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Review

Endothelial cells and cathepsins: Biochemical and biomechanical regulation

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ABSTRACT

Cathepsins are mechanosensitive proteases that are regulated not only by biochemical factors, but are also responsive to biomechanical forces in the cardiovascular system that regulate their expression and activity to participate in cardiovascular tissue remodeling. Their elastinolytic and collagenolytic activity have been implicated in atherosclerosis, abdominal aortic aneurysms, and in heart valve disease, all of which are lined by endothelial cells that are the mechanosensitive monolayer of cells that sense and respond to fluid shear stress as the blood flows across the surfaces of the arteries and valve leaflets. Inflammatory cytokine signaling is integrated with biomechanical signaling pathways by the endothelial cells to transcribe, translate, and activate either the cysteine cathepsins to remodel the tissue or to express their inhibitors to maintain healthy cardiovascular tissue structure. Other cardiovascular diseases should now be included in the study of the cysteine cathepsin activation because of the additional biochemical cues they provide that merges with the already existing hemodynamics driving cardiovascular disease. Sickle cell disease causes a chronic inflammation including elevated TNFα and increased numbers of circulating monocytes that alter the biochemical stimulation while the more viscous red blood cells due to the sickling of hemoglobin alters the hemodynamics and is associated with accelerated elastin remodeling causing pediatric strokes. HIV-mediated cardiovascular disease also occurs earlier in than the broader population and the influence of HIV-proteins and antiretrovirals on endothelial cells must be considered to understand these accelerated mechanisms in order to identify new therapeutic targets for prevention.

Contents

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1. Introduction

According to a 2015 American Heart Association report, cardiovascular disease accounts for more than 17 million deaths per year and is the leading cause of death in the world [1]. It is well established that atherosclerotic plaque formation occurs preferentially at areas of low and oscillatory shear stress, such as those seen at curves and bifurcations within the vasculature; while regions of high, unidirectional fluid shear stress, appear to be atheroprotected [2–8]. Shear stress can be defined as the tangential force of the blood flowing along the vascular wall, and the endothelial cells lining the blood vessel wall are directly exposed to it. These mechanical forces not only cause morphological changes in the endothelium and blood vessel wall, but also trigger biochemical and biological events. Endothelial cells form a monolayer of cells that line blood vessel walls and serve several functions, many of which are induced based on local hemodynamics and shear stress: regulation of cellular adhesion molecules on the cell surface including E-selectin, ICAM-1 and VCAM-1; monocyte recruitment, adhesion, and migration into the vascular wall; inhibition of platelet aggregation, thrombosis, and coagulation; selective transport of macromolecules from the blood into the blood vessel wall; and regulation of vascular tone by stimulating smooth muscle cell contraction or relaxation by producing endothelin-1 or nitric oxide, respectively [3,9–14]. A number of mechanosensitive cellular mechanisms and signaling pathways in endothelial cells have been described and are comprehensively reviewed by Davies [9].

More importantly for this review, however, is the regulation of vascular structure by endothelial cells via production or inactivation of cysteine cathepsins, powerful elastases and collagenases that can remodel the arterial wall and contribute to cardiovascular disease progression. Low and oscillatory shear stress at sites of disturbed flow at bifurcations and branches activates shear-mediated cysteine proteases, the cathepsins, powerful elastases and collagenases which have the ability to remodel extracellular matrix, initiating and promoting elastic lamina fragmentation, neointimal thickening, and plaque progression, while also modifying the mechanical properties of the arterial wall [15–17]. Of note, multiple cathepsins have been implicated in the pathologies of atherosclerosis, abdominal aortic aneurysms (AAA), and heart valve disease, which all preferentially occur at these hemodynamically defined regions. Mechanisms of regulation and the physiological consequences of endothelial cell cysteine cathepsin production by both biomechanical and biochemical influences will be discussed in this review. Additional discussion of endothelial cell cathepsin regulation in HIV-mediated cardiovascular disease and in sickle cell disease vasculopathy will also be included as these are new diseases at the frontier of cysteine cathepsin activity in biochemical and biomechanically driven arterial remodeling that should garner attention.

1.1. Shear stress and endothelial cells

Shear stress is a mechanical, tangential force over the area of the endothelial monolayer as the blood drags across it, and this changes with the cardiac cycle. Differences in magnitude and frequencies of shear stress in the arteries have been linked to a number of cardiovascular health and disease mechanisms [15,16,18–22]. High unidirectional laminar shear stress, such as that found in the straight parts of the arteries, signals the endothelial cells to produce several atheroprotective proteins, including cystatin C, the main protein inhibitor of the cysteine cathepsins. Low or oscillatory shear stress, such as that found at bifurcations or sharp turns in the vascular tree where atherosclerotic plaques are localized, does the inverse: it induces cysteine cathepsin expression and activity as well as cell adhesion molecule expression to promote monocyte adhesion and other local inflammation for atherosclerosis. Certain portions of the vascular tree appear to be differentially regulated by shear stress. The geometry of the proximal ascending aorta produces native regions of oscillatory shear stress. Endothelial cells on the aortic side of the aortic valve are normally subjected to oscillatory shear stress after the valves close, and a loss of this oscillatory stress results in expression of adhesion proteins and cytokines consistent with endothelial activation [23,24]. Cathepsin expression by endothelial cells are ultimately regulated by this complex inflammation cascade and altered biomechanical hemodynamic signaling [15,16,25,26].

1.2. Cathepsins expressed in endothelial cells

Cathepsins K, L, S, and V are of particular focus here; they have unique properties and homeostatic functions, but share 60% sequence homology [27–30]. They are also potent collagenases and elastases that have been highly implicated in cardiovascular diseases and have been shown to be upregulated by endothelial cells at sites of disturbed flow, increasing elastin and collagen degradation *in vitro* and in diseased human arteries [15,16].

1.2.1. Cathepsin synthesis and regulation

Cysteine cathepsins are included in the papain family of proteases that comprises 11 members denoted by letters: cathepsins B, C, F, H, K, L, V, O, S W, and Z (or X). In mammalian cells, cathepsins were first identified in lysosomes, but are now known to play functional roles in other cellular compartments and even in the extracellular space after secretion [31,32]. Cathepsins are synthesized in their inactive form, and the N-terminal propeptide must be enzymatically cleaved to expose the active site for substrate catalysis. This can occur by positive feedback if other, active, proteases cleave the propeptide off of each other [28,33]. Many are also capable of autocatalytically cleaving their own propeptide under acidic conditions to activate themselves [33–35]. Mature, active cathepsins are optimally active at acidic pH, and prefer reducing environments for the –SH group of the active site cysteine to participate in the nucleophilic attack that cleaves peptide bonds, and can be inactivated/denatured due to pH, oxidation, or other mechanisms [36]. If cathepsins escape their intracellular compartments, they are susceptible to inhibition by the cystatins, a family of protein inhibitors that regulate and inhibit intra- and extracellular cathepsin activity, and are usually produced and present in high molar excess to the cathepsins for healthy maintenance of cell and tissue proteins [37–41]. Taken together, cathepsins exist as a system of transiently active enzymes working simultaneously and quickly, but their cell/tissue specificity,

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