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Mini-Review

Atheromas Feel the Pressure

Biomechanical Stress and Atherosclerosis

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Atherosclerosis, a chronic vascular disease, is the underlying cause of over half the deaths in the United States each year. Variations in local vascular hemodynamics predispose select sites in the vasculature to atherosclerosis, and the atherosclerotic lesions, in turn alter the biomechanical functioning of the local microenvironment, the consequences of which are not well understood on a molecular level. Further progress in the field of atherosclerosis will require an understanding of the relationship between biomechanics, the tissue microenvironment, and the cellular and molecular response to these factors. This review summarizes this field, particularly within the context of the vascular smooth muscle cell. ***(Am J Pathol 2010, 177:4–9; DOI: 10.2353/ajpath.2010.090615)***

Biomechanics play a vital role in vascular biology, affecting the cells of arteries and veins under both physiological and pathological conditions. While many studies have shown that the development of atherosclerosis is particularly associated with specific alterations of biomechanical forces, the effect of biomechanics on an established atheroma is less well studied. This minireview aims to describe the role of biomechanics in the vasculature, particularly in vascular smooth muscle cells (VSMCs) of large arteries, in normal and atherosclerotic conditions.

Two of the primary mechanical stimuli experienced by normal large arteries are shear stress and cyclic strain.[1] By contrast, veins experience only very low levels of either.[2] Shear stress is experienced by the endothelium as blood flows through the lumen. While endothelial cells are the primary sensors of shear stress, some stress may be relayed to the VSMCs by transmural transmission through the extracellular matrix (ECM).[3] Unlike shear stress, cyclic strain affects both endothelial cells and VSMCs, as well as, though to a lesser degree, adventitial fibroblasts.[4] The effects of cyclic strain on VSMCs have been the subject of much study in the recent decades, and many methods have been developed for exposing cells and tissues to cyclic strain both *in vitro* and *ex vivo* (an in depth discussion of the topic can be found in a review by Brown).[5] While cyclic strain is a major determinant of normal VSMC physiology, it also plays a pivotal role in various pathologies, including hypertension, vein-graft intimal hyperplasia and failure, restenosis, and atherosclerosis.[6]

VSMCs and Atherosclerosis

Atherosclerosis, the underlying cause of most myocardial infarctions and strokes, is ultimately responsible for up to 50% of all deaths in the United States.[7] In light of this, it is of great importance to understand atherosclerosis to improve detection and treatment of the disease. There are multiple factors affecting initiation and progression of the atherosclerotic lesion. Much of the existing research in the field has focused on the role of lipids and inflammation in atherosclerosis. Less well understood is the role of biomechanical forces, particularly in VSMCs. The underlying principles regarding the effect of biomechanics on atherosclerosis are emerging and these are briefly reviewed here.

Atherosclerosis occurs in large and medium-sized arteries and develops over time, starting with fatty streaks, progressing to intermediate lesions, and eventually proceeding to advanced and complicated lesions at risk of rupture (Figure 1).[8–10] VSMC accumulation is a hallmark

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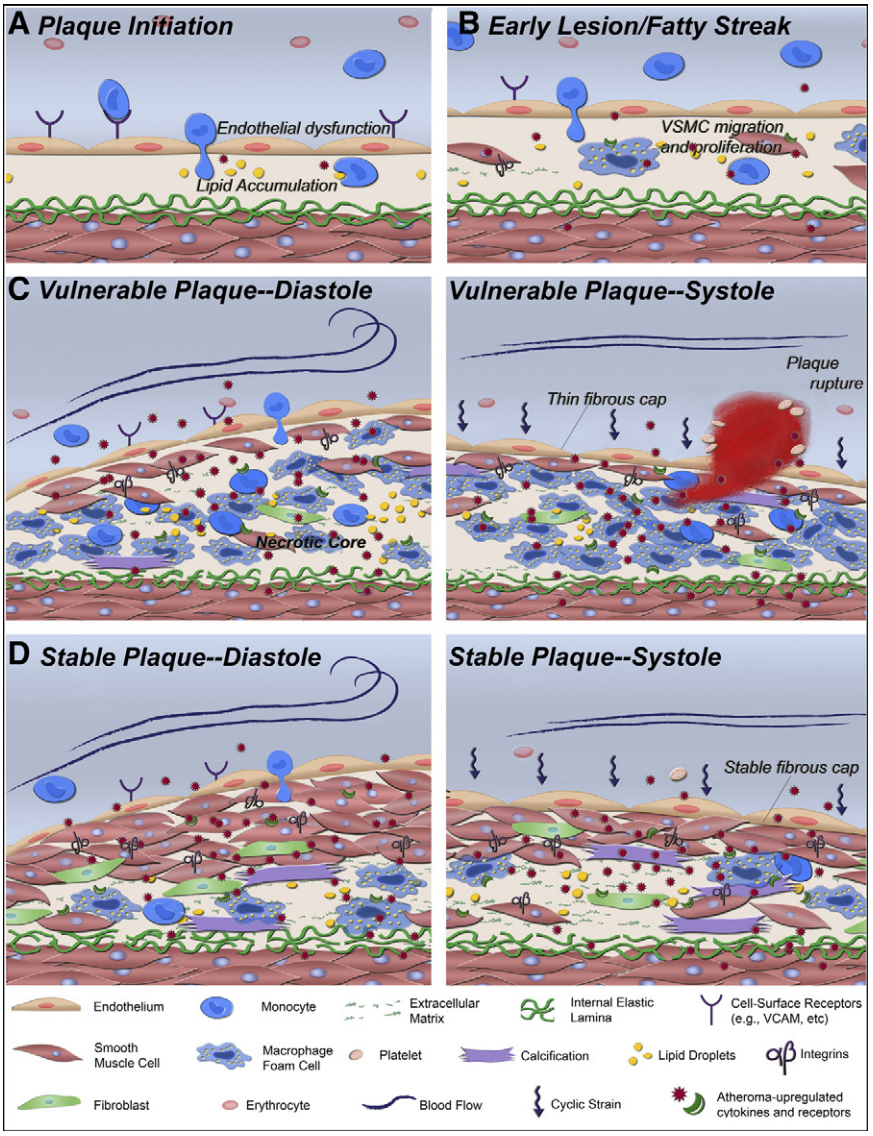

Figure 1. Atherosclerotic progression is a complex process involving many cell types and the ECM. The normal human arterial intima is comprised of the endothelium, ECM (primarily collagens and elastin), and occasional VSMCs. The earliest events in atheroma formation are endothelial dysfunction and lipid accumulation in the arterial intima leading to macrophage infiltration and foam cell formation (**A**). Hallmarks of early lesions include migratory and proliferative VSMCs, as well (eg, integrins) as an up-regulation of cytokines and receptors that are unique to the atheroma microenvironment (**B**). The lesion progresses to a true atheroma and foam cells accumulate as VSMCs continue to proliferate and migrate, thereby increasing plaque size. Furthermore, VSMCs secrete collagen to generate a fibrous cap over the plaque (**C**, **D**). In advancing atherosclerosis, expansion of the plaque into the vessel lumen disrupts laminar blood flow. If the plaque is relatively VSMC-poor (due to apoptosis), especially with a lipid-rich necrotic core and thin fibrous cap, the plaque is vulnerable to fissure and rupture (**C**). Advanced plaques are subject to the dynamics of blood flow, from both shear and cyclic forces; as such plaques can compress during systole (**C**, **D**). However, if VSMCs are abundant within the lesion and actively secrete ECM to generate a thick fibrous cap, then the plaque will remain relatively stable, even in systole, and is unlikely to cause a clinically-recognizable event (**D**).

of moderate to advanced atheromas. Within the plaque, VSMCs act in diverse manners, primarily by modulating proliferation, inflammation, ECM modulation, and contraction.[11] VSMC proliferation and hyperplasia within the plaque is largely mediated by platelet-derived growth factor and transforming growth factor β, which are both sensed and synthesized by the VSMCs.[11] Early in plaque development, VSMCs secrete inflammatory mediators, such as monocyte chemoattractant protein 1, interleukins, and tumor necrosis factor-α.[11] These, along with surface expression of adhesion molecules such as intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, promote macrophage infiltration and accumulation.[11] It has been shown that VSMCs within an atherosclerotic plaque undergo phenotypic switching, moving from a more contractile to synthetic state.[12] As such, VSMCs along with other local cells, such as macrophage foam cells, modify the local atherosclerotic milieu by synthesizing ECM molecules, primarily collagens I and III as well as matrix metalloproteinases, which degrade and remodel the ECM. This remodeling is critical in determining the stability of the plaque. Indeed, increased MMP activity is thought to undermine plaque stability, thereby increasing the risk of rupture.[13] Although they are in a primarily synthetic state, VSMCs within atheromas are still capable of responding to contractile stimuli, such as endothelin-1 and angiotensin II, which are present in the atherosclerotic plaque.[14,15] Thus, the VSMC plays a vital role in atherosclerosis development and progression. Gaining further insight into these cells, particularly as they respond to a lesser-studied stimulant, biomechanical stress, will aid our understanding of atherosclerosis.

Altered Biomechanics and Atherosclerosis

It has long been known that biomechanical forces promote atherogenesis, specifically at curves, branch points, and bifurcations.[16] Thus, atheromas most often arise in the branching coronary and carotid arteries, in the abdominal aorta at the branches for the abdominal

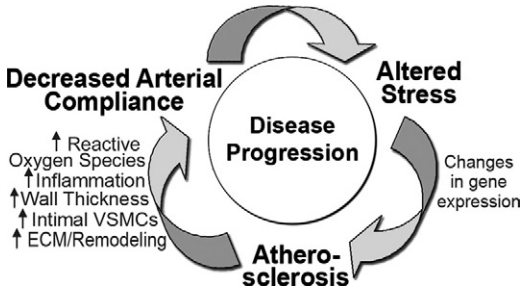

Figure 2. Biomechanic and atherosclerosis: A vicious cycle. Altered shear stress at branch point and curves is a well-known initiating step in atherosclerosis. The atherosclerotic plaque, in turn, promotes increased arterial compliance and distensibility as lipid, cells, and ECM accumulate in the vessel wall. As the vessel wall stiffens, it alters blood flow and changes the local hemodynamics. Altered stress then further promotes atherosclerosis through mechanosensing, resulting in changes in gene expression, thereby promoting increased plaque development.

arteries, and around the iliac bifurcation.[17] Endothelial dysfunction occurs at regions where the blood flow is significantly disrupted and low; turbulent shear stress alters cellular behavior. Aspects of this state include a generalized inflammatory state of endothelial cells, which gives rise to generation of reactive oxygen species, altered surface markers, and increased lipid clearance into the intima.[18] Furthermore, though it is less-well understood, the cyclic strain at these points is also significantly affected, with the direction and magnitude of stretch being different from areas of the arteries that are not atheroma-prone. Hence, these altered biomechanics that impact plaque initiation also impact VSMCs within an established plaque.[19]

An established atherosclerotic plaque itself is subject to alterations in biomechanical stress and such vessels experience distinct stresses as compared with those felt by healthy vessels. The most important cyclic strain is typically circumferential in the normal artery, but the cyclic strain field in a plaque is much more complex, involving extensional and shearing strains. Plaque compression during the high-pressure systolic phase of the cardiac cycle and rebound during diastole can now be directly assessed *in vivo*. The volume compression ratio (plaque volume at diastole minus plaque volume at systole divided by volume at diastole) demonstrates, in real-time, the dynamic and elastic nature of the atherosclerotic plaque, and has been proposed as a means for assessing risk of plaque rupture.[20,21]

Furthermore, studies have shown that biomechanical stress caused by altered flow not only leads to atherosclerosis, but atherosclerosis itself alters local biomechanics (Figure 2).[19,22–24] Recently, sensitive technological innovations have become available, such as intravascular ultrasound, which revealed that even early atherosclerotic lesions significantly affect vessel compliance.[19,22,23] One study has shown decreased arterial distensibility not only at the site of atherosclerosis, but also in proximal normal tissue, though not in distant normal artery.[24]

On the cellular level, there are many factors in the development of atherosclerosis that can affect vessel stiffness. For example, as the disease progresses, VSMC proliferation and inflammatory infiltrates (macrophages and lymphocytes) alter local cellular density. ECM synthesis and remodeling further promote local stiffening. Excess free cholesterol in the plaque can also be taken up into the plasma membranes of the resident cells, which may further alter membrane fluidity of the individual cells.[25] Then, as the plaque progresses, interior necrosis and calcifications further decrease vessel compliance.[11]

Furthermore, generation of a fibrous cap plays an important role both in vessel stiffening and in plaque stability. The fibrous cap is a structure made up of VSMCs and collagen, which separates the lumen from the atheroma and stabilizes the plaque against rupture.[26] A stable plaque is defined by a thick fibrous cap with extensive VSMC content, few macrophages, and a minimal necrotic core. On the other hand, an unstable, rupture-prone, or "vulnerable" plaque is defined by a thin fibrous cap, profound macrophage infiltration, low VSMC content, and a large lipid- and calcium-filled necrotic core.[27] In the absence of a thick, stiff, protective top layer, the unstable plaque is prone to fracturing under the continuous shear and cyclic stresses.[27]

Decreased compliance in a diseased artery leads to disturbed wall motion and shear stress patterns as well as increasing turbulence, thereby further promoting plaque development (Figure 2).[28] These changes in vessel compliance necessarily have an effect on the cells resident in the vessel, such as VSMCs. However, little is understood about the resulting molecular changes of VSMCs as they adapt to plaque biomechanics and their impact on plaque stability.

These changes in plaque stiffness are critical determinants in the propensity for plaque rupture. Moreover, the composition of each of the plaque constituents (eg, fibrous cap, necrotic core, etc) affects the overall plaque stability. For example, studies of the plaque fibrous cap have shown that VSMC-rich caps are 4 to 5 times stiffer than calcified caps, and 1 to 2 times stiffer than hypocellular caps.[29] Moreover, it has been shown that the plaque shoulders are stiffer, and therefore subject to greater stress concentration, than the rest of the plaque. Consistent with this is the finding that the majority (63% in one study of persons who died from coronary thrombosis) of ruptured plaques fissure at the shoulder.[30]

Thus, biomechanical alterations in the vasculature, predominantly in and around atherosclerotic plaques, are of significant biological and clinical interest. Of particular interest is how VSMCs, specifically those within the atherosclerotic microenvironment, sense and adapt to mechanical stress by altering gene regulation and cellular behavior in a way that could alter the plaque structure and stability. Therefore, the remainder of this document will focus on the mechanisms by which VSMCs sense stress and respond to it.

Cellular Changes Resulting from Biomechanical Stress

Many proteins have been implicated in mechanosensing by VSMCs, including the membrane oxidase NADH/NADPH, stretch-activated ion channels, receptor tyrosine

kinases, G-protein coupled receptors, integrins, and others.[31–33] However, within the context of vascular pathologies such as hypertension and atherosclerosis, certain mechanosensors are differentially regulated. For example, the angiotensin type I receptor, which has been shown to be a mechanosensor in VSMCs, is up-regulated in atherosclerosis.[34] Furthermore, spontaneously hypertensive rats were shown to have more sensitive stretch-activated ion channels, compared with Wistar-Kyoto rats.[35] Additionally, it has been shown that expression of integrin $\alpha_1\beta_1$ on VSMCs is limited to atheromas.[31]

In the context of the atherosclerotic plaque, VSMCs are surrounded by ECM, primarily type I collagen, and to a lesser extent elastin, vitronectin, and fibronectin.[8] Cells can relate to and sense this environment through integrin-ECM interactions, thus making this interface an important focus of study.[6] Hence the atheroma microenvironment generates a unique VSMC cellular phenotype (Figure 1). Importantly, extracellular stress and tension can be transmitted through the ECM via integrins to promote intracellular signaling events and alter gene regulation.

Similarly, the forces perceived are transferred to the VSMC cytoskeleton in ways that can influence VSMC biology. Transmission of these forces, particularly cyclic strain, in the context of the local environment produces a distinct set of responses in VSMCs, including altered cytoskeletal arrangement,[36,37] changes in VSMC proliferation,[38,39] apoptosis,[2,40–42] and phenotype[43,44]; most of these responses are determined by altered gene expression. VSMCs modulate an array of genes in atherosclerosis, but only in the presence of the unique plaque microenvironment. For example, our lab and others have demonstrated expression of the type I collagen binding integrin $\alpha_1\beta_1$ by VSMCs within atheromas, and rarely by VSMCs of normal vasculature.[31,45] This is the result of the influence of the atheroma microenvironment, which is rich in various cytokines such as transforming growth factor β, platelet-derived growth factor, monocyte chemoattractant protein 1, and others that modulate VSMC gene expression (Figure 1).[11] The nature of this microenvironment causes biomechanical stress to differentially affect the VSMCs. For example, expression of $\alpha_1\beta_1$ integrin within VSMCs of an atheroma alters signal transduction downstream of cyclic strain and possibly other biomechanical forces as well matrix/cell interactions differentially within the cells comprising the atheroma resulting in unique gene expression.[31] This demonstrates the need to recapitulate multiple features of the *in vivo* microenvironment when studying vascular biology *in vitro*. Not only should the cellular and ECM components be consistent with the physiological context, but the mechanical strains of the system should also be accounted for when working *in vitro*.

The primary manner in which physical changes arise following biomechanical stress is through modulation of gene transcription. For example, many groups have demonstrated upregulation of a variety of genes in VSMCs in response to cyclic strain including α-actinin, extracellular matrix genes, cytoskeletal elements, integrins, monocyte chemoattractant protein 1, protease-activated receptor-1, syndecans 1, 2, and 4, and many other genes.[40,46–50] These changes in gene expression have a variety of effects on VSMCs, including changes in the cytoskeleton, apoptosis, proliferation, and phenotypic state.

In the artery wall, VSMCs are arranged in a helix around the artery and are orientated 50° to 70° relative to the axis of cyclic strain. A well-documented *in vitro* response of VSMCs to cyclic strain is the remodeling of the cytoskeleton such that the cells orient themselves perpendicular to the direction of stretch.[51,52] Furthermore, cytoskeletal proteins themselves can respond to cyclic strain. Rat aortic VSMCs exposed to acute 15% cyclic strain demonstrate translocation of zyxin from focal adhesions to the nucleus, where it affected expression of mechanosensitive genes. However, this was a transient effect; following long-term strain (6 hours), the majority of zyxin returned to the cytoplasm.[53] While not a cytoskeletal element, the transcription factor Egr-1 relocated within the cell in response to stress as well. Egr-1 was not only increased in neonatal rat VSMCs exposed to cyclic strain, but was also shown to translocate to the nucleus in response to the strain.[54]

Modulation of apoptosis and proliferation has also been shown to be regulated by mechanosensing. VSMC apoptosis has various effects on the atherosclerotic plaque, and can affect plaque stability, calcification, and inflammation.[41] Generally, cyclic strain increases VSMC apoptosis. Many groups have studied the mechanisms by which this occurs, with the goal of eventually reversing the effect, thereby promoting plaque stability.[2,52,55,56] In general, changing the rate of apoptosis of VSMCs in an atheroma could be a potential method for regulating plaque stability. VSMC proliferation is a key step in atherogenesis, and a plaque with high VSMC content is generally more stable and, therefore, less likely to initiate a clinical event. Several reports suggest that cyclic strain promotes proliferation in VSMCs, whereas other work suggests that cyclic strain inhibits VSMC proliferation.

The study of VSMCs has revealed a great deal of information into the role of biomechanical stress, particularly cyclic strain, in normal smooth muscle cell biology. It also opens a window into understanding the role of VSMCs in the pathogenesis of mechano-sensitive diseases such as atherosclerosis. These have been extensively addressed in many excellent reviews, and the reader should refer to these for more information.[33,57–59]

Perspectives

The study of the effects of biomechanics on the vasculature, particularly in cases of vascular pathology, is an area still ripe for exploration. The molecular changes arising from biomechanics on VSMCs within an established atheroma remain largely unknown, particularly as the local microenvironment of the plaque changes throughout plaque development and progression. The atherosclerotic plaque has a unique mélange of ECM, cells, cytokines and other inflammatory mediators, dead and dying cells, and lipids. So complex is this microenvironment that it cannot reasonably be recapitulated in completion *in vitro*. A better understanding of the VSMC

response to biomechanical stress within the atherosclerotic milieu may require consideration of their local context. Such insights will promote our understanding of plaque stability and rupture, and lead to the development of better detection and treatment options for atherosclerosis.

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