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Graphical Review

Autophagic regulation of smooth muscle cell biology

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ABSTRACT

Autophagy regulates the metabolism, survival, and function of numerous cell types, including those comprising the cardiovascular system. In the vasculature, changes in autophagy have been documented in atherosclerotic and restenotic lesions and in hypertensive vessels. The biology of vascular smooth muscle cells appears particularly sensitive to changes in the autophagic program. Recent evidence indicates that stimuli or stressors evoked during the course of vascular disease can regulate autophagic activity, resulting in modulation of VSMC phenotype and viability. In particular, certain growth factors and cytokines, oxygen tension, and pharmacological drugs have been shown to trigger autophagy in smooth muscle cells. Importantly, each of these stimuli has a redox component, typically associated with changes in the abundance of reactive oxygen, nitrogen, or lipid species. Collective findings support the hypothesis that autophagy plays a critical role in vascular remodeling by regulating smooth muscle cell phenotype transitions and by influencing the cellular response to stress. In this graphical review, we summarize current knowledge on the role of autophagy in the biology of the smooth muscle cell in (patho)physiology.

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Introduction

Vascular smooth muscle cells (VSMCs) comprise the medial layer of blood vessels. By their contraction or relaxation, VSMCs control vessel tone and blood flow, thereby playing a fundamental role in blood pressure regulation and in nutrient and oxygen delivery [1]. VSMCs also demonstrate significant plasticity and are capable of assuming synthetic, osteochondrogenic, and macrophage-like phenotypes, with such roles called upon during development [2], angiogenesis [3], or disease [4]. In diseases such as atherosclerosis, VSMCs can assume a foam cell phenotype, redolent of the sub-intimal macrophage-derived foam cell. Lesional VSMCs also commonly show increased proliferative, migratory, and/or extracellular matrix-synthesizing capacities, indicative of their conversion to the synthetic phenotype. This form of VSMC is commonly associated with vascular injury and leads to a (re)stenosis of the vessel lumen. In hypertensive vessels, VSMCs

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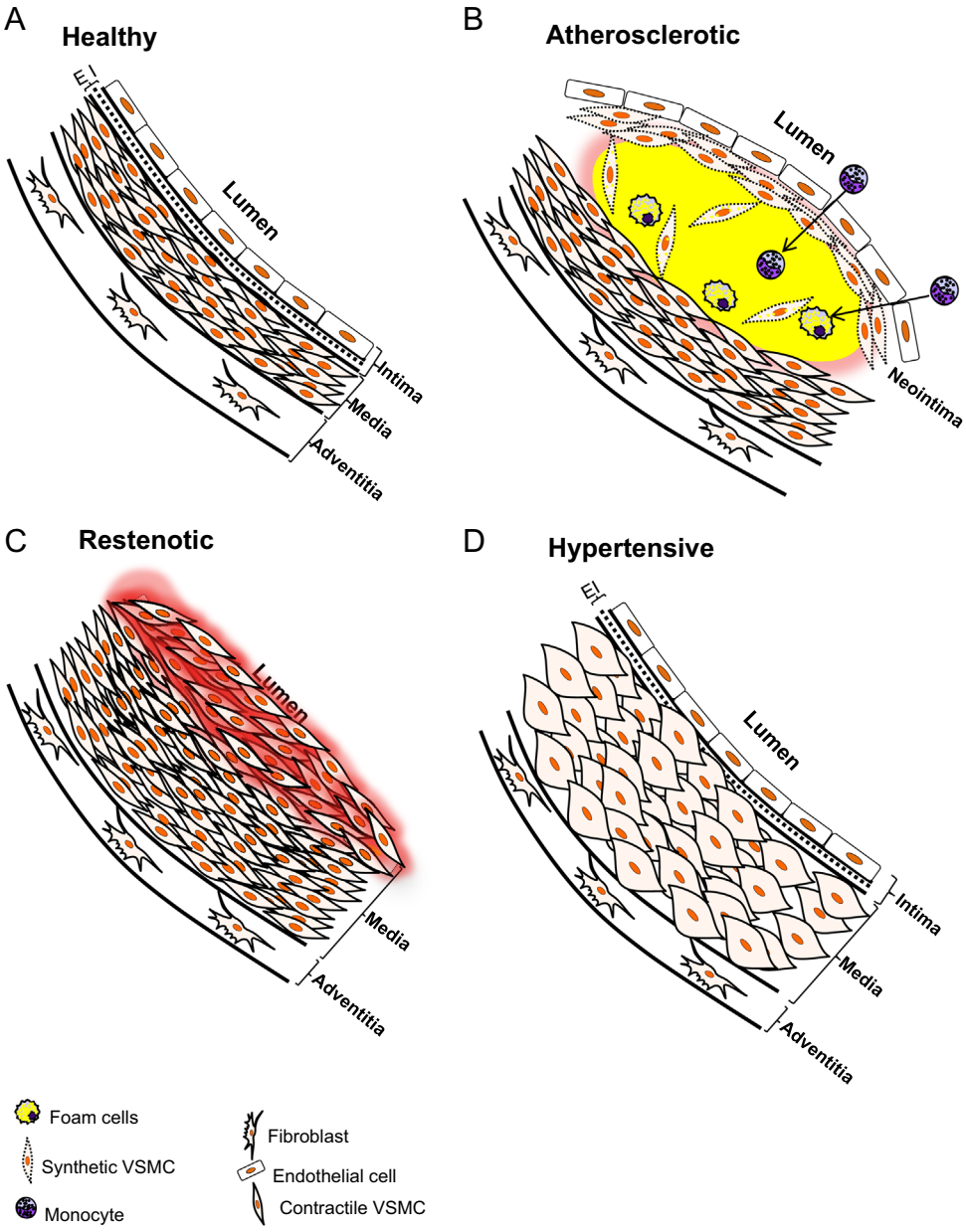

Fig. 1. Illustration of VSMCs in healthy and diseased arteries: (A) the mature, healthy mammalian artery is composed of three principal layers: the intima, which comprises endothelial cells; the media, which is occupied primarily by differentiated VSMCs; and the adventitia, which is composed of fibroblasts and connective tissue. (B) The subintimal and medial layers of the artery are heavily involved in the development of vascular diseases. In atherosclerosis, LDL and its oxidized forms accumulate in the subintimal space, which recruits monocytes and provokes the proliferation and migration of VSMCs. Monocytes differentiate into macrophages which attempt to remove the excess lipids, resulting in the formation of foam cells. The VSMCs also possess an ability to take up lipid and similarly develop into foam-like cells. In addition, synthetic VSMCs migrate to the subintimal space, proliferate, and secrete extracellular matrix, which are thought to help stabilize the atherosclerotic lesion by forming a protective cap around the plaque. Failure to clear excess lipid, debris, and lipid-laden cells, coupled with increased vascular inflammation, could lead to plaque rupture and thrombosis. (C) Severe obstruction of blood flow may occur due to VSMC hyperproliferation after angioplasty or in other vascular injuries where significant tracts of endothelium are removed. The etiology and progression of stenosis is due in part to the phenotypic transition of VSMCs to a synthetic phenotype, which renders VSMCs excessively proliferative and migratory. (D) In hypertension, VSMCs commonly undergo hypertrophy, secrete extracellular matrix, and increase contractile tone. EI=elastic intima.

commonly hypertrophy and increase their contractile tone (Fig. 1).

The unique phenotypic flexibility of VSMCs requires central integration of transcriptional, metabolic, and ultrastructural programs. Autophagy is a principal coordinator of cell homeostasis that could integrate these programs and is finely tuned to respond to stimuli to regulate cell function. Importantly, autophagy is affected in numerous vascular disease states, including restenosis, atherosclerosis, and hypertension [4]. The molecular activation of autophagy is primed via phosphorylation of ULK1 (Atg1), which then coordinates interactions of other critical proteins in the autophagy cascade [5], leading to encapsulation of cellular constituents in a double-membrane vesicle called the autophagosome. The autophagosome then fuses with the lysosome, leading to degradation of the compartmentalized contents and release of essential building blocks such as amino acids for reutilization (Fig. 2). This form of autophagy is commonly activated as a survival mechanism to degrade damaged cellular components and to maintain sufficient nutrient and biosynthetic stores under conditions of bioenergetic distress [6]. Autophagy is also important in regulating the life-cycle of numerous cellular organelles, such as mitochondria, endoplasmic reticulum, and peroxisomes, and it has other specialized roles in the cell that utilize different strategies to