◎総 説

Matrix metalloproteinases (MMPs) and pancreatic diseases

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Abstract : Matrix metalloproteinases (MMPs) is a family of collagenolytic enzymes and are associated with many pathological conditions. Especially, MMPs have a strong relation with tumor progression and invasion. In this review, we focused on association of MMPs and pancreatic diseases, and a potential treatment of MMPs inhibitors for pancreatic cancer.

Key Words : matrix metalloproteinase (MMP), tissue inhibitor of metalloproteinase (TIMP), pancreatic cancer, chronic pancreatitis

Introduction

Matrix metalloproteinases (MMPs) are a family of proteases that degrade the collagen and are associated with many pathological conditions including pancreatic diseases. Recent investigations have revealed the MMPs are associated with the pathogenesis of cancer and inflammation. MMP activity is regulated at multiple steps[1]. The MMP genes are transciptionally responsive to a number of biologically active agents, such as growth factors, hormones and oncogenes[2].

MMP proteins are secreted as inactive zymogens that require proteolytic processing to release the active enzyme. Another mechanism of control is blocking enzyme activity by physiologic MMP inhibitors; the circulating alpha2-macroglobulin or the tissue inhibitors of metalloproteinases (TIMPs). The MMP-inhibitor complex is inactive and unable to bind substrate[3]. We have attempted to investigate MMPs in pancreatic juice of patients with chronic pancreatitis and pancreatic cancer in order to diagnose them at early stage. In addition, MMPs is supposed to be a

new target for anti-cancer therapy. This review is focused on MMPs in pancreatic diseases, and treatment of MMP inhibitors for pancreatic cancer.

Pancreatic cancer and MMPs

Overexpression of several MMPs[4-8] in pancreatic cancer tissues and cancer cell lines has been reported as well as other malignancies[9]. MMPs are thought to play a major role in metastasis by degradation of physiological barriers, promoting invation and entry into and out of blood lymphatic vessels in pancreatic cancer[10]. MMP activity has been correlated with malignant potential in a number of studies[6, 11].

MMP-1 is thought to be an interstitial collagenase, which degrades interstitial collagen. Ito et al.[4] reported that positive staining for MMP-1 protein observed in cancer cells and stromal fibroblasts in pancreatic cancer compared with normal pancreas. They also demonstrated that patients with MMP-1 positivity in the primary site had a significantly poorer prognosis than patients who were MMP-1 negative. These findings suggest that MMP-1 expression is related to the carcinogenesis and prognosis of human pancreatic ductal adenocarcinoma. On the other hand, Bramhall et al.[6] reported that MMP-1 might not play an important role compared with MMP-2 in pancreatic cancer. Imbalance of MMP-1 to TIMP-1 is also important because TIMP-1 inactivated activated MMPs. Increased level of mRNA of TIMP-1 was also reported in pancreatic cancer[5, 6]. Since many cytokines and growth factors are known to affect expression of MMP-1 at the transcriptional level. Comprehensive studies on MMP-1 and pancreatic cancer are needed.

MMP-2 is known to be a type IV collagenase, and plays a crucial role in the invasion of tumor cells because it degrades type IV collagen, which is one of the major components of the basement membranes[12]. Overexpression of MMP-2 mRNA was observed in stromal and tumor cells in pancreatic cancer[5]. Recently, it was found that epithelial cell membrane-bound MMPs, membrane-type MMPs (MT-MMPs) (designated MT1-MMP to MT5-MMP), play crucial roles in the activation of MMP-2. MT-MMPs contain additional transmembrane domain, resulting in cell-surface localization[9]. MT1-MMP is involved in activation of proMMP-2 by forming a complex with TIMP-2 on the cell surface, which serves as a receptor for proMMP-2. An unbound MT1-MMP adjacent to this complex may initiate a second step leading to the activation of proMMP-2[13, 14]. (Figure-1) Recent studies have shown that MT1-MMP itself can degrade the extracellular matrix[15, 16].
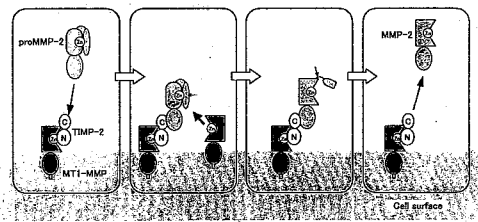

Fig.1. Activation of MMP-2

Overexpression of MT1-MMP mRNA was observed in pancreatic cancer[7] and MT1-MMP is exclusively located to the tumor epithelial cells[6, 9]. A good correlation was found between MT1-MMP and both MMP-2 expression and activity in pancreatic cancer[7]. MMP-2 and MT1-MMP were also overexpressed in hamsters initiated with N-nitrosobis(2-oxopropyl)amine (BOP) which is a rapid-production model for pancreatic duct carcinoma[17]. Koshiba et al.[8] reported that activation ratio of MMP-2 was significantly higher in pancreatic cancer than in chronic pancreatitis and normal pancreas, although latent form of MMP-2 was detected in all samples of pancreatic carcinoma, chronic pancreatitis, and normal pancreatic tissue.

Brook et al.[18] proposed another mechanism of localizing MMP-2 on the cell surface, demonstrating that active MMP-2 binds directly to integrin $\alpha v \beta 3$. MT1-MMP was suggested to be involved activation of integrin-bound MMP-2[19].

Overexpression of MMP-2 was known to be a poor prognostic marker in pancreatic cancer. The MMP-2 activation ratio in pT3 tumors was significantly higher than that in pT1 tumors and also was significantly higher in pancreatic carcinoma specimens with histologically positive regional lymph node metastasis and distant metastasis than those without metastasis[8]. The ratio of type IV collagenase expression (mean of the expression of MMP-2 and MMP-9) to E-cadherin expression (MMP : E-cadherin ratio) at the periphery of the tumors was significantly higher in patients with recurrent disease than in patients who were disease free[20].

MMP-7 is known to be expressed in more than 75 per cent of gastric and colonic carcinomas[21, 22]. According to Bramhall et al.'s report[6], MMP-7 was expressed in 88 per cent of pancreatic carcinoma, suggesting that it may have a role in its invasive phenotype. MMP-7 mRNA was localized to the tumor epithelium, as well as gastric and colonic carcinoma[21]. However, the findings of MMP-7 mRNA expression in normal pancreatic tissues[6, 23] indicates that it may also have physiological role in the pancreas.

There is little evidence supporting expression of stromelysines (MMP-3, MMP-10, and MMP-11) in adenocarcinoma, although in squamous cell carcinoma stromelysin expression was showed to correlate with tumor progression[24]. Gress et al.[25] also failed to detect MMP-3 expression in pancreatic cancer.

Several investigators[5, 26] reported increased level of mRNA of MMP-9 in pancreatic cancer. Overexpression of type II TGF-β receptors was observed in pancreatic cancer, and there was a strong correlation between the expression of type II TGF-β receptors and MMP-9[27]. On the other hand, Koshiba et al.[8, 28] demonstrated that activated MMP-9 was detected in normal pancreatic tissues as well as pancreatic cancer and they concluded that expression of activated MMP-9 was unrelated to pancreatic cancer. In breast cancer, activated MMP-3 is a potent activator of proMMP-9, yielding activated MMP[29]. Furthermore, multiple transcriptional factors including NFκB[30], SP-1[31] and AP-1[31], were known to be associated with regulating transcriptional activation of MMP-9. Taken together, further studies are needed to elucidate the precise mechanism of MMP-9 in pancreatic cancer.

Therapeutic application of MMP inhibitors for pancreatic cancer

As described above, overexpression of MMPs is associated with tumor spread and metastasis. Consequently, inhibitors of MMPs represent an attractive target for a new class of anticancer agents. Therefore, several MMP inhibitors have been developed and preclinical trials have confirmed a reduction in tumor spread and metastases[32]. Marimastat is the first orally available MMP inhibitor (MMP I) to be tested in humans and has been shown to inhibit the spread and growth of pancreatic cancer in animal models[33]. Phase II studies which have used marimastat alone or in combination with other cytotoxic agents, have produced encouraging results with improved survival[34]. Phase III trials are now underway for the use of marimastat in advanced pancreatic cancer and as an adjuvant therapy in patients following resection of pancreatic cancer[33].

Chronic pancreatitis and MMPs

Theoretically, absolute or relative decrease of MMP considered to be reasonable because chronic pancreatitis is characteristic of pancreatic fibrosis. However, the relationship between MMPs and TIMPs, and chronic pancreatitis is controversial. Ishihara et al.[35] reported that positive immunostainings for MMP-2, MMP-9, TIMP-1, and TIMF-2 in ductal epithelia were 15 (75%), five (25%), four (20%), and 10 (50%) of patients with chronic pancreatitis, respectively, whereas no immunostaining was seen in normal pancreas. However, Gress et al.[25] reported that transcripts for MMP-1, MMP-3 and TIMP-1 were not detectable in chronic pancreatitis and control tissues.

Recent studies for pancreatic fibrosis have focused on the pancreatic stellate cell (PSC)[36-39], which are morphologically similar to the hepatic stellate cells that play a central role in liver fibrogenesis[40]. Pancreatic stellate cells are activated on exposure to ethanol[36], which is the major etiological factor in chronic pancreatitis. In liver fibrosis, hepatic stellate cells are reported to product MMPs and TIMPs such as MMP-1[41], MMP-2[42], MMP-3[43], and TIMP-1[44]. Furthermore, MMP-1 mRNA was detected in at early stage, but TIMP-1 mRNA was up-regulated and MMP-1 mRNA became undetectable with activated hepatic stellate cells[41]. Further dynamic studies are needed to be done in pancreatic fibrosis, because treatments of MMP inhibitor for benign diseases such as glomerulonephritis[45], brochial asthma[46], and brain stroke[47], have attempt to be applied.

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マトリックスメタロプロテアーゼと膵疾患

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　マトリックスメタロプロテアーゼ（MMP）は,
コラーゲン分解能を有し, 種々の疾患との関連性
が示唆されている。とりわけ, 癌の浸潤, 転移に
は密接な関係があるとされている。また, MMP
阻害剤を癌の治療に用いる試みもなされている。
本稿ではMMPと膵疾患の関連性, MMP阻害剤
の膵癌への応用の可能性について総説する。
検索用語 : MMP, TIMP, 膵癌, 慢性膵炎