REVIEW

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Biomarkers in VSMC phenotypic modulation and vascular remodeling

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Vascular smooth muscle cells (VSMCs) are not terminally differentiated and can change their phenotype in response to environmental cues. Phenotype switching of VSMCs to less differentiated forms has led to an underestimation of their role in the development of vascular remodeling and many vascular diseases in both humans and animal models of this disease. In recent studies, many factors, such as microRNAs, matrix metalloproteinases, integrins, oxidative stress, autophagy, have been shown to play important roles in the mechanisms of VSMC phenotypic switch and vascular remodeling. This review highlights the current knowledge regarding the molecular mechanisms of VSMC phenotypic modulation in vascular remodeling. In this review, we want to provide effective molecular targets and opportunities for the future development of new therapeutics to regulate vascular remodeling diseases.

1. Introduction

Vascular remodeling is the pathophysiological basis implicated in adverse cardiovascular diseases such as hypertension, atherosclerosis, and restenosis. Four cell types are mainly involved in vascular remodeling: the fibroblasts in the adventitial layer, the smooth muscle cells in the medial layer, the endothelial cells in the intimal layer, and the macrophages in the blood stream (Chen et al. 2013). The main reason for vascular development and remodeling is the phenotypic transition of vascular smooth muscle cells (VSMCs). VSMCs are contractile cells that regulate blood flow and their abnormalities contribute to a range of diseases. "Contractile" VSMCs with low proliferative activity and abundant contractile protein expression adapt to the disease situation by changing to highly proliferative "synthetic" cells that have low contractility and produce large amounts of extracellular matrix (Lehners et al. 2018). During this phenotypic modulation, smooth muscle cells downregulate their contractile markers, including smooth muscle α-actin (α-SMA), myosin heavy chain 11 (MHC11), calponin, and leiomodin, and upregulate the expression of genes involved in extracellular matrix deposition and inflammation (Finney and Orr 2018). Such a phenotypic switch represents one of the main cellular events underlying various VSMC-related pathological conditions, including hypertension, atherosclerosis, post-angioplasty restenosis, and angiogenesis. Molecular mechanisms underlying the cellular phenotypic switch in VSMCs are complex and multifactorial. The precise mechanisms that enable VSMC phenotype switching remain unknown. Herein, we are reviewing the latest molecular targets of VSMC phenotypic switch in the development of vascular remodeling diseases.

2. MicroRNAs

MicroRNAs are small, endogenous, conserved, single-stranded, non-coding RNAs; which degrade target RNAs or inhibit translation post-transcriptionally. MicroRNAs have been shown to modulate VSMC proliferation and migration, and play important roles in the mechanisms of vascular remodeling. Recent studies have demonstrated that microRNAs (miRNAs) expressed in the vascular system are involved in the control of VSMC proliferation (Wang and Atanasov 2019). The transcription factor c-Myb regulates differentiation and proliferation of VSMC by transcriptional activation of miR-143/145 (Chandy et al. 2018). Downregulated expression of the miR143/145 gene cluster promotes phenotypic switching of VSMCs via the TGF-β1 signaling pathway (Zhang and Wang 2019). Moreover, miR-214 significantly inhibits VSMC proliferation, migration and neointima smooth muscle cell hyperplasia after injury by modulating NCK Associated Protein 1 (NCKAP1) (Afzal et al. 2016). However, it was reported that miRNA-214 promotes SMC phenotype switching and proliferation in vascular hyperproliferative disorders including PAH in modulation of MEF2C-MYOCD-LMOD1 signaling (Sahoo et al. 2016). Adenovirus-mediated miR-21 sponge gene therapy effectively reduced neointimal formation in vein grafts, which is characterized by the proliferation and migration of VSMC (Wang et al. 2017). MiR-26a and miR-29b contribute to the PDGF-BB-induced phenotypic switch of VSMCs, respectively, by targeting Smad1 and SIRT1 (Sun et al. 2018; Yang et al. 2017). The expression of miR133a, a muscle-specific miRNA, which is induced by

Table: MiRNAs and their implied targets in phenotypic switching of VSMCs

miRNAs	Implied targets	References
miR-143/145	c-Myb	Chandy et al. 2018
miR-143/145	TGFβ1/TGFβR	Zhang and Wang 2019
miR-214	NCKAP1	Afzal et al. 2016
miR-214	MEF2C-MYOCD-LMOD1 signaling	Sahoo et al. 2016
miR-21	PTEN	Wang et al. 2017
miR-26a	Smad1	Yang et al. 2017
miR-29b	SIRT1	Sun et al. 2018
miR-133a	LDLRAP1	Gabunia et al. 2017
miR-22	MECP2, HDAC4, EVI1	Yang et al. 2018
miR-378a-5p	CDK1/P21	Liu et al. 2019
miR-1281	HDAC4	Li et al. 2018

Abbreviation: transforming growth factor β1/transforming growth factor β receptor (TGFβ1/TGFβR), NCK associated protein 1 (NCKAP1), myocyte enhancer factor **2C-myocardin-leiomodin1 (MEF2C-MYOCD-LMOD1), phosphatase and tensin** homolog (PTEN), Sirtuin 1 (SIRT1), low density lipoprotein receptor adaptor protein 1 (LDLRAP1), methyl-CpG-binding protein 2 (MECP2), histone deacetylase 4 (HDAC4), ecotropic virus integration site-1 (EVI1), cyclin-dependent kinase 1 (CDK1).

IL-19, reduces VSMC proliferation (Gabunia et al. 2017). MiR-22 controls VSMC phenotype and injury-induced arterial remodeling by modulating multiple target genes (MECP2, HDAC4, and EVI1) (Yang et al. 2018). MiR-378a-5p overexpression has significantly promoted VSMC proliferation and migration by targeting CDK1/p21 signaling pathway (Liu et al. 2019). Recently, a novel regulatory axis, phosphatidylinositol 3-kinase–DNA methyltransferase 1–miR-1281–histone deacetylase 4, integrating multiple epigenetic regulators that participate in platelet-derived growth factor BB–stimulated PASMC proliferation and migration and pulmonary vascular remodeling (Li et al. 2018). These important research advances are reviewed below (Table). In addition, adenosine deaminase acting on RNA (ADAR) -mediated RNA editing is an essential mechanism for SMC phenotypic modulation. Blockade of ADAR1 markedly attenuates PDGF-BB-mediated downregulation of SMC contractile proteins and injury-induced vascular remodeling (Fei et al. 2016). Taken together, miRs may serve as promising drug targets or potential biomarkers in prevention and management of VSMC phenotypic switch and vascular disorders.

3. Matrix metalloproteinases (MMPs)

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases that degrade various proteins in the extracellular matrix (ECM) including collagen and elastin. MMPs are often regulated by endogenous tissue inhibitors of metalloproteinases (TIMPs), and the MMP/TIMP ratio often determines the extent of ECM protein degradation. MMPs regulate VSMC proliferation by several mechanisms including promotion of interactions between VSMCs and ECM by integrin-mediated pathway, release and activation of growth factors (Walker et al. 2003; Zhang et al. 2004). MMPs could facilitate the release of cell surface heparin-bound epidermal growth factor (HB-EGF), which in turn stimulates VSMC proliferation (Lucchesi et al. 2004). MMP-9 knockout is associated with inhibition of VSMC proliferation in mice (Liu and Khalil 2017). Other studies have shown that MMP inhibitors inhibit VSMC proliferation *in vitro* and neointima formation in rats (Uglow et al. 2003).

MMPs also play a role in VSMC migration by ECM proteolysis (Shi et al. 2010). The proteolytic effect of MMP-2 on ECM and non ECM components and its contribution in VSMC reshaping and migration may lead to hypertension-induced maladaptive vascular remodeling (Belo et al. 2015). MMP-2/-9 activation signaling promotes a loss of VSMCs and facilitates aortic dilation (Xiong et al. 2012). Impressively, MMP-2 regulates a TGF-β1/ERK-1/-2 non-canonical pathway in VSMCs and facilitates vascular wall dilatation in a fibrillin-1 mutation Marfan syndrome animal model (Patel et al. 2014). MMP-2 cleaves the TGF beta binding protein-1 (LTBP-1) stepwise, leading to the activation of TGF-β1, enhancing increased VSMC production of collagen I, II, and III, and fibronectin (Wang et al. 2015; Wang and Khalil 2018). Young human ASMCs produce active MMP-2 and show a greater migratory capability than aged cells. Treatment of young cells with TIMP-1 and TIMP-2 leads to a migratory behavior that mimics that of aged cells (Haque et al. 2004; Xu et al. 2013a,b). Also, MMP-2 knockout decreases VSMC migration and neointima formation in the mouse carotid ligation model (Johnson and Galis 2004). Furthermore, MMP-9 may also be involved in VSMC migration (Jin et al. 2008; Xu et al. 2013c). Suppression of MMP-9 expression may mediate the inhibitory effects of curcumin on migration of human ASMCs and reduces VSMC migration and neointima formation in mice (Yu and Lin 2010). In addition, Gene transfer of TIMPs reduces VSMC migration *in vitro* and neointma formation and intima thickening *in vivo* (Lucchesi et al. 2004). These important research advances are reviewed in Fig. 1.

Therefore, MMPs are considered to be promising as therapeutic targets, and their inhibition may prevent and ameliorate VSMC phenotypic modulation and its resulting fatal cardiovascular events.

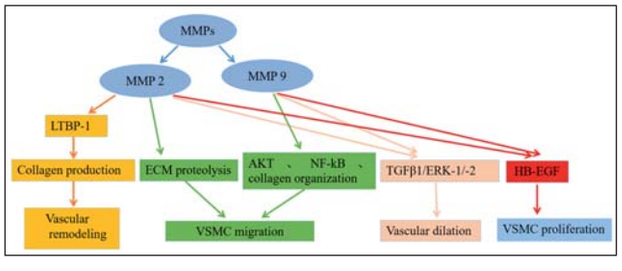

Fig. 1: Modulation of vascular function by MMP 2 and MMP 9. Abbreviation: extracellular matrix (ECM), matrix metalloproteinases (MMPs), heparin-bound epidermal growth factor (HB-EGF), TGF beta binding protein-1 (LTBP-1), vascular smooth muscle cell (VSMC), nuclear factor-k-gene binding (NF-kB).

4. Integrins

Integrins are transmembrane receptors linking the intracellular cytoskeleton to the extracellular matrix and play a significant role in SMC phenotypic changes (Fig. 2). α1β1 and α7β1 integrins (binding to collagen IV and laminin) are highly expressed in contractile VSMCs; their deletion induces VSMCs phenotypic modulation from a contractile phenotype to a synthetic state. It has been reported that α1β1 integrin could be involved in the effect of Ang II-induced arterial wall hypertrophy and VSMC proliferation (Louis et al. 2007; Moraes et al. 2015). α2β1 (binding collagens I and VIII), α5β1 and vβ3 (binding fibronectin) integrins are increased in synthetic VSMCs (Finney et al. 2017; Louis et al. 2007; Moraes et al. 2015; Yu and Lin 2010). Integrin α5β1 was markedly associated with the proliferation and migration of VSMCs (Song et al. 2016). The increased expression of osteopontin (OPN) and integrin β3 promote the migration and adhesion of VSMCs in great saphenous varicose veins (Jiang et al. 2014; Xu et al. 2014a,b). Recombinant osteopontin (rOPN) prevented the vascular smooth muscle phenotypic transformation and improved the neurological outcome, which was possibly mediated by the integrin receptor/ILK/ Rac-1 pathway (Wu et al. 2016). αv integrin (in particular αvβ3) have been implicated in controlling VSMC migration, de-differentiation, contractility, proliferation and apoptosis. The blockage of vβ3 integrin by antibodies or selective peptide ligands prevents VSMC migration (Moraes et al. 2010). α5 and αv integrins cooperate to regulate vascular smooth muscle function and are essential for development of the heart and great vessels (Turner et al. 2015).

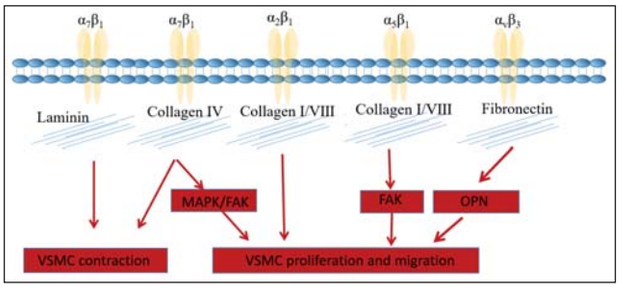

Fig. 2: Representative roles of integrins in VSMC function and phenotypic modulation. Abbreviation: focal adhesion kinase (FAK), osteopontin (OPN), mitogen-activated protein kinase (MAPK).

5. Oxidative stress and H_2O_2 production

Oxidative signaling is critical for cell homeostasis and survival. Advanced glycation end products (AGEs) cause VSMC calcification *in vitro* through increased oxidative stress (Wei et al. 2013). NOXA1-dependent NADPH oxidase activity in VSMC plasticity during restenosis and atherosclerosis, augmenting VSMC proliferation and migration and KLF4-mediated transition to macrophage-like cells, plaque inflammation, and expansion (Vendrov et al. 2019). B-cell lymphoma 6 (BCL6) attenuates proliferation and oxidative stress of VSMCs induced by Angiotensin (Ang) II in hypertension (Chen et al. 2019). Hydrogen peroxide (H_2O_2) has become recognized as a crucial mediator of cellular oxidative signaling. Under normal conditions, constitutive oxidase activities and endogenous scavenger systems maintain steady-state H_2O_2

levels in vascular tissue to maintain VSMC function, such as VSMC proliferation, migration, and differentiation (Ardanaz and Pagano 2006). Upon stimulation, elevation of H_2O_2 in VSMCs leads to VSMC dysfunction and damage in the vasculature. In rat VSMC, H_2O_2 treatment induces an increase in intracellular and extracellular osteopontin and generation of atherosclerotic lesions (Hu et al. 2011). Furthermore, H_2O_2 production from vascular cells initiates a signaling cascade which leads to the inflammatory response through the expression of inflammatory cytokines and adhesion molecules (Park et al. 2011). Increased ROS, particularly H_2O_2, found around calcifying foci, may be attributed to enhanced expression of the oxidases, including Nox2, p22phox, and Nox4 (Liberman et al. 2008; Song et al. 2017; Woo et al. 2015). And H_2O_2 directly induces VSMC calcification in mouse and a phenotypic change of SMC phenotype to an osteogenic phenotype, which is mediated by upregulating Runx2 (Byon et al. 2016; Deng et al. 2015). These observations support a critical role of H_2O_2 produced by VSMC in regulating vascular remodeling. Unveiling H_2O_2–regulated signaling molecule profiles in VSMC and other vascular cells may provide novel molecular insights into the signaling cascades that mediate the pathogenic effects of H_2O_2, and thus leading to identification of molecular targets.

6. Autophagy

Autophagy, which is an evolutionarily conserved mechanism and links to several cellular pathways, impacts vascular smooth muscle cells (VSMCs) survival and function (including proliferation, migration, matrix secretion, contraction/relaxation, and differentiation). Autophagy has a significant influence on the proliferation of VSMCs in response to stimuli as well as matrix secretion and migration (Tai et al. 2016). It has been reported that Long noncoding RNA metastasis-associated lung adenocarcinoma transcript 1 MALAT1 regulated the level of ATG7 and activated autophagy through competitively binding to miR142-3p, leading to the conversion of VSMCs from a contractile to a proliferative phenotype (Song et al. 2018). SCAP knockdown in VSMCs activated autophagy by the ROS/AMPK pathway, inhibited VSMC foam cell formation, and alleviated atherosclerotic plaque development (Li et al. 2019). c-Ski suppresses the oxLDL- or PDGF-induced autophagy and loss of contractile phenotype of VSMC (Li et al. 2014). Defective autophagy in VSMCs accelerates senescence and promotes ligation-induced neointima formation and diet-induced atherogenesis (Grootaert et al. 2015). Stimulation of autophagy could be a valuable new strategy in the treatment of arterial disease. Free fatty acids induce autophagy and LOX-1 upregulation in cultured aortic VSMCs, and then suppress VSMC proliferation (Cheng et al. 2017). However, inhibition of autophagy prevented all the TNF-α-induced phenotype switching in VSMC (García-Miguel et al. 2018). AGEs-induced autophagy accelerated AGEs-stimulated proliferation and migration in VSMCs (Liu et al. 2018). PDGF-induced autophagy activation is associated with enhanced migration and proliferation of VSMCs (Salabei et al. 2013). Autophagy proteins AMBRA1 and beclin 1 were recognized to play a role in the crosstalk between autophagy and cell proliferation by regulation of c-Myc (Cianfanelli et al. 2015). SUMOylation of Vps34 by SUMO1 promotes phenotypic switching of vascular smooth muscle cells by activating autophagy in pulmonary arterial hypertension (Yao et al. 2019). Therefore, it has been assumed that autophagy is essential for VSMC synthetic changes. However, it is still important to uncover how activation of autophagy regulates the expression of synthetic protein markers in VSMCs.

7. Conclusion and perspectives

Vascular remodeling occurs after endothelial injury, resulting in smooth muscle cell (SMC) proliferation and vascular fibrosis. Although much has been learned about mechanisms of vascular remodeling, current cardiovascular therapies are still limited. The smooth muscle cell directly drives the contraction of the vascular wall and hence regulates the size of the blood vessel lumen. VSMCs are highly differentiated and normally maintain a contractile phenotype. Contractile VSMCs are generally referred to as quiescent differentiated cells, whereas the synthetic state is associated with plasticity and appropriately referred to by some as dedifferentiated VSMCs. Several pathologies of the vasculature are associated with VSMC phenotype switching such as atherosclerosis, restenosis, aneurysm and calcification. Most of the studies related to SMC phenotypic modulation have reinforced the concept that intimal SMCs in native atherosclerosis originate locally from the media. VSMCs appear to be much more versatile than expected. Many potential therapeutic strategies are designed to activate or inhibit specific signaling pathways or molecular targets to reduce VSMC phenotypic modulation. In this review, we discussed the importance of the targets such as microRNAs, MMPs, integrins, oxidative stress, and autophagy in the mechanism that leads to VSMC phenotypic switch and vascular remodeling diseases. These molecular targets may serve as biomarkers and potential therapeutic targets for certain vascular disorders.

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