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COMMENTARY

Matrix metalloproteinases and the vascular smooth muscle cell migration in hypertension

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ABSTRACT

Vascular smooth muscle cells (VSMC) migration and proliferation may be the main precursors of the chronic and maladaptive vascular remodeling in hypertension. The proteolysis of extracellular matrix and the phenotype switch of VSMC need to occur in order to allow VSMC migration and the vascular remodeling and hypertrophy. The matrix metalloproteinases (MMPs) are well known to degrade many extracellular matrix and non-extracellular matrix components to favor VSMC migration and their phenotype switch. Targeting MMPs may reduce VSMC migration and the arterial maladaptation caused by hypertension and its cardiovascular events.

Keywords: *Matrix metalloproteinases, vascular smooth muscle cells, hypertension, MMP, VSMC, hypertrophy*

Introduction

Hypertension is characterized by a sustained elevation of arterial pressure[1] which causes mechanical stress within the arterial wall and leads to vascular remodeling.[2] The underlying pathological processes in vascular remodeling are associated with migration and proliferation of vascular smooth muscle cells (VSMC), which are located in the tunica media of arteries.[3] Persistent and severe stretching of the vessel wall caused by hypertension may also result in VSMC hypertrophy, which preferentially occurs in the large conduit arteries, such as aorta.[2, 4] Hypertension-induced hypertrophic remodeling is usually observed as increased arterial wall thickness, cross-sectional area and media to lumen ratio[5, 6] and may be the result of extracellular matrix (ECM) proteolysis and the phenotype switch of contractile to synthetic VSMC.[3] The matrix metalloproteinases (MMPs), a family of zinc-dependent proteases, have been implicated in the chronic vascular remodeling of hypertension due to their proteolytic effects on ECM and non-ECM components, which may contribute to the capacity of VSMC to migrate and proliferate.[7-9]

Role of MMPs in maladaptive vascular remodeling in hypertension

Increased activity of MMPs is generally observed in animal models of hypertension and contributes to excessive ECM proteolysis, VSMC reorganization and hypertrophy.[10, 11] Among many MMPs, the gelatinases (MMP-2 and MMP-9) and MMP-14 were associated with increased arterial media and intima thicknesses of hypertensive animals.[10, 11] Our group showed that treating two-kidney one-clip (2K-1C) hypertensive rats with doxycycline, an MMP inhibitor, inhibited MMP-2-induced chronic maladaptive vascular remodeling by reducing the deposition of elastin and collagen in aortas and the VSMC hyperplasia.[10]

MMPs contribute to VSMC migration: ECM proteolysis and VSMC phenotype switch

The VSMC are the main constituents of the tunica media of the vessels wall and significantly contribute to maintain their scaffold and tone. In the presence of mechanical force or stress and bioactive peptides[3, 12] the VSMC may switch from contractile (differentiated) to synthetic (dedifferentiated) phenotype which migrate, proliferate and produce new ECM, thus contributing to hypertension and its chronic vascular remodeling. In fact, VSMC exposed to cyclic stretch *in vitro* displayed more elongated morphology and a significant proliferation capacity.

For VSMC migration and proliferation, breakdown of their ECM and basement membrane is necessary, which is followed by the switch of VSMC from contractile to synthetic phenotype. MMPs degrade type IV collagen in the basement membrane of VSMC and many ECM and non-ECM components, thus allowing cell migration and ECM re-synthesize.[13] In fact, cultured VSMC transfected with small inhibitory MMP-2 RNA or incubated with a MMP-2 antibody inhibited VSMC migration and their capacity to invade a Matrigel barrier *in vitro*.[14, 15] MMPs may also contribute to VSMC migration by degrading type I collagen as the platelet derived growth factor-mediated VSMC migration in the presence of type I collagen cleavage products and αvβ3 integrins, but not

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in the presence of the native collagen.[16] MMP-2 may also activate transforming growth factor-β that is involved in the phenotype switch of VSMC and the vascular rigidity.[17] Furthermore, in the synthetic phenotype of VSMC, some cytoskeleton and contractile proteins are down-regulated.[3, 18]

Deoxycorticosterone acetate (DOCA) salt rats showed reduced calponin levels in femoral arteries and VSMC proliferation. This event is controlled by many transcriptional regulatory pathways, such as the serum response factor and its cofactor myocardin.[18] DOCA salt rats also showed reduced levels of myocardin throughout the media of femoral arteries and isolated VSMC.[18] MMP-2 may be more abundant in the synthetic than contractile VSMC.[19] Increased MMP activity is associated with reduced cytoskeleton proteins, which resulted in VSMC migration and vascular remodeling of human saphenous vein submitted to an injury by a surgery procedure.[20]

Concluding remarks

Increased MMPs activity induces ECM proteolysis and VSMC phenotype switch and migration, which contribute to the maladaptive vascular remodeling of hypertension. Understanding the mechanisms that underlie the VSMC phenotype switch and migration may contribute to find new strategies to treat hypertension and other cardiovascular diseases. Targeting MMPs may reduce VSMC migration and the arterial maladaptation caused by hypertension and its fatal cardiovascular events.

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