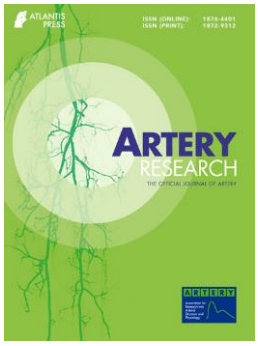

Artery Research

ISSN (Online): 1876-4401 **ISSN (Print): 1872-9312**
Journal Home Page: https://www.atlantis-press.com/journals/artres

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To cite this article: Maryam Heidari, Craig A. Mandato, Stephanie Lehoux (2015) Vascular smooth muscle cell phenotypic modulation and the extracellular matrix, Artery Research 9:C, 14–18, DOI: https://doi.org/10.1016/j.artres.2014.12.002

To link to this article: https://doi.org/10.1016/j.artres.2014.12.002

Published online: 7 December 2019

Artery Research (2015) 9, 14—18

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/artres

REVIEW

Vascular smooth muscle cell phenotypic modulation and the extracellular matrix

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Received 21 December 2011; received in revised form 6 June 2014; accepted 15 December 2014
Available online 3 January 2015

KEYWORDS
Restenosis;
Neointima;
Extracellular matrix;
Remodeling

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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http://dx.doi.org/10.1016/j.artres.2014.12.002

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.

VSMCs proliferate and migrate toward the lumen and form the neointima. Concurrently, endothelial denudation and dysfunction facilitates neointima formation, since healthy endothelium responds to many extracellular signals by activation of endothelial nitric oxide synthase, releasing NO which is both a vasodilator and a modulator VSMC proliferation.[8] Proliferation of VSMCs occurs in 2 phases: in the early phase after injury medial VSMCs proliferate and migrate from media to intima, whereas and in the later phase intimal VSMCs proliferate and thicken the neointima.[9] Interestingly, histopathologic analyses of angioplastied arteries from animals[10,11] or patients[12] indicate that collagen and proteoglycan accumulation appear to contribute to the more prolonged, stenotic response. ECM components may therefore have an important role in regulating the cellular activities including adhesion, proliferation, and migration, associated with restenosis.

VSMC phenotypic modulation and ECM proteins

Within the blood vessel wall, VSMCs are typically surrounded by a strongly adhesive ECM. Under normal conditions, VSMCs make stable contacts with the matrix and remain stationary and quiescent. Strong attachments to the ECM are necessary for transmission of contractile force to structural elements of the vessel wall so that changes in peripheral resistance and blood flow distribution can be controlled by VSMC contraction. However, after vascular injury many of these attachments are disrupted, and VSMCs acquire a motile phenotype to repair the wound. In the process, VSMCs express specialized matrix proteins, matrix-degrading proteases and new cell surface matrix receptors, and they remodel the existing structural elements of the vessel wall.[13] Here the role of some ECM proteins in neointima formation is summarized.

Elastin

The vascular elastic laminae, composed of mainly elastin, contribute to the morphogenesis, regulation of cellular activities, as well as the structural stability, elasticity, and strength of blood vessels.[14] Elastic fibers are organized as concentric layers framed by the internal and external elastic laminae (IEL/EEL). Elastin is produced intracellularly as a tropoelastin and deposited on a microfibrillar scaffold in ECM. Many glycoproteins have been identified in close proximity to or surrounding the elastic fibers. These include fibulin, a family of elastin-associated glycoproteins which has 7 members that are required for assembly and organization of elastic fibers. Among them fibulin-4 and -5 are expressed in the vasculature.

Fibulin-4 is expressed intensely in the outer medial layers towards the adventitia in large blood vessels, whereas, fibulin-5 is expressed in both large and small vessels and is co-localized with all layers of elastic lamina in the vessel wall.[15] It has been shown that in fibulin-$4^{-/-}$ mice there is a general down-regulation of contractile genes in VSMCs, associated with loss of elastic fiber-actin cytoskeleton interaction, normally mediated by integrins, and a shift from fibrillar to globular actin filaments. Globular actins bind to myocardin, a transcription co-factor important for contractile gene expression. Myocardin is thus maintained in the cytoplasm, and prevented from translocating to the nucleus, resulting in the down-regulation of VSMC marker genes and de-differentiation of VSMCs.[16]

De-differentiation of VSMCs has also been shown in fibulin-$5^{-/-}$ mice, for which two distinct mechanisms for VSMC hyperproliferation have been proposed. The first mechanism emphasizes the loss of structural integrity of the vessel wall as a result of disorganization of elastic fibers; in fibulin-$5^{-/-}$ mice, elastic fibers form multiple aggregates instead of smooth, organized lamellar sheets. The second mechanism focuses on the suppressive effect of fibulin-5 on VSMC proliferation and migration, which is absent in knock-out mice.[17]

Consistent findings showed that recombinant tropoelastin, the elastin gene product, inhibited the proliferation and migration of VSMCs *in vitro*.[18] In parallel with these findings, experiments have shown that as a result of deep injury and IEL rupture, neointima thickness was increased.[19] Li and et al. generated mice lacking elastin ($Eln^{-/-}$) and found that animals died from vascular occlusion in the early postnatal phase because of excessive subendothelial proliferation and accumulation of VSMC.[20] Considering these data, it can be concluded that structural integrity of the vessel wall and elastic laminae play an important role in preventing de-differentiation of VSMCs and keeping them in a quiescent phenotype.

Collagen

Collagens I and III are mainly responsible for imparting strength to the vessel wall. The basic unit of fibrillar collagen is the 300 nm triple α-helix. It is produced intracellularly, secreted in the extracellular compartment, and then aggregated in quarter-staggered fibrils. During the formation of intermolecular cross-linking, initiated by lysil oxidase (LOX), collagen fibers become increasingly insoluble and show a progressive increase in tensile strength.[21]

The expression of procollagen mRNA rapidly increases after balloon injury, whereas collagen content increases after 14 days. The delay between increased expression on mRNA level and the actual increase of collagen is likely due to enhanced matrix breakdown within the first weeks after angioplasty.[22] Correspondingly, Lafont and et al. have shown that the collagenous content of media and neointima is greatly increased after angioplasty.[23] LOX is likewise upregulated by balloon injury.[24] Increasing the collagen density of the media and the neointima after vessel angioplasty injury is closely correlated with VSMC phenotype; after angioplasty, synthetic VSMCs start to secret collagen type I and III. The causal link between collagen accumulation and VSMC proliferation was demonstrated recently. In rats treated with an inhibitor of growth factor-induced collagen synthesis, pirfenidone, neointima formation after balloon injury was significantly reduced.[25]

Laminin

The basement membrane, an extracellular structure surrounding ECs and VSMCs, is mainly made of collagen type IV and laminin. Laminin is a trimeric glycoprotein which

contains α-, β-, and γ-chains. In culture, it has been shown that collagen type IV and basement membrane laminin delay, but do not eliminate the transition of VSMCs to the synthetic phenotype in response to growth factors, via the PI3-kinase/AKT pathway.[26] However, the exact role of laminin in restenosis *in vivo* remains to be determined.

Fibronectin

Fibronectin (FN) is an ECM dimeric glycoprotein. It contains 3 module types, and each subunit has a series of repeating modules: 12 type I modules, 2 type II, 15—17 type III, and a variable (V) sequence that is not homologous to other parts of FN. Through interaction with integrins, FN links the ECM to the intracellular cytoskeleton and signaling pathways.[27]

It has been shown that FN derived from serum or coated substrates supports a loss of contractile phenotype. In serum free culture, there is a delay in phenotypic modulation due to lack of FN, and when cultured VSMCs begin to produce their own FN matrix, they lose their contractile apparatus through the P38 MAP kinase signaling pathway.[6,7] Similarly, after *in vivo* vascular injury in rat carotid vessels, immuno-electron microscopy studies have shown a close relation between deposition of FN and the synthetic phenotype of VSMCs.[28]

VSMC phenotypic modulation and integrins

Extracellular matrix receptors on VSMCs help to anchor the cells during contraction and promote cellular migration after vessel injury. Integrins are a group of cell surface glycoproteins that have been implicated as surface receptors, mediating cell adhesion to the ECM and relaying external signals to internal cell signaling response. Each integrin is a heterodimer in which one of several homologous α subunits associates non-covalently with a β subunit. Several integrins can interact with a specific amino acid sequence, Arg-Gly-Asp (RGD), which is located in the cell binding region of fibronectin and vitronectin and is also present in laminin, collagen type I and IV, and other adhesive proteins. In human cells there are eight major subfamilies of integrin receptors, which are defined by their component β chains. The first subfamily includes at least six related complexes, each consisting of a β_1 chain with a distinct companion α chain. Members of the β_1 subfamily include receptors for fibronectin ($\alpha_3\beta_1$, and $\alpha_5\beta_1$), laminin ($\alpha_1\beta_1$, $\alpha_7\beta_1$, and $\alpha_6\beta_1$), and collagen types I and IV ($\alpha_1\beta_1$, $\alpha_2\beta_1$, and $\alpha_3\beta_1$).[29] Integrin subunits α_1, α_3, α_5, and β_1 are the predominant integrins expressed in VSMCs. Expression of $\alpha_1\beta_1$and $\alpha_7\beta_1$ correlates with the differentiated VSMC phenotype.[30]

The role of integrins in VSMC phenotype conversion, proliferation and neointima formation is complex. In some cases, integrin activation is associated with neointima formation. For example, in the adult vasculature, fibronectin comprises a small part of ECM. However, after arterial injury the expression of both fibronectin and its binding mediator $\alpha_5\beta_1$ is induced in the neointima.[31] The ECM-associated protein CCN1 stimulates adhesion and migration of VSMCs, via $\alpha_6\beta_1$. Knockdown of CCN1 inhibits neointima formation in a rat balloon injury model.[32] Blockade of the vitronectin receptor $\alpha_v\beta_3$ with an RGD peptide also reduces neointima formation and lumen narrowing after injury in rabbits.[33] The opposite relationship between integrins and VSMC proliferation has also been documented. Hence cartilage oligomeric matrix protein (COMP), a glycoprotein that binds $\alpha_7\beta_1$ integrin, is decreased in balloon-injured rat carotid arteries, leading to the loss of VSMC differentiation markers, whereas COMP overexpression retards VSMC de-differentiation in response to vascular injury.[34] In agreement, in α_7- knock-out mice the ERK-MAP kinase pathway is activated, which leads to VSMC proliferation and accentuation of neointima formation after carotid artery ligature.[35]

VSMC phenotypic modulation and matrix metalloproteinases

Specialized ECM proteolysis enzymes are key factors involved in atherosclerosis and restenosis. The extracellular proteases are a complex and heterogeneous superfamily of enzymes, including metalloproteinases (matrix metalloproteinases, adamalysins, or pappalysins), serine proteases (elastase, coagulation factors, plasmin, tissue plasminogen activator, urokinase plasminogen activator) and cysteine proteases (cathepsins). Among extracellular proteases relevant to the vasculature, matrix metalloproteinases (MMPs) are most well-characterized. During VSMC phenotypic modulation, the activities of a range of ECM proteinases including members of the serine and cysteine proteinases and MMP-1, -2, -3, -7, -9, and -14 are increased[6] which results in over-proliferation and migration of VSMCs and neointima formation. Blockade of MMPs with a general inhibitors or by specific MMP knockout have all been shown to reduce neointima formation in arterial injury models.[36,37] Moreover, in patients, active MMP-3 and MMP-9 were associated with a history of in-stent restenosis[38] while serum levels of MMP-2 and MMP-9 are associated with increased restenosis rates after implantation of drug-eluting stents.[39]

Conclusion

Restenosis after angioplasty is principally due to neointimal hyperplasia stemming from de-differentiation of vascular smooth muscle cells. Despite the advent of drug-eluting stents, which slow down VSMC proliferation, restenosis remains a major clinical problem. To solve this problem, it is essential to understand the molecular mechanisms that modulate VSMC phenotype modulation after injury. Since vascular cells are embedded in and actively secrete extracellular matrix proteins, the ECM is expected to play an active role in VSMC proliferation and neointima thickening. Given the complex interaction between ECM, MMPs and VSMC proliferation, this field will remain open to further study in the years to come.

For more details see reference.[6]

Acknowledgement

This work was financed by the Canadian Institutes of Health Research (CIHR).

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