Thin-Cap Fibroatheroma Rupture Is Associated With a Fine Interplay of Shear and Wall Stress

Ryan M. Pedrigi, Ranil de Silva, Sandra M. Bovens, Vikram V. Mehta, Enrico Petretto, Rob Krams

Abstract—In this review, we summarized the effect of mechanical factors (shear and wall stress) on thin-cap fibroatheroma formation and rupture. To make this review understandable for a biology-oriented audience, we start with detailed definitions of relevant mechanical metrics. We then describe how biomechanics has supported histopathologic efforts to understand the basis of plaque rupture. In addition to plaque rupture, biomechanics also contributes toward the progression of thin-cap fibroatheroma through a multitude of reported mechanobiological mechanisms. We thus propose a new mechanism whereby both shear stress and wall stress interact to create thin-cap fibroatheromas. Specifically, when regions of certain blood flow and wall mechanical stimuli coincide, they synergistically create inflammation within the cellular environment that can lead to thin-cap fibroatheroma rupture. A consequence of this postulate is that local shear stress is not sufficient to cause rupture, but it must coincide with regions of local tissue stiffening and stress concentrations that can occur during plaque progression. Because such changes to the wall mechanics occur over a micrometer scale, high spatial resolution imaging techniques will be necessary to evaluate this hypothesis and ultimately predict plaque rupture in a clinical environment. (Arterioscler Thromb Vasc Biol. 2014;34:2224-2231.)

Key Words: atherosclerosis ■ biomechanical phenomena ■ cellular mechanotransduction ■ genomics

Coronary heart disease remains the global leading cause of death. In the United States, coronary heart disease accounts for ≈379,000 deaths per year, of which approximately one third are due to acute myocardial infarction, and it incurs annual direct and indirect costs of $195.2 billion. Patients with coronary heart disease frequently present with acute coronary syndromes (ACS), resulting in ≈1.14 million hospitalizations each year in the United States. ACS result from disruption of an atherosclerotic plaque, which leads to a cascade of events including platelet activation, thrombosis, embolism, coronary occlusion, and consequent myocardial infarction. Postmortem and in vivo intracoronary imaging studies have suggested that plaques causing ACS frequently have a large lipid-rich necrotic core covered by a thin and inflamed fibrous cap, termed thin-cap fibroatheroma (TCFA). Additional features of high-risk plaques include large plaque burden, expansive remodeling, neovascularization, intraplaque hemorrhage, adventitial inflammation, and a spotty pattern of calcifications. Plaque rupture is the most commonly observed mechanism of plaque disruption, suggesting a potentially important role for biomechanics to improve the understanding and prediction of this often devastating event.

In humans, TCFA can be observed in multiple locations of the proximal epicardial coronary arteries, in both stable and unstable coronary syndromes, yet the incidence of adverse cardiovascular events over an ≈3-year follow-up period at sites of TCFA is only ≈5%. The reasons underlying this observation remain unknown. Although some studies suggest that plaque erosion and stable plaques may also lead to ACS, this review will predominantly focus on biomechanical factors influencing plaque rupture at sites of TCFA, which is the commonest finding in patients presenting with ACS. It is generally agreed that perturbed tissue mechanics can influence proatherogenic cellular behaviors, which may be important in the pathogenesis of plaque rupture. In this review, we will discuss biomechanical approaches to the study of plaque instability and provide evidence that mechanobiological mechanisms are important in both TCFA development and rupture.

Arterial Biomechanics

Biomechanics is the study of the behavior (or motion) of biological materials under an applied load. The goals are to understand (1) mechanical phenomena within the body and (2) the influence of the tissue mechanical environment on cellular function, during normalcy and disease. The power of biomechanics lies within its ability to describe complex material behaviors under specified conditions of interest. Although
there are numerous applications for this capability in medicine, herein we focus on the role of mechanobiology in the development and instability of TCFA.

Under normal physiological conditions, the coronary artery wall is under constant mechanical loading. The primary externally applied loads are blood pressure and flow (Figure 1). Loads are often described by the metric stress ($\sigma$), which, in one dimension, is defined as a force normalized by the oriented area over which it acts. In this article, stress will always denote mechanical stress, unless otherwise indicated. It is important to realize that external loads applied to a material result in an internal configuration of loads that usually depend on both material properties and geometry, such as curvature. A simple example of an analytic solution for the mean circumferential stress, which is an internal load along the circumferential direction, in an arterial segment is given by Laplace’s law,

$$\sigma_{\theta} = \frac{P r h}{h^2},$$

where $P$ is (externally applied) mean arterial blood pressure, $r$ is lumen radius, and $h$ is vessel wall thickness. A typical value of $P$ is 13.3 kPa and that of the resultant circumferential wall stress is 100 to 150 kPa. $r/h$ has a nearly constant value of 8 in normal vessels, which is reduced in diseased vessels. In addition to blood pressure, the luminal surface of the artery also experiences an externally applied load due to blood flow—shear stress. Shear stress is normally denoted by tau ($\tau$, Pa), and a typical value of shear stress is 1 Pa, which is 4 orders of magnitude lower than blood pressure. Thus, while shear stress affects numerous aspects of vascular mechanobiology (detailed below), it is of insufficient magnitude to alter arterial wall integrity directly. Some arteries also experience external loads due to the motion of the tissues to which they are attached; for example, epicardial coronary arteries experience stress related to torsion of the heart during cardiac contraction, which may also influence atherosclerosis progression.

Finally, it is important to note that the internal stress of an artery wall is dependent not only on the externally applied loads but also on residual stresses of its constituents. Residual stress is defined as the stress that exists within a material body in the absence of an externally applied load. Following Humphrey and Rajagopal, residual stress of a tissue arises from the cellular deposition and organization of matrix proteins (eg, elastin, collagen, and fibronectin) toward a preferred mechanical state. According to Humphrey, these stresses tend to homogenize pressure-induced stress within the arterial wall, which may drive this cellular behavior.

For an elastic material such as the artery wall, the presence of stress (or, more generally, a load) entails the presence of strain (or, more generally, a deformation), which is dependent on the stiffness of the material. Strain is a metric of deformation, which is a function of but not equivalent to stretch (in one dimension, Green strain, $E = (1/2)(\lambda^2 - 1)$, where $\lambda$ is stretch), and stiffness is a mechanical property of a material that describes the amount of deformation that results from a given load (defined as $\sigma / \epsilon$). Importantly, stress, strain, stretch, and stiffness can all be defined pointwise (ie, locally) within a material body.

In summary, to fully define the biomechanics of a material under specific conditions of interest requires knowledge of the geometry, mechanical properties, externally applied loads, and deformation at every point in the material body. In most cases, this cannot be achieved analytically and, thus, it requires the use of numeric methods, such as finite element analysis (FEA), to approximate a solution to the equations of mechanical equilibrium. As detailed below, several groups are using FEA to try to predict plaque vulnerability.

### Plaque Biomechanics

During the development of atherosclerosis, the geometry, stiffness, and loads on the artery wall change. In the case of a TCFA, these changes can lead to a loss of structural integrity.
resulting in plaque rupture. A fundamental question is how plaque biomechanics at locations of rupture differ from those of the normal vessel wall and nonrupture prone plaques.

In clinical practice, coronary angiographic features, such as plaque eccentricity, morphology, ulceration, stenosis severity, and presence of intraluminal thrombi, are routinely used to identify culprit plaques in patients with ACS. Serial coronary angiography studies have suggested that coronary occlusion frequently occurred at sites with less severe stenosis. Coronary angiography can only provide assessment of the coronary lumen rather than a comprehensive characterization of the artery wall, which can now be routinely evaluated using a variety of intracoronary imaging modalities. The same studies have demonstrated that plaques at risk of future ACS present features of large plaque burden and positive remodeling without significant lumen obstruction. These findings are in keeping with histopathologic reports showing that thrombotic plaques are harmless, it actually shows that they are merely a lesser cause of acute events. These observations prompted the development of novel biomechanical models to evaluate stress concentrations within plaques dependent on their composition to predict the risk of rupture at specific locations.

**Plaque Stress Concentrations as a Mechanism for Rupture**

One of the first studies to use mechanical modeling to evaluate stresses within diseased coronary histology sections was performed by Richardson et al., who evaluated ruptured plaques from patients postmortem. They found that ruptured plaques contained a large lipid pool and the site of rupture was at the periphery or center of the overlying fibrous cap. A subsequent FEA, using simulated geometries of diseased arterial cross-sections, demonstrated that stress distributions throughout the vessel section over a physiologically relevant range of blood pressure (70–200 mmHg) were dramatically altered by the presence of the plaque. Furthermore, (high) stress concentrations were found either at the periphery of the fibrous cap or at the center, depending on the choice of constituents and material properties, which correlated well to the actual location of plaque rupture. Subsequent investigations confirmed these results and identified the role of the fibrous cap thickness and the plaque structure (e.g., size of the lipid pool) as primary factors for the occurrence of stress concentrations that may lead to plaque rupture.

More recently, several groups have translated the histology-based modeling techniques described above to begin to understand the mechanics of diseased vessels in vivo. Li et al. used axial 2D MRI of the carotid arteries to perform FEA and showed that peak stresses within plaques from symptomatic patients were double those from asymptomatic patients. In a follow-up study, they also showed a statistically significant difference in peak stress within diseased versus nondiseased vessel segments. Tang et al. performed 3D MRI-based fluid–solid interaction modeling (a type of FEA that incorporates both artery wall and blood flow components) on a cohort of 12 patients scheduled for carotid endarterectomy. Overall, they found a statistically significant increase in predicted stress of ruptured versus nonruptured plaques. Similar studies have been conducted with this advanced form of FEA modeling, and they have also found a good correlation between local maximum stress concentrations and the rupture location. One important limitation of many of these studies, however, is that models of stress distributions within ruptured plaques require an assumption of the prerupture geometry. In many cases, the assumed dimensions of the fibrous cap and lipid core are not well justified. One group, Leach et al., were able to overcome these limitations by obtaining images of and modeling the same diseased vessel before and after plaque rupture, ultimately to corroborate that high stress was indeed present before rupture.

Studies pertaining to healing of ruptured plaques indicate that the healing process initiates a remodeling process that minimizes surface roughness and curvature of plaques probably reducing peak wall stress distribution. There are fewer reports of mechanical modeling studies using invasive imaging modalities. All such studies of vessel wall mechanics use intravascular ultrasound (IVUS) combined with FEA to compute wall stress. For example, a comprehensive analysis was performed by Balocco et al., which showed an inverse relationship between shear stress and wall stress in 10 patients with plaques, an observation that was recently confirmed by Fan et al. Liang et al. used a fluid–solid interaction model in diseased vessel segments of 4 patients and identified increasing stress concentrations with thinning of the cap, and the presence of microcalcifications, as observed previously. Hence, these invasive studies confirmed observations from the noninvasive ones that local stress concentrations occur during plaque development.

Taken together, these studies demonstrate the feasibility of using a variety of in vivo imaging modalities to construct biomechanical models of diseased arteries and determine plaques at risk of rupture. However, accuracy of prediction of local stress peaks in vivo remains a matter of debate as cap thickness and necrotic core size cannot be determined with sufficient accuracy using current imaging modalities. In-plane, IVUS has a reported spatial resolution of ≈150 μm, MRI is ≈400 μm, and angiography is ≈400 μm, but the reported plaque compositions determined from histological studies suggest that stiff (collagen) and soft (lipid core) plaque components may be much more closely situated, and hence, stiffness may vary on the order of just a few microns. Optical coherence tomography has a resolution of 15 μm and so it might be better equipped to serve as a source for mechanical studies, but its penetration depth is too low to visualize the entire vessel wall (particularly with the presence of a plaque). One solution might be to combine optical coherence tomography with IVUS, though this approach would currently require 2 pullbacks within the vessel of interest. This limitation of spatial resolution ultimately limits accurate reconstruction of the plaque geometry and, using techniques such as virtual histology (VH)-IVUS, inferring local variations in stiffness (beyond the fact that using such techniques are controversial in themselves). Moreover, recent biomechanical studies support the view that local variations in plaque stiffness are primary determinants of stress concentrations (see below), again suggesting that current imaging-based determination of stress distributions may not have sufficient resolution to allow accurate prediction of rupture potential. Hence, the image-based FEA studies, especially those based on noninvasive imaging modalities, need to be interpreted.
with caution. Future advancements in imaging to increase spatial resolution, however, may give greater possibility for biomechanical modeling to become a sophisticated diagnostic tool.

**Local Variations in Plaque Stiffness**

Many studies have determined the local (ie, point-to-point) stress distribution in plaques. However, relatively few studies have examined the local tissue stiffness, despite the need for rigorous quantification of both metrics to accurately determine plaque rupture risk. Studies that have examined plaque stiffness show large heterogeneity within individual plaques and between plaques of different composition. For example, Lee et al\(^1\) performed compressive mechanical behavior tests on isolated, whole human plaque caps and found that cap stiffness was dependent on its composition, which was classified as cellular, hypocellular, or calcified. They reported considerable variations in stiffness between specimens within each of these categories, particularly for those lesions classified as calcified. Ebenstein et al\(^1\) later reported similar findings using nanoindentation at multiple locations on human plaques obtained from endarterectomy surgery, and Tracqui et al\(^2\) elegantly demonstrated the high variability of stiffness across individual plaques from aortic cross-sections of an ApoE knockout mouse using atomic force microscopy.

Perhaps the most comprehensive investigation demonstrating plaque stiffness heterogeneity and the associated effect on local stress concentrations was reported by Kelly-Arnold et al,\(^3\) who examined the significance of microcalcifications within human atherosclerotic plaques. They demonstrated a large number and heterogeneous distribution of microcalcifications within each plaque that ranged in size from 1 to 50 \(\mu m\), but most (\(=80\%\)) were in the subcellular (1–2 \(\mu m\)) to cellular (10–15 \(\mu m\)) range. Using FEA,\(^3\) they showed that incorporating such rigid inclusions within an otherwise homogeneous fibrous cap locally increased stress by a factor of 2, regardless of the microcalcification location within the cap. Interestingly, microcalcifications within caps <65 \(\mu m\) thick were found to increase stress beyond 545 kPa, which is within the reported range of 300 to 545 kPa typically cited as the critical stress threshold needed for rupture.\(^3\) A cap thickness <65 \(\mu m\) agrees with the histopathologic reports of Virmani et al,\(^4\) who found in retrospective studies that 95% of ruptured plaques measured from histological sections of deceased patients were <64 \(\mu m\) thick. Thus, mechanical studies of plaque stiffness are consistent with reported histopathologic studies, highlighting that plaque composition and structure are primary determinants of an acute coronary event.\(^2\)

These findings emphasize the need for obtaining single-digit micron resolution of plaques in vivo to accurately assess stiffness and predict rupture potential. Currently, the only method for obtaining such detailed information is by combining in vivo imaging with microscopy-based histology in experimental animal models. Our group has recently introduced the concept of 3D histology,\(^5\) whereby a vessel of interest is imaged in vivo and then excised from the animal for histology after correcting for tissue handling, rotation, and shrinkage. Using these corrections, the histological information can be coregistered and interpolated over the in vivo geometry to identify spatially overlapping regions of cells, lipids, or collagen. This information can be then related to mechanical metrics obtained from FEA to explore the mechanobiology of TCFA development (Figure 2). Intriguingly, preliminary results indicate a different shear stress and strain pattern in murine TCFA, suggesting a possible role for both mechanical factors in TCFA formation. Although mice are a controversial model for studies of TCFA, they are the only practical approach for studying associated signaling pathways of dysfunctional cells. Further, the demonstrated technique may be combined with improved imaging modalities or techniques such as molecular imaging in the future to allow coregistration of such detailed pathobiological information to plaque biomechanics in patients.

Clinically, the ability to obtain such detailed information on plaque composition will likely have to wait for improved resolution of the various imaging modalities available. Nevertheless, in vivo studies have been undertaken to approximate local arterial wall and plaque stiffness. Baldewsing et al\(^6\) used an iterative, inverse-FEA approach whereby IVUS-measured local displacements of the vessel wall and loads (ie, changes in blood pressure over the cardiac cycle) were...
combined within a FEA to predict the stiffness at each point in the 3D reconstruction of the vessel that satisfies the equations of mechanical equilibrium. Using an alternative approach, Paini et al41 used echography (a noninvasive imaging modality that has a higher resolution than IVUS: 21 versus 80 μm, respectively) to assess normal and diseased artery wall mechanics. They found that plaques identified as complex (lipid core, fibrotic, and calcified), as assessed by MRI, experienced reduced strain.42 However, the approach is limited as it provides a finite-element mechanics. They found that plaques identified as complex (lipid core, fibrotic, and calcified), as assessed by MRI, experienced reduced strain. However, the approach is limited by echography only imaging along one radius of the vessel. Overall, these approaches offer promise of quantifying plaque mechanics in vivo for diagnostics, but the accuracy is still limited by the resolution and ability of the imaging modality to provide stiffness over the entire 3D vessel wall, as well as the assumptions made for the various mechanical equations.

Therefore, we propose that determination of local variations in tissue stiffness at a high resolution is one of the key factors needed to accurately predict plaque rupture. While current image-based modeling is providing a foundation for such predictive capability, further developments in imaging technology to improve spatial resolution and identification of plaque constituents within the artery wall may be needed before the full potential of these numeric approaches can be realized and tested prospectively. Given the growing advances in high-resolution imaging, technologies that allow such fine-scale characterization of plaques in vivo may not be far off.

A Unifying Theory of the Role of Biomechanics in the Evolution of a TCFA From Initiation to Rupture

We propose a biomechanical mechanism of TCFA formation and rupture that incorporates both shear stress and wall stress. Specifically, shear stress drives biological mechanisms of endothelial cells that, in turn, will lead to the initiation and progression of a plaque, composed of regions of low stiffness and stress (the lipid core) and high stiffness and stress (the fibrotic cap). These changes in the mechanics of the diseased vessel further promote the errant behaviors of the inflammatory and smooth muscle cells, causing further degradation of the wall and exacerbating regions of stress concentrations (Figure 3). We postulate that when local regions of perturbed shear stress and high wall stress coincide, TCFA may rupture. This hypothesized model may explain the observation that only the minority of TCFAs cause ACS.

Low shear stress has clearly been shown to regulate key processes in atherosclerosis, like adhesion factor expression (vascular cell adhesion molecule-1, E-Selectin, and intercellular adhesion molecule-1), reactive oxygen species production through its influence on nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, SOD3 (superoxide dismutase-3), NQO1 (NADPH dehydrogenase, quinone 1), HMOX1 (heme oxygenase [decelyng] 1), GSTT1 (glutathione S-transferase theta 1), and MGST2 (microsomal glutathione S-transferase 2), and a reduced nitric oxide production through its effect on eNOS (endothelial nitric oxide synthase) expression and phosphorylation. Subsequently, nitric oxide and reactive oxygen species interact in a shear-dependent fashion to form peroxynitrite, and these molecules influence other signaling pathways further promoting the adverse effect of low shear stress on the dysfunctional endothelial cell. This effect is substantial as nitric oxide inhibition has been shown to influence multiple mechanosensitive pathways. In addition to these mechanisms, low shear stress can enhance release of matrix degrading enzymes, as well as promote cytokine and chemokine production (eg, interleukin-1α, interleukin-1R1, interleukin-6, interleukin-8RB, RAGE receptor for advanced glycation endproducts), and monocyte chemoattractant protein-1, leading to an enhanced inflammatory state and increased permeability to low-density lipoprotein. As a consequence, low shear stress produces a milieu where low-density lipoprotein particles are taken up by the vessel wall and...
subsequently oxidized. This then facilitates monocytes entering the subendothelium, where monocytes differentiate predominantly to M1 macrophages prior to TCFA formation. Activation of proinflammatory M1 macrophages is associated with matrix metalloproteinase production and smooth muscle cell apoptosis.43–45 Furthermore, oxidized low-density lipoprotein enhances foam cell formation. The presence of sufficient numbers of M1 macrophages and foam cells will produce local regions of mechanical instability caused by degraded materials that can no longer support the physiological loads (eg, blood pressure) imposed onto the vessel wall. These weak spots induced by shear stress–promoting errant behaviors of endothelial cells may occur in regions of the plaque that lead to significant increases in stress, which is an essential condition to produce plaque rupture.

There is a growing body of evidence demonstrating that cells work to maintain a particular tissue mechanical state during normalcy and perturbations to this state promote pathologic cellular behaviors,12 which supports the hypothesis that perturbed wall mechanics may also influence TCFA formation. For example, several studies have shown that subjecting endothelial cells to increased substrate stress or strain increasingly promotes a proinflammatory phenotype that leads to expression of several important proteins, such as endothelin–1 and reactive oxygen species,46 monocyte chemoattractant protein-1,47,48 and CD-40 (an important endothelial cell surface receptor for the attachment of circulating immune cells that aids their transmigration into the vessel wall).49 Smooth muscle cells have also been shown to be sensitive to the vessel wall and, in vitro, substrate mechanics, wherein increased stress promotes proliferation, migration, and synthesis of matrix proteins (eg, type-I collagen), reactive oxygen species, and matrix metalloproteinases.50–52 Indeed, several studies have now shown that regions of high matrix metalloproteinase expression colocalize to regions of high stress.54–56 This important correlation between matrix metalloproteinase expression and increased wall stress suggests that, in addition to smooth muscle cells, immune cells such as macrophages may also be involved in the mechanobiologically driven degradation of the wall during TCFA formation. However, comprehensive studies and characterization of the mechanobiology of immune cells are still lacking.

It is important to recognize that during TCFA formation local shear stress and wall stress will change, modifying the rate of TCFA development or causing reversion to a stable plaque phenotype. How the different combinations of shear stress and wall stress evolve over time to promote or protect against the development of a TCFA is still unclear and highlights the need for more empirical data on TCFA mechanobiology and the associated pathways of cellular mechanotransduction.

Future Directions in Mechanobiology: Molecular Drivers of TCFA Formation

Boosting the information content and resolution of complementary imaging modalities to construct accurate biomechanical models of arteries will facilitate the characterization of plaques at risk of rupture in experimental models of cardiovascular disease. Toward this end, major advances are expected by integrating mechanical modeling data with high-resolution imaging of relevant systems and tissues. In addition, the rapid generation of genome-scale biological data in single cells, which is increasingly cheaper, motivates investigation of the detailed molecular mechanisms underlying mechanosensitive processes and pathways. Again, the added value comes from the integration of orthogonal data modalities, including, but not limited to, in vivo imaging, mechanical analyses, histopathologic analyses, and cellular level phenotyping (including protein levels and messenger RNAs).

The importance of the mechanical control of gene transcription (ie, mechanosensitive transcriptional control) and its role in cell and tissue function throughout embryogenesis and adult life has been previously proposed.57 For instance, mechanical activation/modulation of several transient receptor potential proteins involved in cardiovascular disease (eg, transient receptor potential C3 in vascular reactivity, transient receptor potential V4 in the regulation of systemic blood pressure, and transient receptor potential C6 in the initiation and progression of cardiac remodeling; reviewed in Inoue et al58) has recently attracted interest as a potential new medium to develop alternative therapeutic strategies. Therefore, deciphering the mechanosensitive signaling pathways underlying TCFA and the specific cellular contexts where they operate (eg, endothelial cells or immune cells) can lead to the development of testable hypotheses on the key molecular drivers (eg, transcription factors and cell-surface receptors) to be potentially targeted for the treatment of a TCFA. We propose that perturbations in both hemodynamics and wall mechanics may operate synergistically to regulate plaque development, where specific combinations of these mechanical stimuli may lead to different plaque phenotypes (TCFA versus stable plaques). Beyond the activation of specific proinflammatory agents and phenotypes (described above), a comprehensive annotation of the genomic landscape of cells affected by the mechanical environment will provide insights into the complex regulatory mechanisms (gene networks and signaling pathways) that may modulate TCFA formation. This is expected to present the opportunity not only to prioritize previously unidentified targets for cardiovascular disease and to map novel pathogenic mechanosensitive pathways but also to predict how those targets and pathways can be manipulated at the cellular level. Thus, more effective drugs can be developed to target specific cell signaling pathways that involve transcription factors as well as cytokines, adhesion molecules, or other signaling factors, through which specific cells interact with biomechanical stimuli to determine the formation of a TCFA.

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Disclosures
None.

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Significance

Plaque rupture is the cause of myocardial infarction, stroke, and intermittent claudication. Remarkably, the plaques associated with rupture—thin-cap fibroatheroma—only rupture in 5% of cases. In this article, we propose a theory to explain this low frequency where both plaque composition-induced peak wall stress values and shear stress-mediated changes in tissue stiffness need to coincide spatially to induce rupture. We subsequently discuss the molecular mechanism underlying both processes because this might help to develop therapies to avoid plaque rupture.
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