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The Gut-Skin Axis

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Several inflammatory gut diseases may be accompanied by cutaneous lesions. For example, 14 percent of patients with ulcerative colitis have skin manifestations, while the percentage is consistently even higher (24%) in Crohn's disease (1). Pyoderma gangrenosum, with one or multiple cutaneous ulcers, is one of the most common skin manifestations of ulcerative colitis. Erythema nodosum, a panniculitis type skin change, is more prevalent in Crohn's disease. Also, psoriasis is more frequently encountered in patients with Crohn's disease than healthy controls. Also celiac disease (CD) has cutaneous manifestations: the blistering rash of dermatitis herpetiformis is encountered in one fourth of patients with CD, and these patients also have an increased frequency of oral mucosal lesions, alopecia and vitiligo (2). Like in linear IgA disease associated with ulcerative colitis, it has been hypothesized that foreign antigens penetrating inflamed bowel mucosa may give rise to production of autoantibodies cross-reacting with cutaneous antigens.

Matrix metalloproteinases (MMPs) are a family of 23 human zinc-dependent endopeptidases. As a group they can degrade all the components of basement membranes and extracellular matrices and are involved in pathologic destruction of tissue in various inflammatory disorders. However, they are also known to be important in wound repair of various organs. Recently, MMPs have been shown to have a diverse range of other roles in cell biology; they mediate cytokine and chemokine activation and inactivation, angiogenesis, they regulate the activity of defensins, cleave adhesion molecules and release of apoptotic ligands (3). MMPs have been implicated in mucosal damage of the intestine caused by excess T-cell activation and secretion of proinflammatory cytokines. Particularly, MMP-3 (stromelysin-1) seems to have a critical role in experimental models of irritable bowel disease (IBD) (4), but recent data also point to the importance of MMPs-1 (collagenase-1), -10 (stromelysin-2) and -12 (metalloelastase) in tissue destruction of IBD (5). Natural inhibitors of MMPs, tissue inhibitors of metalloproteinases, are involved in regulating matrix turnover of lamina propria during inflammation. The ulcer formation in IBD has been suggested to result from disturbed balance between expression of MMPs and their inhibitors (5,6) and indeed downregulation of TIMPS-1 and -3 has been reported in experimental models. Paradoxically, certain MMPs are also important in tissue remodelling (MMP-14) and enterocyte migration (MMP-1, -7 and -10) associated with healing of IBD lesions.

Our group has recently studied two diseases characterized by T-cell-mediated tissue injury, namely CD and graft-versus-host disease (GVHD). The histologic changes of CD, characterized by deepening of crypts and flattening of villi, suggest altered turnover of extracellular matrix. MMP-12 was abundantly expressed in subepithelial macrophages in duodenal lesions of CD while MMP-7, -10 and -13 were absent (7). Furthermore, MMP-1 has previously been shown to contribute to the degradation of collagens and MMP-3 to epithelial cell shedding in CD (8). MMP-12 was also upregulated in both induced and *in vivo* DH blisters. Interestingly, we have previously shown that expression of MMP-1 and -3 is enhanced in basal keratinocytes surrounding neutrophil abscesses in DH skin. These MMPs together with uPA may thus contribute to formation of these blisters by degrading basement membrane components, such as type IV and VII collagens and laminin-1. On the whole, our results demonstrate that the same MMPs are upregulated in association with T-cell-mediated immune responses both in the intestine and skin and may contribute to the histologic changes as effector molecules. Thus, interefering the MMP signal transduction cascades with their synthetic inhibitors and various other drugs (MAPK-inhibitors, tetracycline-analogues) might offer new therapeutic options to dapsone that is still needed in certain cases in addition to a gluten-free diet.

MMP inhibitors have also been demonstrated to prevent lethal acute GVH disease in mice models. In human intestinal GVHD developed after bone marrow transplantation, the predominant MMPs detected in intestinal biopsies are MMP-1 in stromal cells and MMP-19 in the intestinal crypts (9). Both TIMP-1 and TIMP-3 were noted in superficial areas of destroyed mucosa. TIMP-1 and -3 were analogously expressed in the dermis of cutaneous lesions of GVHD. TIMP-3 is also upregulated in cutaneous scleroderma, a disorder characterized by fibrosis, like the chronic lesions of intestinal and cutaneous GVHD.

MMPs are clearly effector molecules in various inflammatory gut disorders in which they control mucosal

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destruction, repair, apoptosis and the degree of inflammation. Selective inhibition of destructive MMPs might alleviate effects of mucosal inflammation without inhibiting the benefial functions of other MMPs involved in repair.

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