



# Endothelial–Vascular Smooth Muscle Cells Interactions in Atherosclerosis

Manna Li<sup>1</sup>, Ming Qian<sup>1</sup>, Kathy Kyler<sup>2</sup> and Jian Xu<sup>1\*</sup>

<sup>1</sup> Department of Medicine, Harold Hamm Diabetes Center, University of Oklahoma Health Sciences Center, Oklahoma, OK, United States, <sup>2</sup> Office of Research Administration, University of Oklahoma Health Sciences Center, Oklahoma, OK, United States

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### \*Correspondence:

Jian Xu  
jian-xu@ouhsc.edu

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Atherosclerosis is a chronic progressive inflammatory process that can eventually lead to cardiovascular disease (CVD). Despite available treatment, the prevalence of atherosclerotic CVD, which has become the leading cause of death worldwide, persists. Identification of new mechanisms of atherogenesis are highly needed in order to develop an effective therapeutic treatment. The blood vessels contain two primary major cell types: endothelial cells (EC) and vascular smooth muscle cells (VSMC). Each of these performs an essential function in sustaining vascular homeostasis. EC-VSMC communication is essential not only to development, but also to the homeostasis of mature blood vessels. Aberrant EC-VSMC interaction could promote atherogenesis. Identification of the mode of EC-VSMC crosstalk that regulates vascular functionality and sustains homeostasis may offer strategic insights for prevention and treatment of atherosclerotic CVD. Here we will review the molecular mechanisms underlying the interplay between EC and VSMC that could contribute to atherosclerosis. We also highlight open questions for future research directions.

**Keywords:** atherosclerosis, cardiovascular disease, cell interactions, endothelial cells, vascular smooth muscle cells

## INTRODUCTION

Atherosclerosis, or hardening of the arterial blood vessel wall, is a chronic progressive inflammatory disorder. The disorder presents with coronary artery disease, carotid artery disease, peripheral artery disease, or combined, cardiovascular disease (CVD) (1). With life-threatening complications, including myocardial infarction and stroke, CVD is the leading cause of death worldwide. Despite available treatments, CVD prevalence continues, suggesting an urgent need to identify the pathogenic molecular mechanisms and develop effective therapeutic approaches. Blood vessel walls are comprised primarily of endothelial cells (EC) and vascular smooth muscle cells (VSMC). Each cell type has an important role in vascular homeostasis. Interaction between these two major cell types is fundamental not only to the development and formation of the vasculature, but also to the function of mature vasculature (2), such as maintaining vessel tone in mature vessels. Their communication is critical for repair and remodeling associated with blood vessel growth. A Compendium on Atherosclerosis (3) recently provided comprehensive reviews on the roles of ECs (4) and VSMCs (5) in the pathological progression of atherogenesis. However, the modes and molecular mechanisms of the EC-VSMC conversation that causes atherosclerosis are less known. Identification of the pathways underlying EC-VSMC interaction-mediated vascular homeostasis in the course of atherogenesis can offer strategic insights for the prevention and treatment of atherosclerotic CVD. While general functions of individual ECs and VSMCs have been extensively

reviewed elsewhere, the present review summarizes the emerging evidence that connects physical (direct) and biochemical (indirect) crosstalk between ECs and VSMCs to atherogenesis, and highlights the unanswered questions that merit future investigations.

## ROLES OF EC AND VSMC IN ATHEROSCLEROSIS

Atherosclerotic lesion formation is a complex process, with initiation and progression dependent on a localized inflammatory response that facilitates changes in the vessel wall (6, 7). Fatty streaks in arterial walls gradually develop into atheroma and characteristic plaques. The acute rupture of these atheromatous plaques causes local thrombosis, leading to partial or total occlusion of the affected artery. The clinical consequences of these plaques depend on their site and the degree and speed of vessel occlusion. The disease has a latency of many years, and frequently coexists in more than one vascular bed. Its major clinical manifestations include ischemic heart disease, ischemic stroke, and peripheral arterial disease.

Abnormal heterotypic cell communication can cause vascular defects (4). A major piece of evidence supporting this notion is that endothelial dysfunction, a well-defined pathological state of the endothelium, underlies vascular impairment in atherosclerosis (8, 9), hypertension, hypercholesterolemia, and diabetes (10). A detectable change in the vascular reactivity and composition of the vascular wall is a common feature of these diseases. It is widely accepted that the effects of endothelial dysfunction on VSMCs are reduction of NO bioavailability and/or augmentation of vasoactive constrictors released from the endothelium (8, 9). Endothelial dysfunction has been positively associated with the pathology of metabolic disorders and the related vascular complications (10, 11). VSMCs, another major type of vascular cell, play a crucial role in the initiation and development of atherosclerosis (6). Mechanistically, normal and controlled VSMC proliferation is beneficial in atherogenesis, while dysregulated VSMC proliferation contributes to plaque formation and aberrant inflammation (5, 12). Thus, endothelial dysfunction contributes to impairment of NO-dependent vasodilatation, cellular glucose uptake, enhanced oxidative stress, and inflammation, leading eventually to atherosclerosis (1, 13–16).

## MODES OF EC-VSMC INTERACTIONS IN ATHEROSCLEROSIS

The individual functions of ECs and VSMCs are dependent on their proper interaction, which is fundamental to the formation and function of the vasculature (2). The early interactions begin at embryogenesis when the blood vessels are forming (2, 17). The intimate EC-VSMC interaction may also determine the outcome of vascular homeostasis under diseased conditions, including atherosclerosis. Great progress has been made in understanding EC-conveyed signals to SMC regulating vascular tone and the basic interplay that occurs during vessel assembly. However,

modes of EC-VSMC communication in adults can be very different from those in developing humans. For vessel assembly, the proliferation and migration of adult EC-VSMC cells are less dynamic. Moreover, physical interactions of EC-VSMC might be blocked by the basement membrane and the internal elastic lamina in mature blood vessels. ECs and VSMCs have evolved various modes of interaction to regulate vascular function and sustain homeostasis. Although it remains largely unclear how defects in EC-VSMC interaction could lead to atherosclerosis, an overview of the mode of EC-VSMC interaction is timely and will help to identify key outstanding problems.

## EC-VSMC INTERACTION VIA DIRECT CONTACT

EC-VSMC interaction *via* direct contact, which has contributed to arterial-venous identity, vascular tip cell specification and sprouting, and VSMC differentiation in vascular development, occurs in embryonic growth (2). In adult vasculature, junctional molecules, such as intercellular adhesion molecules, mediate most of the direct contact between vascular cells (18) N-cadherin, which was believed to mediate EC-VSMC physical adhesion, was found in layers of ECs and VSMCs beneath the internal elastic membrane in adult vasculature (19). Connexins are the next regulator of EC-VSMC interaction in adult blood vessels (20). Connexin 43 post-translational modification by nitrosylation (21) and phosphorylation (22), respectively, alters vascular reactivity. Like ECs, VSMCs also express intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) in atherosclerosis (23), restenosis (24), and transplant vasculopathy (25). There are reports of direct communications between ECs and VSMCs that affect vasculature formation. *In vitro* data suggested that EC-expressed Jagged1 could interact with NOTCH3 on neighboring SMCs, which activated NTOCH signaling, promoting more NTOCH3 expression in the SMCs (26). Another example of contact-dependent interplay involves Ephrin receptor tyrosine kinases (Eph), which are activated by binding to ephrin ligands that are linked to the cell membrane *via* glycosylphosphatidylinositol anchor (ephrin A) or *via* a transmembrane domain (ephrin B) (27). Among well-studied receptor-ligand pairs (28), a reciprocal interaction of EphB4 and ephrin-B2 from both ECs and VSMCs is required in growing blood vessels (29). Both ephrin and receptors have been detected in atherosclerotic plaques (30, 31), indicating a strong association of these proteins with the inflammatory outcome in atherosclerosis (32). A causal role of the direct contact in atherogenesis has yet to be established; however, data for a role of indirect EC-VSMC interaction are emerging.

## EC-VSMC INTERACTION VIA ENOS-DERIVED NO

While developmental signals are required by mature vessels for basal function, they rely on further interactions regulating such vascular functions as vascular tone and blood pressure (33). These signals operate by employing endothelium-derived

hyperpolarizing factor (EDHF) (e.g., eNOS-derived NO) and gap junctions that couple EC-VSMC. Mechanistically, EDHF-induced hyperpolarizing current spreads quickly, leading to vasodilatation and thereby increasing blood flow, while small molecules (e.g.,  $Ca^{2+}$ ) also coordinate changes in diameter and modulate vascular responses. EC-derived NO has also been reported to change flow-dependent vascular remodeling by negatively regulating the platelet-derived growth factor (PDGF) pathway (34). Moreover, increased myoendothelial junctions could be a way of enhancing the interaction, as observed in caudal arteries of spontaneously hypertensive rats (35). In contrast, pharmacological blocking of myoendothelial GAP-junction impaired EC-induced contraction (36). These data suggest EC-mediated SMC hyperpolarization as a mode of EC-VSMC conversation (37, 38).

## EC-VSMC INTERACTION VIA THE EXTRACELLULAR MATRIX (ECM)

A primary feature of atherosclerotic plaques is a transition state of VSMCs, which become proliferative and secrete excess ECM to build up the plaque lesion (6). The ECM was traditionally regarded as a cellular scaffold or foundation to maintain the mechanical properties of blood vessels. It is now known as a source of signaling mediators (39). Alterations in the ECM have structural implications and signaling changes that disrupt EC-VSMC interactions. Both ECs and SMCs synthesize and secrete ECM, which is a complex mixture of components derived from ECs and VSMCs (39, 40), and could influence the function of neighboring cells (41). Indeed, interventional angioplasty to remove diseased plaques may induce EC denudation, damage, and further dysfunction, attributable to the loss of the suppressive effects on VSMC proliferation, thereby causing restenosis (42).

## EC-VSMC INTERACTION VIA EXTRACELLULAR VESICLES

Extracellular vesicles (EVs) are phospholipid bilayer-enclosed membrane sacs that emerged as a mechanism regulating cell-cell communication (43). EVs include exosomes, microparticles, and apoptotic bodies, which carry biomolecules, such as proteins, DNA, mRNA, and noncoding RNA (44). Under physiological conditions, ECs constitutively secrete low concentrations of EVs into the circulation. However, endothelial EV levels increase under various diseases conditions involving endothelial injury or dysfunction (45). EC-derived EVs contain proteins with emerging roles in atherogenesis (43). EVs have been reported to function in post-plaque rupture responses, which promote tissue factor, a rate-limiting enzyme, to initiate the coagulation cascade. Both ECs (46) and VSMCs (47) can release TF-loaded VEs; however, it remains unknown how EC and VSMC talk to each other to control the proper release of the same factor. Notably, one of the cargoes carried by EC-derived EVs is miRNA, a discussion of which follows below.

## EC-VSMC INTERACTION VIA MICRORNAS (MIRNAS)

MiRNAs are evolutionarily conserved and noncoding small RNAs. miRNAs are secreted from cells and can be picked up by other cells (48). MiRNAs function as important regulators and fine-tuners of a range of pathophysiological cellular effects and molecular signaling pathways involved in atherosclerosis (49). Early studies demonstrated that miRNAs mediate atheroprotective communication between EC-VSMC (50). A recent study showed that ECs could inform VSMCs to proliferate *via* a direct secretion of miR-126 from ECs to VSMCs (51), which augments VSMC turnover and worsens atherosclerosis. In line with these findings, atheroprotective shear stress blocked miR-126 release (51). A similar atheroprotective effect was observed when EC-derived miR-143/145 were transferred to VSMCs through an EV-mediated pathway (50). In this regard, miRNAs function similarly to secreted proteins and peptides, which have been considered as major regulators for communication among vascular cells.

## EC-VSMC INTERACTION VIA OTHER FACTORS AFFECTING SMC CELL TURNOVER

EC-VSMC dialogue can alter developmental signaling pathways in mature blood vessels. Hemodynamic force stimulates ECs to produce heparin sulfate proteoglycans, which promote vascular growth and hypertrophy (52). This was achieved by enhancing the VSMC response to growth signals from transforming growth factor beta (TGF- $\beta$ ) (52). Manipulation of EC can promote excessive VSMC turnover in plaque formation. The EC injury-activated PDGF signaling pathway is associated with VSMC proliferation and ECM synthesis (53). Similarly, loss of EC-expressed Apelin, an endogenous ligand for G protein-coupled receptors, causes defects in vascular maturation and VSMC recruitment (54), suggesting an overlap with the PDGF pathway. In contrast, EC-FGF receptor signaling accelerates atherosclerosis (55), whereas EC-overexpression of FasL decreases atherosclerosis in *ApoE*<sup>-/-</sup> mice (56). Homocysteine activates VSMCs by DNA demethylation of PDGF in ECs (57). Another atheroprotective mode of EC-VSMC interaction is supported by evidence showing EC-induced suppression of SMC proliferation and, thus, vascular injury. These effects have been accomplished with blood vessel re-endothelialization by blocking cell migration (58) and restenosis (59), elevating peroxiredoxin activity (60), and inducing VSMC apoptosis (61), respectively. These data further support the therapeutic potential of promoting EC regrowth after tissue damage.

Wnt-signaling is involved in many aspects of the atherogenesis (62–64) including EC dysfunction (65), macrophage activation (66), and VSMC proliferation (67). For example, canonical Wnt/ $\beta$ -catenin pathway regulates VSMC proliferation and survival *via* a crosstalk between the Wnt cascade and NF- $\kappa$ B signaling, mediated through  $\beta$ -TrCP1, an

E3-ligase (68). Wnt-signaling dependent EC-VSMC interaction, however, is less known. Recent studies showed that EC-derived non-canonical Wnt ligand regulated vascular formation in an autocrine manner (69). In line with these results, enhancement of Wnt-signaling in ECs through R-spondin3 was required for vascular stability during vasculature remodeling (70). Given the EC-VSMC interplay in atherogenesis, components of the Wnt signaling cascade may represent novel targets for atherosclerosis (71).

In an analogy to transdifferentiation of VSMCs to macrophage-like cells during atherogenesis (72), ECs have been shown to have certain plasticity through interacting with ECM and/or cues from supporting cells. Indeed, transdifferentiation of mature vascular ECs has been detected in pulmonary hypertension, which plays an important role in pulmonary arterial remodeling (73). This likely happens due to downregulation of EC-cadherin (74) or regulation by myocardin in hypoxia-induced pulmonary vascular remodeling (75). However, the causal role of EC-derived VSMC in atherogenesis, if any, remains poorly understood (5).

## EC-VSMC TWO-WAY INTERACTION

It is widely accepted that EC dysfunction is a leading cause of atherosclerosis (76). The resultant dysfunctional VSMCs contribute to atherogenesis (5). Specifically, loss of endothelial cell function elicits abnormal expression of adhesion proteins that recruit leukocytes from the blood into vascular tissue, wherein these cells promote VSMC-mediated vascular wall remodeling. As such, atherosclerosis is characterized by chronic vascular wall inflammation, progressive narrowing of the vessel lumen, and eventual plaque formation. However, EC-VSMC communication is not unidirectional from blood into the vascular wall in atherogenesis, or simply from EC to VSMC. Changes that occur in VSMCs may ultimately affect the other side of the conversation. In a mouse model of thoracic aortic aneurysm, elevated endoplasmic reticulum stress in VSMC stimulated the release of EVs, which contributed to EC apoptosis and the infiltration of inflammatory cells (77). VSMC-secreted ECM can buffer the high-pressure load of circulating blood, which prevents physical EC permeability in large vessels (78). Given the critical role of the two major cell types in atherogenesis, in-depth studies of the VSMC-derived impacts on ECs in atherosclerosis, a less-investigated area, should be encouraged.

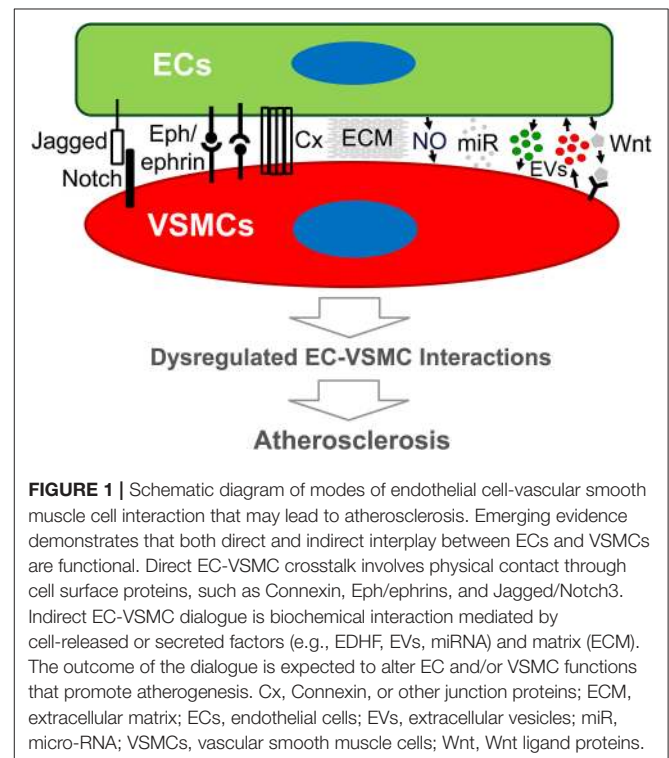
## EC-VSMC INTERACTION: GENETIC EVIDENCE

Defects in EC-VSMC interactions cause certain genetic diseases. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited disease caused by *NOTCH3* mutations that lead to vascular dementia and stroke due to SMC degeneration in small arteries (79). Patients with CADASIL exhibit endothelial dysfunction (80). Animal models of CADASIL exhibit disruptions in vascular tone and increased incidence of ischemic stroke

(81, 82). In addition, patients with Marfan syndrome have defects in the gene encoding ECM protein fibrillin-1, which cause structural abnormalities of the vessel wall, likely due to elevated TGF-signaling (83, 84). Endothelium-dependent vasomotor dysfunction was found in the small arteries of a mouse model of Marfan syndrome, suggesting defects in heterotypic cell communication (85). Endoglin is a TGF- $\beta$  receptor for the TGF-mediated signaling pathway and is highly expressed in EC (86). *Endoglin* mutations cause hereditary hemorrhagic telangiectasia (HHT), which is an autosomal-dominant disorder. Patients with HHT manifest with dilations of the vascular lumen (87) and thinning of blood vessel wall (88), which lead to arteriovenous malformations and hemorrhage (89). Mutations in other mediators of TGF- $\beta$  signaling could induce HHT (90). *Endoglin*-KO mice present with defects in EC-dependent SMC recruitment (91). Interestingly, heterozygous *endoglin* mutation has impaired NO-dependent reactivity (92), suggesting an additional function to maintain vascular tone in mature vessels.

## OUTSTANDING QUESTIONS AND FUTURE DIRECTIONS

Our understanding of atherogenesis has progressed significantly. The endothelium is recognized and implicated in the regulation of physiologic and pathologic processes *via* its signals and metabolic cues (93, 94) to their residing organs in development and function. Loss of endothelial function thus contributes to CVD (95, 96). This review focuses on EC-VSMC interaction-promoted atherogenesis, a less-explored, but potentially



important, field. The existence of genetic disorders due to EC-VSMC interaction defects indicates the clinical significance of the modes of interplay. The reviewed pathways that ECs and VSMCs use to communicate in vascular functionality support an essential role for their interaction in atherosclerotic plaque formation (**Figure 1**). There are other major cell types in different stages of atherogenesis. The modes of interaction may well apply to the dialogue of ECs with other cell types in atherogenesis. Since a selected pathway or target may have opposing effects in different cell types, a promising therapeutic target would promote (net) beneficial outcomes in multiple cell types. Outstanding questions that warrant future exploration are listed below.

Endothelial dysfunction ultimately leads to atherosclerotic CVD. Treatment of endothelial dysfunction has focused mainly on reducing known CVD risk factors, because this approach could be associated with improved vascular endothelial functions (97). However, treatment specifically targeting the EC-dependent mechanism is not available. Can these drugs modulate the crosstalk between ECs and VSMC, and translate to the prevention and treatment of atherosclerosis? Emerging discoveries, including EC-mediated signaling (98), EC metabolism (99, 100), EC-mediated re-endothelialization (as seen in the treatment of stroke) (101), EC-regulated blood flow sensor function (102), EC-induced metabolic changes (103), and EC-vascular integrity, may be linked to the EC-VSMC crosstalk reviewed here (104–107). Could a better and/or more effective target be identified based on EC-centered mechanisms for atherosclerosis?

There are challenges to determining an authentic EC-VSMC interplay that causes vascular injury. The disruptions in signaling between ECs and VSMCs are difficult to precisely define, due to the contribution of other cell types, e.g., inflammatory cells, monocytes, and lymphocytes. An array of approaches from various perspectives has been reported, e.g., using a co-culture system to identify contributing cell type (108), using endothelial dysfunction as an early predictor of vascular cell conversation (109), text mining to identify genes associated with atherogenesis (110), and further classifying sub-population(s) of SMCs linking to their specificity (111). Would systematic consideration and/or application of these approaches be a better way to identify a causal role of EC-VSMC interaction in vascular injury?

Vascular cell communication confers on the blood vessel wall the ability to act as a functional entity. In addition to ECs and VSMCs, there are other major cell types in different stages of atherogenesis. The modes of interaction may well apply to the dialogue of ECs with other cell types, such as effector macrophages (112) and vascular first responder platelets (113),

which significantly contribute to atherogenesis. Macrophages are the major and important type of cell that determines the progression of atherosclerosis by interplay with both ECs (4) and VSMCs (5). How is EC-VSMC signaling integrated with macrophages to determine the fate of atherosclerosis?

To date, therapies in the atherosclerosis field have mainly focused on drugs that control blood lipids (e.g., statins), which fail to significantly reduce disease prevalence. Anti-inflammatory strategies targeting macrophages and other immune cells remain unproven. Can we shift the paradigm to identify the factors and mechanisms that can promote beneficial vascular cell interactions, such as those between EC-VSMC, which can either enhance or replace current conventional anti-atherosclerotic therapies?

It has been recognized that VSMCs of different embryological origin may undergo specific processes at different stages and in different regions of the plaque during atherogenesis (5). These processes are associated with VSMC phenotypic switching, cell proliferation, migration, cell death, and cell senescence. What is the role and mechanism of ECs in these processes that eventually lead to atherosclerosis?

The impact of sex and gender differences has been widely described in cardiovascular diseases, including atherosclerosis (114–116). Although work with most available animal models (117) cannot address a sex-specific impact in atherogenesis [e.g., more plaque erosion in younger women (118)], emerging evidence has shown that sex affects cells that are involved in atherogenesis in humans (119). What is the role and mechanism of sex and gender differences in the EC-VSMC interaction that contributes to atherosclerosis?

In conclusion, atherosclerosis is a chronic arterial disease and a leading cause of vascular death. Our deeper understanding of the defects in EC-VSMC interaction that induce atherosclerosis may allow us to design proper targets for the treatment and prevention of atherosclerotic CVD.

## AUTHOR CONTRIBUTIONS

JX contributed to the conception. ML, MQ, KK, and JX wrote the article.

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