The role of gastrointestinal bacterial ecology in Inflammatory bowel disease (IBD)

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The pathogenesis of inflammatory bowel disease (IBD) is not yet fully understood A genetic predisposition, some environmental factors and microbial flora of the grit are the key factors. The presence of bacteria in the intestinal lumen is a prerequisite for the development of IBD. In animal models, mice incapable of expressing IL, or IL invariably develop a colitis- or Crohn-like inflammation. No inflammation occurs if they grow up in a pathogen free environment or if they are fed with Lactobacillus sp when exposed to environmental bacteria. Thus, the absence of liminal bacteria or a different make-up there of prevents the development of inflammatory bowel disease in this model. Patients with IBD have been found to have a decreased stool excretion Lactobacillus andlor Bifidobacteria.

Furthermore, an increased number of bacteria adherents to the mucosa and within the epithelium has been demonstrated in quantitative studies. It appears that these bacteria trigger a strong abnormal mucosal immunological response, leading to intestinal epithelial cell injury mediated by activated T-cells, mononuclear cells and macrophages. If this response can not be down regulated by regulatory T-cells, mononuclear inflammatory cytokines are activated by stimulation of the intracellular transcription factor NF-kB. Recently it was shown that bacterial lipopolysaccharides can activate NF-kB by binding to two specific receptors on the cell membrane (Toll-like receptors [TLR's]) or intracellular receptors (NOD's).

New insights of the role of bacteria in IBD became available by identifying susceptibility genes for IBD. Several IBD susceptibility loci were recently identified. The IBD-l locus on chromosome 16 shows positive evidence for linkage in Crohn's disease and IBD-2 locus on chromosome l2 for ulcerative colitis. The evidence for' an association with Crohn's disease at the IBD-I locus have been shown to be attributed to mutations in the CARDI5/NOD2 gene. This gene is exressed in peripheral blood monocytes and in intestinal epithelial cells and serves as a key factor of innate mucosal response to luminal bacteria as an antibacterial factor.

The intact intercellular NOD2 protein binds LPS and activates NF-kB. This activation of the NF-kB signalling pathway in response to bacterial components plays a protective role in the mucosal epithelial cells for the host against inviting pathogens and an increased apoptosis of infected cells. There is evidence, that the defective NOD2 protein variants increase the susceptibility to pathogen invasion and a decrease in cellular apoptosis.

NF-kB plays a dual role in IBD. On the mucosal epithelial cells, bacterial components bind on NOD2 proteins and protect bacterial invasion. If this barrier mechanism is not intact, the bacterial invasion stimulates via TLR- and NOD2 receptors in immune-active cells (macrophages, T-cells and monocytes) NF-kB and triggers an aberrant inflammatory response leading to tissue damage. These new insights in the pathogenesis in IBD have led to new treatment possibilities including pre- and probiotics.

These therapies are aimed at directly modulating the host immune system to suppress intestinal inflammation. This has prompted considerable interest in manipulating the enteric microenvironment as a

novel therapeutic strategy Several clinical studies showed promising results rising pre- and probiotics in patients with ulcerative colitis, pouchitis and Crohn's disease. The introduction of genetically engineered probiotic organism to produce and deliver anti-inflammatory cytokines or other biological relevant molecules to the mucosa offers further new potential for the treatment of IBD.