

# IgG4 and Autoimmunity

1: J Clin Immunol 2008 Jun;

Impact of Three Anti-TNFalpha Biologics on Existing and Emergent Autoimmunity in Rheumatoid Arthritis and Spondylarthropathy Patients.

Bacquet-Deschryver H, Jouen F, Quillard M, Ménard JF, Goëb V, Lequerré T, Mejjad O, Daragon A, Tron F, Le Loët X, Vittecoq O

Department of Rheumatology, Rouen University Hospital & Inserm U905 (IFRMP 23), Institute for Biomedical Research, University of Rouen, 76031, Rouen Cedex, France.

**OBJECTIVE:** The objective of this study was to analyze the effects of 3 anti-TNFalpha agents on markers of autoimmunity in rheumatoid arthritis (RA) and spondylarthropathy (SPA) patients. **METHODS:** First-time anti-TNFalpha biologics (infliximab, etanercept, or adalimumab) were prescribed to 156 RA and 95 SPA (58 ankylosing spondylarthritides, 37 psoriatic arthritides). During 1-2 years of follow-up, clinical, biological [antinuclear (ANA) and anti-double-stranded (dsDNA) antibodies, rheumatoid factors (RF), and anti-cyclic citrullinated peptide (CCP) for RA], and therapeutic data were collected biannually. **RESULTS:** ANA appeared or ANA and anti-dsDNA titers increased significantly ( $P < 0.001$ ) more under infliximab than etanercept in both rheumatism and than adalimumab in RA patients. During the 2-year follow-up, ANA appeared more in RA patients taking adalimumab than etanercept ( $P = 0.003$ ), but independently of the anti-TNFalpha used; anti-dsDNA titers rarely became positive. Under etanercept or infliximab, ANA and anti-dsDNA were not influenced by the underlying pathology nor were they affected by infliximab intensification over 18 months. Only one case of cutaneous lupus was observed in a patient having IgG anti-dsDNA. The therapeutic responses were independent of ANA and anti-dsDNA titers for all rheumatism and biologics. In RA patients, RF titers, but not anti-CCP levels, declined with the therapeutic response for all biologics. **CONCLUSION:** This is the first study that has evaluated the impact of three TNFalpha blockers on ANA and anti-dsDNA antibodies in RA and SPA patients. Autoimmunity was more induced with infliximab than etanercept and to a lesser degree to adalimumab but, more importantly, this emergent autoimmunity was exceptionally associated to clinical manifestations of lupus.

PMID: 18587633 [found with GoPubMed]

2: Clin Endocrinol (Oxf) 2008 Sep;

Characterization of macroprolactin and assessment of markers of autoimmunity in macroprolactinaemic patients.

Kavanagh-Wright L, Smith TP, Gibney J, McKenna TJ

Department of Endocrinology St. Vincent's University Hospital, Elm Park, Dublin 4, Ireland.

Objective: It has been reported that macroprolactin is a complex of prolactin and an immunoglobulin G (IgG). This study further characterises macroprolactin and evaluates for other markers of autoimmunity using a cohort of macroprolactinaemic sera. Patients and normal subjects: Following treatment of hyperprolactinaemic sera (n=66) with polyethylene glycol (PEG), prolactin values fell from 524-13546mU/L (Range) to 302-8455mU/L, while in macroprolactinaemic sera (n=59), prolactin concentration fell from 525-5747mU/L to 98-468mU/L (PEG treated normoprolactinaemic reference range, 68-390mU/L). Design: Prolactin was measured in sera prior to and following gel filtration chromatography, ultrafiltration, treatment with protein A-sepharose, protein G-sepharose, anti-human IgG-agarose and sodium thiocyanate (NaSCN). The binding of radio-labelled prolactin in macroprolactinaemic sera was also measured. Sera were assayed for anti-thyroid and anti-nuclear antibodies. C-reactive protein (CRP) and CD5 positive B cells were also measured. Comparisons were made between values obtained in normal, hyperprolactinaemic and macroprolactinaemic sera. Results: Macroprolactinaemic sera indicated the presence of an IgG molecule and/or IgG fragments with one or more molecules of prolactin. In 97% of the sera macroprolactin had a molecular weight of 204kDa. Treatment of macroprolactinaemic sera with NaSCN caused dissociation of macroprolactin, releasing monomeric prolactin. Macroprolactinaemic sera did not yield evidence of an increase in markers of autoimmunity when compared with hyperprolactinaemic or normal sera. Conclusions: Comprehensive analysis of macroprolactin confirmed its composition as an IgG molecule or fragment with a prolactin molecule. The occurrence of macroprolactin does not appear to be associated with autoimmunity.

PMID: 18771565 [found with GoPubMed]

3: Clin Biochem 2008 Mar;

Hydroxyl radical damaged Immunoglobulin G in patients with rheumatoid arthritis: Biochemical and immunological studies.

Rasheed Z, Ali R

Department of Biochemistry, Faculty of Medicine, A.M.U., Aligarh-202002, U.P., India.

OBJECTIVES: The role of hydroxyl radical (OH) damaged Immunoglobulin G (IgG) in rheumatoid arthritis (RA) has been investigated. DESIGN AND METHODS: The study was hypothesized that oxidative by-products, like OH-damage IgG, help to initiate autoimmunity in RA. To test this hypothesis, IgG was modified by OH. Immunogenicity of native and modified IgG was probed by inducing polyclonal antibodies in rabbits. Autoantibodies from 77 RA sera were screened by direct binding and competition ELISA. RESULTS: The OH caused extensive damage to IgG. The OH-IgG was found to be highly immunogenic in rabbits as compare to native IgG. High degree of specific binding by 72.7% RA sera autoantibodies towards OH-IgG was observed, in comparison to its native analogue (p<0.05). CONCLUSION: The OH modification of IgG causes perturbations, resulting in the generation of neo-epitopes, and making it a potential immunogen. The IgG modified with the .OH may be one of the factors for the induction of circulating RA autoantibodies.

PMID: 18359293 [found with GoPubMed]

4: Cell Host Microbe 2008 May;3(5):304-15

Liver autoimmunity triggered by microbial activation of natural killer T cells.

Mattner J, Savage PB, Leung P, Oertelt SS, Wang V, Trivedi O, Scanlon ST, Pendem K, Teyton L, Hart J, Ridgway WM, Wicker LS, Gershwin ME, Bendelac A

Howard Hughes Medical Institute, Committee on Immunology, Department of Pathology, University of Chicago, Chicago, IL 60637, USA.  
jochen.mattner@cchmc.org

Humans with primary biliary cirrhosis (PBC), a disease characterized by the destruction of small bile ducts, exhibit signature autoantibodies against mitochondrial Pyruvate Dehydrogenase Complex E2 (PDC-E2) that crossreact onto the homologous enzyme of *Novosphingobium aromaticivorans*, an ubiquitous alphaproteobacterium. Here, we show that infection of mice with *N. aromaticivorans* induced signature antibodies against microbial PDC-E2 and its mitochondrial counterpart but also triggered chronic T cell-mediated autoimmunity against small bile ducts. Disease induction required NKT cells, which specifically respond to *N. aromaticivorans* cell wall alpha-glycuronosylceramides presented by CD1d molecules. Combined with the natural liver tropism of NKT cells, the accumulation of *N. aromaticivorans* in the liver likely explains the liver specificity of destructive responses. Once established, liver disease could be adoptively transferred by T cells independently of NKT cells and microbes, illustrating the importance of early microbial activation of NKT cells in the initiation of autonomous, organ-specific autoimmunity.

PMID: 18474357 [found with GoPubMed]

5: Diabetologia 2008 Feb;

Cytomegalovirus infection in early infancy: risk of induction and progression of autoimmunity associated with type 1 diabetes.

Aarnisalo J, Veijola R, Vainionpää R, Simell O, Knip M, Ilonen J

Immunogenetics Laboratory, University of Turku, MediCity, BioCity 4th floor, Tykistökatu 6A, 20520, Turku, Finland, johanna.aarnisalo@utu.fi.

**AIMS/HYPOTHESIS:** Type 1 diabetes is an autoimmune disease resulting from a complex interplay between genetic and environmental factors. Cytomegalovirus (CMV) infection is one of the environmental factors implicated in the development of type 1 diabetes, although the association remains unproven. We aimed to clarify the possible correlation between CMV infections and type 1 diabetes-associated autoimmunity at the time point of autoantibody appearance in young children with HLA-conferred disease susceptibility. **METHODS:** CMV-specific IgG antibodies were analysed from serum samples of 169 children who had developed the first type 1 diabetes-associated autoantibody by the age of 2 years and who turned positive for multiple autoantibodies during later follow-up. We also studied 791 control children matched for sex, age and HLA genotype. The subsequent progression to clinical diabetes was analysed. The serum specimens used were collected at the time of autoantibody seroconversion or within the next 6 months. **RESULTS:** The frequency of CMV antibodies was similar in both study groups at the time of the first autoantibody appearance. Of the index children, 38 (22.5%) were CMV IgG antibody-positive, while the figure for control children was 206 (26.0%;  $p = 0.38$ ). No association between perinatal CMV infection and progression to type 1 diabetes was observed. **CONCLUSIONS/INTERPRETATION:** According to these results, perinatal CMV infections are not associated with early serological signs of beta cell

autoimmunity or progression to type 1 diabetes in children with diabetes risk-associated HLA genotype.

PMID: 18278478 [found with GoPubMed]

6: J Exp Med 2008 Mar;

Distinct cell-specific control of autoimmunity and infection by Fc{gamma}RIIb.

Brownlie RJ, Lawlor KE, Niederer HA, Cutler AJ, Xiang Z, Clatworthy MR, Floto RA, Greaves DR, Lyons PA, Smith KG

Cambridge Institute for Medical Research and the Department of Medicine, University of Cambridge School of Clinical Medicine, Addenbrooke's Hospital, Cambridge CB2 2OY, England, UK.

FcgammaRIIb is an inhibitory Fc receptor expressed on B cells and myeloid cells. It is important in controlling responses to infection, and reduced expression or function predisposes to autoimmunity. To determine if increased expression of FcgammaRIIb can modulate these processes, we created transgenic mice overexpressing FcgammaRIIb on B cells or macrophages. Overexpression of FcgammaRIIb on B cells reduced the immunoglobulin G component of T-dependent immune responses, led to early resolution of collagen-induced arthritis (CIA), and reduced spontaneous systemic lupus erythematosus (SLE). In contrast, overexpression on macrophages had no effect on immune responses, CIA, or SLE but increased mortality after *Streptococcus pneumoniae* infection. These results help define the role of FcgammaRIIb in immune responses, demonstrate the contrasting roles played by FcgammaRIIb on B cells and macrophages in the control of infection and autoimmunity, and emphasize the therapeutic potential for modulation of FcgammaRIIb expression on B cells in inflammatory and autoimmune disease.

PMID: 18362174 [found with GoPubMed]

7: PLoS ONE 2008;3(2):e1637

A novel immunoglobulin-immunoglobulin interaction in autoimmunity.

Kawa S, Kitahara K, Hamano H, Ozaki Y, Arakura N, Yoshizawa K, Umemura T, Ota M, Mizoguchi S, Shimozuru Y, Bahram S

Center for Health, Safety and Environmental Management, Shinshu University, Matsumoto, Japan.

Well over six decades since its first description, the Rheumatoid Factor (RF)-autoantibodies recognizing Fc (constant) portion of IgG through their own Fab (antigen binding variable segments)-is believed to have come of age. Autoimmune pancreatitis is a unique form of pancreatitis, biologically characterized by an elevated serum IgG4 concentration. Given the fact that IgG4 myeloma proteins can act as RF, we initially hypothesized that IgG4 in autoimmune pancreatitis might do likewise, hence potentially contributing to disease pathogenesis. Indeed Western blotting clearly showed that IgG4 binds to IgG1 kappa, IgG2 kappa, IgG3 kappa myeloma proteins, as well as to IgG Fc, in line with a typical RF activity. Further experiments however unraveled the unexpected fact that unlike hitherto known RF, IgG4 does not engage IgG Fc through its Fab, but its very own Fc. These data therefore collectively describe a Novel RF (NRF) in autoimmune pancreatitis. In the

future, the relevance of NRF, beyond autoimmune pancreatitis, in both diagnosis/prognosis as well as pathophysiology of autoimmune and other systemic diseases where IgG4's role seems paramount, needs to be systematically assessed.

PMID: 18297131 [found with GoPubMed]

8: J Cell Mol Med 2008 Feb;

Interphotoreceptor retinoid binding protein as biomarker in systemic autoimmunity with eye afflictions.

Descamps FJ, Kangave D, Cauwe B, Martens E, Geboes K, El-Asrar AA, Opdenakker G

Department of Microbiology and Immunology, Rega Institute for Medical Research, University of Leuven, Leuven, Belgium.

Autoimmune diseases of the eye, exemplified by Behçet disease and Vogt-Koyanagi-Harada disease, are a major cause of blindness. We studied interphotoreceptor retinoid binding protein (IRBP), a dominant autoimmune antigen in the eye. Aqueous humor samples from 28 patients with active uveitis were analysed for immunoglobulin G (IgG) content as a marker for blood-ocular barrier breakdown and by gelatinase B zymography for the detection of inflammation. The data were correlated with the presence of intact IRBP ( asymptotically equal to 140 kD) as determined by Western blot analysis and with the clinical disease activity. Aqueous humor samples from control eyes and eyes with low disease activity showed positive immunoreactivity for intact IRBP. The IRBP signal weakened or disappeared with higher disease activity. Significant positive correlations were observed between disease activity and levels of matrix metalloproteinase-9 ( $r(s) = 0.713$ ;  $p < 0.001$ ) and IgG ( $r(s) = 0.580$ ;  $p = 0.001$ ). Significant negative correlations were found between levels of IRBP and disease activity ( $r(s) = -0.520$ ;  $p = 0.005$ ) and levels of MMP-9 ( $r(s) = -0.727$ ;  $p < 0.001$ ) and of IgG ( $r(s) = 0.834$ ;  $p < 0.001$ ). Whereas neutrophil elastase converted intact IRBP into an immunoreactive 55 kD peptide in vitro, the conversion by neutrophil degranulates resembled more the in vivo context with a complete degradation of IRBP. Reversal of inflammation with immunosuppressive therapy was accompanied with reappearance of intact IRBP and disappearance of IgG and MMP-9. The analysis of IRBP proteolysis is useful as a biomarker for uveitis and suggests that inhibition of proteinases might become a therapeutic strategy in an inflammatory context of a damaged blood-ocular barrier.

PMID: 18266969 [found with GoPubMed]

9: Arch Neurol 2008 Jan;65(1):78-83

Neuromyelitis optica and non organ-specific autoimmunity.

Pittock SJ, Lennon VA, de Seze J, Vermersch P, Homburger HA, Wingerchuk DM, Lucchinetti CF, Zéphir H, Moder K, Weinshenker BG

Department of Neurology, Mayo Clinic College of Medicine, 200 First St SW, Rochester, MN 55905. weinb@mayo.edu.

BACKGROUND: Neuromyelitis optica (NMO) is often associated with other clinical or serological markers of non-organ-specific autoimmunity.  
OBJECTIVE: To evaluate the relationship between NMO spectrum disorders

(NMOSDs), including NMO, longitudinally extensive transverse myelitis, and recurrent optic neuritis, and autoimmune disease. We concentrated on the association with systemic lupus erythematosus (SLE), Sjögren syndrome (SS), or serological evidence of these disorders, which commonly is a source of diagnostic confusion. DESIGN: Retrospective blinded serological survey. SETTING: Mayo Clinic College of Medicine, Rochester, and Centre Hospitalier Régional Universitaire de Lille. METHODS: Group 1 included 153 US patients with NMOSDs (78 with NMO and 75 with longitudinally extensive transverse myelitis) and 33 control subjects with SS/SLE. Group 2 included 30 French patients with SS/SLE, 14 with NMOSDs (6 with NMO, 6 with longitudinally extensive transverse myelitis, and 2 with recurrent optic neuritis), 16 without NMOSDs, and 4 with NMO without SS/SLE. RESULTS: For group 1, NMO-IgG was detected in 66.7%, antinuclear antibodies in 43.8%, and Sjögren syndrome A (SSA) antibodies in 15.7% of patients with NMO and longitudinally extensive transverse myelitis. Five NMO-IgG-seropositive patients with NMOSDs had coexisting SLE, SS, or both. Antinuclear antibodies and SSA antibodies were more frequent in NMO-IgG-seropositive patients than in NMO-IgG-seronegative patients ( $P = .001$ ). For group 2, NMO-IgG was detected in 5 of 14 patients (35.7%) with NMOSDs and SS/SLE and in 2 of 4 patients (50.0%) with NMO without SS/SLE ( $P = .59$ ). We detected NMO-IgG only in patients with NMOSDs and not in 49 controls with SS/SLE but without optic neuritis or myelitis from the 2 cohorts ( $P = .01$ ). CONCLUSION: Neuromyelitis optica spectrum disorders with seropositive findings for NMO-IgG occurring with SS/SLE or non-organ-specific autoantibodies is an indication of coexisting NMO rather than a vasculopathic or other complication of SS/SLE.

PMID: 18195142 [found with GoPubMed]

10: Br J Nutr 2007 Aug;:1-8

Lactobacillus casei Shirota administered during lactation increases the duration of autoimmunity in rats and enhances lung inflammation in mice.

Ezendam J, van Loveren H

National Institute for Public Health and the Environment (RIVM), Laboratory for Health Protection Research, Bilthoven, The Netherlands.

Probiotics are considered to have beneficial effects on the immune system. An association between the composition of microflora and allergies has been demonstrated and modulation of microflora of infants by probiotics might reduce the risk of allergies. To investigate immune effects of probiotics administered early after birth two animal models were used: a mouse model for respiratory allergy; a rat model for experimental autoimmune encephalomyelitis (EAE). Administration of the probiotic Lactobacillus casei Shirota (LcS) started during lactation and allergy or autoimmunity were induced at an adult age. Results were compared with similar studies in rats and mice that were exposed from an adult age. Early administration of LcS significantly increased lymphocytes in the lungs of female mice and eosinophils in the lungs of male mice. LcS had no effects on ovalbumin-specific serum IgE levels and on ovalbumin-specific cytokine production by spleen cells. In adult mice, LcS enhanced ovalbumin-specific cytokine production by the spleen, whereas other parameters were not affected. Early administration of LcS to rats significantly increased the duration of clinical symptoms of EAE. This was also demonstrated previously in adult rats exposed to LcS. Timing of administration of LcS induced divergent effects on respiratory allergy and only early administration of LcS exacerbated lung inflammation. In the EAE model, LcS stimulated autoimmunity independent of the timing of administration. Our data show that immune effects of probiotics do not necessarily induce beneficial

effects. It is therefore important that, in the evaluation of probiotics, efficacy and safety should be demonstrated.

PMID: 17678568 [found with GoPubMed]

11: J Immunol 2007 Dec;179(11):7568-76

The Rheumatoid Arthritis-Associated Autoantigen hnRNP-A2 (RA33) Is a Major Stimulator of Autoimmunity in Rats with Pristane-Induced Arthritis.

Hoffmann MH, Tuncel J, Skriner K, Tohidast-Akrad M, Türk B, Pinol-Roma S, Serre G, Schett G, Smolen JS, Holmdahl R, Steiner G

Department of Rheumatology, Medical University of Vienna, Vienna, Austria;

A single intradermal injection of the mineral oil pristane in susceptible DA.1F rats induces erosive arthritis closely mimicking rheumatoid arthritis (RA). Pristane-induced arthritis (PIA) is driven by autoreactive T cells but no autoantigen has been identified to date. We therefore analyzed B and T cell responses to autoantigens potentially involved in the pathogenesis of RA, including IgG, citrullinated proteins, stress proteins, glucose-6-phosphate isomerase, and heterogeneous nuclear ribonucleoprotein (hnRNP)-A2 (RA33). IgG and IgM autoantibodies to hnRNP-A2 were detectable in sera of pristane-primed DA.1F rats already 1 wk before disease onset, reached maximum levels during the acute phase, and correlated with arthritis severity. Apart from rheumatoid factor, autoantibodies to other Ags were not observed. CD4(+) lymph node cells isolated 10 days after pristane injection produced IFN-gamma but not IL-4 in response to stimulation with hnRNP-A2, whereas none of the other candidate Ags elicited cytokine secretion. Surprisingly, hnRNP-A2 also stimulated lymph node cells of naive animals to produce inflammatory cytokines in a MyD88-dependent manner. Furthermore, hnRNP-A2 was highly overexpressed in the joints of rats injected with pristane. Overexpression coincided with the appearance of anti-RA33 Abs and preceded the onset of clinical symptoms of PIA by several days. Taken together, these data suggest hnRNP-A2 to be among the primary inducers of autoimmunity in PIA. Therefore, this Ag might play a pivotal role in the pathogenesis of PIA and possibly also human RA.

PMID: 18025202 [found with GoPubMed]

12: Immunology 2007 May;

Chronic exposure in vivo to thyrotropin receptor stimulating monoclonal antibodies sustains high thyroxine levels and thyroid hyperplasia in thyroid autoimmunity-prone HLA-DRB1\*0301 transgenic mice.

Flynn JC, Gilbert JA, Meroueh C, Snower DP, David CS, Kong YC, Paul Banga J

Department of Immunology and Microbiology, Wayne State University School of Medicine, Detroit, MI, USA.

We have examined the induction of autoimmunity and the maintenance of sustained hyperthyroidism in autoimmunity-prone human leucocyte antigen (HLA) DR3 transgenic non-obese diabetic (NOD) mice following chronic stimulation of the thyrotropin receptor (TSHR) by monoclonal thyroid-stimulating autoantibodies (TSAbs). Animals received weekly injections over the course of 9 weeks of monoclonal antibodies (mAbs) with strong thyroid-stimulating properties. Administration of the mAbs KSAb1 (IgG2b) or KSAb2 (IgG2a), which have similar stimulating properties but different TSH-

binding blocking activity, resulted in significantly elevated serum thyroxine (T(4)) levels and thyroid hyperplasia. After the first injection, an initial surge then fall in serum T(4) levels was followed by sustained elevated levels with subsequent injections for at least 63 days. Examination of KSAb1 and KSAb2 serum bioactivity showed that the accumulation of the TSAbs in serum was related to their subclass half-lives. The thyroid glands were enlarged and histological examination showed hyperplastic follicles, with minimal accompanying thyroid inflammation. Our results show that chronic in vivo administration of mAbs with strong thyroid-stimulating activity resulted in elevated T(4) levels, suggesting persistent stimulation without receptor desensitization, giving a potential explanation for the sustained hyperthyroid status in patients with Graves' disease. Moreover, despite the presence of HLA disease susceptibility alleles and the autoimmune prone NOD background genes, chronic stimulation of the thyroid gland did not lead to immune cell-mediated follicular destruction, suggesting the persistence of immunoregulatory influences to suppress autoimmunity.

PMID: 17535305 [found with GoPubMed]

13: J Autoimmun 2008;30(1-2):51-7

Antinucleosome antibodies in primary antiphospholipid syndrome: A hint at systemic autoimmunity?

Andreoli L, Pregnotato F, Burlingame RW, Allegri F, Rizzini S, Fanelli V, Radice A, Corace C, Sinico RA, Meroni PL, Tincani A

Rheumatology and Clinical Immunology Unit, Spedali Civili, Piazzale Spedali Civili 1, University of Brescia, 25123 Brescia, Italy.

**BACKGROUND:** Antinucleosome antibodies (anti-NCS) are reported to be highly sensitive and specific for systemic lupus erythematosus (SLE) and to correlate with disease activity. They may appear in early stages of the disease, in particular before anti-dsDNA antibodies, being a potential marker for identifying patients susceptible to SLE. Patients with primary antiphospholipid syndrome (PAPS) may develop full-blown SLE but there is no evidence for markers predictive for that. **AIM:** To evaluate whether anti-NCS may be predictors for full-blown or lupus like disease (LL) in a cohort of PAPS patients. **METHODS:** A multicentric cohort of 105 PAPS patients was tested for IgG/IgM anti-NCS by using a home made assay with H1-stripped chromatin as antigen. **RESULTS:** Eighty-one out of 105 (77%) of the patients were positive for anti-NCS; medium-high titre results were present only in 49/105 (46%). Anti-NCS were more frequently detected in PAPS+LL, but no relationship with clinical/serological features was found, except for a weak correlation with anti-dsDNA antibodies. Two PAPS patients evolved into full-blown SLE during the follow-up and displayed high titre anti-NCS many years before. **CONCLUSIONS:** Our findings suggest that anti-NCS might be added to the mosaic of autoimmune phenomena characterizing PAPS patients and in particular those with more chance to evolve to SLE.

PMID: 18191541 [found with GoPubMed]

14: Isr Med Assoc J 2008 Jan;10(1):13-9

The mosaic of autoimmunity: prediction, autoantibodies, and therapy in autoimmune diseases--2008.



Shoenfeld Y, Blank M, Abu-Shakra M, Amital H, Barzilai O, Berkun Y, Bizzaro N, Gilburd B, Zandman-Goddard G, Katz U, Krause I, Langevitz P, Mackay IR, Orbach H, Ram M, Sherer Y, Toubi E, Gershwin ME

Department of Medicine B and Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, Israel. shoenfel@post.tau.ac.il

PMID: 18300564 [found with GoPubMed]

15: J Invest Dermatol 2007 Jul;

A Pathogenic Role for IgE in Autoimmunity: Bullous Pemphigoid IgE Reproduces the Early Phase of Lesion Development in Human Skin Grafted to nu/nu Mice.

Fairley JA, Burnett CT, Fu CL, Larson DL, Fleming MG, Giudice GJ

[1] 1Department of Dermatology, Medical College of Wisconsin, Milwaukee, Wisconsin, USA [2] 4Dermatology Section, Veterans Affairs Medical Center, Milwaukee, Wisconsin, USA.

Bullous pemphigoid (BP) is an autoimmune disease characterized by subepidermal blistering. Based on previous work, IgG autoantibodies directed against BP180 are thought to be the primary pathogenic agent in BP. In addition to these IgG autoantibodies, however, most BP patients produce IgE class autoantibodies that also react with BP180, and total IgE levels are often elevated in this disease. To directly test whether BP IgE is pathogenic, 6 ng of total IgE isolated from two BP and two normal sera were injected into human skin grafted onto athymic, nude mice. Twenty-four hours after injection, erythematous, elevated plaques were observed in all human skin grafts receiving BP IgE (n=11), but not control IgE (n=9). Histologic and ultrastructural examination of the lesions showed engorgement of blood vessels and a dermal infiltrate composed of neutrophils, eosinophils, and mast cells, many of which were degranulated. At a higher dose of BP IgE (47 ng), histological separation of the epidermis from the dermis was observed in two of the three grafts. The BP IgE-induced erythematous plaques were reminiscent of those clinically seen in BP. This provides early evidence of a direct demonstration of a pathogenic role for IgE class autoantibodies in a human autoimmune disease. *Journal of Investigative Dermatology* advance online publication, 5 July 2007; doi:10.1038/sj.jid.5700958.

PMID: 17611576 [found with GoPubMed]

16: J Paediatr Child Health 2007 Oct;43(10):716-8

Congenital rubella syndrome, hyper-IgM syndrome and autoimmunity in an 18-year-old girl.

Palacin PS, Castilla Y, Garzón P, Figueras C, Castellví J, Español T

Paediatric Immunology and Infectious Disease Unit, Vall d'Hebron Hospital, Barcelona, Spain.

Congenital rubella syndrome can be associated with dysgammaglobulinaemia and autoimmune phenomena in adult and paediatric population. The aim of this article is to present the association between a congenital rubella syndrome with hypogammaglobulinaemia and hyper IgM diagnosed at the age of 8 months and autoimmune manifestations in an 18-year-old girl. A medical

chart review of this patient since admission at our institution at 8 months of age was carried out. During infancy she presented the classical manifestations of a rubella syndrome (sensorineural deafness and brain calcifications in basal ganglia) with respiratory and gastrointestinal infections. She was also diagnosed of localised scleroderma and thyroiditis. She has been on intravenous immunoglobulin since diagnosis, with rapid normalisation of IgG and IgM levels, decreased incidence of infectious processes, but with persistent autoimmune phenomena. At 18 years of age she was admitted because of a thyroid mass. Fine needle aspiration biopsy was not conclusive and thyroidectomy was performed. Pathology studies showed no malignancy. She is now on replacement therapy with thyroid hormones. Our aim is to emphasise the importance of the association between autoimmune phenomena in patients with immunodeficiencies, even secondary to some infections, and the increased frequency of malignancies owing to the persistent immunologic defect in this syndrome.

PMID: 17854460 [found with GoPubMed]

17: Ann N Y Acad Sci 2007 Sep;1110:410-25

Harnessing autoimmunity (vitiligo) to treat melanoma: a myth or reality?

Ram M, Shoenfeld Y

FRCP, Head, Department of Medicine "B" and Center for Autoimmune Diseases, Chaim Sheba Medical Center, Tel-Hashomer 52621, Israel.  
shonfel@post.tau.ac.il.

Melanoma is a highly malignant tumor derived from skin melanocytes (pigment-producing cells), which is associated with a significant rate of systemic metastases and death. Various therapeutic approaches for melanoma have been attempted in recent years, including the use of chemotherapy, immunotherapy, and ablative surgical and radiation treatments. However, in many cases these treatments fail as the tumor becomes resistant to the treatment and rapidly spreads and causes death. Reports in the medical literature have documented the unique immunogenic nature of melanoma where antigens, antibodies, and immune complexes seem to play a major role in the course of the disease. Anti-melanoma antibodies can cross-react with antigens on normal melanocytes, therefore causing the appearance of an associated hypopigmentation that resembles vitiligo. Vitiligo is a dermatological disorder characterized by local, dispersed, or diffuse white patches on the skin as a result of the destruction of melanocytes. This disease is believed to be an autoimmune disorder since autoantibodies against membrane components of melanocytes are found in the sera of patients with vitiligo. Melanoma triggers an anti-tumor response in many patients. Unfortunately, such anti-tumor response is insufficient to elicit tumor regression and the tumor continues to proliferate. Since the prognosis of melanoma in patients and animals with vitiligo is more favorable than in the general population, it was hypothesized that sera from patients with vitiligo may react against melanoma cells. Such studies have demonstrated that exposure of tumor cells to the sera resulted in inhibition of proliferation of the melanoma cells in vitro and in regression of melanoma metastases in mice presumably on account of the presence of the high titer of anti-melanoma antibodies in the sera used in these studies. In this review we discuss the known data and hypothetical assumptions related to the use of vitiligo-associated antibodies against melanoma, as well as characterize the immune mechanisms involved in this process.

PMID: 17911456 [found with GoPubMed]

18: Minerva Gastroenterol Dietol 2008 Dec;54(4):375-87

Serology in autoimmune pancreatitis.

Raina A, Greer JB, Whitcomb DC

University of Pittsburgh School of Medicine, Division of Gastroenterology, Hepatology and Nutrition, Pittsburgh, PA, USA whitcomb@pitt.edu.

Autoimmune pancreatitis (AIP) is the pancreatic manifestation of a systemic immune-driven, inflammatory process that can involve organs such as the bile duct, salivary glands and lymph nodes, in addition to the pancreas. Many of the presenting signs and symptoms of AIP, including painless jaundice, weight loss and mild epigastric pain, are characteristic of pancreatic adenocarcinoma; thus, obtaining an accurate diagnosis to avoid unnecessary surgery is imperative. AIP responds very well to steroid treatment, although it may recur in up to 20% to 40% of cases. The diagnostic criteria for AIP are histological, radiographic, clinical and laboratory-based in nature. Although no international consensus on diagnostic criteria has yet been made, some of the diagnostic features of AIP include elevated gamma globulin, immunoglobulin, and, in particular, immunoglobulin G4 fraction (IgG4). The search for a distinct serological marker of AIP has included antibodies to a wide range of antigenic stimuli. To date, there have been studies of AIP and antibodies to lactoferrin, carbonic anhydrase isoforms II and IV, pancreatic secretory trypsin inhibitor (PSTI or SPINK) as well as to less sensitive or specific markers of autoimmunity, such as antinuclear antibody and rheumatoid factor. Although there are some preliminary strengths of association with PSTI antibodies, none of these biomarkers appears to be sensitive or specific enough to serve as distinctive evidence of AIP. At the current time, elevations of IgG4 to greater than 280 mg/dL remain the most reliable and reproducible indicator that a patient has AIP.

PMID: 19047979 [found with GoPubMed]

19: Minerva Gastroenterol Dietol 2008 Dec;54(4):359-64

Autoimunné pancreatitis.

Dite P, Trna J, Novotny I

Department of Hepatogastroenterology, University Hospital of Brno, Brno, Czech Republic pdite@med.muni.cz.

Since Sarles et al. in 1961 reported a particular type of pancreatitis with hypergammaglobulinemia, many investigators have suggested that an autoimmune mechanism may be involved in some patients with pancreatitis. Recently, the concept of autoimmune pancreatitis (AIP) has been proposed in which several unique clinical, biochemical and imaging signs have been shown. In the TIGARO risk factor classification system of chronic pancreatitis proposed in 2001, autoimmunity was categorized as one of six of the risk factors. AIP is a chronic fibroinflammatory condition primarily affecting pancreas. It is an atypical form of chronic pancreatitis characterized by sonolucent swelling of the pancreas, diffuse irregular narrowing of the pancreatic duct, and high serum IgG4 concentrations. Co-occurrence of extrapancreatic involvement, such as sclerosing cholangitis, retroperitoneal fibrosis, or salivary gland swelling were found: Histopathologic examinations detected extrapancreatic lesions such as lymphoplasmacytic inflammation and fibrosis, similar to those present in

the pancreatic tissue, suggesting a common pathogenesis. These findings suggest that the disease involves a general involvement of the digestive system, although the presence of such involvement has not been fully elucidated. Steroids are a main therapeutic option in AIP.

PMID: 19047977 [found with GoPubMed]

20: Blood 2008 Aug;

The majority of cutaneous marginal zone B cell lymphomas express class switched immunoglobulins and develop in a T helper type 2 inflammatory environment.

van Maldegem F, van Dijk R, Wormhoudt TA, Kluin PM, Willemze R, Cerroni L, van Noesel CJ, Bende RJ

Department of Pathology, Academic Medical Center, Amsterdam, Netherlands.

Extranodal marginal zone B cell lymphomas (MZBCLs) arise on a background of chronic inflammation due to organ-specific autoimmunity, infection, or by unknown causes. Well known examples are salivary gland MZBCL in Sjogren's sialadenitis and gastric MZBCL in *Helicobacter pylori* gastritis. MZBCLs express CXCR3, a receptor for IFN-gamma-induced chemokines highly expressed in the chronic inflammatory environment. The immunoglobulin variable heavy/light chain (IgVH/IgVL) gene repertoire of salivary gland- and gastric- MZBCL appears restricted and frequently encodes BCRs with rheumatoid factor (RF) reactivity. Primary cutaneous marginal zone B cell lymphomas (PCMZLs) are regarded as the skin-involving counterpart of extranodal MZBCL. Although PCMZLs have been associated with *Borrelia burgdorferi* dermatitis, PCMZLs generally arise due to unknown causes. We studied an extensive panel of PCMZLs and show that PCMZLs do not conform to the general profile of extranodal MZBCL. Whereas most non-cutaneous MZBCLs express IgM, PCMZL in majority express IgG, IgA and IgE, and do not show an obvious immunoglobulin repertoire bias. Furthermore, the isotype-switched PCMZLs lack CXCR3 and seem to arise in a different inflammatory environment, as compared to other extranodal MZBCL.

PMID: 18687986 [found with GoPubMed]

21: Nat Med 2008 Oct;

Molecular mimicry in pauci-immune focal necrotizing glomerulonephritis.

Kain R, Exner M, Brandes R, Ziebermayr R, Cunningham D, Alderson CA, Davidovits A, Raab I, Jahn R, Ashour O, Spitzauer S, Sunder-Plassmann G, Fukuda M, Klemm P, Rees AJ, Kerjaschki D

Department of Pathology, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Wien, Austria.

Pauci-immune focal necrotizing glomerulonephritis (FNGN) is a severe inflammatory disease associated with autoantibodies to neutrophil cytoplasmic antigens (ANCA). Here we characterize autoantibodies to lysosomal membrane protein-2 (LAMP-2) and show that they are a new ANCA subtype present in almost all individuals with FNGN. Consequently, its prevalence is nearly twice that of the classical ANCAs that recognize myeloperoxidase or proteinase-3. Furthermore, antibodies to LAMP-2 cause pauci-immune FNGN when injected into rats, and a monoclonal antibody to human LAMP-2 (H4B4) induces apoptosis of human microvascular endothelium in

vitro. The autoantibodies in individuals with pauci-immune FNGN commonly recognize a human LAMP-2 epitope (designated P(41-49)) with 100% homology to the bacterial adhesin FimH, with which they cross-react. Rats immunized with FimH develop pauci-immune FNGN and also develop antibodies to rat and human LAMP-2. Finally, we show that infections with fimbriated pathogens are common before the onset of FNGN. Thus, FimH-triggered autoimmunity to LAMP-2 provides a previously undescribed clinically relevant molecular mechanism for the development of pauci-immune FNGN.

PMID: 18836458 [found with GoPubMed]

22: Ann Neurol 2008 Sep;64(3):332-43

Autoantibodies in gluten ataxia recognize a novel neuronal transglutaminase.

Hadjivassiliou M, Aeschlimann P, Strigun A, Sanders DS, Woodroffe N, Aeschlimann D

Department of Neurology, Royal Hallamshire Hospital, Sheffield, UK.

**OBJECTIVE:** Gluten sensitivity typically presents as celiac disease, a chronic, autoimmune-mediated, small-intestinal disorder. Neurological disorders occur with a frequency of up to 10% in these patients. However, neurological dysfunction can also be the sole presenting feature of gluten sensitivity. Development of autoimmunity directed toward different members of the transglutaminase gene family could offer an explanation for the diversity in manifestations of gluten sensitivity. We have identified a novel neuronal transglutaminase isozyme and investigated whether this enzyme is the target of the immune response in patients with neurological dysfunction. **METHODS:** Using recombinant human transglutaminases, we developed enzyme-linked immunosorbent assays and inhibition assays to analyze serum samples of patients with gluten-sensitive gastrointestinal and neurological disorders, and various control groups including unrelated inherited or immune conditions for the presence and specificity of autoantibodies. **RESULTS:** Whereas the development of anti-transglutaminase 2 IgA is linked with gastrointestinal disease, an anti-transglutaminase 6 IgG and IgA response is prevalent in gluten ataxia, independent of intestinal involvement. Such antibodies are absent in ataxia of defined genetic origin or in healthy individuals. Inhibition studies showed that in those patients with ataxia and enteropathy, separate antibody populations react with the two different transglutaminase isozymes. Furthermore, postmortem analysis of brain tissue showed cerebellar IgA deposits that contained transglutaminase 6. **INTERPRETATION:** Antibodies against transglutaminase 6 can serve as a marker in addition to human leukocyte antigen type and detection of anti-gliadin and anti-transglutaminase 2 antibodies to identify a subgroup of patients with gluten sensitivity who may be at risk for development of neurological disease.

PMID: 18825674 [found with GoPubMed]

23: Autoimmunity 2008 Sep;41(6):484-9

Immunoabsorption as treatment option in dilated cardiomyopathy.

Felix SB, Staudt A

Department of Internal Medicine B, Ernst-Moritz-Arndt-University of Greifswald, Greifswald, Germany.

Abnormalities of the cellular and humoral immune system have been described in patients with dilated cardiomyopathy (DCM). Various circulating cardiac autoantibodies have been detected among DCM patients. Circulating antibodies are extractable by immunoabsorption (IA). Recent open controlled pilot studies have consequently shown that removal of circulating antibodies by IA induces improvement of cardiac function in DCM. IA, furthermore, decreases myocardial inflammation. In vitro data indicate that cardiodepressive antibodies play an important role in cardiac dysfunction of DCM patients; removal of these antibodies may accordingly represent the essential mechanism of IA in DCM. Furthermore, detection of cardiodepressive antibodies predicts hemodynamic benefits during IA. These antibodies belong to immunoglobulin G subclass 3. Recent data indicate that newly detected sarcolemmal Fc(gamma) receptors IIa are involved in the functional effects of cardiac autoantibodies.

PMID: 18781476 [found with GoPubMed]

24: Clin Chim Acta 2008 May;

Up-regulation of adhesion molecule expression and induction of TNF-alpha on vascular endothelial cells by antibody against human parvovirus B19 VP1 unique region protein.

Tzang BS, Tsai CC, Shi JY, Hsu TC

Institutes of Biochemistry and Biotechnology, Chung Shan Medical University, Taichung, Taiwan, ROC.

BACKGROUND: Human parvovirus B19 infection has been frequently described as a cause or trigger of various autoimmune diseases. In previous studies, we have postulated the association among human parvovirus B19 (B19)-VP1 unique region (VP1u), production of anti-beta2-glycoprotein I (anti-beta2GPI) antibody and anti-phospholipid syndrome (APS)-like autoimmunity. However, the precise role of B19-VP1u in induction of APS is still obscure. METHODS: To further elucidate the pathogenic roles of VP1u in B19 infection and autoimmunity, we examined the effect of anti-B19-VP1u IgG antibodies on endothelial cells that is recognized to play crucial roles in APS. Human vascular endothelial cells, ECV-304, were incubated with various preparations of purified human or rabbit IgG. The activation of endothelial cells and production of cytokines were assessed by flow cytometry and ELISA, respectively. RESULTS: Purified IgG from rabbits immunized with recombinant B19-VP1u proteins can up-regulate ICAM-1 (CD54), VCAM-1 (CD106), E-selectin (CD62E), MHC class II (HLA-DR, DP, DQ) molecule expression, and TNF-alpha production in endothelial cells as compared to those endothelial cells cultured with control IgG. Additionally, significantly increased phosphorylated-P38 mitogen-activated protein kinase (P38 MAPK) and iNOS were observed in both human anti-beta2GPI IgG and rabbit anti-B19-VP1u IgG treated-ECV-304 cells, respectively. CONCLUSIONS: These experimental results imply that antibodies against B19-VP1u play important roles in the immunopathological processes as well as human anti-beta2GPI IgG that leads to development of APS by involving p38 phosphorylation and iNOS activation. It could provide a clue in understanding the role of anti-B19-VP1u antibodies in APS manifestations.

PMID: 18538665 [found with GoPubMed]

25: Hum Exp Toxicol 2008 Sep;27(9):701-7

Toxicological evaluation of the immune function of pesticide workers, a European wide assessment.

Steerenberg P, van Amelsvoort L, Colosio C, Corsini E, Fustinoni S, Vergieva T, Zaikov C, Pennanen S, Liesivuori J, Van Loveren H

National Institute of Public Health and the Environment, Bilthoven, The Netherlands.

In this study, the prolonged low-dose exposure of mixtures of pesticides has been examined on hematological parameters and components of the immune defense in occupationally exposed humans. This investigation was carried out in five field studies in: the Netherlands (flower bulb growers, mainly re-entry workers), Italy (vineyard workers), Finland (potato farmers), and Bulgaria (workers from a zineb factory and greenhouse workers). Immunotoxicity was studied by measuring hematological parameters, complement, immunoglobulins, lymphocyte subpopulations, natural killer cells, autoimmunity, and antibody responses to hepatitis B vaccination. The total study population consisted of 248 pesticide-exposed and 231 non-occupationally exposed workers. As a surrogate measure of pesticide exposure the urinary excretion of ethylenethiourea (ETU), the main metabolite ethylenebisdithiocarbamates was measured. A significantly higher level of ETU in occupationally exposed subjects compared with controls (2.7 +/- 8.1 mug/g vs 0.5 +/- 3.7 mug/g creatinine) was found. Statistically significant differences, albeit very low, were found for complement C3 and C4 and the immunoglobulin classes IgG4 and IgA. For complement and IgG4, the levels were slightly increased and the level of IgA was decreased. In the lymphocyte populations, the CD8 subpopulation was increased. No effects were found on autoimmune antibodies and antibody response to hepatitis vaccination. In conclusion, pesticide exposure under various work place conditions in Europe was associated only with some subtle effects on the immune system, which may suggest that occupational exposure to pesticides does not influence the immunologic system in a clinically significant fashion, and does not pose a significant health risk to the exposed subjects.

PMID: 19042952 [found with GoPubMed]

26: J Clin Immunol 2008 Jun;

Renal Expression of Adhesion Molecules in Anca-Associated Disease.

Arrizabalaga P, Solé M, Abellana R, Ascaso C

Service of Nephrology, Hospital Clínic and the Biomedical Investigation Institute August Pi i Sunyer, c/ Villarroel, 170, 08036, Barcelona, Spain, parriza@clinic.ub.es.

INTRODUCTION: Anti-neutrophil cytoplasmic autoantibodies (ANCA)-associated disease among other manifestations can underlie rapidly progressive glomerulonephritis (RPGN), with crescentic and necrotizing GN. Differences in pathogenic immune mechanisms in RPGN may provide differences in the renal expression of adhesion molecules mediating these lesions. METHODS: Renal intercellular adhesion molecule 1 (ICAM-1; CD54) and vascular cell adhesion molecule 1 (VCAM-1; CD106) were assessed in 40 patients with type I RPGN (anti-glomerular basement membrane antibodies, n = 4), type II (immune complexes, n = 17), and type III (ANCA, n = 19). Enzyme-linked immunosorbent assay (ELISA) for detection of immunoglobulin G antibodies against the Goodpasture's antigen and indirect immunofluorescence and ELISA for myeloperoxidase (MPO) and proteinase 3 (PR3) were performed for ANCA testing. Ten normal renal tissues were used as controls. Relationships

between ICAM-1 and VCAM-1, histopathologic features, and CD18, CD14, and CD3 cells were analyzed. RESULTS: Abnormal ICAM-1 and VCAM-1 in tubule was seen in >80% of biopsies with RPGN. Abnormal VCAM-1 in glomerular tuft was seen in >60% of biopsies with RPGN. Glomerular ICAM-1 was associated with less glomerulosclerosis (chi (2) = 6.719, p = 0.01), less interstitial fibrosis (chi (2) = 4.322, p < 0.05), and less tubular atrophy (chi (2) = 8.547, p < 0.005). Glomerular VCAM-1 was associated with glomerular leukocyte infiltration (chi (2) = 4.698, p < 0.05). Glomerular tuft stains of ++/+++ for VCAM-1 was observed in 10% from MPO-ANCA-GN patients but in 60% from PR3-ANCA-GN (Fi = 8.538, p = 0.03). CONCLUSIONS: The following conclusions can be made from this study. (1) The renal expression of ICAM-1 and VCAM-1 is upregulated in RPGN, and this is associated with the histological activity. (2) De novo expression of VCAM-1 on glomerular tuft suggests that endothelial cells play a role in RPGN. (3) De novo tubular expression of ICAM-1 and VCAM-1 suggests that epithelial cells may participate in adhesive interactions in RPGN. (4) De novo expression of VCAM-1 at the glomerular tuft in PR3-ANCA positive patients seems greater than in MPO-ANCA positive patients, which suggests that testing specific immune activation mechanisms may play a role in ANCA-associated GN.

PMID: 18574676 [found with GoPubMed]

27: J Clin Immunol 2008 Jun;

IgA Anti-b2GPI Antibodies in Patients with Autoimmune Liver Diseases.

Gabeta S, Norman GL, Gatselis N, Liaskos C, Papamichalis PA, Garagounis A, Zachou K, Rigopoulou EI, Dalekos GN

Department of Medicine, Research Laboratory of Internal Medicine, Medical School, University of Thessaly, Larissa, Greece.

INTRODUCTION: Recently, we reported a high prevalence of immunoglobulin G and/or immunoglobulin M anticardiolipin antibodies (aCL) in patients with autoimmune liver diseases, namely, autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC), which were independent of the respective isotypes of antibodies against beta2-glycoprotein I (anti-b2GPI). Immunoglobulin A (IgA) aCL and IgA anti-b2GPI are the least studied of the three specific isotypes either in antiphospholipid syndrome (APS) or in other conditions. METHODS: Therefore, we investigated the prevalence and clinical significance of IgA anti-b2GPI and IgA aCL by enzyme-linked immunosorbent assays in another set of Caucasian patients with autoimmune liver diseases (59 AIH, 96 PBC, and 37 PSC). The disease controls group consisted of 50 hepatitis C virus (HCV) patients, 50 hepatitis B virus (HBV), 30 alcoholic liver disease (ALD), 30 non-alcoholic steatohepatitis (NASH), and 110 healthy controls. RESULTS AND DISCUSSION: IgA anti-b2GPI prevalence was higher in AIH (50.8%) compared to PBC (p = 0.005), PSC (p = 0.008), NASH (p = 0.004), ALD (p = 0.01), and HCV (p = 0.002). The titers were also significantly higher in AIH compared to any other group of the study. IgA aCL prevalence was higher in AIH (33.9%) compared to PBC (p = 0.005), PSC (p = 0.014), NASH (p = 0.001), ALD (p = 0.004), and HCV (p < 0.001). IgA anti-b2GPI or IgA aCL were not associated with APS features in patients with liver autoimmunity. Of note, IgA anti-b2GPI and IgA aCL were associated with clinical and biochemical markers of disease severity in AIH and PBC. We demonstrated a high prevalence and high titers of IgA anti-b2GPI in patients with AIH compared to any other liver disease of the study. CONCLUSION: IgA anti-b2GPI and IgA aCL were associated with the severity and biochemical activity of AIH and PBC, but long-term prospective studies are needed to address whether this new finding is of clinical importance in AIH and PBC patients.



PMID: 18551357 [found with GoPubMed]

28: J Clin Immunol 2008 Aug;

IgA Deficiency: Correlation Between Clinical and Immunological Phenotypes.

Aghamohammadi A, Cheraghi T, Gharagozlou M, Movahedi M, Rezaei N, Yeganeh M, Parvaneh N, Abolhassani H, Pourpak Z, Moin M

Department of Pediatrics, Division of Immunology and Allergy, Children Medical Center Hospital, Tehran University of Medical Sciences, 62 Gharib St, Keshavarz Blvd, 14194, Tehran, Iran, aghamohammadi@sina.tums.ac.ir.

**BACKGROUND:** IgA deficiency (IGAD) is the most common primary antibody deficiency. Although many affected individuals have no apparent symptom, selected patients suffer from recurrent mucosal infections, allergies, and autoimmune diseases. We aimed to investigate the clinical features in relation to immune function of Iranian patients with symptomatic IGAD. **METHODS:** Thirty-seven patients (21 male and 16 female), aged 4-32 years, were evaluated in this study. Patients were followed for a total of 131 patient years with a mean follow-up of 3.5 years per patient. **RESULTS:** The most prevalent presentations were recurrent infections occurring in 27 subjects, followed by allergy in eight cases and autoimmunity in two patients. However, during the follow-up period, 35 patients developed infections in respiratory and gastrointestinal tracts, necessitating medical care. Apart from infections, allergy was the most frequent complaint (31 cases); the major features were asthma, atopic dermatitis, and allergic rhinoconjunctivitis. Autoimmune diseases were documented in ten cases; thyroiditis was the most common. In 31 patients who received unconjugated pneumococcal polyvalent vaccine, antibody response against polysaccharide antigen was measured before and 28 days after vaccination. One fourth of vaccinated patients were hyporesponsive to vaccine; four of these patients developed bronchiectasis. The patients with IGAD were classified into two groups: group 1 (14 cases) consisted of patients with IGAD and other associated immune defects, such as immunoglobulin G (IgG) subclass deficiency and defective specific antibody production. Group 2 (23 cases) had isolated IGAD without other immunological abnormalities. There was a significantly increased number of lower respiratory tract infections in group 1 compared with group 2 ( $P = 0.006$ ). Moreover, four patients of group 1 had bronchiectasis whereas none of the patients in group 2 developed this complication ( $P = 0.015$ ). **CONCLUSION:** Subclassification of IGAD regarding the existence of associated immune defects is useful in terms of morbidity and planning for medical care. IgA-deficient patients with concomitant immune defects such as defects in specific antibody production have higher rates of recurrent infections and bronchiectasis, which necessitates more effective monitoring.

PMID: 18683032 [found with GoPubMed]

29: Clin Calcium 2008 Aug;18(8):1169-75

[Daily practice along the guideline for prevention and treatment of osteoporosis. The effects of anti-TNF therapy on bone and joint manifestations in rheumatoid arthritis.]

S Soen

Kinki University School of Medicine, Nara Hospital, Department of Orthopaedic Surgery and Rheumatology.

Patients diagnosed as RA should be started with disease modifying anti-rheumatic drugs (DMARDs) as early as possible. Among the DMARDs, methotrexate (MTX) is considered the anchor drug and should be used first in patients as risk of developing persistent disease. The main goal of DMARDs treatment is to achieve remission and monitoring of disease activity and adverse events should guide decisions on choice and changes in treatment strategies. However, treatment of RA with DMARDs including MTX often fails to control disease activity and prevent structural damage in a some population of patients. Therefore, more effective treatment strategies are needed. Tumor necrosis factor-alpha (TNF-alpha) , a representative pro-inflammatory cytokine, plays a pivotal role in the pathological process of RA by mediating initiation to autoimmunity, lymphocyte accumulation and angiogenesis in the inflamed synovium, and joint destruction. Treatment of RA patients with TNF inhibitors have been efficacious for a) a prolonged improvement in disease activity and an induction to remission, b) inhibition of radiographic progression, when they are used in combination with MTX. Thus, the combined use of the TNF-inhibitor and MTX has brought about a paradigm shift in the treatment goal of RA. However, their small but definite risks of serious infections are also clear and their occurrence mandates that TNF-inhibitors should be supervised by physicians with experience in their use.

PMID: 18677056 [found with GoPubMed]

30: J Immunol 2008 Aug;181(3):1767-79

IL-21-Induced Isotype Switching to IgG and IgA by Human Naive B Cells Is Differentially Regulated by IL-4.

Avery DT, Bryant VL, Ma CS, de Waal Malefyt R, Tangye SG

Immunology and Inflammation Group, Garvan Institute of Medical Research, Sydney, New South Wales, Australia;

Naive B cells can alter the effector function of their Ig molecule by isotype switching, thereby allowing them to secrete not only IgM, but also the switched isotypes IgG, IgA, and IgE. Different isotypes are elicited in response to specific pathogens. Similarly, dysregulated production of switched isotypes underlies the development of various diseases, such as autoimmunity and immunodeficiency. Thus, it is important to characterize mediators controlling isotype switching, as well as their contribution to the overall B cell response. Isotype switching in human naive B cells can be induced by CD40L together with IL-4, IL-10, IL-13, and/or TGF-beta. Recently, IL-21 was identified as a switch factor for IgG1 and IgG3. However, the effect of IL-21 on switching to IgA, as well as the interplay between IL-21 and other switch factors, remains unknown. We found that IL-4 and IL-21 individually induced CD40L-stimulated human naive B cells to undergo switching to IgG, with IL-4 predominantly inducing IgG1(+) cells and IL-21 inducing IgG3. Culture of naive B cells with CD40L and IL-21, but not IL-4, also yielded IgA(+) cells. Combining IL-4 and IL-21 had divergent effects on isotype switching. Specifically, while IL-4 and IL-21 synergistically increased the generation of IgG1(+) cells from CD40L-stimulated B cells, IL-4 concomitantly abolished IL-21-induced switching to IgA. Our findings demonstrate the dynamic interplay between IL-4 and IL-21 in regulating the production of IgG subclasses and IgA, and suggest temporal roles for these cytokines in humoral immune responses to specific pathogens.

PMID: 18641314 [found with GoPubMed]

31: Mol Immunol 2008 Jul;

Genetic interactions of KIR and G1M immunoglobulin allotypes differ in obese from non-obese individuals with type 2 diabetes.

Romero V, Zúñiga J, Azocar J, Clavijo OP, Terreros D, Kidwai H, Pandey JP, Yunis EJ

Department of Cancer Immunology and AIDS, Dana-Farber Cancer Institute, Boston, MA 02115, USA.

We analyzed the natural killer cell immunoglobulin-like receptor (KIR) genes and immunoglobulin allotypes in the development of type 2 diabetes (T2D) based on body mass index (BMI) measurements (obese vs. non-obese) in Puerto Rican Americans. Genetic interactions between the KIR haplotype A homozygotes (HAH) and its fraction containing two inhibitory receptors 2DL3 and 2DL1 and the activating receptor 2DS4 with immunoglobulin allotypes were studied. We found a significant association between the HAH and T2D ( $p=0.002$ ;  $OR=7.97$ ) and its interaction with the immunoglobulin allotype z: GM f/f (-) ( $p<0.0001$ ;  $OR$ , not determined) only in non-obese individuals. This association were due to the interactions between the 2DL3/2DL3, 2DL1/2DL1, and 2DS4 fragment with GM f/f (-) in T2D patients ( $p=0.0017$ ;  $OR=3.45$ ). Analysis based on BMI demonstrated associations in both obese ( $p=0.037$ ;  $OR=2.43$ ; 95%  $CI=0.97-6.31$ ) and non-obese individuals ( $p<0.0001$ ;  $OR=8.38$ ; 95%  $CI=2.49-29.31$ ). By contrast, the interaction of the GM allotype f/f (-) with the HAH fragment was associated with T2D only in non-obese individuals ( $p<0.0001$ ;  $OR=18.2$ ; 95%  $CI=3.71-113.4$ ). As expected, interaction of both HAH and its fragment with HLA-C group's ligands were significant. We used informative short tandem repeats (STRs) that distinguish major populations to determine genetic admixture and found that there was no genetic stratification in our cohort. Our findings are consistent with the possibility of an autoimmune and/or innate immune component in the pathogenesis of T2D: NK receptors with chronic inflammation in obese and genetic interactions with G1M allotype in T2D non-obese possibly mediating autoimmunity.

PMID: 18632158 [found with GoPubMed]

32: Am J Reprod Immunol 2008 Apr;

Treatment with Tumor Necrosis Factor Inhibitors and Intravenous Immunoglobulin Improves Live Birth Rates in Women with Recurrent Spontaneous Abortion.

Winger EE, Reed JL

Alan E. Beer Center for Reproductive Immunology & Genetics, San Francisco, CA, USA.

Problem The purpose of this study was to investigate whether treatment with tumor necrosis factor (TNF) inhibitors combined with intravenous immunoglobulin (IVIG) increases live birth rates among women with recurrent spontaneous abortion (RSA) concurrently treated with anticoagulants (AC). Method of study Seventy-five pregnancies in patients with a history of RSA were retrospectively evaluated. The population was divided into three groups: group I: 21 patients treated with AC (anticoagulants), group II: 37 patients treated with AC and IVIG, and group III: 17 patients treated with AC, IVIG and the TNF inhibitor Etanercept (Enbrel((R))) or Adalimumab (Humira((R))). In groups II and III, IVIG was administered at least once

during the cycle of conception and/or at least once after a positive pregnancy test. In group III, either Adalimumab or Etanercept was administered by subcutaneous injection according to standard protocols. Statistical analysis of pregnancy outcome was performed using Fisher's exact test. Results Patient populations in the three treatment groups were similar in terms of age, past miscarriages, inherited thrombophilia and autoimmunity. The live birth rate was 19% (4/21) in group I, 54% (20/37) in group II, and 71% (12/17) in group III. There was significant improvement in pregnancy outcome in group II versus group I (P = 0.0127) and in group III versus group I (P = 0.0026). The live birth rate in group III compared to group II was not significantly different (P = 0.3723). Side effects of AC, IVIG and TNF inhibitor treatment were minimal in these patients, and no birth defects were identified in their offspring. Conclusion In women with RSA, addition of either IVIG or a TNF inhibitor + IVIG to the AC regimen appears to improve live birth rates compared to the treatment with AC alone. The positive effect of IVIG and TNF inhibitor therapy on pregnancy outcome merits further study in prospective clinical trials.

PMID: 18422811 [found with GoPubMed]

33: Arthritis Rheum 2008 Jun;58(7):2131-2141

Regulation of B cell tolerance by 129-derived chromosome 1 loci in C57BL/6 mice.

Fossati-Jimack L, Cortes-Hernandez J, Norsworthy PJ, Cook HT, Walport MJ, Botto M

Imperial College, London, UK.

OBJECTIVE: Systemic lupus erythematosus is a multifactorial disease with a strong genetic component. Previous studies have shown that a 129-derived chromosome 1 interval (Sle16) on the C57BL/6 (B6) background is sufficient to induce humoral autoimmunity. The aim of the present study was to elucidate the mechanisms by which this locus contributes to the loss of peripheral tolerance. METHODS: Anti-single-stranded DNA (anti-ssDNA)-knockin transgenic mice (V(H)3H9R/Vkappa8R and V(H)3H9R) were crossed with a B6 congenic line named B6.129chr1b that carries the Sle16 locus. A parallel study of a gene-targeted animal, whose mutated gene is located within the 129chr1b interval on chromosome 1, was also performed. RESULTS: The combination of V(H)3H9R/Vkappa8R with the 129chr1b interval resulted in impaired B cell anergy, and transgenic IgM and IgG anti-ssDNA antibodies were found in the circulation. The presence of IgG2a(a) anti-ssDNA and IgM(a) anti-Sm antibodies in sera indicated that the autoreactive transgenic B cells underwent class switching and epitope spreading. The 129chr1b locus appeared to have a dominant effect, since transgenic antibodies were also detected in mice carrying a single allele. The gene-targeted animals showed a similar phenotype. CONCLUSION: The presence of a single 129chr1b locus on the B6 background impaired B cell anergy, prevented deletion of anti-DNA transgenic B cells, and induced receptor revision. The findings of this study also emphasize that the autoimmune phenotype observed in mice with targeted genes located on chromosome 1 may simply arise from epistatic interactions between the 129 and B6 parental strains.

PMID: 18576325 [found with GoPubMed]

34: J Immunol 2008 Jun;180(12):8361-8

Defective generation of a humoral immune response is associated with a reduced incidence and severity of collagen-induced arthritis in microsomal prostaglandin e synthase-1 null mice.

Kojima F, Kapoor M, Yang L, Fleishaker EL, Ward MR, Monrad SU, Kottangada PC, Pace CQ, Clark JA, Woodward JG, Crofford LJ

Division of Rheumatology, Department of Internal Medicine and.

Microsomal PGE synthase-1 (mPGES-1) is an inducible enzyme that acts downstream of cyclooxygenase and specifically catalyzes the conversion of PGH(2) to PGE(2). The present study demonstrates the effect of genetic deletion of mPGES-1 on the developing immunologic responses and its impact on the clinical model of bovine collagen-induced arthritis. mPGES-1 null and heterozygous mice exhibited decreased incidence and severity of arthritis compared with wild-type mice in a gene dose-dependent manner. Histopathological examination revealed significant reduction in lining hyperplasia and tissue destruction in mPGES-1 null mice compared with their wild-type littermates. mPGES-1 deficient mice also exhibited attenuation of mechanical nociception in a gene dose-dependent manner. In addition, mPGES-1 null and heterozygous mice showed a marked reduction of serum IgG against type II collagen, including subclasses IgG1, IgG2a, IgG2b, IgG2c, and IgG3, compared with wild-type mice, which correlated with the reduction in observed inflammatory features. These results demonstrate for the first time that deficiency of mPGES-1 inhibits the development of collagen-induced arthritis, at least in part, by blocking the development of a humoral immune response against type II collagen. Pharmacologic inhibition of mPGES-1 may therefore impact both the inflammation and the autoimmunity associated with human diseases such as rheumatoid arthritis.

PMID: 18523303 [found with GoPubMed]

35: Cancer Immunol Immunother 2007 Oct;

Vaccination with metastasis-related tumor associated antigen TPD52 and CpG/ODN induces protective tumor immunity.

Payton LA, Lewis JD, Byrne JA, Bright RK

Department of Microbiology and Immunology, Texas Tech University Health Sciences Center, 3601 4th Street, MS 6591, Lubbock, TX 79430, USA, robert.bright@ttuhsc.edu.

Tumor protein D52 (TPD52) is involved in transformation and metastasis and has been shown to be over-expressed in tumor cells compared to normal cells and tissues. Murine TPD52 (mD52) shares 86% protein identity with the human TPD52 orthologue (hD52). To study TPD52 protein as a target for active vaccination recombinant, mD52 was administered as a protein-based vaccine. Naïve mice were immunized with either mD52 protein and CpG/ODN as a molecular adjuvant or CpG/ODN alone. Two weeks following the final immunization, mice were challenged s.c. with syngeneic tumor cells that over-express mD52. Two distinct murine tumor cell lines were used for challenge in this model, mKSA and 3T3.mD52. Half of the mice immunized with mD52 and CpG/ODN rejected or delayed onset of mKSA s.c. tumor cell growth, and 40% of mice challenged with 3T3.mD52 rejected s.c. tumor growth, as well as the formation of spontaneous lethal lung metastases. Mice immunized with mD52 and CpG/ODN generated detectable mD52-specific IgG antibody responses indicating that mD52 protein vaccination induced an adaptive immune response. In addition, mice that rejected tumor challenge generated tumor-specific cytotoxic T lymphocytes' responses. Importantly, microscopic and gross evaluation of organs from mD52 immunized mice revealed no

evidence of autoimmunity as assessed by absence of T cell infiltration and absence of microscopic pathology. Together, these data demonstrate that mD52 vaccination induces an immune response that is capable of rejecting tumors that over-express mD52 without the induction of harmful autoimmunity.

PMID: 17962942 [found with GoPubMed]

36: Clin Rev Allergy Immunol 2008 Jan;

Histidine-Rich Glycoprotein Modulation of Immune/Autoimmune, Vascular, and Coagulation Systems.

Blank M, Shoenfeld Y

The Autoimmune Disease Center and Internal Medicine B, Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel.

Histidine-rich glycoprotein (HRG) is plasma glycoprotein that has a multidomain structure, interacts with many ligands, and exhibit many modulatory functions in diverse biological systems. HRG ligands include Zn(2+), tropomyosin, heparin and heparan sulphate, plasminogen, plasmin, fibrinogen, thrombospondin, IgG, FcγR, and complement. In many cases, the histidine-rich region of the molecule enhances ligand binding after interaction with Zn(2+) or exposure to low pH, conditions associated with sites of tissue injury or tumor growth. The multidomain nature of HRG and diverse ligand binding properties indicates that it can act as an extracellular adaptor protein, bridging together different ligands mainly on cell surfaces. Apart from cell surface molecules, HRG can differentially target IgG, preventing generation of insoluble immune complexes. HRG binds to most cells primarily via heparan sulphate proteoglycans. HRG can enhance clearance of apoptotic and necrotic phagocytes as well as immune complexes. The anti-angiogenic properties of HRG are well established in vitro and in vivo. HRG can modulate other physiological processes such as cell adhesion and migration, fibrinolysis and coagulation, complement activation. This review presents an update on the molecular, structural, biological, and clinical properties of HRG and associated autoimmunity conditions.

PMID: 18219588 [found with GoPubMed]

37: Cytokine 2008 Apr;

The significance of persistent newly developed autoantibodies in JIA patients under long-term anti-TNF treatment.

Kanakoudi-Tsakalidou F, Tzimouli V, Pratsidou-Gertsis P, Chronopoulou E, Trachana M

First Department of Pediatrics, Aristotle University, Ippokration General Hospital, 49 Konstantinoupoleos str., 54642 Thessaloniki, Greece.

Objective: To study the significance of persistent (12 months) new autoantibodies, in Juvenile Idiopathic Arthritis (JIA) patients treated with either Infliximab (INFL) or Etanercept (ET) for 2 years. Patients-methods: 26 children under INFL (n=12) or ET (n=14) were prospectively studied. A large panel of autoantibodies was tested using indirect immunofluorescence (ANA, anti-dsDNA, anti-ENA, SMA, LKM, AMA, PCA, anti-R1, ATA), ELISA (ANA, anti-ENA, anti-cardiolipin, ANCA), immunoblotting assay (anti-ENA: anti-Ro, anti-La, anti-Sm, anti-URNP, anti-Jo, anti-Scl70, anti-

centromere, anti-ribosomal and anti-histone) and rate nephelometry (RF). Results: Apart from the positive patients for ANA (13/26) and RF (2/26) prior to anti-TNF treatment, 6/26 patients (23%) developed new autoantibodies (SMA, anti-R1, ATA) which persisted for 12-50 months. None developed antibodies to nuclear antigens. In only one case, ATA was associated with the development of Hashimoto's thyroiditis. Conclusions: These findings indicate that in JIA patients in contrast to adult RA patients, development of new autoantibodies to various nuclear antigens is rare. Other non relevant to rheumatic diseases autoantibodies, may appear and persist for >12 months, but very rarely they may be related to clinical entities, especially in the presence of a positive family history of autoimmunity.

PMID: 18445529 [found with GoPubMed]

38: *Reprod Biomed Online* 2008 Jun;16(6):817-24

Multiple endometrial antigens are targeted in autoimmune endometriosis.

Gajbhiye R, Suryawanshi A, Khan S, Meherji P, Warty N, Raut V, Chehna N, Khole V

Department of Reproductive Endocrinology and Infertility, National Institute for Research in Reproductive Health, Indian Council of Medical Research, J. M. Street, Parel, Mumbai, India, 400 012.

Endometriosis is defined as the growth of endometrial glands and stroma in ectopic locations. Its aetiology is multifactorial, but autoimmunity has been shown to play a role in its onset and development. The present study aimed to investigate the presence of both IgG and IgM anti-endometrial antibodies in sera of endometriosis patients in comparison with age-matched controls, and to also investigate the cognate endometrial proteins involved. Sera from these groups were screened by western blot and immunohistochemistry. Thirteen out of the 40 sera tested were positive for IgG isotype, and 10/27 IgG negative patients were positive for IgM isotype. These findings indicate that endometrial antibodies of IgG and IgM classes could be detected in almost 60% of endometriosis patients. Of the various identified endometrial antigens, 30 and 45 kDa antigens were immunodominant in both IgG and IgM positive endometriosis patients. With immunohistochemistry, positive sera showed reactivity in luminal epithelium, glandular epithelium and stroma. These anti-endometrial antibodies might be partially responsible for failure of implantation leading to infertility. Identification of specific targets would be a help in understanding the pathophysiology of endometriosis, and would also help in setting up a non-invasive test for the diagnosis of endometriosis.

PMID: 18549691 [found with GoPubMed]

39: *Orv Hetil* 2008 May;149(19):873-6

[Autoimmune pancreatitis.]

Igaz P, Tulassay Z

Semmelweis Egyetem, Általános Orvostudományi Kar II. Belgyógyászati Klinika Budapest Szentkirályi u. 46. 1088.

Autoimmune pancreatitis is a rare form of chronic pancreatitis. Its clinical relevance, however, cannot be dismissed, as it can be difficult to

distinguish autoimmune pancreatitis from malignant pancreatic cancer and in contrast with the majority of chronic pancreatitis forms it can be efficiently treated, even complete remission can be achieved on steroid therapy. The clinical picture of autoimmune pancreatitis is not characteristic, obstructive jaundice, abdominal pain, weight loss are frequently observed. Imaging studies often show diffuse pancreas enlargement and irregular narrowing of the main pancreatic duct. Elevated serum IgG4 immunoglobulin concentrations, some autoantibodies and the presence of IgG4 positive immune cells were observed in addition to other histological features. Apart from pancreatic manifestations, other organs may also be affected, thus associations with sclerosing cholangitis, sialoadenitis, retroperitoneal fibrosis, Riedel thyroiditis and inflammatory bowel diseases have been described. Based on these findings, autoimmune pancreatitis should be regarded as a systemic disease, as a manifestation of systemic IgG4-related sclerosing disease.

PMID: 18450546 [found with GoPubMed]

40: Brain Nerve 2008 May;60(5):527-37

[Neuromyelitis optica and anti-aquaporin 4 antibody--an overview]

Misu T, Fujihara K, Itoyama Y

Department of Neurology and Multiple Sclerosis Therapeutics, Tohoku University Graduate School of Medicine, 11 Seiryomachi, Aoba-ku, Sendai 980-8574, Japan.

Neuromyelitis optica (NMO) is an inflammatory disease mainly affecting optic and spinal cords, and was originally described by Devic in 1894. There has been long controversy about whether NMO is a subtype of multiple sclerosis (MS) or a distinct disease. In Japan and other Asian countries, relapsing NMO has been called as optic-spinal form of MS (OSMS), but we reported in 2002 that OSMS was heterogeneous and it comprised both typical NMO and MS with optic spinal presentation. Recently, a highly specific serum autoantibody marker, NMO-IgG, was found in the sera of Caucasian NMO and Japanese OSMS cases, and the target antigen was identified as the water channel protein aquaporin (AQP) 4. So in NMO and OSMS, similar autoimmune backgrounds were revealed. In our anti-AQP4 antibody assay using HEK293 cells transfected with human AQP4, we found that the sensitivity and specificity of anti-AQP4 antibody was 91% and 100%, respectively, which was superior to the original immunohistological assay using mouse brain slices (NMO-IgG). The titre of AQP4 antibody correlated with the length of spinal cord lesions and relapse rate. We also studied the expression of AQP4 in autopsied cases of NMO and MS and revealed that AQP4 and GFAP, an astrocytic marker protein, were completely lost at the acute inflammatory lesions surrounding immunoglobulin and complement-deposited dilated vessels, but the myelin basic protein was relatively preserved. Those results suggest that astrocytic damage associated with autoimmunity to AQP4 may be involved in the pathogenesis of NMO, which is distinct from MS, primarily demyelinating disease. After the long history of confusion, NMO became clearly discriminated disease from MS. In this review, we focus on the historical changes of the disease concept and new knowledge gained from the clinical or immunological analyses of NMO.

PMID: 18516975 [found with GoPubMed]

41: Can J Neurol Sci 2008 May;35(2):220-5



Effect of ALS IgG on motor neurons in organotypic spinal cord cultures.

Li B, Liu XY, Li Z, Bu H, Sun MM, Guo YS, Li CY

Department of Neurology, the Second Hospital of Hebei Medical University, Shijiazhuang, Hebei, People's Republic of China.

**OBJECTIVE:** Reports about the role of autoimmunity in amyotrophic lateral sclerosis (ALS) are inconsistent. The aim of this work was to investigate the effect of IgG from patients with ALS on motor neurons in a physiological-like surrounding. **METHODS:** Using affinity chromatography, IgG from six ALS patients, four disease controls and five healthy subjects was purified. Organotypic spinal cord cultures, which conserve the structure of the spinal cord in a horizontal plane and are suitable for studies with long-term treatment, were used and IgG with different concentrations ranging from 0.05 mg/mL to 0.5 mg/mL was added to the culture medium. Ventral motor neuron survival was evaluated by morphology and SMI-32 immunohistochemistry staining. Lactate dehydrogenase (LDH) level in the culture medium was measured by colorimetry. **RESULTS:** After cultures were treated with ALS IgG for three weeks, the number and morphology of motor neurons showed little change. In addition, there was no significant difference in lactate dehydrogenase release between cultures treated with medium alone, normal control IgG, disease control IgG or ALS IgG. **CONCLUSIONS:** The results indicate that IgG from these ALS patients was insufficient per se to induce motor neuron death in organotypic slice cultures. However, this does not preclude the possibility that other changes may have occurred in the motor neurons. This work offered a new model to evaluate the role of IgG in the pathogenesis of ALS. Organotypic cultures contribute to study of the impact of IgG on motor neurons by mimicking physiological conditions.

PMID: 18574938 [found with GoPubMed]

42: Clin Exp Immunol 2008 Mar;

Depletion of CD4(+) CD25(+) regulatory T cells inhibits local tumour growth in a mouse model of B cell lymphoma.

Heier I, Hofgaard PO, Brandtzæg P, Jahnsen FL, Karlsson M

LIIPAT, Institute of Pathology, University of Oslo, Rikshospitalet University Hospital, Oslo, Norway.

Regulatory T cells (T(regs)) may inhibit immunity against cancer. Induction and expansion of T(regs) in the immunosuppressive microenvironment created by a growing tumour appear to be one of the mechanisms by which it can evade host defence. We studied the impact of CD25(+) T(regs) in a B cell lymphoma model in which Rag2(-/-) mice received adoptive transfer of wild-type spleen cells with or without CD25(+) cells, and concurrently subcutaneous inoculation of the B cell lymphoma cell line A20. We also examined the effect of engaging the glucocorticoid-induced tumour necrosis factor receptor (GITR) - an approach reported previously to abrogate the suppressive effects of T(regs). Mice that received spleen cells depleted of CD25(+) T(regs) showed significantly slower tumour growth and increased survival compared with mice that received unsorted spleen cells. The T(reg)-depleted group also had significantly more CD8(+) T cells infiltrating the tumours and higher levels of serum immunoglobulin G subclasses. The anti-GITR treatment had no significant effect on tumour growth, survival or immunoglobulin production. In the CD25-depleted group four of 10 mice developed clinical signs of autoimmunity, in contrast to none in the non-depleted group. Forkhead box P3(+) T cells were found in

tumour-draining lymph nodes in mice in the CD25-depleted group, suggesting an in vivo induction or expansion of rare transferred donor T(regs). Thus, our study showed that removal of CD25(+) T(regs) enhanced anti-tumour immunity against local growth of a B cell lymphoma and that induction or expansion of T(regs) could be one mechanism by which the growing tumour evades immune surveillance.

PMID: 18341610 [found with GoPubMed]

43: J Clin Immunol 2008 Mar;

Autoimmune Manifestations in Common Variable Immunodeficiency.

C Cunningham-Rundles

Mount Sinai School of Medicine, 1425 Madison Avenue, New York City, 10029, USA, Charlotte.Cunningham-Rundles@mssm.edu.

INTRODUCTION: About 20% of subjects with common variable immune deficiency (CVID) develop an autoimmune complication, most often immune thrombocytopenia or hemolytic anemia. While the pathogenesis of autoreactivity is unknown for CVID subjects in general, and to a greater extent in those with autoimmunity, there is a loss of switched memory B cells. DISCUSSION: About 7-8% of CVID subjects have mutations in the transmembrane activator and calcium-modulating cyclophilin ligand interactor (TACI), a significant association with this immune defect, although the same mutations may be found in normal relatives and rarely in healthy blood donors. In addition to generalized B cell dysfunction, defective elimination of autoimmune B cells has been demonstrated.

PMID: 18322785 [found with GoPubMed]

44: Mycoses 2008 May;51(3):228-35

Innate and adaptive immunity in patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.

Perniola R, Congedo M, Rizzo A, Sticchi Damiani A, Faneschi ML, Pizzolante M, Lobreglio G

Paediatric Unit, V. Fazzi Regional Hospital, Lecce, Italy.  
rperniola@hotmail.com

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is an autosomal recessive syndrome characterised by chronic mucocutaneous candidiasis (CMC) and multiple endocrine failures. While the spectrum and modalities of autoimmunity are the main objects of current research into APECED, unequivocal data on the efficiency of immune responses to infectious agents are still elusive. The in vitro ability of monocytes and polymorphonuclear leucocytes to phagocytise and kill bacteria and fungi, and the degree of activation of lymphocytes cultured with mitogens and *Candida albicans* were investigated by flow cytometry in 11 APECED patients and healthy subjects. In addition, a comparison of gamma-globulin and immunoglobulin (Ig) concentrations was performed, and a correlation was sought between oral fungal load and the anti-*Candida* antibody titre. No difference between APECED patients and healthy subjects was observed in the phagocyte function, although the patients had a larger number of monocytes. Similarly, cultured lymphocytes were equally activated in the two groups. The concentration of gamma-globulins was higher among APECED patients, and

anti-Candida IgM and IgG correlated with current and past oral candidiasis respectively. APECED patients have efficient innate and adaptive immune responses against exogenous stimuli, and currently, the mechanisms of mucocutaneous anergy leading to the high prevalence of CMC in this syndrome remain to be elucidated.

PMID: 18399903 [found with GoPubMed]

45: Scand J Immunol 2008 May;67(5):509-15

Autoimmune markers in lymphoid malignancies.

Sjöberg K, Roth EB, Gustavsson L, Jönsson C, Simán H, Henriksson G, Stenberg P, Lindblom A, Svensson P

Department for Clinical Sciences, Section of Medicine, Lund University, Malmö University Hospital, Malmö, Sweden. klas.sjoberg@med.lu.se

Chronic immune stimulation such as *Helicobacter pylori* (hp) infection, Sjögren's syndrome or coeliac disease may initiate non-Hodgkin lymphoma (NHL). The opposite (appearance of autoimmunity) has also been reported. The aim of this study was to describe the pattern of these immune markers in patients with lymphoid malignancies. Sera from 96 patients with NHL (median age 72, range 38-88, F/M 41/55) were analysed with ELISA to determine the frequency of antibodies against guinea pig (gp) and human recombinant (hr) transglutaminase type 2 (Tg2), and hr factor XIII subunit a\* (part of the Tg-family), extractable nuclear antigen (ENA), and hp. As hp antibodies decrease in younger age cohorts a sex- and age-matched control group of 768 persons was used. The control population for transglutaminase antibodies consisted of 59 blood donors, (median 42 years, range 19-65) was analysed with a commercial kit. Gp-Tg2-IgG positivity was documented in 72% and hr-Tg2-IgG positivity in 15% (5% positive controls for both;  $P < 0.001$  and ns, respectively). For IgA 3% had gp-Tg2 and 4% hr-Tg2 (5% in controls: ns for both). Anti-FXIII-IgA positivity was found in 22% (5% in controls;  $P = 0.03$ ). Unspecific anti-ENA-IgG positivity was found in 24% ( $P < 0.001$ ), while only 2% had specific ENA autoantibodies. Moreover, 36% were positive for anti-hp-IgG, while controls were positive in 54% ( $P < 0.001$ ). The frequency of unspecific autoantibodies was increased. No differences could be noted in specific autoantibodies (hr-Tg2-IgA). In contrast, fewer than expected were anti-hp-positive. A defective immune response, similar to that in autoimmune diseases, could contribute to the pathogenesis of lymphoid malignancies.

PMID: 18405328 [found with GoPubMed]

46: Cancer Biol Ther 2007 Jan;7(4)

Heterophilic NeuGcGM3 ganglioside cancer vaccine in advanced melanoma patients: Results of a Phase Ib/IIa Study.

Osorio M, Gracia E, Rodríguez E, Saurez G, Arango MD, Noris E, Torriella A, Joan A, Gómez E, Anasagasti L, González JL, Melgares MD, Torres I, González J, Alonso D, Rengifo E, Carr A, Pérez R, Fernández LE

Clinical Trials Unit, National Institute of Oncology and Radiobiology, Havana City, Cuba.

NeuGcGM3 ganglioside is especially attractive because it is expressed on melanoma cells but is minimally or not expressed at all on most normal

human tissues. A Phase Ib/IIa clinical trial was carried out in patients with advanced cutaneous and ocular malignant melanomas, to evaluate immunogenicity and toxicity of an intramuscularly administered cancer vaccine and composed by NeuGcGM3 in a proteoliposome of Neisseria meningitides with Montanide ISA 51 as adjuvant. Twenty two patients were included, twelve at dose level of 200 mug and 10 at 400mug. The first five doses were administered every other week and then monthly until 9 doses. 12 patients received additional immunizations. . Vaccination induced specific anti-NeuGcGM3 IgM, IgG and IgA antibodies responses. Titers of IgM were greater for the highest vaccine doses. Vaccination also elicited DTH response in 45.5 % of patients in the lower doses and 77,8 % in the higher doses. Toxicities were mostly grade 1 or 2, according CTC-NCI criteria. Interestingly, 3 patients developed vitiligo at the lower dose (none in the highest dose) although the nominal antigen NeuGcGM3 is not present in melanocytes. Survival analysis was not the goal of this Phase I trial; nevertheless, the fact that seven patients are alive for more than 2 years after inclusion is noteworthy. Safety and immunogenicity with NeuGcGM3 vaccine treatment in advanced melanoma patients was established. The prognostic value of autoimmunity and the possibilities of dissociating anti-tumor immunity from autoimmunity deserve further research.

PMID: 18285705 [found with GoPubMed]

47: Int J Immunopathol Pharmacol 2008;21(2):279-88

Antibodies as predictors of complex autoimmune diseases.

A Vojdani

Immunosciences Lab., Inc., Beverly Hills, CA, USA.

Emerging evidence has suggested environmental factors such as infections and xenobiotics and some dietary proteins and peptides in the pathogenesis of many autoimmune diseases. Considering the fact that autoantibodies can often be detected prior to the onset of a disease, in this study an enzyme immunoassay was used for measurement of antibodies against different highly purified antigens or synthetic peptides originating not only from human tissue, but also from cross-reactive epitopes of infectious agents, dietary proteins and xenobiotics. The measurement of antibodies against a panel of antigens allows for identification of patterns or antibody signatures, rather than just one or two markers of autoimmunity, thus establishing the premise for increased sensitivity and specificity of prediction, as well as positive predictive values. This panel of different autoantibodies was applied to 420 patients with different autoimmune diseases, including pernicious anemia, celiac disease, thyroiditis, lupus, rheumatoid arthritis, osteoarthritis, Addisons disease, type 1 diabetes, cardiovascular disease and autoimmunity, which are presented in this article. In all cases, the levels of these antibodies were significantly elevated in patients versus controls. Antibody patterns related to neuroautoimmune disorders, cancer, and patients with somatic hypermutation will be shown in a subsequent article. We believe that this novel 96 antigen-specific autoantibody or predictive antibody screen should be studied for its incorporation into routine medical examinations. Clinicians should be aware that the detection of antibodies should not automatically mean that a patient will definitely become ill, but would rather give a percentage of risk for autoimmune disease over subsequent months or years.

PMID: 18547471 [found with GoPubMed]

48: Muscle Nerve 2007 Dec;

Autoantibody-mediated bowel and bladder dysfunction in a patient with chronic, nondiabetic neuropathy.

Jackson MW, Gordon TP, McCombe PA

Autoimmunity Research Laboratory Department of Immunology, Allergy and Arthritis, Flinders Medical Centre and Flinders University, GPO Box 2100, Adelaide, South Australia 5001, Australia.

Physiological techniques can be used to detect novel autoantibodies causing alteration of autonomic function after passive transfer to mice. Previously, such antibodies have been detected in patients with type I diabetes mellitus, myasthenia gravis, and Sjogren's syndrome. We now describe a patient with an idiopathic nondiabetic neuropathy with prominent autonomic symptoms, including bladder and bowel dysfunction. Physiological assays of whole colon and bladder were used to determine the presence in the patient serum of functional autoantibodies capable of mediating autonomic dysfunction. Immunoglobulin G (IgG) from this patient was able to disrupt bladder and bowel function on passive transfer to mice. This is a new pattern of autoantibody-mediated abnormality. Although the target antigen is unknown, it is likely to be a cell-surface receptor or ion channel. This case highlights the usefulness of passive transfer studies in detecting functional antibodies in patients with autonomic neuropathy. Muscle Nerve, 2007.

PMID: 18061937 [found with GoPubMed]

49: Asian Pac J Allergy Immunol 2008 Mar;26(1):19-22

Autoantibodies to the high-affinity IgE receptor in patients with asthma.

Sun RS, Chen XH, Liu RQ, Cheng TM, Ran XZ, Yang T

Department of Dermatology, Institute of Battle Surgery, Daping Hospital, the Third Military Medical University, Chongqing 400042, People's Republic of China..

Autoimmune diseases have been implicated as a cause of intrinsic asthma; however, there is little data on the role of autoimmunity in the pathogenesis of asthma. The purpose of this study was to investigate circulating autoantibodies against the high-affinity IgE receptor Fc(epsilon)RI in patients with asthma. Seventy-eight patients with asthma and 32 healthy individuals as control subjects were included. All subjects were tested with basophil histamine releasing assay and immunoblotting to assess for the potential presence of receptor Fc(epsilon)RI autoantibodies. Of the 78 asthma patients total subjects, 25 (32.1%) had a positive by basophil histamine releasing assay and 23 (29.5%) by immunoblotting. Both of them were significant higher than the positive rate, 9.4% ( $p < 0.05$ ) and 9.4% ( $p < 0.05$ ), respectively. Our data demonstrated that aberrant autoantibodies against the high-affinity IgE receptor Fc(epsilon)RI were found in some patients with asthma implies that the autoimmunity may be one factor in intrinsic asthma pathogenesis.

PMID: 18595526 [found with GoPubMed]

50: J Immunol 2008 Feb;180(3):1373-81

Autoantigen-Specific IL-10-Transduced T Cells Suppress Chronic Arthritis by Promoting the Endogenous Regulatory IL-10 Response.

Guichelaar T, Ten Brink CB, van Kooten PJ, Berlo SE, Broeren CP, van Eden W, Broere F

Department of Infectious Diseases and Immunology, Utrecht University, Utrecht, The Netherlands.

Deficient T cell regulation can be mechanistically associated with development of chronic autoimmune diseases. Therefore, combining the regulatory properties of IL-10 and the specificity of autoreactive CD4(+) T cells through adoptive cellular gene transfer of IL-10 via autoantigen-specific CD4(+) T cells seems an attractive approach to correct such deficient T cell regulation that avoids the risks of nonspecific immunosuppressive drugs. In this study, we studied how cartilage proteoglycan-specific CD4(+) T cells transduced with an active IL-10 gene (T(IL-10)) may contribute to the amelioration of chronic and progressive proteoglycan-induced arthritis in BALB/c mice. TCR-transgenic proteoglycan-specific T(IL-10) cells ameliorated arthritis, whereas T(IL-10) cells with specificity for OVA had no effect, showing the impact of Ag-specific targeting of inflammation. Furthermore, proteoglycan-specific T(IL-10) cells suppressed autoreactive proinflammatory T and B cells, as T(IL-10) cells caused a reduced expression of IL-2, TNF-alpha, and IL-17 and a diminished proteoglycan-specific IgG2a Ab response. Moreover, proteoglycan-specific T(IL-10) cells promoted IL-10 expression in recipients but did not ameliorate arthritis in IL-10-deficient mice, indicating that T(IL-10) cells suppress inflammation by propagating the endogenous regulatory IL-10 response in treated recipients. This is the first demonstration that such targeted suppression of proinflammatory lymphocyte responses in chronic autoimmunity by IL-10-transduced T cells specific for a natural Ag can occur via the endogenous regulatory IL-10 response.

PMID: 18209031 [found with GoPubMed]

51: J Neuroimmunol 2008 Jan;

Inhibitory IgG receptor FcgammaRIIB fails to inhibit experimental autoimmune myasthenia gravis pathogenesis.

Li J, Tüzün E, Wu XR, Qi HB, Allman W, Saini SS, Christadoss P

Department of Microbiology and Immunology, University of Texas Medical Branch, Galveston, TX, 77555-1070, USA.

Deficiency of the inhibitory FcgammaRIIB renders mice susceptible to autoimmune disorders characterized with cellular infiltration of target tissue. To analyze the role of FcgammaRIIB in an antibody-mediated autoimmune disease, experimental autoimmune myasthenia gravis (EAMG), FcgammaRIIB knockout (KO) and wild-type mice were immunized with acetylcholine receptor (AChR). In contrast with previous reports, FcgammaRIIB KO mice were mildly resistant to EAMG despite preserved anti-AChR antibody production and neuromuscular junction complement deposition capacity. EAMG resistance was associated with reduced lymph node cell IL-6 and IL-10 production and increased CD4(+)CD25(+) cell ratios in lymph nodes. Our data suggest that FcgammaRIIB promotes antibody-mediated autoimmunity.

PMID: 18207575 [found with GoPubMed]

52: Am J Respir Crit Care Med 2007 Nov;

Autoantibodies in Patients with Chronic Obstructive Pulmonary Disease.

Feghali-Bostwick CA, Gadgil AS, Otterbein LE, Pilewski JM, Stoner MW, Csizmadia E, Zhang Y, Sciruba FC, Duncan SR

Division of Pulmonary, Allergy and Critical Care, University of Pittsburgh Medical Center, Pittsburgh, PA, USA.

BACKGROUND: Adaptive immune responses are present in patients with chronic obstructive pulmonary disease (COPD), and it has been postulated these processes could be autoreactive. OBJECTIVES: To ascertain if humoral autoimmunity could play a role in COPD pathogenesis. METHODS: Circulating IgG autoantibodies were detected by immunofluorescence and immunoprecipitation. Immunohistochemistry and immunofluorescence were used to evaluate intrapulmonary IgG and complement (C3) deposition in human lung explants. Autoantibody pathogenicity was also investigated with an antibody-dependent cell-mediated cytotoxicity (ADCC) assay. MEASUREMENTS AND MAIN RESULTS: The prevalence of anti-HEp-2 epithelial cell autoantibodies in 47 smokers/former smokers with COPD (GOLD Stages 1-4) was greater than among eight subjects with a smoking history but normal spirometry, and 21 healthy, Never-Smoke Controls (68% vs. 13% vs. 10%, respectively,  $p < 0.0001$ ). Antibodies against primary pulmonary epithelial cells were found in 12/12 COPD vs. 3/12 Never-Smoke Controls ( $p < 0.001$ ). Self-antigens immunoprecipitated from 34/35 (97%) of COPD plasmas (vs. 0/12 Never-Smoke Controls). Antibodies against a particular 130 kDa autoantigen ( $n=7$ ) were associated with decreased body mass index ( $23.2 \pm 2.1$  vs.  $29.5 \pm 1.0$  kg/M<sup>2</sup>),  $p=0.007$ ). Intrapulmonary immune complexes were present in 6/6 and C3 was seen in 5/6 COPD lung explants, unlike 0/6 and 1/6 normals, respectively. Cytotoxicity of pulmonary epithelial cells by allogeneic mononuclear cells also increased 46% after incubation with COPD plasmas ( $n=10$ ), compared to identical treatments with eight normal specimens ( $p=0.03$ ). CONCLUSIONS: IgG autoantibodies with avidity for pulmonary epithelium, and the potential to mediate cytotoxicity, are prevalent in COPD patients. Autoreactive adaptive immune responses may be important in the etiology of this disease.

PMID: 17975205 [found with GoPubMed]

53: Ann Rheum Dis 2007 Aug;

Loss-of-function mutations in the Filaggrin gene: no contribution to disease susceptibility, but to autoantibody formation against citrullinated peptides in early rheumatoid arthritis.

Hüffmeier U, Böiers U, Lascorz J, Reis A, Burkhardt H

Institute of Human Genetics, University Erlangen-Nuremberg, Germany.

OBJECTIVES: Autoantibody formation to citrullinated (pro)filaggrin has proven to be a highly specific serological marker for rheumatoid arthritis (RA). To test the potential relevance of mutations of the filaggrin (FLG) gene for disease susceptibility and elicitation of humoral autoimmunity in RA, an association study of three loss-of-function FLG variants was performed in case-control design. METHODS: DNA was obtained from 282 patients with early RA (mean disease duration: 6.5 months) and from 376 control individuals. Three loss-of-function variants of the FLG gene (\*R501X, \*2282del14 and \*3702del1) were genotyped. RESULTS: No significant differences in genotype frequencies were observed between control probands

and the population of RA-patients. The FLG\*3702del1 allele was not identified in any of the patients nor controls, and none of the probands was homozygous or compound heterozygous. In the RA cohort, heterozygous carriers of either of the FLG variants exhibited a significantly elevated prevalence of autoantibodies to citrullinated peptides (CCP-2) (80%) compared to non-carriers (51.9%) [p=0.018, Odds ratio: 3.71 [1.20-11.46]]. CONCLUSIONS: The investigated FLG variants do not confer an overall risk for the development of RA. However, loss-of-function mutations in the FLG gene may contribute to the development of humoral autoimmunity targeting citrullinated determinants in early RA.

PMID: 17704064 [found with GoPubMed]

54: Curr Dir Autoimmun 2008;10:182-94

*Pemphigus foliaceus*.

Dasher D, Rubenstein D, Diaz LA

Department of Dermatology, University of North Carolina - Chapel Hill School of Medicine, Chapel Hill, N.C., USA.

*Pemphigus foliaceus* (PF) and its endemic form *fogo selvagem* (FS) are autoimmune diseases characterized clinically by transient cutaneous superficial blisters. As opposed to *pemphigus vulgaris* (PV), patients lack mucosal involvement. Acantholysis in the upper epidermis is appreciated histologically. The serologic hallmark of PF and FS is the demonstration of IgG autoantibodies against the cell surface of keratinocytes. The specific target of these autoantibodies is desmoglein (Dsg) 1, one of the four known desmosomal cadherins, a family of transmembrane glycoproteins that play an important role in the dynamic regulation of intercellular adhesion. Compelling evidence has been compiled suggesting anti-Dsg1 autoantibodies in patients with PF and FS are pathogenic. The mechanism by which anti-Dsg autoantibodies induce loss of cell-cell adhesion in PF is under active investigation and is beginning to be elucidated. The study of the pathogenesis of PF and FS provides a unique opportunity to uncover insights that may contribute to our greater understanding of autoimmunity.

PMID: 18460886 [found with GoPubMed]

55: Immunity 2008 Jan;28(1):40-51

The Lupus-Related *Lmb3* Locus Contains a Disease-Suppressing Coronin-1A Gene Mutation.

Haraldsson MK, Louis-Dit-Sully CA, Lawson BR, Sternik G, Santiago-Raber ML, Gascoigne NR, Theofilopoulos AN, Kono DH

Department of Immunology, The Scripps Research Institute, La Jolla, CA 92037, USA; Department of Clinical Microbiology, Division of Immunology, Umeå University, SE-901 87 Umeå, CH-1211, Sweden.

Here, we show that a lupus-suppressing locus is caused by a nonsense mutation of the filamentous actin-inhibiting Coronin-1A gene. This mutation was associated with developmental and functional alterations in T cells including reduced migration, survival, activation, and Ca(2+) flux. T-dependent humoral responses were impaired, but no intrinsic B cell defects were detected. By transfer of T cells, it was shown that suppression of autoimmunity could be accounted for by the presence of the *Coro1a(Lmb3)*



mutation in T cells. Our results demonstrate that Coronin-1A is required for the development of systemic lupus and identify actin-cytoskeleton regulatory proteins as potential targets for modulating autoimmune diseases.

PMID: 18199416 [found with GoPubMed]

56: Isr Med Assoc J 2008 Jan;10(1):65-8

A latitudinal gradient study of common anti-infectious agent antibody prevalence in Italy and Colombia.

Pordeus V, Barzilai O, Sherer Y, Luiz RR, Blank M, Bizzaro N, Villalta D, Anaya JM, Shoenfeld Y

Pro Cardiaco Hospital Research and Training Center-PROCEP, Rio de Janeiro, Brazil.

**BACKGROUND:** Infectious agents are important in the pathogenesis of autoimmune disease since they are a major part of the environmental trigger of autoimmunity. A negative relationship between latitude and infectious diseases species richness has been suggested. **OBJECTIVES:** To examine whether their prevalence differs in two latitudinally different populations. **METHODS:** The prevalence of infections with *Toxoplasma gondii*, rubella virus, cytomegalovirus, Epstein-Barr virus and *Treponema pallidum* was compared between subjects from Italy and Colombia. **RESULTS:** We found high titers of antibodies against four of five microorganisms tested, *Toxoplasma gondii* (50.8%), rubella virus (German measles) (75%), cytomegalovirus (86.3%), Epstein-Barr virus (83.3%) and *Treponema pallidum* (6.3%) in completely healthy individuals from a tropical country (Colombia) and a European country (Italy). Differences between two groups of volunteers were noted regarding two infectious agents. The prevalence of immunoglobulin G anti-rubella antibodies was significantly higher among Italian subjects (85% vs. 67.9%,  $P = 0.002$ ), whereas antibodies against CMV were less prevalent among Italian as compared to Colombian subjects (77% vs. 92.9%,  $P < 0.001$ ). **CONCLUSIONS:** These differences might also result in a different tendency towards development of autoimmune diseases associated with these infectious agents in different populations.

PMID: 18300578 [found with GoPubMed]

57: J Investig Allergol Clin Immunol 2008;18(4):266-71

Alterations in humoral immunity in relatives of patients with common variable immunodeficiency.

Aghamohammadi A, Sedighipour L, Saeed SE, Kouhkan A, Heydarzadeh M, Pourpak Z

Immunology, Asthma and Allergy Research Institute, Medical Sciences/University of Tehran, Tehran, Iran.

**BACKGROUND AND OBJECTIVES:** It has been reported that there is a high prevalence of immunodeficiency and autoimmunity in relatives of patients with common variable immunodeficiency (CVID). The aim of this study was to determine the prevalence of immunoglobulin deficiency in relatives of patients with CVID in Iran, where there is a high rate of consanguineous marriage. **METHODS:** A descriptive study was undertaken in 64 family members of 23 unrelated CVID patients. The group contained 17 fathers, 18 mothers,

18 sisters, 9 brothers, and 2 children. Serum immunoglobulin levels were measured by nephelometry. Immunoglobulin (Ig) G subclass levels were measured in a subgroup of 36 individuals. Serum IgA levels were confirmed by enzyme-linked immunosorbent assay for subjects with suspected IgA deficiency. RESULTS: The rate of consanguineous marriage in families containing relatives with antibody deficiencies was significantly higher than in those families in whom relatives did not have immune deficiencies. IgA deficiency was observed in 2 relatives of patients with CVID. Also CVID was observed in 2 family members. In 3 fathers and 1 brother, IgM levels were lower than normal. Three relatives had IgG4 deficiency and 1 person had combined IgG4 and IgG2 deficiency. Twenty percent of the relatives had hypogammaglobulinemia (including IgA deficiency, CVID, decreased levels of IgM, and IgG subclass deficiencies). CONCLUSION: In our study, alteration in humoral immunity in relatives of CVID patients was higher than previously reported, and this could be attributed to the high rate of consanguineous marriage in Iran. Since the family members of CVID patients are at high risk of hypogammaglobulinemia, it is advisable that they be evaluated for immunodeficiency disorders and monitored throughout their lifetimes.

PMID: 18714534 [found with GoPubMed]

58: Methods Mol Biol 2008;441:175-92

The "reverse capture" autoantibody microarray : an innovative approach to profiling the autoantibody response to tissue-derived native antigens.

Ehrlich JR, Tang L, Caiazzo RJ, Cramer DW, Ng SK, Ng SW, Liu BC

Molecular Urology Laboratory, Division of Urology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.

Recently, we reported the development and use of a "reverse capture" antibody microarray for the purpose of investigating antigen-autoantibody profiling. This platform was developed to allow researchers to characterize and compare the autoantibody profiles of normal and diseased patients. Our "reverse capture" protocol is based on the dual-antibody sandwich immunoassay of enzyme-linked immunosorbent assay (ELISA), and we have previously reported its use to detect autoimmunity to epitopes found on native antigens derived from tumor cell lines. In this protocol, we used ovarian cancer as a model system to adapt the "reverse capture" procedure for use with native antigens derived from frozen tissue samples. The use of this platform in studies of autoimmunity is valuable because it allows for the detection of autoantibody reactivity with epitopes found on the post-translational modifications (PTMs) of native antigens, a feature not present with other protein array platforms. In the first step in the "reverse capture" process, tissue-derived native antigens are immobilized onto the 500 monoclonal antibodies that are spotted in duplicate on the array surface. Using the captured antigens as "baits," we then incubate the array with labeled IgG from test and control samples, and perform a two-slide dye-swap to account for any dye effects. Here, we present a detailed description of the "reverse capture" autoantibody microarray for use with tissue-derived native antigens.

PMID: 18370319 [found with GoPubMed]

59: Pediatr Cardiol 2007 Aug;

Chronic Granulomatous Disease Associated with Atypical Kawasaki Disease.

Yamazaki-Nakashimada MA, Ramírez-Vargas N, De Rubens-Figueroa J

Department of Clinical Immunology, Instituto Nacional de Pediatría,  
Insurgentes Sur 3700-C C.P, 04530, Col. Insurgentes Cuicuilco, Mexico City,  
Mexico, yzki71@yahoo.com.mx.

Chronic granulomatous disease (CGD) is an infrequent inherited disorder characterized by recurrent infections and abnormal granuloma formation. Patients with CGD have an exuberant inflammatory response and an increased risk of developing autoimmunity. We present the case of a 1-year-old boy with CGD who developed several of the characteristic clinical features of Kawasaki Disease. His illness responded to intravenous immunoglobulin, aspirin, and corticosteroids.

PMID: 17676373 [found with GoPubMed]

60: Physiol Res 2008 Feb;

Anti-Helicobacter pylori, anti-thyroid peroxidase, anti-thyroglobulin and anti-gastric parietal cells antibodies in Czech population.

Sterzl I, Hrdá P, Matucha P, Ceřovská J, Zamrazil V

Institute of Immunology and Microbiology, First Faculty of Medicine,  
Charles University, Prague, Czech Republic. ister@lf1.cuni.cz.

Autoimmune thyropathies are frequently linked to many infections, such as Helicobacter pylori, which are also supposed to play also a role in their pathogenesis. The aim of this study was to evaluate the relationships between thyroid and gastric autoimmunity and H. pylori infection on a large sample of Czech population (n=1621) by monitoring the autoantibodies against thyroglobulin (anti-Tg) and thyroid peroxidase (anti-TPO) and gastric parietal cell (anti-GPC, representing thyrogastric syndrome) in correlation with antibodies against Helicobacter pylori (anti-H. pylori) of classes IgG and IgA. The interrelation between autoantibodies and H. pylori antibodies was assessed by H. pylori seropositivity. In H. pylori seropositive persons as compared to seronegative irrespective of age and sex, a higher occurrence of anti-TPO (10.4 % vs. 5.8 %, p=0.001) and anti-GPC (6.1 % vs. 1.7 %, p<0.001) was found. Differences in anti-TPO occurrence were significant in both men (7.0 % vs. 3.3 %, p=0.03) and women (12.7 % vs. 8.0 %, p=0.02), differences in anti-GPC occurrence were significant only in women (7.2 % vs. 1.7 %, p<0.001). Results of this study support the idea of a connection between infection of H. pylori and the occurrence of anti-TPO autoantibodies representing thyroid autoimmunity and gastric parietal cells autoantibodies representing the thyrogastric syndrome. This paper is scheduled for Physiological Research, Vol. 57, Supplement 1 (2008).

PMID: 18271683 [found with GoPubMed]

61: Genes Immun 2007 Aug;

Sle3 and Sle5 can independently couple with Sle1 to mediate severe lupus nephritis.

Liu K, Li QZ, Yu Y, Liang C, Subramanian S, Zeng Z, Wang HW, Xie C, Zhou XJ, Mohan C, Wakeland EK

1Department of Immunology, The University of Texas Southwestern Medical Center, Dallas, TX, USA.

Genetic analyses of the lupus-prone NZM2410 mouse have identified multiple susceptibility loci on chromosome 7, termed Sle3 and Sle5. Both of these loci were contained within a large congenic interval, originally termed as Sle3 that strongly impacts a variety of myeloid and T-cell phenotypes and mediates fatal lupus nephritis when combined with Sle1. We have now produced two subcongenic strains, B6.Sle3 and B6.Sle5, carrying the Sle3 and Sle5 intervals separately and characterized their phenotypes as monocongenic strains and individually in combination with Sle1. Neither B6.Sle3 nor B6.Sle5 monocongenic strain develop severe autoimmunity; however, both of these intervals cause the development of severe glomerulonephritis when combined with Sle1. Thus, B6.Sle1Sle3 and B6.Sle1Sle5 exhibit splenomegaly, expansion of activated B and CD4+ T-cell populations and high levels of IgG and IgM autoantibodies targeting multiple nuclear antigens, intact glomeruli and various other autoantigens. In addition, B6.Sle1Sle3 mice also produced higher levels of IgA antinuclear autoantibodies, which were implicated in the development of IgA nephropathy. Our results indicate that Sle3 and Sle5 can independently complement with Sle1, through shared and unique mechanisms, to mediate the development of severe autoimmunity. Genes and Immunity advance online publication, 30 August 2007; doi:10.1038/sj.gene.6364426.

PMID: 17728789 [found with GoPubMed]

62: Immunity 2007 Dec;27(6):912-26

Opposing Functions of the T Cell Receptor Kinase ZAP-70 in Immunity and Tolerance Differentially Titrate in Response to Nucleotide Substitutions.

Siggs OM, Miosge LA, Yates AL, Kucharska EM, Sheahan D, Brdicka T, Weiss A, Liston A, Goodnow CC

John Curtin School of Medical Research and Australian Phenomics Facility, The Australian National University, Canberra 2601, Australia.

Null mutations that cripple T cell receptor (TCR) signaling explain rare primary immunodeficiencies, but it is not understood why more common polymorphisms that lead to subtle TCR signaling defects are paradoxically associated with autoimmunity. Here we analyzed how a series of Zap70 variants with step-wise decreases in TCR signaling impacted upon opposing TCR functions of immunity and tolerance. One Zap70 variant, murdock, moderately decreased TCR signaling and thymic selection without compromising immunological tolerance, whereas a more severe Zap70 defect, mrtless, abolished thymic-positive selection and led to immunodeficiency. Signaling capacities between these two thresholds disproportionately compromised negative selection and Foxp3(+) regulatory T cell formation, creating a cellular imbalance between immunogenic and tolerogenic functions that resulted in the excessive production of autoantibodies and immunoglobulin E (IgE). The pleiotropic functions of ZAP-70 and their differential response to graded variation provide a paradigm for understanding the complex outcomes of human genetic variation.

PMID: 18093540 [found with GoPubMed]

63: J Immunol 2007 Dec;179(11):7959-66

Lack of chromatin and nuclear fragmentation in vivo impairs the production of lupus anti-nuclear antibodies.

Frisoni L, McPhie L, Kang SA, Monestier M, Madaio M, Satoh M, Caricchio R

Division of Rheumatology, Department of Medicine, University of Pennsylvania, and.

Nuclear autoantigens in systemic lupus erythematosus are thought to derive primarily from apoptotic cells, yet there is no direct evidence that interfering with apoptosis impairs the generation of lupus autoantibodies. Here we use a mouse model that lacks the endonuclease caspase-activated DNase (CAD), resulting in an absence of chromatin and nuclear fragmentation during apoptotic cell death. We show that in this mouse, production and release into circulation of chromatin is impaired after exposure to several apoptotic triggers, but that the absence of CAD does not interfere with upstream steps of apoptosis or immune system function. Finally we show that in CAD-mutant mice, impaired lupus autoimmunity is skewed toward known cytoplasmic components, and autoimmunity toward membrane autoantigens is preserved, while autoimmunity toward chromatin and other lupus nuclear targets is severely impaired or absent. We also show, as control, that the induction of experimental autoimmune encephalomyelitis is not affected by the absence of CAD. Thus, our work in vivo strongly suggests that apoptotic molecular steps during cell death generate nuclear autoantigens to sustain the specific autoimmune response in systemic lupus erythematosus.

PMID: 18025244 [found with GoPubMed]

64: J Neuroimmunol 2007 Nov;

Abnormality of circulating CD4(+)CD25(+) regulatory T cell in patients with Guillain-Barré syndrome.

Chi LJ, Wang HB, Zhang Y, Wang WZ

Department of Neurology, the Second Affiliated Hospital of Harbin Medical University, Harbin 150086, China.

CD4(+)CD25(+) T regulatory cells (Tregs), a subset of CD4(+) T cells expressing high levels of CD25 and the transcription factor Foxp3, are critical in maintaining immunologic homeostasis and preventing autoimmunity by suppressing self-reactive T cells. Guillain-Barré syndrome (GBS) is thought to be a self-limiting, autoimmune disease of the peripheral nervous system. We hypothesized that altered frequency and/or function of Tregs play a role in the breakdown of immunologic self-tolerance in GBS patients. To characterize Tregs in GBS patients, we used flow cytometry to evaluate peripheral numbers of Tregs, real-time polymerase chain reaction to assay mRNA expression of FOXP3, and coculture to analyze functional suppressive properties of Tregs. The results showed that acute-stage patients with AMAN and AIDP exhibited significantly reduced numbers of peripheral Tregs as compared with healthy donors, but marked improvement was observed in stable-stage patients with GBS after treatment with intravenous immunoglobulin (IVIG), concomitantly with improvement of neuropathic symptoms. On the other hand, GBS-derived Tregs and Tregs from healthy individuals exhibited equal FOXP3-expression of mRNA and their ability of suppressing the proliferation and cytokine secretion of CD4 (+) effector T cells was unimpaired in GBS patients. These results suggest that short-term reduced circulating Tregs may be associated with the pathogenesis of two subtypes of GBS. Reversible number and intact function of Tregs presumably contribute to monophasic self-limiting course in GBS.

PMID: 17997492 [found with GoPubMed]

65: Am J Reprod Immunol 2007 Nov;58(5):447-59

Decline in Number of Elevated Blood CD3(+) CD56(+) NKT Cells in Response to Intravenous Immunoglobulin Treatment Correlates with Successful Pregnancy.

van den Heuvel MJ, Peralta CG, Hatta K, Han VK, Clark DA

Department of Pediatrics, University of Western Ontario, London, ON, Canada.

Problem Patients with elevated blood natural killer (NK) cells may be offered intravenous immunoglobulin (IVIG) treatment, but there is controversy about the utility of blood NK cell testing. Human CD56(+) NK cells include several subpopulations that include the putatively cytotoxic CD56(+) CD16(+) subset. In mouse models of pregnant failure, NKT cells appear to be important. However, a mouse model may only be pertinent to a subset of patients, as recurrent pregnancy failure is a heterogeneous group. Method of study An ethics-approved observational study was done to observe the effect of treatment on total blood lymphoid cells, and subsets of CD56(+) blood lymphocytes including CD56(+) CD3(+) NKT cells determined by flow cytometry, and to correlate with pregnancy outcome. Fifteen fertile women with a history of successful pregnancy and thirty-one women suffering from repeated implantation failure or recurrent spontaneous abortion provided serial blood samples during one menstrual cycle or prior to and during treatment. IVIG was administered to the latter group with or without heparin/ aspirin. Results Eight of thirty infertile women presented with high numbers of CD56(+) CD3(+) NKT cells, which declined after treatment with IVIG. The elevated NKT cell group with or without concomitant autoimmunity achieved a significantly higher successful pregnancy rate over the course of the study, as compared to women with average numbers of NKT cells and no evidence of autoimmunity (P = 0.018). Elevated NKT levels alone was an independent predictor of success on treatment (P = 0.003). Conclusion Elevated NKT cells in recurrent pregnancy loss or implantation failure can be ameliorated with IVIG treatment, and result in successful pregnancy. Assay of NKT cell numbers may identify patients who are more likely to benefit from IVIG therapy and merits further examination in randomized phase II studies.

PMID: 17922698 [found with GoPubMed]

66: J Immunol 2007 Nov;179(9):6336-42

Decline in the Frequencies of *Borrelia burgdorferi* OspA161 175-Specific T Cells after Antibiotic Therapy in HLA-DRB1\*0401-Positive Patients with Antibiotic-Responsive or Antibiotic-Refractory Lyme Arthritis.

Kannian P, Drouin EE, Glickstein L, Kwok WW, Nepom GT, Steere AC

Center for Immunology and Inflammatory Diseases, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114.

Synovitis in patients with antibiotic-refractory Lyme arthritis persists for months to several years after antibiotic therapy. This course, which may result from infection-induced autoimmunity, is associated with T cell recognition of *Borrelia burgdorferi* outer surface protein A (OspA(161-175)) and with HLA-DR molecules that bind this epitope, including the DRB1\*0401 molecule. In this study, we used tetramer reagents to determine the

frequencies of OspA(161-175)-specific T cells in samples of PBMC and synovial fluid mononuclear cells (SFMC) from 13 DRB1\*0401-positive patients with antibiotic-responsive or antibiotic-refractory arthritis. Initially, three of the six patients (50%) with antibiotic-responsive arthritis and four of the seven patients (57%) with antibiotic-refractory arthritis had frequencies of OspA(161-175)-specific CD4(+) T cells in peripheral blood above the cutoff value of 4 per 10<sup>5</sup> cells. Among the five patients with concomitant PBMC and SFMC, four (80%) had OspA tetramer-positive cells at both sites, but the mean frequency of such cells was 16 times higher in SFMC, reaching levels as high as 1,177 per 10<sup>5</sup> cells. In the two patients in each patient group in whom serial samples were available, the frequencies of OspA(161-175)-specific T cells declined to low or undetectable levels during or soon after antibiotic therapy, months before the resolution of synovitis in the two patients with antibiotic-refractory arthritis. Thus, the majority of patients with Lyme arthritis initially have increased frequencies of OspA(161-175)-specific T cells. However, the marked decline in the frequency of such cells with antibiotic therapy suggests that persistent synovitis in the refractory group is not perpetuated by these cells.

PMID: 17947711 [found with GoPubMed]

67: J Virol 2007 Sep;

Influenza virus induced type I IFN leads to polyclonal B cell activation but does not break B cell tolerance.

Woods A, Monneaux F, Soulas-Sprauel P, Muller S, Martin T, Korganow AS, Pasquali JL

INSERM U737, Université Louis Pasteur, Hôpitaux universitaires de Strasbourg, Strasbourg, France; CNRS UPR 9021, Institut de Biologie cellulaire et moléculaire, Strasbourg, France.

Objective : The link between infection and autoimmunity is yet not well understood. This study was designed to evaluate if an acute viral infection known to induce type I interferon production, like influenza, can, by itself, be responsible for the breakdown of immune tolerance and for autoimmunity. Methods : We first tested the effects of influenza virus on B cells in vitro. We, then, infected different transgenic mice expressing human Rheumatoid Factors (RF) in the absence or in the constitutive presence of the autoantigen (human IgG) and young lupus prone mice (NZB/NZW F1) with influenza virus and looked for B cell activation. Results : In vitro, the virus induces B cell activation through type I interferon production by non B cells, but does not directly stimulate purified B cells. In vivo, both RF and non-RF B cells were activated in an autoantigen-independent manner. This activation was abortive since IgM and IgM-RF productions were not increased in infected mice compared to uninfected controls, whether or not anti influenza human IgG were detected, and even after viral rechallenge. As in RF tg mice, acute viral infection of NZB/NZW F1 mice induced only an abortive activation of B cells, and no increase in autoantibody production compared to uninfected animals. Conclusion : Taken together, these experiments show that virus induced acute type I interferon production is not able by itself to break down B cell tolerance in both normal and autoimmune genetic backgrounds.

PMID: 17855528 [found with GoPubMed]

68: Clin Exp Immunol 2007 Aug;

Gold causes genetically determined autoimmune and immunostimulatory responses in mice.

Havarinasab S, Johansson U, Pollard KM, Hultman P

Departments of Clinical and Experimental Medicine, and Molecular and Immunological Pathology, Linköping University, Linköping, Sweden.

Natrium aurothiomaleate (GSTM) is a useful disease-modifying anti-rheumatic drug, but causes a variety of immune-mediated adverse effects in many patients. A murine model was used to study further the interaction of GSTM with the immune system, including induction of systemic autoimmunity. Mice were given weekly intramuscular injections of GSTM and controls equimolar amounts of sodium thiomaleate. The effects of gold on lymphocyte subpopulations were determined by flow cytometry. Humoral autoimmunity was measured by indirect immunofluorescence and immunoblotting, and deposition of immunoglobulin and C3 used to assess immunopathology. Gold, in the form of GSTM, stimulated the murine immune system causing strain-dependent lymphoproliferation and autoimmunity, including a major histocompatibility complex (MHC)-restricted autoantibody response against the nucleolar protein fibrillarin. GSTM did not cause glomerular or vessel wall IgG deposits. However, it did elicit a strong B cell-stimulating effect, including both T helper 1 (Th1)- and Th2-dependent isotypes. All these effects on the immune system were dependent on the MHC genotype, emphasizing the clinical observations of a strong genetic linkage for the major adverse immune reactions seen with GSTM treatment.

PMID: 17680821 [found with GoPubMed]

69: Sci Total Environ 2007 Jun;

Non-positive autoimmune responses against CYP2E1 in refrigeration mechanics exposed to halogenated hydrocarbons.

Gunnare S, Vidali M, Lillienberg L, Ernstgård L, Sjögren B, Hagberg M, Albano E, Johanson G

Work Environment Toxicology, Institute of Environmental Medicine, Karolinska Institutet, SE-171 77 Stockholm, Sweden; National Institute for Working Life, SE-113 91 Stockholm, Sweden.

The aim of the study was to determine if occupational exposure to hydrofluorocarbons (HFC) and hydrochlorofluorocarbons (HCFC) generates autoimmune responses against CYP2E1. HFCs and HCFCs have replaced the chlorofluorocarbons (CFC) in e.g. refrigeration installations and air-conditioning systems. During the substitution period, refrigeration mechanics reported symptoms like asthma, influenza-like reactions, and joint troubles. These symptoms resemble those of chronic inflammatory diseases with an autoimmune component. Since exposure to structurally similar chemicals, e.g. halothane, has previously been associated with autoimmune responses and diseases, autoimmunity among the refrigeration mechanics might hypothetically explain the reported inflammatory symptoms. Serum from 44 Swedish men, occupationally exposed to halogenated hydrocarbons, was screened for antibodies against CYP2E1 with enzyme-linked immunosorbent assay. Thirty of the workers had asthma, joint problems or influenza-like symptoms whereas 14 of them had no such symptoms. They were all selected from a cohort of 280 refrigeration mechanics. Unexposed, healthy, Swedish men (n=35) constituted control group. The study was approved by the Ethics Committee at Karolinska Institutet. No increase in autoantibodies against CYP2E1 was detected among the occupationally exposed



workers as compared to the unexposed controls. Further, there was no difference in antibody titer between the exposed workers with symptoms and the exposed, asymptomatic workers or the unexposed controls. The present study does not completely exclude a connection between exposure and effect but makes the relation less likely at these exposure levels.

PMID: 17582468 [found with GoPubMed]

70: Ann N Y Acad Sci 2007 Sep;1110:151-158

Genetic Control of Immune Response in Carriers of the 8.1 Ancestral Haplotype: Correlation with Levels of IgG Subclasses: Its Relevance in the Pathogenesis of Autoimmune Diseases.

Candore G, Campagna AM, Cuppari I, Carlo DD, Mineo C, Caruso C

Laboratorio di Immunopatologia, Dipartimento di Biopatologia e Metodologie Biomediche, Università di Palermo, Corso Tukory 211, 90134 Palermo, Italy. gcandore@unipa.it.

Ancestral haplotype (AH) 8.1(HLA-A1, Cw7, B8, TNFAB\*a2b3, TNFN\*S, C2\*C, Bf\*s, C4A\*Q0, C4B\*1, DRB1\*0301, DRB3\*0101, DQA1\*0501, DQB1\*0201) seems to be associated with susceptibility to autoimmune diseases. Different mechanisms are probably involved in increasing autoimmunity, such as unbalanced cytokine production and the lack of C4A protein. So AH 8.1 modifies immune response in many ways. In this study we demonstrate that IgG2 serum levels were significantly lower in 8.1 AH carriers than in 8.1 AH non-carriers. On the contrary, as regards IgG1, IgG3, IgG4 serum levels, no significant differences were observed between the two groups. In AH 8.1 carriers low IgG2 levels might take to slower clearance of the infectious agent and hence to a lasting presence of it. The persistence of infectious antigens could determine an increased production of autoantibodies with a higher risk of cross-reactions.

PMID: 17911430 [found with GoPubMed]

71: Blood 2007 Sep;110(5):1595-602

Macrophages prevent the differentiation of autoreactive B cells by secreting CD40 ligand and interleukin-6.

Kilmon MA, Wagner NJ, Garland AL, Lin L, Aviszus K, Wysocki LJ, Vilen BJ

Activation of the innate immune system promotes polyclonal antibody secretion to eliminate invading pathogens. Inherent in this process is the potential to activate autoreactive B cells and induce autoimmunity. We showed previously that TLR-stimulated dendritic cells and macrophages regulate B cell tolerance to Smith antigen, in part through the secretion of interleukin-6 (IL-6). In this manuscript, we show that neutralization of IL-6 fails to abrogate macrophage-mediated repression and identify soluble CD40 ligand (CD40L) as a second repressive factor secreted by macrophages. CD40L selectively repressed Ig secretion by chronically antigen-experienced (anergic) immunoglobulin transgenic and nontransgenic B cells but not by transiently stimulated B cells. The importance of macrophages in maintaining B cell tolerance was apparent in lupus-prone MRL/lpr mice. Compared with C57BL/6 mice, macrophages from MRL/lpr mice were significantly less efficient at repressing immunoglobulin secretion coincident with diminished IL-6 and CD40 ligand production. These data indicate that macrophages regulate autoreactive B cells by secreting

repressive factors that prohibit terminal differentiation of B cells. The regulation of autoreactive B cells by macrophages is diminished in lupus-prone mice suggesting a role in autoimmunity.

PMID: 17712049 [found with GoPubMed]

72: Science 2008 Oct;322(5899):271-5

CTLA-4 control over Foxp3+ regulatory T cell function.

Wing K, Onishi Y, Prieto-Martin P, Yamaguchi T, Miyara M, Fehervari Z, Nomura T, Sakaguchi S

Department of Experimental Pathology, Institute for Frontier Medical Sciences, Kyoto University, Kyoto 606-8507, Japan.

Naturally occurring Foxp3+CD4+ regulatory T cells (Tregs) are essential for maintaining immunological self-tolerance and immune homeostasis. Here, we show that a specific deficiency of cytotoxic T lymphocyte antigen 4 (CTLA-4) in Tregs results in spontaneous development of systemic lymphoproliferation, fatal T cell-mediated autoimmune disease, and hyperproduction of immunoglobulin E in mice, and it also produces potent tumor immunity. Treg-specific CTLA-4 deficiency impairs in vivo and in vitro suppressive function of Tregs in particular, Treg-mediated down-regulation of CD80 and CD86 expression on dendritic cells. Thus, natural Tregs may critically require CTLA-4 to suppress immune responses by affecting the potency of antigen-presenting cells to activate other T cells.

PMID: 18845758 [found with GoPubMed]

73: Int Immunol 2008 Sep;

Autoreactive B-cell elimination by pathogenic IgG specific for the same antigen: implications for peripheral tolerance.

Ota T, Aoki-Ota M, Tsunoda K, Nishikawa T, Koyasu S, Amagai M

Department of Dermatology.

Harmful pathogenic IgG auto-antibodies are produced against desmoglein 3 (Dsg3) in pemphigus vulgaris, an autoimmune blistering disease. Dsg3 is a cadherin-type cell adhesion molecule expressed in desmosomes of the skin and mucous membranes. In AK7-transgenic mice expressing non-pathogenic AK7 IgM against Dsg3, autoreactive transgenic B cells escape from the deletion or inactivation and exist in the periphery. However, when a pathogenic anti-Dsg3 IgG1 mAb (AK23) capable of inducing blisters was injected into AK7-transgenic mice, AK7 B cells were eliminated from the bone marrow (BM) and spleen only when Dsg3 was expressed in the periphery. In contrast, non-pathogenic IgG mAbs (AK7, AK9) failed to eliminate AK7 B cells. Interestingly, the AK23-mediated elimination of mature AK7 B cells in the spleen was significantly diminished in AK7-transgenic mice on a Rag2(-/-) background while BM B cells were still eliminated, suggesting the presence of T-cell-dependent and -independent mechanisms. T cell transfer studies into AK7-Rag2(-/-) mice revealed that autoreactive B-cell elimination in the periphery requires CD4(+) T cells from wild-type mice but not from gld (FasL mutant) mice. The B-cell elimination was impaired in both BM and periphery when Bcl2 was over-expressed in AK7 B cells. These findings suggest that autoreactive B cells exist unless they are harmful, but once

harmful or dangerous events such as tissue destruction are sensed, the mature autoreactive B cells in the periphery are eliminated via a Fas-mediated process in a CD4(+) T cell-dependent manner.

PMID: 18765425 [found with GoPubMed]

74: Clin Immunol 2008 Jul;

Memory B cells in common variable immunodeficiency: Clinical associations and sex differences.

Sánchez-Ramón S, Radigan L, Yu JE, Bard S, Cunningham-Rundles C

Department of Medicine, Pediatrics and Immunobiology Center, Mount Sinai Medical School, New York, NY, USA; Clinical Immunology Unit, Department of Immunology, General University Hospital Gregorio Marañón, Madrid, Spain.

Common variable immunodeficiency (CVID) is a heterogeneous syndrome characterized by impaired antibody responses, recurrent infections, inflammatory, autoimmune and malignancy-related conditions. We evaluated the relationship between memory B cell phenotype, sex, age at diagnosis, immunologic and clinical conditions in 105 CVID subjects from one medical center. Reduced numbers of switched memory B cells (cutoff  $\leq 0.55\%$  of B cells) were an independent risk factor of granulomas, autoimmune diseases and splenomegaly ( $p < 0.001$ ). Not previously noted, CVID females had significantly more switched memory cells ( $p = 0.007$ ) than males. Splenectomized subjects did not have fewer IgM memory B cells and these numbers were not related to the development of lung disease, as previously proposed. Lower baseline serum IgG was an independent predictor of pneumonia ( $p = 0.007$ ) and severe infections ( $p = 0.001$ ). We conclude that outcomes in CVID depend on an interplay of factors including sex, numbers of switched memory B cells, and baseline serum IgG and IgA levels.

PMID: 18620909 [found with GoPubMed]

75: Cytometry A 2008 Jun;

Intracellular Phospho-Flow cytometry reveals novel insights into TCR proximal signaling events. A comparison with Western blot.

Haas A, Weckbecker G, Welzenbach K

Novartis Institutes for Biomedical Research, Autoimmunity, Transplantation and Inflammation, Basel, Switzerland.

Phospho-site specific antibodies become increasingly available, enabling the study of signaling events by Western blotting (WB) or intracellular flow cytometry (Phospho-Flow). Here we compared data generated by WB or Phospho-Flow regarding the kinetics and degree of phosphorylation of membrane proximal TCR signaling molecules. Phosphorylation events in Jurkat T cells were triggered by anti-CD3 stimulation (OKT3) or by oxidative stress ( $H_2O_2$ ) and were analyzed by Phospho-Flow or WB. Both techniques showed that OKT3- or  $H_2O_2$ -induced, transient phosphorylation of ZAP70 or LAT was dependent on functional Lck. Phospho-Flow data revealed differences in the kinetics and the degree of  $H_2O_2$ - or OKT3-mediated protein phosphorylation compared with WB data. In addition, using Phospho-Flow we discovered that  $H_2O_2$ -induced phosphorylation of TCR signaling proteins was inhibited by small molecular weight kinase inhibitors far more potently than OKT3-triggered protein phosphorylation, despite a superior

induction of phosphorylation by H<sub>2</sub>O<sub>2</sub>. This finding was confirmed by WB. Interestingly, we identified by Phospho-Flow that, in P116 Jurkat cells lacking ZAP70 protein expression, H<sub>2</sub>O<sub>2</sub> potently triggered the phosphorylation of ZAP70 residues Y493 and Y292 but not Y319. The phosphorylation of these ZAP70 tyrosine residues cells was blocked by an Lck inhibitor, suggesting the existence of an Lck-coupled truncated ZAP70 protein or a novel isoform of ZAP70 in P116 cells. Phospho-Flow is a largely quantitative technology with excellent throughput, highly suited in studying the function or inhibition of TCR signaling pathways and allowing the detection of novel pathway insights. It can serve as a good complement to Western blot analysis. (c) 2008 International Society for Advancement of Cytometry.

PMID: 18548611 [found with GoPubMed]

76: J Invest Dermatol 2008 Apr;

Humoral Autoimmune Responses to the Squamous Cell Carcinoma Antigen Protein Family in Psoriasis.

El-Rachkidy RG, Young HS, Griffiths CE, Camp RD

1Department of Infection, Immunity and Inflammation, University of Leicester, Leicester, UK.

Substantial evidence indicates that psoriasis is a T-lymphocyte-mediated autoimmune disease. However, longstanding data also indicate IgG and complement deposition in upper epidermis of psoriasis plaques. This led us to propose that autoantigen-autoantibody interactions in the skin may also be of pathogenic importance. Here, we have confirmed the presence of IgG in upper lesional epidermis and used high-resolution two-dimensional immunoblotting of extracts from this tissue, and laser desorption mass spectrometry of tryptic peptides, to define a series of epidermal proteins that bind IgG from psoriatic serum. The most prominent of these autoantigens are homologues of the serpin, squamous cell carcinoma antigen (SCCA), the other autoantigens identified including arginase 1, enolase 1, and keratin 10. Blood levels of IgG autoantibodies that bind to SCCA proteins were significantly higher in psoriasis than healthy controls (P=0.005), but were not detectable in sera from patients with active atopic dermatitis. To our knowledge, SCCA proteins have not previously been described as autoantigenic in animals or humans and form complexes with IgG that are associated with complement deposition. These findings expose potentially pathogenic humoral immunologic events and thus possible therapeutic targets in psoriasis. Journal of Investigative Dermatology advance online publication, 3 April 2008; doi:10.1038/jid.2008.71.

PMID: 18385761 [found with GoPubMed]

77: Nippon Naika Gakkai Zasshi 2008 Aug;97(8):1830-7

[Immunotherapy for paraneoplastic neurological syndromes]

K Nomura

PMID: 18833703 [found with GoPubMed]

78: Autoimmunity 2008 Aug;41(5):395-404

Effect of anti-CD134L mAb and CTLA4Ig on ConA-induced proliferation, Th cytokine secretion, and anti-dsDNA antibody production in spleen cells from lupus-prone BXSB mice.

Zhou YB, Ye RG, Li YJ, Xie CM, Wu YH

Department of Internal Medicine, First Affiliated Hospital, Sun Yat-sen University, Guangzhou, People's Republic of China. sumszyb@yahoo.com.cn

We sought to evaluate the effects of combined downregulation of CD134 and cytotoxic T lymphocyte-associated antigen 4 (CTLA4) on the autoimmune process of lupus. Concanavalin A (ConA)-induced proliferation, T helper cell cytokine secretion, and anti-double stranded DNA (dsDNA) antibody production were measured in cultures of splenic lymphocytes derived from lupus-prone BXSB mice. Splenocytes from six prednisone-treated and six untreated male lupus-prone BXSB mice, as well as from six syngeneically normal C57BL/6 male mice, were stimulated with ConA. BXSB splenocytes from untreated mice were exposed to anti-CD134L mAb, CTLA4 linked to the Fc portion of IgG1 (CTLA4Ig), or both. The magnitude of splenocyte proliferation and the levels of IFN-gamma, IL-6, and anti-dsDNA antibody were: (1) significantly higher in cultures of ConA-stimulated control and other cells than in unstimulated cells, (2) similar in cultures of normal and BXSB cells treated with anti-CD134 and CTLA4Ig or prednisone and (3) significantly reduced in cultures of ConA-stimulated and unstimulated cells treated with anti-CD134L and CTLA4Ig or prednisone compared with cells treated with CD134L or CTLA4Ig alone. Like corticosteroids, anti-CD134L mAb or CTLA4Ig can inhibit T- and B-cell activation by blocking the CD134-CD134L or CD28/CTLA4-B7 co-stimulatory pathway. The combined immune intervention described herein may prove useful for the treatment of autoimmune diseases such as systemic lupus erythematosus.

PMID: 18568645 [found with GoPubMed]

79: Autoimmunity 2008 Aug;41(5):341-52

A role for DRAK2 in the germinal center reaction and the antibody response.

Al-Qahtani A, Xu Z, Zan H, Walsh CM, Casali P

Center for Immunology, University of California, Irvine, CA, USA.

DAP-related apoptotic kinase-2 (DRAK2), a death-associated protein kinase family member, is highly expressed in B and T lymphocytes in the human and the mouse. To determine whether DRAK2 plays a role in B-cell activation and differentiation, we analyzed germinal centers (GCs) and the specific antibody response to NP in drak2<sup>-/-</sup> mice immunized with the thymus-dependent (TD) conjugated hapten NP16-CGG. In drak2<sup>-/-</sup> mice, spleen GCs were normal in size and morphology, but their number was reduced by as much as 5-fold, as compared to their wild-type littermates. This was not due to a defect in B-cell proliferation, as the BrdU uptake was comparable in DRAK2-deficient and wild-type B cells. Rather, the proportion of apoptotic GC B and T cells in drak2<sup>-/-</sup> mice was significantly higher than that in wild-type control mice, as shown by 7-AAD and terminal deoxynucleotide transferase dUTP nick end labeling (TUNEL) staining. In drak2<sup>-/-</sup> mice, the generation high affinity IgG antibodies was impaired in spite of the seemingly normal somatic hypermutation and class switch DNA recombination machineries in drak2<sup>-/-</sup> B cells. In NP16-CGG-immunized drak2<sup>-/-</sup> mice, T-cell-intrinsic Bcl-xL transgene expression increased the number of GCs and rescued the high affinity IgG response to NP. These findings suggest a novel role for DRAK2 in regulating the GC reaction and the response to TD

antigens, perhaps through increased survival of T cells and enhanced B-cell positive selection. They also suggest that DRAK2-deficiency is not involved in regulating intrinsic B-cell apoptosis.

PMID: 18568639 [found with GoPubMed]

80: J Cardiovasc Med (Hagerstown) 2008 Jul;9(7):666-71

Myocarditis and dilated cardiomyopathy: possible connections and treatments.

Castellano G, Affuso F, Di Conza P, Fazio S

Department of Internal Medicine, School of Medicine, University of Naples Federico II, Naples, Italy.

Myocarditis is an inflammatory heart muscle disease, resulting from various etiologies, both noninfectious and infectious, which may be associated or not with cardiac dysfunction. Its course is unpredictable: it may spontaneously resolve or evolve into dilated cardiomyopathy and heart failure. A possible connection between myocarditis and dilated cardiomyopathy has long been postulated, but the intimate mechanisms linking these two conditions are still poorly understood. Viral myocarditis could induce a dilated cardiomyopathy through viral persistence and/or by triggering an autoimmune process. Understanding the mechanisms underlying the relationship between myocarditis and dilated cardiomyopathy will help in identifying an effective strategy of treatment aimed to stop and prevent cardiac damage. Specifically, we need to (a) evaluate the potential role of autoantibodies in disease prevention and progression, and understand their importance as markers of disease progression; (b) clarify the role of immunoregulation in exacerbating the disease.

PMID: 18545064 [found with GoPubMed]

81: J Neurol 2008 Jul;255 Suppl 3:3-6

Advances in the understanding of the mechanism of action of IVIg.

HP Hartung

Department of Neurology, Heinrich-Heine-University, Moorenstr. 5, 40225, Duesseldorf, Germany. hans-peter.hartung@uni-duesseldorf.de

The IgG molecule is the main component of IVIg. Commercial preparations of IVIg are derived from a pool of donors and subsequently, IVIg products contain smaller amounts of IgA and IgM antibodies as well as Th2 cytokines and cytokine antagonists that may also contribute to therapeutic effects. Numerous targets for IVIg include: T-cells, cytokines, immune cell trafficking, B-cells, complement and Fc-receptors. IVIg has been demonstrated to inactivate auto-reactive T-cells by competing for and interrupting their interaction with antigen presenting cells. The balance of cytokines also appears to be restored by IVIg, with studies showing that IVIg contains antibodies and antagonists to pro-inflammatory cytokines. In addition, IVIg is thought to interfere with and prevent the passage of auto-immune T-cells into the blood-nerve barrier. The effects of exogenous antibodies on B-cells have been well studied; IVIg is thought to down-regulate antibody production by B-cells, interfere with B-cell proliferation via a blockade of cell surface receptors and prevent the activation of certain subtypes of B-cell. In addition, IVIg can affect

innate immunity by interrupting the steps in the complement activation cascade and blocking Fc-receptor mediated activity, which results in down-regulation of macrophage activity. In conclusion, IVIg has numerous modes of action, which culminate in the down-regulation of the immune response; many of which may be relevant to neuromuscular disorders and immune neuropathies.

PMID: 18685919 [found with GoPubMed]

82: J Rheumatol 2008 May;35(5):745-51

Serum Antibodies Against Intact Human Collagen IX Are Elevated at Onset of Rheumatoid Arthritis But Are Not Related to Development of Erosions.

Jäälinoja J, Nissilä M, Kauppi MJ, Hakala M, Laiho K, Karttunen R, Hörkkö S, Ala-Kokko L

From the Departments of Rheumatology and Cardiology, Hospital Son Llàtzer, and the Departments of Cardiac Surgery and Genetics, Hospital Son Dureta, Palma de Mallorca, Balearic Islands, Spain.

**OBJECTIVE:** Objective. To measure the presence of autoantibodies binding to intact human recombinant collagen IX and assess their usefulness as a diagnostic marker and an indicator of disease activity in rheumatoid arthritis (RA). **METHODS:** Recombinant human full-length collagen IX (rCIX) was produced in a baculovirus expression system and purified for use in ELISA developed to detect antibodies to native and denatured collagen IX. Fifty-three patients with recent-onset rheumatoid factor-seropositive RA were analyzed for the presence of rCIX antibodies of the IgG type at the time of initial diagnosis and after 3, 6, 12, and 24 months of followup. The RA sera were accompanied by 30 controls. Associations were determined between patients' antibody titers, development of erosions in the hands and feet, and various clinical and laboratory markers. **RESULTS:** Serum antibody levels among patients with RA at time of diagnosis were 1.78 times higher against native rCIX ( $p < 0.001$ ) and 1.71 times higher against denatured rCIX ( $p < 0.001$ ) than in the controls, and they remained high during the followup. No correlation was seen between antibody levels and clinical and laboratory findings. **CONCLUSION:** Our data show that patients with recent-onset RA have significantly elevated levels of autoantibodies to human rCIX. These autoantibodies were observed already at the early stages of the disease, which may reflect their diagnostic potential in RA.

PMID: 18381798 [found with GoPubMed]

83: Histol Histopathol 2008 Apr;23(4):411-22

Autoimmune glomerulonephritis induced in congenic mouse strain carrying telomeric region of chromosome 1 derived from MRL/MpJ.

Ichii O, Konno A, Sasaki N, Endoh D, Hashimoto Y, Kon Y

Laboratory of Anatomy, Department of Biomedical Sciences, Graduate School of Veterinary Medicine, Hokkaido University, Sapporo, Japan.

In lupus erythematosus-prone mice, including the BXSB, NZW and NZB strains, telomeric regions of chromosome 1 (Chr.1) contain major glomerulonephritis susceptibility loci such as Bxs3, Sle1, and Nba2. To assess whether strain MRL, a model for lupus erythematosus, had glomerulonephritis susceptibility loci on Chr.1, we created B6.MRLc1(82-100) congenic mice carrying MRL/MpJ

Chr.1 (82-100 cM) based on the C57BL/6 background and investigated renal pathology. From 6 months of age, B6.MRLc1 (82-100) showed the onset of diseases such as splenomegaly due to proliferation of CD3- or B220-positive cells, glomerular damage, and an increased serum anti-dsDNA antibody concentration, and these were earlier and severer in females. The score for glomerular damage was higher in B6.MRLc1(82-100) mice over 12 months old than in C57BL/6 or even in wild-type MRL/MpJ. Immune-complex depositions were demonstrated on glomerular basement membrane in B6.MRLc1(82-100) by immunohistochemistry and electron microscopy. For the percentage of IgG1-positive glomeruli, B6.MRLc1 (82-100) had significantly higher values than C57BL/6. In evaluations of clinical parameters, serum levels of blood urea nitrogen and the anti-dsDNA antibody in B6.MRLc1(82-100) were significantly higher than those in C57BL/6. In conclusion, B6.MRLc1(82-100) clearly developed autoimmune-mediated glomerulonephritis, and we demonstrated that MRL Chr.1 contained a novel glomerulonephritis susceptibility locus. We named this locus Mag (MRL autoimmune glomerulonephritis) and it provided new insights into the genetic basis and pathogenesis of lupus nephritis.

PMID: 18228198 [found with GoPubMed]

84: Trends Immunol 2008 Mar;

Therapeutic cleavage of IgG: new avenues for treating inflammation.

Nandakumar KS, Holmdahl R

Medical Inflammation Research, I-11, BMC, Lund University, Lund, Sweden;  
and Medical Inflammation Research, Department of Medical biochemistry and Biophysics, Karolinska Institutet, Scheeles väg 2, Stockholm, Sweden.

Autoantibodies developing in humans contribute to the pathogenesis of several diseases, and injected therapeutic antibodies can also trigger adverse side effects. An efficient and rapid elimination of these antibodies are therefore critically needed. Antibody removal by plasmapheresis and immunoadsorption are commonly used methods but have their own limitations. Bacterial enzymes that can cleave IgG molecules or remove carbohydrate moieties to ameliorate their immunogenicity or effector functions in vivo offer new avenues for drug development. Recent discoveries highlight the possibility of cleaving or modifying IgG in vivo by injection of enzymes. Such an approach opens up new therapeutic possibilities not only for the control of pathogenic antibody-mediated inflammatory diseases but also allograft rejection or the treatment of side-effects of 'biologicals' such as monoclonal antibodies.

PMID: 18328782 [found with GoPubMed]

85: Ideggyogy Sz 2008 Mar;61(3-4):136-9

PARP activation and inflammatory reaction in selective neurodegeneration.

J Soós

Albert Szent-Györgyi Center for Medical and Pharmaceutical Sciences,  
Department of Neurology, University of Szeged, Szeged.

PMID: 18459454 [found with GoPubMed]



86: Immunol Lett 2008 Jan;

An antibody-based construct carrying DNA-mimotope and targeting CR1(CD35) selectively suppresses human autoreactive B-lymphocytes.

Voynova E, Tchorbanov A, Prechl J, Nikolova M, Baleva M, Erdei A, Vassilev T

Department of Immunology, Institute of Microbiology, Bulgarian Academy of Sciences, Bulgaria.

There is an urgent and unmet need for therapeutic agents targeting selectively disease-associated B-lymphocytes in autoantibody-mediated diseases. We have constructed a chimeric molecule able to cross-link cell surface immunoglobulin with the inhibitory complement receptor type 1 (CD35) on DNA-specific B cells from SLE (systemic lupus erythematosus) patients with the aim of selectively silencing them. This engineered molecule is made of copies of the DNA-mimotope peptide DWEYSVWLSN coupled to a monoclonal anti-CD35 antibody. We found that the DNA-like peptide chimera induced a dose-dependent decrease in the number of IgG anti-dsDNA antibody producing cells when PBMCs of lupus patients were cultured in its presence. Our data present evidence that clustering BCR and the inhibitory CR1 on disease-associated autoreactive B-lymphocytes selectively suppresses autoantibody production.

PMID: 18262286 [found with GoPubMed]

87: Ann Allergy Asthma Immunol 2008 Mar;100(3):280-2

Clinical assessment and management of abnormal IgA levels.

FM Schaffer

Section of Pulmonary, Allergy, and Immunology, Department of Pediatrics, Medical University of South Carolina, Charleston 29425, USA.  
schaffer@musc.edu

PMID: 18426148 [found with GoPubMed]

88: PLoS ONE 2008;3(2):e1692

IdeS: A Bacterial Proteolytic Enzyme with Therapeutic Potential.

Johansson BP, Shannon O, Björck L

Division of Infection Medicine, Department of Clinical Sciences, Biomedical Center (BMC), Lund University, Lund, Sweden.

**BACKGROUND:** IdeS, a proteinase from *Streptococcus pyogenes*, cleaves immunoglobulin (Ig)G antibodies with a unique degree of specificity. Pathogenic IgG antibodies constitute an important clinical problem contributing to the pathogenesis of a number of autoimmune conditions and acute transplant rejection. To be able to effectively remove such antibodies is therefore an important clinical challenge.

**METHODOLOGY/PRINCIPAL FINDINGS:** IdeS was found to specifically and efficiently cleave IgG in human blood in vitro (20 microg of IdeS caused a complete degradation of IgG in one ml of human whole blood in 15 minutes) and to clear IgG from the blood stream of rabbits in vivo (no IgG was detected six hours following an intravenous injection of 5 mg of IdeS)

without any side effects. In a mouse model of immune thrombocytopenic purpura (ITP), polyclonal IgG antibodies against platelet surface antigens were used to induce a lethal disease. These profoundly thrombocytopenic animals were treated and cured by a single injection of IdeS.

CONCLUSIONS/SIGNIFICANCE: Novel information is provided concerning the IgG-cleaving activity of IdeS in vitro and in vivo. The highly specific and rapid elimination of IgG in vivo, the dramatic effect in a mouse model of ITP, and the lack of side effects in the treated animals, indicate that IdeS could also be used to treat IgG-driven diseases in humans.

PMID: 18301769 [found with GoPubMed]

89: Autoimmunity 2008 Feb;41(1):80-6

VH gene usage and CDR3 analysis of B cell receptor in the peripheral blood of patients with PBC.

Foreman AL, Lemercier B, Lim A, Kourlisky P, Kenny T, Gershwin ME, Gougeon ML

Division of Rheumatology, Allergy and Clinical Immunology, University of California at Davis School of Medicine, CA 95616, USA.

We have analyzed the IgM, IgG and IgA BCR repertoire in PBC patients by means of quantitative RT-PCR and CDR3-spectratyping with immunoscope technology. PBMC from 35 PBC patients and 18 normal controls were analyzed. Quantitative B cell repertoire analysis of IgM from healthy donors showed the preferential usage of VH3a, VH3b and VH4 families. Very similar VH family usage was observed in IgM B cells from PBC patients. CDR3-spectratyping of IgM BCR rearrangements showed a Gaussian distribution for dominant VH families in control donors, and similar diversity was found for the VH3b family in PBC patients. In contrast, VH3a and VH4 families showed oligoclonal expansions in some patients. Quantitative B cell repertoire analysis of IgG and IgA did not reveal any difference in VH chain distribution in PBC patients as compared to the control donors. Immunoscope profiles of CDR3 length distribution showed several peak expansions in B cells from control donors, particularly for the VH3a and VH4 families. CDR3 length distribution profiles of IgG and IgA from PBC patients were oligoclonal too, with expansions throughout the various VH chains. However, no common expansions within the CDR3 region were found intraindividually between IgG, IgA and IgM, and between patients. In conclusion, immunoscope technology does provide, for the first time, a sensitive and rapid method for detailed immunoglobulin gene usage analysis in peripheral B cells from PBC patients. This study failed to demonstrate preferential B cell rearrangements in the blood of patients with PBC, but this technology may be more successful if applied to the analysis of compartmental B cells (i.e. liver infiltrating B cells).

PMID: 18176868 [found with GoPubMed]

90: Acta Dermatovenerol Croat 2008 May;16(2):65-71

Chronic Autoimmune Urticaria in Children.

Dodig S, Richter D

Slavica Dodig, BPharm, PhD, Srebrnjak Children's Hospital, Reference Center for Pediatric Allergology of the Ministry of Health and Social Welfare, Srebrnjak 100, HR-10000 Zagreb, Croatia; slavica.dodig@zg.t-com.hr.

Results of determination of circulating histamine releasing autoantibodies using histamine release urticaria test in 12 children (aged 3 to 18 years, mean age 8.5 years; 7 female and 5 male) with chronic urticaria are presented. Standard work-up including detailed history, allergy testing and routine laboratory findings did not disclose any plausible cause of chronic/recurrent urticarial eruption in these children. All children underwent serum-induced basophil histamine release urticaria test. At serum dilution of 12.5%, the mean percent of histamine liberation was 40.8% (range 18%-77%; normal <16.5%), which indicated the presence of autoantibodies to FcepsilonRI and/or to the IgE-FcepsilonRI complex. The percent of histamine release did not correlate with patient age or duration and severity of symptoms. Thus the autoimmune basis of chronic urticaria was established. Associated antithyroid autoantibodies were found in two patients. Complete or partial remission was obtained with treatment that included antihistamines, low salicylate-low preservative diet in all, and high dose intravenous immunoglobulin in 3 children.

PMID: 18541101 [found with GoPubMed]

91: Ann Neurol 2008 Jan;63(1):16-25

Homogeneity of active demyelinating lesions in established multiple sclerosis.

Breij EC, Brink BP, Veerhuis R, van den Berg C, Vloet R, Yan R, Dijkstra CD, van der Valk P, Bö L

Department of Molecular Cell Biology and Immunology, Vrije Universiteit Medical Center, Amsterdam, the Netherlands.

**OBJECTIVE:** Four different patterns of demyelination have been described in active demyelinating lesions of multiple sclerosis (MS) patients that were biopsied shortly after disease onset. These patterns were suggested to represent heterogeneity of the underlying pathogenesis. The aim of this study was to determine whether lesion heterogeneity also exists in an unselected collection of autopsy material from patients with established MS. **METHODS:** All MS brain tissue available in the VU Medical Center was assessed for the presence of active demyelinating lesions using magnetic resonance imaging-guided sampling and immunohistochemistry. Tissue blocks containing active demyelinating lesions were evaluated for the presence of complement and antibody deposition, oligodendrocyte apoptosis, differential loss of myelin proteins, and hypoxia-like damage using histology, immunohistochemistry, and confocal microscopy. Blocks with active demyelinating lesions were compared with blocks with active (nondemyelinating) and inactive lesions. **RESULTS:** Complement and antibodies were consistently associated with macrophages in areas of active demyelination. Preferential loss of myelin proteins, extensive hypoxia-like damage, and oligodendrocyte apoptosis were absent or rare. This pattern was observed in all tissue blocks containing active demyelinating lesions; lesion heterogeneity between patients was not found. **INTERPRETATION:** The immunopathological appearance of active demyelinating lesions in established MS is uniform. Initial heterogeneity of demyelinating lesions in the earliest phase of MS lesion formation may disappear over time as different pathways converge in one general mechanism of demyelination. Consistent presence of complement, antibodies, and Fcγ receptors in phagocytic macrophages suggests that antibody- and complement-mediated myelin phagocytosis is the dominant mechanism of demyelination in established MS. Ann Neurol 2008;63:16-25.

PMID: 18232012 [found with GoPubMed]

92: Exp Dermatol 2008 Jan;17(1):35-43

IgG against extracellular subdomains of desmoglein 3 relates to clinical phenotype of pemphigus vulgaris.

Müller R, Svoboda V, Wenzel E, Müller HH, Hertl M

Department of Dermatology and Allergology, University of Marburg, Marburg, Germany.

Pemphigus vulgaris (PV) is associated with autoantibodies against desmoglein (Dsg) 3 inducing epidermal loss of adhesion. The major pathogenic epitopes of Dsg3 are presumably dependent of their conformation. The aim of this study was to characterize the IgG reactivity of sera from a cohort of clinically well-characterized PV patients against presumably non-conformational subdomains of the Dsg3 ectodomain including recently described NH(2)-terminal immunodominant epitopes. By ELISA, IgG reactivity against distinct subdomains of Dsg3 was related to disease activity and the clinical phenotype of PV patients. Our findings suggest that (i) autoantibody from PV sera react with non-conformational epitopes of Dsg3; (ii) IgG reactivity against the NH(2)-terminus and the extracellular domains (EC) 2-4 of Dsg3 was associated with active PV, while IgG titres were not strictly correlated with disease activity and (iii) IgG reactivity against the EC1-4 was associated with mucosal dominant PV and was decreased in cutaneous dominant PV. The findings may help to define more refined serological disease markers of PV.

PMID: 18095943 [found with GoPubMed]

93: Immunopharmacol Immunotoxicol 2008;30(1):13-25

Differential anti-Golgi complex autoantibody production following murine lactate dehydrogenase-elevating virus infection.

Nozawa K, Fritzler MJ, Ikeda K, Takasaki Y, Satoh M, Chan EK

Institute for Environment and Gender Specific Medicine, Juntendo University Graduate School of Medicine, Chiba, Japan. kazunozawa@juntendo-urayasu.jp

Lactate dehydrogenase-elevating virus (LDV) causes asymptomatic infection and persistent viremia in mice with unique infectious specificity directed to a certain subpopulation of macrophages leading to chronic infection and an immunological disorder that includes hyperimmunoglobulinemia and production of autoantibodies. Infection with a species of LDV originally isolated from mice carrying an LDV-contaminated transplantable tumor (LDV-W) was reported to induce anti-Golgi complex antibody (AGA) production. In contrast, infection with the most common LDV species (LDV-P) was not associated with AGA production. Here we performed the first independent side by side comparison of the effects of the two LDV strains on their hosts as an initial approach to investigating the production of AGA. After viral inoculation, both LDV-W and LDV-P infected mice exhibited similar changes in lactate dehydrogenase in plasma suggesting similar viral activity. However, AGA production was observed in only the LDV-W infected mice and these mice exhibited plasma IgG elevation and immune complex formation. These data validated the differential potential of LDV-W and LDV-P in the production of AGA. Future comparative characterizations in the immune processing of Golgi complex autoantigens using these viral strains

may be useful in obtaining specific insights in the specific anti-Golgi complex autoimmune responses.

PMID: 18306101 [found with GoPubMed]

94: J Immunol 2008 Jan;180(1):580-9

Targeting Immune Complex-Mediated Hypersensitivity with Recombinant Soluble Human Fc{gamma}RIA (CD64A).

Ellsworth JL, Maurer M, Harder B, Hamacher N, Lantry M, Lewis KB, Rene S, Byrnes-Blake K, Underwood S, Waggle KS, Visich J, Lewis KE

Department of Autoimmunity and Inflammation.

Binding of Ag-Ab immune complexes to cellular FcgammaR promotes cell activation, release of inflammatory mediators, and tissue destruction characteristic of autoimmune disease. To evaluate whether a soluble FcgammaR could block the proinflammatory effects of immune complexes, recombinant human (rh) versions of FcgammaRIA, FcgammaRIIA, and FcgammaRIIIA were prepared. Binding of rh-FcgammaRIA to IgG was of high affinity ( $K(D) = 1.7 \times 10^{-10}$  M), whereas rh-FcgammaRIIA and rh-FcgammaRIIIA bound with low affinity ( $K(D) = 0.6-1.9 \times 10^{-6}$  M). All rh-FcgammaR reduced immune complex precipitation, blocked complement-mediated lysis of Ab-sensitized RBC, and inhibited immune complex-mediated production of IL-6, IL-13, MCP-1, and TNF-alpha by cultured mast cells. Local or systemic delivery only of rh-FcgammaRIA, however, reduced edema and neutrophil infiltration in the cutaneous Arthus reaction in mice. (125)I-labeled rh-FcgammaRIA was cleared from mouse blood with a rapid distribution phase followed by a slow elimination phase with a  $t(1/2)_{\text{gamma}}$  of approximately 130 h. The highest percentage of injected radioactivity accumulated in blood approximately liver approximately carcass > kidney. s.c. dosing of rh-FcgammaRIA resulted in lower serum levels of inflammatory cytokines and prevented paw swelling and joint damage in a murine model of collagen Ab-induced arthritis. These data demonstrate that rh-FcgammaRIA is an effective inhibitor of type III hypersensitivity.

PMID: 18097060 [found with GoPubMed]

95: Blood 2007 Aug;

Excessive exposure to anionic surfaces maintains autoantibody response to {beta}2-Glycoprotein I in patients with antiphospholipid syndrome.

Yamaguchi Y, Seta N, Kaburaki J, Kobayashi K, Matsuura E, Kuwana M

Department of Environmental immuno-dermatology, Yokohama City University Graduate School of Medicine, Yokohama, Japan.

Antiphospholipid syndrome (APS) is an autoimmune prothrombotic disorder associated with autoantibodies to phospholipid (PL)-binding proteins, such as beta2-glycoprotein I (beta2GPI). We have recently reported that binding of beta2GPI to anionic PL facilitates processing and presentation of the cryptic beta2GPI epitope that activates pathogenic autoreactive T cells. To clarify mechanisms that induce sustained presentation of the dominant antigenic beta2GPI determinant in APS patients, T cell proliferation induced by beta2GPI-treated phosphatidylserine liposome (beta2GPI/PS) was evaluated in bulk peripheral blood mononuclear cell cultures. T cells from APS patients responded to beta2GPI/PS in the presence of IgG anti-beta2GPI

antibodies derived from APS plasma, and this response was completely inhibited either by the depletion of monocytes or by the addition of anti-FcγRI antibody. These findings indicate that efficient presentation of the cryptic determinants can be achieved by monocytes undergoing FcγRI-mediated uptake of beta2GPI-bound anionic surfaces in the presence of IgG anti-beta2GPI antibodies. Finally, beta2GPI-bound oxidized LDL or activated platelets also induced the specific T-cell response. Continuous exposure to these anionic surfaces may play a critical role in maintaining the pathogenic anti-beta2GPI antibody response in APS patients.

PMID: 17726161 [found with GoPubMed]

96: Autoimmun Rev 2007 Dec;7(2):137-42

B cells in rheumatoid arthritis.

Bugatti S, Codullo V, Caporali R, Montecucco C

Chair and Division of Rheumatology, University of Pavia, IRCCS Fondazione Policlinico San Matteo, Piazzale Golgi 2, 27100 Pavia, Italy.

Though its etiology remains unknown thus far, the role that autoimmune processes play in rheumatoid arthritis (RA) pathogenesis has been widely proven. Given the easier accessibility of humoral components, the first feature of this contribution to be recognized has been the occurrence of the so-called rheumatoid factor in a large proportion of RA patients. This antibody recognizes the Fc portion of human IgG. By investigating RA pathologic processes and also through experimental models where immune complexes play a fundamental role, many other autoantibodies have then come to our knowledge to be associated with the disease. Their presence and persistence implies that clones of autoreactive B cells survive and proliferate in RA patients under a continuous stimulation. Whether this is a mechanism of disease initiation or just an epiphenomenon is still unclear but no doubt exists that autoantibodies represent a very useful tool in both diagnostic and prognostic terms. Being much more than simple autoantibody producers, B cells are able to secrete many important cytokines and to efficiently present antigens to T lymphocytes in the synovial environment. All of these functions are essential in the development of RA, and lately have claimed attention as B cell depletion has become a common and effective strategy of treatment in RA.

PMID: 18035324 [found with GoPubMed]

97: Curr Opin Immunol 2007 Nov;

Protective mechanisms of IVIG.

R Clynes

Columbia University, College of Physicians and Surgeons, Departments of Medicine and Microbiology, P & S Building Room 8-510, 630 West 168th Street, New York, NY 10032, United States.

PMID: 18032008 [found with GoPubMed]

98: Eur J Immunol 2007 Nov;37(12):3330-3333

Autoreactive B cells get activated in extrafollicular sites.

Weisel F, Wellmann U, Winkler TH

Hematopoiesis Unit, Institute for Biology, Nikolaus-Fiebiger-Center for Molecular Medicine, University Erlangen-Nuremberg, Germany.

Autoreactive B cells are prevented from producing autoantibodies that may cause pathogenicity in autoimmune diseases by the induction of tolerance. When autoreactive B cells escape regulation in autoimmune-prone individuals, large amounts of autoantibodies are produced with somatic mutations in their variable regions. In this issue of the European Journal of Immunology, a new and very useful model is presented that induces activation and hypermutation of autoreactive B cells upon injection of chromatin-containing immune complexes. The differentiation and hypermutation of autoreactive B cells takes place at extrafollicular sites. See accompanying article: <http://dx.doi.org/10.1002/eji200737752>.

PMID: 18050163 [found with GoPubMed]

99: Eur J Immunol 2007 Nov;

Anti-chromatin antibodies drive in vivo antigen-specific activation and somatic hypermutation of rheumatoid factor B cells at extrafollicular sites.

Herlands RA, William J, Hershberg U, Shlomchik MJ

Section of Immunobiology, Yale University School of Medicine, New Haven, USA.

A dominant type of spontaneous autoreactive B cell activation in murine lupus is the extrafollicular generation of plasmablasts. The factors governing such activation have been difficult to identify due to the stochastic onset and chronic nature of the response. Thus, the ability to induce a similar autoreactive B cell response with a known autoantigen in vivo would be a powerful tool in deciphering how autoimmune responses are initiated. We report here the establishment and characterization of a system to initiate autoreactive extrafollicular B cell responses, using IgG anti-chromatin antibodies, that closely mirrors the spontaneous response. We demonstrate that exogenously administered anti-chromatin antibody, presumably by forming immune complexes with released nuclear material, drives activation of rheumatoid factor B cells in AM14 Tg mice. Anti-chromatin elicits autoreactive B cell activation and development into antibody-forming cells at the T zone/red pulp border. Plasmablast generation occurs equally in BALB/c, MRL/+ and MRL/lpr mice, indicating that an autoimmune-prone genetic background is not required for the induced response. Importantly, infused IgG anti-chromatin induces somatic hypermutation in the absence of a GC response, thus proving the extrafollicular somatic hypermutation pathway. This system provides a window on the initiation of an autoantibody response and reveals authentic initiators of it.

PMID: 18034429 [found with GoPubMed]

100: Clin Exp Immunol 2007 Aug;

Mercury exposure as a model for deviation of cytokine responses in experimental Lyme arthritis: HgCl<sub>2</sub> treatment decreases T helper cell type

1-like responses and arthritis severity but delays eradication of *Borrelia burgdorferi* in C3H/HeN mice.

Ekerfelt C, Andersson M, Olausson A, Bergström S, Hultman P

Division of Clinical Immunology, and Unit of Autoimmunity and Immune Regulation, Department of Molecular and Clinical Medicine, Faculty of Health Sciences, University Hospital, Linköping, Sweden.

Lyme borreliosis is a complex infection, where some individuals develop so-called 'chronic borreliosis'. The pathogenetic mechanisms are unknown, but the type of immune response is probably important for healing. A strong T helper cell type 1 (Th1)-like response has been suggested as crucial for eradication of *Borrelia* and for avoiding development of chronic disease. Many studies aimed at altering the Th1/Th2 balance in Lyme arthritis employed mice deficient in cytokine genes, but the outcome has not been clear-cut, due possibly to the high redundancy of cytokines. This study aimed at studying the importance of the Th1/Th2 balance in murine *Borrelia* arthritis by using the Th2-deviating effect of subtoxic doses of inorganic mercury. Ninety-eight C3H/HeN mice were divided into four groups: *Borrelia*-infected (Bb), *Borrelia*-infected exposed to HgCl<sub>2</sub> (BbHg), controls exposed to HgCl<sub>2</sub> alone and normal controls. Mice were killed on days 3, 16, 44 and 65 post-*Borrelia* inoculation. Arthritis severity was evaluated by histology, spirochaetal load determined by *Borrelia* culture, IgG2a- and IgE-levels analysed by enzyme-linked immunosorbent assay (ELISA) and cytokine-secreting cells detected by enzyme-linked immunospot (ELISPOT). BbHg mice showed less severe histological arthritis, but delayed eradication of spirochaetes compared to Bb mice, associated with increased levels of IgE (Th2-induced) and decreased levels of IgG2a (Th1-induced), consistent with a Th2-deviation. Both the numbers of Th1 and Th2 cytokine-secreting cells were reduced in BbHg mice, possibly explained by the fact that numbers of cytokine-secreting cells do not correlate with cytokine concentration. In conclusion, this study supports the hypothesis that a Th1-like response is required for optimal eradication of *Borrelia*.

PMID: 17672870 [found with GoPubMed]