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Vascular matrix metalloprotease inhibition, a new mechanism for how PPAR γ protects target organ damage

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Of the cardiovascular complications attributable to hypertension, vascular remodeling is believed to be a crucial precursor for hypertension-associated end-organ damage. Alterations in the arterial wall include enhanced arterial wall thickness and stiffening associated with collagen deposition, endothelial dysfunction, and perivascular/adventitial fibrosis and inflammation, ultimately contributing to elevations in blood pressure and exacerbation of cardiovascular complications such as those in heart and kidney¹. Among the key contributors to vascular remodeling, the roles of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) in extracellular matrix (ECM) homeostasis appear essential. It has been recognized that during the development of hypertension, environment in the vessel wall and cell types favor excessive activity of MMPs with commensurate up-regulation of TIMPs leading to an altered balance between MMPs and TIMPs. Specifically, enhanced degradation of ECM enables vascular smooth muscle cells to migrate and proliferate, and inflammatory cells to infiltrate the arterial wall during the remodeling process². Alternatively if TIMPs override MMPs, a depressed degradation of collagen type I may facilitate aortic stiffness and organ fibrosis in hypertension². Indeed MMP9 knockout enhances vascular collagen accumulation, hypertension and pulse pressure³, whereas TIMP-3 knockout attenuates, hypertension, vascular hypertrophy and fibrosis upon AngII infusion⁴. Thus translational approaches to target either TIMPs or MMPs could lead to beneficial outcomes in hypertensive patients.

In this issue of Hypertension, Katsawatsomkron et al⁵ highlight a novel pathway involving TIMP-4 by which pathophysiological vascular remodeling is exacerbated in a mouse model of DOCA-Salt-induced hypertension. They observed that transgenic mice carrying a dominant-negative mutation of PPAR γ (P467L) under control of the smooth muscle myosin heavy chain promoter leads to enhanced hypertension and vascular remodeling compared to control mice. This transgenic mouse has been utilized to demonstrate the cell type-specific protective role of vascular smooth muscle PPAR γ activation in several models of cardiovascular disease⁶. While the observed phenotypic alterations in mice were in line with previous literature, the authors further identified that TIMP-4 is a missing target of vascular smooth muscle PPAR γ which appears responsible for its vascular protection. Intriguingly, the authors noticed mice harboring the P467L mutation show diminished

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TIMP-4 expression when paneling TIMP-1 to TIMP-4 in the vasculature. This diminished TIMP-4 expression was inversely correlated with induction of MMP-9, but not MMP-2. Further analysis identified a PPAR γ response element in close proximity to the TIMP-4 promoter. This is a novel and relevant finding as PPAR γ has not been previously attributed with directing TIMP expression. In vitro analysis showed that TIMP-4 overexpression decreased vascular smooth muscle cell (VSMC) migration, whereas PPAR γ P467L mutant overexpression resulted in increased migration of VSMCs. Thus, it is plausible to reason that smooth muscle PPAR γ induced TIMP-4 is an endogenous protective mechanism that suppresses VSMC migration⁵. This role for TIMP-4 is supported with a previous report in which overexpression of TIMP-4 in rat VSMCs resulted in decreased migration. Additionally, increased expression of TIMP-4 was noted in the carotid arteries of rats subjected to balloon injury⁷. Similarly, Ciglitazone, a PPAR γ agonist, elicited elevations in TIMP-4 and reductions in MMP-2 and MMP-9 in glomeruli and ameliorated diabetic nephropathy in mice receiving alloxan⁸. These findings thus contrast against the above-mentioned protective balance (MMPs>TIMPs) in hypertension^{3,4}, which may be too simplistic to understand the complex regulations in TIMPs and MMPs in contributing to hypertension and its complication.

TIMPs bind to and inhibit activities of MMPs, ADAM (a disintegrin and metalloproteinase) and the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motif)⁹. The interesting question to this study is which protease(s) is/are the target(s) of TIMP-4 and critical for hypertensive vascular remodeling. Although an inverse relationship between TIMP-4 and MMP-9 expression has been noted, MMP-9 may not be the responsible target of TIMP4 according to a previous report³. The known high affinity (K_i or $IC_{50} < 5$ nM) TIMP4 targets include MMP-1, MMP-2, MMP-3, MMP-14 (aka, MT1-MMP) and MMP-26¹⁰. Of the MMPs discussed, decreased MMP-1 and MMP-2 activity was reported in mammary arteries obtained from hypertensive patients². However, it is also important to appreciate the TIMP functions via protein-protein interactions independently from MMP inhibition⁹.

As noted, the contribution of vascular smooth muscle PPAR γ in hypertension has been explored previously. Using the same gene-engineered mice, vascular smooth muscle P467L mutation is reported to enhance angiotensin type 1 receptor-mediated extracellular signal-regulated kinase-1/2 activation⁶, which is a well-studied signaling mechanism associated with vascular alteration¹¹. It is intriguing that the inhibition of vascular PPAR γ is a common contributing factor to both angiotensin II/angiotensin type 1 receptor and aldosterone/mineralocorticoid receptor-dependent hypertension, which leads to speculation that TIMP-4 might have a conserved counter-regulatory role against these two types of receptors in hypertension (Figure 1). However, systemic TIMP-4 deletion in mice does not alter angiotensin II-induced hypertension⁴, which could be due to a compensation by other TIMP(s) as the authors speculated⁵.

TIMP-4 has been the least studied of TIMPs¹⁰. Separate from vascular examination, limited information is available. TIMP-4 is an important component to cardiac homeostasis as absence of TIMP-4 compromises recovery from myocardial ischemia/reperfusion injury through increased inflammation, fibrosis, hypertrophy, and oxidative stress. TIMP-4

knockout hearts show significant increases in pro and cleaved MMP-2 mRNA in response to ischemia/reperfusion, whereas MMP-9 elevation in mRNA is not significant¹², suggesting that TIMP-4 downstream signaling is tissue specific.

Ultimately, further emphasis needs to be placed on discerning the direct role of TIMP-4 induced by PPAR γ in vascular protection against hypertension. One such way is through the use of TIMP-4 knockout mice, or ideally vascular specific TIMP-4 knockout mice in order to observe if a similar phenotype is created as seen in the study. Furthermore, direct target(s) of TIMP-4 should be elucidated in order to provide a clue for translational approaches for treating hypertension and the associated vascular complications.

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Figure 1.

Schematic diagram of PPAR γ -mediated TIMP-4 induction in VSMCs potentially protecting hypertensive vascular remodeling and end-organ damage induced by the renin angiotensin aldosterone system. Since aldosterone is able to enhance TIMP-4 expression in VSMCs, this cascade seems to be a critical negative-feed back mechanism against hypertension complication accelerated by aldosterone and angiotensin II. Bold fonts indicate the findings from the manuscript. MR indicates mineralocorticoid receptor; AT1, angiotensin II type-1 receptor; ERK1/2, extracellular signal-regulated kinase-1/2.