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SERUM LEUCOTRIENS (B4,C4-D4-E4-F4) AND THROMBAXANE B2 LEVELS IN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER.

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Familial mediterranean fever (FMF) is an inflammatory disease characterized by recurrent fever episodes and polyserositis, autosomal recessive inheritance with unknown etiology especially seen in Turks, Arabs, Jewish and Armenians. Since its pathogenesis and etiology is not certainly known, current treatment modalities are only palliative. To search for pathogenesis of disease, inflammatory mediators of arachidonic acid metabolites, LT B4, LT C4-D4-E4-F4 and Tx B2 were studied in a group of 40 patients with FMF. 14 patients with FMF attack (Group I), 15 asymptomatic without taking colchicine therapy (Group II) and 11 asymptomatic with colchicine therapy (Group III), 10 patients with sepsis (Group IV) and 14 healthy controls (Group V). Detailed results were shown in Table 1. There was no difference among groups statistically. But the mean values of leucotriens were higher and TX B2 was lower than the healthy controls. In conclusion, the role of inflammatory mediators LT B4, LT C4-D4-E4-F4 and Tx B2 was not confirmed, but some clues from this study may lead to detailed searches for certain conclusion.

Table. Mean values of LT B4, LT C4-D4-E4-F4 and Tx B2 in patients with FMF and controls.

Groups	LT B4(pg/ml)	LT C4-D4-E4-F4(pg/ml)	Tx B2(pg/ml)
Group I	856.3±67.3	543.0±44.8	49.8±5.8
Group II	882.6±53.1	496.8±31.6	52.1±4.9
Group III	825.5±117.9	525.7±27.7	54.5±6.0
Group IV	948.2±77.4	534.1±15.8	53.1±4.9
Group V	784.0±73.4	471.2±15.8	60.9±3.4

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REGULATION OF A MUCUS SECRETAGOGUE BY SOMATOSTATIN IN A HUMAN MACROPHAGE HYBRIDOMA CELL LINE.

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Somatostatin (SST) is protective against a variety of injuries to the gastrointestinal tract. One possible mechanism for this effect is through SST's stimulation of mucus secretion into the epithelial/mucus barrier. Our group has isolated a protein (MMS-68), synthesized by intestinal macrophages, which stimulates mucus secretion by a variety of epithelia (Gastroenterology 1993;104:12-17). Further, we have created a human macrophage hybridoma cell line (clone 63) which secretes this factor (J Immunol Meth 1990;129:31-40). We tested the effects of SST on MMS-68 secretion in Clone 63 cells to test whether SST mediates its effects on mucus secretion through stimulation of MMS-68. Methods: Clone 63 cells were grown in supplemented RPMI and treated with SST (Sigma, St. Louis, MO) at 10^{-5} to 10^{-8} M for 4 hours. Supernatants were then added to [3 H]glucosamine labeled HT-29 colon cells for 1 hour, TCA-precipitated and read in a scintillation counter. Extracted RNA from lysed cells were tested for SST receptor subtype 2 (SSTR2) by RT-PCR using specific human SSTR2 21mer primers. Since we and others have detected SST mRNA in mouse macrophages, we tested SST mRNA expression by RT-PCR in Clone 63 cells followed by Southern blotting for confirmation. Human colonic RNA was used as a positive control for SST and SSTR2 expression. Results: SSTR2 and SST mRNA's were expressed by Clone 63 cells by RT-PCR and confirmed by Southern blotting using specific probes. SST stimulated mucin release from [3 H]glucosamine labeled HT-29 cells in a dose-dependent manner which could be blocked by anti-MMS-69 I-D-10 monoclonal antibody. SST mRNA was itself stimulated by SST administration (dose-dependent). Conclusions: SST and its subtype 2 receptor are expressed in a human macrophage hybridoma cell line. SST regulates mucus secretion through MMS-68 in HT-29 cells. SST also regulates its own expression, suggesting an autocrine regulatory pathway. We believe this is the first report of SST expressed in human macrophages.

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REGULATED PRODUCTION OF THE TH2-LYMPHOCYTE CHEMOATTRACTANT MACROPHAGE DERIVED CHEMOKINE (MDC) BY HUMAN INTESTINAL EPITHELIAL CELLS.

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MDC is a ligand for CCR4 expressed on antigen presenting cells and T cells of the Th2 subset. MDC selectively induces the chemotaxis of IL-4-producing, but not IFN- γ -producing T cells. The intestinal epithelium can secrete chemokines that attract acute inflammatory cells, but little is known about the ability of epithelial cells to produce chemokines that attract T cells, particularly those secreting anti-inflammatory cytokines such as IL-4. The aim of this study was to characterize regulated MDC production by human intestinal epithelial cells. **METHODS:** HT-29 and HCA-7 cells were stimulated with cytokines, or infected with the pathogens *Salmonella dublin* or enteroinvasive *Escherichia coli*. Expression of MDC mRNA was determined by RT-PCR, and protein secretion by ELISA. **RESULTS:** HT-29 and HCA-7 cells did not constitutively express mRNA for MDC. Stimulation with TNF α , IL-1 α , or IFN- γ upregulated MDC mRNA expression after 3 h and expression was maximal at 12 h. Epithelial MDC secretion was increased synergistically after stimulation of cells with IFN- γ plus TNF α or IL-1 α , with maximal levels at 24 h reaching > 500 ng/ml. To chemoattract Th2 lymphocytes, epithelial MDC predictably should be secreted in the basolateral direction. To test this, HCA-7 cells grown as polarized monolayers on filter supports were stimulated with cytokines. Greater than 90% of MDC was secreted basolaterally, rather than apically. Infection with *S. dublin* or enteroinvasive *E. coli* also elicited MDC secretion from HT-29 cells, and synergy was observed between bacterial infection and stimulation with IFN- γ . The Th2 cytokine IL-4 inhibited MDC secretion elicited by TNF α and IFN- γ , but had no effect on MDC secretion by itself, suggesting Th2 cell recruitment in response to MDC may be regulated by a negative feedback loop. **CONCLUSION:** Pro-inflammatory stimuli induce the production of the Th2 chemoattractant MDC from human intestinal epithelial cells. Epithelial cell derived MDC may recruit Th2-type T cells to the epithelium, and through the release of IL-4 have anti-inflammatory functions, including the control of inflammatory responses to pathogenic stimuli. Supported by NIH grant DK35108, DK07202, the CCFA, and a MRC of Canada Fellowship (MCB).

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PROTECTIVE EFFECT OF DIETARY NITRIC OXIDE ON EXPERIMENTAL GASTRITIS IN RATS.

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Nitric oxide (NO) stimulates blood flow, increases mucus secretion and decreases acid secretion at gastric level, and may consequently display anti-inflammatory properties. Dietary nitrates are transformed into NO in the gastric lumen. The aim of the study was to determine whether nitrate ingestion protects against an experimental gastritis induced in rats by iodoacetamide and whether these effects are mediated through NO. **Methods.** 8 groups of male Wistar rats (200-250 g) were used. Groups 1-4 received intragastrically, for 7 days, iodoacetamide (25 mg/kg/d) alone (group 1) or associated with KNO₃, 250 mg/kg/d (group 2), sodium nitroprusside, 2 mg/kg/d (SNP, a NO donor, group 3), KNO₃ and haemoglobin, 150 mg/kg/d (a NO scavenger, group 4). Groups 5-8 received water alone (group 5) or associated with KNO₃ (group 6), SNP (group 7) or haemoglobin (group 8). On day 8, rats were sacrificed and strips of gastric antrum were taken for measurement of myeloperoxidase (MPO) activity according to the method of Bradley et al, 1982. Results. Daily administration of iodoacetamide for 7 days significantly increased ($P < 0.0001$) gastric MPO activity (3190 ± 247 vs 1008 ± 113 units/g protein in controls). KNO₃ and SNP treatments significantly reduced ($P < 0.005$) the increase in MPO induced by iodoacetamide (1246 ± 96 and 1763 ± 278 MPO units/g protein, respectively). Haemoglobin treatment associated with KNO₃ suppressed the reduction of iodoacetamide-induced inflammation by KNO₃ (2590 ± 456 MPO units/g protein). Treatments with KNO₃, SNP, or haemoglobin alone, in absence of iodoacetamide, did not modify significantly ($P > 0.05$) the MPO activity in comparison with controls receiving water. **Conclusion.** Our results indicate that intragastric nitrate reduces an experimental gastric inflammation induced by iodoacetamide in rats. These effects are very likely mediated by NO coming from nitrate transformation since they are reproduced by a NO donor and abolished by a NO scavenger. Dietary NO may indeed play a protective role in gastritis.