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ACE Inhibitors to Block MMP-9 Activity: New Functions for Old Inhibitors

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Since the early 1990's, angiotensin converting enzyme (ACE) inhibitors have been used clinically to improve survival and reduce adverse left ventricular (LV) remodeling following myocardial infarction (MI). Seminal studies performed by the Pfeffer laboratory clearly demonstrated a survival benefit post-MI for both rats and humans treated with ACE inhibitors.[1,2] Several avenues of research have since sprouted to better understand the underlying mechanisms behind this benefit. Patten and colleagues demonstrated that both the ACE inhibitor enalapril and the angiotensin II type I receptor inhibitor losartan prevented LV hypertrophy and decreased collagen I gene expression compared to placebo-treated controls, suggesting that these events signaled through the angiotensin II type I receptor.[3] Yoshiyama and colleagues then showed that, in mice deficient for the angiotensin type I receptor, treatment with an ACE inhibitor prevented remodeling post-MI, indicating that ACE inhibitors also block angiotensin receptor-independent remodeling pathways.[4] In this issue, Dr. Yamamoto and colleagues examined the ability of the ACE inhibitor imidapril to directly bind to the matrix metalloproteinase MMP-9.[5] The importance of these findings is that ACE inhibition may also inhibit MMP-9, which provides a common link between strategies to prevent adverse remodeling post-MI (Figure 1). Adverse remodeling post-MI leading to congestive heart failure remains a leading cause of long-term morbidity and mortality.[6]

ACE and MMP-9 are both zinc-dependent endopeptidases, both stimulate remodeling post-MI, and both process angiotensin I to form angiotensin II.[7] Matrix metalloproteinases are a family of 25 proteolytic enzymes defined by their ability to cleave individual extracellular matrix (ECM) components. MMP-9, also known as gelatinase B, processes multiple extracellular substrates, including denatured collagen I, fibronectin, and laminin.[8] Adding another layer of complexity, MMP-9 also cleaves non-ECM components, including cytokines and growth factors, to regulate multiple cell functions.[9] MMP-9 is inhibited in the tissue by binding one of four tissue inhibitors of metalloproteinases (TIMPs). Of the 4 TIMPs identified

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to date, TIMP-1 binds MMP-9 with greatest affinity.[10] MMPs have assigned roles in many cardiovascular diseases, including atherosclerosis, myocardial infarction, and heart failure [11]. Ample evidence has demonstrated a direct cause and effect relationship between MMP-9 and LV remodeling: 1) MMP-9 levels increase early post-MI[12], 2) MMP inhibition improves post-MI outcomes[13], and 3) MMP-9 gene deletion reduces remodeling and stimulates post-MI angiogenesis.[14] Furthermore, Blankenberg and colleagues have shown that MMP-9 is also a novel predictor of cardiovascular mortality, as patients with coronary artery disease who had the highest MMP-9 levels at baseline showed the greatest cardiovascular mortality rates at follow-up.[15] While global non-selective MMP inhibition studies have not fared well, strategies that specifically limit MMP-9 activity may prove beneficial.

Dr. Yamamoto and colleagues have previously published their prediction that, based on modeling studies, lisinopril, another ACE inhibitor, directly binds to MMP-9.[16] The S1′ substrate recognition site on MMP-9 forms a deep hydrophobic pocket that is compatible with the hydrophobic moieties present in ACE inhibitors. For example, both lisinopril and imidapril have a phenyl ethyl group that will bind to this hydrophobic pocket. The current study builds on this past report by adding imidapril to the list of ACE inhibitors that bind MMP-9 and also be providing additional information on the predicted complex structures. Differential binding affinities were seen for the two inhibitors, indicating that different ACE inhibitors will inhibit MMP-9 to different degrees. Lisinopril was shown to be stabilized in the active site of MMP-9 by specific hydrogen bonds and hydrophobic interactions.[16] Specifically, the hydrophobic group in lisinopril interacted preferentially with the S1 site, compared to the S1′ site. The fact that imidapril binds with greater affinity than lisinopril indicates that hydrophobic interactions with the S1 site of MMP-9 may be important for enhancing the inhibitory affect of the ACE inhibitor. This detail may be useful for the design of ACE inhibitors with increased affinity for MMP-9. Extending the earlier observational binding studies, the authors also demonstrated that use of imidapril in a unique hamster MI model resulted in decreased MMP-9 levels (both pro and active) and improved function.

These results are intriguing and raise new questions to be answered in future studies. First, it will be important to determine how selective and specific ACE inhibitors are for MMP-9. We will need to evaluate whether ACE inhibitors also bind any of the other 24 MMPs, whether ACE inhibitors are able to bind members of other metalloproteinase families, and whether MMP inhibitors can block ACE activity. The MMP-9 hydrophobic pocket is smaller than the pockets of other MMPs, indicating that selectivity may be achievable.

Second, further study is needed to better understand the multiple overlapping roles of ACE in the post-MI left ventricle. This effort is complicated by the fact that chymase also increases in the infarct region, chymase generates angiotensin II, and chymase inhibition also improves post-MI outcomes.[17,18] Chymase-dependent angiotensin II formation has been reported to account for over 90% of total myocardial levels, although chymase levels do vary among species.[19] Chymase from human, dog, and hamster all hydrolyze the Phe^{8}-His^{9} bond of angiotensin I to efficiently produce angiotensin II.[20] In contrast, rodent chymase cleaves angiotensin I at the Tyr^{4}-Ile^{5} bond to generate inactive angiotensin fragments.[20] Also, mast cells are the major source of chymase, and the fact that rodents have very few mast cells in the left ventricle further defines species differences.[21] Chymase has been shown to process MMP-9 to its active form[22], indicating that the connection between angiotensin II and MMP-9 is further complicated. Studies evaluating ACE and MMP-9 connections will also need to take into account chymase activity.

Third, the effects of ACE inhibitors on blocking MMP-9 function at different, longer time points post-MI need investigation. Yamamoto and colleagues only evaluated effects at day 1 post-MI, when most of the MMP-9 in the infarcted myocardium is derived from infiltrated

polymorphonuclear leukocytes.[12] It would be interesting to determine effects at day 3 through 7, when fibroblast, macrophage, and endothelial cell-derived MMP-9 likely play important roles in post-MI remodeling. In addition, Yamamoto *et al* showed that ACE expression did not increase until day 3 and remained elevated at day 7. Therefore, we do not know whether inhibiting both ACE and MMP-9 when both are elevated would show additive benefits, or whether there would be competitive binding of the two enzymes. Evaluating effects of the ACE inhibitor when both MMP-9 and ACE levels are high would indicate the relative *in vivo* affinities of the inhibitor for the different enzymes.

In conclusion, the findings that ACE inhibitors are able to bind directly to MMP-9 and that the ACE inhibitor imidapril decreases MMP-9 levels *in vivo* following MI emphasize the potential non-specific and non-selective nature of ACE inhibitors. It is important to consider both ACE and MMP systems when evaluating LV remodeling and when designing new drugs that target either or both systems. A novel therapeutic strategy may be to use currently available ACE inhibitors as the backbone on which to design new drugs that also target MMP-9.

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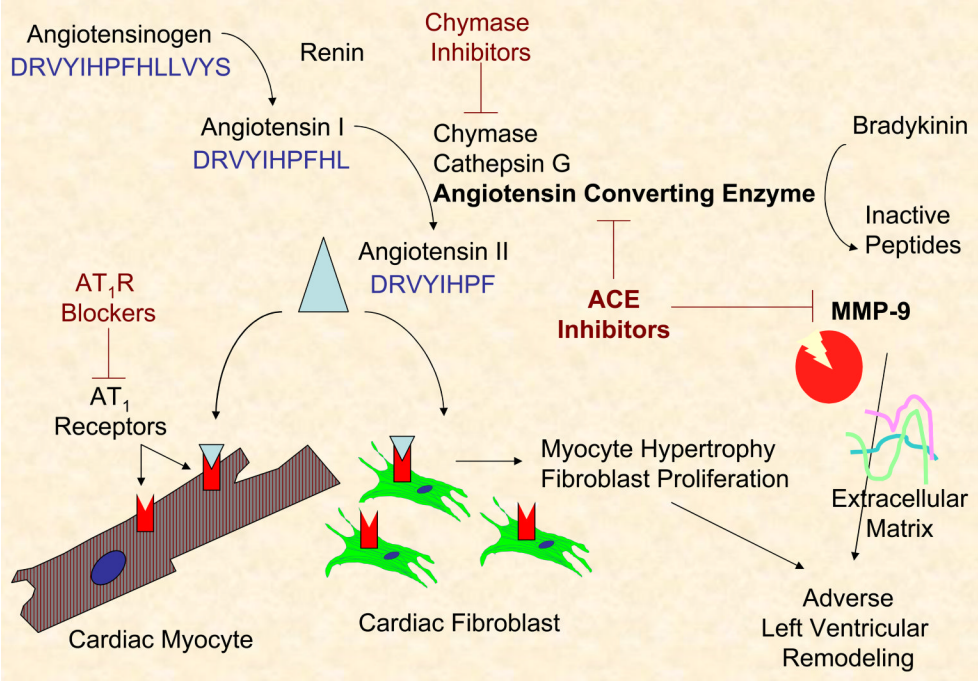

Figure 1.
Schematic demonstrating the relationship between angiotensin II, matrix metalloproteinase-9 (MMP-9), and angiotensin converting enzyme (ACE) inhibitors in preventing adverse LV remodeling.