



Adventitial dysfunction: an evolutionary model for understanding atherosclerosis

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Summary Endothelial and smooth muscle dysfunctions are widely implicated in the pathogenesis of atherosclerosis. Modern mechanical and pharmacologic treatments aim to remodel abnormalities of the vessel intima and media. We hypothesize that adventitial dysfunction comprises the dominant source of atherosclerosis by originating many endothelial and smooth muscle abnormalities. The autonomic nervous system innervates the adventitia, and autonomic dysfunction induces many end-organ dysfunctions including inflammation and thrombosis. The link between diabetes and atherosclerosis may operate through adventitial autonomic neuropathy. Smoking may promote atherosclerosis by inducing adventitial autonomic dysfunction related to nicotine-mediated compensatory upregulation of sympathetic bias independent of endothelial injury induced by purported tobacco toxins. While hypertension is thought to cause atherosclerosis, the two conditions may instead represent independent consequences of autonomic dysfunction. The link between aging and atherosclerosis may operate through adventitial dysfunction induced by autonomic dysregulations. Exercise may ameliorate atherosclerosis by restoring adventitial autonomic function, thereby normalizing adventitial regulation of medial and intimal biology. Feed-forward adventitial vascular baroreceptor and chemoreceptor dysregulation may further exacerbate atherosclerosis as intimal plaque interferes with these sensors. Since penetrating external physical injury likely represented a dominant selective force during evolution, the adventitia may be preferentially equipped with sensors and response systems for vessel trauma. The convergent response of adrenergia, inflammation, and coagulation, which is adaptive for physical trauma, may be maladaptive today when different stressors trigger the cascade. Endoluminal therapies including atherectomy, angioplasty, and stent deployment involve balloon expansion that traumatizes all layers of the vessel wall. These interventions may paradoxically reinitiate the cascade of atherogenesis that begins with adventitial dysfunction and leads to restenosis. Methods to reduce adventitial trauma, a maladaptive trigger of adventitial dysfunction, may reduce the risk of restenosis. We envision novel mechanical and biopharmaceutical solutions that target the adventitia to prevent or treat atherosclerosis including novel drug delivery strategies, exo-stents that wrap vessels, and neuromodulation of vessels. © 2005 Elsevier Ltd. All rights reserved.

Hypothesis

Endothelial and smooth muscle dysfunction are widely implicated in the pathogenesis of

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atherosclerosis [1,2]. Modern mechanical and pharmacologic interventions aim to remodel abnormalities of the vessel intima and media to treat atherosclerosis. We hypothesize that adventitial dysfunction comprises the dominant source of atherosclerosis by originating many endothelial and smooth muscle abnormalities.

Evidence

Atherosclerosis is a major driver of cardiovascular disease in humans and occurs with greater frequency with increasing age, diabetes, smoking, and hypertension [3–6]. Theories to explain atherosclerosis initially centered on dysregulation of lipid metabolism [7–9]. Etiologic paradigms have gradually evolved to include consideration of the roles of endothelial cells, smooth muscle cells, and inflammation in pathogenesis [10–12]. Accordingly, studies have increasingly focused on dysfunctions of the intima and media to elucidate the mechanism of atherogenesis [13,14].

As with the intima [15], the adventitia has historically been seen as an inert structural element of the blood vessel, but emerging evidence indicates that its role in the regulation of vessel biology has also been underappreciated. Porcine models show that adventitial remodeling precedes remodeling of the media and intima in the setting of hypercholesterolemia and hypertension [16]. Adventitial fibroblasts are recruited by local inflammation to modulate vascular smooth muscle cells and endothelium [17], and other adventitial cells can undergo direct transformation into smooth muscle cells [18,19]. Adventitial inflammation appears to associate with more unstable plaques [20]. Adventitial injury appears to promote neointimal proliferation [17] and fibroblast migration [21], predisposing to plaque formation.

The fundamental basis of adventitial dysfunction and the consequent atherosclerotic cascade in the media and intima may result from autonomic dysfunction and sympathetic bias. The adventitia is a target for autonomic innervation [22]. The autonomic nervous system exhibits a progressive shift towards sympathetic bias in conjunction with aging [23]. Sympathetic bias appears to contribute to the gradual deterioration of many end-organ systems [24] and is associated with thrombosis and inflammation [25]. The convergence of these pathways may have emerged during prehistoric evolution when trauma was a dominant selective force and the co-regulation of adrenergia, inflammation, and thrombosis en-

abled rapid control of blood pressure, hemostasis, and microbial defense.

From a teleologic standpoint, the outer location of the adventitia may make it a suitable location for sensors and response systems for environmental stimuli such as trauma or infection. Indeed, the adventitia contains toll-like receptors that appear to induce intimal remodeling and plaque formation in response to elements such as bacterial lipopolysaccharide [26]. Baroreceptor nerve endings terminate in the vascular adventitia [27]. In modern times, when non-traumatic triggers of this cascade including chronic diseases or autonomic dysfunction have emerged, the co-regulated pathways may behave maladaptively and initiate nefarious self-propelling dysfunction.

Once adrenergia-induced inflammation and thrombosis are triggered, the cascade may self-propagate for a number of reasons. For instance, luminal compromise can induce downstream hypoxia, which is one of the triggers for adrenergia. While hypoxia-induced adrenergia is adaptive in the setting of hemorrhagic trauma or acute respiratory insult, in the setting of atherosclerosis-induced hypoxia the resulting adrenergia can further exacerbate vasoconstriction, inflammation, and thrombosis as seen in acute coronary syndromes.

Physical interposition of atherosclerotic plaques between the blood and adventitial sensors such as baroreceptors and chemoreceptors may also induce feed-forward maladaptive cycles. Empirically, atherosclerotic plaques preferentially develop at sites where vessels bifurcate [28,29]. Sensors positioned at bifurcations, such as carotid baroreceptors, function to adaptively modulate intravascular volume via control of sympathetic activity. Baroreceptors would misinterpret pressures due to dampening of measurement secondary to irregular wall thickening and plaque formation.

Chemoreceptors would misinterpret the degree of oxygenation due to alterations of pH imposed by stasis and coagulation within the vessel lumen due to non-laminar flow. In both cases, the barrier effects of the plaque leading to sensor misregistration could induce control system failure and autonomic dysfunction. Inappropriate invocation of sympathetic activity would produce vasoconstriction, inflammation, and thrombosis at these sites, leading to further vascular stasis and remodeling [25], yielding a vicious circle of pathology.

Adventitial autonomic dysfunction may represent a unifying explanatory framework for the myriad of predisposing factors associated with atherosclerosis that are currently attributed to disparate theories. Independent of causing oxidative

stress that leads to endothelial dysfunction [30], diabetes may lead to the development of atherosclerosis by inducing autonomic neuropathy through pathways such as increased sympathetic tone [31]. In like fashion, smoking may promote atherosclerosis via paradoxical upregulation of sympathetic bias as a compensatory response to intermittent nicotine use [32]. While hypertension is thought to cause atherosclerosis, the two conditions may instead represent independent consequences of autonomic dysfunction. The link between aging and atherosclerosis may operate through adventitial dysfunction induced by autonomic dysregulation. Interestingly, the accelerated atherosclerosis attributed to lipid dysfunction in HIV-infected patients may also be explained by the virus-induced systemic sympathetic bias [33]. The underlying sympathetic bias also provides an explanation for the benefits of exercise. By restoring autonomic balance in the adventitia with consequent normalization of adventitial function, exercise may mitigate atherosclerosis.

Implications

Potential implications regarding existing therapeutic modalities are apparent in light of our adventitial autonomic hypothesis. The sensitivity of adventitia to trauma may have served an adaptive function during prehistoric evolution when external physical trauma was a leading variable in natural selection. The presence of autonomic innervation in the adventitia may partially reflect this teleologic purpose. On the other hand, balloon-based endoluminal interventions such as atherectomy, angioplasty, and stent deployment have emerged as evolutionarily unanticipated sources of vessel trauma, potentially involving all layers of the vessel wall. The resulting activation of the trauma response, however, can paradoxically reinitiate the cascade of atherogenesis that begins with adventitial dysfunction and leads to restenosis. Interventional methods that minimize adventitial injury while reducing the atherosclerotic plaque burden may ultimately hold greater promise for durable results.

We envision novel mechanical and biopharmaceutical solutions that target the adventitia to prevent or treat atherosclerosis, including novel drug delivery strategies, exo-stents that wrap vessels, and neuromodulation of vessels. The differential response of the adventitia compared to the intima with respect to known agents [34–36] suggests the potential for rediscovery or rede-

ployment of ignored or marginalized agents to achieve greater activity and selectivity. A variety of potential mechanical and biopharmaceutical approaches remain unexplored, including administration of agents to the external rather than the internal aspect of vessels, utilization of polymers, meshes, or coatings that enclose or encase vessels rather than line them, and deployment of agents with a greater emphasis on neuromodulation. Studies have shown that agents delivered exclusively within the adventitia can influence the whole of vessel biology [37,38], further demonstrating the fundamental role played by the adventitia.

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