The Tortuous Ways of the Vascular Wall

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The concept that blood pressure influences vessel wall composition and structure is well established. Any alterations in stretch (caused by changes in blood pressure) solicit counteracting radial and tangential forces, driving transformations in the vessel wall that aim to accommodate the new conditions and to ultimately restore basal levels of tensile stress. Thus, when tensile stress increases because of a rise in arterial pressure, smooth muscle cell hypertrophy and collagen and elastin contents augment. Inversely, when the circumferential stress falls, the wall undergoes atrophy.

Understanding how vessel wall remodeling occurs is valuable because it relies on the delicate balance between reorganization and overcompensation. For instance, vascular accumulation of type I, III, and IV collagen in hypertensive patients and in animal models of hypertension effectively counteracts the distending force of blood pressure, but at length it also results in increased vascular stiffness. Clinically, vascular stiffness translates to greater pulse wave velocity, which is an independent predictor of mortality in patients with end-stage renal failure, hypertension, and diabetes, as well as in older individuals. In this issue of *Atherosclerosis, Thrombosis and Vascular Biology*, Jackson et al show that the opposite holds true for vessels in which arterial pressure-induced MMP-9 in isolated carotid arteries contributes to increased vessel distensibility points to a role for matrix degrading enzymes in the early stages of hypertensive vascular remodeling. These data concur with observations made in vivo in a model of arterial longitudinal stretch. Before studying tension off-loading, Jackson et al found that increased axial strain in rabbit carotid arteries caused an increase in the area of fenestrae in the internal elastic lamina, leading to vessel stretch, concurrent with a transient rise in MMP-2 and MMP-9 activity. And indeed, cultured VSMCs under sustained strain display increased levels of MMP-2 and MMP-9. MMP activation and enhanced distensibility may thus be hallmarks of early hypertensive remodeling, allowing the vessel to expand to accommodate the new pressure setting.

Strangely enough, MMP-2 and MMP-9 levels correlate with aortic and brachial pulse wave velocity in patients with isolated systolic hypertension, and even in healthy normotensive subjects serum elastase activity and MMP-9 are independent predictors of arterial stiffness. One way of explaining this paradox is that reduced tensile stress caused by MMP activity, particularly in the presence of concomitant hypertension, stimulates VSMCs to produce ECM. Certainly, collagen and elastin synthesis is enhanced in hypertensive subjects and proceeds as long as blood pressure is elevated. Furthermore, tensile strain probably contributes to this effect, because extracellular matrix synthesis is stimulated in vessels exposed to cyclic stretch. In all probability, excessive upregulation of ECM proteins contributes to rigidification of the vessel wall typical of hypertension.

Insofar as high blood pressure drives early vessel expansion through MMP activation, it turns out that many of the same processes regulate the response to reduced axial strain. MMP-2 is activated in cultured whole vessels in which intraluminal pressure is maintained at 10 mm Hg compared with 80 mm Hg. Similarly, cufing rabbit carotid arteries such that circumferential wall tension is off-loaded results in artery remodeling including apoptosis, wall atrophy, and increased activity of MMP-2 and MMP-9, much like what wall, excess of these enzymes prevents proper vessel reorganization.

The balance between matrix synthesis and degradation after changes in mechanical strain is complex. In young humans with mild to moderate hypertension, increased collagen deposition is actually associated with reduced vessel stiffness. This was hypothesized to reflect a pressure-dependent fibrillar collagen recruitment or changes in vascular smooth muscle cell (VSMC)-matrix anchoring as hypertension progresses. But a recent demonstration that high intraluminal pressure-induced MMP-9 in isolated carotid arteries contributes to increased vessel distensibility points to a role for matrix degrading enzymes in the early stages of hypertensive vascular remodeling. These data concur with observations made in vivo in a model of arterial longitudinal stretch. Before studying tension off-loading, Jackson et al found that increased axial strain in rabbit carotid arteries caused an increase in the area of fenestrae in the internal elastic lamina, leading to vessel stretch, concurrent with a transient rise in MMP-2 and MMP-9 activity. And indeed, cultured VSMCs under sustained strain display increased levels of MMP-2 and MMP-9. MMP activation and enhanced distensibility may thus be hallmarks of early hypertensive remodeling, allowing the vessel to expand to accommodate the new pressure setting.
occurs in arteries elongated with an interpositional graft.\textsuperscript{10} Hence, a plausible explanation for irreversible tortuosity in off-loaded arteries would be that MMPs over-degrade the ECM, making it impossible for vessel structure to recover despite concomitant ECM synthesis. Indeed, MMP inhibition restores axial strain in these vessels.\textsuperscript{10} But intriguingly, the pattern of vascular cell apoptosis, MMP activation, DNA, elastin and collagen synthesis, and internal elastic lamina fenestration is virtually identical between off-loaded arteries presented by Jackson et al\textsuperscript{10} and stretched arteries that do recover normal strain.\textsuperscript{13} So other differences in conditions between overstretched and understretched arteries dictate whether or not axial strain will return to normal levels (Figure). Maintained tortuosity in unloaded vessels could relate to a loss of VSMC contractile phenotype caused by absence of mechanical stimulation. In arteries cultured at low intraluminal pressure, a condition of low axial strain, the content of smooth muscle marker proteins h-caldesmon and filamin decreases over three to six days, whereas loss of these proteins is prevented in vessel segments kept at physiological intraluminal pressure.\textsuperscript{21} Production of MMPs by VSMCs may actually contribute to their phenotypic modulation to a synthetic state.\textsuperscript{22,23} Alternatively, differential activation kinetics of MMP-2 and MMP-9 could influence ECM remodeling; MMP-2 activity appears to increase with time in unloaded arteries\textsuperscript{10} but not in strained arteries.\textsuperscript{13} On the other hand, MMP-9 alone can regulate collagen organization by VSMCs.\textsuperscript{24} Ultimately, MMP activation in the context of tensile strain unloading engages a series of events that impede vascular recovery.

In humans, two conditions that are characterized by vessel tortuosity and dilatation are varicose veins and arterial tortuosity syndrome. Defining a role for MMPs in the development of varicose veins is complicated by conflicting reports. One study showed that the balance between TIMPs and MMPs actually favored the former in varicose veins compared with normal vessels, varicose veins showing higher TIMP-1 and lower MMP-2 levels.\textsuperscript{22} In other studies, expression levels of MMP-1, MMP-2, MMP-9, MMP-12, TIMP-1, and TIMP-2 were found to be equivalent between normal and varicose veins, but tissue distribution of MMP-1 and MMP-9 differed between the two groups and varicose veins displayed fragmentation of elastic laminae.\textsuperscript{26,27} Still others showed increased MMP-2 activity in varicose veins.\textsuperscript{28} Finally, there is evidence that VSMCs derived from varicose veins produce more collagen I but less collagen III,\textsuperscript{29} and elastin content is reduced in varicose veins.\textsuperscript{30} Either way, it is most likely that imbalance between ECM protein synthesis and degradation contributes to the progression of this disease.

Fragmentation of the internal elastic lamina and elastic fibers of the tunica medial of large arteries is a hallmark of arterial tortuosity syndrome, a rare autosomal recessive disease characterized by generalized tortuosity and elongation of all major arteries.\textsuperscript{31} However, this syndrome is not associated with abnormalities in elastin gene, nor of fibronectin-1 or collagen type I, II, III, V, or VI for that matter,\textsuperscript{32} but maps to chromosome 20q13.\textsuperscript{33} Amazingly, the role for MMP-9, which lies in the 20q13 region, has not yet been evaluated in this syndrome. Although elastin content is preserved, disruption of the architecture could be key in inducing such potent vascular structural changes. Case in point, mice deficient in Fibulin-5, a key elastin-binding protein, show fragmented and disorganized elastin fibers and tortuosity and elongation of the aorta.\textsuperscript{34,35}

In summary, it is clear that maintaining the equilibrium between matrix protein synthesis (making up the vessel wall) and organization and MMP activity (breaking up the vessel wall) is crucial to preserving normal vessel structure and function. In the course of development and throughout adulthood, changes in tensile strain can tip the balance to one side or another, but this only becomes problematic in the case of aberrant accumulation or degradation of the ECM. Mice deficient for MMPs or ECM components will certainly prove to be useful tools to uncover the specific roles of these enzymes and proteins in responding to and shaping the mechanical environment of blood vessels.

References

5. Leung DY, Glagov S, Mathews MB. Elastin and collagen accumulation in rabbit ascending aorta and pulmonary trunk during postnatal growth:
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