

Expression of Interleukin 6 and chronic intestinal Inflammation

1: Gastroenterology 2005 Jul;129(1):204-19

Growth hormone reduces the severity of fibrosis associated with chronic intestinal inflammation.

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BACKGROUND & AIMS: Growth hormone (GH) is used to treat growth delay in children with Crohn's disease and in patients with short-bowel syndrome. GH can increase collagen accumulation in intestinal mesenchymal cells, raising concern that GH therapy could exacerbate fibrosis in patients with Crohn's disease. We tested if GH treatment altered inflammation or fibrosis during chronic, experimental granulomatous enterocolitis. **METHODS:** Ileum and cecum of Lewis rats were subserosally injected with peptidoglycan-polysaccharide (PG-APS) or control human serum albumin. At the onset of chronic PG-APS-induced inflammation, rats were administered recombinant human GH or vehicle for 14 days. Fibrosis and inflammation were quantified by gross gut disease scoring, histologic scoring, type I collagen, and cytokine expression in cecum. Abundance and localization of suppressor of cytokine signaling-3 (SOCS-3) messenger RNA and/or protein were determined in cecum. Effect of GH, cytokines, or PG-APS on SOCS-3 synthesis was measured in intestinal myofibroblasts. Myofibroblasts overexpressing SOCS-3 were used to test whether SOCS-3 inhibits collagen accumulation. **RESULTS:** In PG-APS-injected rats, GH modestly reduced gross adhesions and mesenteric contractions, cecal fibrosis score, and collagen expression, but had no effect on intestinal inflammation. GH increased SOCS-3 messenger RNA and protein abundance in PG-APS rats and SOCS-3 messenger RNA was localized to the periphery of granulomas. GH in combination with cytokines or PG-APS, but not alone, induced SOCS-3 synthesis in intestinal myofibroblasts. Myofibroblasts overexpressing SOCS-3 showed reduced cytokine-induced collagen accumulation. **CONCLUSIONS:** GH modestly reduces intestinal fibrosis associated with chronic experimental enterocolitis and stimulates expression of antifibrogenic SOCS-3, suggesting that GH therapy in inflammatory bowel disease should not exacerbate fibrosis.

PMID: 16012948 [found with GoPubMed]

2: J Gastrointest Surg 2006 Jan;10(1):46-53

Immune-enhancing diet and cytokine expression during chronic sepsis: an immune-enhancing diet containing L-arginine, fish oil, and RNA fragments promotes intestinal cytokine expression during chronic sepsis in rats.

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Chronic feeding with enteral immune-enhancing diets (IEDs) provides benefits based on composition of the diet, route of feeding, and timing of feeding in relation to timing of trauma or surgery. Our prior studies of acute feeding in naïve rats demonstrated that IED promotes blood flow and

proinflammatory cytokines in the ileum. We hypothesized that chronic feeding with IED would shift gut immune status to an anti-inflammatory state during chronic sepsis, resulting in an altered state of cytokine expression in the gut. Five days prior to feeding, gauze was implanted subcutaneously in the backs of male Sprague-Dawley rats, which were fed for 3 days with either control diet (CD, Boost; Mead-Johnson, Evansville, IL) or IED (Impact; Novartis) and randomly assigned to one of four groups: saline control (NS) + control diet (CD), sepsis (EC) + CD, NS + IED, or EC + IED. EC rats were inoculated with 10(9) CFU Escherichia coli and 10(9) CFU Bacteroides fragilis in 2 ml normal saline into the back sponge while NS rats received 2 mL normal saline alone. After 3 days, animals were anesthetized and gut tissue samples were harvested and frozen at -80 degrees C. Tissue protein was extracted and ELISA was performed for interleukin (IL-1beta, IL-5, IL-6, IL-10, tumor necrosis factor (TNF)-alpha, and interferon (IFN)-gamma. In saline controls, IED feeding decreased IL-1beta, IL-5, IL-6, TNF-alpha, and IFN-gamma and increased IL-10 compared with CD-fed animals. In septic animals, IED feeding increased IL-5 and IL-6, while decreasing IFN-gamma and IL-10 in the distal third of the small intestine compared with CD-fed septic rats, whereas IL-1beta and TNF-alpha levels were unchanged. Chronic IED feeding produced a anti-inflammatory state via decreased IFN-gamma and increased IL-5 and IL-6, which both promote gut IgA class switching, suggesting that the gut is shifted toward humoral immunity during chronic IED feeding in septic rats.

PMID: 16368490 [found with GoPubMed]

3: Gastroenterology 2002 Jan;122(1):134-44

Role of tumor necrosis factor receptor 2 (TNFR2) in colonic epithelial hyperplasia and chronic intestinal inflammation in mice.

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BACKGROUND & AIMS: Tumor necrosis factor (TNF) induces multiple effects including cell proliferation and death by ligation with TNF receptor type II (TNFR2). We studied the role of TNFR2 in chronic inflammation-induced colonic epithelial alteration. METHODS: TNFR2 expression in colonic epithelial cells (CECs) was assessed by ribonuclease protection assay (RPA) and immunohistochemistry (IHC) in patients with inflammatory bowel disease (IBD) and murine colitis models. TNFR2 expression was also analyzed using COLO205 cells. The role of TNFR2 in colonic epithelial homeostasis was examined by generating interleukin 6-deficient TCR alpha KO (alpha IL-6DKO) or TNFR2-deficient TCR alpha (alpha TNFR2DKO) mice. RESULTS: TNFR2 expression was up-regulated in CEC in both human ulcerative colitis and Crohn's disease. In vitro studies showed that TNFR2 expression was up-regulated by a cooperative effect of key proinflammatory cytokines. By RPA, the increased expression of TNFR2 was detectable in TCR alpha KO mice with colitis compared with TCR alpha KO mice without colitis or wild-type mice. In alpha IL-6DKO mice, TNFR2 expression, proliferation, and nuclear factor kappa B activation of CECs were markedly reduced compared with TCR alpha KO mice. alpha TNFR2 mice also showed significantly less colonic epithelial proliferation compared with TCR alpha KO mice. CONCLUSIONS: Expression of TNFR2 is consistently increased on CECs in both murine colitis models as well as patients with IBD. TNFR2 may play an important role in colonic inflammation-associated alteration in the intestinal epithelium.

PMID: 11781288 [found with GoPubMed]

4: J Lipid Res 2008 Jan;

Phospholipid transfer protein deficiency ameliorates diet-induced hypercholesterolemia and inflammation in mice.

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Phospholipid transfer protein (PLTP) facilitates transfer of phospholipids from triglyceride-rich lipoproteins (TRL) into HDL. PLTP has been shown to be an important factor in lipoprotein metabolism and atherogenesis. Here we report that chronic high fat high cholesterol diet feeding markedly elevated plasma cholesterol levels in C57BL/6 mice. PLTP deficiency attenuated diet-induced hypercholesterolemia by dramatically reducing ApoE-rich lipoproteins (-88%), and to a lesser extent LDL (-40%) and HDL (-35%). Increased biliary cholesterol secretion, indicated by increased hepatic ABCG5/ABCG8 gene expression, and decreased intestinal cholesterol absorption may contribute to the lower plasma cholesterol in PLTP deficient mice. The expression of pro-inflammatory genes (ICAM-1 and VCAM-1) is reduced in aorta of PLTP knockout mice compared to wild type mice fed with either a chow or high cholesterol diet. Furthermore, plasma IL-6 levels are significantly lower in PLTP deficient mice, indicating reduced systemic inflammation. These data suggest that PLTP appears to be playing a pro-atherogenic role in diet induced hyperlipidemic mice.

PMID: 18198166 [found with GoPubMed]

5: Life Sci 2006 Oct;79(21):2032-42

Localized colonic inflammation increases cytokine levels in distant small intestinal segments in the rat.

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Local inflammation in the colon has been associated with nutrient malabsorption and altered motility in the small bowel. These remote effects suggest the release of mediators which can act (or alter) the function of intestinal segments located far from the primary area of inflammation. This study describes the changes in the expression of pro-inflammatory cytokines in the colon and in various segments of the small intestine in two rat models of experimental colitis. Colitis was induced by the intracolonic administration of 100 microL of 6% iodoacetamide or 250 microL of 2, 4, 6-trinitrobenzene sulfonic acid. Levels of interleukin one beta, interleukin 6, and tumor necrosis factor alpha were measured by ELISA in tissue homogenate sampled from duodenum, jejunum, ileum and colon at different time intervals. In homogenates of strips isolated from duodenum, jejunum and ileum, tumor necrosis alpha and interleukin-6, increased significantly 3-6 h after iodoacetamide or TNBS administration and remained elevated until the colonic inflammation subsided. Interleukin one beta showed comparable but delayed increase. Similar, but more pronounced increase of the three cytokines was noticed in areas of the colon adjacent to the ulcer. Histologic examinations revealed important inflammatory changes in the colon; however, examination of sections from the small intestines did not reveal significant differences between controls and rats with colitis. In conclusion, expression of pro-inflammatory cytokines is increased in

remote segments of the small intestines during colitis. The findings may provide a partial explanation or a molecular substrate for the associated small bowel dysfunction.

PMID: 16904127 [found with GoPubMed]

6: IUBMB Life 2005 Jul;57(7):499-503

Systemic regulation of intestinal iron absorption.

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The intestinal absorption of the essential trace element iron and its mobilization from storage sites in the body are controlled by systemic signals that reflect tissue iron requirements. Recent advances have indicated that the liver-derived peptide hepcidin plays a central role in this process by repressing iron release from intestinal enterocytes, macrophages and other body cells. When iron requirements are increased, hepcidin levels decline and more iron enters the plasma. It has been proposed that the level of circulating diferric transferrin, which reflects tissue iron levels, acts as a signal to alter hepcidin expression. In the liver, the proteins HFE, transferrin receptor 2 and hemojuvelin may be involved in mediating this signal as disruption of each of these molecules decreases hepcidin expression. Patients carrying mutations in these molecules or in hepcidin itself develop systemic iron loading (or hemochromatosis) due to their inability to down regulate iron absorption. Hepcidin is also responsible for the decreased plasma iron or hypoferremia that accompanies inflammation and various chronic diseases as its expression is stimulated by pro-inflammatory cytokines such as interleukin 6. The mechanisms underlying the regulation of hepcidin expression and how it acts on cells to control iron release are key areas of ongoing research.

PMID: 16081371 [found with GoPubMed]

7: Vet Immunol Immunopathol 1996 Jan;49(4):331-45

Increased intestinal TNF-alpha, IL-1 beta and IL-6 expression in ovine paratuberculosis.

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Mycobacterium avium subspecies paratuberculosis is an intracellular parasite of intestinal macrophages and causes a chronic granulomatous enteritis in sheep and other ruminants (paratuberculosis or Johne's disease). Macrophages can be produced a variety of immunoregulatory cytokines that may influence mycobacterial killing and produce disordered inflammation within the gut. In this study, messenger RNA (mRNA) was extracted from intestinal tissue from control and multibacillary diseased sheep and profiles for the cytokines tumour necrosis factor-alpha (TNF-alpha), interleukin-1 beta (IL-1 beta), IL-6, transforming growth factor-beta1 (TGF-beta1) and granulocyte-macrophage colony stimulating factor (GM-CSF) were semi-quantified using reverse transcriptase polymerase chain reactions (RT-PCR). Infected intestinal tissues had significantly increased

mRNA for TNF-alpha, IL-1beta and IL-6 but TGF-beta1 and GM-CSF mRNA levels were significantly different from controls. Supernatants from in vitro intestinal cultures were assayed for TNF-alpha activity using the PK(15)-1512 cytotoxicity bioassay and levels were significantly raised in diseased samples. TNF-alpha was not detected in any serum samples. Further analysis on intestinal tissues from sheep with the different, paucibacillary, form of the disease showed significant elevation of TNF-alpha mRNA but not other cytokines tested. Increased pro-inflammatory cytokine expression in the intestine coincident with a failed or misdirected immune response may contribute to the pathogenesis of paratuberculosis and the persistence of a chronic inflammatory state.

PMID: 8677635 [found with GoPubMed]

8: Am J Pathol 2007 Nov;

Gastrointestinal Disease in Simian Immunodeficiency Virus-Infected Rhesus Macaques Is Characterized by Proinflammatory Dysregulation of the Interleukin-6-Janus Kinase/Signal Transducer and Activator of Transcription3 Pathway.

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Gastrointestinal disease and inflammation are common sequelae of human and simian immunodeficiency virus (SIV) infection. Nevertheless, the molecular mechanisms that lead to gastrointestinal dysfunction remain unclear. We investigated regulation of the interleukin (IL)-6-JAK-STAT3 pathway in jejunum and colon, collected at necropsy, from 10 SIV-infected macaques with diarrhea (group 1), 10 non-SIV-infected macaques with diarrhea (group 2), and 7 control uninfected macaques (group 3). All group 1 and 2 macaques had chronic diarrhea, wasting, and colitis, but group 1 animals had more frequent and severe lesions in the jejunum. A significant increase in IL-6 and SOCS-3 gene expression along with constitutive STAT3 activation was observed in the colon of all group 1 and 2 macaques and in the jejunum of only group 1 macaques compared to controls. Further, in colon, histopathology severity scores correlated significantly with IL-6 (groups 1 and 2) and SOCS-3 (group 2) gene expression. In jejunum, a similar correlation was observed only in group 1 animals. Phosphorylated STAT3 (p-STAT3) was localized to lymphocytes (CD3(+)) and macrophages (CD68(+)), with fewer CD3(+) lymphocytes expressing p-STAT3 in group 1 macaques. Despite high SOCS-3 expression, STAT3 remained constitutively active, providing a possible explanation for persistent intestinal inflammation and immune activation that may favor viral replication and disease progression.

PMID: 18055558 [found with GoPubMed]

9: Oncogene 2007 Feb;

Suppressor of cytokine signaling 3 (SOCS3) limits damage-induced crypt hyper-proliferation and inflammation-associated tumorigenesis in the colon.

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Intestinal injury or chronic inflammation induce cytokines that promote crypt regeneration and mucosal repair. If excessive or prolonged, such mechanisms may increase colon cancer risk. Factors that terminate or limit cytokine action in intestinal epithelial cells (IEC) may protect against crypt hyperplasia and neoplasia. We hypothesized that suppressor of cytokine signaling-3 (SOCS3) is such a factor. Mice with Vilin-promoter/Cre-recombinase (VC)-mediated IEC-specific SOCS3 gene disruption (VC/HO), WT/HO littermates with floxed but intact SOCS3 genes and VC/WT mice were studied. Colon was examined after acute dextran sodium sulfate (DSS)-induced mucosal injury or after azoxymethane (AOM) and chronic DSS. Signaling pathways were examined in colon, cultured IEC or colon cancer cell lines. VC/HO mice showed no basal phenotype. After acute DSS, VC/HO exhibited enhanced crypt proliferation and crypt hyperplasia and reduced transforming growth factor (TGF) beta expression in colon. Inflammation and mucosal damage were similar across genotypes. Following AOM/DSS, VC/HO mice had increased size, number and load of colonic tumors and increased STAT3 and nuclear factor-kappa B (NF-kappaB) activation in colon. In vitro, SOCS3 overexpression reduced proliferation, IL-6-mediated STAT3 activation and tumor necrosis factor (TNF) alpha-mediated NF-kappaB activation. We conclude that cytokine induction of SOCS3 normally provides an intrinsic mechanism to limit injury-induced crypt hyperproliferation and inflammation-associated colon cancer by regulating both STAT3 and NF-kappaB pathways. *Oncogene* advance online publication, 12 February 2007; doi:10.1038/sj.onc.1210286.

PMID: 17297444 [found with GoPubMed]

10: *Gastroenterology* 2006 Sep;131(3):788-96

Increased adipose tissue expression of hepcidin in severe obesity is independent from diabetes and NASH.

Bekri S, Gual P, Anty R, Luciani N, Dahman M, Ramesh B, Iannelli A, Staccini-Myx A, Casanova D, Ben Amor I, Saint-Paul MC, Huet PM, Sadoul JL, Gugenheim J, Srai SK, Tran A, Le Marchand-Brustel Y

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BACKGROUND & AIMS: Hepcidin is an acute-phase response peptide. We have investigated the possible involvement of hepcidin in massive obesity, a state of chronic low-grade inflammation. Three groups of severely obese patients with or without diabetes or nonalcoholic steatohepatitis were investigated. **METHODS:** Hepcidin expression was studied in liver and adipose tissue of these patients. Hepcidin regulation was investigated in vitro by adipose tissue explant stimulation studies. **RESULTS:** Hepcidin was expressed not only in the liver but also at the messenger RNA (mRNA) and the protein levels in adipose tissue. Moreover, mRNA expression was increased in adipose tissue of obese patients. The presence of diabetes or NASH did not modify the hepcidin expression levels in liver and adipose tissue. In adipose tissue, mRNA expression correlated with indexes of inflammation, interleukin-6, and C-reactive protein. Interleukin-6 also promoted in vitro hepcidin expression. A low transferrin saturation ratio was observed in 68% of the obese patients; moreover, 24% of these patients presented with anemia. The observed changes in iron status could be due to the role of hepcidin as a negative regulator of intestinal iron absorption and macrophage iron efflux. Interestingly, a feedback control mechanism on hepcidin expression related to low transferrin saturation occurred in the liver but not in the adipose tissue. **CONCLUSIONS:** Hepcidin is a

proinflammatory adipokine and may play an important role in hypoferrremia of inflammation in obese condition.

PMID: 16952548 [found with GoPubMed]

11: J Immunol 2003 Sep;171(6):3194-201

IL-6 induces NF-kappa B activation in the intestinal epithelia.

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IL-6 is a potent proinflammatory cytokine that has been shown to play an important role in the pathogenesis of inflammatory bowel disease (IBD). It is classically known to activate gene expression via the STAT-3 pathway. Given the crucial role of IL-6 in the pathogenesis of chronic intestinal inflammation, it is not known whether IL-6 activates NF-kappaB, a central mediator of intestinal inflammation. The model intestinal epithelial cell line, Caco2-BBE, was used to study IL-6 signaling and to analyze whether suppressor of cytokine signaling 3 (SOCS-3) proteins play a role in the negative regulation of IL-6 signaling. We show that IL-6 receptors are present in intestinal epithelia in a polarized fashion. Basolateral IL-6 and, to a lesser extent, apical IL-6 induces the activation of the NF-kappaB pathway. Basolateral IL-6 stimulation results in a maximal induction of NF-kappaB activation and NF-kappaB nuclear translocation at 2 h. IL-6 induces polarized expression of ICAM-1, an adhesion molecule shown to be important in the neutrophil-epithelial interactions in IBD. Using various deletion constructs of ICAM-1 promoter, we show that ICAM-1 induction by IL-6 requires the activation of NF-kappaB. We also demonstrate that overexpression of SOCS-3, a protein known to inhibit STAT activation in response to IL-6, down-regulates IL-6-induced NF-kappaB activation and ICAM-1 expression. In summary, we demonstrate the activation of NF-kappaB by IL-6 in intestinal epithelia and the down-regulation of NF-kappaB induction by SOCS-3. These data may have mechanistic and therapeutic implications in diseases such as IBD and rheumatoid arthritis in which IL-6 plays an important role in the pathogenesis.

PMID: 12960348 [found with GoPubMed]

12: Am J Physiol 1999 Jul;277(1 Pt 1):G245-55

Bacterial cell wall polymers promote intestinal fibrosis by direct stimulation of myofibroblasts.

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Normal luminal bacteria and bacterial cell wall polymers are implicated in the pathogenesis of chronic intestinal inflammation. To determine the direct involvement of bacteria and their products on intestinal fibrogenesis, the effects of purified bacterial cell wall polymers on collagen and cytokine synthesis were evaluated in intestinal myofibroblast cultures established from normal fetal and chronically inflamed cecal tissues. In this study, the intestines of Lewis rats were intramurally

injected with peptidoglycan-polysaccharide polymers. Collagen and transforming growth factor (TGF)-beta1 mRNA levels were measured and correlated with mesenchymal cell accumulation by immunohistochemistry. The direct effects of cell wall polymers on fibrogenic cytokine and collagen alpha1 (type I) expression were evaluated in intestinal myofibroblast cultures. We found that intramural injections of bacterial cell wall polymers induced chronic granulomatous enterocolitis with markedly increased collagen synthesis and concomitant increased TGF-beta1 and interleukin (IL)-6 expression. Intestinal myofibroblast cultures were established, which both phenotypically and functionally resemble the mesenchymal cells that are involved in fibrosis in vivo. Bacterial cell wall polymers directly stimulated collagen alpha1 (I), TGF-beta1, IL-1beta, and IL-6 mRNA expression in the intestinal myofibroblasts derived from both normal and inflamed cecum. Neutralization of endogenous TGF-beta1 inhibited in vitro collagen gene expression. From our results, we conclude that increased exposure to luminal bacterial products can directly activate intestinal mesenchymal cells, which accumulate in areas of chronic intestinal inflammation, thus stimulating intestinal fibrosis in genetically susceptible hosts.

PMID: 10409173 [found with GoPubMed]

13: Int J Surg 2007 Aug;5(4):216-24

Heme oxygenase-1 upregulation protects against intestinal ischemia/reperfusion injury: A laboratory based study.

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OBJECTIVES: Tissue damage caused by ischemia/reperfusion injury (IRI) of the intestine may lead to organ dysfunction in several clinical conditions, and is associated with increased incidence of chronic rejection after transplantation. Heme oxygenase-1 (HO-1) is a stress-inducible protein capable of modulating inflammation, oxidative stress, and cell death. The aim of the present study was to assess the effects of HO-1 upregulation on intestinal IRI. **METHODS:** Lewis rats (seven groups, n=6 each) underwent intestinal warm ischemia induced by clamping the superior mesenteric artery and by ligating the inferior mesenteric artery for 60min. After 120 or 240min of reperfusion, tissue samples were collected for analysis. Cobalt protoporphyrin (CoPP) was administered IP at 10 or 20mg/kg 24h before IRI, to induce HO-1 upregulation. Control animals received vehicle alone. Tissue injury measurements included the following: histological changes, tissue myeloperoxidase (MPO) activity, nitrate/nitrite levels, and IL-6 levels. **RESULTS:** A significant HO-1 upregulation was demonstrated in pre-treated animals (p<0.05, 95% CI: -0.84 to -0.05). Intestinal IL-6 mRNA expression levels were significantly reduced in animals treated with CoPP 20mg/kg after 240min of IRI (p<0.05, 95% CI: 0.09-2.25). Significant reduction in MPO activity and NO products was observed in treated animals when compared to controls (p<0.01, 95% CI: 0.07-0.24 and p<0.01, 95% CI: 5.58-12.75, respectively). **CONCLUSIONS:** Induction of HO-1 by CoPP administration before IRI resulted in a significant reduction of intestinal tissue injury. Developing strategies to induce HO-1 upregulation before surgery will be important to reduce IRI in the clinical setting.

PMID: 17660127 [found with GoPubMed]

14: Am J Pathol 2007 Feb;170(2):497-504

Repression of repulsive guidance molecule C during inflammation is independent of Hfe and involves tumor necrosis factor-alpha.

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Genetic iron overload, or hemochromatosis, can be caused by mutations in HFE, hemojuvelin, and hepcidin genes. Hepcidin, a negative regulator of intestinal iron absorption, is found to be inappropriately low in both patients and in animal models, indicating that proper control of basal hepcidin levels requires both hemojuvelin and HFE. In mice, repulsive guidance molecule c (Rgmc, the hemojuvelin mouse ortholog) and hepcidin levels are transcriptionally regulated during inflammation. Here, we report that basal Rgmc levels in Hfe-deficient mice are normal and that these mice retain the ability to suppress Rgmc expression after lipopolysaccharide (LPS) challenge. Thus, Rgmc regulation by LPS is Hfe-independent. The response of Rgmc to LPS involves signaling through toll-like receptor 4 (Tlr4), because Tlr4-deficient mice do not show altered Rgmc expression after LPS administration. We further show that tumor necrosis factor-alpha, but not interleukin-6, is sufficient to cause Rgmc down-regulation by LPS. These results contrast with previous data demonstrating that hepcidin levels are directly regulated by interleukin-6 but not by tumor necrosis factor-alpha. The regulation of iron-related genes by different cytokines may allow for time-dependent control of iron metabolism changes during inflammation and may be relevant to chronic inflammation, infections, and cancer settings, leading to the development of anemia of chronic disease.

PMID: 17255318 [found with GoPubMed]

15: Blood Cells Mol Dis 2005;35(1):47-56

Regulation of hepcidin and ferroportin expression by lipopolysaccharide in splenic macrophages.

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Acute and chronic inflammatory states are associated with many changes in intracellular iron metabolism including sequestration of iron in the mononuclear-phagocyte system (MPS) and a decline in serum iron. Previous work in rodent models of acute inflammation has demonstrated inflammation-induced downregulation of intestinal and MPS iron exporter, ferroportin 1, mRNA and protein. In addition, these models have also demonstrated hepatic induction of mRNA of the small 25 amino acid peptide hepcidin. Hepcidin has been hypothesized to be the mediator of iron- and inflammation-induced changes in iron metabolism. The molecular details of the connection between iron metabolism, hepcidin and inflammation have become clearer with the recent finding of hepcidin-induced internalization and degradation of FPN1. The work presented here demonstrates that the lipopolysaccharide-induced splenic macrophage FPN1 mRNA downregulation is not dependent upon the action of a single cytokine such as IL-6, IL-1 or TNF-alpha because mice deficient in these pathways downregulate FPN1 normally. Furthermore, hepcidin is also synthesized in the spleen of normal mice and induced by lipopolysaccharide. Additionally, in vitro, splenic adherent cells produce

hepcidin in response to lipopolysaccharide in an IL-6-dependent manner. There appear to be both probable transcriptional and post-transcriptional control of FPN1 expression by lipopolysaccharide-induced inflammation. The former effect is on mRNA expression and is independent of hepcidin, whereas the latter is IL-6- and hepcidin-dependent.

PMID: 15932798 [found with GoPubMed]

16: Liver Transpl 2005 Jul;11(7):800-6

Ischemia-reperfusion of rat liver modulates hepcidin in vivo expression.

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The recently identified acute-phase response antimicrobial peptide hepcidin has been postulated to maintain iron homeostasis by modulating iron absorption at both the intestinal and macrophage levels. Hepcidin has also been reported to be responsible for anemia associated with chronic inflammatory diseases, and in anemia in patients with hepatic adenomas. Since Kupffer cells are known to be the primary contributor to early-phase ischemia-reperfusion injury in the liver and iron is known to modulate Kupffer cell production of proinflammatory cytokine and reactive oxygen species, we investigated hepcidin in vivo expression in the well-established rat partial-liver ischemia-reperfusion model. We found that both liver ischemia alone and liver ischemia-reperfusion significantly induced serum and liver hepcidin levels. Furthermore, currently proposed mediators of in vivo hepcidin expression, such as interleukin-6, signal transducers and activators of transcription-family transducers, and CCAAT/enhancing binding protein-alpha do not appear to modulate hepcidin expression in the liver ischemia-reperfusion acute inflammatory model. In this study we report the first in vivo evidence of liver ischemia and liver ischemia-reperfusion modulation of hepcidin expression. In conclusion, in the well-characterized liver ischemia-reperfusion model of acute inflammation, mechanism(s) other than interleukin-6 signal transduction via signal transducers and activators of transcription-3 may be responsible for hepcidin induction.

PMID: 15973703 [found with GoPubMed]

17: Gut 2002 Sep;51(3):379-85

Activation of signal transducer and activator of transcription (STAT) 1 in human chronic inflammatory bowel disease.

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BACKGROUND: Increased expression of proinflammatory cytokines, including tumour necrosis factor alpha, interleukin 6, and interferon gamma, as well as activation of proinflammatory signalling molecules such as nuclear factor kappa B, is characteristic of inflammatory bowel disease (IBD).

AIMS: To investigate expression and activation of signal transducer and

activator of transcription (STAT) 1 in patients with IBD. PATIENTS: Patients with active IBD (n=42), disease specificity controls (n=8), and normal controls (n=12) were investigated. METHODS: Expression and activation of STAT1 were assessed by western blotting and electrophoretic mobility shift assays in extracts of endoscopic colonic biopsies. Cellular localisation was determined by immunohistochemistry. RESULTS: Western blots and immunohistochemical staining revealed an increase in STAT1 expression and activation in mucosal samples from ulcerative colitis and to a lesser extent in Crohn's disease patients. High levels of suppressor of cytokine signalling (SOCS)-3 expression, an inhibitor of STAT activation, were observed in Crohn's disease patients and normal controls in western blot experiments whereas no differences were observed for SOCS-1 expression. Phosphorylated (p) STAT1 was mainly detected in monocytic cells and neutrophils in the inflamed mucosa. Induction of remission by systemic glucocorticoids led to a decrease in levels of pSTAT1. In vitro studies indicated a direct effect of steroid treatment on STAT1 activation. CONCLUSIONS: Expression and activation of STAT1 are predominantly heightened in ulcerative colitis and may therefore play an important role in the pathophysiology of colonic inflammation.

PMID: 12171960 [found with GoPubMed]

18: J Exp Med 2008 Aug;

The transcription factor NFATc2 controls IL-6-dependent T cell activation in experimental colitis.

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The nuclear factor of activated T cells (NFAT) family of transcription factors controls calcium signaling in T lymphocytes. In this study, we have identified a crucial regulatory role of the transcription factor NFATc2 in T cell-dependent experimental colitis. Similar to ulcerative colitis in humans, the expression of NFATc2 was up-regulated in oxazolone-induced chronic intestinal inflammation. Furthermore, NFATc2 deficiency suppressed colitis induced by oxazolone administration. This finding was associated with enhanced T cell apoptosis in the lamina propria and strikingly reduced production of IL-6, -13, and -17 by mucosal T lymphocytes. Further studies using knockout mice showed that IL-6, rather than IL-23 and -17, are essential for oxazolone colitis induction. Administration of hyper-IL-6 blocked the protective effects of NFATc2 deficiency in experimental colitis, suggesting that IL-6 signal transduction plays a major pathogenic role in vivo. Finally, adoptive transfer of IL-6 and wild-type T cells demonstrated that oxazolone colitis is critically dependent on IL-6 production by T cells. Collectively, these results define a unique regulatory role for NFATc2 in colitis by controlling mucosal T cell activation in an IL-6-dependent manner. NFATc2 in T cells thus emerges as a potentially new therapeutic target for inflammatory bowel diseases.

PMID: 18710929 [found with GoPubMed]

19: J Immunol 2008 Sep;181(5):3586-94

Gp130 signaling promotes development of acute experimental colitis by facilitating early neutrophil/macrophage recruitment and activation.

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IL-6 is known to play a crucial role in the pathogenesis of chronic intestinal inflammation by modulating T cell functions. In this study, we investigated the role of gp130, the common signal transducer for all IL-6 cytokines, in a murine model of acute T cell independent colitis to better characterize the impact of gp130 on innate immune cells and the early stages of inflammation. Experimental colitis was induced by dextran sulfate sodium treatment of mice with inducible systemic deletion of gp130 (MxCre/gp130(-/-)), macrophage/neutrophil-specific gp130-deficiency (LysCre/gp130(-/-)), or bone marrow chimeric mice and compared with wild-type controls (gp130(f/f)). Systemic deletion of gp130 (MxCre/gp130(-/-)) protected mice from severe colitis and wasting and attenuated the mucosal inflammatory infiltrate as well as local cytokine, chemokine, and adhesion molecule expression. Experiments in newly generated macrophage/neutrophil-specific gp130-deleted animals (LysCre/gp130(-/-)) and gp130 bone marrow chimeric mice, revealed a dual mechanism of proinflammatory effects mediated by gp130. Leukocyte recruitment was impaired in gp130-deleted animals and gp130-deleted recipients of wild-type bone marrow, demonstrating a central role of gp130-dependent signals in nonmyeloid cells for directing leukocytes to sites of inflammation, which was further confirmed in a model of sterile peritonitis. In contrast, macrophage/neutrophil-specific gp130 deficiency delayed and attenuated the disease but only marginally affected the inflammatory infiltrate, indicating a defective activation of mucosal leukocytes. We provide evidence that IL-6 cytokines acting via gp130 are required in the acute stages of intestinal inflammation by modulating the dynamics of innate immune cell recruitment and activation.

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20: J Clin Invest 2008 Jun;

The transcription factor IFN regulatory factor-4 controls experimental colitis in mice via T cell-derived IL-6.

Mudter J, Amoussina L, Schenk M, Yu J, Brüstle A, Weigmann B, Atreya R, Wirtz S, Becker C, Hoffman A, Atreya I, Biesterfeld S, Galle PR, Lehr HA, Rose-John S, Mueller C, Lohoff M, Neurath MF

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The proinflammatory cytokine IL-6 seems to have an important role in the intestinal inflammation that characterizes inflammatory bowel diseases (IBDs) such as Crohn disease and ulcerative colitis. However, little is known about the molecular mechanisms regulating IL-6 production in IBD. Here, we assessed the role of the transcriptional regulator IFN regulatory factor-4 (IRF4) in this process. Patients with either Crohn disease or ulcerative colitis exhibited increased IRF4 expression in lamina propria CD3(+) T cells as compared with control patients. Consistent with IRF4

having a regulatory function in T cells, in a mouse model of IBD whereby colitis is induced in RAG-deficient mice by transplantation with CD4(+)CD45RB(hi) T cells, adoptive transfer of wild-type but not IRF4-deficient T cells resulted in severe colitis. Furthermore, IRF4-deficient mice were protected from T cell-dependent chronic intestinal inflammation in trinitrobenzene sulfonic acid- and oxazolone-induced colitis. In addition, IRF4-deficient mice with induced colitis had reduced mucosal IL-6 production, and IRF4 was required for IL-6 production by mucosal CD90(+) T cells, which it protected from apoptosis. Finally, the protective effect of IRF4 deficiency could be abrogated by systemic administration of either recombinant IL-6 or a combination of soluble IL-6 receptor (sIL-6R) plus IL-6 (hyper-IL-6). Taken together, our data identify IRF4 as a key regulator of mucosal IL-6 production in T cell-dependent experimental colitis and suggest that IRF4 might provide a therapeutic target for IBDs.

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21: Gastroenterology 2005 Sep;129(3):1005-18

Differential regulation of gastric tumor growth by cytokines that signal exclusively through the coreceptor gp130.

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BACKGROUND & AIMS: We have shown that mice with a mutation in gp130 (gp130(757F/F)), the signal transducing receptor for interleukin (IL)-6 family cytokines, have chronic gastric inflammation and develop distal stomach tumors associated with deregulated phosphorylated STAT3 expression. This model recapitulates many characteristics of intestinal-type gastric cancer in humans. **METHODS:** To evaluate the role of IL-6 and IL-11 as ligands regulating tumor growth and submucosal invasion, we compared tumor characteristics of gp130(757F/F) mice with gp130(757F/F) mice lacking IL-6 or mature T and B cells. **RESULTS:** As a result of the gp130(757F/F) mutation, expression of IL-6 and IL-11 was greatly up-regulated concomitant with activation of STAT3 and development of tumors. However, the lack of IL-6 or T and B cells did not impact on tumor growth. While IL-6 did not regulate tumor growth or tumor vascularization, gp130(757F/F)/IL-6(-/-) mice showed approximately 10-20-fold more submucosal tumor invasion, reduced mononuclear inflammatory cell infiltrate, and greater IL-11 and matrix metalloproteinase (MMP)-13 and MMP-9 synthesis than gp130(757F/F) mice. Expression of MMP-13 was largely restricted to tumor-associated stroma, but MMP-9 was also expressed in polymorphonuclear cells and a subset of epithelial cells. In addition, treatment with recombinant IL-11 stimulated expression of MMP-13 and MMP-9 in stomachs of wild-type mice. **CONCLUSIONS:** Increased submucosal invasion in gp130(757F/F)/IL-6(-/-) mice could not be explained by increased vascularization or reduced immunosurveillance but was most likely facilitated by augmented metalloproteinase activity driven by elevated IL-11 levels.

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22: Clin Rev Allergy Immunol 2005 Jun;28(3):187-96

Involvement of IL-6 in the pathogenesis of inflammatory bowel disease and colon cancer.

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Inflammatory bowel disease (IBD), which consists of Crohn's disease and ulcerative colitis, is defined as a chronic inflammation of the gastrointestinal tract. The etiopathogenetic mechanisms underlying the development of IBD are still not completely understood, and the therapeutic strategies used thus far have been limited to mostly evidence-based principles. There is growing evidence that the pro-inflammatory cytokine interleukin (IL)-6 plays a crucial part in the uncontrolled intestinal inflammatory process, which is a main characteristic of IBD. There is elevated production of IL-6 and its soluble receptor (sIL-6R) by intestinal macrophages and CD4+T-cells. The increased formation of IL-6-sIL-6R complexes that interact with gp130 on the membrane of CD4+T-cells (trans-signaling) lead to an increased expression and nuclear translocation of STAT3, which causes the induction of anti-apoptotic genes, such as Bcl-xl. This leads to an augmented resistance of lamina propria T-cells to apoptosis. The ensuing T-cell expansion contributes to the perpetuation of chronic intestinal inflammation. This understanding concerning the predominant pathogenic role of an IL-6-dependent inflammatory cascade may lead to the development of new therapeutic strategies in the treatment of this disease. Recent studies have also suggested a potential role of IL-6-sIL-6R in the pathogenesis of colon cancer and, therefore, imply a possible novel therapeutic strategy targeting the sIL-6R and ensuing IL-6 trans-signaling.

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23: Carcinogenesis 2007 Aug;

Cytokine mediated rapid reversal of epithelial invasion in a mouse model of microbially-induced colon carcinoma.

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Chronic inflammation of mucosal surfaces renders them increasingly susceptible to epithelial cancers both in humans and mice. We have previously shown that anti-inflammatory CD4+CD45RBloCD25+ regulatory (Treg or T(R)) lymphocytes down-regulate inflammation and block development of bacteria-triggered colitis and colorectal carcinoma (CRC) in 129/SvEv Rag2-/- mice. Interestingly, CD4+CD25+ cells from Interleukin (IL)-10-deficient cell donors not only failed to suppress carcinogenesis but instead promoted invasive mucinous colonic carcinoma in male mice. Here we show that peritoneal invasion by mucinous carcinoma arose rapidly and consistently after treatment with IL10-/- T(R) cells, which were found to express Foxp3+ and localize throughout tumor tissue. Carcinogenesis was dependent on IL-6 and rapidly reversible by transfer of wild type IL10-competent T(R) cells. Likewise, treatment with IL10-Ig fusion protein was sufficient to revert the lesions histologically and restore inflammatory cytokine and oncogene expression levels to base line levels. These studies indicate an essential role for IL-6 in this male predominant CRC phenotype. Interleukin-10-competent T(R) cells are important for constructive remodeling of bowel following tumorigenic microbial insults. These data provide insights into etiopathogenesis of inflammation-associated epithelial invasion and maintenance of epithelial homeostasis.

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24: Orv Hetil 2006 Jul;147(30):1395-403

[Molecular biology background of inflammatory bowel disease]

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The exact pathological background of inflammatory bowel disease has not been clarified yet. Many aspects of genetical and environmental factors, as well as certain alterations of the functions of epithelial cells and immunoregulation which may attenuate chronic inflammation in the gastrointestinal tract are known. These three components have many connecting points. Among the inflammatory bowel disease genes we know only the function of the NOD2/CARD gene, and we have some idea about the OCTN and DRG genes. The function of the intestinal epithelial cells is changed in inflammatory bowel disease. The latter two genes may have a role in the increased permeability, so as the tumor necrosis factor alpha, interferon gamma may play affect it. The interleukin-10 helps the mucosal integrity. The interleukin-6 production is elevated in these diseases, and the interleukin-8 level can be elevated in case of mutation of toll like receptor 5. The tumor necrosis factor alpha, interferon gamma and lymphotoxin-3-alpha increased the chemokine secretion and adhesion molecule expression also. The amount of certain cytokines are changed in inflammatory bowel disease. There were no association between the incidence and phenotype of Crohn's disease and cytokine gene polymorphisms, except the interleukin 6 gene. It seems that these alterations are secondary, and don't play a major role in the pathogenesis of inflammatory bowel disease.

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25: J Endocrinol 2003 Dec;179(3):405-15

Interleukin-1beta (IL-1beta) and IL-6 modulate insulin-like growth factor-binding protein (IGFBP) secretion in colon cancer epithelial (Caco-2) cells.

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Chronic inflammation is characterised by modifications in cytokine concentrations, whereas growth is mainly dependent on the GH-IGF axis. IGF-I bioavailability is modulated by a family of IGF-binding proteins (IGFBPs). The aim of the present study was to evaluate the interactions among interleukin-1beta (IL-1beta), IL-6 and IGFBP secretion by intestinal cells to assess whether cytokines modulate IGFBP secretion, and in turn IGF-I and IGF-II bioavailability. The human colon carcinoma derived cell line Caco-2 was used as an in vitro model for its capacity to differentiate spontaneously. Experiments were carried out on day 4 (undifferentiated state) and day 14 (differentiated state) after plating. Carcinoembryonic antigen (CEA) was used as a marker of differentiation and increased in the conditioned media (CM) from days 4 to 14 (0.2+/-0.01 ng/ml per 10⁵ cells

vs 3.3±0.2 ng/ml per 10⁵ cells, P<0.05). IGFBP-2 and IGFBP-4 secretion decreased concomitantly. Cells were stimulated with IL-1β and IL-6 at 1, 10 and 50 ng/ml, and with IL-1β and IL-6 in combination at the same dose of 1 and 10 ng/ml. IGF-I at 50 ng/ml was used as a control. Caco-2 cells expressed and secreted mainly IGFBP-2 and IGFBP-4 into the CM. On day 4, IL-1β (1 ng/ml) and IL-6 (10 and 50 ng/ml) reduced IGFBP-2 by 29±8%, and by 32±9 and 38±8% respectively (P<0.05). IGFBP-4 was also reduced by IL-1β at 1 and 50 ng/ml (-14±4% and -46±11% vs serum free medium (SFM) respectively, P<0.05), and IL-6 at 50 ng/ml (-46±15%, P<0.05). Both IGFBP-2 and IGFBP-4 were reduced by IL-1β and IL-6 in combination at 1 and 10 ng/ml (P<0.05). On day 14, IGFBP-2 band intensity was reduced at 10 ng/ml of IL-1β (-22±15% vs SFM, P<0.05) and at 50 ng/ml of both cytokines (-33±8% and -13±13% vs baseline respectively, P<0.05). IGFBP-4 band intensity decreased with 10 and 50 ng/ml of IL-1β (-35±11% and -46±15% vs SFM respectively) and IL-6 (-36±10% and -46±15% vs SFM respectively). IL-1β and IL-6 in combination at 1 and 10 ng/ml reduced both IGFBP-2 and IGFBP-4. In conclusion, IGFBP-2 and IGFBP-4 secretion in CM decreased with Caco-2 cell differentiation. IGFBP-2 and IGFBP-4 were significantly decreased by IL-1β and IL-6 treatment in both the undifferentiated and differentiated state. Furthermore, these cytokines increased cell proliferation whereas total protein content was significantly reduced only at the higher concentrations of IL-6 and IL-1β. These findings suggest that interleukins modulate the IGF-IGFBP system in Caco-2 cells in vitro.

PMID: 14656210 [found with GoPubMed]

26: Leukemia 1999 Sep;13(9):1307-15

Hematopoietic, immunomodulatory and epithelial effects of interleukin-11.

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Interleukin 11 (IL-11) is a pleiotropic cytokine with biological activities on many different cell types. Recombinant human IL-11 (rhIL-11) is produced by recombinant DNA technology in *Escherichia coli*. Both in vitro and in vivo, rhIL-11 has shown effects on multiple hematopoietic cell types. Its predominant in vivo hematopoietic activity is the stimulation of peripheral platelet counts in both normal and myelosuppressed animals. This activity is mediated through effects on both early and late progenitor cells to stimulate megakaryocyte differentiation and maturation. rhIL-11 has been approved for the treatment of chemotherapy-induced thrombocytopenia. The hematopoietic effects of rhIL-11 are most likely direct effects on progenitor cells and megakaryocytes in combination with other cytokines or growth factors. rhIL-11 also induces secretion of acute phase proteins (ferritin, haptoglobin, C-reactive protein, and fibrinogen) from the liver. The induction of heme oxidase and inhibition of several P450 oxidases have been reported from in vitro studies. In vivo, rhIL-11 treatment decreases sodium excretion by the kidney by an unknown mechanism and induces hemodilution. rhIL-11 also exhibits anti-inflammatory effects in a variety of animal models of acute and chronic inflammation, including inflammatory bowel disease, inflammatory skin disease, autoimmune joint disease, and various infection-endotoxemia syndromes. rhIL-11 has trophic effects on non-transformed intestinal epithelium under conditions of mucosal damage. The mechanism of the anti-inflammatory activity of rhIL-11 has been extensively studied. rhIL-11 directly affects macrophage and T cell effector function. rhIL-11 inhibits tumor necrosis factor-α (TNF-α), interleukin 1β (IL-1β), interleukin 12 (IL-12), interleukin 6 (IL-6), and nitric oxide (NO) production from activated macrophages in

vitro. The inhibition of cytokine production was associated with inhibition of nuclear translocation of the transcription factor, nuclear factor kappa B (NF-kappaB). The block to NF-kappaB nuclear translocation correlates with the ability of rhIL-11 to maintain or enhance production of the inhibitors of NF-kappaB, IkappaB-alpha and IkappaB-beta. In addition to effects on macrophages, rhIL-11 also reduces CD4+ T cell production of Th1 cytokines, such as IFN gamma induced by IL-12, while enhancing Th2 cytokine production. rhIL-11 also blocks IFN gamma production in vivo. The molecular effects of rhIL-11 have also been studied in a clinical trial. Molecular analysis of skin biopsies of patients with psoriasis before and during rhIL-11 treatment demonstrates a decrease in mRNA levels of TNF alpha, IFN gamma and iNOS. These activities suggest that in addition to its thrombopoietic clinical use, rhIL-11 may also be valuable in the treatment of inflammatory diseases. The clinical utility of the anti-inflammatory properties of rhIL-11 is being investigated in patients with Crohn's disease, psoriasis and rheumatoid arthritis. These diseases are believed to be initiated and maintained by activated CD4+ Th1 cells in conjunction with activated macrophages.

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27: Cancer Res 2006 Dec;66(24):11580-4

Nrf2-deficient mice have an increased susceptibility to dextran sulfate sodium-induced colitis.

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Inflammatory bowel diseases, chronic inflammatory disorders, have been strongly linked with an increased risk of the development of colorectal cancer. Understanding the etiology of these diseases is pivotal for the improvement of currently available strategies to fight against inflammatory bowel disease, and more importantly, to prevent colorectal cancer. Nuclear factor-erythroid 2-related factor 2 (Nrf2) has been known to be a transcriptional factor which plays a crucial role in cytoprotection against inflammation, as well as oxidative and electrophilic stresses. The aim of this study is to investigate the role of Nrf2 in the regulation of dextran sulfate sodium (DSS)-induced experimental colitis in mice. Nrf2-deficient mice were found to be more susceptible to DSS-induced colitis as shown by the increased severity of colitis following 1 week of oral administration of 1% DSS. The increased severity of colitis in Nrf2(-/-) mice was found to be associated with decreased expression of antioxidant/phase II detoxifying enzymes including heme-oxygenase-1, NAD(P)H-quinone reductase-1, UDP-glucosyltransferase 1A1, and glutathione S-transferase Mu-1. In addition, proinflammatory mediators/cytokines such as COX-2, inducible nitric oxide, interleukin 1beta, interleukin 6, and tumor necrosis factor alpha were significantly increased in the colonic tissues of Nrf2(-/-) mice compared with their wild-type (Nrf2+/+) counterparts. In summary, we show for the first time that mice lacking Nrf2 are more susceptible to DSS-induced colitis. Our data suggests that Nrf2 could play an important role in protecting intestinal integrity, through regulation of proinflammatory cytokines and induction of phase II detoxifying enzymes.

PMID: 17178849 [found with GoPubMed]

28: Int J Mol Med 2002 Nov;10(5):631-4

Interleukin (IL)-4 and IL-17 synergistically stimulate IL-6 secretion in human colonic myofibroblasts.

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There is increasing evidence that interleukin (IL)-4 can aid in Th1-type inflammatory responses in chronic colitis models. In this study, we evaluated the effects of IL-4 and/or IL-17 on IL-6 secretion in human colonic myofibroblasts. IL-6 secretion was determined by ELISA and Northern blotting. IL-6 secretion was rapidly induced by either IL-4 or IL-17. IL-17 induced IL-6 mRNA expression within 1 h after stimulation, and reached a maximum at 3 h. IL-6 mRNA induction by IL-4 occurred more rapidly. A maximum induction of IL-6 mRNA by IL-4 was observed at 1 h after stimulation, and this was rapidly decreased. The combination of IL-4 plus IL-17 greatly enhanced IL-6 secretion and mRNA expression. In conclusion, IL-4, in particular IL-4 plus IL-17, induced IL-6 secretion in human colonic myofibroblasts. Th2 immune responses might play an important role in the pathogenesis of gut inflammation.

PMID: 12373306 [found with GoPubMed]

29: Proc Natl Acad Sci U S A 2002 Jan;99(2):1053-8

Anti-inflammatory role in septic shock of pituitary adenylate cyclase-activating polypeptide receptor.

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Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) are two mediators synthesized by immune cells, specially under inflammatory and antigen stimulation conditions. Reports have shown that neuropeptides attenuate the deleterious consequences of septic shock both by down-regulating the production of proinflammatory mediators and by stimulating the production of anti-inflammatory cytokines by activated macrophages. In this study, we used a knockout for the PACAP receptor (PAC1(-/-)) to demonstrate an important protective role for PAC1 receptor in endotoxic shock. Moreover, our results indicate that PAC1 receptor acts in vivo as an anti-inflammatory receptor, at least in part, by attenuating lipopolysaccharide (LPS)-induced production of proinflammatory IL-6, which appears to be the main cytokine regulating the expression of the majority of the acute phase protein genes, which are an important deleterious component of septic shock. Besides, our findings point to endogenously produced VIP and PACAP as participants of the natural anti-inflammatory machinery. Because VIP and PACAP are two attractive candidates for the development of therapies against acute and chronic inflammatory diseases, septic shock, and autoimmune diseases, this paper represents a contribution to the understanding of the mechanism of action of these anti-inflammatory agents.

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