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Development of Chymase Inhibitor as a Potent Agent for Preventing Vascular Diseases

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Abstract: Chymase activates not only angiotensin I to angiotensin II but also pro-matrix metalloproteinase-9 to matrix metalloproteinase-9. A clinical trial of an angiotensin II receptor blocker for preventing restenosis after percutaneous coronary intervention was successful, but that of an angiotensin-converting enzyme inhibitor was not. After balloon injury in dog arteries, chymase activity was significantly increased in the injured artery and a chymase inhibitor and an angiotensin II receptor blocker were effective in preventing the vascular proliferation, but an angiotensin-converting enzyme inhibitor was ineffective. In dog grafted veins, chymase activity and angiotensin II concentration along with vascular proliferation were significantly increased, while they were significantly suppressed by a chymase inhibitor. In human and animal atherosclerosis, chymase activity and mRNA level were also significantly increased, whereas a chymase inhibitor suppressed the atherosclerosis in a hamster model. Although both angiotensin II and matrix metalloproteinase-9 are thought to be closely involved in the pathogenesis of abdominal aortic aneurysms, a chymase inhibitor significantly suppressed not only chymase activity but also aneurysms in a hamster aneurysmal model. Both angiotensin II and matrix metalloproteinase-9 are also induced the development of angiogenesis, but chymase inhibition results in suppressing the angiogenesis in experimental animal models. Thus, chymase may become a very important target for preventing vascular diseases.

Key words: Angiotensin II, chymase, inhibitor, metalloproteinase

INTRODUCTION

Chymase (EC 3.4.21.39) is a chymotrypsin-like enzyme that is expressed in the secretory granule of mast cells. chymase is stored as an inactive enzyme in secretory granules, because the pH within the granule is regulated at pH 5.5, in which chymase has no enzymatic activity[1,2]. The optimal pH of chymase is between 7 and 9 and its activity shows almost a maximum level immediately upon release into the extracellular matrix (pH 7.4), when the mast cells are activated in injured or inflammatory vascular tissues[3,4]. However, strong chymase inhibitors such as serine protease inhibitors are contained in blood and the activity of chymase is immediately inhibited. Therefore, chymase has enzymatic activity only in local tissues.

Angiotensin II is a vasoconstricting peptide derived from angiotensinogen by renin and Angiotensin-Converting Enzyme (ACE) and the latter is a well-known enzyme for conversion from angiotensin I to angiotensin II. However, chymase can produce angiotensin II from angiotensin I in human and animal cardiovascular tissues[5-12]. Angiotensin II also plays an important role in vascular hypertrophy[13]. In clinical studies, an Angiotensin II Receptor Blocker (ARB) was successful in preventing restenosis after Percutaneous Coronary Intervention (PCI)[14]. On the other hand, ACE inhibitors could not suppress the restenosis after PCI[15]. These studies suggest the significance of chymase-dependent angiotensin II formation on an important role in the development of vascular hypertrophy in the injured dessels. On the other hand, chymase also contributes the conversion of pro-matrix metalloproteinase (pro-MMP)-9 to matrix metalloproteinase (MMP)-9[16-18]. MMP-9 is closely involved in the developments of abdominal aortic aneurysm and angiogenesis. Therefore, chymase inhibitors may be useful for preventing vascular diseases.

Restenosis after balloon injury: Patients with ischemic heart disease are offered with Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Grafting (CABG). An ACE inhibitor cilazapril failed to suppress the restenosis after percutaneous coronary intervention in a clinical trial, the mercator study[14], but an ARB valsartan was successful in preventing the restenosis in a clinical trial, the Val-Prest trial[15]. More recently, in the Valvace trial, the restenosis rate after bare metal stent

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implantationwas significantly lower in valsartan than ACE inhibitors[19]. ACE inhibitors are not able to suppress chymase-dependent angiotensin II formation. We speculated that chymase-dependent angiotensin II-formation may play an important role in the development of vascular proliferation after percutaneous coronary intervention. In our dog balloon-injury model, chymase activity, but not ACE activity, was significantly increased in the arteries injured by a balloon catheter[20]. In this model, an ARB candesartan significantly suppressed the development of neointimal formation after injury by a balloon catheter, while an ACE inhibitor enalapril did not[21,22]. The difference in the inhibitory action of candesartan and enalapril is thought to be that ACE inhibitor suppresses only the angiotensin II action produced by ACE but that ARB can suppress the angiotensin II action produced by chymase in addition to that by ACE. These results indicated that local angiotensin II production by chymase is involved in the intimal hyperplasia seen in the injured arteries. In fact, in this dog model, a chymase inhibitor NK3201 significantly reduced intimal hyperplasia in the injured arteries[20]. ACE inhibitors and ARBs are known to reduce blood pressure and to increase plasma renin activity, while NK3201 did not affect blood pressure or plasma renin activity[20]. Therefore, chymase inhibitors may be useful for preventing restenosis after PCI.

Stenosis in vein graft: Patients with ischemic heart disease are offered with CABG or PCI. In CABG, the internal thoracic artery and saphenous vein have been frequently used as coronary artery bypass conduits. However, the poor performance of the saphenous vein compared with the internal thoracic artery is well known[23,24]. The chymase activity and total angiotensin II-forming activity, but not the ACE activity, is significantly higher in human saphenous vein than in the internal thoracic artery[25]. In isolated human saphenous vein, the contractile response of angiotensin II is greater than that in the internal thoracic artery, suggesting that the saphenous vein exhibits greater angiotensin II-mediated action than the internal thoracic artery[26]. This high level of total angiotensin II-forming activity in the saphenous vein is thought to be dependent on the upregulated chymase activity. In a dog grafted model, each dog underwent right common carotid artery bypass grafting with the ipsilateral external jugular vein after anesthetizing[27]. The ACE activity in the grafted veins was significantly decreased up to 7 days after the operation and especially after 1 and 3 days, it was suppressed in the grafted veins to less than 10% of the control value[28]. The reason why the ACE activity was decreased at acute periods after the operation is thought to be dependent on the loss of the endothelium. Because the endothelium in grafted veins is put under arterial pressure, thus resulting in the loss of the endothelium including ACE[29]. On the other hand, 7 days after the operation, the chymase activity was significantly increased in the grafted veins. Considering these findings, up to 7 days after the operation, the angiotensin II formation in the grafted veins is thought to depend mainly on the chymase-dependent angiotensin II-forming pathway. Moreover, the angiotensin II concentration and the mRNA levels of fibronectin, collagen I and collagen III, all of which are induced by an increase of angiotensin II action[30], were significantly increased in the grafted veins 7 days after the operation. These findings suggest that chymase-dependent angiotensin II formation may play an important role in increase of extracellular matrix such as fibronectin, collagen I and collagen III in vascular tissues. In fact, a chymase inhibitor, Suc-Val-Pro-Phe^{P}(OPh)$_2$, completely suppressed the angiotensin II concentration and the mRNA levels of fibronectin, collagen I and collagen III in the grafted vein 7 days after the operation[28]. Chymase activities in the grafted veins was activated at acute phase after grafting and the angiotensin II-forming activity via chymase was especially accelerated, suggesting that the activated angiotensin II formation via chymase may be important in the development of vascular proliferation. In fact, a single treatment with Suc-Val-Pro-Phe^{P}(OPh)$_2$ into grafting veins maintained the suppression of chymase activity and vascular proliferation even 3 months after the operation[30]. On the otherhand, oral administration of chymase inhibitors, NK3201 and TY-51184, could also prevent both the chymase activity and the vascular proliferation in the grafted veins[31,32]. Therefore, chymase inhibitors may be useful for the prevention of stenosis in vein graft.

Atherosclerosis: The number of activated mast cells was increased in human atherosclerotic lesions and a chymase gene variant was associated with atherosclerosis[33,34]. In animal atherosclerotic models, the chymase activities and mRNA levels were increased in atherosclerotic legions, whereas a chymase inhibitor, SUN-C8257, significantly suppressed the development of atherosclerosis[8,35]. Angiotensin II is well known to induce atherosclerosis and ARBs prevent the development of atherosclerosis in animal atherosclerotic models[36-38]. Thus, an increase of local angiotensin II formation by chymase may play an important role in the development of atherosclerosis.

Abdominal Aortic Aneurysm: Human Abdominal Aortic Aneurysms (AAA) which represents a chronic

degenerative condition associated with atherosclerosis is characterized by segmental weakening and dilatation of the aortic wall and carries a life-threatening risk of rupture[39]. The pathophysiology of AAA includes aortic atherosclerosis, chronic inflammation within the outer aortic wall and an imbalance between the production and degradation of structural extracellular matrix proteins[40]. In human AAA, chymase activity is significantly increased[41-43]. Chymase-positive mast cells are hardly detected in the normal vessels and only in the adventitial area[42]. However, in the AAA, chymase-positive mast cells were detected in the medial area in addition to the adventitial area and the number of mast cells was obviously increased in comparison with the normal aorta[41]. The increased chymase activity in the AAA is thought to be dependent on the accumulation of chymase-positive mast cells. The number of macrophages is also increased in the AAA and angiotensin II activates macrophages[44,45]. The activated macrophages induce nuclear factor-κB and this in turn induces an inflammatory cytokine, interleukin-1 and a chemokine, monocyte chemoattractant protein (MCP)-1[46]. Interleukin-1 produced by activated macrophages induces tissue damage and MCP-1 induces the activation and migration of monocytes, resulting in an accumulation of macrophages[47,48]. ARBs were found to reduce gene expression of MCP-1 and reduced the accumulation of macrophages[49,50]. Infusion of angiotensin II leads to development of aortic aneurysm in apolipoprotein E-deficient mice, but an ARB can suppress progression of the abdominal aortic aneurysm[51,52]. Chymase activity is involved not only in angiotensin II formation but also in the processing of MMP-9[17-19]. An MMP inhibitor and a targeted gene disruption of MMP-9 limited expansion of experimental AAA[53,54] and MMP-9 is thought to be closely involved in the pathogenesis of AAA. In a hamster aneurysmal model, chymase activity in AAA was significantly higher than that in normal aorta, whereas a chymase inhibitor significantly suppressed both the chymase activity and the aortic diameter[55]. Thus, the inhibition of chymase may also be useful for preventing the promotion of AAA.

Angiogenesis: Angiotensin II enhances neovascularization via induction of vascular endothelial growth factor in several animal models and increases blood flow in ischemia-induced angiogenesis[56-58]. Moreover, angiotensin II receptor signaling-dependent induction of vascular endothelial growth factor in stroma is relevant to tumor-associated angiogenesis and tumor growth, an ARB candesartan inhibited tumor growth, angiogenesis and metastasis[59,60]. In a hamster sponge implant model, exogenous injection not only of angiotensin II but also of angiotensin I directly into the sponges enhanced angiogenesis, whereas chymase inhibitors partially prevented the angiogenesis induced by angiotensin I, but not by angiotensin II[61,62]. This finding suggests the importance of chymase-dependent angiotensin II formation for angiogenesis. Chymase also acts as a pro-angiogenic factor, because the injections of the chymase gene or of purified chymase into implanted sponges strongly facilitate angiogenesis[62]. However, this chymase-induced angiogenesis could only be prevented by 50% by an ARB[62]. Furthermore, a maximum dose of an ARB or a chymase inhibitor partially prevented the angiogenesis induced by basic fibroblast growth factor and a combination of an ARB and a chymase inhibitor could inhibit more strongly than either agent alone[62]. Chymase-induced angiogenesis may depend not only on angiotensin II formation but also on activation of other factors such as MMP-9.

CONCLUSIONS

Chymase released from mast cells functions as an angiotensin II-forming enzyme or an MMP-9-activating enzyme and is involved in the development of vascular diseases such as vascular wall remodeling and angiogenesis. Therefore, chymase inhibition may promise the therapeutic benefits against vascular diseases.

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