The Role of Vascular Smooth Muscle Cells on The Pathogenesis of Atherosclerosis

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ABSTRACT

Atherosclerosis is the leading cause of death and disability. The lesions of atherosclerosis represent a series of highly specific cellular and molecular responses. The earliest changes that precede the formation of lesions of atherosclerosis take place in the endothelium (EC), with resultant endothelial dysfunction. The EC-induced injury can result in increased lipid permeability, macrophage recruitment, formation of foam cells, and recruitment of T-lymphocytes and platelet. After intimal injury, different cell types, including ECs, platelets, and inflammatory cells release mediators, such as growth factors and cytokines that induce multiple effects including phenotype change of vascular smooth muscle cells (VSMC) from the quiescent "contractile" phenotype state to the active "synthetic" state, that can migrate and proliferate from media to the intima. The inflammatory response stimulates migration and proliferation of VSMC that become intermixed with the area of inflammation to form and intermediate lesion. These responses continue uninhibited and is accompanied by accumulation of new extra cellular matrix (ECM).

The migratory and proliferative activities of VSMC are regulated by growth promoters such as platelet derived growth factors (PGF), endothelin-1 (ET-1), thrombin, fibroblast growth factor (FGF), interleukin-1 (IL-1) and inhibitors such as, heparin sulfates, nitric oxide (NO), transforming growth factor (TGF)-β. The matrix metallo proteinases (MMPs) could also participate in the process of VSMC migration. MMPs could catalyze and remove the basement membrane around VSMC and facilitate contacts with the interstitial matrix. This could promote a change from quiescent, contractile VSMC to cells capable of migrating and proliferating to mediate repair.

The VSMC regulation is a very complex process, VSMC are stimulated to proliferate and migrate by some kind of cytokines, growth factors, and angiotensin II (Ang-II). Together with apoptosis, proliferation and migration of VSMC are vital to the pathogenesis of atherosclerosis and plaque rupture. Rupture of the plaque is associated with increased fibrous cap macrophage, increased VSMC apoptosis, and reduced fibrous cap VSMC. VSMC are the only cells within plaques capable of synthesizing structurally important collagen isoforms, and the apoptosis of VSMC might promote plaque rupture.

Key words: *vascular smooth muscle cells, atherosclerosis.*

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INTRODUCTION

Atherosclerosis is the leading cause of death and disability in the developed world. Despite familiarity with this disease, some of its fundamental characteristics remain poorly recognized and understood.[1] Atherosclerosis lesions (atheroma) are asymmetric focal thickenings of the innermost layer of the artery, the intima. They consist of cells, connective-tissue elements, lipids, and debris.[2] The lesions of atherosclerosis represent a series of highly specific cellular and molecular responses. Atherosclerosis can develop in response to endothelial cell (EC) injury caused by many different stimuli including diabetes mellitus (DM), hypertension, and dyslipidemia. After initial injury, different cell types, including EC, platelets, and inflammatory cells release mediators, such as growth factors and cytokines that induce multiple effects. These growth factors and cytokines will promote the changes of vascular smooth muscle cells (VSMC) from the quiescent contractile state to the active synthetic state, VSMC proliferation and migration, and extracellular matrix (ECM) protein deposition.[3-5] Blood-borne inflammatory and immune cells constitute an important part of atheroma, the remainder being vascular EC and VSMC. In the center of atheroma, foam cells and extracellular lipid droplets form a core region, which is surrounded by a cap of VSMC and collagen-rich matrix. T cells, macrophages, and mast cells infiltrate the lesion and are particularly abundant in the shoulder region where atheroma grows.[2,6]

VSMC exist in a diverse range of phenotypes.[7,8] In normal mature blood vessels, the predominant

phenotype is the quescent or noted as contractile or differentiated VSMC, which has as its major function the regulation of blood vessel diameter (vasodilation and vasoconstriction) and blood flow.[9-11] The synthetic, migratory and proliferative phenotype is present during response to injury. During this pathogenic vascular remodeling (ie, arteriosclerosis), VSMC with noncontractile or synthetic phenotype generate intimal vascular lesions.[9,10] These noncontractile or synthetic phenotype of VSMC also termed as dedifferentiated cells, and have reduced expression of protein required for normal regulation of contractile function. These synthetic phenotype of VSMC have increased capacity to generate extracellular matrix (ECM) protein.[7,8] Synthetic phenotype of VSMC do not regulate contraction but instead control vascular construction.[12]

The synthetic phenotype of VSMC, migration and proliferation are key elements in atherosclerosis and restenosis.[13] Dysregulation of vascular smooth muscle function is exacerbated by impairment in sympathetic nervous system function.[14] The VSMC regulation is a very complex process, VSMC are stimulated to proliferate and migrate by some kind of growth factors, and Ang-II.[5] Together with apoptosis, proliferation and migration of VSMC are vital to the pathogenesis of atherosclerosis.[15]

The present review will focus on the regulation of VSMC in correlation with the development of atherosclerosis, highlighting molecular mechanism of VSMC migration, proliferation, and apoptosis.

STRUCTURE OF THE ARTERY

The formation of functional blood vessels during embryogenesis requires the assembly of EC and VSMC. The initial steps of this process involve the formation of a new endothelial network through angiogenesis, the generation process of new vessels from differentiated EC of existing vessels, or vasculogenesis, the formation of vessels from circulating EC progenitors. These primitive endothelial tubes recruit supporting cells, the pericytes or smooth muscle cells,[16] make a network and subsequent branching angiogenesis.[17] As part of remodeling process, VSMC migrate toward these sites and align around the endothelial cells from a multilayered vessel wall. The recruitment of VSMC and further interactions between the two cellular layers of the nascent vasculature are mediated through secreted signaling molecules and ECM constituents. Osteopontin and vitronectin are examples of ECM adhesion molecules with known regulatory functions during blood vessel development and remodeling.[18]

The general architecture and cellular composition of blood vessels are the same throughout the cardiovascular system. However, certain features of the vasculature vary with and reflect distinct functional requirements at different locations. The basic components of the wall of blood vessels are EC, VSMC, and ECM, including elastin, collagen, and glycosoaminoglycans. The three concentric layers, intima, media, and adventitia, are most clearly defined in the larger vessels, particularly arteries.[19]

The normal intima of large arteries has continued endothelial monolayer seated on basement membrane. In human, the intima is focally thickened by hyaluronan-rich matrix with sparse VSMC. All basement membranes contain type IV collagen, laminin, and heparin sulfate proteoglycans, such as perlecan, and syndecan.[20,21] The intima is separated from the media by dense elastic membrane called the internal elastic intima.

The normal media contains contractile VSMC surrounded by their own basement membrane, a few of macrophages, and fibroblasts.[22] The medial interstitial matrix contains types I and III collagen, a variety of glycoproteins, such as fibronectin, vitronectin, tenascin, thrombospondin, together with chondroitin sulfate proteoglycans, such as versican.[23] Elastin is also arranged into distinct layers (lamellae). The VSMC layers of the media near the vessel lumen receive oxygen and nutrients by direct diffusion from the vessel lumen, facilitated by holes in the internal elastic membrane. However, diffusion from the lumen is inadequate for the outer portions of the media in large and medium sized arteries. Therefore, these areas are nourished by small arterioles arising from outside the vessel coursing into the outer one half to two thirds of the media.[19]

External of the media is adventitia. The normal adventitia consisting of connective tissue with nerve fibers, small blood vessels (vasa vasorum), and fat in loose interstitial matrix.[24]

PATHOGENESIS OF ATHEROSCLEROSIS

Atherosclerotic lesions (atheroma) are asymmetric focal thickenings of the intermostlayer of the artery, the intima. The response to injury hypothesis considers atherosclerosis to be a chronic inflammatory response of the arterial wall initiated by injury caused by hyperglycemia, hypertension, modified low density lipoprotein (LDL), and other stimuli to EC.

The earliest changes that precede the formation of lesions of atherosclerosis take place in the endothelium, with resultant EC dysfunction. The initial response of EC to injury can result in decreased production of nitric

oxide (NO), increased permeability to lipoprotein and other plasma constituents,[25] leukocyte adhesion, and thrombotic potential.[19] The EC injury make dysfunction of the cells and leads to compensatory responses that alter the normal homeostatic properties of the endothelium. The injury increases the adhesiveness of the EC with respect to leukocytes or platelets, as well as permeability. It is an adaptive response to a variety of adverse physical and biochemical stimuli acting on the vessel wall.

In the early atherogenic process arterial EC begin to express intracellular adhesion molecules (ICAM)-1 that bind various classes of leukocytes. Vascular cell adhesion molecule (VCAM)-1 binds monocyte and T-lymphocyte. After monocytes adhere to EC, they migrate between EC to localize in the intima, transform into macrophages after stimulated by chemokines, and avidly engulf oxidized lipoprotein especially oxidized LDL. Macrophages produce interleukin (IL)-1, and tumor necrosis factor (TNF) which increases adhesion of leukocytes. Macrophages also generate several chemokines, including monocytes chemotactic protein (MCP)-1, that recruit more leukocytes into the plaque. Toxic oxygen species produced by macrophages cause oxidation of the LDL.[19]

When LDL particles become trapped in the vessel wall, they undergo progressive oxidation and be internalized by macrophages through scavenger receptors on the surface of the cells, lead to the formation of lipid peroxides and facilitate the accumulation of cholesterol ester, resulting in the formation of foam cells.[26-28] The next process is the fatty streak formation. Fatty streak initially consists of lipid-laden monocytes and macrophages that engulf oxidized LDL (foam cells) together with T-lymphocytes. Later they are joined by various numbers of VSMC.[25] In the center of an atheroma, foam cells and extracellular lipid droplets form a core region, which is surrounded by a cap of smooth muscle cells and a collagen rich matrix.[29] Cholesterol accumulation in the plaque reflects an imbalance between influx and efflux, and high density lipoprotein (HDL) likely helps clear cholesterol from these accumulations. Foam cells of atheromatous plaque are derived from macrophages via very low density lipoprotein (VLDL) and LDL modifications recognized by their scavenger receptors.

The injury also induce the EC to have procoagulant instead of anticoagulant and to form vasoactive substances, the cytokines, and growth factors. The inflammatory response stimulates migration and proliferation of VSMC that become intermixed with the area of inflammation to form and intermediate lesion. If these responses continue uninhibited, and accompanied by accumulation of new ECM,[30] the artery wall will be thickened.[31]

When the inflammatory process still continues and results in increased number of macrophages, lymphocytes, and platelets recruitment,[3,32] which emigrate from the blood and multiply within the lesion. The cycles of mononuclear cell accumulation, VSMC still migrate to the intima, proliferate, and produce ECM, converting fatty streak into mature fibrofatty atheroma leading to further enlargement and restructuring of the lesion.

As fatty streaks progress to intermediate and advanced lesion, they tend to form a fibrous cap that walls the lesion from the lumen. This represent a type of healing or fibrous response to the injury. The fibrous cap covers a mixture of leukocytes, lipid, and debris, which may form a necrotic core. These lesions expand at their shoulders by means of continued leukocyte adhesion and entry to the lesion. The factors associated with macrophage accumulation include macrophage colony stimulating factor (MCSF), MCP-1, and oxidized LDL. The necrotic core represents the result of increased activity of platelet derived growth factor (PDGF), transforming growth factor (TGF)-β, IL-1, TNF-α, osteopontin, and of decreased connective tissue degradation.[25]

In most patients, myocardial infarctions occur as a result of erosion or uneven thinning and rupture of the fibrous cap, that often happen at the shoulders of the lesion where macrophages enter, accumulate, and are activated and where apoptosis of the cells including VSMC may occur.[33] Activated T-lymphocytes stimulates macrophages to produce MMPs in the lesions, which promotes plaque instability and further implicates immune response.[34] Thinning of fibrous cap is apparently due to the continuing influx and activation of macrophages, which release matrix metalloproteinases (MMPs) and other proteolytic enzymes at these sites[25] such as collagenases, elastases, and stromelysins[35] that could degrade the fibrous cap.

Apoptotic VSMCs are evident in advanced human plaques, prompting the suggestion that VSMC apoptosis in advanced atherosclerotic plaques may promote plaque rupture.[36] Atherosclerosis plaque ruptures are associated with increased infiltration of the fibrous cap by macrophages, and T-lymphocytes with reduced number of VSMC fibrous cap[25] that make the thinning of VSMC-rich fibrous cap overlying the core.

THE ROLE OF VASCULAR SMOOTH MUSCLE CELLS IN ATHEROMA EVOLUTION AND COMPLICATIONS

VSMC are the predominant cellular elements of the vascular media. Responsible for vasoconstriction and dilation in response to normal or pharmacologic

stimuli. During blood vessel formation, the phenotype of VSMC in the medial layer of the wall changes such that secretion of ECM protein is reduced and the formation of intracellular myofilament is increased. This transition, from synthetic to a contractile state, is required for the VSMC to perform its primary function, contraction and dilation of the blood vessel wall to regulate blood pressure and flow. Under pathological conditions, cells in mature vessels can undergo a reverse phenotypic shift from the normal contractile state to synthetic, proliferative cells that can migrate from the media into the intimal region.[37] In the synthetic state, they also synthesize collagen, elastin, proteoglycans, and elaborate growth factors and cytokines. VSMC can migrate to the intima and proliferate following vascular injury.[19]

Although the fatty streaks commonly precedes the development of a more advanced atherosclerotic plaque, not all fatty streaks progress to form complex atheroma. While accumulation of lipid-laden macrophages is the hallmark of the fatty streaks, accumulation of fibrous tissue typifies the more advanced atherosclerotic lesion. The VSMC synthesizes the bulk of the ECM of the complex atherosclerosis lesions. The arrival of VSMC and their elaboration of ECM probably provides a critical transition, yielding a fibrofatty lesion in place of simple accumulation of macrophage-derived foam cells.[1] Recent research has provided insight into the mechanism that may trigger migration and proliferation of VSMC and the MMPs that have important role to catalyze and removel of the basement membrane around VSMC and facilitate migration of the cells.[38]

Vascular Smooth Muscle Cell Migration and Atherosclerotic Lesion Growth

In the native vessel, VSMC are surrounded by a complex, highly structured ECM consisting largely of collagens type I and III, elastin and proteoglycans. These matrix molecules are important in maintaining tissue structure but also play key roles in guiding cell function. Cell binds to the ECM via specific integrin receptors, and this binding can directly affect cell function.[37]

The MMPs are produced by a variety of cell types, are localized to the cell surface, and have been noted to degrade a variety of ECM. MMPs are implicated in a variety of vascular processes. The MMPs could participate in the process of VSMC migration. MMPs could catalyze and remove of the basement membrane around VSMC and facilitate contacts with the interstitial matrix. This could promote a change from quiescent, contractile VSMC to the active, synthetic state cells that capable of migrating and proliferating. The mammalian MMPs are a family of at least 25 secreted or surface-bound proteases, of which 14 have been characterized in vascular cells.[39] Most MMPs are expressed as inactive, latent proforms, although MMP-11, 21, 23, 27, and membrane-type MMPs (MT-MMPs) are active. Most pro-MMPs are likely to be activated biologically by tissue or plasma proteinases, including other MMPs.[40] Two MMPs that associated particularly with VSMC migration are MMP-2 and membrane-type MMP.[41] VSMC constitutively express the gelatinase MMP-2.[42,43] Upregulation of MMP-2 production and induction of other gelatinase, MMP-9, occur rapidly after mechanical injury.[44,45]

After intimal injury, different cell types, including EC, platelets, and inflammatory cells release mediators, such as growth factors and cytokines that induce multiple effects including phenotypic change of VSMC from contractile state to the active, synthetic state, ECM protein deposition, and VSMC migration and proliferation from the media into the intima.[46] Inflammatory cytokines, such as interleukin (IL)-1, IL-4, and tumor necrosis factor (TNF)-α, act synergistically with growth factors, such as platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF)-2, induce a broad range of MMPs.[43,47-48] The presence of both inflammatory cytokines and growth factors in atherosclerotic bloods vessels could therefore increase the production of MMPs with the ability to remodel basement membranes and the components of interstitial matrix.

VSMC migrate from the media to the intima, where they proliferate and deposit ECM components, converting fatty streak into mature fibrofatty atheroma, and contribute to the progressive growth of atherosclerotic lesions.[19] Migration of VSMC from the media to the intima is an essential part of both pathologic processes. The migratory and proliferative activities of VSMC are regulated by growth promoters and inhibitors. The promoters such as PDGF, endothelin (ET)-1, thrombin, FGF, interferon gamma (IFN-γ), and IL-1. The inhibitors include heparin sulfates, nitric oxide (NO), and transforming growth factor (TGF)-β. The other regulators include angiotensin (AT)-II, catecholamines, the estrogen receptor, and osteopontin, a component of the ECM.[49]

Extracellular ligands bind cell-surface receptors to stimulate VSMC migration through a process commonly referred to as intracellular signal transduction. The intracellular signal transduction predominantly involve two receptor-coupled systems, guanosine 5'itriphosphate (GTP)-binding protein (G-protein)-coupled and tyrosin kinase-coupled proteins. The signal transduction pathways from these two systems appear to intersect as signals are transmitted. Some of the cytoplasmic and

membrane-bound signaling proteins most associated with cell migration, including the small G-proteins, GTP-ases (Ras, Rho), Cdc42, focal adhesion kinase (FAK), phosphatidylinositol 3-kinase (PI3K), protein kinase-C (PKC), and MAPKs (ERK1/2, p38).[46]

VSMC migration involves a dominant plasma membrane leading lamellae, or leading edge, protruding in contact with an extracellular substrate, and binding by way of integrin transmembrane receptors to form focal complexes and secure focal adhesions.[46] A cascade of intracellular signal transduction, including G-protein and tyrosine-kinases, result in actin filament alignment and myosin contraction within the leading edge, disengagement of focal adhesions over remainder of the cell surface, and contractile forces propelling the cell forward in the direction of the anchoring leading edge.[50,51] VSMC synthesize ECM molecules that stabilize atherosclerotic plaques. However, activated inflammatory and immune cells in the plaque can lead to the death of intimal VSMC by apoptosis.[52]

Smooth Muscle Cell Proliferation and The Development of The Intermediate and Advance Atherosclerotic Lesion

VSMC proliferation and neo-intima formation are important events in the pathophysiological course of atherosclerosis and restenosis after balloon angioplasty. After EC activation, locally produce growth factors and cytokines mediate an inflammatory response within the vessel wall, which involves monocyte recruitment, stimulation of macrophage proliferation, migration of VSMC from the medial layer of the vessel and finally deposition of collagen and other ECM proteins leading to the formation of fibrous cap.[25] Diverse signal transduction systems have been proposed to translate the mitogenic stimulus within VSMC that control VSMC proliferation, among them nuclear factor kappa (NFk)-B,[53,54] the mitogen activated protein kinase (MAPK) (Koyama, 1998; Che, 2001), or the phosphatidylinositol-3-kinase (PI3K) pathways.[55-57]

A role of MAPKs in induction of cellular proliferation has been described not only in VSMCs, but also in a variety of cell types and tissues after interaction of growth factors with their receptors. The main feature of the extracellular signal regulated kinase (ERK) cascade, to distinguish it from other MAPKs, involves activation of Raf, which then initiates a series of phosphorylation steps, resulting in the activation of ERK1 and ERK2, which in turn act on everal substrates including transcription factors, protein kinase C (PKC) or p90 ribosomal S6 kinase.[58]

Several growth factors have been implicated in the proliferation of VSMC, including PDGF (released by platelet adherent to locus of endothelial leakage, ECs, macrophages, and VSMC), FGF, and TGF-β.[19] The growth factors trigger activation of PI3K followed by generation of phosphatidylinositol diphosphate and triphosphate in the cell membrane. Although much information is available about growth factors and cytokines that stimulate VSMC migration and proliferation, less is known about the intracellular protein that controls these functions.[59] Protein kinase-B (PKB or Akt) is recruited to the cell membrane, where it is phosphorylated and activated by phosphoinositide-dependent kinase (PDK) (Anderson, 1998). One target of activated PKB is ribosomal p70-S6 kinase, which is associated with a mitogenic signal transduction cascade.[60] Study by Itoh (2001), showed that PKC activation also enhances proliferation of human VSMC. Heparin might block VSMC proliferation by interfering with PKC pathway through a selective direct inhibition of the PKC-α isoenzyme.[61]

The inflammatory response stimulates migration and proliferation of VSMC that becomes intermixed with the area of inflammation to form an intermediate lesion. If these responses still continue, they can thicken the artery wall, which compensates by gradual dilation, and the diameter of the lumen remains unaltered.[62] The cycles of accumulation of mononuclear cells, proliferation of VSMC, and formation of fibrous tissue lead to further enlargement and restructuring of the lesion that becomes covered by fibrous cap that overlies a core lipid and necrotic tissue, lead to the advanced complicated lesion formation.[25]

Smooth Muscle Cell Apoptosis and Plaque Rupture

Apoptosis, or programmed cell death, is a process through which multicellular organism disposes of cells efficiently. Much has been discovered about the molecular control of apoptosis since its initial description as a series of morphological events. VSMC within the vessel wall can both divide and undergo apoptosis throughout life. However, the normal adult artery shows very low apoptotic and mitotic indices. In diseased tissue many factors are present both locally, and systemically. The local factors such as inflammatory cells, cytokines, and modified cholesterol, and the systemic factors include hyperglycemia, blood pressure and flow. These factors substantially alter the normal balance of proliferation and apoptosis, and the apoptosis in particular may predominate.[63]

The regulation of apoptosis can be simplified into two major pathways. First, apoptosis via membrane death

receptors of the tumor necrosis receptor (TNF) family such as Fas (CD95), TNF-R1, or death receptors (DR)3-6. The binding of these receptors to their ligands causing receptor aggregation, and subsequent recruitment of adaptor proteins such as Fas-FADD, TNF-R1, TRADD, etc, through protein-protein interaction.[64] TNF-α acts through two receptors, TNF-R1 and TNF-R2. Both TNF-R1 and TNF-R2 are homologous to Fas.[65] TNF-R1 has a death domain that initiates assembly of death induced signaling complex, thus activating caspases.[66] TNF-R2 lacks of death domain. The mechanism for the proapoptotic effect of TNF-R2, by way of tumor necrosis receptor associated factor (TRAF) adaptor molecules, produce proapoptotic effects. TNF-R1 and TNF-R2 cooperatively also interact to induce apoptosis through TRAF.[67] Fas, the prototypic member of the TNF death receptor family, binds to its ligand. Recruitmentof adapter molecules FADD and pro-caspase-8 results in activation of the latter. Caspase-8 activation directly activates downstream caspase (3, 6, and 7) which results in DNA fragmentation and cleavage of cellular proteins. Caspase-8 activation also results in cleavage of Bid, which translocates and interacts with Bcl-2 family members.

The second pathway is via mitochondrial amplification. Anti apoptotic members of the Bcl-2 family, such as Bcl-2 and Bcl-x, are located on the mitochondrial outer membrane. Here they act to prevent the release of apoptogenic factors from the inner mitochondrial space. Binding of the pro-apoptotic protein Bid, after cleavage by caspase-8 or Bad after dephosphorylation, to Bcl-2 reduces the protective effect of Bcl-2 and triggers release of cytochrome-c and Smac/DIABLO.[68] Cytochrome-c in concert with adapter protein caspase-9 activates caspase-3, and the downstream caspase cascade. Smac/DIABLO inhibits inhibitor of apoptotic protein (IAP), which in turn inhibits caspase activities, thus will induce apoptosis.[63]

VSMC within vessel wall can both divide and undergo apoptosis throughout life. The normal adult artery shows very low apoptotic and mitotic indices. In diseased tissue additional factors are present both locally, such as inflammatory cytokines, inflammatory cells, and the presence modified cholesterol. These factors substantially alter the normal balance of proliferation and apoptosis.[63] VSMC derived from atherosclerotic plaques are intrinsically sensitive to apoptosis, compared with cells from normal vessels.[68] Human VSMC express death receptors, and inflammatory cells within the atherosclerotic plaque express death ligands. Physiologically, combinations of cytokines such as interleukin (IL)-1β, interferon (IFN)-γ, and TNF-α increase surface death receptors, possibly via nitric oxide (NO) and p-53 stabilization.[69] Interaction between membrane bound ligands and receptors may therefore induce VSMC death.

The effect of VSMC apoptosis is clearly context dependent. Atherosclerosis plaque ruptures are associated with increased infiltration of the fibrous cap by macrophages, and T-lymphocytes with reduced number of VSMC fibrous cap.[25] An important mode of loss of plaque in VSMC is through apoptosis.[70] Rupture of atherosclerotic plaques is associated with a thinning of VSMC-rich fibrous cap overlying the core. Rupture occurs particularly at the plaque shoulders, which exhibits lack of VSMCs and the presence of inflammatory cells. Apoptotic VSMCs are evident in advanced human plaques including the shoulder regions, prompting the suggestion that VSMC apoptosis in advanced atherosclerotic plaques may promote plaque rupture.[36]

CONCLUSION

Atherosclerotic is an inflammatory disease. The lesion of atherosclerosis represents a series of highly specific cellular and molecular responses.

Pathophysiologic observation in human and animals led to the formulation of the response to the injury hypothesis, which initially proposed that EC denudation was the first step in atherosclerosis. EC damage results in lower production of nitric oxide, which inhibits thrombosis, inflammation, and VSMC growth and migration. The expression of ICAM-1 and VCAM-1 is being increased. The adhesion molecule promotes the attachment of circulating monocytes, macrophages, and platelets. An inflammatory reaction ensues, along with the production of chemokines, chemoattractant protein-1 (MCP-1), which directs migration of the attached monocytes/macrophages into the vascular wall.

LDL which may be modified by oxidation becomes trapped in an artery, that can undergo progressive oxidation and be internalized by macrophage to form foam cells. The lipid-laden foam cells break down inside the vessel wall to form fatty streaks.

VSMC migrate from the media to the intima, where they proliferate and form a neointima with increased ECM production, leading to the development of an organized atherosclerotic plaque. VSMC become intermixed with the area of inflammation to form an intermediate lesion. These VSMC changes are through to constitute a late event in atherosclerotic process. The cycles of accumulation of mononuclear cells, proliferation of VSMC, and formation of fibrous tissue leads to further enlargement and restructuring of the lesion that

becomes covered by fibrous cap that overlies a core lipid and necrotic tissue, leads to the advanced complicated lesion formation. Atherosclerosis plaque ruptures are associated with increased infiltration of the fibrous cap by macrophages, and T-lymphocytes with reduced number of VSMC fibrous cap. An important mode of loss of plaque in VSMC is through apoptosis. Rupture of atherosclerotic plaques is associated with a thinning of VSMC-rich fibrous cap overlying the core.

It can be concluded that VSMC are involved not only in the atherosclerotic lesion growth but also in the process of plaque rupture.

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