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Reassessing the Mechanisms of Acute Coronary Syndromes: The "Vulnerable Plaque" and Superficial Erosion

Peter Libby[*], **Gerard Pasterkamp**[†], **Filippo Crea**[¶], and **Ik-Kyung Jang**[‡]

[*]Brigham and Women's Hospital, Harvard Medical School, Boston, MA [†]University Medical Center Utrecht, Utrecht, The Netherlands [¶]F. Policlinico Gemelli – IRCCS, Università Cattolica del Sacro Cuore, Roma [‡]Massachusetts General Hospital, Harvard Medical School, Boston, MA

Abstract

The mechanisms that underlie superficial erosion, a cause of coronary thrombosis quite distinct from plaque rupture, have garnered recent interest. In an era of improved control of traditional risk factors such as low-density lipoprotein, plaque erosion may assume greater clinical importance. Plaques complicated by erosion tend to be matrix-rich, lipid-poor, and usually lack prominent macrophage collections, unlike plaques that rupture, which characteristically have thin fibrous caps, large lipid pools, and abundant foam cells. Thrombi that complicate superficial erosion appear more platelet-rich than the fibrinous clots precipitated by plaque rupture. The pathogenesis of plaque rupture probably does not pertain to superficial erosion, a process heretofore little understood mechanistically. We review here data that support a substantial shift in the mechanisms of the thrombotic complications of atherosclerosis. We further consider pathophysiologic processes recently implicated in the mechanisms of erosion. Multiple mechanisms likely predispose plaques to superficial erosion including experiencing disturbed flow, basement membrane breakdown, endothelial cell death, and detachment potentiated by innate immune activation mediated through pattern-recognition receptors and endothelial-to-mesenchymal transition. Monocytes/macrophages predominate in the pathogenesis of plaque rupture and consequent thrombosis, but polymorphonuclear leukocytes likely promote endothelial damage during superficial erosion. The formation of neutrophil extracellular traps (NETs) probably perpetuate and propagate intimal injury and potentiate thrombosis due to superficial erosion. These considerations have profound clinical implications. Acute coronary syndromes (ACS) due to erosion may not require immediate invasive therapy. Understanding the biological bases of erosion points to novel therapies for ACS due to erosion. Future research should probe further the mechanisms of superficial erosion, and develop point-of-care tests to distinguish ACS due to erosion vs. rupture that may direct more precision management. Future clinical investigations should evaluate intervening on the targets that have emerged from experimental studies and the management strategies that they inform.

Corresponding Author: Peter Libby, Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 77 Avenue Louis Pasteur, Boston, MA 02115; Phone: (617) 525-4383; Fax: (617) 525-4400; plibby@bwh.harvard.edu.

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The thrombotic complications of atherosclerosis bring our patients to us with the most dramatic presentations such as the acute coronary syndromes (ACS). For many decades, the concept the “vulnerable plaque” has dominated our clinical and investigative thinking about the mechanisms of the ACS.[1] The typical “vulnerable plaque” has a large lipid core filled with macrophage foam cells and debris accumulated due to their death (Figure 1, top). A fibrous cap, rich in extracellular matrix macromolecules such as interstitial collagens, typically overlies the lipid-rich “necrotic” core of the plaque. These morphologic characteristics gave rise to the nomenclature “thin-capped fibroatheroma,” abbreviated TCFA. This term has entered daily clinical argot. Rupture of the so-called “vulnerable plaque” exposes blood with its coagulation factors to thrombogenic material residing within the plaque. These disruptive events trigger the thrombus that provokes the ischemia characteristic of ACS.

A great deal of effort devoted to unraveling the pathophysiology of rupture of TCFAs supports a pathophysiologic picture predicated on decreased synthesis and increased breakdown of interstitial collagen in the plaque’s fibrous cap.[2] The T lymphocyte-derived mediator interferon gamma (IFN-γ) inhibits production of interstitial collagen by vascular smooth muscle cells, the major source of this extracellular matrix macromolecule in arteries. Macrophages and other cells in plaques overexpress members of the matrix metalloproteinase (MMP) and other protease families capable of degrading interstitial collagen when stimulated by inflammatory mediators. Moreover, tissue factor, a potent pro-coagulant implicated in triggering thrombosis in ACS, produced in the plaque by macrophages and to a lesser extent by smooth muscle cells, also undergoes exquisite regulation by inflammatory mediators. [3–6] Also, systemic inflammation begets the heightened production of fibrin, the precursor of clots, and of plasminogen activator inhibitor-1 (PAI-1), the major endogenous inhibitor of fibrinolysis. Thus, inflammation provokes a perfect storm: decreased synthesis and increased breakdown of the collagen fibrils that protect the plaque from rupture, increased thrombogenicity in the “solid state” of the plaque, and increased fibrinogen and PAI-1 stimulating clot formation and inhibiting thrombolysis in the fluid phase of blood. [7] This satisfying scenario gained considerable ascendency as a pathophysiologic schema that underlies the acute coronary syndromes.[2]

Experimental and clinical studies have demonstrated that lipid lowering can limit inflammation and ameliorate many components of the plaque rupture scenario.[289] In experimental animals and in humans, as shown by intracoronary imaging and by magnetic resonance studies, lipid lowering, particularly statin therapy, lessens the lipid core and augments the relative amount of fibrous tissue in atherosclerotic plaques. Yet, even in an era of profound LDL lowering potential, a residual burden of ACS events persists.[10, 11] Of course, the implementation of preventive therapies including lipid lowering, control of hypertension, and smoking cessation and decreased exposure to secondhand smoke is imperfect. In addition, some of the burden of “residual risk” doubtless results from initiation

of preventive therapies later in the course of evolution of atherosclerotic disease. Nonetheless, the persistent burden of cardiovascular events in the face of highly effective control of conventional risk factors suggests that mechanisms less responsive to control of classical risk factors might underlie a proportion of ACS and contribute to the residual burden of risk. Such considerations have stimulated interest in mechanisms beyond the lipid-rich "vulnerable plaque" that might provoke ACS.[12, 13]

Emerging technologies and data in addition to the considerations above have engendered a re-examination of the primacy of the TCFA in ACS pathogenesis. The concept of the "vulnerable plaque" arose originally from autopsy studies. Compelling images and data derived from post-mortem examination associated fatal acute myocardial infarction with fibrous cap rupture.[14–16] Plaques that ruptured and caused death due to ACS tended to have thin fibrous caps and other characteristics of the morphology attributed to "vulnerable plaques." Of course, inclusion in an autopsy series requires death as an entrance criterion. Thus, we lacked a "denominator": the number of plaques with TCFA morphology that do not rupture and cause a fatal ACS.

Advances in intravascular imaging helped to close this gap. In particular, the PRECISION study used the radiofrequency backscatter from intravascular ultrasound to perform an estimation of the character of tissue in coronary atherosclerotic plaques. [17] The practitioners of this technique, known as "virtual histology," devised criteria for delineation of TCFA. In the PROSPECT study, follow up of TCFA over a 3.4-year observation period showed that less than 5% of TCFA actually provoked a clinical event. Thus, the term "vulnerable plaque" is a misnomer. Indeed, most TCFA appear quite stable and remain unlikely to provoke a clinical event. Serial intravascular imaging studies also suggested that the morphology of human coronary atheromata can evolve in time.[18] Plaques appear able to shift from TCFA to a less "vulnerable" morphology, observations that indicate that the morphological characteristics of plaques (be they "stable" or "unstable") represent a snapshot in time of a moving target. [19]

This reconsideration of the "vulnerable plaque" concept heightened interest in another pathoanatomic substrate for coronary thrombosis previously relegated to minority status, namely superficial erosion (Figure 1, bottom). The pathological picture of superficial erosion varies distinctly from that of the typical TCFA.[20, 21] Plaques complicated by erosion tend to be matrix-rich rather than depleted of fibrous tissue. Excellent studies substantiated an increased content of proteoglycan and glycosaminoglycans including hyaluronic acid in lesions complicated by erosion as well as increased expression of the hyaluronan receptor CD44.[22, 23] Rather than containing abundant mononuclear phagocytes (monocytes/macrophages), eroded plaques have few inflammatory cells.[24] Regions of thin fibrous caps in human atheromata contain few arterial smooth muscle cells. Eroded plaques, however, have abundant smooth muscle cells. Even the type of thrombus associated with superficial erosion differs from that characteristic of plaque rupture. Aspirated thrombi tend to show more platelet-rich "white" thrombus, complicating eroded lesions versus predominantly fibrin-rich "red" thrombi typically associated with TCFA.[25, 26] Furthermore, thrombi overlying eroded plaques are much richer in myeloperoxidase-positive inflammatory cells as compared to fissured plaques.[27] These various observations all suggest marked differences

in the pathophysiology of lesions that provoke erosion compared to those associated with fibrous cap rupture.

In addition, the epidemiology of erosion appears to differ from that of plaque rupture. Based on autopsy studies, often referred from medical examiners, superficial erosion has associated more with women than men.[24] The clinical presentation of ACS due to superficial erosion may also tend to differ from that due to plaque rupture. Another advance in intracoronary imaging has shed considerable new light on these questions. Optical coherence tomography (OCT) provides a near-microscopic, near-field image of the intimal surface. This invasive technique, which usually requires a contrast flush, readily visualizes discontinuities in the plaque's fibrous cap typical of plaque rupture. The delineation of superficial erosion presents some challenges, but practitioners of OCT have evolved criteria for delineating definite superficial erosion or probable superficial erosion. OCT definitively identifies plaque rupture as a discontinuity in the region of the fibrous cap, but the OCT diagnosis of plaque erosion by OCT remains a diagnosis of exclusion: an ACS and mural thrombus without a discernable plaque fissure. [28]

Thus, OCT has sharpened our ability to the characterization of the culprit lesions of ACS in living patients. This advantage obviates some of the obvious biases that autopsy studies entail. In contemporary cohorts, erosion appears to account for as high at one-third of ACS. [28] Characterization of culprit lesions by OCT supports the concept that erosion associates more commonly with non-ST segment myocardial infarction (NSTEMI) while plaque rupture predominantly provokes ST segment myocardial infarction (STEMI).[13] The application of OCT has challenged the notion that superficial erosion occurs more commonly in women, findings that arose from autopsy studies.[28]

In sum, superficial erosion has gained more prominence from both a clinical and investigative perspective in an era of excellent control of the risk factors associated with "vulnerable plaques." Numerous observational studies have shown a shift coincident with the advent of effective lipid lowering and other preventive therapies from a predominance of STEMI to an ascendency of NSTEMI. Contemporary data suggest that plaque erosion—rather than accounting for a fifth of ACS—now appears to cause approximately a third of ACS. [28] Thus, as plaque rupture recedes, in part because of better control of classical risk factors, the proportion of ACS due to superficial erosion may be on the rise. LDL elevation may be permissive to atheroma formation, and likely contributes to all causes of plaque disruption. Yet, the relatively lipid-poor lesions associated with erosion and the decrease in the lipid content and relative increase in fibrous tissue in the plaques of patients who have undergone intensive LDL lowering raises the possibility that erosion might contribute particularly to the residual burden of ACS events in individuals despite highly effective lipid control. [13, 29]

From an investigative perspective, research over decades has unraveled the complex pathogenesis of plaque rupture as described above. Yet we have very limited knowledge of the mechanisms of superficial erosion. Hence, there exists an immense opportunity to learn more about this mechanism underlying ACS that may account for a greater proportion of current thrombotic complications of atherosclerosis, and which may respond less well to

lipid lowering than the typical TCFA with its abundant foamy macrophages and lipid-engorged central core.

Potential Mechanisms of Superficial Erosion

At the outset of a consideration of the mechanisms of superficial erosion, one must plead ignorance. The lack of an intact endothelial monolayer on the intimal surface at autopsy does not prove that endothelial loss preceded the thrombotic event. Even if not the initiating factor in superficial erosion, the loss of integrity of the endothelial monolayer most likely contributes to the amplification and propagation of thrombi associated with coronary atheromata with intact fibrous caps. Therefore, this discussion postulates a primary role of endothelial cell loss as even if not the initial event in inciting erosion, the pathogenesis of this process ultimately involves impaired endothelial integrity.

The lack of a multitude of macrophages in plaques complicated by erosion suggests that inflammation may have less of a role in the pathophysiology of this type of ACS compared to plaque rupture. Evolving evidence suggests, however, the participation of a distinct set of innate immune reactions in plaque erosion versus rupture. Early hypotheses envisaged two mechanisms that could heighten the risk of endothelial desquamation in the context of superficial erosion: scission of the tethers of the basal surface of the endothelial cell to the subjacent basement membrane, and endothelial cell death (Figure 2).[30] One important adhesive interaction that glues the endothelial cell to the underlying membrane comprises a ligand/receptor dyad consisting of integrin family members, prominently beta 1 integrins, and macromolecules prominent in the arterial basement membrane including non-fibrillar type IV collagen and laminin.

Although interstitial collagenases that attack collagens I and III likely contribute to plaque rupture, erosion could involve degradation of non-fibrillar collagen, such as collagen IV, a major constituent of the basement membrane upon which luminal endothelial cells reside. A major type IV collagenase, matrix metalloproteinase (MMP)-2 (gelatinase A), rather than MMPs 1, 8, and 13, could participate in plaque erosion. [2, 31] Indeed, pro-inflammatory cytokines or minimally oxidized LDL can induce the expression of MMP-14, an activator of pro-MMP-2.[32] MMP-14 facilitates the processing of the inactive zymogen to mature MMP-2 that can degrade basement membrane non-fibrillar collagen. These data implicate MMP-14-mediated activation of MMP-2 in mechanisms related to superficial erosion. Endothelial cell death, particularly by apoptosis, might also contribute to disruption of the continuity of the endothelial monolayer in the context of superficial erosion. Hypochlorous acid (HOCl), a potent oxidant species produced by myeloperoxidase (MPO), can promote endothelial cell apoptosis and produce an agonal burst of tissue factor gene expression by human endothelial cells in culture. [33] Thus, MPO action might spur endothelial apoptosis in superficial erosion.

The findings above lend credence to the concept that despite the sparse population of inflammatory cells in eroded plaques aspects of innate immunity might nonetheless participate in this process. Seeking stimuli that might instigate a local innate immune response that could contribute to superficial erosion, we sought clues in the literature. An

important observation of Tedgui's group published in 2000 showed a striking accentuation of endothelial cells bearing markers of apoptosis, programmed cell death, downstream of a stenosis in an analysis of human carotid endarterectomy specimens.[34] The percentage of cells with signs of apoptosis in the upstream lumenal lining was 2.7 ± 1.2 versus 18.8 ± 3.3 in the downstream region ($p<0.001$). While they studied only 8 specimens, this important observation pointed toward flow disturbance as a potential contributor to endothelial cell death and hence superficial erosion. A recent human study using computational fluid dynamics and OCT compared endothelial shear stress (ESS), ESS gradient (ESSG), and oscillatory shear index (OSI) in eroded plaques. In 78% of the cases, thrombus localized between a high ESS zone and distal high OSI.[35] These results suggest that *in vivo* in humans both ESS and plaque geometry can contribute to the pathogenesis of erosion.

A review of innate immune pathways regulated by shear stress led us to consider the elegant work of Adam Mullick that established regional overexpression of the innate immune receptor toll-like receptor 2 (TLR2) in the endothelial cells of atherosclerotic mice at sites of disturbed flow.[36, 37] This work also showed that loss of TLR2 function led to lower leukocyte accumulation in atheromata. Together, these observations inspired a series of experiments that tested the hypothesis that engagement of TLR2 could contribute to endothelial cell dysfunction related to superficial erosion.[3839] Stimulation of human endothelial cells in culture with TLR2 ligands such as lipoteichoic acid (LTA) or peptidoglycan stimulated the expression of leukocyte adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) or E-selectin. [40] Exposure of human endothelial cells to these TLR2 agonists also augmented expression of the gene encoding interleukin-8, a granulocyte chemoattractant. The magnitude of induction of these mediators of leukocyte recruitment by TLR2 agonists was much lower than that elicited by a strong pro-inflammatory stimulus such as tumor necrosis factor (TNF). This observation suggested that TLR2 engagement yielded a low level, smoldering innate immune activation of endothelial cells that contrasted with the acute and severe endothelial derangement such as that elicited by a key mediator of septic shock like TNF (Figure 3b). TLR2 ligation further primed endothelial cells for desquamation (Figure 3c). The protein Vascular Endothelial Cadherin (VE-cadherin, CD144) contributes to the integrity of endothelial monolayers. [41] Exposure to LTA reduced surface VE-cadherin in human endothelial cells by more than 50% and boosted their tendency to detach from a monolayer. Given the augmented mechanisms for recruitment of granulocytes elicited by TLR2 stimulation, we added human PMN to endothelial monolayers stimulated by TLR2 agonists and found that the presence of the leukocytes accentuated the decrease in VE-cadherin and augmented endothelial cell detachment.

When endothelial cells slough, neighboring cells rapidly mobilize to migrate and recover the gap in intimal integrity. We tested the hypothesis that TLR2 agonism would impair this process. Using a standardized *in vitro* wounding of a monolayer of human endothelial cells we observed retarded repair of the wounded monolayer when the cells were exposed to TLR2 agonists. Together, these observations indicated a role for TLR2 stimulation in functions of endothelial cells hypothesized to contribute to superficial erosion. [40]

The quest for an endogenous ligand for TLR2 that might have relevance for superficial erosion recalls the observation of Virmani, Wight, and colleagues that eroded plaques accumulate proteoglycans and hyaluronan.[2223] Hyaluronan fragments can act as endogenous danger signals by engaging TLR2. [42, 43] Coupling these two observations led to the hypothesis that hyaluronan could serve as an endogenous contributor to endothelial dysfunctions related to erosion. Indeed, endothelial cells cultured on a hyaluronan matrix showed increased E-selectin, VCAM-1, and interleukin-8 expression and activation of caspase-3, a "machinery" enzyme implicated in apoptosis. Further studies indicated that lower molecular weight fragments of this glycosaminoglycan stimulated these inflammatory functions of human endothelial cells to a greater extent than large molecular weight fractions of hyaluronan.[38, 44]

Beyond hyaluronan fragments other endogenous danger-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs) could ligate TLR2 or other innate immune receptors to contribute to a smoldering endothelial activation in relation to superficial erosion.[45] Such candidates could include oxidized lipids, fatty acids, or bacterial products derived from pathogens or from the endogenous microbiome. Peptidoglycans comprise a major component of the cell wall of Gram-positive bacteria that ubiquitously inhabit human mucosae. Human atheromata also contain peptidoglycans.[46] Peptidoglycans can engage CD14, a co-receptor for bacterial lipopolysaccharides on macrophages, and elicit production of proinflammatory cytokines and matrix metalloproteinases. Peptidoglycan activation of inflammatory cells increases their adhesive and migratory capacities.[47]

The concepts that emerged from a synthesis of such studies prompted postulation of a "2-hit" schema for the pathogenesis of superficial erosion. As a working model, low level innate immune activation of the luminal endothelial cells could comprise a first "hit" (Figure 3b). Flow disturbance impinging on endothelial cells can contribute to their activation and help provoke desquamation or sloughing of luminal endothelial cells (Figure 3c). The neighboring cells could have impaired ability to recover the exposed sub-intima.

In a second wave, chemokines such as IL-8 elaborated by activated endothelial cells could aid local recruitment of leukocytes. Granulocytes adherent to the intimal surface could then aggravate injury by elaboration of reactive oxygen species, proteinases, and by formation of neutrophil extracellular traps (NETs) (Figure 3d and 3e). These structures derive from granulocytes undergoing NETosis, a specialized form of cell death. Polymorphonuclear leukocytes (PMN) undergoing NETosis elaborate strands of nuclear DNA decorated with proteins derived from the neutrophil-including myeloperoxidase, a source of the pro-oxidant hypochlorous acid (HOCl), and a series of serine proteinases (Figure 4).[48, 49] NETs can also acquire tissue factor from the blood. They also contain pro-inflammatory cytokines including active interleukin-1-α derived from the PMN itself. [50, 51] NETs can also entrap platelets and fibrin contributing to local thrombus formation (Figures 3f and 4). [52, 53] Our observations on human atherosclerotic plaques showed evidence for more abundant NETs in those with characteristics of erosion than in those with the morphology associated with rupture. [40]. Some evidence suggests that statins may actually augment the susceptibility of granulocytes to form NETs.[54] While statin treatment indubitably lessens the risk of overall ACS in broad categories of individuals, and furnishes the foundation of anti-atherosclerotic

drug therapy, the use of these agents could theoretically augment thrombotic risk due to eroded plaques by facilitating NETosis.

Platelets adherent to the exposed subendothelium can become activated and release their granular contents which include a number of pro-inflammatory mediators, in addition to bridging to one another, aggregating, and forming platelet-rich “white” thrombi (Figure 3d and 3e). In this manner, a microscopic defect in endothelial integrity produced by a combination of innate immune activation and flow disturbance could lead to a pro-inflammatory and pro-thrombotic cascade that could amplify and propagate a limited mural thrombus into a persistent clot that could provoke an acute coronary syndrome (Figures 1 bottom and 3f).

Testing this “2-hit” hypothesis used an *in vivo* preparation in mice. We created intimal lesions in mouse carotid arteries using an adventitial electrical injury in mice to create an intimal lesion reminiscent of a human substrate associated with superficial erosion.[38] These expanded intimas had abundant hyaluronan, few macrophages, and numerous smooth muscle cells, characteristics of human plaques that have undergone erosion. After creating these “tailored” intimas, we introduced a peri-arterial cuff with a restricted lumen that created a flow disturbance downstream. Using this preparation, we could demonstrate that disturbed flow favors neutrophil accumulation on the surface of the arteries with the fibrous intimal thickening. We found impaired barrier function in the region of disturbed flow, as well as evidence for thrombosis in situ, with fibrin deposition downstream of the cuff. Depletion of granulocytes reduced endothelial cell death and improved the continuity and barrier function of the endothelial monolayer. Mice with genetically induced loss of function of the innate immune receptor TLR2 showed inhibition of vascular cell adhesion molecule (VCAM) −1 expression, an indicator of endothelial cell activation. Further experiments using bone marrow chimeric animals demonstrated that it was TLR2 in intrinsic vascular cells such as the endothelium that mediated the muted arterial inflammatory responses to TLR2 engagement. Moreover, endothelial cells expressed TLR2 vectorially, exposed on the basal surface, enabling contact with the hyaluronan found in high quantities in the intimal lesions associated with superficial erosions in humans and in our experimentally tailored intimas. Furthermore, animals deficient in TLR2 signaling showed impaired neutrophil accumulation after introduction of flow disturbance and preserved endothelial barrier function.

Subsequent *in vivo* experiments probed the role of NETs in the pathophysiology of superficial erosion.[5556] NET generation depends on an enzyme known as peptidyl arginine deiminase-4 (PAD-4) that converts arginine, a positively charged amino acid abundant in histones, to neutral citrulline. The action of this enzyme disrupts the ionic interactions between negatively charged DNA with its plentiful phosphate groups and the histones around which strands of DNA usually entwine. Analysis of human atherosclerotic plaques revealed greater markers of NET formation in those associated with erosion than those with rupture prone characteristics. Using bone marrow chimeric mice lacking PAD-4 in hematopoietic cells, we abrogated NETosis in experimental atherosclerotic plaques but did not impede the evolution of experimental atherosclerotic lesions in mice. Yet, study of carotid arteries with the tailored intima followed by flow perturbation showed that PAD-4

deficiency abrogated the NETosis and prevented endothelial injury and thrombosis formation in the region of flow disturbance that occur in mice wild type for PAD-4. The deficiency in PAD-4 also lessened the impairment of endothelial barrier function in the region of flow disturbance in arteries with the tailored intima. Administration of deoxyribonuclease, an enzyme that can degrade the DNA strands that form the backbone of NETs, also diminished NET formation in the region of flow disturbance. These observations provided additional support for the hypothesis that NETs can promote pathophysiology related to superficial erosion *in vivo*. Other experiments implicated complement formation in intimal injury at sites of flow disturbance, providing another pathway of innate immune activation related to endothelial desquamation and hence superficial erosion.

Mature endothelial cells can exhibit considerable heterogeneity and can transdifferentiate into mesenchymal-like cells, a biological process called Endothelial-to-Mesenchymal Transition (EndMT) (Figure 5). Transforming growth factor-beta (TGF-β) signaling participates importantly in EndMT. FGF signaling maintains the classical endothelial phenotype and function, while inhibition of FGF signaling initiates EndMT. Repression of endothelial FGF signaling by loss of function of the FGF adaptor protein FRS2 or the FGF1 receptor leads to the activation of TGF-β signaling and subsequent EndMT. [57, 58] Inflammatory cytokines, such as TNF-α, IFN-γ, or IL-1β, can limit FGF signaling which in turn can promote TGF-β actions. Indeed, favoring EndMT may contribute to the mechanisms by which these cytokines participate in atherogenesis. EndMT involves disassembly of adherens junctions due to disruption of VE-cadherin, leading to loss of endothelial integrity, favoring local thrombus formation. [59, 60] Lineage tracing experiment for endothelial cells provide support for the presence of EndMT-derived fibroblast-like cells in mouse atherosclerotic plaques. Cells that express both endothelial markers such as PECAM and fibroblast markers such as FSP-1 also reside in human atherosclerotic lesions.

Many questions remain regarding the pathophysiology of superficial erosion. The animal preparation described above aims to probe mechanisms rather than to provide a “model” of human superficial erosion. A good deal more analysis of human eroded lesions and further mouse experimentation should affirm the findings described above and extend our knowledge of mechanisms that relate to superficial erosion. In particular, we need to expand the menu of potential activators of innate immune responses in endothelial cells and triggers of NETosis in relation to superficial erosion and explore other pharmacologic approaches to attacking the pathways implicated in arterial thrombus due to erosion identified by our experimental work.

Therapeutic and Clinical Implications of Superficial Erosion

As is the case with many human diseases such as tuberculosis, rheumatic fever, and endocarditis, the current clinical picture of ACS has shifted over time.[12, 13] We currently witness an evolution in the epidemiology of ACS, a family of conditions that now affects more and younger women, and has spread worldwide beyond developed countries and affects increasingly individuals of varied ethnicity. The clinical presentation of the ACS has also changed over the last few decades from a predominance of ST segment elevation myocardial infarction to an increasing proportion of non-ST segment elevation myocardial

infarction. The risk factor profile of ACS patients has also shifted, now encompassing more individuals with diabetes or components of the “metabolic syndrome” cluster, and in some countries less exposure to tobacco smoke. Although control of hypertension remains imperfect, we have many tools to manage blood pressure and have increased success in controlling this important risk factor for atherosclerosis. Most dramatically, low-density lipoprotein (LDL) control has, like blood pressure, come under much better control in the current era. We now possess highly effective tools for addressing LDL: statins, a cholesterol-absorption inhibitor, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitory strategies. These and other advances have led to a secular decrease in LDL in various populations.[61, 62] We have argued that the underlying pathophysiology of ACS may be evolving in parallel, and that a gradual waning of plaque rupture and increase in superficial erosion may reflect some of the changes in the epidemiology and risk factor shifts noted above, and account for some of the changes in clinical presentation of ACS.[13] Furthermore, early data suggest that plaque fissure portends poorer prognosis in ACS compared to ACS produced by culprit lesions with intact fibrous caps.[63]

This recognition has profound implications for “personalized” or “precision” medicine. As the pathophysiology of ACS due to plaque rupture appears to differ distinctly from that of superficial erosion, the optimum treatments may also vary. Perhaps anti-platelet therapy can combat the more platelet-rich “white” thrombus associated with erosion than the thrombi associated with the rupture of macrophage- and lipid-rich so-called “vulnerable” plaques. Perhaps immediate invasive revascularization may not yield equivalent benefits in outcome in ACS due to erosion versus rupture. Perhaps interventions that target NETs could have greater efficacy in ACS due to erosion than those provoked by rupture.

Indeed, recent preliminary clinical observations support the concept that intensified anti-platelet therapy rather than urgent invasive revascularization may manage ACS due to erosion as an initial approach.[64] In the EROSION study, the burden of thrombus in individuals presenting with STEMI due to erosion as ascertained by OCT had a striking reduction in thrombus burden after 30 days following treatment with intense anti-platelet therapy but no invasive revascularization. [65, 66] While this and other smaller studies have lacked sufficient power to assess outcomes, they provide a rationale for a large-scale and systematic study testing the efficacy of this non-interventional management of ACS due to erosion. Such a segmentation of the ACS population based on pathophysiologic mechanisms rather merely relying on venerable electrocardiographic criteria has profound implications for clinical care and the well-recognized costs and complications of acute invasive revascularization. [67, 68]

The widespread deployment of distinct strategies for the management of ACS due to erosion versus rupture could benefit enormously from development and validation of biomarkers that indicate the underlying pathophysiology of ACS. For example, previous early studies have shown that patients with plaque erosion have more myeloperoxidase in peripheral blood than those with plaque fissure, while those with fissure have higher C-reactive concentrations. [27, 69] Thus, markers of NETosis in peripheral blood (e.g. myeloperoxidase) might reflect erosion to a greater extent than rupture. Markers of NETs could include double-stranded DNA, or citrullinated histones. Proteomic strategies applied to coronary arterial blood

samples suggest distinct patterns of protein release in patients with ACS due to erosion versus rupture. [70] Beyond anti-platelet therapy, individuals with markers indicating substantive NETosis with ACS could undergo treatment with deoxyribonuclease (DNase) or inhibitors of PAD4. While these notions remain highly conjectural, they merit consideration as we strive to a more targeted treatment of individual segments of patients with ACS and have achieved success with current management strategies for ACS, rendering it unlikely that further intensification of management of traditional risk factors will yield increasing inroads into residual risk.

Implications for Research of the Recognition of the Role of Superficial Erosion in ACS

In laboratory research, much recent work has focused on the regulation of characteristics of experimental atherosclerotic plaques produced by hypercholesterolemia in mice, in swine, and in rabbits. We have learned a great deal from these studies about the cellular and molecular contributors to plaques rich in lipids and macrophages, characteristics associated with the rupture-prone human plaque. The levels of plasma cholesterol generally used in such experimental studies generally exceed by some twenty-fold that which we encounter in contemporary clinical practice in the current era.

The literature regarding experimental atherosclerosis often refers to a “vulnerable plaque phenotype” versus a “stable plaque phenotype” based on anatomo-pathological characteristics gleaned from autopsy studies of ruptured human plaques conducted in the pre-statin era. Seldom do the experimental studies actually assess the biomechanical properties of plaques, nor do animals with experimental atherosclerosis actually undergo plaque rupture except under unusual circumstances. Perhaps, to move forward in dissecting the mechanisms of ACS in the experimental laboratory we should take into consideration the striking changes in clinical ACS including the risk factor burden rather than persist in the study of animals with levels of cholesterol strikingly higher than those encountered in clinical practice. In the laboratory, we should strive to study the disease of today and tomorrow rather than the lipid- and macrophage-rich lesions which appear to have driven ACS to a greater extent in times gone by. [12]

Conclusion

This review summarizes the challenges and opportunities presented by ACS due to superficial erosion. We have achieved a great deal of detailed knowledge of plaque rupture over the last several decades. Unraveling the pathogenesis of superficial erosion both experimentally and in the clinic provides a path to considerable new understanding of ACS in the contemporary era. We need to develop and validate the biomarkers that can distinguish probabilities of superficial erosion versus rupture that can be used at point of care and not require invasive imaging, for example by OCT. We need to undertake clinical investigation of different therapies for superficial erosion. The comparative studies of different management strategies for ACS due to erosion versus rupture could provide an advance towards the goal of “precision” medicine, and ultimately improve outcomes in patients presenting with ACS.

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Non-standard Abbreviations and Acronyms

(ACS)	acute coronary syndromes
(IFN-γ)	interferon gamma
(MMP)	matrix metalloproteinase
(PAI-1)	plasminogen activator inhibitor-1
(OCT)	optical coherence tomography
(HOCl)	hypochlorous acid
(MPO)	myeloperoxidase
(ESS)	endothelial shear stress
(ESSG)	ESS gradient
(OSI)	oscillatory shear index
(TLR2)	toll-like receptor 2
(LTA)	lipoteichoic acid
(ICAM-1)	intercellular adhesion molecule-1
(TNF)	tumor necrosis factor
(VE-cadherin)	vascular endothelial cadherin
(DAMPs)	danger-associated molecular patterns
(PAMPs)	pathogen-associated molecular patterns
(NETs)	neutrophil extracellular traps
(PMN)	polymorphonuclear leukocytes
(HOCl)	hypochlorous acid
(VCAM)	vascular cell adhesion molecule
(PAD-4)	peptidyl arginine deiminase-4
(EndMT)	Endothelial-to-Mesenchymal Transition
(PCSK9)	proprotein convertase subtilisin/kexin type 9
(DNase)	deoxyribonuclease

References:

1. Bentzon JF, Otsuka F, Virmani R and Falk E. Mechanisms of plaque formation and rupture. Circ Res 2014;114:1852–1866. [PubMed: 24902970]
2. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. N Engl J Med 2013;369:2004–2013.
3. Drake TA, Morrissey JH and Edgington TS. Selective cellular expression of tissue factor in human tissues. Implications for disorders of hemostasis and thrombosis. Am J Pathol 1989;134:1087–1097. [PubMed: 2719077]
4. Wilcox JN, Smith KM, Schwartz SM and Gordon D. Localization of tissue factor in the normal vessel wall and in the atherosclerotic plaque. Proc Natl Acad Sci U S A 1989;86:2839–2843. [PubMed: 2704749]
5. Mach F, Schoenbeck U, Bonnefoy J-Y, Pober J and Libby P. Activation of monocyte/macrophage functions related to acute atheroma complication by ligation of CD40. Induction of collagenase, stromelysin, and tissue factor. Circulation 1997;96:396–399. [PubMed: 9244201]
6. Schonbeck U, Mach F, Sukhova GK, Herman M, Graber P, Kehry MR and Libby P. CD40 ligation induces tissue factor expression in human vascular smooth muscle cells. Am J Pathol 2000;156:7–14. [PubMed: 10623647]
7. Libby P and Theroux P. Pathophysiology of coronary artery disease. Circulation 2005;111:3481–3488. [PubMed: 15983262]
8. Nilsson J. Atherosclerotic plaque vulnerability in the statin era. Eur Heart J 2017;38:1638–1644. [PubMed: 28387815]
9. Lee SE, Chang HJ, Sung JM, Park HB, Heo R, Rizvi A, Lin FY, Kumar A, Hadamitzky M, Kim YJ, Conte E, Andreini D, Pontone G, Budoff MJ, Gottlieb I, Lee BK, Chun EJ, Cademartiri F, Maffei E, Marques H, Leipsic JA, Shin S, Choi JH, Chinnaiyan K, Raff G, Virmani R, Samady H, Stone PH, Berman DS, Narula J, Shaw LJ, Bax JJ and Min JK. Effects of Statins on Coronary Atherosclerotic Plaques: The PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging) Study. JACC Cardiovasc Imaging 2018.
10. Bohula EA, Giugliano RP, Leiter LA, Verma S, Park JG, Sever PS, Pineda AL, Honarpour N, Wang H, Murphy SA, Keech A, Pedersen TR and Sabatine MS. Inflammatory and Cholesterol Risk in the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk). Circulation 2018.
11. Pradhan AD, Aday AW, Rose LM and Ridker PM. Residual Inflammatory Risk On Treatment with PCSK9 Inhibition and Statin Therapy. Circulation 2018;in press.
12. Libby P and Pasterkamp G. Requiem for the ‘vulnerable plaque’. Eur Heart J 2015;36:2984–2987. [PubMed: 26206212]
13. Pasterkamp G, den Ruijter HM and Libby P. Temporal shifts in clinical presentation and underlying mechanisms of atherosclerotic disease. Nat Rev Cardiol 2017;14:21–29. [PubMed: 27762311]
14. Falk E, Shah P and Fuster V. Coronary plaque disruption. Circulation 1995;92:657–671. [PubMed: 7634481]
15. Davies MJ. Stability and instability: the two faces of coronary atherosclerosis. The Paul Dudley White Lecture, 1995. Circulation 1996;94:2013–2020. [PubMed: 8873680]
16. Virmani R, Burke AP, Farb A and Kolodgie FD. Pathology of the unstable plaque. Prog Cardiovasc Dis 2002;44:349–356. [PubMed: 12024333]
17. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z and Serruys PW. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226–235. [PubMed: 21247313]
18. Kubo T, Maehara A, Mintz GS, Doi H, Tsujita K, Choi SY, Katoh O, Nasu K, Koenig A, Pieper M, Rogers JH, Wijns W, Bose D, Margolis MP, Moses JW, Stone GW and Leon MB. The dynamic nature of coronary artery lesion morphology assessed by serial virtual histology intravascular ultrasound tissue characterization. J Am Coll Cardiol 2010;55:1590–1597. [PubMed: 20378076]

19. Chang HJ, Lin FY, Lee SE, Andreini D, Bax J, Cademartiri F, Chinnaiyan K, Chow BJW, Conte E, Cury RC, Feuchtner G, Hadamitzky M, Kim YJ, Leipsic J, Maffei E, Marques H, Plank F, Pontone G, Raff GL, van Rosendael AR, Villines TC, Weirich HG, Al'Aref SJ, Baskaran L, Cho I, Danad I, Han D, Heo R, Lee JH, Rivzi A, Stuijfzand WJ, Gransar H, Lu Y, Sung JM, Park HB, Berman DS, Budoff MJ, Samady H, Shaw LJ, Stone PH, Virmani R, Narula J and Min JK. Coronary Atherosclerotic Precursors of Acute Coronary Syndromes. J Am Coll Cardiol 2018;71:2511–2522. [PubMed: 29852975]
20. Farb A, Burke AP, Tang AL, Liang TY, Mannan P, Smialek J and Virmani R. Coronary plaque erosion without rupture into a lipid core. A frequent cause of coronary thrombosis in sudden coronary death. Circulation 1996;93:1354–1363. [PubMed: 8641024]
21. Arbustini E, Dal Bello B, Morbini P, Burke AP, Bocciarelli M, Specchia G and Virmani R. Plaque erosion is a major substrate for coronary thrombosis in acute myocardial infarction. Heart 1999;82:269–272. [PubMed: 10455073]
22. Kolodgie FD, Burke AP, Farb A, Weber DK, Kutys R, Wight TN and Virmani R. Differential accumulation of proteoglycans and hyaluronan in culprit lesions: insights into plaque erosion. Arterioscler Thromb Vasc Biol 2002;22:1642–1648. [PubMed: 12377743]
23. Kolodgie FD, Burke AP, Wight TN and Virmani R. The accumulation of specific types of proteoglycans in eroded plaques: a role in coronary thrombosis in the absence of rupture. Curr Opin Lipidol 2004;15:575–582. [PubMed: 15361794]
24. Virmani R, Burke AP and Farb A. Plaque rupture and plaque erosion. Thromb Haemost 1999;82 Suppl 1:1–3.
25. Hu S, Yonetsu T, Jia H, Karanasos A, Aguirre AD, Tian J, Abtahian F, Vergallo R, Soeda T, Lee H, McNulty I, Kato K, Yu B, Mizuno K, Toutouzas K, Stefanadis C and Jang IK. Residual thrombus pattern in patients with ST-segment elevation myocardial infarction caused by plaque erosion versus plaque rupture after successful fibrinolysis: an optical coherence tomography study. J Am Coll Cardiol 2014;63:1336–1338. [PubMed: 24361315]
26. Jia H, Abtahian F, Aguirre AD, Lee S, Chia S, Lowe H, Kato K, Yonetsu T, Vergallo R, Hu S, Tian J, Lee H, Park SJ, Jang YS, Raffel OC, Mizuno K, Uemura S, Itoh T, Kakuta T, Choi SY, Dauerman HL, Prasad A, Toma C, McNulty I, Zhang S, Yu B, Fuster V, Narula J, Virmani R and Jang IK. In vivo diagnosis of plaque erosion and calcified nodule in patients with acute coronary syndrome by intravascular optical coherence tomography. J Am Coll Cardiol 2013;62:1748–1758. [PubMed: 23810884]
27. Ferrante G, Nakano M, Prati F, Niccoli G, Mallus MT, Ramazzotti V, Montone RA, Kolodgie FD, Virmani R and Crea F. High levels of systemic myeloperoxidase are associated with coronary plaque erosion in patients with acute coronary syndromes: a clinicopathological study. Circulation 2010;122:2505–2513. [PubMed: 21126969]
28. Partida RA, Libby P, Crea F and Jang IK. Plaque erosion: a new in vivo diagnosis and a potential major shift in the management of patients with acute coronary syndromes. Eur Heart J 2018;39:2070–2076. [PubMed: 29329384]
29. Libby P. How does lipid lowering prevent coronary events? New insights from human imaging trials. Eur Heart J 2015;36:472–474. [PubMed: 25575600]
30. Libby P, Ganz P, Schoen FJ and Lee RT. The vascular biology of the acute coronary syndromes. In: Topol EJ., ed. Acute Coronary Syndromes 2nd ed. New York: Marcel Dekker, Inc.; 2000: 33–57.
31. Lindsey ML and Libby P. Matrix Metalloproteinases in Cardiovascular Diseases. In: Brinckerhoff CE., ed. Matrix Metalloproteinases in Health and Disease: World Scientific Publishing; 2017: 187–225.
32. Rajavashisth TB, Liao JK, Galis ZS, Tripathi S, Laufs U, Tripathi J, Chai NN, Xu XP, Jovinge S, Shah PK and Libby P. Inflammatory cytokines and oxidized low density lipoproteins increase endothelial cell expression of membrane type 1-matrix metalloproteinase. J Biol Chem 1999;274:11924–11929. [PubMed: 10207013]
33. Sugiyama S, Kugiyama K, Aikawa M, Nakamura S, Ogawa H and Libby P. Hypochlorous acid, a macrophage product, induces endothelial apoptosis and tissue factor expression: involvement of myeloperoxidase-mediated oxidant in plaque erosion and thrombogenesis. Arterioscler Thromb Vasc Biol 2004;24:1309–1314. [PubMed: 15142860]

34. Tricot O, Mallat Z, Heymes C, Belmin J, Leseche G and Tedgui A. Relation between endothelial cell apoptosis and blood flow direction in human atherosclerotic plaques. Circulation 2000;101:2450–2453. [PubMed: 10831515]
35. Yamamoto E, Thondapu V, Poon E, Sugiyama T, Fracassi F, Dijkstra J, Lee H, Ooi A, Barlis P and Jang IK. Endothelial Shear Stress and Plaque Erosion: A Computational Fluid Dynamics and Optical Coherence Tomography Study. JACC Cardiovasc Imaging 2018;in press.
36. Mullick AE, Tobias PS and Curtiss LK. Modulation of atherosclerosis in mice by Toll-like receptor 2. J Clin Invest 2005;115:3149–3156. [PubMed: 16211093]
37. Mullick AE, Soldau K, Kiosses WB, Bell TA, 3rd, Tobias PS and Curtiss LK. Increased endothelial expression of Toll-like receptor 2 at sites of disturbed blood flow exacerbates early atherogenic events. J Exp Med 2008;205:373–383. [PubMed: 18250194]
38. Franck G, Mawson T, Sausen G, Salinas M, Masson GS, Cole A, Beltrami-Moreira M, Chatzizisis Y, Quillard T, Tesmenitsky Y, Shvartz E, Sukhova GK, Swirski FK, Nahrendorf M, Aikawa E, Croce KJ and Libby P. Flow Perturbation Mediates Neutrophil Recruitment and Potentiates Endothelial Injury via TLR2 in Mice - Implications for Superficial Erosion. Circ Res 2017;121:31. [PubMed: 28428204]
39. Bentzon JF and Falk E. Plaque Erosion - New Insights From the Road Less Travelled. Circ Res 2017;121:8–10. [PubMed: 28642322]
40. Quillard T, Araujo HA, Franck G, Shvartz E, Sukhova G and Libby P. TLR2 and neutrophils potentiate endothelial stress, apoptosis and detachment: implications for superficial erosion. Eur Heart J 2015;36:1394–1404. [PubMed: 25755115]
41. Giannotta M, Trani M and Dejana E. VE-cadherin and endothelial adherens junctions: active guardians of vascular integrity. Dev Cell 2013;26:441–454. [PubMed: 24044891]
42. Taylor KR, Trowbridge JM, Rudisill JA, Termeer CC, Simon JC and Gallo RL. Hyaluronan fragments stimulate endothelial recognition of injury through TLR4. J Biol Chem 2004;279:17079–17084. [PubMed: 14764599]
43. Scheibner KA, Lutz MA, Boodoo S, Fenton MJ, Powell JD and Horton MR. Hyaluronan fragments act as an endogenous danger signal by engaging TLR2. The Journal of Immunology 2006;177:1272–1281. [PubMed: 16818787]
44. Quillard T, Franck G, Mawson T, Folco E and Libby P. Mechanisms of erosion of atherosclerotic plaques. Curr Opin Lipidol 2017.
45. Bertheloot D and Latz E. HMGB1, IL-1alpha, IL-33 and S100 proteins: dual-function alarmins. Cell Mol Immunol 2016.
46. Laman JD, Schoneveld AH, Moll FL, van Meurs M and Pasterkamp G. Significance of peptidoglycan, a proinflammatory bacterial antigen in atherosclerotic arteries and its association with vulnerable plaques. Am J Cardiol 2002;90:119–123. [PubMed: 12106839]
47. Nijhuis MM, Pasterkamp G, Sluis NI, de Kleijn DP, Laman JD and Ulfman LH. Peptidoglycan increases firm adhesion of monocytes under flow conditions and primes monocyte chemotaxis. J Vasc Res 2007;44:214–222. [PubMed: 17337907]
48. Wright HL, Moots RJ, Bucknall RC and Edwards SW. Neutrophil function in inflammation and inflammatory diseases. Rheumatology (Oxford) 2010;49:1618–1631. [PubMed: 20338884]
49. Borregaard N, Sorensen OE and Theilgaard-Monch K. Neutrophil granules: a library of innate immunity proteins. Trends Immunol 2007;28:340–345. [PubMed: 17627888]
50. Naegelen I, Beaume N, Plancon S, Schenten V, Tschirhart EJ and Brechard S. Regulation of Neutrophil Degranulation and Cytokine Secretion: A Novel Model Approach Based on Linear Fitting. J Immunol Res 2015;2015:817038. [PubMed: 26579547]
51. Folco EJ, Mawson TL, Vromman A, Bernardes-Souza B, Franck G, Persson O, Nakamura M, Newton G, Luscinskas FW and Libby P. Neutrophil Extracellular Traps Induce Endothelial Cell Activation and Tissue Factor Production through Interleukin-1α and Cathepsin G. Arterioscler Thromb Vasc Biol 2018;38:1901–1912. [PubMed: 29976772]
52. Fuchs TA, Brill A, Duerschmied D, Schatzberg D, Monestier M, Myers DD, Jr., Wrobleski SK, Wakefield TW, Hartwig JH and Wagner DD. Extracellular DNA traps promote thrombosis. Proc Natl Acad Sci U S A 2010;107:15880–15885. [PubMed: 20798043]

53. Martinod K and Wagner DD. Thrombosis: tangled up in NETs. Blood 2014;123:2768–2776. [PubMed: 24366358]
54. Chow OA, von Kockritz-Blickwede M, Bright AT, Hensler ME, Zinkernagel AS, Cogen AL, Gallo RL, Monestier M, Wang Y, Glass CK and Nizet V. Statins enhance formation of phagocyte extracellular traps. Cell Host Microbe 2010;8:445–454. [PubMed: 21075355]
55. Franck G, Mawson TL, Folco EJ, Molinaro R, Ruvkun V, Engelbertsen D, Liu X, Tesmenitsky Y, Shvartz E, Sukhova GK, Michel J-B, Nicoletti A, Lichtman AH, Wagner DD, Croce KJ and Libby P. Roles of PAD4 and NETosis in Experimental Atherosclerosis and Arterial Injury: Implications for Superficial Erosion. Circ Res 2018;123:33–42. [PubMed: 29572206]
56. Soehnlein O, Bazioti V and Westerterp M. A Pad 4 Plaque Erosion. Circ Res 2018;123:6–8. [PubMed: 29929967]
57. Chen PY, Qin L, Barnes C, Charisse K, Yi T, Zhang X, Ali R, Medina PP, Yu J, Slack FJ, Anderson DG, Kotelianski V, Wang F, Tellides G and Simons M. FGF regulates TGF-β signaling and endothelial-to-mesenchymal transition via control of let-7 miRNA expression. Cell Rep 2012;2:1684–1696. [PubMed: 23200853]
58. Cooley BC, Nevado J, Mellad J, Yang D, St Hilaire C, Negro A, Fang F, Chen G, San H, Walts AD, Schwartzbeck RL, Taylor B, Lanzer JD, Wragg A, Elagha A, Beltran LE, Berry C, Feil R, Virmani R, Ladich E, Kovacic JC and Boehm M. TGF-beta signaling mediates endothelial-to-mesenchymal transition (EndMT) during vein graft remodeling. Sci Transl Med 2014;6:227ra234.
59. Wesseling M, Sakkers TR, de Jager SCA, Pasterkamp G and Goumans MJ. The morphological and molecular mechanisms of epithelial/endothelial-to-mesenchymal transition and its involvement in atherosclerosis. Vascul Pharmacol 2018;106:1–8. [PubMed: 29471141]
60. Evrard SM, Lecce L, Michelis KC, Nomura-Kitabayashi A, Pandey G, Purushothaman KR, d'Escamard V, Li JR, Hadri L, Fujitani K, Moreno PR, Benard L, Rimmele P, Cohain A, Mecham B, Randolph GJ, Nabel EG, Hajjar R, Fuster V, Boehm M and Kovacic JC. Endothelial to mesenchymal transition is common in atherosclerotic lesions and is associated with plaque instability. Nat Commun 2016;7:11853. [PubMed: 27340017]
61. Schreiner PJ, Jacobs DR, Jr., Wong ND and Kiefe CI. Twenty-Five Year Secular Trends in Lipids and Modifiable Risk Factors in a Population-Based Biracial Cohort: The Coronary Artery Risk Development in Young Adults (CARDIA) Study, 1985–2011. J Am Heart Assoc 2016;5.
62. Hopstock LA, Bonaa KH, Eggen AE, Grimsgaard S, Jacobsen BK, Lochen ML, Mathiesen EB, Njolstad I and Wilsgaard T. Longitudinal and secular trends in total cholesterol levels and impact of lipid-lowering drug use among Norwegian women and men born in 1905–1977 in the population-based Tromso Study 1979–2016. BMJ Open 2017;7:e015001.
63. Niccoli G, Montone RA, Di Vito L, Gramegna M, Refaat H, Scalone G, Leone AM, Trani C, Burzotta F, Porto I, Aurigemma C, Prati F and Crea F. Plaque rupture and intact fibrous cap assessed by optical coherence tomography portend different outcomes in patients with acute coronary syndrome. Eur Heart J 2015;36:1377–1384. [PubMed: 25713314]
64. Prati F, Uemura S, Souteyrand G, Virmani R, Motreff P, Di Vito L, Biondi-Zoccai G, Halperin J, Fuster V, Ozaki Y and Narula J. OCT-based diagnosis and management of STEMI associated with intact fibrous cap. JACC Cardiovasc Imaging 2013;6:283–287. [PubMed: 23473109]
65. Jia H, Dai J, Hou J, Xing L, Ma L, Liu H, Xu M, Yao Y, Hu S, Yamamoto E, Lee H, Zhang S, Yu B and Jang IK. Effective anti-thrombotic therapy without stenting: intravascular optical coherence tomography-based management in plaque erosion (the EROSION study). Eur Heart J 2017;38:792–800. [PubMed: 27578806]
66. Jia H, Kubo T, Akasaka T and Yu B. Optical Coherence Tomography Guidance in Management of Acute Coronary Syndrome Caused by Plaque Erosion. Circ J 2018;82:302–308. [PubMed: 29332908]
67. Braunwald E. Coronary plaque erosion: recognition and management. JACC Cardiovasc Imaging 2013;6:288–289. [PubMed: 23473110]
68. Libby P. Superficial erosion and the precision management of acute coronary syndromes: not one-size-fits-all. Eur Heart J 2017;38:801–803. [PubMed: 28053187]
69. Niccoli G, Montone RA, Cataneo L, Cosentino N, Gramegna M, Refaat H, Porto I, Burzotta F, Trani C, Leone AM, Severino A and Crea F. Morphological-biohumoral correlations in acute

coronary syndromes: pathogenetic implications. Int J Cardiol 2014;171:463–466. [PubMed: 24439867]

70. Chandran S, Watkins J, Abdul-Aziz A, Shafat M, Calvert PA, Bowles KM, Flather MD, Rushworth SA and Ryding AD. Inflammatory Differences in Plaque Erosion and Rupture in Patients With ST-Segment Elevation Myocardial Infarction. J Am Heart Assoc 2017;6.

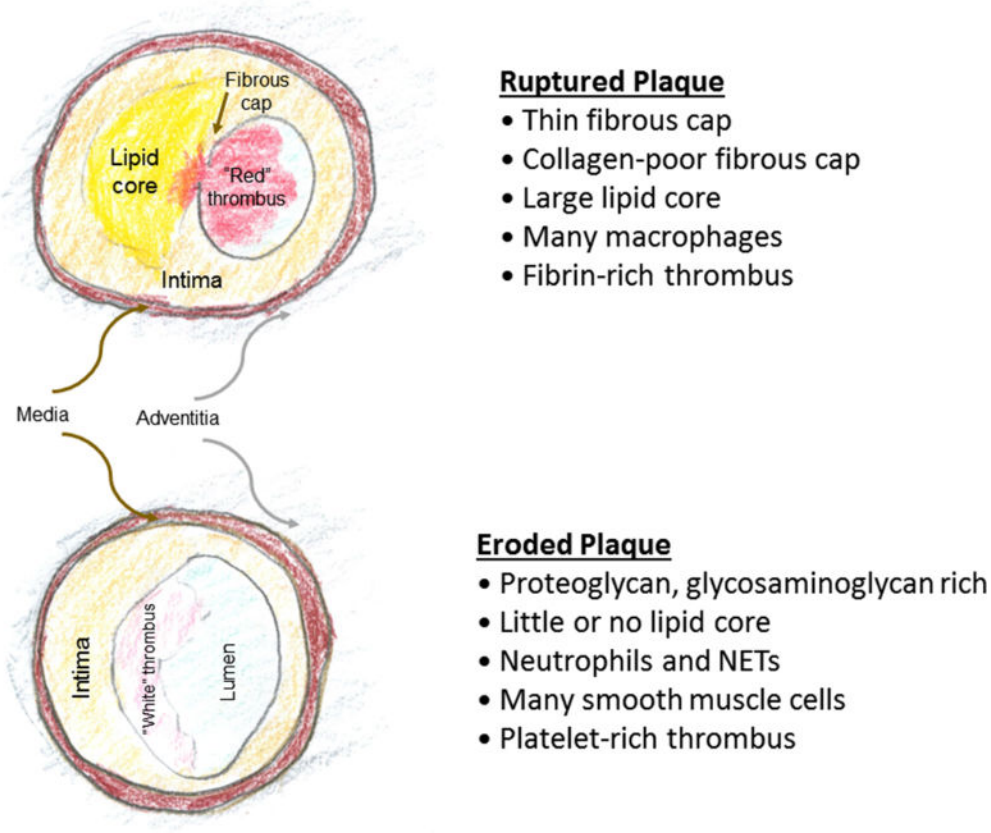

Figure 1. Comparison of the characteristics of human atheromata complicated by thrombosis due to plaque rupture (top) or superficial erosion (bottom).

The column on the left highlights some of the characteristics demonstrated by analyses of human coronary arterial lesions that have undergone thrombosis by these two diverse mechanisms. NETs = neutrophil extracellular traps (Illustration Credit: Ben Smith).

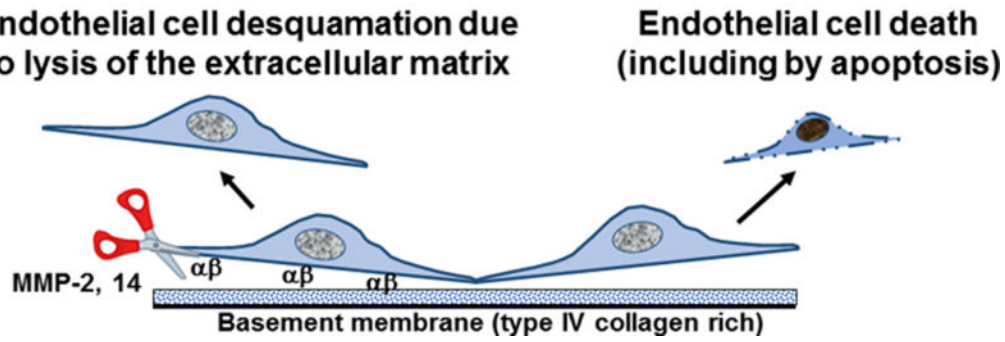

Figure 2. Some possible mechanisms of endothelial cell desquamation associated with superficial erosion and arterial thrombosis.

The left side of this diagram shows proteolysis affected by enzymes such as the matrix metalloproteinases that can degrade the integrins on the basal surface of endothelial cells represented by the α and β, or the constituents of the basement membrane to which the endothelial cells adhere through integrin/matrix binding. Basement membranes contain about 40% of Type IV collagen, a substrate of matrix metalloproteinase-2 (MMP-2) a Type IV collagenase that undergoes activation by the membrane associated proteinase MMP-14. The right side of this diagram depicts endothelial cell death by apoptosis or other mechanisms that can lead to sloughing of the luminal endothelial cells affording access of the blood and its formed elements including platelets to the subjacent intimal layers. (Illustration Credit: Ben Smith).

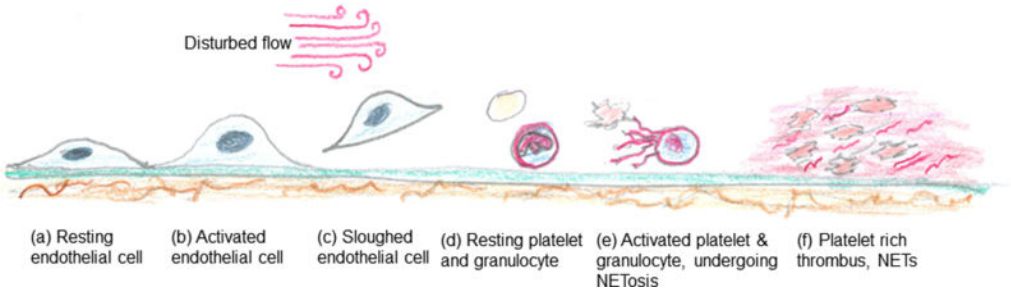

Figure 3. A hypothetical timeline of events that can promote thrombosis due to superficial erosion.

This hypothetical timeline depicts a possible sequence of events (from left to right) that can lead to thrombosis due to superficial erosion. Endothelial cells can undergo low-grade smoldering activation as depicted by assuming a less squamous and more columnar morphology. Candidate stimuli include TLR2 ligands such as hyaluronan fragments among other innate immune activators including damage-associated molecular patters (DAMPs.) Endothelial cells with severed tethers to the basement membrane or those that have undergone various forms of cell death as depicted in Figure 2 can desquamate allowing access of platelets and neutrophils to subendothelial structures. Activation of platelets by contact with collagen and triggering of NETosis in the localized granulocytes can initiate and propagate the formation of a platelet-rich thrombus depicted on the right-hand side of this diagram showing activated platelets that can bridge through fibrin binding and adhere to collagen through glycoprotein VI. The red spiral structures in the platelet-rich thrombus depict DNA strands derived from NETs, decorated with thrombogenic and pro-inflammatory mediators as shown in Figure 4. (Illustration Credit: Ben Smith).

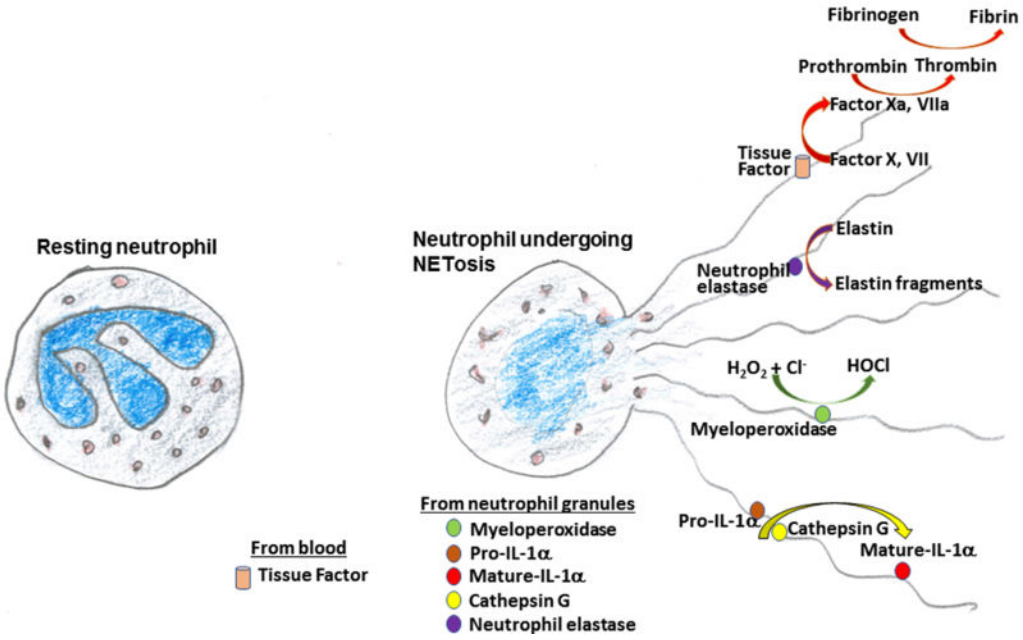

Figure 4. Formation of neutrophil extracellular traps and selected mediators associated with NETs that can participate in local arterial thrombosis.

NETs can bear proteins contained in neutrophil granules released during neutrophil activation. These proteins include those derived from azurophilic or primary granules including myeloperoxidase, Cathepsin G, neutrophil elastase (NE), and proteinase 3 (PR3), among other hydrolytic enzymes including a series of phospholipases that can generate biologically active lipid mediators of inflammation. NETs can also acquire proteins from extra-neutrophilic sources including tissue factor (TF) that can activate Factor VII and through activation of Factor Xa lead to local thrombin generation that produce fibrin locally. NE and other extracellular matrix-degrading proteins such as neutrophil collagenase and gelatinases can further degrade the basement membrane and underlying extracellular matrix macromolecules including basement membrane constituents and fibrillar collagens. (Elastin fragments may promote chemoattraction of further granulocytes.) Myeloperoxidase generates the highly pro-oxidant species hypochlorous acid (HOCl). Pro- interleukin-1-alpha (IL-1α) derived from neutrophils can bind to the DNA strands that comprise NETs. NETs can activate pro-inflammatory functions of endothelial cells through stimulation by IL-1α. The neutrophil serine proteinase Cathepsin G can enhance the local activity of IL-1α by cleaving the pro- form to produce the more active mature form of this pro-inflammatory cytokine. (Illustration Credit: Ben Smith).

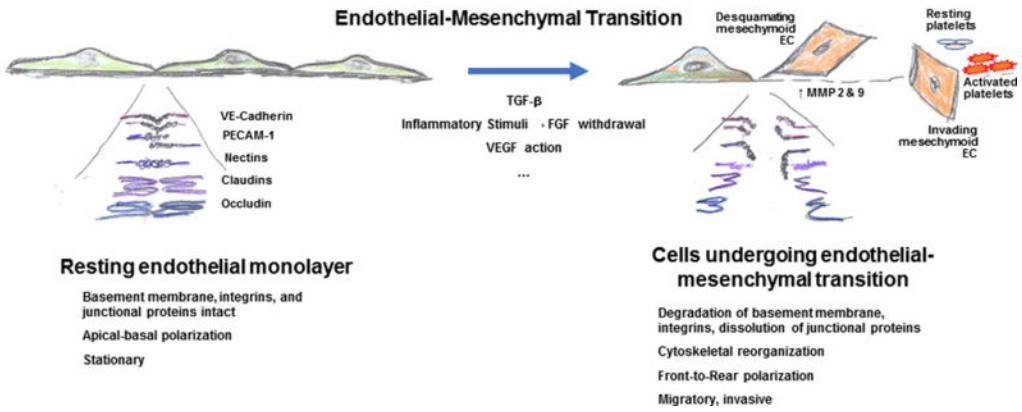

Figure 5. Endothelial-mesenchymal transition may contribute to superficial erosion.

The left-hand part of this diagram depicts a resting endothelial monolayer tightly adherent to the underlying basement membrane. A number of junctional proteins including those depicted here contribute to the barrier function of an intact resting endothelial monolayer. These resting endothelial cells have a squamous morphology with apical-basal polarization. In response to signals such as transforming growth factor beta (TGF-β), withdrawal or loss of function of fibroblast growth factor, or augmented vascular endothelial growth factor (VEGF) signaling, the cells express higher levels of matrix metalloproteinases (MMPs) 2 and 9, enzymes capable of degrading basement membrane constituents. These and other proteinases can disturb the integrin molecules localized on the basal aspect of the endothelial cells that tether them to the basement membrane, as depicted in Figure 2. These stimulated cells lose their squamous morphology and apical-basal polarization that characterize the resting endothelial cell, and acquire front to rear polarization. The endothelial cells can slough due to the interrupted binding to the basement membrane. Local permeability of the endothelial monolayer increases due to dissolution of the junctional proteins that determine the barrier function of the intimal interface with blood. The loss of endothelial cell coverage permits contact with subjacent structures in the intima that may promote platelet activation as depicted on the right side of this diagram. The cells that have acquired the mesenchymal character can invade and penetrate into the underlying atherosclerotic plaque in the intima. (Illustration Credit: Ben Smith).

Table 1:

Therapeutic interventions that might mitigate superficial erosion

Anti-platelet therapy without percutaneous intervention
Deoxyribonuclease (DNAse I)
Inhibition of peptidyl arginine deiminase-4 (PAD-4)
Inhibition of myeloperoxidase (MPO)
Anti-cytokine therapy (e.g. targeting IL-1 isoforms, IL-8, or IL-6)

Table 2:

Research needs regarding superficial erosion

Expanded experimental preparations
Deeper mechanistic understanding of triggers and effectors
Identification and validation of biomarkers that would permit non-invasive point-of-care differentiation of ACS due to plaque erosion vs. rupture
Develop and validate preventive strategies and treatments for ACS caused by erosion
Prospective biomarker-guided therapeutic trials