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Changing paradigms in atherothrombosis: inflammation and neovascularization in plaque progression, rupture and regression

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Summary

Coronary atherothrombosis remains the most frequent cause of ischemic heart disease. Plaque rupture/erosion with superimposed thrombosis is the main cause of acute coronary syndromes and sudden cardiac death. New findings have recently introduced exciting concepts that could have major impact on the treatment of the disease. We will discuss the mechanisms that lead to the development of atherothrombosis and those responsible for the acute coronary syndromes. In particular we will give some insight in the role of arterial remodeling as well as the involvement of the media/adventitia, vasa vasorum and tissue factor in atherothrombosis. Finally, we discuss the current mechanisms involved in the process of plaque regression.

Resumen

PARADIGMAS CAMBIANTES EN LA ATEROTROMBOSIS:
INFLAMACIÓN Y NEOVASCULARIZACIÓN EN LA
PROGRESIÓN, RUPTURA Y REGRESIÓN DE LA PLACA

La aterotrombosis coronaria sigue siendo la causa más frecuente de enfermedad isquémica. La ruptura/erosión de la placa con trombosis superpuesta es la causa principal de los síndromes coronarios agudos y de la muerte súbita cardíaca. Los nuevos hallazgos han introducido conceptos que podrían impactar de manera muy importante el tratamiento de esta patología. Discutiremos los mecanismos que desencadenan en el desarrollo de la aterotrombosis y en aquellos responsables del síndrome coronario agudo. En particular, se revisará la participación de la remodelación arterial así como el papel de la media/adventicia y de los tejidos en la aterotrombosis. Finalmente, se discuten los mecanismos actuales participantes en la regresión de la placa.

Key words: Atherothrombosis. Inflammation. Neovascularization.
Palabras clave: Aterotrombosis. Inflamación. Neovascularización.

Introduction

Atherothrombosis is a systemic disease of the vessel wall that is characterized by the tendency to accumulate lipids, inflammatory cells, smooth muscle cells (SMC) and extracellular matrix within the subendothelial space and the media, and to progress in an unpredictable way to different stages. The molecular and biological mechanisms involved in

the initiation and progression of atherosclerotic disease have been extensively studied during the past decades leading to the introduction of new concepts that form the basis for research efforts in the field of vascular biology.¹⁻³ Some of these new concepts derived from *in vivo* observations using new imaging technologies, such as high-resolution magnetic resonance (MR), which has emerged as a leading imaging

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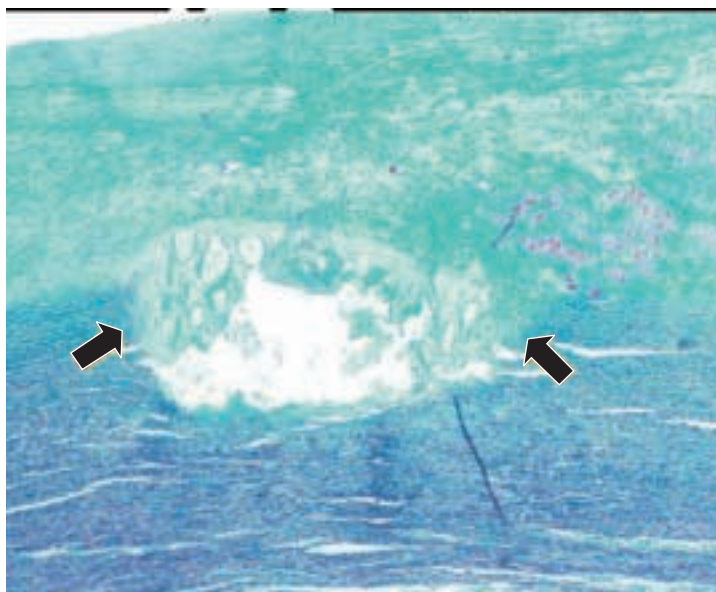


Fig. 1. Human atherosclerotic plaque showing extensive rupture of the internal elastic lamina (arrows) with expansion of the atherosclerotic process from the tunica intima to the tunica media (Elastic Trichrome Stain).

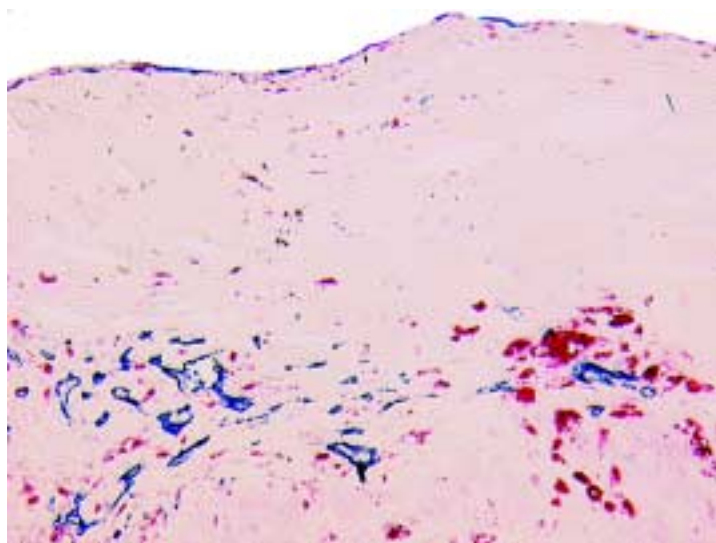


Fig. 2. Histologic examples of plaque neovascularization and inflammation identified by light microscopy in double immunostained sections using CD-34 antibodies link to a blue chromogen (neovessels), and CD68/CD3 linked to a red chromogen (macrophages and T cells).

modality for atherosclerotic plaque characterization.⁴

Initiation of atherosclerotic lesions

The initiation of atherosclerotic plaque has been correlated with the presence of a number of cardiovascular risk factors (such as hyperlipidemia,

diabetes mellitus, hypertension, aging and others) leading to endothelial dysfunction. Dysfunctional endothelium shows increased permeability, reduced synthesis and release of nitric oxide, and over-expression of adhesion molecules (such as intracellular adhesion molecule-1, vascular cell adhesion molecule-1, and selectins) and chemoattractants (such as monocyte chemoattractant protein-1, macrophage colony stimulating factor, IL-1/-6, and INF- α /- γ). These processes facilitate the recruitment and internalization of circulating monocytes and low density lipoprotein.^{3,5} The lipid material accumulated within the sub-endothelial space becomes oxidized and triggers an inflammatory response that induces the release of different chemotactic and proliferative growth factors. In response to these factors, smooth muscle cells and macrophages will activate, migrate and proliferate resulting in the thickening of the arterial wall.

Arterial remodeling: revival of an old concept

The normal vessel wall is an active, integrated organ composed of endothelial, smooth muscle, and fibroblast cells coupled to each other in a complex autocrine-paracrine set of interactions. The vasculature is capable of sensing changes within its milieu, integrating these signals by intercellular communication, and changing itself through the local production of mediators that influence structure and function. Vascular remodeling is an active process of structural alteration that involves changes in at least four cellular processes — cell growth, cell death, cell migration, and production or degradation of extracellular matrix — and is dependent on a dynamic interaction between locally generated growth factors, vasoactive substances, and hemodynamic stimuli.⁶ In diseased vessels, arterial remodeling allows for plaque growth without significant obstruction of the arterial lumen.⁷ Atherosclerotic plaques undergoing remodeling are characterized by large lipid core, less smooth muscle cells and increased macrophage infiltration.^{8,9} As a result, remodeling is considered a high-risk feature for plaque rupture and thrombosis.

Tronc et al demonstrated that increased activity of metalloproteinases, by digesting the internal elastic lamina (IEL), modulates the process of arterial remodeling.¹⁰ More recently our group introduced the new concept of disruption of the IEL as a trigger of plaque rupture in advanced

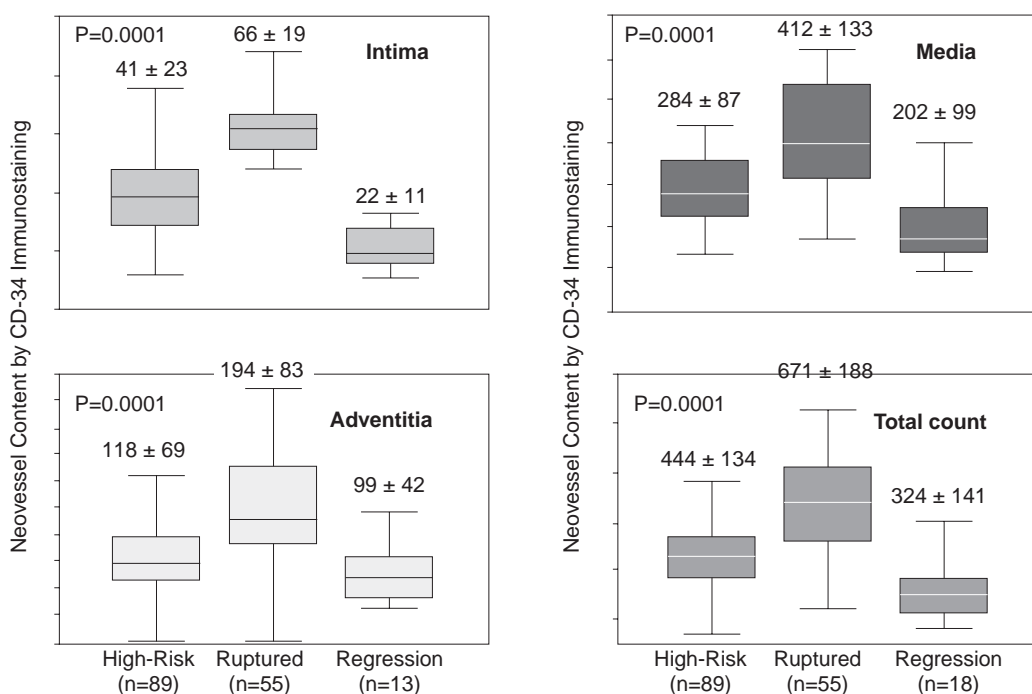


Fig. 3. Neovessel content (mean \pm standard deviation) in high-risk plaques compared to ruptured plaques and regression-type plaques. Neovessel content values are presented in the tunica intima (upper left), tunica media (upper right), tunica adventitia (lower left) and all 3 areas combined as total count (lower right). Please note that neovessel content is highest in ruptured plaques and lowest in regression-type plaques ($P = 0.0001$ for all comparisons). Adapted from reference # 29.

atherosclerosis.¹¹ A strong association between the histological evidence of IEL disruption and plaque rupture leading to thrombus formation was found in 598 human aortic plaques studied (Fig. 1). Concordantly, Burke et al demonstrated that marked expansion of the IEL occurred in plaque hemorrhages with or without rupture, whereas, in erosions and total occlusions there was shrinkage of the IEL.¹² Interestingly, the plaque components most strongly associated with remodeling were macrophage infiltration, degree of fibrous calcification, and amount of lipid core, confirming the concept of instability. The percentage of fibrous plaque area was strongly negatively correlated with remodeling, while calcified lipid core and medial atrophy were less strongly associated with remodeling.

The role of vasa vasorum

A further intriguing new concept in the pathogenesis of atherothrombosis derives from experimental observations of adventitial inflammation and increased plaque invasion of vasa vasorum. Neovascularization may have a crucial role in the pathogenesis of early atherosclerosis.¹³⁻²² The

vasa vasorum surrounds and penetrates the adventitia and outer media of large vessels including the aorta, coronary, femoral and carotid arteries.²³ Vasa can originate from several different sites. In the coronary arteries, vasa originate from bifurcation segments of epicardial vessels; in the ascending aorta, vasa originate from coronary and brachiocephalic arteries; in the descending thoracic aorta, vasa originate from intercostal arteries, and in the abdominal aorta vasa arise from the lumbar and mesenteric arteries. There are two anatomically distinct patterns of vasa vasorum; first order vasa run longitudinally to the lumen of the host vessel; while second order vasa are arranged circumferentially around the host vessel.²³ Their main function is to nurture the vessel wall with a number of vasa vasorum that remains constant throughout life.²⁴ However, in diseased vessels, vasa can proliferate leading to extensive neovascularization involving the tunica media and the intima of diseased vessels.²⁵

Studies of vasa vasorum in complex atherosclerosis using double immunohistochemistry have identified increased neovessel content in ruptured plaques from the human aorta, as shown in

*Figure 2.*²⁶ High-risk features of plaque vulnerability including inflammation, fibrous cap thickness, lipid core area and neovessel content were studied simultaneously to identify predictors of plaque rupture. Multiple logistic regression analysis identified neovessel content as a powerful independent predictor of plaque rupture.²⁷ Furthermore, plaques from patients with diabetes mellitus were characterized by increased neovessel content, higher inflammation and intra-plaque hemorrhage suggesting a microangiopathic process in diabetes atherosclerosis.²⁸ Vasa vasorum may also be involved in the process of plaque regression. When compared to lipid-rich plaques, fibrocalcific lesions with reduced lipid area -are also known as regression type lesions- had the lowest microvessel content, as seen in *Figure 3.*²⁹ Of clinical relevance, this latter observation is in agreement with insightful observations by Corti, et al., using sequential MRI testing in patients undergoing aggressive lipid lowering therapy for 24 months.³⁰ These studies documented for the first time, *in-vivo* the morphological pathway for plaque regression. Plaque area was reduced from the adventitia before improving lumen area. More recently, the Reversal trial confirmed the same inverse Glagovian phenomena for plaque regression after aggressive lipid lowering therapy in coronary artery disease.³¹ Therefore, vasa vasorum may serve as a potential pathway for reverse lipid transport. As cholesterol exits the plaque, neovascularization may also experience regression. This observation, previously validated in experimental animal models may also apply for human disease.³²

Plaque rupture and thrombosis

A major finding of the last two decades was the recognition that plaque composition, rather than severity of stenosis, may determine the risk of thrombotic complications associated with ACS. It is now well established that plaque rupture and superimposed thrombus formation play a key role in the pathogenesis of ACS.³³ Ambrose et al³⁴ and Little et al³⁵ first demonstrated that in approximately half the cases of myocardial infarction the lesions leading to occlusion were less than 50% stenotic. Other groups have shown similar results and today it is accepted that in approximately 70% of cases the clot responsible for an acute coronary event occurs in a plaque that is less than 50% stenotic.

Inflammation has been clearly associated with

all steps of the development of atherosclerotic plaques, beginning with plaque initiation and ending in plaque rupture leading to thrombus formation. Consequently, the definition of plaque vulnerability is bound to morphological characteristics such as a large lipid content covered by a thin fibrous cap and high content of inflammatory cells. Activated inflammatory cells produce proteolytic enzymes able to digest the extracellular matrix and further weaken the fibrous cap. After rupture, the highly thrombogenic plaque content is exposed to circulating blood, triggering thrombus formation. Changes in the geometry of a disrupted plaque, as well as organization of the mural thrombus by connective tissue, can lead to rapid plaque progression resulting in more occlusive and fibrotic lesions.

Thrombosis on non-disrupted plaques

In one third of ACS, particularly in acute sudden coronary death, no plaque rupture but just a superficial erosion of a fibrotic plaque is responsible for the thrombotic event.³⁶ Thrombosis due to endothelial erosion is more commonly seen in women at a younger age and in men with some pro-thrombotic risk factors (smoking, diabetes, hypercholesterolemia). Thus, thrombus formation in these cases where plaque rupture is absent may depend on a hyperthrombogenic state triggered by systemic factors. Indeed, systemic factors, including elevated LDL, cigarette smoking, hyperglycemia, hemostasis, and others are associated with increased blood thrombogenicity. Diabetes mellitus, for instance is associated with platelet hyperaggregability, increased PAI-1, fibrinogen and von Willebrand's Factor, and decreased antithrombin III activity.³⁶ Improvement of glycemic control is associated with a reduction in blood thrombogenicity.³⁷ Significant evidence exists to link hyperlipidemia with a hypercoagulable and prothrombotic state, and this association has been substantiated by normalization of this hypercoagulability with treatment of the hypercholesterolemic state.³⁸

Role of tissue factor in thrombosis

Recently, cardiovascular risk factors have been associated with increased blood tissue factor (TF) activity in humans.³⁹ Our group showed that the thrombogenicity of disrupted atherosclerotic plaques is modulated by their TF content, and furthermore, specific inhibition of the TF pathway

significantly reduces their thrombogenicity.⁴⁰ Roque et al showed that inhibition of TF reduces thrombus formation and intimal hyperplasia after porcine coronary angioplasty.⁴¹ Upon disruption, the atheromatous gruel, abundant in macrophages and TF, is the most thrombogenic component of an atherosclerotic plaque.⁴² TF, the most potent trigger of the coagulation cascade, forms a high affinity complex with coagulation factors, triggering both the intrinsic and extrinsic blood coagulation cascade.⁴³ Activation of the clotting cascade by TF results in the generation of thrombin, platelet activation and fibrin deposition.

The importance of TF in thrombosis has been significantly enhanced by the recent description of a blood-borne pool of TF that may play a critical role in the propagation of thrombosis.⁴⁴ Rauch et al reported that polymorphonuclear leukocytes might be involved in the transport of circulating TF to platelets by a CD15-dependent mechanism.⁴⁵ Higher plasma levels of TF antigen have been reported in ACS patients compared to patients with stable angina or those without coronary artery disease.⁴⁶ Furthermore, circulating TF-positive microparticles with procoagulant activity have been described in patients with ACS.⁴⁷ Because of the key position of TF as an initiator of the extrinsic coagulation pathway leading to clot formation after injury, specific inhibitors of the TF pathway have been recently proposed as having theoretical advantages over therapies that target more “downstream” components of coagulation cascade.⁴⁸

One major question relates to the source of the circulating pool of TF. Mallat et al linked apoptotic phenomena to atherothrombosis and to the production of TF.⁴⁹ More recently, Hutter et al showed that apoptosis of plaque macrophages co-localize with TF expression, suggesting a potential pathogenic mechanism leading to increased plaque thrombogenicity.⁵⁰ Apoptotic death of macrophages within lesions leads to shedding of membrane microparticles causing exposure of phosphatidylserine on the cell surface and conferring a potent procoagulant activity. The shed particles account for almost all the TF activity present in plaque extract and may be a major contributor in initiating the coagulation cascade following plaque disruption.⁵¹

Lipid lowering and plaque regression

With the advent of high-resolution MR imaging to monitor the effects of lipid lowering by statins

in asymptomatic hypercholesterolemic patients, our group documented a significant decrease in the plaque size in both carotid and aortic lesions before changes lumen area, which increased only at 24 months.³⁰ The significant reduction in lesion size and slight increase in the lumen seems to be mediated by a reduction in lipid content of the plaques, indicative of structural changes favoring their stabilization.³¹ Prospective angiographic studies demonstrated that simvastatin abolished progression of stenotic coronary lesions and, recently, Brown et al confirmed that simvastatin and niacin taken together can stop the progression of luminal narrowing in patients with coronary artery disease.⁵²

Recent observations have highlighted the role of high-density lipoproteins (HDL) and reverse cholesterol transport, as they are responsible for the removal of free cholesterol from the blood. A low plasma level of HDL has been associated with increased cardiovascular risk, but only recently has this been recognized as a major risk factor requiring adequate treatment. Several experimental studies have demonstrated the potential antiatherogenic properties of HDL, which is able to prevent plaque formation and even induce plaque regression.⁵³ Spieker et al demonstrated that HDL administration restores normal endothelial function by increasing bioavailability of nitric oxide in hypercholesterolemic patients.⁵⁴ New potent antiatherosclerotic drugs with a novel mechanism of action have been proposed. Peroxisomal proliferator-activated receptors (PPAR) are steroid hormone nuclear receptors that act as ligand-activated transcription factors controlling the expression of specific target genes that in turn regulate a variety of cellular functions. Considering their pivotal role in atherogenesis, PPAR are considered the nuclear transcriptional regulators of atherothrombosis. Three subfamilies have been described with different tissue distribution and effects: PPAR- α , PPAR- δ and PPAR- γ . The subfamily member PPAR- γ plays a central role in adipogenesis and lipid metabolism, and is highly expressed in endothelial cells, SMC, lymphocytes, and macrophages. The PPAR- γ -activators may reduce plaque inflammation, inhibit expression of adhesion molecules and cytokines, and reduce production of MMP. Evidence indicates that PPAR- γ -activators can decrease thrombogenicity by reducing plasminogen activator inhibitor-1 (PAI-1) and fibrinogen concentrations to improve fibrinolysis. In

addition, PPAR- γ -activators may reduce production of endothelin-1, a potent vasoconstrictor and important atherogenic stimulus. Crucially, PPAR- γ -activators may reduce lipid content of plaques by enhancing reverse cholesterol transport and by up-regulating the genes responsible for scavenger receptor class B type I human homologue, for adenosine triphosphate-binding cassette transporter-1 and for apolipoprotein A1, thereby facilitating efflux of free cholesterol from the plaque and its transport to the liver. Using high-resolution MR, we recently observed plaque regression and features of plaque stabilization in the atherosclerotic rabbit model exposed to a new selective PPAR- γ - activator.⁵⁵

Conclusion

Multiple evolving concepts have emerged in the pathophysiology of atherothrombosis. Plaque neovascularization is now considered a major fac-

tor in progression of the disease and may offer potential avenues for stabilization and regression. Circulating tissue factor increases blood thrombogenicity through several pathways including leucocyte-platelet interaction and monocyte apoptosis. Most importantly, increased blood thrombogenicity can be reduced with proper therapy, setting a new therapeutic target for patients with traditional risk factors including diabetes, cigarette smoking and hypercholesterolemia. The mechanisms of plaque regression are now emerging after several decades of clinical evidence. The use of potent imaging techniques have shown that plaque regression follows an inverse Glagovian phenomena in which reverse lipid transport may be supported by adventitial-derived neovascularization. The use of novel antiatherosclerotic drugs including statins and peroxisomal proliferator-activated receptors (PPAR) may be crucial for optimal clinical results in the chronic treatment of atherothrombosis.

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