Atherosclerotic Plaque Rupture
Local or Systemic Process?

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Abstract—It is generally established that the unstable plaque is the major cause of acute clinical sequelae of atherosclerosis. Unfortunately, terms indicating lesions prone to plaque instability, such as "vulnerable plaque," and the different phenotypes of unstable plaques, such as plaque rupture, plaque fissuring, intraplaque hemorrhage, and erosion, are often used interchangeably. Moreover, the different phenotypes of the unstable plaque are mostly referred to as plaque rupture. In the first part of this review, we will focus on the definition of true plaque rupture and the definitions of other phenotypes of plaque instability, especially on intraplaque hemorrhage, and discuss the phenotypes of available animal models of plaque instability. The second part of this review will address the pathogenesis of plaque rupture from a local and a systemic perspective. Plaque rupture is thought to occur because of changes in the plaque itself or systemic changes in the patient. Interestingly, contributing factors seem to overlap to a great extent and might even be interrelated. Finally, we will propose an integrative view on the pathogenesis of plaque rupture. **(*Arterioscler Thromb Vasc Biol.* 2003;23:2123-2130.)**

Key Words: atherosclerosis ■ inflammation ■ pathology

Definition of Plaque Rupture

In 1995, the American Heart Association (AHA) Committee on Vascular Lesions developed a numerical classification of the composition and structure of human atherosclerotic lesions. In this classification, "complicated lesions" (type VI lesions), responsible for most of the morbidity and mortality from atherosclerosis, were defined as atheromata (type IV lesions) or fibroatheromata (type V lesions), containing 1 or more surface defects and/or hematoma-hemorrhage and/or thrombus.[1]

In 2000, the classification was updated by Stary[2] and modified by Virmani et al.[3] They introduced a more detailed description of atherothrombotic plaques. In contrast to the AHA classification of 1995, the definition of "plaque rupture" is stricter, and the possibilities for atherothrombotic events are extended. Atherothrombotic events are clearly separated into plaque rupture, erosion, and eruptive calcified nodules. Moreover, intraplaque hemorrhages are described as phenomena in lesions that are not necessarily associated with plaque rupture (Figure 1).

Because terms like "plaque instability," "plaque vulnerability," "plaque rupture," and "intraplaque hemorrhage" are often used interchangeably, one explanation for the apparent confusion in the literature is the use of a different definition of atherosclerotic plaque rupture. In this review, the stricter definitions of plaque rupture and intraplaque hemorrhage as proposed by Virmani et al[3] are used. Plaque rupture is defined as "an area of fibrous cap disruption whereby the overlying thrombus is in continuity with the lipid core".[3] Intraplaque hemorrhage is defined as the deposition of blood products inside the plaque and is not necessarily associated with atherosclerotic plaque rupture.[2] Because the pathogenesis of plaque erosion and calcified nodules is hardly known, these are excluded from this review.

Animal Models of Plaque Rupture: Do They Exist?

Until the last decade, the most widely used animal models of primary atherosclerosis were cholesterol-fed rabbits, pigs, and nonhuman primates. These models, except for primates, develop only minimal disease and require >1 year to develop significant lesions. The development of genetically engineered mice that lack genes important in lipid metabolism, like apolipoprotein E (apo E) and the LDL receptor, was a major step forward.[4] Not only do these mouse models develop widespread atherosclerotic lesions in a reproducible way, but also their lesion progression shows features reminiscent of human atherogenesis.

However, one of the major drawbacks of these animal models is the lack of end-stage atherosclerosis with spontaneous plaque rupture that is characterized by an area of fibrous cap disruption, whereby the overlying thrombus is in continuity with the lipid core. However, a kind of spontaneous plaque rupture in apoE−/− mice has been reported by several groups.[5–7] These plaque ruptures predominantly occur in the brachiocephalic artery after a prolonged period (age 30

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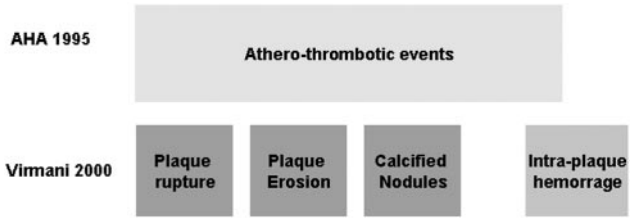

Figure 1. Outline of the different subtypes of the definition of atherothrombosis (AHA classification and Virmani classification).

to 59 weeks) of a lipid-rich diet (containing 0.15% cholesterol and 21% lard).[5] The same phenomenon was observed in apoE−/− mice fed a normal chow diet for 42 to 60 weeks.[6] These plaques are reported to show loss of fibrous cap continuity, intraplaque hemorrhage, and buried fibrous caps, which are interpreted as evidence of prior plaque rupture. In the mouse studies, plaque rupture was defined as the "disruption of the fibrous cap accompanied by the intrusion of blood products into the plaque itself",[5] which is a broader definition than the strict definition of plaque rupture discussed earlier. In fact, observations thus far suggest that spontaneous plaque rupture in mice is merely an intraplaque hemorrhage and not a true plaque rupture. The presence of luminal thrombi occurs only rarely in mice, and when present, thrombi are mostly not organized and nonocclusive. Part of this might be explained by the differences between humans and mice in their regulation of coagulation.[8]

In addition to the genetically engineered mouse models of spontaneous plaque rupture, models in which acute plaque rupture is induced mechanically or by vasoconstriction have been developed. In atherosclerotic mice, mechanical plaque rupture was induced by gently squeezing the plaque-bearing aortic segment of the abdominal aorta between blunt forceps.[9] In this model, the plaque ruptures reproducibly and gives rise to fibrin-rich thrombi that protrude into the lumen, which is plaque rupture in a stricter sense. Some interventions also induce intraplaque hemorrhage and plaque rupture by altering the atherosclerotic plaque phenotype. In a model of accelerated atherosclerosis, a collar was placed around the carotid artery of apoE−/− mice. After a plaque had developed caudal from the collar, an adenoviral vector expressing p53, an oncosuppressor gene involved in apoptosis, was introduced. Overexpression of p53 induced fibrous cap thinning, and triggering with phenylephrine, a vasoconstrictor, caused the thin, fibrous cap to rupture.[10] Although a limited number of organized, luminal thrombi were observed, most of the ruptures were merely intraplaque hemorrhages (Figure 2). Other interventions include treatment of apoE−/− mice with a soluble transforming growth factor-β receptor (TGFβRII:Fc). Inhibition of TGF-β also induced thin, fibrous caps and large lipid cores, with intraplaque hemorrhage, intraplaque fibrin, iron deposition, and disruption of the endothelium.[11,12] The absence of Gas6, a platelet-response amplifier,[13] induced large intraplaque hemorrhages in plaques of apoE−/− mice in the absence of fibrous cap fissuring.[14] ApoE−/− mice deficient in scavenger receptor BI develop severe occlusive coronary atherosclerotic lesions containing cholesterol clefts and fibrin, resulting in myocardial infarctions already at the age of 5 weeks.[15] The same phenotype was observed in LDL receptor−/−/apoE−/− mice, particularly after endothelin infusion at 7 to 12 months of age.[16] However, whether this occlusive coronary artery disease is the result of true plaque rupture or is caused by excess lipid accumulation or vasoconstriction (induced plaque rupture) remains to be determined.

In cholesterol-fed rabbits, intravenous injection with Russell's Viper venom in combination with the vasoconstrictors histamine, angiotensin II, or serotonin induced acute plaque rupture.[17,18] Another approach to induce plaque rupture in cholesterol-fed rabbits is balloon injury to a preexisting lesion or embedding of a balloon into a lesion followed by inflation when the lesion has progressed.[19,20] All 3 models of plaque rupture in the rabbit result in rupture of the fibrous cap and in the formation of an organized thrombus that protrudes into the lumen, features that fit into the stricter definition of plaque rupture.

Although some features of plaque rupture occur spontaneously in genetically engineered mouse models of atherosclerosis, they should not be defined as plaque rupture according to the strict definition as proposed by Virmani et al.[3] Mouse and rabbit models of acute plaque rupture resemble human ruptured lesions but require mechanical intervention or the use of vasoconstricting agents, which might not reflect pathogenesis in humans.

Nonfatal Plaque Rupture, Intraplaque Hemorrhage, and Plaque Growth

It is important to realize that plaque rupture does not always imply a fatal event. In patients who died of noncardiovascular causes, plaque rupture was present in 10% of atherosclerotic lesions.[21] Nonfatal lesions can contain areas of (repeated)

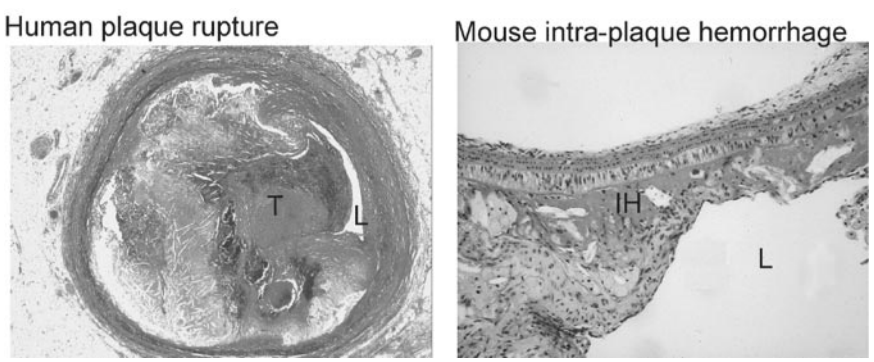

Figure 2. Photographs showing a human coronary artery (left) with a true plaque rupture and a mouse atherosclerotic plaque (brachiocephalic artery; right, ×10) containing an intraplaque hemorrhage. L indicates lumen, T indicates thrombus, IH indicates intraplaque hemorrhage.

plaque rupture and thrombosis. If a thrombus remains mural rather than occlusive and its lysis is incomplete, reendothelialization followed by fibrous thrombus organization results in exponential plaque growth.[3]

The same exponential plaque growth can be observed after intraplaque hemorrhage. Factors triggering intraplaque hemorrhage are largely unknown, but one suggested mechanism is that intraplaque hemorrhage is the result of leakage of plasma owing to rupture of the vasa vasorum and plaque neovessels.[22] In the first stages of atherosclerotic plaque development, cells in the plaque receive oxygen by diffusion from the arterial lumen. From experimental and human pathology studies, it is known that the number of both adventitial vasa vasorum and of intraplaque capillaries increases with plaque progression.[23,24] When intimal thickness increases beyond the critical diffusion limits, vasa vasorum and intraplaque neovessels appear to oxygenate the plaque. However, parts of advanced plaques do become hypoxic.[25] In advanced plaques, hypoxia-inducible factor (HIF)-α as well as vascular endothelial growth factor are upregulated, suggesting activation of hypoxia and angiogenesis pathways.[24] These neovessels can rupture or leak and cause intraplaque hemorrhage. Consequently, plaques will grow expansively, plaque hypoxia and neovascularization will redevelop, and new intraplaque hemorrhages will occur. This cycle might eventually lead to total occlusion of the arterial lumen.

Intraplaque neovessels are also detected in advanced lesions of apoE−/− mice with the use of different markers, such as von Willebrand factor, VE-cadherin, CD31, and Flt-1.[26–29] The amount of neovascularization is positively correlated with the extent of inflammatory cells.[26] Angiogenesis inhibitors such as endostatin, TNP-470, and angiostatin reduce plaque neovascularization and plaque growth, whereas stimulation of angiogenesis by vascular endothelial growth factor or nicotine promotes atherosclerosis.[26–29] Mouse models of spontaneous plaque rupture resemble nonfatal human plaque rupture and intraplaque hemorrhage to some extent. Although it has not been proved, it is tempting to speculate that the accumulation of blood products in the plaque and small fissures of the fibrous cap that are observed in apoE−/− mice might be the result of leakage/rupture of intraplaque microvessels.

Pathophysiology of Plaque Rupture: A Local or Systemic Phenomenon?

In the second part of the review, we will address the pathogenesis of atherosclerotic plaque rupture from a local and a systemic perspective.

Local Perspective

From a local perspective, plaque rupture is attributed to changes that occur in the atherosclerotic plaque. Most of the knowledge of this process is obtained from RNA and protein expression studies in human atherosclerotic plaques and from intervention studies in animal models of atherosclerosis. The mechanisms that have been tested most extensively are those that involve inflammation and matrix turnover in plaque progression and plaque rupture. Moreover, the coagulation system also seems to be able to trigger plaque rupture.

Inflammatory Mediators

The influx of inflammatory cells, macrophages, and T lymphocytes in atherosclerotic plaques increases with plaque progression and is increased at sites of plaque rupture.[30–32] A broad spectrum of inflammatory mediators, such as leukocyte adhesion molecules (P- and E-selectins, intercellular adhesion molecule-1 [ICAM-1], vascular cell adhesion molecule), chemokines (monocyte chemoattractant protein-1, CC chemokine receptor-2 [CCR-2], interleukin [IL]-8, CXCR3, CX3CR1), cytokines (granulocyte macrophage colony stimulating factor, IL-1, IL-6, IL-18, tumor necrosis factor-α, interferon-γ, CD40, CD40L),[30,33] and C-reactive protein (CRP)[34] are expressed in human atherosclerotic lesions, and most of these show increased expression at sites of plaque rupture.[33] Intervention studies in atherosclerotic mouse models in which one of these molecules, such as P-selectin,[35,36] ICAM-1,[35] granulocyte macrophage colony stimulating factor,[37] or IL-1β,[38] was inhibited (genetically or pharmacological) showed a decrease in plaque progression. Moreover, after inhibition of CD40L,[39–41] interferon-γ,[42] IL-18,[43] monocyte chemoattractant protein-1,[44] CCR-2,[45]CXCR2,[46] and CX3CR1,[47,48] a change of plaque composition toward a collagen-rich plaque phenotype with a relative paucity of inflammatory cells and lipids was observed.

Mediators of Fibrosis

The second local regulator in the development of plaque rupture is matrix turnover. TGF-β, an inducer of collagen synthesis, is expressed in all atherosclerotic lesion types, but expression of its receptors decreases with lesion progression.[49] Decreased plasma levels of TGF-β are associated with a poor outcome in coronary artery disease.[50] Proteinases, such as the family of matrix metalloproteinases (MMP-1, -2, -3, -7, -8, -9, -12, and -14)[51,52] and the cathepsin family (cathepsins S and K),[53] as well as their specific inhibitors, such as tissue inhibitors of MMPs (TIMPs)[51] and cystatin C[54] (a cathepsin inhibitor), are expressed in human atherosclerotic lesions. Moreover, the expression of MMP-1, -3, and -9, as well as cathepsins K and S, is increased in the vulnerable shoulder region.[51,53] It is assumed that proteolytic activity is driven by inflammatory activity in the plaque and that this process is responsible for the degradation and thinning of the fibrous cap, thereby favoring plaque rupture.[55] Inhibition of TGF-β in apoE−/− mice induces a plaque phenotype with increased inflammation, thin fibrous caps, and intraplaque hemorrhages.[11,12]

Modulation of the MMP family in atherosclerotic mice has clear effects on aneurysm formation, whereas the effects on atherogenesis are ambivalent. Inhibition of MMPs with a broad-spectrum inhibitor does not affect plaque progression in LDL receptor−/− mice but merely affects medial elastin degradation.[56] Furthermore, overexpression of MMP-1 in macrophages of apoE−/− mice reduces atherosclerosis.[57] The absence of MMP-3 in apoE−/− mice did not affect plaque progression or phenotype but reduced aneurysm formation.[58] In TIMP-1−/−/apoE−/− mice, atherosclerosis

was either not affected[59] or reduced.[58] In both studies, the absence of TIMP-1 induced aneurysm formation.[59,60]

Until now, the mechanisms of aneurysm formation and atherosclerotic plaque rupture have not been linked. However, processes involved in their pathogenesis overlap. Proteolysis is involved in both processes, although elastolysis seems more important in aneurysm formation, whereas collagenolysis is more important in plaque rupture. ApoE−/− mice suffering from severe atherosclerosis develop abdominal aneurysms. Moreover, angiotensin II infusion not only accelerates and aggravates atherosclerosis in apoE−/− mice but also induces aneurysm formation, indicating that both processes might be interrelated.[61] Cathepsins B, D, L, and S show increased expression in the vasculature of apoE−/− mice.[62] Furthermore, cathepsin B activity could be detected in atherosclerotic lesions of apoE−/− mice in vivo by near-infrared tomography.[63] Cathepsin S−/−/LDL receptor−/− mice developed smaller atherosclerotic plaques that exhibited less inflammation.[64]

Coagulation

A third group of local modulators of plaque rupture are those involved in coagulation.[65] Both tissue factor and tissue factor pathway inhibitor (TFPI) are expressed in advanced human atherosclerotic lesions and are abundant at sites of plaque rupture.[66] Protein levels of prothrombin were increased in advanced human atherosclerotic lesions, whereas the anticoagulants antithrombin III and α_2-macroglobulin were decreased.[67] Tissue plasminogen activator, urokinase-type plasminogen activator, and plasminogen activator inhibitor (PAI) were increased in advanced human plaques.[68]

In apoE−/− mice, injection of activated platelets exacerbated atherosclerotic plaque progression.[69] Furthermore, TFPI+/−/apoE−/− mice[70] and PAI-1−/−/apoE−/− mice[71] had increased atherosclerosis. Deficiency of plasminogen attenuated transplant arteriosclerosis,[72] whereas thrombin inhibition by warfarin did not affect atherosclerosis.[73] The absence of Gas6, a platelet-response amplifier,[13] had no effect on atherosclerosis extent, but it did induce intraplaque hemorrhage.[14]

Gene Profiling

Recently, we were able to identify genes that were differentially expressed between stable and ruptured human atherosclerotic plaques by using the suppressive subtraction hybridization technique. This study suggested an important role not only for perilipin and cathepsin K in plaque rupture but also for many unknown genes, such as vasculin.[74,75] From expression data in human plaques and interventions in animal models, it is clear that molecules of inflammation, matrix turnover, and coagulation and yet-unknown molecules are involved in plaque progression and the development of plaque rupture. The major limitation of these studies is that we do not know when and how these processes become critical and induce plaque rupture.

Systemic Factors Associated With Plaque Rupture

From a systemic perspective of the pathogenesis of plaque rupture, it is stated that plaque rupture does not occur as an isolated phenomenon but rather as a systemic disease. In this view, it is preferred to refer to the "vulnerable patient" instead of a patient with a localized, vulnerable atherosclerotic plaque.

Vulnerable patients often present with multiple ruptured plaques. In an angiography study of patients with an acute coronary syndrome (ACS), 39.5% of the patients had multiple complex plaques that were associated with an increased incidence of recurrent ACSs.[76] In another study with intravascular ultrasound, 79% of the patients presenting with an ACS had multiple ruptured plaques at sites other than the culprit lesion that caused the clinical symptoms.[77] It can therefore be postulated that the occluding thrombus at the culprit lesion determines the clinical presentation but that it is only a focal manifestation of an underlying systemic disease process that includes several rupture-prone or vulnerable lesions.

Systemic factors that are correlated with plaque rupture are altered blood rheology, increased coagulability, increased systemic inflammation, and recurrent infections. These unfavorable systemic changes often interact synergistically with risk factors of atherosclerosis and plaque rupture, such as hyperlipidemia, smoking, and diabetes.[78–80]

Because the systemic status of a patient seems to influence the incidence of plaque rupture, attention has focused on several plasma markers that can help predict individuals at increased risk of plaque rupture. Elevated levels of the inflammatory markers CRP,[81] P-selectin,[82] soluble ICAM-1, soluble vascular cell adhesion molecule-1,[83] IL-6,[84] tumor necrosis factor-α,[85] IL-18,[86] and soluble CD40L[87] have been shown to predict future cardiovascular risk in a variety of clinical settings. Although most of these inflammatory markers are derived from the liver (CRP, IL6), low levels might also be derived from other sources, including adipose tissue, activated endothelium, and the plaque itself. Other sets of markers that seem to predict cardiovascular risk are those associated with the coagulation cascade or those involved in proteolysis. Increased plasma levels of fibrinogen,[88] von Willebrand factor,[89] PAI-1,[90] tissue factor,[91] and tissue plasminogen activator,[92] as well as increased plasma levels of MMP-9,[93] indicate an increased risk of cardiovascular events.

Until now, therapies that are most successful in preventing cardiovascular events have been based on improvement of systemic parameters.[94] Lowering of plasma LDL levels by 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) has been proved to prevent ACSs in severe hypercholesterolemic patients,[95] but it is also beneficial for patients with acceptable LDL cholesterol levels.[96,97] Anticoagulation therapy with aspirin,[98] heparins,[99] or platelet antagonists like clopidogrel[100] and glycoprotein IIb/IIIa inhibitors has been proved to prevent acute cardiovascular events in a variety of settings.[101] Moreover, angiotensin-converting-enzyme inhibitors (HOPE trial),[102] angiotensin II type 1 inhibitors, β-blockers, cyclooxygenase-2 inhibitors, and thiazolidinediones have been shown to prevent (recurrent) cardiovascular events. In accordance with the systemic perspective, systemic treatment often lowers serum markers that are correlated with plaque vulnerability/rupture. For example, statin therapy is able to reduce plasma levels of CRP[103] and serum levels of soluble CD40L.[104]

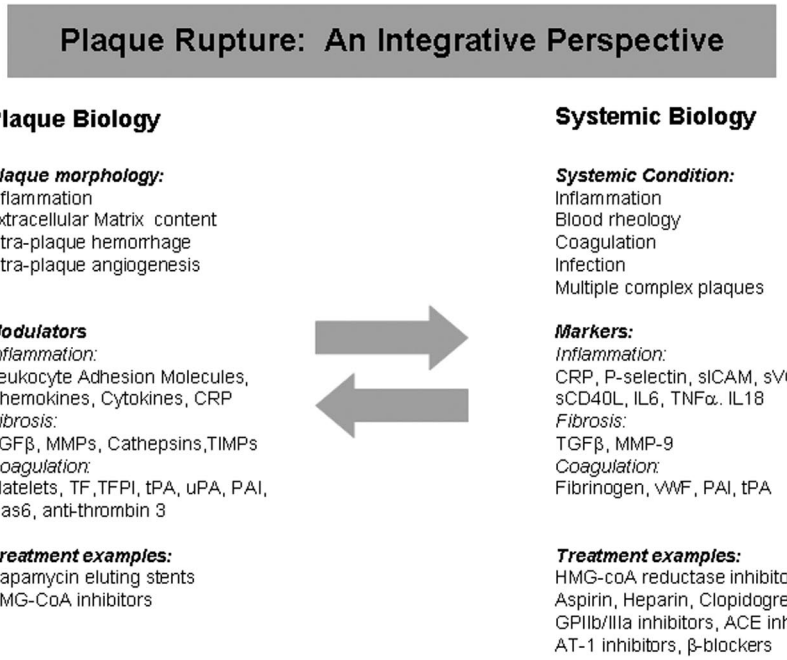

Figure 3. Plaque rupture from an integrative perspective.

The fact that these systemic therapies are most successful in preventing adverse cardiovascular events and are capable of lowering serum markers associated with cardiovascular risk stresses the systemic aspects of the disease. Plaque vulnerability might be expected to develop in a multifocal pattern, resulting in multiple ruptured plaques. Any one of these lesions might progress to the culprit lesion that is responsible for the fatal cardiovascular event.

Integrative Perspective of Atherosclerotic Plaque Rupture

Although systemic markers and systemic treatment seem to predict and prevent cardiovascular events and therefore plaque rupture, its basic mechanism is still unknown. On the other hand, it has been proved that modulation of local plaque-associated factors is capable of changing plaque progression and plaque composition, thereby preventing or inducing plaque rupture. Local therapy with rapamycin-eluting stents was able to prevent restenosis after percutaneous transluminal coronary angioplasty for at least 12 months.[105]

In the integrative view of plaque rupture, it is realized that factors that modulate plaque rupture locally are, to a large extent, the same factors that are also circulating systemically. This suggests a parallel local and systemic pathogenesis of plaque rupture. Alternatively, modulation of systemic modulators might have an effect on local plaque biology and vice versa. Many modulators of inflammation, fibrosis, and coagulation, such as CD40L, MMP-9, and tissue factor, are not only used as systemic biomarkers of atherosclerotic events but are also locally active partakers in the development of plaque rupture. Some studies have investigated the effects of proven beneficial systemic treatment on local plaque biology. For example, treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors not only has a favorable effect on serum lipids but is also able to reduce local plaque inflammation, increase fibrous cap thickness, and induce plaque regression.[106]

In conclusion, by strictly applying the classification proposed by Virmani et al,[3] confusion about definitions of plaque instability, plaque rupture, and intraplaque hemorrhages can be avoided. By this definition, mouse models of spontaneous plaque rupture merely reflect intraplaque hemorrhage without true plaque rupture. Lastly, the pathogenesis of plaque rupture and its clinical symptoms are most likely a combination of (similar) changes in intraplaque and systemic biology (Figure 3). Future studies on the mechanism of plaque rupture should focus on both local plaque and systemic factors.

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