

Autoimmunity and Food Allergy

1: Curr Gastroenterol Rep 2004 Jun;6(3):254-60

Novel foods to treat food allergy and gastrointestinal infection.

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The gastrointestinal tract communicates directly with the external environment. Necessary nutrients must be absorbed and commensal bacteria tolerated, and foreign proteins, antigens, and pathogens must be simultaneously excluded or destroyed. Immaturity or disruption of the mucosal immune defenses increases vulnerability to food allergy, intolerance, and infectious disease. Diseases resulting from ingested foreign proteins and organisms are increasing and cause morbidity and mortality worldwide. There is no specific treatment for food allergy other than avoidance. Vaccination for infectious disease is limited by the cost and logistics of distribution and administration, particularly in developing countries. Novel strategies are being explored to modulate the gut mucosal immune system by altering protein expression in food. Crops are being developed to remove deleterious allergens to prevent immunogenic exposure while preserving nutritional quality. Local food plants that express protein fragments of pathogens might provide an effective means to stimulate gut mucosal immunity while increasing vaccine accessibility.

PMID: 15128494 [found with GoPubMed]

2: J Pediatr 2003 Jul;143(1):39-47

A consistent pattern of minor immunodeficiency and subtle enteropathy in children with multiple food allergy.

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OBJECTIVE: Although immunoglobulin (Ig)E-mediated allergies are readily identifiable, non-IgE-mediated allergies present more diagnostic difficulty. We performed a formal retrospective analysis to determine whether there is a recognizable clinical pattern in children. **METHODS:** We studied 121 children (mean age, 17.3 months) with multiple food allergies who were recruited on the basis of adequate immunological assessment by using case notes and parental questionnaire. **RESULTS:** Group 1 (n=44) had rapid reactions to dietary antigens, of whom 41 also showed delayed reactions. Group 2 (n=77) had delayed reactions only. Mean IgE was increased in group 1 but both groups otherwise shared a pattern of increased IgG1, decreased IgG2/4, and low-normal IgA. Lymphocyte subsets were skewed, with an increased percentage of CD4 and CD19 and decreased CD8

and natural killer cells. Gastroesophageal reflux, esophagitis, subtle enteropathy, and constipation were frequent in both groups. Of 55 exclusively breast-fed infants, 44 sensitized before weaning. Twenty-one of the mothers suffered from autoimmunity. CONCLUSIONS: There appears to be a recognizable pattern of immune deviation and minor enteropathy in children with multiple food allergy, irrespective of the speed of reactions. Disturbed gut motility is particularly common, as is a maternal history of autoimmunity.

PMID: 12915822 [found with GoPubMed]

3: Can J Physiol Pharmacol 1997 Apr;75(4):241-54

Adverse reactions to food constituents: allergy, intolerance, and autoimmunity.

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Food allergies and intolerance represent important health concerns to consumers who are predisposed to these illnesses. Unlike many current food safety issues, food sensitivities are complicated by both complex and multiple individual adverse reactions, which can vary from emotional to pathophysiological ailments. In some instances, the underlying mechanisms that result in the development of food allergies or intolerance have marked differences but produce common symptoms. The present-day diagnosis of these disorders can be impeded by intrinsic limitations in generating accurate information from patient history and biochemical, physicochemical, and immunochemical tests. Oral challenge tests represent effective methods for confirming and testing food allergens and food intolerance; however, these procedures are often restricted to clinical trials. It is important to be able to distinguish among food allergy, intolerance, and autoimmune disease in the management of these disorders. The role of food in the development of autoimmune disease may be exemplified by celiac disease, a food-induced enteropathy, requiring exposure to prolamins in wheat, rye, and barley. Various wheat and soy protein sources, including the soy protein isolates used to make infant formulas, have been related to juvenile or insulin-dependent diabetes mellitus (IDDM), a common chronic disease of childhood. Employing food process technologies to eliminate food constituents with potential for intolerance in some individuals is a potentially viable approach for reducing risk to food-related disorders. Finally, the development of food labelling regulations that require the identification of potential food allergens or agents for intolerance in the ingredient declaration on prepackaged food is a positive step toward the prevention of severe adverse reactions in hypersensitive individuals.

PMID: 9196849 [found with GoPubMed]

4: Gastroenterology 2007 May;132(5):1705-1717

Severe Food Allergy as a Variant of IPEX Syndrome Caused by a Deletion in a Noncoding Region of the FOXP3 Gene.

Torgerson TR, Linane A, Moes N, Anover S, Mateo V, Rieux-Laucat F, Hermine O, Vijay S, Gambineri E, Cerf-Bensussan N, Fischer A, Ochs HD, Goulet O, Ruedemle FM

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Background & Aims: Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX; OMIM 304930) syndrome is a congenital syndrome characterized by autoimmune enteropathy, endocrinopathy, dermatitis, and other autoimmune phenomena. In the present work, we aimed to uncover the molecular basis of a distinct form of IPEX syndrome presenting at the edge of autoimmunity and severe allergy. **Methods:** The FOXP3 gene was sequenced, FOXP3 messenger RNA (mRNA) was quantified by real-time polymerase chain reaction (PCR), and protein expression in peripheral blood lymphocytes was analyzed by flow cytometry after intracellular staining. In coculture experiments (CD4(+)CD25(-) and CD4(+)CD25(+) cells), the functions of regulatory T cells were analyzed. Expression of interferon gamma and interleukin 2 and 4 mRNA within the inflamed intestinal mucosa was quantified by real-time PCR. **Results:** Here, we describe a distinct familial form of IPEX syndrome that combines autoimmune and allergic manifestations including severe enteropathy, food allergies, atopic dermatitis, hyper-IgE, and eosinophilia. We have identified a 1388-base pair deletion (g.del-6247_-4859) of the FOXP3 gene encompassing a portion of an upstream noncoding exon (exon -1) and the adjacent intron (intron -1). This deletion impairs mRNA splicing, resulting in accumulation of unspliced pre-mRNA and alternatively spliced mRNA. This causes low FOXP3 mRNA levels and markedly decreased protein expression in peripheral blood lymphocytes of affected patients. Numbers of CD4(+)CD25(+)FOXP3(+) regulatory T cells are extremely low, and the CD4(+)CD25(+) T cells that are present exhibit little regulatory function. **Conclusions:** A new mutation within an upstream noncoding region of FOXP3 results in a variant of IPEX syndrome associating autoimmune and severe immunoallergic symptoms.

PMID: 17484868 [found with GoPubMed]

5: J Clin Invest 2000 Dec;106(12):R75-81

JM2, encoding a fork head-related protein, is mutated in X-linked autoimmunity-allergic dysregulation syndrome.

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X-linked autoimmunity-allergic dysregulation syndrome (XLAAD) is an X-linked recessive immunological disorder characterized by multisystem autoimmunity, particularly early-onset type 1 diabetes mellitus, associated with manifestations of severe atopy including eczema, food allergy, and eosinophilic inflammation. Consistent with the allergic phenotype, analysis of two kindreds with XLAAD revealed marked skewing of patient T lymphocytes toward the Th2 phenotype. Using a positional-candidate approach, we have identified in both kindreds mutations in JM2, a gene on Xp11.23 that encodes a fork head domain-containing protein. One point mutation at a splice junction site results in transcripts that encode a truncated protein lacking the fork head homology domain. The other mutation involves an in-frame, 3-bp deletion that is predicted to impair the function of a leucine zipper dimerization domain. Our results point to a critical role for JM2 in self tolerance and Th cell differentiation.

PMID: 11120765 [found with GoPubMed]

6: Pediatrics 2006 Jun;117(6):2175-82

Timing of initial exposure to cereal grains and the risk of wheat allergy.

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OBJECTIVE: Early exposure to solid foods in infancy has been associated with the development of allergy. The aim of this study was to examine the association between cereal-grain exposures (wheat, barley, rye, oats) in the infant diet and development of wheat allergy. **METHODS:** A total of 1612 children were enrolled at birth and followed to the mean age of 4.7 years. Questionnaire data and dietary exposures were obtained at 3, 6, 9, 15, and 24 months and annually thereafter. The main outcome measure was parent report of wheat allergy. Children with celiac disease autoimmunity detected by tissue transglutaminase autoantibodies were excluded. Wheat-specific immunoglobulin E levels on children reported to have wheat allergy were obtained. **RESULTS:** Sixteen children (1%) reported wheat allergy. Children who were first exposed to cereals after 6 months of age had an increased risk of wheat allergy compared with children first exposed to cereals before 6 months of age (after controlling for confounders including a family history of allergic disorders and history of food allergy before 6 months of age). All 4 children with detectable wheat-specific immunoglobulin E were first exposed to cereal grains after 6 months. A first-degree relative with asthma, eczema, or hives was also independently associated with an increased risk of wheat-allergy development. **CONCLUSIONS:** Delaying initial exposure to cereal grains until after 6 months may increase the risk of developing wheat allergy. These results do not support delaying introduction of cereal grains for the protection of food allergy.

PMID: 16740862 [found with GoPubMed]

7: Curr Drug Targets Inflamm Allergy 2005 Oct;4(5):577-83

Prophylaxis and therapy of allergy by mucosal tolerance induction with recombinant allergens or allergen constructs.

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The mucosal immune system, present along the respiratory, gastrointestinal and genitourinary tract, has to discriminate between harmful pathogens and innocuous antigens, such as food, airborne antigens or the commensal bacterial flora. Therefore the mucosal immune system has acquired two opposing immunological functions, i.e. the induction of immunity and defence of mucosal pathogens, and the induction and maintenance of tolerance to environmental antigens and bacterial flora. As described for autoimmunity a breakdown or failure of tolerance induction is believed to lead also to allergies and food enteropathies. Based on the physiological role to prevent hypersensitivity reactions, tolerance induction via the

mucosa has been proposed as a treatment strategy against inflammatory diseases, such as allergies. The aim of our research is to develop mucosal allergy vaccines based on the induction of mucosal tolerance and/or the induction of counter-regulatory immune responses with or without the use of certain mucosal antigen delivery systems, such as lactic acid bacteria. The use of recombinant allergens instead of allergen extracts with varying allergen content and composition may be essential for improvement of the treatment efficacy. In the present review we give examples of different animal models of type I allergy/asthma. Using these models we demonstrate that recombinant allergens or hypoallergenic variants thereof can be successfully used to induce mucosal tolerance in a prophylactic as well as a therapeutic treatment regime. That the concept of mucosal tolerance induction/mucosal vaccine delivery may in principal also function in humans is supported by recent clinical trials with locally (sublingual) applied immunotherapy.

PMID: 16248826 [found with GoPubMed]

8: *Pediatr Allergy Immunol* 2002 Feb;13(1):68-71

Severe food-induced vasculitis in two children.

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Food-induced vasculitis seems to be rare and is considered by some as controversial. The reported cases in the literature are few and mostly on adult patients. Described in this report are two children with severe vasculitis caused by specific foods. They were diagnosed at two separate allergy centers that have a special interest in food allergies. Case 1 was an 8-year-old girl with a 9-month history of cutaneous vasculitis with large joints involvement. Case 2 was a 23-month-old girl with an 8-month history of multiple hospitalizations for recurrent acute severe cutaneous and mucous membrane vasculitis with large joints involvement. In both patients, skin biopsy showed leucocytoclastic vasculitis. In neither of the patients could the symptoms be attributed to drug intake, infection, autoimmunity, or other systemic disease. Case 1 had a moderately elevated serum total immunoglobulin E (IgE) level and strongly positive skin test and radioallergosorbent test (RAST) to cow's milk and hen's egg, both of which were proven to be the cause by elimination-challenge tests. Case 2 had a slightly elevated serum total IgE level, but negative skin tests to foods, including chocolate that was suspected by the mother. Avoidance of chocolate resulted in remission, except following accidental ingestion of cocoa-containing products. These findings support the few previous reports on food-induced vasculitis, an entity that seems rare but may be more common than currently realized.

PMID: 12000502 [found with GoPubMed]

9: *Toxicol Lett* 2000 Mar;112-113:433-42

Predictive testing for pathogenic autoimmunity: the morphological approach.

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The term autoimmunity refers to physiologically normal immune processes against self-antigens. In rare cases, the regulatory mechanisms become defective and the uncontrolled production of autoantibodies or activation of autoreactive T-cells can subsequently cause disease. Substances may be capable of evoking autoimmune disease, and it is a challenge in routine toxicology to recognize such substances. In in vivo toxicity studies, uncommon inflammation in exposed animals should be discussed in terms of non-immune toxicity (e.g. irritation), infection, allergy and autoimmunity, taking into account that a response in even a few animals may be significant. Moreover, early morphological indicators of inflammation and lymphoid organ alterations can direct further investigation.

PMID: 10720763 [found with GoPubMed]

10: Ann N Y Acad Sci 2005 Jun;1051:211-7

Decreased serum leptin levels in primary biliary cirrhosis: a link between metabolism and autoimmunity?

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Primary biliary cirrhosis (PBC) is an autoimmune liver disease of unknown etiology resulting in the progressive destruction of the intrahepatic bile ducts and leading to chronic cholestasis and ultimately liver cirrhosis and failure. The immune response in PBC seems to be mediated by autoantibodies as well as autoreactive T lymphocytes directed against mitochondrial antigens in biliary epithelial cells, primarily PDC-E2. Experimental evidence suggests a role of the hormone/cytokine leptin in autoimmune diseases. Leptin is an adipocyte-derived molecule that acts as a hormone influencing food intake and energy metabolism as well as a cytokine with pro-inflammatory, immune-regulatory functions. To study serum leptin in PBC and its association with disease severity, we evaluated serum levels in 37 patients with PBC (27 with no signs of fibrosis or cirrhosis at histologic examination) and 37 age- and sex-matched healthy controls using a validated ELISA method. We found that patients with PBC had significantly lower leptin serum levels compared with healthy controls (13.6 +/- 13.8 vs. 17.6 +/- 11.6; P < 0.05). No correlation between disease severity and serum leptin levels was found. This study has demonstrated that leptin levels are decreased in the serum of patients with PBC but do not seem to be associated with disease severity. Data do not seem to indicate a direct role of leptin in the perpetuation of the autoimmune response in PBC. However, further studies are warranted to further characterize the functions of leptin during the natural history of autoimmunity.

PMID: 16126961 [found with GoPubMed]

11: Allergy Asthma Proc 2003;24(3):171-4

The syndrome of thyroid autoimmunity and idiopathic chronic urticaria and angioedema presenting as anaphylaxis.

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Previous observations have shown that the syndrome of thyroid autoimmunity and idiopathic urticaria and angioedema (ICUA) can be associated with a marked worsening of reactive airway disease. Possibly, mediators released in this syndrome may contribute to acute bronchospasm and associated respiratory symptoms in some patients. In this study, two patients presenting with overlapping clinical presentations of the syndrome of thyroid immunity and ICUA are described in whom a diagnosis of anaphylaxis to food and antibiotics, respectively, was initially suspected but ruled out by testing and challenges. These cases illustrate clinical overlap between presentations of ICUA and anaphylaxis. We suggest that patients with idiopathic anaphylaxis be evaluated for the presence of antithyroid microsomal (peroxidase) antibodies or antithyroglobulin antibodies, particularly because the diagnosis of thyroid antibody-positive ICUA may suggest additional therapeutic options.

PMID: 12866319 [found with GoPubMed]

12: Ann N Y Acad Sci 2002 Apr;958:47-58

Oral tolerance, systemic immunoregulation, and autoimmunity.

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Convincing clinical and experimental evidence suggests that the disturbance of important immunoregulatory and suppressive immunological events induced after oral (mucosal) antigen exposure (oral tolerance) may lead to allergic and autoimmune diseases. Within a variety of factors, age of the host and timing of antigen (food) administration are important characteristics in the development of food allergic disease. Induction of tolerance is seen as a Th2 skewed response, which on one side may prevent harmful mucosal immune reactions but on the other side may contribute to adverse responses in the susceptible individual. The primary mechanisms by which tolerance may be mediated include deletion, anergy, suppression, "ignorance," and apoptosis. Cell-mediated delayed hypersensitivity reactions (Th1), which are implicated in the development of autoimmune and gastrointestinal diseases, are particularly well suppressed. Regulatory events after mucosal exposure of antigen are not well characterized and remain controversial. The balance between tolerance (suppression) and sensitization (priming) is dependent on several factors, such as: (a) genetic background, (b) nature and dose of antigen, (c) frequency of administration, (d) age at first antigen exposure, (e) immunological status of the host, (f) antigen transmission via breast milk, and others. Overall there is evidence in rodents that multiple low-dose feeds are more likely to induce regulatory cytokines (e.g., TGF-beta, IL-10, IL-4) in part secreted by CD4+CD25+ T regulatory cells. Despite the powerful suppressive effects of oral autoantigen exposure observed in experimental models of autoimmune diseases (including bystander suppression), their translation into clinical trials of autoimmune diseases has not yet yielded the expected beneficial results.

PMID: 12021083 [found with GoPubMed]

13: Exp Dermatol 1998 Aug;7(4):139-42

Most chronic urticaria is food-dependent, and not idiopathic.

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Although chronic urticaria is generally thought to be mostly idiopathic, we have recently provided convincing evidence that in the majority of patients, food ingredients provoke the symptoms and sustain the disease. On a diet largely avoiding preservatives, dyes and natural pseudoallergens, 73% of patients experienced remission of more than 6 months duration, starting within the first 3 weeks after initiation of the diet. This response rate is clearly higher than the reported 24% spontaneous remission rate over the same time period. The specificity of the dietary effect was proven 1) by double-blind provocation with pureed pseudoallergen-low versus -rich food and 2) by induction of a clinical response to a 3-week diet low in pseudoallergens, but not to a standard diabetes diet in 3 patients studied in a double-blind crossover design. On double-blind, placebo controlled oral provocation, only 18% of diet-responsive patients reacted to known food preservatives and dyes, but 71% to pureed tomatoes and 44% to their steam extracts. These findings identify naturally occurring pseudoallergens in food as major elicitors of chronic urticaria. In contrast, autoantibodies against Fc epsilonRIalpha have been identified in only about 30% of chronic urticaria patients, and evidence for their truly causative role is still lacking since therapeutic measures work in patients irrespective of the presence or absence of the autoantibodies. For both food intolerance and Fc epsilonRIalpha-autoantibodies in chronic urticaria, the associated pathomechanisms are however still in need of clarification. Meanwhile, the diet-responsiveness in the majority of patients opens new perspectives for the management of chronic urticaria.

PMID: 9758408 [found with GoPubMed]

14: Pediatr Allergy Immunol 2008 Feb;

The importance of early complementary feeding in the development of oral tolerance: Concerns and controversies.

Prescott SL, Smith P, Tang M, Palmer DJ, Sinn J, Huntley SJ, Cormack B, Heine RG, Gibson RA, Makrides M

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Rising rates of food allergies in early childhood reflect increasing failure of early immune tolerance mechanisms. There is mounting concern that the current recommended practice of delaying complementary foods until 6 months of age may increase, rather than decrease, the risk of immune disorders. Tolerance to food allergens appears to be driven by regular, early exposure to these proteins during a 'critical early window' of development. Although the timing of this window is not clear in humans, current evidence suggests that this is most likely to be between 4 and 6 months of life and that delayed exposure beyond this period may increase the risk of food allergy, coeliac disease and islet cell autoimmunity. There is also evidence that other factors such as favourable colonization and continued breastfeeding promote tolerance and have protective effects during this period when complementary feeding is initiated. This discussion paper explores the basis for concern over the current recommendation to delay complementary foods as an approach to preventing allergic disease. It will also examine the growing case for introducing complementary foods from around 4 months of age and maintaining breastfeeding during this early feeding period, for at least 6 months if possible.

PMID: 18266825 [found with GoPubMed]

15: Antonie Van Leeuwenhoek 1999;76(1-4):199-205

Intestinal microflora and the interaction with immunocompetent cells.

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The intestinal mucosal surface is colonised by the comensal microflora that attains very high numbers of bacterial cells in the distal intestine, more specifically in the colon. At the same time these extensive areas are the interface with the external environment, through which most pathogens initiate infectious processes in mammals. Intestinal mechanisms of defense need to discriminate accurately between comensal, symbiotic microflora, and exogenous pathogens. Today we do not fully understand the essence of the mechanism of discrimination but, probably, innate as well as adaptive immune responses participate in this process. We have explored, in in vitro models, the capacity of mucosal immunocompetent cells to discriminate amongst signals delivered by different types of bacteria. We have found at least two different patterns of innate response to gram-negative and gram-positive bacteria, and within this last group big differences are observed between species. We have only worked with non-pathogenic bacteria in what may represent the modulation of the physiological host status. The understanding of these modulatory functions could render a unique possibility for the use of food-borne bacteria to prevent or correct intestinal problems associated with food allergy, inflammatory bowel disease, and autoimmunity.

PMID: 10532379 [found with GoPubMed]

16: Int Arch Allergy Appl Immunol 1989;88(1-2):256-8

Immune reactions in a changing environment. USA initiatives.

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Environmental hazards occurring as an undesirable consequence of economic progress, urbanization and pollution have become a worldwide concern. In the US, this is evident from the campaign against smoking which has focused attention on the lung in part because the lung as a target organ is constantly exposed to many visible environmental hazards. On the other hand, environmental hazards which are not lethal, but cause their effects in an insidious fashion, may be difficult to study and identify. Among the disciplines available to assess adverse health consequences of xenobiotics ('strange' substances in our environment), application of modern immunological methods in concert with traditional toxicologic studies have to date demonstrated significant progress in drug allergy, food allergy, environmentally induced lung diseases and autoimmunity. These successes have come from the collaboration of immunologists, allergologists, pulmonologists, pharmacologists and toxicologists. In fact, a newer discipline of immunotoxicology has emerged in order to deal with these complex issues. The National Institutes of Health, through a series of workshops and research initiatives, and in collaboration with other US

government agencies, including the Environmental Protection Agency, the National Institute of Environmental Health Sciences, and the National Academy of Sciences, is attempting to foster research aimed at enhancing progress in the field of immunotoxicology. The overall aim is to encourage the use of modern immunologic approaches to the study of the alleged harmful effects of xenobiotics on the immune system. Success will permit the development of improved diagnostic tools followed by initiatives concerned with prevention. Apart from their scientific implications the results are expected to have an impact on social, legal and economic issues within society.

PMID: 2707890 [found with GoPubMed]

17: Rev Chilena Infectol 2007 Jun;24(3):215-9

[Recurrent oral ulcer: clinical characteristic and differential diagnosis.]

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Recurrent aphthous stomatitis (RAS), are common inflammatory lesions of the oral mucous, usually round or ovoid, circumscribed by an erythematous halo with a yellow-grey floor and mostly painful. The RAS has reached an incidence about 20% in general population, present on any aged group, especially adolescents and young adults. Etiopathogenesis of RAS is not entirely understood. Some factors involved include immune system anomalies, infections, nutritional deficiency, mucous traumatism, food or contact allergy, autoimmunity illness and cancer; together with psychiatric, genetic and environment agents. In this article, main clinical features, etiology related factors, differential diagnosis and initial study of patients consulting for RAS are presented.

PMID: 17554441 [found with GoPubMed]

18: Am J Physiol Gastrointest Liver Physiol 2000 Feb;278(2):G191-6

Nutrient tasting and signaling mechanisms in the gut V. Mechanisms of immunologic sensation of intestinal contents.

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Immune perception of intestinal contents reflects a functional dualism with systemic hyporesponsiveness to dietary antigens and resident microflora (oral tolerance) and active immune responses to mucosal pathogens. This facilitates optimal absorption of dietary nutrients while conserving immunologic resources for episodic pathogenic challenge. Discrimination between dangerous and harmless antigens within the enteric lumen requires continual sampling of the microenvironment by multiple potential pathways, innate and adaptive recognition mechanisms, bidirectional lymphoepithelial signaling, and rigorous control of effector responses. Errors in these processes disrupt mucosal homeostasis and are associated with food hypersensitivity and mucosal inflammation. Mechanisms of mucosal immune perception and handling of dietary proteins and other antigens have several practical and theoretical implications including vaccine design, therapy of systemic autoimmunity, and alteration of enteric flora with probiotics.

PMID: 10666042 [found with GoPubMed]

19: Clin Exp Immunol 2007 Jun;

Spleen lymphocyte function modulated by a cocoa-enriched diet.

Ramiro-Puig E, Pérez-Cano FJ, Ramírez-Santana C, Castellote C, Izquierdo-Pulido M, Permanyer J, Franch A, Castell M

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Previous studies have shown the down-regulating in vitro effect of cocoa flavonoids on lymphocyte and macrophage activation. In the present paper, we report the capacity of a long-term rich cocoa diet to modulate macrophage cytokine secretion and lymphocyte function in young rats. Weaned rats received natural cocoa (4% or 10% food intake), containing 32 mg flavonoids/g, for 3 weeks. Spleen immune function was then evaluated through the analysis of lymphocyte composition, their proliferative response and their ability to secrete cytokines and Ig. In addition, the status of activated peritoneal macrophages was established through tumour necrosis factor (TNF)-alpha secretion. The richest cocoa diet (10%) caused a reduction of TNF-alpha secretion by peritoneal macrophages showing anti-inflammatory activity. Similarly, although a 10% cocoa diet increased lymphocyte proliferation rate, it down-regulated T helper 2 (Th2)-related cytokines and decreased Ig secretion. These changes were accompanied by an increase in spleen B cell proportion and a decrease in Th cell percentage. In summary, these results demonstrate the functional activity of a cocoa-high dosage in down-regulating the immune response that might be beneficial in hypersensitivity and autoimmunity.

PMID: 17565606 [found with GoPubMed]

20: J Investig Allergol Clin Immunol 2004;14(1):50-4

Skin test positivity to aeroallergens in the patients with chronic urticaria without allergic respiratory disease.

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The etiology of chronic urticaria and angioedema remains uncertain in most of the patients. There are several agents and factors including medications, foods and food additives, infections, contactants, inhalants, physical factors and autoimmunity that implicated in provoking urticaria symptoms. In addition, the possible role of house dust mites has been considered in a few reports. We investigated skin test positivity to house dust mites and other inhalants in 259 patients with chronic idiopathic urticaria and angioedema but without allergic rhinitis and/or asthma. Results were compared with both 300 healthy controls and 300 atopic patients. Immediate cutaneous reactivity to one or more allergens was detected in 71 patients in the study group (27.4%). The most common allergens were house dust mites (24.7%). Skin prick test sensitivity to other inhalant allergens including pollens, molds and cockroach were 7.7%, 0.4% and 0.8%, respectively. In the healthy control group 7% of patients were found as atopic with respect to skin prick test results. The most

common allergens in healthy controls were pollens (6%), and house dust mites (4.7%). In atopic control group, pollens and mites are also the most common allergens detected in skin prick test (62% and 50.3%, respectively). The difference between study and healthy control group was statistically significant with respect to presence of atopy and mite sensitivity ($p < 0.001$). Similar differences were not established in other inhalant allergens. Significant mite sensitivity in the study group is not a coincidence. Because, ratio of skin test positivity to house dust mites in the study group was higher than the healthy controls, but was not as high as atopic patients. Furthermore, the rate of skin reactivity to other aeroallergens was not different from healthy controls. Urticaria as a sole clinical manifestation in mite sensitive patients was unusual.

PMID: 15160442 [found with GoPubMed]

21: Med Lav 2002;93(3):225-32

[Immunologic effects of exposure to low levels of inorganic mercury]

Soleo L, Colosio C, Alinovi R, Guarneri D, Russo A, Lovreglio P, Vimercati L, Birindelli S, Cortesi I, Flore C, Carta P, Colombi A, Parrinello G, Ambrosi L

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OBJECTIVE: The immune system is a target for the toxic effects of inorganic mercury, both in humans and animals. In humans it has been observed that occupational and environmental exposure to inorganic mercury may cause both clinical (autoimmunity, hypersensitivity) and subclinical effects (cellular and humoral immunologic variable modifications). To obtain a better definition of these effects with respect to the exposure levels, a multicentre study was performed on 117 workers exposed to very low doses of inorganic mercury and 172 subjects from the general population of the same geographical area with environmental exposure to mercury from dental amalgams and dietary fish intake. **RESULTS:** The white blood cell count was included in the normality range for all subjects and there was no difference between exposed and non exposed subjects. The immunologic variables studied showed an increase of the CD4+ and CD8+ number in exposed workers compared to non-exposed subjects, with a statistically significance only for CD4+, while no difference was observed regarding CD4+, CD8+, NK+ percentage and CD4+/CD8+ ratio. A significative decrease of serum IL-8 and an inverse correlation between serum levels of this cytokine and HgU were observed in exposed workers compared to non exposed subjects. No association between immunologic variables and both dental amalgams and dietary fish intake was found in subjects not occupationally exposed to inorganic mercury. **DISCUSSION:** The decrease in IL-8 serum levels observed in exposed workers might suggest an immunosuppressive effect of occupational exposure to very low doses of inorganic mercury. This result suggests the need to revise of current HgU BEI after further definition of its prognostic significance.

PMID: 12197272 [found with GoPubMed]

22: Nat Immunol 2001 Mar;2(3):216-22

An unexpected version of horror autotoxicus: anaphylactic shock to a self-peptide.

Pedotti R, Mitchell D, Wedemeyer J, Karpuj M, Chabas D, Hattab EM, Tsai M, Galli SJ, Steinman L

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EAE can refer either to experimental autoimmune encephalomyelitis or experimental allergic encephalomyelitis. Although EAE is classically a prototypic T helper 1 (TH1) cell-mediated autoimmune disease, it can also be induced by TH2 cells. Characteristically, the most severe manifestation of allergy, anaphylaxis, is associated with exposure to a foreign antigen that is often derived from medication, insect venom or food. We report here that, after self-tolerance to myelin is destroyed, anaphylaxis may be triggered by a self-antigen, in this case a myelin peptide. "Horror autotoxicus", which was initially described by Ehrlich, may not only include autoimmunity to self, it may also encompass immediate hypersensitivity to self, which leads to shock and rapid death.

PMID: 11224520 [found with GoPubMed]

23: Schweiz Med Wochenschr 1999 Sep;129(36):1271-9

[Importance of laboratory investigations and trigger factors in chronic urticaria]

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Urticaria is one of the most frequent skin disorders. Whereas for the acute form a cause is usually found, the aetiology of chronic urticaria often remains obscure. Infectious or autoimmune origin are presumed aetiologies, whereas trigger factors such as pressure, cold or food additives often induce an urticarial episode. In this study, we investigated the significance of laboratory and supplementary analysis in relation to the aetiology and classification of chronic urticaria. We also looked at a correlation of trigger factors with the aetiology and course of chronic urticaria. Out of 170 patients with chronic urticaria referred to our outpatient allergy clinic within 3 1/4 years, 95 were female (56%) and 75 male (44%). The average age was 37 years. Based on history and clinical signs, laboratory, allergo-immunological, stool and urine samples were performed, as well as allergological skin and physical tests. Of the laboratory parameters, total leukocyte count, C-reactive protein (CRP) and alanine-amino-transferase (ALAT) were the findings most often out of the normal range. In 25% (43/170) chronic urticaria could be attributed to a possible cause (infection [15%], autoimmunity [8%], allergy [1%], urticaria pigmentosa [1%]). Trigger factors were found in 84/170 (49%) patients (physical [29%], pseudoallergic [12%], combination of both [8%]). Follow-up after an average of 22.3 months revealed that 84 patients (63%) no longer suffered from urticarial disorders, while 49 (37%) still complained of hives. In conclusion, laboratory and supplementary investigations were rarely helpful in identifying aetiological agents, although in 25% chronic urticaria was classified. Trigger factors are not of predictive value either for aetiology or course of chronic urticaria. However, the longer chronic urticaria lasts, the rarer are remissions. In younger patients, chronic urticaria tends to last less long than in elderly persons.

PMID: 10519182 [found with GoPubMed]

24: Environ Health Perspect 1998 Feb;106 Suppl 1:85-109

Integrated defense system overlaps as a disease model: with examples for multiple chemical sensitivity.

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The central nervous, immune, and endocrine systems communicate through multiple common messengers. Over evolutionary time, what may be termed integrated defense system(s) (IDS) have developed to coordinate these communications for specific contexts; these include the stress response, acute-phase response, nonspecific immune response, immune response to antigen, kindling, tolerance, time-dependent sensitization, neurogenic switching, and traumatic dissociation (TD). These IDSs are described and their overlap is examined. Three models of disease production are generated: damage, in which IDSs function incorrectly; inadequate/inappropriate, in which IDS response is outstripped by a changing context; and evolving/learning, in which the IDS learned response to a context is deemed pathologic. Mechanisms of multiple chemical sensitivity (MCS) are developed from several IDS disease models. Model 1A is pesticide damage to the central nervous system, overlapping with body chemical burdens, TD, and chronic zinc deficiency; model 1B is benzene disruption of interleukin-1, overlapping with childhood developmental windows and hapten-antigenic spreading; and model 1C is autoimmunity to immunoglobulin-G (IgG), overlapping with spreading to other IgG-inducers, sudden spreading of inciters, and food-contaminating chemicals. Model 2A is chemical and stress overload, including comparison with the susceptibility/sensitization/triggering/spreading model; model 2B is genetic mercury allergy, overlapping with: heavy metals/zinc displacement and childhood/gestational mercury exposures; and model 3 is MCS as evolution and learning. Remarks are offered on current MCS research. Problems with clinical measurement are suggested on the basis of IDS models. Large-sample patient self-report epidemiology is described as an alternative or addition to clinical biomarker and animal testing.

PMID: 9539008 [found with GoPubMed]

25: Food Chem Toxicol 1988 Jun;26(6):527-39

Identification of immunotoxic effects of chemicals and assessment of their relevance to man.

Trizio D, Basketter DA, Botham PA, Graepel PH, Lambré C, Magda SJ, Pal TM, Riley AJ, Ronneberger H, Van Sittert NJ

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Immunotoxicity is defined as the adverse effects of foreign substances (xenobiotics) on the immune system. Two types of effects are possible: immunosuppression (which may result in an increased susceptibility to infection or to the development of tumours) and immunopotentialiation (which may manifest as an allergy or as autoimmunity). There is, as yet, little evidence that well controlled occupational exposure to industrial chemicals has led to clinically significant immunosuppression. In contrast, a number of industrial chemicals have been shown to cause immunopotentialiation in exposed populations, producing occupational asthma and contact dermatitis and possibly autoimmunity. In experimental models, immunosuppression (usually assessed by in vivo or in vitro immune function tests) has been induced by a wide range of chemicals but there are a few reports of the

immunosuppression leading directly to an increased susceptibility to infection or to the development of tumours. Predictive experimental models are available for type IV allergic reactions, but the identification of chemicals that have a potential to cause other types of allergy or autoimmune reactions requires further research and the development and validation of new animal models. It is considered that routine subacute and chronic toxicity studies should include a full gross and histopathological assessment of the lymphoid organs to more accurately detect the potential of a chemical to cause immunotoxicity. Should such studies indicate that a substance has affected the immune system directly, an assessment of overall immune competence and function tests may be necessary using dose levels below those which cause frank toxicity. However, precise interpretation of immune function tests in terms of their relevance to human health requires an improved understanding of the extent of the functional reserve of the immune system. A strategy for assessing immunotoxicity in exposed human populations demonstrates a need for reliable clinical assessment, accurate medical record-keeping, an environmental and biological monitoring for levels of contaminating chemicals and the judicious use of well-validated immune function tests.

PMID: 3049276 [found with GoPubMed]

26: Curr Diab Rep 2007 Apr;7(2):91-8

Mucosal exposure to antigen: cause or cure of type 1 diabetes?

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The human gut offers more than 200 m² of mucosal surface, where direct interactions between the immune system and foreign antigens take place to eliminate pathogens or induce immune tolerance toward food antigens or normal gut flora. Therefore, mucosally administered antigens can induce tolerance under certain circumstances. In autoimmune diabetes, mucosal vaccination with autoantigens elicits some efficacy in restoring tolerance in mice, but it never succeeded in humans. Furthermore, in some instances autoimmunity can be precipitated upon oral or intranasal autoantigen administration. Therefore, it is difficult to predict the effect of mucosal vaccination on autoimmunity and much effort should be put into establishing better assays to reduce the risk for possible adverse events in humans and enable a rapid and smooth translation.

PMID: 17425912 [found with GoPubMed]

27: Nestle Nutr Workshop Ser Pediatr Program 2007;60:139-55

The influence of gluten: weaning recommendations for healthy children and children at risk for celiac disease.

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In most developed countries, gluten is currently most commonly introduced between 4 and 6 months of age, in spite of little evidence to support this

practice. As for infants at risk of developing food allergies, there is clear evidence that introducing solid foods before the end of the 3rd month is detrimental and should be avoided. A recent growing body of evidence however challenges the notion that solids (and among them, gluten-containing foods) should be introduced beyond the 6th month of life. Another important aspect of gluten introduction into the diet has to do with its possible role in causing type-1 diabetes (IDDM). Recently, a large epidemiological investigation in a cohort of children at risk for IDDM found that exposure to cereals (rice, wheat, oats, barley, rye) that occurred early (≤ 3 months) as well as late (≥ 7 months) resulted in a significantly higher risk of the appearance of islet cell autoimmunity compared to the introduction between 4 and 6 months. As for celiac disease, the protective role of breastfeeding can be considered ascertained, especially the protection offered by having gluten introduced while breastfeeding is continued. Evidence is emerging that early (≤ 3 months) and perhaps even late (7 months or after) first exposure to gluten may favor the onset of celiac disease in predisposed individuals. Additionally, large amounts of gluten at weaning are associated with an increased risk of developing celiac disease, as documented in studies from Scandinavian countries. In celiac children observed in our center, we could show that breastfeeding at the time of gluten introduction delays the appearance of celiac disease and makes it less likely that its presentation is predominantly gastrointestinal. Based on current evidence, it appears reasonable to recommend that gluten be introduced in small amounts in the diet between 4 and 6 months, while the infant is breastfed, and that breastfeeding is continued for at least a further 2-3 months.

PMID: 17664902 [found with GoPubMed]

28: J Clin Invest 2004 Oct;114(8):1090-7

A new model for dermatitis herpetiformis that uses HLA-DQ8 transgenic NOD mice.

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Dermatitis herpetiformis (DH) is an autoimmune blistering skin disorder that is associated with gluten sensitivity. It presents as a papulovesicular rash and is often associated with enteropathy. The rash resolves when the patient is placed on a gluten-free diet and/or dapsone. DH, as well as celiac disease, is tightly associated with DQ2 and DQ8. A novel mouse model for DH is described that utilizes the NOD background and the HLA-DQ8 transgene. The addition of DQ8 contributes sensitivity to gliadin, and the addition of the NOD background contributes to autoimmunity and pathogenesis. Fifteen NOD DQ8+ mice of 90 that were sensitized to gluten developed blistering pathology similar to that seen in DH. Neutrophil infiltration of the dermis, deposition of IgA at the dermal-epidermal junction, and a complete reversal of the blistering phenomenon with the administration of a gluten-free diet with or without dapsone were observed. None of the 3 blistering mice examined had small-bowel pathology. This animal model of DH will be useful to determine the specificity of the IgA deposits, as well as the pathogenic mechanisms that occur in the skin as a result of gluten ingestion.

PMID: 15489956 [found with GoPubMed]

29: Clin Rev Allergy Immunol 2002 Oct;23(2):185-93

Evaluating chronic urticaria patients for allergies, infections, or autoimmune disorders.

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Urticaria is a common disorder affecting one-fifth of the world's population. The pathophysiology is characterized by an increased propensity for mast cell degranulation with the release of potent mediators into the dermal and subdermal tissues with resulting vasoactive, chemotactic, and inflammatory effects. The final clinical manifestation of the typical urticarial lesion is the effect of several diverse effects and causes. The general classification is acute, chronic, and physical urticaria. In general, allergenic triggers can be identified in between 60-80% of acute urticarias. Physical urticarias are characterized by the onset after the specific inciting stimulus, which can reproduce the characteristic lesion which is usually of shorter duration (with the exception of delayed pressure urticaria). Chronic idiopathic urticaria is associated with thyroid autoimmunity and, more recently, anti-mast cell receptor antibodies. An extensive work-up is usually not indicated or helpful in identifying a cause. Food or other allergens are rare causes of this type of presentation. The evaluation and work-up is dependent on clues identified by history. The treatment is removal of specific and non-specific triggers and the use of symptomatic medications generally attenuating the mediator effects.

PMID: 12221863 [found with GoPubMed]

30: Int J Neurosci 1994 Jun;76(3-4):231-6

Handedness and allergic response.

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Previous reports have linked nonright-handedness with allergies including hay fever, asthma, eczema and urticaria. The present study examined reactions to 20 common allergens (e.g., food, animal fur, dust, drugs, etc.) in a sample of 430 subjects. Individuals who were left-handed or not consistently right-handed showed an elevated frequency of allergic reactions. The criteria used to determine handedness and the existence of allergies are both important factors. The stringent criterion of consistent right-handedness versus nonright-handedness was a more sensitive measure in detecting allergic individuals than was the simple dichotomy of left-versus right-handed. The association with handedness was stronger for individuals with more than one allergy.

PMID: 7960479 [found with GoPubMed]

31: Allerg Immunol (Paris) 2007 Oct;39(8):253-8

Urticaria and urticaria related skin condition/disease in children.

Novembre E, Cianferoni A, Mori F, Calogero C, Bernardini R, Di Grande L, Pucci N, Azzari C, Vierucci A

PMID: 18237002 [found with GoPubMed]

32: Allerg Immunol (Paris) 2006 Apr;38(4):124-5

Collagenous colitis: possible link with isotretinoin.

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A case of collagenous colitis in a young man treated by isotretinoin raises the hypothesis of an isotretinoin induced excess on the possible account of atopy and auto-immunity in the family.

PMID: 16805418 [found with GoPubMed]

33: Orv Hetil 2001 Oct;142(43):2357-67

[Gastrointestinal immunology]

A Pár

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The paper is devoted to the actual questions of gastrointestinal immunology. In the first part, structure and function of gut-associated mucosal tissue (GALT), including the role of secretory immunoglobulins and importance of oral tolerance are shown. In the second part, the pathogenesis of unknown origin gastrointestinal and liver diseases (gluten sensitive enteropathy, inflammatory bowel diseases, autoimmune liver diseases, autoimmune pancreatitis) is described. Then the immunology of some gastrointestinal infections (*Helicobacter pylori*, hepatitis virus B and C, and HIV) and of alcoholic and drug induced, liver diseases is briefly summarized.

PMID: 11760453 [found with GoPubMed]

34: ORL J Otorhinolaryngol Relat Spec 2001;63(1):19-24

No increased serum levels of antifeed antibodies in patients with Ménière's disease.

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The etiology of Ménière's disease (MD) is still unknown, but it is likely to be multifactorial, one of the factors being an immunological causation. Antifeed allergens as well as anti-baker's yeast antibodies are humoral

factors that may be linked with allergenic disorders and other autoimmune conditions. To determine their possible role in MD activity, we investigated 29 MD sera for the presence of antibodies against gliadin, beta-lactoglobulin, albumin, ovalbumin, soya, and Dermatophagoides pteronyssinus and Saccharomyces cerevisiae strains using an ELISA technique. The patients were compared with 29 healthy individuals matched for sex and age. A serum was regarded as positive if the absorbance was two standard deviations higher than values obtained with sera from healthy subjects. Historical data, including factors which the patients believed to provoke their Ménière's symptoms, were obtained from patients' questionnaires. MD patients showed no significant symptoms of allergenic disorders suggesting allergies when compared to controls ($p > 0.05$). IgG and IgA antibody levels were not significantly raised in MD patients as compared with healthy controls ($p > 0.05$) for gliadin, beta-lactoglobulin, soya, albumin, ovalbumin, and D. pteronyssinus and S. cerevisiae strains. These data do not convincingly support a hypothesis of increased serum levels of antifood antibodies in patients with MD, as very few patients were antibody positive.

PMID: 11174058 [found with GoPubMed]

35: Allergy 1996 Aug;51(8):590-2

Anaphylactoid reaction in relation to sialolithiasis.

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PMID: 8874666 [found with GoPubMed]

36: Acta Paediatr Suppl 1996 May;412:10-4

Latent and potential coeliac disease.

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Under the umbrella of coeliac disease (CD), or gluten-sensitive enteropathy, the concepts of silent, latent and potential CD have recently been introduced. While silent CD is marked by severe damage to the jejunal mucosa in the absence of clinical symptoms, both latent and potential CD are characterized by jejunal mucosa that would be reported as normal by most clinical pathologists in an individual on a gluten-containing diet. As opposed to potential coeliac patients, latent subjects sometimes in their life have had a flat jejunal biopsy which recovered on a gluten-free diet. Latent coeliac patients are often symptomatic; neither high titres of gliadin antibodies nor mucosal changes (including raised intraepithelial lymphocyte counts) are obligate features of latent CD, although the presence of elevated endomysial antibodies is probably the best predictor of progression towards villous atrophy. The term potential CD has been proposed for those subjects who do not have, and have never had, a jejunal biopsy consistent with overt CD, and yet have immunological abnormalities similar to those found in coeliac patients. Good markers of potential CD include the presence of serum endomysial antibodies, a high count of intraepithelial lymphocytes and subtle pathological alteration such as

increased density of intraepithelial lymphocytes expressing gamma delta T cell receptor, signs of activated mucosal cell-mediated immunity, coeliac-like intestinal antibody pattern, and positive rectal gluten challenge.

PMID: 8783748 [found with GoPubMed]

37: Nature 1992 Sep;359(6392):194-5

Diabetes. Breast may well be best.

Baxter AG, Cooke A

PMID: 1528258 [found with GoPubMed]