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Basic and Clinical Aspects of Mucosal Inflammation and Healing in Crohn's Disease

In the thesis of Qiang Gao studies are described on immunopathogenic aspects of inflammatory bowel disease (IBD), i.e., Crohn's disease (CD) and ulcerative colitis (UC), as well as on efficacy mechanisms of infliximab, an anti-tumor necrosis factor (TNF)-α antibody, for the treatment of CD. The focus was on three groups of factors, fibroblast growth factor and its receptors, the gelatinase-type of matrix metalloproteinases (MMPs), and TNF-α, which are all believed to be important mediators in the mucosal processes in IBD. The following observations were made:

1. The ternary complex of bFGF-FGFR-syndecan-1 is actively involved in the inflammatory and healing processes of the intestinal IBD mucosa. A shift in the expression of the bFGF-FGFR-syndecan-1 complex was observed, at both the protein and mRNA level, from mature epithelial cells in normal tissue to cells of the lamina propria in IBD tissue, particularly at sites with increased inflammation. This change in the predominant location of the bFGF-complex is thought to be related to coordinated reparative mechanisms as angiogenesis, tissue reconstitution, cell-cell and cell-matrix interaction in the intestinal mucosa. Healing of fistulizing/perianal CD is reflected by a decrease in high serum bFGF, particularly in relation to treatment with infliximab (anti-TNF-α). In contrast, serum bFGF levels do not relate with response in patients with active CD. These observations confirm that bFGF, in concert with TNF-α, plays a role in the inflammation and tissue repair process in CD patients with a fistulizing disease phenotype. *In vitro* experiments illustrated further that LPS regulates the expression of bFGF at both the transcriptional (mRNA) and/or post-transcriptional (protein) level in leucocytes from patients with CD and from healthy controls. The transcription regulation of bFGF was found to be mediated to a large extent by TNF-α, as exemplified by interference of infliximab.

2. The determination of TNF-α by immunosorbent assays is strongly interfered by infliximab. The presence of infliximab does not influence the capability of peripheral blood cells, however, to produce TNF-α.

3. Comprehensive tissue analysis showed that MMP-2 and MMP-9 are markedly increased and thus actively involved in the inflammatory and remodelling processes in intestinal IBD mucosa. MMP-2 was found to participate in the stromal processes, whereas MMP-9 was predominantly associated with the leucocyte-mediated inflammatory process. An enhanced MMP-9 secretion by blood leucocytes of CD patients through LPS stimulation was found to be independent of TNF-α inhibition by infliximab. The induction of MMP-9 mRNA transcription in leucocytes after longer LPS stimulation, however, was TNF-α dependent. Treatment of CD patients with infliximab resulted in an inverse changing pattern of serum MMP-2 and MMP-9, i.e., an increase of MMP-2 and a decrease of MMP-9, the latter also in the intestine. However, these changes were not strictly associated with the clinical response, i.e., improvement, to treatment with infliximab.

These observations may be helpful to understand the role of proteolytic enzymes and immunological regulatory peptides in the pathological processes of IBD (Figure 1). In addition, the *in vitro* and *in vivo* studies with infliximab provide further insight into mechanisms of anti-pro-inflammatory cytokine directed immunological therapy for Crohn's disease.

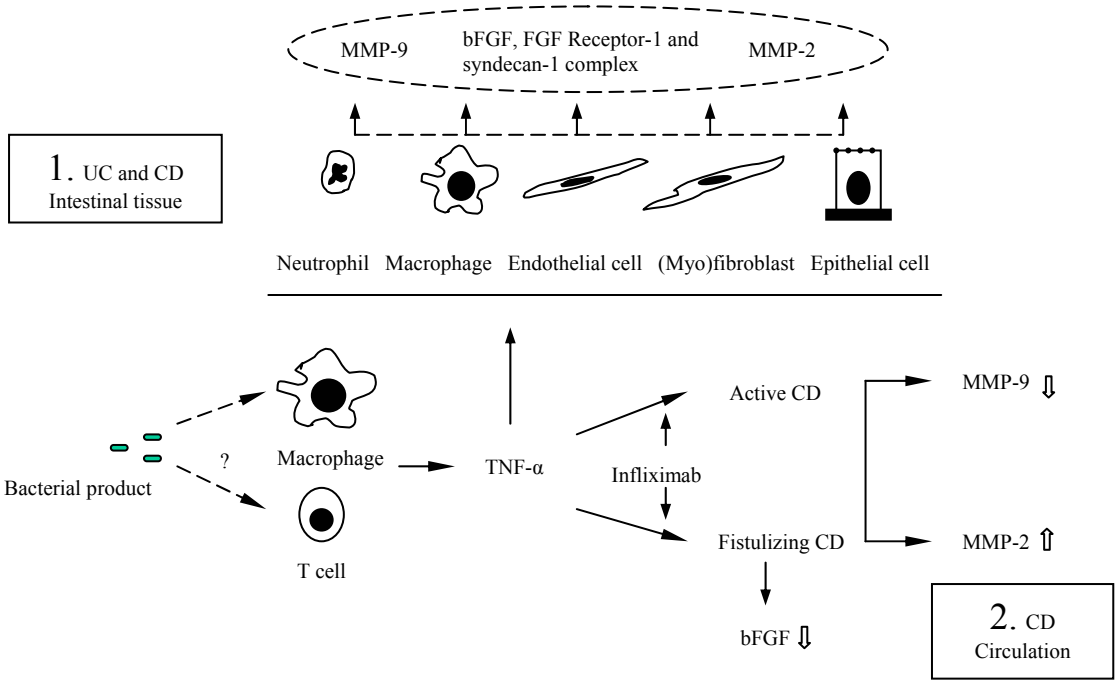

Figure 1. The outline of the results described in this thesis: MMP-2, MMP-9 and the complex of bFGF, FGF Receptor-1 and syndecan-1 were found to actively participate in the inflammatory process, both tissue destruction and healing, of IBD; 1) in intestinal tissues of UC and CD the elevated expression of MMP-2 and -9, and a heterogenic expression of the complex was observed; 2) after treatment with infliximab, serum bFGF was decreased in fistulizing patients who respond to the therapy, whereas serum MMP-2 and -9 in CD patients exhibited an inverse changing partten, i.e., an increase of MMP-2 and a decrease of MMP-9. (© Q.Gao and H.W.Verspaget)

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