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The Role of Smooth Muscle Cells in the Initiation and Early Progression of Atherosclerosis

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Abstract

The initiation of atherosclerosis results from complex interactions of circulating factors and various cell types in the vessel wall, including endothelial cells, lymphocytes, monocytes and smooth muscle cells (SMCs). Recent reviews highlight the role of activated endothelium and inflammatory cell recruitment in the initiation of and progression of early atherosclerosis. Yet, human autopsy studies, *in vitro* mechanistic studies and *in vivo* correlative data suggest an important role for SMCs in the initiation of atherosclerosis. SMCs are the major producers of extracellular matrix within the vessel wall and in response to atherogenic stimuli can modify the type of matrix proteins produced. In turn, the type of matrix present can affect the lipid content of the developing plaque and the proliferative index of the cells that are adherent to it. SMCs are also capable of functions typically attributed to other cell types. Like macrophages, SMCs can express a variety of receptors for lipid uptake and can form foam-like cells, thereby participating in the early accumulation of plaque lipid. Like endothelial cells, SMCs can also express a variety of adhesion molecules such as VCAM-1 and ICAM-1 to which monocytes and lymphocytes can adhere and migrate into the vessel wall. In addition, through these adhesion molecules, SMCs can also stabilize these cells against apoptosis, thus contributing to the early cellularity of the lesion. Like many cells within the developing plaque, SMCs also produce many cytokines such as PDGF, TGFβ, IFNγ; and MCP-1 all of which contribute to the initiation and propagation of the inflammatory response to lipid. Recent advances in SMC-specific gene modulation have enhanced our ability to determine the role of SMCs in early atherogenesis.

Introduction

Understanding the molecular and cellular mechanisms that lead to the development of atherosclerosis is critical for identifying strategies to limit disease progression before it leads to clinical consequences. Studies have revealed that many different cell types, including macrophages, lymphocytes, endothelial cells and smooth muscle cells (SMCs), are involved in atherosclerotic lesion formation [1]. Most reviews on atherosclerosis focus on the role of endothelial and inflammatory cells in the initiation of atherosclerosis and discuss SMCs largely in the context of late atherosclerosis when they migrate into the neointima and secrete matrix proteins to stabilize the plaque [1-6]. Histological studies of autopsy specimens of human coronary arteries ranging from infants to adults provide evidence that regions prone to the development of atherosclerosis contain abundant SMCs while regions that are more resistant to atherosclerosis contain few [7-9], raising the interesting question: Do SMCs in areas of intimal

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thickening play a pathogenic role in the increased development of atherosclerosis at these sites? The potential role of SMCs in early lesion initiation has not been extensively reviewed. This article reviews existing *in vitro* and *in vivo* data implicating a role for SMCs in early atherogenesis. While many of the mechanisms discussed herein may be involved not only in early atherosclerosis but also at later stages, we will focus on the role SMCs play in the development of early stage I through III lesions, prior to the formation of stage IV "atheroma" (see Table 1).

Intimal SMCs: Harbingers of lesion development?

Although the majority of SMCs in the vessel wall of humans are contained within the medial layer, a significant number of SMCs exist within the intima as well. These areas, known as "intimal thickenings" can be either "eccentric" or "diffuse", although these two types are often contiguous and can be difficult to distinguish from each other. Eccentric intimal thickenings tend to be focal and involve up to half of the circumference of the arterial wall [7]. They are found in conserved locations, including branchpoints and areas of turbulent blood flow [7, 10-13]. Eccentric intimal thickenings have been identified as early as 36 weeks' gestation and are present in nearly all humans by one year of age [7, 13, 14]. Most interestingly, regions of eccentric intimal thickening correlate with the locations in which advanced atherosclerotic lesions are later observed [7, 15]. Unlike eccentric thickenings, diffuse intimal thickenings occur throughout the vasculature, particularly in older patients, suggesting that it may be part of the normal aging process [7, 10, 12, 16, 17]. Both types of intimal thickening consist almost exclusively of SMCs and the proteoglycans that they produce [7]. Investigation into the character of the SMCs within these thickenings suggest that within a particular area, the SMCs present are of a monoclonal nature while the SMCs within the underlying media are polyclonal [14, 18]. These monoclonal regions could result from any one of several scenarios, including: somatic mutation resulting in a neoplastic-type proliferation, selection of a rare cell that proliferates in response to a particular stimulus or the migration and trapping of rare cells during development [19]. These topics have been concisely reviewed in two papers by Schwartz et al [16, 19]. While the migration and trapping hypothesis is widely favored, definitive evidence confirming this is lacking. Progress in this area, as with all atherosclerosis research, has been hindered by the lack of an ideal animal model. It is important to note that not all animal models of atherosclerosis develop intimal thickening as a precursor to lesion formation. While intimal thickening is observed in primate and chicken models, it is not found in any of the commonly used rodent models [7]. Many investigators over the years have attempted to study atherosclerosis in rodent models by injuring vessels and disrupting the internal elastic lamina, thus producing a robust proliferation of SMCs from the media. While many reports in the literature utilize this strategy, the plaques that result from this injury model differ significantly from spontaneous atherosclerosis in cellular content. Because of this, we will attempt to limit our review to those articles which do not rely solely on the injury model. Independent of how intimal thickenings arise, the effect of the presence of intimal SMCs on the subsequent development of atherosclerosis remains an interesting question.

Phenotype of SMCs within atherosclerotic lesions

Current evidence suggests that intimal SMCs differ significantly from medial SMCs and as such, may have unique atherogenic properties that make them fertile ground for the initiation of plaques [20]. While human medial SMCs predominantly express proteins involved in the contractile function of the cell such as smooth muscle myosin heavy chain (SM-MHC) or smooth muscle α-actin (SM-αA), those SMCs found in the intima express lower levels of these proteins, have a higher proliferative index and a greater synthetic capacity for extracellular matrix, proteases and cytokines [6, 21, 22]. Follow on studies, predominantly *in vitro*, have gone on to show that rat and mouse SMCs can switch between the "contractile" and "synthetic"

phenotypic states in response to a variety of atherogenic stimuli including extracellular matrix [23, 24], cytokines [25-27], shear stress [28], reactive oxygen species [29] and lipids [30]. In addition, this "phenotypic switching" correlates with the ability of SMCs to perform a variety of functions. These "synthetic" SMCs migrate and proliferate more readily than "contractile" SMCs and can synthesize up to 25 to 46 times more collagen [6, 31]. In addition, they express a greater proportion of VLDL, LDL and scavenger receptors allowing more efficient lipid uptake and foam cell formation [21, 32]. Therefore, transition to the "synthetic" state facilitates many of the pathogenic roles of SMCs. Recently, an *in vivo* study confirmed the ability of lipids to induce phenotypic switching of SMCs [30]. Using a pluronic gel system, the authors demonstrated that local exposure of rat carotid arteries to the oxidized phospholipid 1-palmytoyl-2-(5-oxovaleroyl)-sn-glycero-3-phosphocholine (POVPC) caused SMCs to downregulate SM-αA and SM-MHC.

Lipid uptake by smooth muscle cells

While the majority of foam cells in the atherosclerotic lesion are thought to be derived from macrophages, SMCs also give rise to a significant number of lipid laden cells [9]. This phenomenon has been established by co-localization studies *in vitro* and *in vivo* by demonstrating simultaneous staining for smooth muscle markers and lipids [32-35].

Smooth muscle cells from humans, rats and rabbits have been demonstrated to express a variety of cholesterol uptake receptors, including the LDL receptor [36], VLDL receptor [37], CD36 [38, 39], type I and type II scavenger receptors [39, 40] and CXCL16/SR-PSOX[41]. In diet-induced models of atherosclerosis, SMCs derived from rabbits fed a 'Western diet' were shown to have increased levels of scavenger receptor [42]. Similarly, in the presence of atherogenic cytokines including interleukin-1β (IL-1β), tumor necrosis factor-α (TNFα) and macrophage colony stimulating factor (MCSF), the expression of LDL and VLDL receptors is increased in rats and rabbits [36, 37, 41, 43]. In addition to enhancing expression of the LDL receptor, TNFα and MCSF also increase the binding of LDL to SMCs, therefore promoting foam cell formation [43]. Cholesterol uptake studies have confirmed that these receptors are indeed functional and in the presence of various forms of cholesterol, SMCs can become 'lipid laden' [32]. *In vitro*, the LDL receptor on SMCs can mediate the uptake of unmodified LDL [36], acetylated LDL [44], enzymatically modified LDL [35] as well as chylomicron remnants [45-47] in the same manner demonstrated in macrophages. The scavenger receptor CXCL16/SR-PSOX, which is found in atherosclerotic but not healthy vessels, is also associated with the uptake of oxidized LDL into human SMCs [41].

In addition to cholesterol uptake, smooth muscle cells also express the necessary components of the reverse cholesterol transport pathway, including the ATP binding cassette (ABC) transporter, ABCA1 [48]. The reverse transport pathway, extensively studied in macrophages, is the means by which lipid laden cells can metabolize lipid and export it to carriers that recycle it to the liver. In macrophages, these cellular transporters are downregulated as atherosclerosis progresses, leading to foam cell formation. After initial cholesterol loading, mouse SMCs upregulate ABCA1 and ABCG1 while downregulating the typical smooth muscle markers including smooth muscle α-actin, α-tropomyosin and myosin heavy chain [32]. With continued lipid loading in a pro-atherogenic milieu, these SMCs go on to downregulate the levels of the cholesterol transporters, enhancing foam cell formation [48]. These data suggest that lipid accumulation in SMC may contribute to atherosclerosis development.

Retention of monocytes and macrophages by SMCs

Interaction of monocytes with cells of the vascular wall allows these cells to move from the bloodstream into the intima where they differentiate into macrophages. While endothelial cells are thought to be the major cell type responsible for interacting with macrophages, SMCs are

also capable of doing so. Electron microscopic and immunohistochemical analysis of human atherosclerotic plaques have shown that SMCs and macrophages are in direct contact [9]. This process is mediated by the expression of a variety of adhesion molecules on endothelial cells and smooth muscle cells, including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule (VCAM-1) and fractalkine (CX3CL1).

VCAM-1 and ICAM-1 have been well characterized on endothelium as adhesion molecules that are induced in response to inflammatory cytokines and enable endothelial cell:monocyte as well as endothelial cell:lymphocyte interactions [49]. The expression of VCAM-1 and ICAM-1 has also been detected on human smooth muscle cells, indicating that they are capable of interacting with leukocytes by this mechanism [50]. This fact, taken together with their co-localization with monocytes within the intima, suggest that smooth muscle cells could play an important role in retaining monocytes and macrophages within the lesion [51, 52].

VCAM-1 has been shown to be expressed by intimal smooth muscle cells within the atherosclerotic coronaries, aorta and carotids of both mice and men, but is not found in healthy medial SMCs [53, 54]. In addition, the presence of VCAM-1 has been detected on smooth muscle cells within lesion prone areas of the aorta of ApoE$^{-/-}$ mice, suggesting that this event occurs early in atherogenesis [50]. In fact, expression of VCAM-1 in medial SMCs was found to occur prior to or coincident with mononuclear cell infiltration, providing further support for this idea [50]. Like VCAM-1, ICAM-1 is also expressed by SMCs in the intima of lesions, but is not found in healthy aorta. Its expression is confined to areas prone to lesion formation and is upregulated prior to mononuclear infiltration [55].

Fractalkine (CX3CL1) is a ligand for the chemokine receptor CX3CR1 that is expressed on human smooth muscle cells but unlike ICAM-1 and VCAM-1 is not expressed on endothelial cells [56]. In the presence of oxidized lipids, human monocytes upregulate expression of CX3CR1, enabling them to bind to SMCs and accumulate in the vessel wall under hyperlipidemic conditions [57]. Likewise, SMCs in healthy regions of arteries do not express fractalkine, however it is significantly upregulated on those found in regions of atherosclerotic plaque [58]. *In vitro*, monocyte adhesion to mouse SMCs can be inhibited by blocking fractalkine on SMCs prior to incubation with monocytes and *in vivo*, CX3CR1$^{-/-}$ ApoE$^{-/-}$ mice have reduced monocyte accumulation within lesions [58].

Anti-apoptotic effect of smooth muscle cells on monocytes and macrophages

In addition to being able to bind and retain monocytes within the developing atherosclerotic lesion, SMCs are also able to protect them from apoptosis. One group observed that very few apoptotic monocytes were found in early atherosclerotic lesions when SMCs are abundant, leading them to propose that local interactions between these two cell types may protect the monocytes [59]. This potential anti-apoptotic phenomenon could be part of the mechanism of monocyte accumulation in early atherosclerosis after migration to the subendothelial layer [51, 52, 59]. Recent *in vitro* studies have demonstrated that SMCs can in fact protect monocytes from apoptosis. Serum deprived peripheral blood monocytes rapidly undergo apoptosis, but when co-cultured with human SMCs, the monocytes survive [51]. This effect was found to be mediated by an increase in Bcl-2 expression and increased activity of the Akt and MAPK pathways. Furthermore, the effect was blocked by a neutralizing antibody to VCAM-1, suggesting that the VCAM-1/VLA_4 interaction may be essential [51]. In addition, several stimuli, including angiotensin II, PDGF-BB and 12/15 lipoxygenase activation, were found to increase monocyte binding to SMCs and prevent apoptosis [52].

Cytokine production by smooth muscle cells

Atherosclerosis is a form of chronic inflammation associated with the secretion of many cytokines, which are produced by T cells, macrophages, endothelial cells and smooth muscle cells. Smooth muscle cells in particular produce cytokines that attract and activate leukocytes, induce proliferation of SMCs, promote endothelial cell dysfunction and stimulate production of extracellular matrix components. While SMCs are capable of producing many cytokines, some of the most important are: platelet derived growth factor (PDGF), transforming growth factor-β (TGFβ), macrophage inhibitory factor (MIF), interferon gamma (IFNγ) and monocyte chemoattractant protein (MCP-1). All of these cytokines can also be produced by other cells within the lesion, therefore while a role for SMC production of these cytokines seems probable, their precise contribution remains unknown (Table 2). Recently, an excellent review by Raines, et al detailed many of the cytokines produced by SMCs under atherogenic conditions [60].

Extracellular matrix production by smooth muscle cells

One of the major roles of smooth muscle cells is to produce extracellular matrix, which accumulates over the course of lesion progression [3, 61]. Although endothelial cells, macrophages and smooth muscle cells all contribute to ECM production, SMCs are known to be the major producers of connective tissue both in the healthy and atherosclerotic vessel [2]. While most of the ECM within a healthy artery is type I and type III fibrillar collagen, atherosclerotic lesions tend to contain mostly proteoglycans with scattered type I collagen fibrils and fibronectin [43]. This transition can alter not only the architecture of the vessel, but also the lipid content and the proliferative index.

ECM within the developing lesion of humans, monkeys and rodents can trap and retain lipoproteins [62]. As atherosclerosis progresses, the presence of many atherogenic cytokines stimulate SMCs to favor the production of proteoglycans and fibronectin as well as enhance the rate of ECM synthesis [60]. Once present in the vessel wall, proteoglycans entrap additional LDL via ionic interactions with the LDL core proteins, ApoB100 and ApoE. When bound, LDL can be quickly oxidized, enhancing lipid uptake by macrophages and foam cell formation [63, 64]. OxLDL, in turn, stimulates SMCs to secrete larger and more highly sulfated proteoglycans, which increases their affinity for LDL [64, 65]. Therefore, alterations in SMC production of ECM can increase lipid content and accelerate lesion progression.

ECM content can in turn influence the cellularity of the lesion. When SMCs are bound to healthy fibrillar collagen or laminin, they quickly become arrested in G1. This cell cycle arrest was found to be concomitant with SMC upregulation of cdk2 inhibitors and subsequent phosphorylation of these proteins by cyclin E associated kinase in rodents and primates [66, 67]. In contrast, when SMCs are bound to fibronectin and proteoglycan as in an atherosclerotic plaque, cdk2 inhibitors such as $p27^{kip1}$ are downregulated in order to promote SMC proliferation [66-69]. In turn, proliferating SMCs produce more proteoglycan than quiescent cells, amplifying the effect [64, 70, 71].

SMCs: Guilt by association or truly guilty?

Specific regions of the vascular tree are more susceptible to the development of atherosclerosis than others and these regions are found to have abundant SMCs in the intima. *In vitro* mechanistic and *in vivo* correlative data provide evidence that these phenotypically modulated SMCs participate in functions that can lead to atherogenesis as outlined above. While these data suggest a key role for SMCs in the initiation and early progression of atherosclerosis, mechanistic *in vivo* data confirming the role of SMCs in these processes are just recently surfacing. These studies have been hindered by the fact that lesions are complex and many SMC functions that would lead to atherosclerosis initiation and progression are redundant with

other cell types that participate in early lesion development. More definitive studies involving the depletion of a specific cell type, as has been done with specific inflammatory cell populations to confirm their role in atherosclerosis, are not feasible for SMCs since any such mutation would be lethal in embryonic stages. Recent *in vivo* studies utilizing SMC-specific gene modulation in mice have provided some insights into the role of SMCs in vascular pathologies. SMC-specific knockout of connexin43 results in an increased neointimal response to injury [72]. SMC-specific overexpression of genes involved in the production of reactive oxygen species, Nox1 and catalase, can alter the hypertrophic and hypertensive response to Angiotensin II [73, 74]. These data highlight the fact that the use of this technology is feasible for studying the *in vivo* role of SMC in atherosclerosis. Yet, there is still a dearth of literature utilizing these tools to confirm the *in vitro* mechanistic studies reviewed herein.

Reasons for the relative lack of this *in vivo* data are explored in more detail in a recent review by Wamhoff, et al [75]. First, there is no single gene that marks the SMC lineage, making it difficult to select a target promoter to drive cell-specific expression. For example, SM-αA and smooth muscle 22-α (SM22α) are restricted to SMCs in the adult animal, but are expressed in a variety of tissues including cardiomyocytes and skeletal myoblasts during development [6, 75]. Smooth muscle myosin heavy chain, while more specific than most other markers, is still expressed in some atrial myocytes [76]. Such promiscuous expression raises the question of whether the resulting phenotype can be truly attributed to a SMC-specific phenomenon or it is due at least in part to effects in other tissues over the course of development. Secondly, as discussed above, SMCs retain a certain degree of plasticity even in the adult animal, altering their expression of cell-specific genes in response to many stimuli. Therefore, overexpression studies utilizing transgenes driven by these SMC-specific promoters could be affected by the pathophysiological state of the animal. Indeed, studies have shown significant variation in expression following vascular injury, which is known to induce phenotypic switching of SMCs [77]. This is a significant consideration in the choice of promoter construct for studying SMCs in atherosclerosis, since phenotypic modulation of SMCs within lesions is known to be an early phenomenon [6]. Lastly, exogenous Cre recombinase expressed by cells lining the reproductive tract of parent mice can result in high levels of recombination that are not specific to SMCs in their offspring. To date, the reason for this is unproven, although Wamhoff et al have postulated that it may be due to transplacental leakage from the SMC-rich uterus [75].

To circumvent the problems associated with SMC-specific gene targeting, conditional or inducible gene targeting has been employed. Wolfsgruber, et al crossed SM22α-CreER$^{T2(ki)}$ mice with ApoE$^{-/-}$ mice expressing a floxed cGMP-dependent protein kinase. When fed a western diet, these animals were found to have decreased plaque size due to a decrease in cGMP-dependent protein kinase mediated nitric oxide production [78]. Another study by Feil, et al bred SM22α-CreER$^{T2(ki)}$ mice to each other, generating inducible SM22α knockouts. They found that the lack of SM22α significantly increased the amount of atherosclerosis in these animals [79]. Clarke, et al have utilized SMC promoter technology to induce SMC-specific cell death in atherosclerotic plaques. By placing the human diphtheria toxin receptor under the control of a minimal SM22α promoter, the authors generated transgenic mice whose vascular SMCs would be susceptible to cell death in the presence of diphtheria toxin. When crossed to the ApoE$^{-/-}$ background and fed a western diet for 12 weeks, these animals developed advanced atherosclerotic plaques. Upon subsequent administration of diphtheria toxin to these animals, 50-70% of their SMCs underwent apoptosis. While overall plaque size remained unchanged, the investigators noted that SMC death was enough to induce increased macrophage content, increased necrotic core volume, decreased matrix content and significant thinning of the fibrous cap [80]. No thrombosis, disruption of elastic laminae or inflammation was detected. While the study by Clarke is focused on the function of SMCs in late atherosclerosis and plaque stability, it illustrates the feasibility of this type of technique to study SMC-specific function *in vivo*. In addition, the studies by Wolfsgruber and Feil, which both

modified SMC function prior to the development of atherosclerosis, provide evidence that SMCs may contribute to the earlier stages of atherogenesis and that these types of conditional gene manipulation can be successfully utilized for the study of SMCs in early disease.

These recent studies, coupled with significant *in vitro* mechanistic data and *in vivo* correlative data reviewed herein provide strong evidence that SMCs are indeed important in early atherogenesis. SMCs are the first cells present in locations destined to develop atherosclerotic plaques. These SMCs, more than medial SMCs, secrete extracellular matrix that traps lipid from the bloodstream and can take up this lipid to form foam-like cells just as macrophages do in more advanced atheroma. SMCs can also enhance the accumulation of monocytes and macrophages within the early lesion by secreting cytokines to attract them from the bloodstream, secreting matrix to which these cells can attach and by direct SMC:monocyte contact that retains and stabilizes these cells. At the same time, these studies also underscore a key role for conditional SMC-specific gene modification in providing further *in vivo* mechanistic data to confirm these various functions and isolate their role from that of other cell types during the initiation and early progression of atherosclerosis.

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Table 1

American Heart Association Classification of Atherosclerotic Lesions [7-9,15]

	Lesion Type		Cellular Composition	
I	Initial Change		Isolated macrophage foam cells	
II	Minimal Change	**IIa:** Progression-prone	Multiple layers of foam cells Few lymphocytes	Abundant SMCs
		IIb: Progression-resistant	Isolated mast cells	Few SMCs
III	Preatheroma		Isolated pools of densely packed extracellular lipids SMCs accumulate lipid droplets	
IV	Atheroma		Confluent core of extracellular lipids Increased number of lymphocytes SMCs decrease in number, remaining SMCs have thick basement membranes	
V	Fibroatheroma		Fibrous tissue and collagen added Intimal SMCs increase in number	
VI	Hemorrhagic/Thrombotic Lesion		Lesion becomes fissured and/or thrombotic	
VII	Calcific Lesion		Calicification predominates	
VIII	Fibrotic Lesion		Fibrous tissue changes predominate Lipid core is nearly absent	

Table 2

Atherogenic cytokines elaborated by smooth muscle cells

Cytokine	Cellular Sources	Effects	References
IFNγ	SMC, M, T	↑ SMC migration and proliferation ↑ ECM remodeling ↑ adhesion molecule expression	60, 81–83
IL-1	SMC, EC, M, T, B	↑ SMC migration and proliferation ↑ monocyte accumulation ↑ adhesion molecule expression	84, 85
IL-18	SMC, EC, M	↑ adhesion molecule expression ↑ SMC accumulation ↑ ECM remodeling	86–88
MCP-1	SMC, EC, M, T	↑ recruitment of monocytes ↑ ECM remodeling	60, 89–91
MIF	SMC, EC, M, T	↑ recruitment of monocytes ↑ SMC migration ↑ ECM synthesis and remodeling	60, 92–94
PDGF-BB	SMC, EC, M	↑ SMC migration and proliferation	95–98
TGFP	SMC, EC, M, T	↑ SMC migration and proliferation ↑ ECM synthesis	60, 87, 99, 100

SMC: smooth muscle cell; **EC**: endothelial cell; **M**: macrophage; **T**: T lymphocyte, **B**: B lymphocyte