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Review Article

Vascular endothelium, hemodynamics, and the pathobiology of atherosclerosis

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ABSTRACT

The localization of atherosclerotic lesion formation to regions of disturbed blood flow associated with certain arterial geometries, in humans and experimental animals, suggests an important role for hemodynamic forces in the pathobiology of atherosclerosis. There is increasing evidence that the vascular endothelium, which is directly exposed to various fluid mechanical forces generated by pulsatile blood flow, can discriminate among these different biomechanical stimuli and transduce them into genetic regulatory programs that modulate endothelial function. In this brief review, we discuss how biomechanical stimuli generated by blood flow can influence endothelial functional phenotypes, and explore the working hypothesis of "atheroprone" hemodynamic environments as "local risk factors" in atherogenesis. In addition, we consider the therapeutic implications of the activation of "atheroprotective genes" and their role as "critical regulatory nodes" in vascular homeostasis.

1. Introduction

Atherosclerosis, the most common form of large vessel pathology responsible for syndromes of vital organ ischemic damage (e.g., myocardial infarction and stroke), remains a leading cause of mortality and morbidity in industrialized societies. Although its histopathologic features have been appreciated since the time of Virchow [1], mechanistic insights into its pathogenesis, at the cellular and molecular level, have been gained only relatively recently. While early pathogenetic theories (e.g., "lipid insudation" and "fibrin incrustation") focused on the prominent microscopic features of advanced lesions, more recent working hypotheses have utilized the tools of modern cell biology and molecular genetics to probe the pathogenetic mechanisms of fibromuscular scarring and lipid accumulation that ultimately result in plaque instability and thrombotic sequelae [2–5].

An important organizing principle that has emerged is that the vascular endothelium is a *dynamically mutable interface*—whose structural and functional properties are responsive to a variety of stimuli, both local and systemic, and that its phenotypic modulation to a dysfunctional state can constitute a major risk factor for vascular diseases such as atherosclerosis [6]. Manifestations of *endothelial dysfunction* extend well beyond altered nitric oxide metabolism and vascular reactivity, and encompass increased lipoprotein permeability and oxidation, enhanced mononuclear leukocyte adhesion and intimal accumulation, altered extracellular matrix metabolism, and dysregulation of the hemostatic–thrombotic balance. Pathophysiologic stimuli of arterial endothelial dysfunction that are especially relevant to atherogenesis include proinflammatory cytokines, bacterial products and viruses, advanced glycation end products generated in diabetes and aging, hypercholesterolemia (per se), as well as oxidized lipoproteins and their components (e.g., lysophosphatidylcholine) that accumulate within the arterial wall [7]. In addition to these biochemical stimuli, it is now clear that biomechanical forces, generated by flowing blood, can also influence the structure and function of endothelial cells and, remarkably, can act, at the level of complex transcriptional regulation, to orchestrate the pattern of expression of pathophysiologically relevant genes in atherogenesis [8].

The notion that hemodynamic forces can function as pathophysiologic stimuli for endothelial dysfunction provides a conceptual basis for the long-standing observation that the earliest lesions of atherosclerosis develop in a distinctive, nonrandom pattern, the geometry of which correlates with branch points and other regions of altered blood flow [9,10]. This strikingly localized pattern of lesion formation, across various species and in the face of systemic risk factors such as elevated plasma cholesterol, has intrigued experimental pathologists and fluid mechanical engineers alike, for decades, and has motivated the search for mechanistic links between hemodynamic forces and atherogenesis. In this brief review, we highlight our current understanding of the interrelationships of hemodynamics, endothelial pathobiology, and atherogenesis, with a view to future therapeutic implications.

2. Hemodynamics, endothelium, and vascular pathobiology

The pulsatile flow of blood through the branched tubular geometry of the arterial vasculature generates various types of hemodynamic

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forces—wall shear stresses, hydrostatic pressures, and cyclic strains—that can impact vessel wall biology [11]. As the cellular layer in intimate contact with blood, the endothelium in particular bears the frictional forces (wall shear stresses) imparted by the flow of this viscous fluid. Blood flow patterns can vary from the relatively uniform (time-averaged) well-developed laminar flows that occur in the unbranched portions of medium-sized arteries, to the complex disturbed laminar flow patterns (involving regions of flow separation, recirculation, and reattachment) that result in significant temporal and spatial gradients of wall shear stresses over relatively short distances [12]. The latter disturbed laminar flow patterns occur near branch points, bifurcations, and major curvatures—arterial geometries that are typically associated with the earliest appearance (and subsequent progression) of atherosclerotic lesions (Fig. 1A). In contrast, the unbranched, tubular portions of arteries that carry uniform laminar flow typically are relatively protected from atherogenesis (at least at the early stages of disease) [13,14]. For many years, the common wisdom therefore held that "low shear" areas (e.g., complex geometries in which the time-averaged fluctuations in wall shear stresses were small, due to forward–reverse flow cycles) were especially *atherosclerosis susceptible*, whereas "high shear" areas were relatively *atherosclerosis resistant* (Fig. 1B). Interestingly, this nonrandom pattern of lesion development is observed not only in various experimental animal models (dietary and/or genetic), across multiple animal species, but also is a feature of the natural history of atherosclerotic disease in humans, thus underscoring its potential pathogenetic significance [15].

Various in vivo observations suggest that the structure and function of the endothelial lining is modulated by hemodynamic forces. Strikingly, endothelial cell morphology appears to reflect local flow conditions, with ellipsoidal cell (and nuclear) shape and coaxial alignment in the primary flow direction seen in laminar flow regions, and disruption of this orderly pattern in regions of disturbed flow [16,17] (Fig. 1C). Surgical manipulation of vascular architecture (e.g., the creation of coarctations or arteriovenous shunts) results in acute and chronic changes in the vessel wall that appear (at least in part) to be endothelial dependent. And, in the presence of hypercholesterolemia, these surgically modified vascular geometries can also develop atherosclerotic-like lesions [18]. While these in vivo observations are consistent with an effect of blood flow on arterial wall (patho)biology, evidence of the direct action of hemodynamic forces on endothelium has come primarily from in vitro studies. In the early 1980s, our group, in collaboration with colleagues in Fluid Mechanical Engineering at the Massachusetts Institute of Technology, utilized a modified cone-plate viscometer to subject cultured human and animal endothelial cells to defined fluid mechanical stimulation [19] and began to explore the resultant changes in endothelial structure and function [20]. Our early studies established that unidirectional, steady laminar shear stresses could induce time- and force-dependent cell-shape changes and alignment that mimicked those observed in the arterial vasculature in vivo [21]. Further studies by our group, and several others, went on to document that hemodynamic forces could significantly influence a spectrum of the vital properties of vascular endothelium that encompass its functions as a blood-compatible container, a selectively permeable barrier, and a metabolically active cellular component of the arterial wall [22]. This essentially established a new paradigm in vascular (patho)biology—biomechanical regulation of endothelial phenotype [23].

3. Endothelial gene regulation by biomechanical forces

In addition to eliciting immediate responses (e.g., the secretion of biologically active endothelial metabolites such as prostacyclin and nitric oxide via enzymatic regulation), in vitro applied shear stresses appeared to strongly influence endothelial cell gene expression [11]. Mechanistic analyses of this phenomenon revealed the existence of "shear-stress response elements" in the promoters of pathophysiologically relevant genes, such as the platelet-derived growth factor and vascular cell adhesion molecule-1 (VCAM-1), that acted to up- or down-regulate gene transcription [24,25]. Other studies revealed the presence of various "mechano-transducers" and downstream signaling pathways that link the externally applied mechanical stimuli to intracellular and, ultimately, intranuclear events [12,26,27]. Interestingly, individual genes as well as groups of multiple genes appeared to be *differentially* responsive to the spatial and temporal properties of applied shear stresses—suggesting a complex and dynamic system of biomechanical endothelial gene regulation.

A major logistical step forward was the move from single (candidate) gene analyses to high-throughput molecular biological

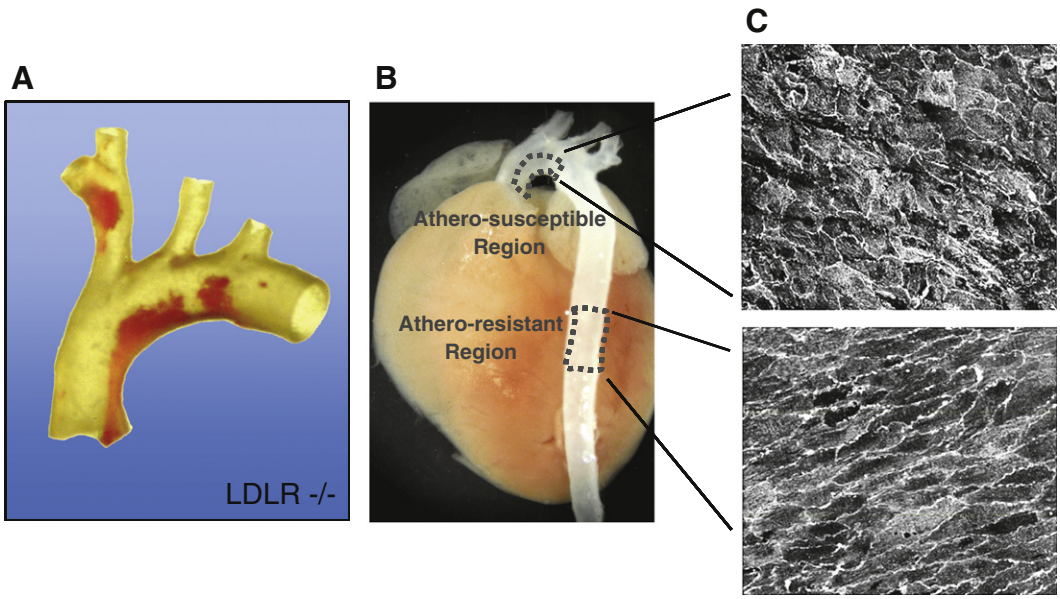

Fig. 1. Nonrandom pattern of early atherosclerotic lesion development in mouse aorta. (A) Dissected aortic arch from a LDL receptor-deficient (LDLR−/−) mouse fed a cholesterol-rich diet stained with oil red-O to mark early atherosclerotic lesions (adapted from Ref. [65]). (B) Location of "atherosclerosis-resistant" and "atherosclerosis-susceptible" regions, indicated on an intact mouse aorta, corresponding to the descending thoracic aorta and the lesser curvature of the aortic arch, respectively. (C) En face confocal microscopy of the endothelium of these regions showing distinct cell shapes (cell junctions stained for CD31).