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REVIEW PAPER

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Inflammatory bowel disease: the function of metalloproteinases

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Abstract

Introduction. Inflammatory bowel disease (IBD) is a group of inflammatory conditions of the colon and small intestine.

Aim. The aim of this work was to review the current literature regarding matrix metalloproteinases. The databases such as PubMed, ScienceDirect and Springer were utilized to search the literature for relevant articles.

Materials and methods. An analysis of literature. We collected information, data, and examples of the function of metalloproteinases.

Results. Herein we show that metalloproteinases play a role in such processes as the immune response, angiogenesis, the epithelial barrier function, fibrosis induced by the inflammatory process, and in the process of carcinogenesis.

Conclusions. Further studies on the role of metalloproteinases in the process of carcinogenesis associated with inflammatory bowel diseases are required.

Keywords. inflammatory bowel disease, matrix metalloproteinases, extracellular matrix

Introduction

Matrix metalloproteinases (MMPs) are the main group of enzymes responsible for collagen and other protein degradation in the extracellular matrix (ECM).[1-5] Matrix metalloproteinases are also responsible for the activation or inhibition of the function of numerous cytokines, chemokines, receptors, adhesion molecules or signaling substances affecting inflammatory processes in the intestine.[6-10] A typical structure of MMPs consists of several distinct domains. The MMP family can be divided into six groups: collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs, and other non-classified MMPs. [10-14] The MMP functions are listed in the Table 1.

Invading neutrophils produce large amounts of matrix metalloproteinase MMP8 and MMP9, which proteolytically cleave collagen into small fragments.[25] These collagen fragments are further cleaved to the tripeptide, PGP, by epithelial- and neutrophil-derived prolyl endopeptidase (PE).[26]

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Table 1. MMP functions[1-42]

MMPs name	Function
MMP 1	inhibition of fibrosis[17,18]
MMP 2	inhibition of angiogenesis, influence on the epithelial barrier function, inhibition of fibrosis[17,18]
MMP 3	outflow to the production of Endostatin[19]
MMP 7	alpha-defensin activation, chemokine expression, ulcer healing, Endostatin production[20]
MMP 8	neutrophil infiltration[21]
MMP 9	Chemokine expression, neutrophil infiltration, production of anti-angionenic factors, processing, VEGF-A activation, inhibition of goblet cell differentiation, inhibition of fibrosis[21]
MMP 10	healing of ulcers[22,23]
MMP 13	TNF-alpha activation and Endostatin production[24]
MMP 20	Endostatin production[24]

The role of metalloproteinases in fibrosis in non-specific inflammatory bowel diseases

Fibrosis is the process of pathological collection of the substance in the intracellular sow in the intestinal wall, which accompanies chronic inflammatory processes. Expression of MMP and the balance between their level and the level of metalloproteinase inhibitors (TIMPs and others) play an essential role in ECM homeostasis. Disruption of this balance leads to the deposition of collagen and fibrosis. Despite advances in the treatment of inflammatory bowel disease (IBD), there are no medications to prevent or reverse the process of fibrosis. In ulcerative colitis, fibrosis affects the mucosa and submucosa. Crohn's disease affects the entire thickness of the intestinal wall and can lead to intestinal stenosis. Treatment of stenosis is a surgical procedure. The increase in ALK5, TIMP, Smad-2, Smad-3 phosphorylation leads to collagen accumulation in the intestinal wall.[27-29] Glutamine has an effect that lowers fibrosis in induced TNBC enteritis by reducing overexpression of TGF-beta, Smad and TIMP phosphorylation.[30-31] Interleukin-13 also participates in fibrosis processes by affecting the concentration of MMP-1 and TIMP-1.[28-32] The cytokine may inhibit the expression of MMP-1, MMP-2, MMP-9. MMP-2 is reduced in the form of a narrowing Crohn's disease.[29-33] In studies on DSL-induced dextran sulfate, an increase in gelatinase expression (MMP-2 and MMP-9) may prevent fibrosis by collagen degradation.[28-33]

The role of metalloproteinases in the process of carcinogenesis, colitis associated cancer (CAC)

Patients with IBD have an increased risk of colorectal cancer compared to the entire population.[39] The risk of cancer in ulcerative colitis increases significantly 8-10 years from the beginning of the disease and increases as the disease progresses. It also depends on the extent of changes in the intestine, the higher risk occurs in the extensive form (E3-classification of ulcerative colitis depending on the extent of the disease) compared to left-sided (E 2), in disease located only in the rectum (E 1) does not increase. Colon cancer is the cause death of 1 in 6 patients with colitis ulcerosa.[40]

An increase in MMP-9 expression is observed during the carcinogenesis process and the adenocarcinoma sequence. MMP-9 may be a marker of early stages of carcinogenesis.[41] However, cancer associated with chronic inflammation does not arise as a sporadic or genetically determined adenoma-dysplasia carcinoma, but as an inflammation-dysplasia-carcinoma (where the p53 mutation plays a key role in the early stage of carcinogenesis).[40]

Metalloproteinase 9, which is a mediator of inflammatory bowel process, may also play a protective role in the process of carcinogenesis (Colitis Associated Cancer - CAC). MMP-9 may have a double meaning in CAC. In experiments in mice, MMP-9 -/- individuals have been shown to be more susceptible (in comparison to individuals able to produce MMP-9) to develop CAC. It is emphasized that it protects the development of CAC by activating the Notch-1 molecule with subsequent inhibition of beta-catenin expression. Notch-1 activation by MMP-9 also leads to increased expression of p53 protein, increase in p21 Waf / Cip1 protein (regulator), a cell cycle inhibitor), as well as an increase in Bax family proteins (Bcl-2 family proteins that accelerate apoptosis).[41]

In contrast to the protective role of MMP-9 in the development of CAC, in experiments on mice, it was found that the activation of neutrophilia by CXCL2 chemokines increases the production of MMP-9, which in turn through the activation of VEGF (vascular epithelial growth factor) accelerates neoangiogenesis. This process has essential in the development of cancer.

There was also an effect on the expression of MMP-9, integrin linked kinase (ILK) - a protein responsible for such cellular processes as migration, proliferation and adhesion. ILK through MMP-9, MMP-2 and MMP3 promotes neoplasia (carcinogenesis, tumorigenesis).[29]

Infliximab (anti-TNF-alpha antibody) as well as celecoxib (gelatinase inhibitor) may have been shown to be preventive in the case of CAC by decreasing the concentration of metalloproteinase.[32]

Metalloproteinase -10 may have an inhibitory effect on the carcinogenesis process, it may also act to inhibit the development of dysplastic changes in IBD.[42]

Conclusions

Further studies on the role of metalloproteinases in the process of carcinogenesis associated with inflammatory bowel diseases are required.

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