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REVIEW ARTICLE

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# Phenotypic switching of vascular smooth muscle cells in atherosclerosis, hypertension, and aortic dissection

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## Abstract

Vascular smooth muscle cells (VSMCs) play a critical role in regulating vasotone, and their phenotypic plasticity is a key contributor to the pathogenesis of various vascular diseases. Two main VSMC phenotypes have been well described: contractile and synthetic. Contractile VSMCs are typically found in the tunica media of the vessel wall, and are responsible for regulating vascular tone and diameter. Synthetic VSMCs, on the other hand, are typically found in the tunica intima and adventitia, and are involved in vascular repair and remodeling. Switching between contractile and synthetic phenotypes occurs in response to various insults and stimuli, such as injury or inflammation, and this allows VSMCs to adapt to changing environmental cues and regulate vascular tone, growth, and repair. Furthermore, VSMCs can also switch to osteoblast-like and chondrocyte-like cell phenotypes, which may contribute to vascular calcification and other pathological processes like the formation of atherosclerotic plaques. This provides discusses the mechanisms that regulate VSMC phenotypic switching and its role in the development of vascular diseases. A better understanding of these processes is essential for the development of effective diagnostic and therapeutic strategies.

**KEYWORDS**

aneurysm, cardiovascular disease, extracellular matrix, migration, theranostics

## 1 | INTRODUCTION

Vascular smooth muscle cells (VSMCs) are critical regulators of blood flow and distribution, as well as blood pressure (Brown et al., 2018). In adult vessels, VSMCs express specific signaling molecules, ion channels, and proteins that influence blood vessel contraction, as well as exhibiting modest synthetic activity and proliferative rates (Zhang et al., 2021). Additionally, differentiated VSMCs have a high degree of plasticity, allowing them to alter phenotypes in response to local changes in the environment (Owens et al., 2004).

VSMCs display distinct phenotypic characteristics depending on their location within the vessel wall and their functional role, as depicted in Figure 1 (Owens et al., 2004). Vascular tone and diameter are tightly controlled by contractile VSMCs, which are primarily situated in the tunica media of the vessel wall. Contractile VSMCs have a spindle-shaped morphology and are characterized by the expression of smooth muscle-specific contractile proteins such as α-smooth muscle actin (α-SMA), smooth muscle myosin heavy chain (SM-MHC), and calponin (Chamley-Campbell et al., 1979). In contrast, synthetic or secretory phenotypes are found in the tunica intima and adventitia and involved in vascular repair

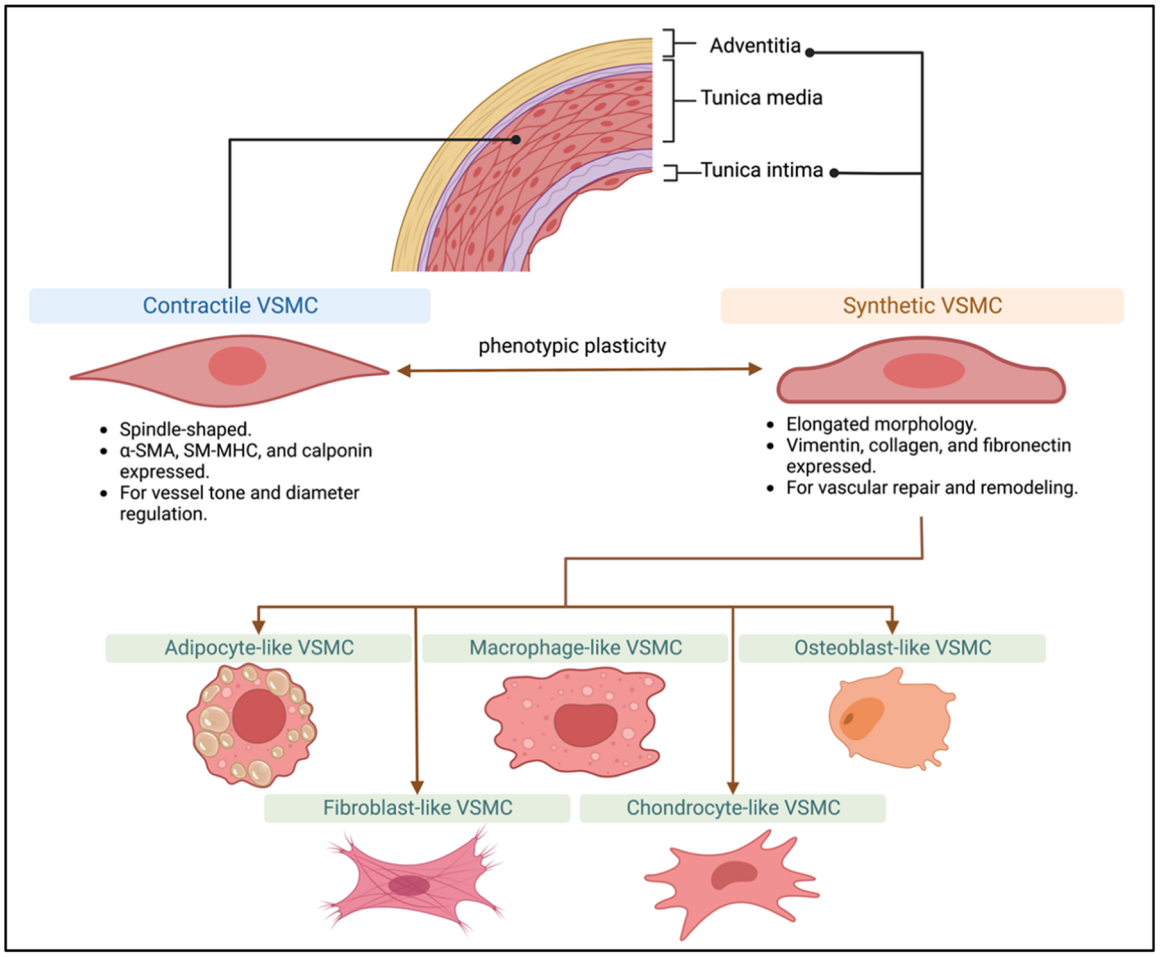


**FIGURE 1** The two main types of VSMCs: contractile and synthetic. Contractile VSMCs are predominantly found in the tunica media, whereas the synthetic VSMCs are found in the tunica intima and adventitia. While the contractile cells function mainly to regulate vasotone, the synthetic ones are important during repair and remodeling. VSMC, vascular smooth muscle cell.

and remodeling (Milutinović et al., 2020). Synthetic VSMCs exhibit a more elongated morphology and express proteins such as vimentin, collagen, and fibronectin. They also secrete growth factors and cytokines that contribute to the development of vascular diseases such as atherosclerosis (Milutinović et al., 2020).

The ability to switch between contractile and synthetic phenotypes allows VSMCs to respond to changing environmental cues, regulate vascular tone, promote growth, and facilitate repair. This phenotypic plasticity becomes especially important in response to certain insults and stimuli, such as injury or inflammation, two instigators of vascular disease (Owens et al., 2004). When the reparative process is completed, VSMCs revert to their non-proliferating contractile phenotype (Iyemere et al., 2006). However, in other circumstances, VSMC restoration is dysregulated, resulting in the transition of synthetic VSMCs into other cell types, such as fibroblast-like, macrophage-like, adipocyte-like, and chondrocyte-like cells (Zhang et al., 2021).

Phenotypic switching is implicated in numerous vascular diseases including atherosclerosis, hypertension, and aortic dissection (Coll-Bonfill et al., 2016; Gomes et al., 2017; Lu et al., 2022; Mosse et al., 1985; Napoli et al., 1997; Zhang et al., 2013). This switching, shown in Figure 1, is associated with reduced expression of SMC-specific markers, and a shift from spindle-shaped to epithelial-like morphology (Bochaton-Piallat et al., 1996). Populations of dedifferentiated VSMCs within an injured or diseased vasculature can be exceedingly variable, especially in the phenotypic divergence and dedifferentiation grade (Zhang et al., 2021). VSMCs can indeed transdifferentiate into other cell types such as chondrocytes, macrophages, and foam cells (Zhang et al., 2021). It has been postulated that VSMCs constitute at least a portion of the foam cells in atherosclerotic plaques (Wissler, 1967). Indeed, co-localization of the macrophage marker CD68 and the smooth muscle cell marker SMA was discovered in atherosclerotic human aortic cells (Andreeva et al., 1997). Additionally, VSMCs have shown the ability to transdifferentiate into osteoblast/chondrocyte-like cells (Bobryshev et al., 2008; Bobryshev, 2005; Speer et al., 2009).

VSMC switch is influenced by a variety of chemicals and environmental variables including inflammatory mediators, growth factors, lipids, retinoids, blood flow shear stress, oxidative

stress, and cell-to-cell contacts (Zhang et al., 2021). Understanding the mechanisms and signaling cascades that lead to a specific phenotype could uncover important avenues for designing effective interventions for vascular diseases. Therefore, this paper dissects the association between VSMC phenotypes and a battery of vascular diseases, and sheds light on the possibility of utilizing our emerging understandings for a better theranostics.

## 2 | MOLECULAR BASIS OF VSMC PHENOTYPIC SWITCH

There are several molecular and cellular parameters that contribute to the phenotypic plasticity of VSMCs. These include platelet-derived growth factor BB (PDGF-BB), insulin-like growth factor (IGF), insulin receptor substrate (IRS), basic fibroblast growth factor (bFGF), Angiotensin II (Ang. II), epidermal growth factor (EGF), lysophosphatidic acid (LPA), heparan sulfate proteoglycan (HSPG), transforming growth factor-β 1 (TGF-β1), receptor tyrosine kinases (RTKs), G-protein coupled receptors (GPCRs), TGF-β receptor, as well as extracellular matrix (ECM) proteins like fibronectin, vimentin, Type IV collagen, and laminin (Beamish et al., 2009; Krajnik et al., 2023; Li et al., 2023; McDaniel et al., 2007; Rabkin, 2023). Integrins and metalloproteinases are also well-known to control VSMC behavior and phenotype (Li et al., 2023). Signaling messengers like cyclic AMP and cyclic GMP as well as inflammatory cues, metabolic pathways, and reactive oxygen species are also involved (Aboukhater et al., 2023; Al Attar et al., 2022; Anwar et al., 2017, 2018; Aramouni et al., 2023; Badran et al., 2019, 2020; Bhagani et al., 2020; Lincoln, 2006; Maaliki et al., 2019; Shaito et al., 2022; Wehbe et al., 2020). Importantly, two main transcription factors that modulate expression of various genes implicated in phenotypic switch are serum response factor (SRF-2) and myocardin (Liang et al., 2022; Liu et al., 2023).

Of these aforementioned players, we focus here on TGF-β, PDGF-BB, IRS, and Ang II. These regulators interact with various signaling pathways and molecular mechanisms to control VSMC phenotypic switching in response to injury or disease. More importantly, aberrant regulation of these players can lead to adverse vascular remodeling and the development of cardiovascular pathologies.

### 2.1 | Role of TGF-β in VSMC phenotypic switch

TGF-β superfamily is a class of secreted polypeptides that function by activating downstream SMAD-dependent and SMAD-independent signaling pathways, such as PI3K/Akt, p38, and ERK1/2 (Zhang et al., 2020; Zhu et al., 2015). TGF-β, through PI3K-Akt signaling, reduces the expression of α-SMA and SM22α, two contractile markers, while at the same time, it increases the expression of synthetic marker protein osteopontin (OPN) (Zhu et al., 2015). These changes in protein levels mark the switch from a contractile to synthetic phenotypic.

### 2.2 | Role of PDGF-BB and IRS in VSMC phenotypic switch

PDGF-BB is an extensively studied and well-established cytokine that induces migration, proliferation, and phenotypic switching of VSMCs (Hwang et al., 2023; Ji et al., 2021; Song, Gao, et al., 2020; Zhao et al., 2011). For instance, PDGF-BB inhibits the expression of α-SMA in VSMC, while promoting markers of the synthetic phenotype (Hao et al., 2002). Mediators of these effects of PDGF have been identified, and they include JAK2/STAT3, ERK1/2, RhoA (Ouyang et al., 2014; Song, Cui, et al., 2020; Tong & Qi, 2018) among many others. Interestingly, accumulating evidence points to a role of microRNA in PDGF-induced phenotypic switch. For instance, PDGF-BB drives VSMC migration by promoting epithelial-mesenchymal transition (EMT) via partially suppressing microRNA 214 (miR-214) expression (Zhou et al., 2021). Additionally, miR-26a (Yang et al., 2017), miR-27b-3p (Li et al., 2021), miR-335-5p (Ma et al., 2022), miR-92 and others (Deng et al., 2019).

The role of PDGF-BB in VSMC phenotypic switching is further elicited by its intricate interplay with insulin receptor signaling components. For instance, PDGF induces dysregulation of insulin receptor substrate-1 (IRS-1) and IRS-2, key elements in insulin signaling. Interestingly, activation of Akt and p70S6kinase, two mediators of PDGF-induced phenotypic switch, promotes serine phosphorylation of IRS-1 and IRS-2, ultimately leading to IRS-2 downregulation in VSMCs. Moreover, IRS-1 downregulation potentiates VSMC proliferation via insulin-like growth factor-I (IGF-I)-induced activation of ERK1/2 (Radhakrishnan et al., 2010), another mediator of PDGF's effects. Indeed, the IRS-1-sequestered SHP-2 phosphatase is released when IRS-1 is downregulated. This release promotes the formation of a signaling complex that drives IGF-I-induced ERK-mediated VSMC proliferation (Hayashi et al., 2004).

### 2.3 | Role of Ang II in VSMC phenotypic switch

Ang II is well-known to contribute to physiological and pathological aspects of VSMC behavior. These cells express two receptors, type 1 (AT1) and 2 (AT2), which are the primary targets of Ang II on the cell surface of VSMCs (Ardaillou, 1999; Eguchi et al., 2023). While AT1 is primarily implicated in VSMC contraction (Hughes, 1998; Yu et al., 2012), a characteristic of differentiated phenotype, AT2 is known to promote proliferation or hypertrophy of these cells (Chow & Allen, 2016; Lemarié & Schiffrin, 2010; Nguyen Dinh Cat & Touyz, 2011; Ruiz-Ortega et al., 2003). The underlying molecular mechanisms for this Ang II-mediated phenotypic switch involve several players and signaling molecules including calcium, myocardin, fibronectin, SM-MHC, among others (Chassagne et al., 2002; Ha et al., 2017; Hu et al., 2000; Li et al., 2010; Shyu et al., 2015; Xu et al., 2019; Zhou et al., 2022).

### 2.4 | Role of other proteins in VSMC phenotypic switch

There are several other proteins that are also involved. One such protein is the SET and MYND domain containing protein 2 (SMYD2), a histone lysine methyltransferase. SMYD2, known for its roles in regulating carcinogenesis and inflammation, also plays a role in regulating VSMC behavior. For example, deletion of SMYD2 results in a significant increase in both proliferation and migration of VSMCs (Zhou et al., 2023). Conversely, overexpression of SMYD2 exerts a marked inhibitory effect PDGF-BB-induced proliferation and migration. Notably, SMYD2 deletion significantly influences the expression of myocardin and other genes implicated in differentiation of VSMCs (Toghill et al., 2018). In this context, it was recently reported that SMYD2's ability to suppress VSMC hyperplasia and neointima formation is mediated by myocardin (Liang et al., 2022; Zhou et al., 2023).

## 3 | ROLE OF PHENOTYPIC SWITCH IN ATHEROSCLEROSIS

Atherosclerosis is the leading cause of death in the developed world (Libby et al., 2011; Virmani et al., 2000). It is a chronic progressive inflammatory disease where lesions develop in the wall of large- and medium-sized arteries (Tabas et al., 2015). Although the exact cause of atherosclerosis is unknown, risk factors for atherosclerosis include obesity, high blood pressure, cigarette smoking, diabetes, elevated inflammatory markers, high levels of low-density lipoprotein (LDL), and low levels of high-density lipoprotein (HDL), as well as vascular aging, which is a significant contributor to the development and progression of atherosclerotic cardiovascular diseases (CVD) (Rafieian-Kopaei et al., 2014; Wang & Bennett, 2012). Although vascular aging hastens the progression of the disease, the developmental mechanisms that regulate atherosclerotic lesions are complicated (Childs et al., 2015). These lesions may lead to narrowing of the blood vessel, and consequently blockage of blood flow due to the buildup of atheromatous plaque (Lusis, 2000).

Clinical implications of atherosclerosis are caused by thrombotic events associated with rapid rupture or erosion of an unstable plaque, rather than by steady narrowing of the lumen (Bennett et al., 2016). As a thrombus clogs the artery, coronary artery disease, stroke, peripheral artery disease or renal infarction may ensue, depending on which vessels are affected (Bentzon et al., 2014). Several variables contribute to plaque instability and its consequent rupture. Some of these factors include a large necrotic core and a fragmented fibrous cap composed of smooth muscle actin-positive cells (Bennett et al., 2016).

Two preatherosclerotic lesions that are important in the development of atherosclerosis are intimal xanthomas and diffuse intimal thickenings (DITs) (Figure 2) (Ikari et al., 1999). While the former ones are present in areas that are prone to atherosclerosis and can develop into plaques, the latter are largely considered as the most likely precursor of such plaques (Velican, 1981; Virmani et al., 2000). DITs contain VSMCs, proteoglycans, and elastin but lack macrophages and thrombus (Ikari et al., 1999; Virmani et al., 2000). VSMCs of the DIT are clonal and are assumed to be derived from local medial VSMCs (Ikari et al., 1999; Kaur et al., 2017; Murry et al., 1997). Although there is variation among these cells, the majority display features of synthetic VSMCs compared with contractile VSMCs, which suggests a shift toward a synthetic phenotype (Mosse et al., 1985). These synthetic VSMCs are thought to be the predominant source of ECM in DITs during the preatherosclerotic stage, accounting for much of the increase in intimal thickness (Skålén et al., 2002). Furthermore, synthetic VSMCs metabolize lipids differently from contractile VSMCs, largely due to reduced amounts of the cholesterol efflux transporter ATP-binding cassette transporter ABCA1 (Campbell et al., 1983). This results in an increased inclination to convert into foam-like cells (Campbell et al., 1985).

Progression of DIT to pathological intimal thickening (PIT) is a key event in the early stage of atherosclerosis, as shown in Figure 2. Synthetic VSMCs are the primary cell type found within the plaque during early atherosclerosis and are responsible for producing atherogenic, lipid-retentive ECM rich in glycosaminoglycans and proteoglycans (Langley et al., 2017; Little et al., 2002; Skålén et al., 2002). This matrix can retain LDL apolipoproteins, which interact with VSMC-derived proteoglycans, leading to the retention and subsequent oxidation of LDL in the intimal layer (Napoli et al., 1997). Oxidized LDL is taken up by more VSMCs, leading to further transformation into foam-like cells and eventually inducing apoptosis (Basatemur et al., 2019).

As the intimal layer thickens, the change from DIT to PIT is also associated with a decrease or increase in VSMC or macrophage markers, respectively (Figure 2) (Gomez et al., 2013; Okura et al., 2000; Shankman et al., 2015). In atherosclerotic plaques, VSMCs account for 30%–70% of cells expressing macrophage markers, as well as 30%–40% of $CD68^+$ cells and 50% of foam cells (Allahverdian et al., 2014; Chappell et al., 2016; Shankman et al., 2015). This dedifferentiation is a crucial event in the progression of atherosclerosis since it causes a loss of contractile function in VSMCs, which are replaced by macrophages that produce ECM-degrading enzymes. Together with the accumulated lipids and inflammatory cells, these enzymes contribute to the formation of the lipid-rich necrotic core (Basatemur et al., 2019).

Late atherosclerosis is characterized by the progression from PIT to fibroatheroma, resulting in the formation of a fibrous cap and necrotic core, shown in Figure 2. Defective efferocytosis of apoptotic cells is associated with the formation of the fibrous cap and necrotic core by the extracellular lipid pools (Ait-Oufella et al., 2008; Basatemur et al., 2019; Clarke et al., 2010). VSMCs dedifferentiation into chondrocyte-like cells is an important event in fibroatheroma formation, and this shift is associated with the initiation of calcification and the formation of microcalcifications in the necrotic core of the atherosclerotic plaque (Rattazzi et al., 2005).

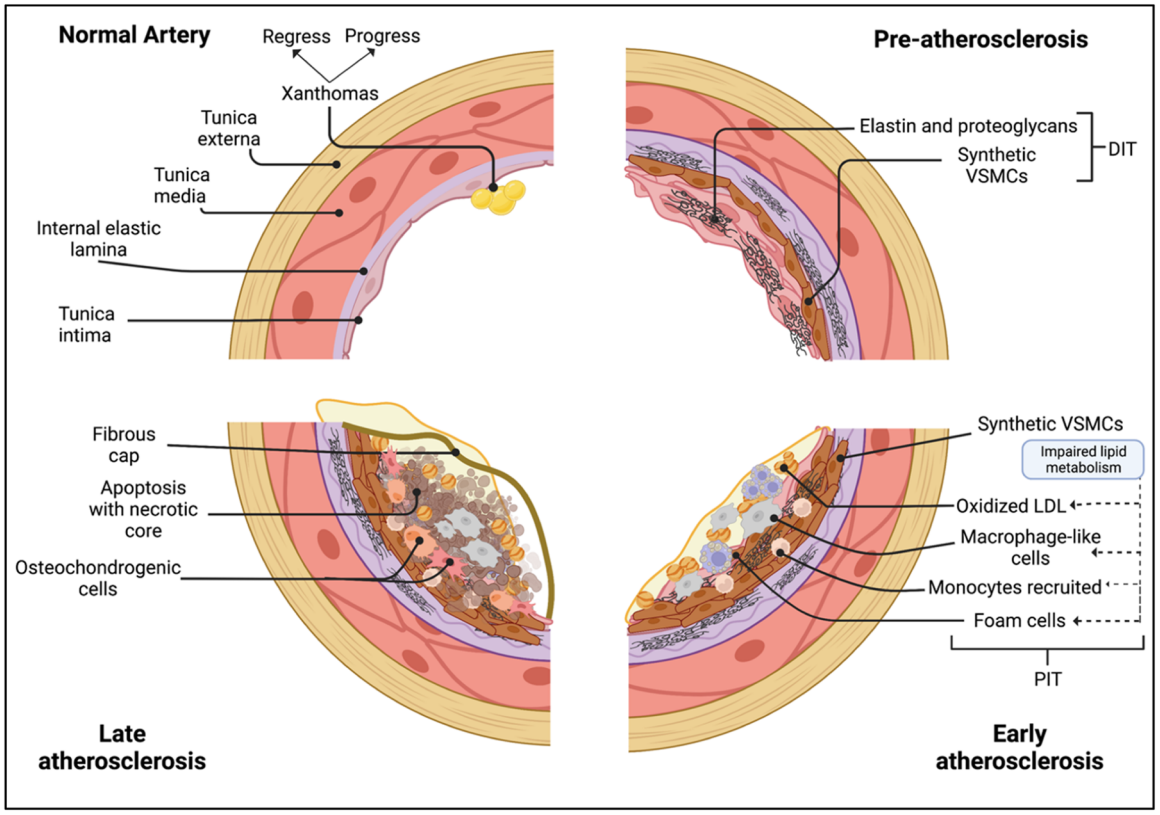


**FIGURE 2** Stages of atherosclerosis and the changes occurring with each stage. In the preatherosclerotic stage, the main change is DIT which is characterized by increasing population of synthetic VSMCs. In early atherosclerosis, the second stage there is a transition from DIT to PIT that has increasing differentiation of synthetic VSMCs to macrophage-like cells along with monocyte recruitment. In late atherosclerosis, there is increasing lipid accumulation, inflammation, and apoptosis of VSMCs with differentiation to osteochondrogenic cells and fibrous cap formation. DIT, diffuse intimal thickening; PIT, pathological intimal thickening; VSMC, vascular smooth muscle cell.

The osteochondrogenic phenotype of VSMCs is characterized by the expression of key genes involved in the formation of bone and cartilage, such as alkaline phosphatase, osteocalcin, and collagen type X (Hutcheson et al., 2016; New et al., 2013). Moreover, VSMCs also exhibit a marked increase in the expression of Runx2, a transcription factor that is essential for osteoblast differentiation and bone formation (Qin et al., 2020). In advanced atherosclerotic plaques, VSMCs can differentiate into chondrocyte-like cells, which express Sox9 and collagen type II, two markers of chondrogenesis. Contextually, SOX9 promotes chondrocytic differentiation while inhibiting VSMC differentiation into other cell lineages (Xu et al., 2012).

## 4 | ROLE OF PHENOTYPIC SWITCH IN HYPERTENSION

Systemic arterial hypertension, more commonly known as hypertension, is a leading cause of morbidity and mortality in the world, and the most common avoidable risk factor for CVD, chronic kidney disease (CKD), and cognitive decline (Forouzanfar et al., 2016). Globally, there are 1.4 billion estimated cases of hypertension; however, only 14% of those cases are under control (Forouzanfar et al., 2016). All prediction models have shown that blood pressure significantly contributes to CVD risk and that the association between hypertension and CVD is independent of other risk variables (Goff et al., 2014).

There are several etiologies for hypertension with 90%–95% of individuals have primary hypertension that has a complicated etiology, including interactions between genes and the environment (Oparil et al., 2018). On the other hand, secondary hypertension is a sequel of other illnesses that affect the endocrine, cardiovascular, or renal systems. Declines in arterial compliance brought on by aging and pathology have a significant role in determining the systolic component of hypertension (O'Rourke & Nichols, 2005). Therefore, arterial wall remodeling has a major role in the emergence and progression of hypertension-related complications.

The process of cellular phenotypic transition in hypertension is governed by multiple molecular pathways. These pathways can be activated by various stimuli such as vasoactive substances like Ang II, norepinephrine, and endothelin 1, as well as growth factors like IGF-1, EGF, and PDGF (Wynne et al., 2009). In addition, mechanical and physical factors such as stretch, pressure, and shear stress can also contribute to the process (Kennedy et al., 2016). These activities lead

to changes in the expression and functionality of genes that regulate ion channels, transporters, transcription factors, cell membrane receptors, ECM components, and growth signaling pathways—all of which are crucial for vascular remodeling in hypertension (Touyz et al., 2018).

VSMCs have the ability to differentiate into a phenotype that can endure high blood pressure in hypertensive patients (Reho et al., 2014). The contractile genes expressed by VSMCs in large arteries produce a tonic VSMC phenotype, while VSMCs in arterioles produce a phasic VSMC phenotype. However, VSMCs can lose their contractility markers and revert to a synthetic phenotype when exposed to vascular damage or biological stress signals (Owens et al., 2004). Synthetic VSMCs exhibit repressed contractile markers but greater levels of signaling molecules that promote cell proliferation, migration, fibrosis, and inflammation. These signaling molecules include cyclins, mitogen-activated protein kinases (MAPKs), transcription factors, and matrix metalloproteinases (MMPs) (Owens et al., 2004). MMPs, such as collagenases and elastases, may account for the synthetic VSMC phenotype's tendency to migrate toward damaged vasculature where they actively restructure the ECM (Willis et al., 2004).

α-SMA, SM-MHC, and calponin are key markers of differentiated contractile VSMCs, as they are vital for smooth muscle contraction (Rensen et al., 2007). Reduced expression of these markers causes increased VSMC proliferation and vascular remodeling (Bennett et al., 2016). Interestingly, several studies show that synthetic VSMCs in vessels subjected to high blood pressure show diminished expression of these markers (Cao et al., 2022). This argues for the close relationship between the low expression of these proteins and dysregulated vascular function.

One other key player in the phenotypic transition of VSMCs is the noncoding genome (Coll-Bonfill et al., 2016). Noncoding RNAs (ncRNAs) control several aspects of gene expression, including transcription, RNA processing, and translation (Albinsson et al., 2010; Statello et al., 2021). Numerous long noncoding RNAs (lncRNAs), such as H19, ANRIL, lncRNA-p21, lncRNA-362, and GAS5, have been linked to hypertension and VSMCs differentiation or proliferation (Gomes et al., 2017). Although most lncRNAs are expressed globally, smooth muscle and endothelial cell-enriched migration/differentiation-associated lncRNA (SENCR) seems uniquely expressed in VSMCs and endothelial cells (Bell et al., 2014). In this context, many Ang II-regulated lncRNAs have been associated with vascular remodeling in hypertension (Gangwar et al., 2018). In particular, lncRNA-GAS5 (growth arrest-specific 5) has been discovered as a regulator of hypertension-induced vascular remodeling, which, when knocked down, results in hypertension (Wang et al., 2016).

Chronic phenotypic transition leads to vascular dysfunction and arterial remodeling in hypertension and other clinical diseases linked to vascular damage (Touyz et al., 2018). The medial thickening, neointimal hyperplasia, and vascular stiffness associated with hypertension may occur due to an unchecked cell cycle with subsequent uncontrolled proliferation and resultant accumulation of dedifferentiated VSMCs in the vascular wall, as shown in Figure 3 (Nemenoff et al., 2011). Studies utilizing in vivo cell-tracking models have shown that >80% of VSMCs in arterial damage or vascular remodeling display characteristics of dedifferentiation (Shankman et al., 2015). Moreover, excessive VSMC-mediated remodeling of ECM within arterial walls may result in increased arterial stiffness (Lacolley et al., 2017), resulting in systolic hypertension and altered hemodynamic conditions in end organs such as the brain, kidneys, and heart (Smulyan et al., 2016).

Arterial calcification is frequent in hypertension and is associated with cardiovascular morbidity and mortality (Kang & Hata, 2012). Calcified lesions within vessels express higher levels of osteogenic and chondrogenic genes but lower levels of contractile markers as the calcification degree increases (Lee et al., 2019; Shen et al., 2011). This process can be triggered by various factors, including high calcium and phosphate levels, and can lead to the formation of microcalcifications that can grow into macrocalcifications (Jiang et al., 2012). VSMCs may transition into osteogenic or chondrogenic phenotypes during this process, exhibiting different markers and protein expression levels than their normal, contractile phenotype (Doherty et al., 2004). Osteogenic VSMCs, for example, show higher levels of alkaline phosphatase and Bone Morphogenetic Protein-2 (BMP-2) but lower expression of proteins that inhibit calcification (Doherty et al., 2004; Shanahan et al., 2011).

Vascular calcification is also facilitated by extracellular vesicles (EVs) produced by VSMCs. These EVs have been detected in the intimal and medial layers of the vessel wall (Kapustin et al., 2017) and are released from VSMCs when their phenotypic profile shifts toward a synthetic or osteogenic phenotype (Schurgers et al., 2018). Because they can bind calcium and produce ECM comparable with osteoblasts, EVs formed from VSMCs are similar to EVs obtained from osteoblasts. Before transitioning to an osteoblast-like state, the contractile VSMCs may first transdifferentiate into stem cells or other intermediate phenotypes.

## 5 | ROLE OF PHENOTYPIC SWITCH IN AORTIC DISSECTION

Aortic dissection is a relatively uncommon vascular disease with an incidence of around 5–30 cases per 1 million people per year (Baliyan et al., 2018). It is a catastrophic disorder that results from the separation of tunica intima and media, leading to internal hemorrhage (Cambria, 2002; Wu, 2018). Mortality in aortic dissection is not uncommon because the condition can lead to severe hemodynamic compromise (Mehta et al., 2002). The separated layers can be located at the ascending aorta, aortic arch, descending thoracic, and/or abdominal aortae. The DeBakey classification divides aortic dissection into three main types according to the location of the disorder (Pape et al., 2015). Type I is when the dissection involves the ascending aorta, aortic arch, descending thoracic aorta and may progress to involve the abdominal aorta. Type II occurs when the disorder is limited to the ascending aorta. While both types IIIa and

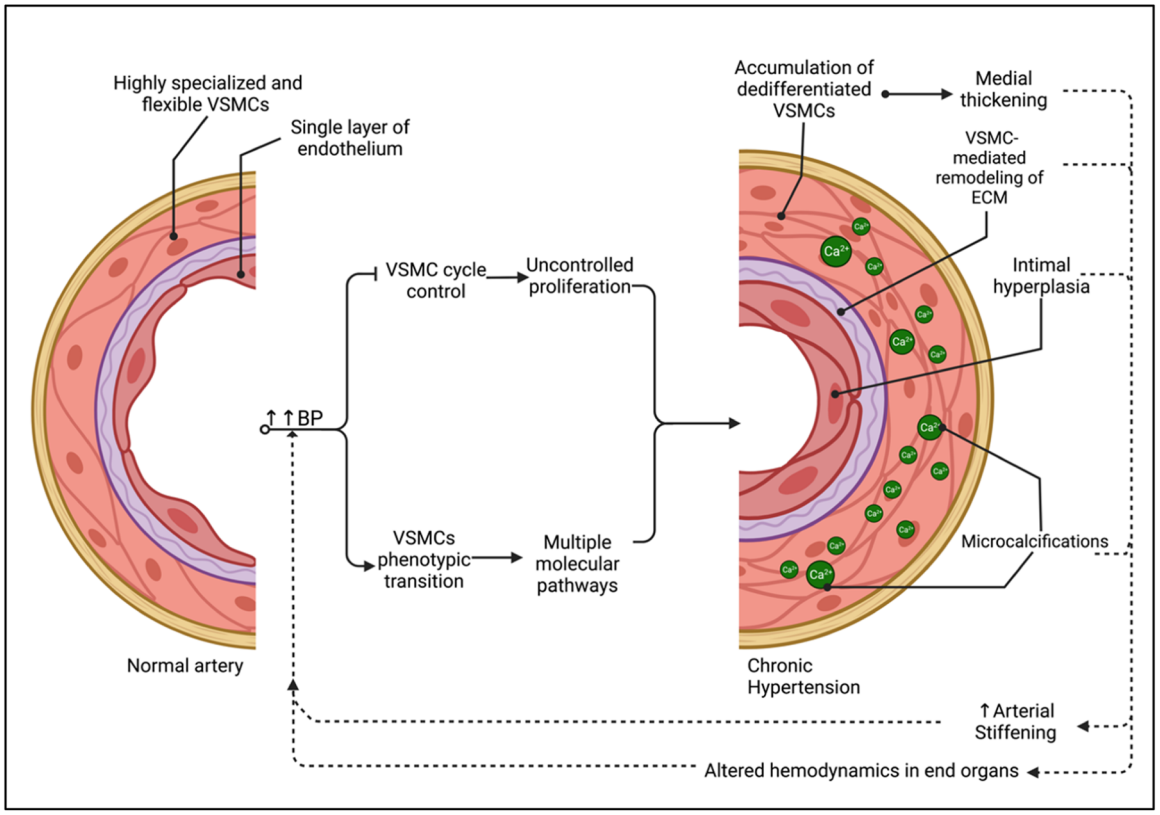


**FIGURE 3** The vicious process of changes in the arterial wall seen with chronic hypertension. The cell cycle of neointimal and medial cells is altered in chronic hypertension, leading to unchecked cellular proliferation and through multiple molecular pathways can induce VSMCs phenotypic transition. The net results of these mechanisms are accumulation of dedifferentiated VSMCs which causes medial thickening, as well as ECM remodeling, intimal hyperplasia, and microcalcification which collectively cause arterial stiffening and altered hemodynamic conditions in end organs leading to a further increase in blood pressure. ECM, extracellular matrix; VSMC, vascular smooth muscle cell.

IIIb involve the thoracic and abdominal aortae distal to the left subclavian artery, type IIIa takes place proximal to the celiac artery compared with type IIIb, which occurs distal to the celiac artery.

It is well-established that phenotypic switching is implicated in the pathogenesis of aortic dissection. Indeed, weakening of the aortic wall is characterized by loss of VSMCs due to apoptosis and ECM degradation within the medial layer of the aortic wall (Figure 4). A delicate balance in VSMC phenotypes is key to maintain aortic physiology, and imbalance as in phenotypic switching can precipitate or exacerbate aortic dissection (Frismantiene et al., 2018). Indeed, during the progression of aortic dissection, the balance between contractile and synthetic VSMCs is shifted toward synthetic VSMCs with increased proteolytic enzyme production by those VSMCs, as depicted in Figure 4. Additionally, VSMCs in the medial layer of the aortic wall in aortic dissection patients show decreased contractile function and increased proliferation and migration (Lu et al., 2022; Zhang et al., 2013).

In aortic dissection patients, the expression of osteoblast-like and chondrocyte-like markers such as alkaline phosphatase and type X collagen has been shown to be increased (Chen et al., 2022; Yu et al., 2015). Moreover, the presence of calcified regions in the aortic wall, suggestive of osteoblast-like VSMCs, could predict poor outcomes and increased mortality (Alves et al., 2014). Likewise, chondrocyte-like VSMCs have been shown to contribute to the formation of neointima (Beazley et al., 2013; Kuro-o et al., 1991). In relevance to this, neointima has been observed in aortic dissection patients, particularly in those with chronic or recurrent dissection (Horiuchi et al., 2005). Additionally, although contractile VSMCs undergoes apoptosis, synthetic VSMCs with osteoblast- or chondrocyte-like phenotypes have been shown to be resistant to apoptosis, which may contribute to the accumulation of these cells in the arterial wall and the progression of aortic dissection (Bennett & Boyle, 1998; Bennett et al., 1995).

The exact mechanisms underlying VSMC phenotypic switching in aortic dissection are not fully understood, but several factors have been implicated. For instance, oxidative stress, which is increased in aortic dissection, can promote VSMC phenotypic switching by inducing the expression of pro-inflammatory cytokines and growth factors such as interleukin-1β (IL-1β) and transforming growth factor-β (TGF-β) (Lu et al., 2021). Additionally, MMPs have been shown to promote VSMC phenotypic switching by releasing growth factors from the ECM (Cai & Wang, 2017).

Multiple studies suggest that levels of legumain (LGMN), a lysosomal cysteine protease, are significantly upregulated in aortic

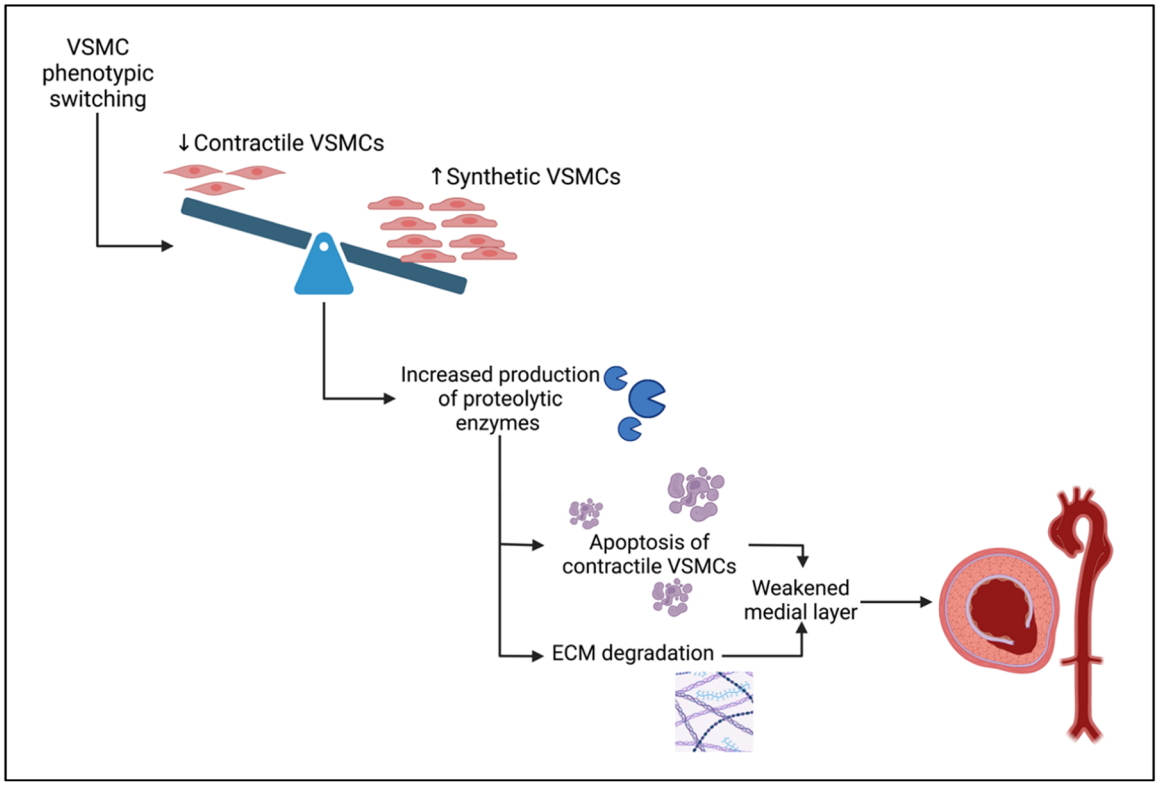


**FIGURE 4** Role of VSMC pathophysiology in aortic dissection. The initial step seems to involve phenotypic switching from contractile to synthetic VSMCs that occurs due to unclear mechanisms. Synthetic VSMCs causes increased production of proteolytic enzymes that leads to ECM degeneration and VSMCs apoptosis. These changes over time lead to weakening of the medial layer and increases the risk of aortic dissection. ECM, extracellular matrix; VSMC, vascular smooth muscle cell.

tissues with thoracic aortic dissection (TAD) compared with those from patients without TAD or healthy controls (Lunde et al., 2017; Pan et al., 2022). Another study that specifically looked at the effect of LGMN deficiency on phenotype switch in VSMCs showed that homozygous knockout of LGMN represses VSMC phenotypic switch in mice (Pan et al., 2022). Importantly, in these knock-out cells, levels of key markers of contractile phenotypes are upregulated (Pan et al., 2022). These include myocardin, a determinant of VSMC contractile phenotype, MYH11 (myosin-11), SM22α (smooth muscle 22α), and calponin 1 (Pan et al., 2022). This supports the hypothesis that LGMN plays a role in the development of TAD (Pan et al., 2022).

Another protein that is implicated in abdominal aortic dissection (AAD) and VSMC phenotype switching is aldehyde dehydrogenase 2 (ALDH2). In a case-control study, ALDH2 deficiency was shown to reduce the risk of AAD by 50% compared with wild-type alleles (Tsai et al., 2020). It appears that one mechanism by which ALDH2 regulates phenotypic switch is involves miR-31-5p (Yang et al., 2020). Indeed, ALDH2 loss-of-function significantly diminishes the expression of miR-31-5p, which itself is known to suppress myocardin (Yang et al., 2020). Together, these findings shows that the ALDH2-miR-31-5p-myocardin is an important parameter in the onset of phenotypic switch.

## 6 | PHARMACOLOGIC INTERVENTIONS

VSMC phenotypic switching is a complex and multifactorial process regulated by various intracellular and extracellular mechanisms (Kawai-Kowase & Owens, 2007). The modulation of VSMC phenotypes is crucial for mitigating the substantial impact of CVD on human health. Traditional therapeutic strategies for CVD primarily center on managing risk factors like blood pressure, lipid levels, and glucose. Recent advancements in technologies such as fate mapping and single-cell transcriptomics have identified fundamental pathways that influence VSMC phenotype, providing novel therapeutic targets for the effective treatment of CVD (Chakraborty et al., 2021).

### 6.1 | Drug-eluting stents (DES)

An effective approach addressing VSMC phenotypic switching involves the utilization of DES in coronary artery revascularization. These devices work to prevent restenosis by locally delivering antiproliferative agents to the vascular site via coated stents. Specifically, rapamycin-eluting stents and paclitaxel-eluting stents stand as the forefront technology in preventing restenosis during coronary revascularization (Khan et al., 2012). Rapamycin (sirolimus), a macrolide antibiotic with well-characterized antiproliferative and

immunosuppressive effects, exerts its effects by binding to FK-binding-protein, thereby inhibiting the kinase activity of mTORC1 (Lamming, 2016). By targeting mTOR signaling, rapamycin-eluting stents induce cell cycle arrest at the G1/S transition and consequently inhibit VSMC proliferation, in addition to suppressing migration, and phenotypic switching (Martin et al., 2004). It is for these reasons that rapamycin-eluting stents are a preferred choice for preventing restenosis (Windecker et al., 2005).

Paclitaxel is a microtubule-stabilizing chemotherapeutic agent that selectively binds to beta subunits of tubulin proteins, impairing microtubule disassembly and thereby inducing mitotic arrest. In addition, by virtue of its effects on the cytoskeleton, paclitaxel has been shown to suppress VSMC migration (Axel et al., 1997). These findings prompted the utilization of paclitaxel-eluting stents for prevention of restenosis. Indeed, evidence demonstrates clinical efficacy of these stents in preventing in-stent restenosis (Bernabeu et al., 2017). However, recent reviews of randomized controlled trials have raised concerns about the safety of paclitaxel-coated stents in limb revascularization, associating them with increased all-cause mortality following lower limb endovascular interventions (Katsanos et al., 2018; Nordanstig et al., 2020). As such, usage of DES has moved away from paclitaxel- to Limus-based stents.

## 6.2 | Epigenetic regulators

Targeting epigenetic regulators that influence gene expression, such as DNA methylation, histone acetylation, and ncRNA, represents a promising approach in addressing VSMC phenotypic switching. DNA methylation, a process mediated by DNA methyltransferases (DNMTs) and counteracted by the ten-eleven translocation (TET) family of proteins, plays a crucial role in controlling VSMC phenotype by regulating the expression of numerous genes (Alexander & Owens, 2012). Specifically, both in vivo and in vitro studies show that knockdown of TET2 promotes VSMC phenotypic switching. This occurs by inhibiting the expression of key genes, including myocardin and SRF, while concurrently increasing the expression of KLF4. Conversely, TET upregulation induces a contractile phenotype by exerting opposing effects (Liu et al., 2013). In $ApoE^{-/-}$ mice, inhibiting DNMT using 5-aza-2'-deoxycytidine has been shown to ameliorate the methylation status of the TET2 promoter, thereby preventing VSMC dedifferentiation (Zhuang et al., 2017).

Targeting histone modifications represents another potential avenue for controlling VSMC phenotypic switch and mitigating vascular diseases. Histone acyltransferases (HATs) and histone deacetylases (HDACs) play pivotal roles in modifying chromatin structure through the regulation of histone acetylation, influencing eukaryotic gene expression. Several studies have highlighted the close relationship between HDACs and the phenotypic transition of VSMCs, with HDAC inhibitors proving successful in preventing VSMC dedifferentiation (Findeisen et al., 2011; Yoon & Eom, 2016). In addition to histone modification, HDACs can modify nonhistone proteins in VSMCs, further influencing cellular behavior. In particular, class II HDACs (HDAC 4, 5, 7, and 9) have been shown to interact with myocardin, suppressing its promyogenic activity and inhibiting the expression of contractile genes (Cao et al., 2005). Conversely, HDAC inhibition, such as with trichostatin A, rescues myocardin and helps maintain smooth muscle gene expression that promotes VSMC differentiation (Spin et al., 2010). Another class of proteins, the Bromodomain and Extra Terminal (BET) family, binds to acetylated histones, acting as molecular scaffolds for transcription factors and cofactors to regulate transcription. Numerous BET inhibitors are currently undergoing testing in preclinical and clinical trials, showing promise for the treatment of CVD (Lin & Du, 2020; Schooling & Zhao, 2019; Wang et al., 2015). A notable example is apabetalone (RVX-208), a bromodomain 2-selective BET inhibitor, which has undergone a phase III clinical trial. This trial demonstrated that apabetalone is associated with decreased rates of cardiovascular death and myocardial infarction compared with a placebo, leading the US Food and Drug Administration to grant apabetalone a breakthrough therapy designation (Nicholls et al., 2018).

In addition to the aforementioned regulators, microRNAs (miRNAs) have recently emerged as crucial modifiers of VSMC phenotype, offering potential targets for finely tuning the complex pathway of VSMC behavior. Notably, miRNA 221/222 have been demonstrated to promote VSMC phenotypic switch by inhibiting negative regulators of the cell cycle, such as p27, p57, and c-kit (Davis et al., 2009). In the context of atherosclerosis, miRNA 221/222 have demonstrated a propensity to promote neointimal hyperplasia (Liu et al., 2012). Conversely, knockdown of miRNA 221/222 has been found to mitigate neointimal hyperplasia in balloon-injured rat carotid arteries (Liu et al., 2009). Similarly, studies have unveiled that miRNA 21 plays a role in promoting neointimal growth through its proliferative effects on VSMCs. As such, knocking out miRNA 21 could prevent neointimal hyperplasia in mice carotid arteries after balloon angioplasty (Cheng & Zhang, 2010). On the contrary, miRNA 143/145 have been identified as promoters of VSMC differentiated and contractile phenotype. This is mediated by promoting myocardin expression while concurrently suppressing the expression of Krüppel-like factor 4 (KLF4) and calmodulin kinase II-δ (Rangrez et al., 2011). More recently, miRNA 128 has emerged as a novel regular of VSMC phenotype. Overexpression of miRNA 128 significantly decreases VSMC proliferation and migration while promoting a contractile phenotype (Farina et al., 2020). Collectively, these miRNAs add a layer of complexity to our understanding of VSMC phenotypic switching, presenting potential avenues for targeted interventions in CVD.

## 6.3 | Transcription factors

The phenotypic characteristics of VSMCs are defined by a delicate balance between genes that promote growth and proliferation and those that encode contractile proteins. Different transcriptional pathways have been demonstrated to promote distinct pattern of gene expression in VSMCs, thus modulating their phenotypic transition (Zhang et al., 2016). The Hippo pathway, originally identified in

*Drosophila melanogaster*, plays a crucial role in VSMC phenotypic switching. At its core, activation of this pathway inhibits VSMC proliferation and migration (Kimura et al., 2016). Mechanistically, the activation of Hippo pathway initiates a kinase cascade, resulting in the phosphorylation of two key transcriptional coactivators, Yes-associated protein (YAP), and transcriptional coactivator with PDZ-binding motif (TAZ). Phosphorylated YAP/TAZ undergo functional inactivation, preventing their excessive entry into the nucleus and inhibiting their interaction with the TEAD 1-4 (transcription enhancer activation domain). Consequently, YAP/TAZ lose their ability to promote cell proliferation (Ma et al., 2019). Studies in human umbilical arterial smooth muscle cells (HUASMCs) showed that increased arterial wall stress induces VSMC phenotypic switching through YAP/TAZ activation. Knockdown of YAP/TAZ significantly attenuated the stretch-induced remodeling process (Wang et al., 2018). Animal studies demonstrated YAP upregulation in response to experimental arterial injury, and YAP knockdown attenuated injury-induced intima formation (Osman et al., 2021). Recent reports emphasize the role of prostacyclin in promoting the Hippo pathway, thereby inhibiting VSMC proliferation and promoting differentiation (Fetalvero et al., 2007). PGL2, through binding to its specific receptor (IP) on the VSMC surface, activates adenylyl cyclase (AC), leading to the formation of the second messenger cAMP (cyclic adenosine monophosphate) and stimulating cAMP-dependent protein kinase PKA. Elevated cAMP promotes YAP/TAZ phosphorylation and degradation, thereby suppressing gene expression facilitated by the YAP/TAZ-TEAD signaling pathway, and inhibiting VSMC proliferation (Fetalvero et al., 2006). Conversely, thromboxane A2 (TxA2) has been demonstrated to play a significant role in inducing VSMC proliferation and migration after vascular injury (Owens et al., 2004). Thromboxane's operation through the TP receptor prevents YAP/TAZ phosphorylation, influencing the normal physiological process of wound healing in response to vascular injury. However, excessive YAP/TAZ activation mediated by TP under pathological circumstances has been associated with VSMCs migration and proliferation, ultimately contributing to neointima formation and restenosis after angioplasty (Garas et al., 2001). Furthermore, mice models overexpressing TP receptor demonstrated an exaggerated proliferative response of VSMCs to vascular injury, and this can be inhibited by the TP receptor antagonist S18886 (Cheng et al., 2002). In animal models of atherosclerosis, treatment with S18886 demonstrated substantial regression in the progression of atherosclerotic lesion (Cayatte et al., 2000; Egan et al., 2005). Additionally, the administration of terutroban (a TP receptor antagonist) to spontaneously hypertensive rats prevented hypertension-induced vascular hypertrophy and fibrosis (Gelosa et al., 2011).

Peroxisome proliferator-activated receptors (PPARs)-γ are another class of transcription regulators that play multiple roles beneficial to VSMC phenotype. Thiazolidinedione (TZD), a PPAR activator, enhances insulin sensitization in diabetic patients and exerts substantial effects on VSMCs by modulating inflammatory processes. In mice models with cuff-induced injury, PPAR agonist pioglitazone abrogated neointima formation by inhibiting VSMC hyperplasia (Kubota et al., 2016). Similarly, rosiglitazone administration to mini-pigs undergoing internal carotid artery stenting resulted in significant reduction of neointima formation by attenuating local and systemic inflammatory response and VSMC proliferation (Wu et al., 2017). In-vitro experiments revealed that rosiglitazone inhibit VSMC dedifferentiation by counteracting PDGF-induced reduction of protein kinase G level (Yang et al., 2013). Conversely, SMC-PPARγ deletion is associated with exaggerated vascular dysfunction and lesion formation in hypertensive or atherosclerotic mice models (Mukohda & Ozaki, 2021). Systematic reviews and meta-analyses of human clinical trials demonstrate that TZDs significantly attenuate in-stent restenosis in diabetic and nondiabetic patients undergoing coronary revascularization (Geng et al., 2009; Rosmarakis & Falagas, 2007). Interestingly, the beneficial effects of TZDs have been reported to be partially mediated by adiponectin (Kubota et al., 2016). Adiponectin is a cardioprotective adipokine secreted primarily by adipocytes and to a lesser degree by VSMCs, and it has shown to influence VSMC function through autocrine or paracrine modes (Sowka & Dobrzyn, 2021). In particular, adiponectin promotes the contractile phenotype of VSMC and inhibits dedifferentiation by inhibiting mTORC1 through activation of AMP-activated protein kinase (AMPK) (Ding et al., 2012). It is well established that adiponectin levels are increased with TZDs treatment (Combs et al., 2002; Phillips et al., 2003). In animal models with experimental vascular injury, oral administration of AdipoRon (an adiponectin receptor agonist) was associated with significant reduction of injury-induced neointima formation by inhibiting mTOR signaling independent of AMPK (Fairaq et al., 2017). Furthermore, a recent meta-analysis of randomized controlled trials confirmed a notable increase in plasma adiponectin concentrations following statin use, contributing to the pleiotropic effects exerted by statins (Chruściel et al., 2016).

## 7 | CONCLUSIONS AND PERSPECTIVES

The link between VSMC phenotype and vascular disease is ever evident. The ability to switch between different phenotypes in response to various stimuli underscores VSMCs' importance in maintaining vascular homeostasis. It also provides new opportunities for theranostics and precision medicine, as there will be a pressing need to develop novel disease-specific therapies that target selected VSMC phenotypes more effectively. Thus, further research into this phenotypic switching and its role in the pathogenesis of vascular disease is still warranted and encouraged.

### AUTHOR CONTRIBUTIONS

**Mohamed Elmarasi**: Writing original draft. **Ibrahim Elmakaty**: Writing original draft. **Basel Elsayed**: Writing original draft. **Abdelrahman Elsayed**: Writing original draft. **Jana Al Zein**: Writing original draft. **Ammar Boudaka**: Writing: review and editing. **Ali H. Eid**: Conceptualization; writing original draft; writing: review and editing; resources; supervision; project administration.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of Interest.

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