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Tissue Inhibitor of Metalloproteinase-1: actions beyond matrix metalloproteinase inhibition

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Matrix metalloproteinases (MMPs) are a family of zinc-dependent enzymes, which include 25 current members. MMPs degrade structural components of extracellular matrix and process bioactive molecules including cytokines, chemokines, and growth factors [1]. MMP activity is tightly controlled by endogenous tissue inhibitors of metalloproteinases (TIMPs), which are composed of four homologous members (TIMP-1, TIMP-2, TIMP-3, and TIMP-4). The dynamic balance between MMPs and TIMPs controls extracellular matrix turnover and maintains tissue homeostasis. Alterations in the balance between MMPs and TIMPs are implicated in the pathogenesis of cardiovascular disease [2].

In the manuscript that is the focus of this editorial, Wang and colleagues investigated whether plasma MMP-9 and TIMP-1 levels as well as the MMP-9/TIMP-1 ratio could be used as biomarkers to predict future cardiovascular events in Chinese patients with mild to moderate coronary artery stenosis [3]. Immediately after diagnosis, plasma levels of MMP-9 and TIMP-1 were measured, and the patients were followed for a median of 64 months. Patients with median TIMP-1 levels above 37.6 ng/mL had an increased incidence of major adverse cardiac events (MACEs) during the follow-up period, which was further supported by multivariate Cox proportional hazards analysis after adjustment of covariates. In contrast, no correlation was observed between MMP-9 or MMP-9/TIMP-1 ratio and the incidence of MACEs. Therefore, TIMP-1 may serve as a promising biomarker to predict the outcomes of patients with mild to moderate coronary artery lesions.

TIMP-1, a 28-kDa glycoprotein, is produced by cardiac myocytes and fibroblasts in the normal heart [2]. TIMP-1 binds with active MMPs in a non-covalent 1:1 stoichiometric relation to inhibit MMP activity. Post-myocardial infarction (MI), TIMP-1 mRNA levels

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increase as early as 6 h due to neutrophil infiltration. TIMP-1 deficiency accelerates remodeling and dilation of the left ventricle (LV), and this effect could be rescued by MMP inhibition [4]. TIMP-1 overexpression reduces atherosclerotic lesions in apolipoprotein E deficient mice, accompanied by reduction in MMP-2, MMP-3, and MMP-13 content [5]. Combined, these studies define that TIMP-1-dependent favorable effects are mediated by inhibiting MMP activity.

Independent of inhibiting MMP activity, TIMP-1 can also modulate a broad range of biological processes, including cell growth, proliferation, apoptosis, migration, and angiogenesis, by binding to unidentified receptors and inducing specific signaling cascades [6]. *In vitro*, TIMP-1 displays growth-promoting activity in a wide range of cells, mediated through receptor tyrosine kinase/mitogen activated protein kinase signaling pathway [7,8]. TIMP-1, but not a MMP inhibitor, induces proliferation of aortic smooth muscle cells involving the phosphoinositide 3-kinase pathway [9]. TIMP-1 directly induces smooth muscle actin expression and stimulates Smad-3 phosphorylation in cardiac fibroblasts, as well as inhibits apoptosis in myocytes [10]. Of note, TIMP-1 suppresses microvascular endothelial cell migration through both MMP-dependent and MMP-independent mechanisms [11]. The MMP independent roles of TIMP-1 may, at least partially, explain why TIMP-1, but not MMP-9, independently predicted MACEs risk in the Wang *et al.* study [3].

The findings that TIMP-1 acts as an independent predictor for future MACEs are supported by previous studies. The Framingham Heart Study revealed that plasma TIMP-1 levels are higher in men than women, and increase with age, body mass index, and total/high density lipoprotein-cholesterol ratio [12]. Subjects who smoke or have diabetes have higher plasma TIMP-1 levels. More importantly, after adjusting for age, sex, and height, plasma TIMP-1 is positively correlated with LV mass, wall thickness, end-systolic diameter, and the risk of having increased LV end-diastolic diameter or wall thickness, but negatively associated with fractional shortening [12]. Lubos *et al.* report that higher mean concentrations of TIMP-1 predispose patients with suspected coronary artery disease to a higher chance of MACEs, which is age- and sex-independent [13]. Kelly *et al.* have shown that plasma TIMP-1 levels positively associate with the occurrence of MACEs in patients presenting with acute MI [14]. TIMP-1 concentrations increase with quartiles of Global Registry of Acute Coronary Events (GRACE) score, and combination of TIMP-1 with GRACE score displays a greater area under the receiver operator characteristic curve [14]. This indicates that TIMP-1 offers information in addition to GRACE score systems to assess prognosis.

MMP-9, one of the most studied MMPs, is involved in cardiac aging and multiple cardiovascular diseases such as MI, atherosclerosis, and hypertension [1,15]. During cardiac aging, circulating and cardiac MMP-9 increase, and MMP-9 deletion abolishes age-induced diastolic dysfunction, which may be mediated by facilitating anti-inflammatory M2 macrophage polarization and inhibiting collagen deposition [15,16]. MMP-9 expression substantially increases post-MI, and MMP-9 deletion attenuates cardiac dilation and dysfunction in both young (8–10 weeks) and aged (11–36 months) mice, indicating detrimental roles of MMP-9 [17,18]. The potential mechanisms are strongly associated with promoting M2 macrophage polarization and suppressing inflammation [18]. However,

transgenic overexpression of MMP-9 in macrophages also shows beneficial impact on post-MI cardiac remodeling and function, signifying biphasic functions of MMP-9 [19]. Therefore, in the MI setting, MMP-9 may exert different roles depending on its cellular source and spatiotemporal expression. In atherosclerosis, MMP-9 mainly derives from macrophage-derived foam cells, smooth muscle cells, and endothelial cells, and positively correlates with increased plaque vulnerability and cardiovascular mortality [20]. MMP-9 activity is induced at a very early stage of hypertension development, promoting collagen breakdown and arterial destruction. Hypertensive patients have higher serum levels of MMP-9, which positively associates with aortic stiffness [21].

Due to critical roles MMP-9 plays in cardiovascular disease, evaluating MMP-9 as a biomarker has attracted much attention. Post-mortem examination revealed that patients with infarct rupture after MI have higher cardiac MMP-9 activity and increased inflammatory cell numbers than non-rupture patients [22]. This suggests that inflammatory cells generate MMP-9, which destructs collagen to impair infarct formation. In a clinical study of 1127 patients with coronary artery disease, median concentrations of plasma MMP-9 are significantly higher in patients who subsequently experienced a fatal cardiovascular event than in those who did not [23]. Patients with the highest quartile of MMP-9 have the highest mortality rates during the follow-up period. After adjustment for clinical and therapeutic confounders, MMP-9 levels are independently associated with high mortality [23]. Patients with acute coronary syndrome have higher levels of MMP-9 in serum (median, 4000 pg/mL) than patients with stable angina pectoris (900 pg/mL) and healthy controls (87 pg/mL), and the patients presenting acute coronary syndrome with higher MMP-9 levels have poor outcomes (recurrent ischemic attacks, congestive heart failure, or death) [24]. An MMP-9 cutoff value of 3100 pg/mL has been proposed to distinguish MI from unstable angina, while the best prognostic utility is set at 4700 pg/mL, indicating high potential for MMP-9 as a diagnosis and prognosis marker. Of interest, the current study by Wang *et al.* did not find a correlation between plasma MMP-9 concentrations and future cardiovascular events in the patient cohort examined [3]. This discrepancy could be partially explained by differences in patient inclusion criteria, patient race, and other confounding factors. For example, the study by Blankenberg *et al.* enrolled German patients with a stenosis of >30%, while the study by Wang *et al.* enrolled Chinese patients with a stenosis of 20%–70% in a major coronary artery [3,23]. Further investigation to determine why these different cohorts relied differently on MMP-9 could shed further mechanistic insight into its roles in cardiovascular disease. A proteomics approach would be ideal for this investigation.

This study has several minor limitations that should be taken into consideration. First, TIMP-1 and MMP-9 levels were measured at one time point only; this time point was right after diagnosis. Multiple time point measurements during the follow-up period would be better to understand the correlation between TIMP-1 and MMP-9 with MACEs in patients at specific times along the pathology continuum. Second, large-scale multicenter clinical trials are warranted to validate the findings in larger populations and to better understand if different populations use TIMP-1 and MMP-9 differently.

In conclusion, the manuscript by Wang *et al.* demonstrated that TIMP-1, but not MMP-9, can serve as an independent biomarker to predict MACEs in Chinese patients with mild to moderate coronary artery stenosis [3].

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