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REVIEW

Vascular smooth muscle cell phenotypic modulation and the extracellular matrix

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Abstract Intervascular stents provide clinical benefits in preventing occlusive coronary artery disease after angioplasty, but intimal hyperplasia and restenosis after stent implantation remains an unresolved problem. Vascular smooth muscle cells (VSMCs), the main component of medial layer of arteries, play an important role in neointimal hyperplasia. After arterial injury, quiescent, contractile VSMCs undergo a change in phenotype; they proliferate and migrate from the media to the intima. It has been shown that the extracellular matrix (ECM) plays a key role in tissue formation, homeostasis and repair. The adhesion, proliferation, and migration of VSMCs are strongly influenced by interaction with ECM components including proteoglycans, glycoproteins such as fibronectin, collagen, elastic fibers (laminae). This interaction is further diversified under the influence of multiple transmembrane receptors and matrix proteinases. Hence, the coordinated regulation of VSMC function by these matrix components is an essential process for controlling the development and remodeling of the vascular system. Here the role of ECM in VSMC phenotypic modulation and neointimal hyperplasia will be reviewed.

Contents

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Introduction

Restenosis

Soon after the first percutaneous transluminal coronary angioplasty was applied in 1977 to unblock coronary arteries, investigators discovered that a considerable percentage of patients experienced recurrent ischemia due to acute reocclusion in treated artery.[1] This phenomenon, which is called restenosis, occurs within 6 months after angioplasty. Pathophysiologically, restenosis comprises a cascade of molecular and cellular events within the vessel wall. Replacement of hyaluronic acid with collagen fibers in ECM, adventitial thickening, and constriction of the external elastic lamina area, compounded by neointimal hyperplasia, are among the proposed mechanisms of vascular remodeling after angioplasty.[1] In-stent restenosis (ISR) was classified by visual estimate on angiography. Class I corresponds to focal ISR defined by formation of restenotic plaque (<10 mm) on the stent body or on the edges. Class II comprises diffuse intrastent ISR with a lesion (>10 mm) positioned on the stent body. Class III identifies diffuse proliferative ISR in which a lesion (>10 mm) extends beyond the stent margin(s). Finally, class IV represents an occluded ISR.[2]

To minimize vascular remodeling and to prevent elastic lamina recoil, the bare metal stent (BMS) was first used as a scaffold to maintain the artery's patency. However, BMS implantation bears an in-stent restenosis rate of around 25%. Restenosis was significantly reduced to the one-digit range (<10%) by drug-eluting stents (DES). Drug-eluting stents provide localized pharmacotherapy to minimize the response of the vessel to injury. However, their efficiency to reduce restenosis depends on different parameters including drug type, dosage, drug release kinetics, flow dynamics, and local drug delivery. The effect of different generations of DESs on rate and pattern of restenosis have been reviewed extensively,[3,4] and in a fully bioabsorbable stents the rate of restenosis can be as low as 3.5%.[3]

Table 1 VSMC markers in different phenotype markers.

VSMC contractile phenotype marker	VSMC synthetic phenotype marker
SM-22- α	Vimentin
SM- α-actin	Non-muscle myosin HC
SM-MHC	Caldesmon light chain
Calponin	Tropomyosin 4
Smoothelin	Cellular-retinol binding protein-1
Caldesmon	

VSMC phenotypic modulation

Despite the extensive studies on neointimal hyperplasia, the exact mechanism of this complex pathological process remains to be fully understood.

VSMCs are the main component of the artery medial layer. They have both contractile (quiescent) and synthetic (proliferative) properties (Table 1), and in different stages of vascular development they show a wide range of different phenotypes between these two extremes. In the adult, VSMCs are fully differentiated. However, in response to environmental signals, they are able to switch back to a synthetic phenotype. This plasticity allows cells to maintain homeostasis of the vessel, but imbalance between these two VSMC phenotypes in favor of the proliferative cells may lead to wall dysfunction and vessel disease.

In the contractile state, VSMCs express contractile proteins such as smooth muscle-α-actin (SM-α-actin), smooth muscle myosin heavy chain (SM-MHC), SM22, calponin, and smoothelin. The cytoplasm of contractile VSMCs contains minimal endoplasmic reticulum, Golgi apparatus, and ribosomes, and cells possess dense fusiform morphology associated with tightly bundled myofilaments. In contrast, in synthetic VSMCs the expression of contractile marker genes, especially SM-MHC, SM22α, and SM-α-actin, is downregulated,[5] whereas expression of ECM proteins (collagen type I and III, fibronectin) and matrix metalloproteinases (MMPs) -1, -2, -3, -7, -9, -14 are extensively increased.[6] This change in phenotype allows VSMCs to proliferate and migrate. Synthetic VSMCs are fibroblast-like, and their cytoplasm is rich in endoplasmic reticulum, Golgi, and ribosomes. The change in VSMC phenotype can be modulated by different factors including inflammatory mediators, growth factors, growth inhibitors, mechanical forces, cell—cell interactions, and cell-ECM interactions.[7]

Angioplasty and stent implantation ruptures the atherosclerotic plaque, and initiates platelet adhesion and activation, secretion of cytokines, recruitment of inflammatory cells, and up-regulation of adhesion molecules in VSMCs of the injured vessel. The activated platelets release mitogens, including thromboxane A2, serotonin, and platelet-derived growth factor, which promote the smooth muscle cell phenotypic shift[6] from contractile to synthetic.