



Inflammation and plaque vulnerability

Citation

Hansson, G. K., P. Libby, and I. Tabas. 2015. "Inflammation and Plaque Vulnerability." *Journal of Internal Medicine* 278 (5) (August 11): 483–493. Portico. doi:10.1111/joim.12406.

Published Version

10.1111/joim.12406

Permanent link

<http://nrs.harvard.edu/urn-3:HUL.InstRepos:23792479>

Terms of Use

This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Open Access Policy Articles, as set forth at <http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#OAP>

Share Your Story

The Harvard community has made this article openly available.
Please share how this access benefits you. [Submit a story](#).

[Accessibility](#)

INFLAMMATION AND PLAQUE VULNERABILITY

Göran K Hansson¹, Peter Libby² and Ira Tabas³

- 1) Department of Medicine and Center for Molecular Medicine, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden;
- 2) Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA;
- 3) Department of Medicine, Department of Pathology and Cell Biology, and Department of Physiology, Columbia University Medical Center, New York, NY, USA.

Correspondence:

Professor Göran K Hansson
Center for Molecular Medicine L8:03
Karolinska University Hospital
SE-17176 Stockholm
Sweden
e-mail: goran.hansson@ki.se

Atherosclerosis: chronic inflammation in the artery wall

Atherosclerosis is a maladaptive, non-resolving chronic inflammatory disease that occurs at sites of blood flow disturbance. The atherogenic process is thought to be triggered by the subendothelial retention of cholesterol-containing plasma lipoproteins at these sites and by flow-mediated inflammatory changes in endothelial cells^{1,2}. The lesions contain monocyte-derived macrophages and T cells interspersed with acellular regions containing lipids and debris from dead cells, embedded in an extracellular matrix composed of collagen fibers and other constituents produced primarily by vascular smooth muscle cells^{3,4}. The collagenous matrix typically forms a fibrous cap that overlies the lipid rich region in the plaque core. Lesions generally remain covered by an intact endothelium until the late stages of the disease. The eventual breakdown of endothelial continuity can promote lesion progression and complication.

Cells of the atherosclerotic lesion display features of ongoing inflammation, with macrophages and T cells producing a host of mediators including proinflammatory cytokines, costimulatory factors for immune activation, eicosanoids, and reactive oxygen and nitrogen species^{5,6}. In addition, many of the macrophages internalize cholesterol through their scavenger receptors and some also produce anti-inflammatory cytokines. Furthermore, certain T cells of the regulatory phenotype display anti-inflammatory and immunosuppressive features. This delicate balance between pro- and anti-inflammatory signals results in a slowly progressive, non-resolving, chronic inflammation⁷.

Innate and adaptive reactions in the artery

Several reactions link lipid accumulation to inflammation. In the macrophage, pattern recognition receptors selected in evolution for handling components of microbial pathogens also mediate internalization of modified lipoproteins^{5,6}. These scavenger receptors evade suppression due to increases in intracellular cholesterol concentrations, and can therefore mediate continued lipoprotein uptake that permits overloading the cell with lipids. At a certain point, intracellular cholesterol precipitates as microcrystals. Analogously with urate

crystals, these cholesterol microcrystals can activate an inflammasome, i.e. a cytosolic molecular machine that cleaves a proform of interleukin (IL)-1 beta, converting it into bioactive IL-1beta that can be secreted by the cell⁸. When released in the arterial intima, IL-1beta induces production of a set of other proinflammatory molecules, including the cytokine IL-6 and the proinflammatory eicosanoid, PGE₂^{9,10}. IL-1 beta also promotes expression of leukocyte adhesion molecules and matrix-degrading metalloproteinases. Thus, cholesterol accumulation begets inflammation and tissue remodelling.

Another set of pattern recognition receptors, the Toll-like receptors, may bind modified lipoprotein particles in the arterial intima¹¹⁻¹⁴, triggering phosphorylation cascades that elicit expression of a set of proinflammatory genes similar but not identical to that elicited by IL-1 beta. For instance, TNF induces expression of matrix metalloproteinases that degrade collagen and promotes tissue remodelling¹⁵. TNF has crucial pathogenetic importance in rheumatoid arthritis and other inflammatory diseases and also impacts atherosclerosis substantially¹⁶⁻¹⁸.

Presentation by dendritic cells of fragments of LDL particles to T cells in lymph nodes draining the atherosclerotic lesion calls adaptive immunity into action^{19,20}. Clones of T cells that recognize peptide fragments of the main LDL apoprotein (apoprotein B) that can act as autoantigens. This encounter tends to differentiate the T cells into proinflammatory Th1 effector cells under the influence of proinflammatory mediators such as IL-12 found in plaque^{20,21}. Effector T cells patrol the body, enter at sites such as the plaque, where endothelial cells express leukocyte adhesion molecules. These T cells may undergo reactivation by LDL fragments. Such renewed activation prompts the Th1 cell to produce large amounts of TNF and also another proinflammatory cytokine, interferon-gamma^{21,22}. This interferon strongly stimulates macrophages and also profoundly effects vascular endothelial and smooth muscle cells, causing them to express leukocyte adhesion molecules, modulate their fibrinolytic properties, reduce proliferation, and in the case of the smooth muscle cell, inhibit fibrillar collagen formation^{23,24}. Interestingly, in keeping with the counterbalancing forces mentioned above, lesional dendritic cells can

also promote the development of pro-resolving regulatory T cells in early atherosclerosis^{25, 26}, but ultimately the effector:regulatory T cell balance promotes progressive inflammation.

In the advanced atherosclerotic plaque, infiltrating mast cells contribute to the proinflammatory milieu²⁷. Upon activation, these cells release a host of mediators and enzymes, including histamine, serotonin, thromboxane and other eicosanoids, cytokines, and a set of serine proteases, all of which may profoundly affect the atherosclerotic lesion.

The concerted action of all proinflammatory signals operating in the plaque not only enhances inflammation but also hampers renewal of the structural elements that support the mechanical stability of the inflamed tissue.

Clinical and histopathological features of culprit lesions

The atherosclerotic process typically lies silent for months, years, and even decades, and may never result in clinical manifestations². Yet, if the plaque's surface is damaged, thrombotic occlusion of the artery may ensue. Surface continuity may be damaged by fissuring (so-called plaque rupture, observed in 60 to 80% of cases of acute coronary syndrome) or surface erosion (present in 20 to 40% of cases with coronary thrombosis, especially in women and young victims of sudden coronary death)^{28, 29}. Figures 1-2 depict these two different types of discontinuity of the plaque surface. Recent studies suggest that the proportion of infarctions caused by rupture vs erosion is changing, with more cases due to erosion and fewer to overt plaque rupture³⁰.

Fissures and erosions trigger atherothrombosis by exposing thrombogenic material inside the plaque, such as phospholipids, tissue factor, and matrix molecules, to platelets and coagulation factors². Platelet aggregates precipitating on these exposed surfaces are stabilized by fibrin networks. Tissue factor, expressed by macrophages and by vascular smooth muscle cells in the atherosclerotic plaque, can initiate the blood coagulation cascade that leads to fibrin formation³¹. Atherothrombi expand rapidly and can fill the lumen within minutes, thereby leading to ischemia and infarction.

A range of factors may contribute to atherothrombosis. Disturbance of the balance between prothrombotic and fibrinolytic activity on the plaque surface probably plays an important role for precipitating the thrombotic event³², but the precise sequence of events that operate in vivo is not yet known.

The “vulnerable plaque”

Thrombi precipitate on damaged vascular surfaces, as recognized by Rudolf Virchow in 1856³³. The cause of the damage leading to plaque rupture or erosion remains incompletely understood, despite considerable progress in this regard. Constantinides, Davies, Falk and their colleagues observed that ruptured plaques display thin fibrous caps and large lipid core regions³⁴⁻³⁶. These findings highlighted structural abnormalities in the vessel wall as a cause of atherothrombosis. Subsequent investigations have revealed that culprit lesions of fatal thrombi in coronary arteries contain reduced amounts of mature, crosslinked collagen and increased levels of collagen-degrading enzymes.

In vivo imaging technology now offers approaches to the analysis of major plaque components. For example, optical coherence tomography (OCT) and magnetic resonance imaging can identify thin-cap plaques. Computerized tomographic angiography can identify outward arterial remodelling, radiolucency, and spotty calcification associated with coronary events. Such approaches, albeit incompletely validated, currently see used to obtain surrogate endpoint data on effects of putative plaque-stabilizing therapies³⁷⁻³⁹.

Histopathologic analysis of lesions that have provoked fatal myocardial infarction (MI) shows stigmata of inflammation including accumulation of macrophages, activated T cells, dendritic cells, and mast cells as well as reduced thickness of the fibrous cap and increased neovascularization at sites of plaque rupture and thrombosis⁴⁰ (Fig. 1). Matrix metalloproteinases and cysteine proteinases, products of activated macrophages, localize at sites of plaque rupture⁴¹. Several of these enzymes digest fibrillar collagen, thus reducing the mechanical stability of the plaque^{41, 42}. These proteinases likely render plaques susceptible to rupture, but have complex effects on the composition and size of lesions in mouse experiments.

Lesional cell death

Cell death may also predispose to plaque rupture^{7, 43}. Smooth muscle cells (SMC) synthesize the bulk of the arterial extracellular matrix. Site of fatal plaque rupture display depletion of SMC needed to repair and maintain the collagen that comprises the plaque's fibrous cap. Apoptosis of SMC documented in atherosclerotic lesions, may thus lead to their relative lack at sites of plaque rupture. Rapid phagocytosis usually clears the remnants of cells that have undergone apoptosis, a process known as efferocytosis⁴⁴. If this process fails, secondary necrosis ensues, contributing to the formation of the plaque's lipid core, also known as the "necrotic core." Computational analyses indicate that lipid core accumulation can reduce the mechanical integrity of the plaque.

Plaque necrosis results from death of lesional cells, mostly macrophages. Cell death can lead to necrosis by at least two mechanisms: apoptosis followed by defective phagocytic clearance ("efferocytosis") of the apoptotic cells; and a process called primary necrosis⁷. Macrophage apoptosis occurs in lesions of all stages. A number of plaque factors are likely to trigger lesional macrophage apoptosis, including excessive inflammation, oxidized lipids, and cholesterol, often in combination through a "multi-hit" process. Observational data in human atherosclerotic lesions and molecular-genetic causation data in mouse models of advanced atherosclerosis indicate that one of the hits caused by these factors is chronic endoplasmic reticulum (ER) stress⁴⁵. In particular, the ER stress effector CHOP is tightly associated with cell death and plaque necrosis in human coronary artery lesions, and genetic deletion of CHOP in mice protects against advanced lesional macrophage apoptosis and plaque necrosis⁴⁵.

In early atherosclerosis, the apoptotic cells are properly cleared by neighboring phagocytes, which prevents post-apoptotic necrosis and triggers pro-resolving processes that are linked to efferocytosis⁴⁶. In advanced plaques, however, efferocytosis is defective, leading to cell necrosis, release of pro-inflammatory damage-associated molecular patterns (DAMPs), and lack of efferocytosis-mediated pro-resolving signaling⁴⁷⁻⁴⁹. Collectively, these processes promote the type of inflammatory, necrotic lesions that are characteristic of vulnerable plaques (see below). The mechanisms of defective efferocytosis in advanced

atherosclerotic lesions are not known and are likely to be multi-factorial. A recent study provided correlative evidence in human atheromata suggesting a role for ADAM17-mediated cleavage of MerTK, a macrophage efferocytosis receptor shown to be important in the progression of murine atherosclerosis⁴⁹⁻⁵¹. It is also interesting to note that defective efferocytosis is a cardinal sign of defective inflammation resolution⁵², and that a therapeutic strategy that enhanced resolution in advanced murine plaques markedly suppressed plaque necrosis⁵³.

Whereas, defective efferocytosis leads to plaque necrosis through secondary necrosis of uncleared apoptotic cells, cells can undergo another process in which necrosis develops as a primary event. In this case, a signaling cascade involving RIP1 and RIP3 kinases is involved, and when RIP3 kinase was genetically targeted in fat fed LDL receptor null mice, plaque necrosis was partially suppressed⁵⁴. These data suggest that, at least in advanced murine atheroma, both secondary and primary apoptosis contribute to plaque necrosis.

Plaque erosion

Plaques that have disrupted due to fibrous cap fracture tend to have a large lipid core³⁰, and the potent procoagulant tissue factor localizes in these cores⁷ (Fig. 1). Those disrupted by erosion, another substrate for thrombus formation, do not have a large lipid core and show less inflammatory cell accumulation than fissured plaques (Fig. 2). Plaques frequently rupture without clinical manifestations, possibly reflecting variation in the thrombotic response depending on the thrombogenicity of exposed plaque constituents, local hemorheology, shear-induced platelet activation systemic clotting activity, fibrinolytic function, and sensitivity of the end organ to ischemia.

Plaques displaying endothelial erosion seem to differ from rupturing ones in some important aspects²⁹. They appear to be less inflamed but contain proliferating smooth muscle cells, abundant proteoglycans and hyaluronan, and substantial neovascularization. Therefore, pathogenetic mechanisms may differ between these two conditions and we will consider them separately.

Why do plaques rupture?

Most of our knowledge about plaque rupture comes from studies of human autopsy specimens and surgical material. Key histopathological findings associated with regions of fatal disruption include a thin fibrous cap (< 50-60 microns), increased signs of inflammatory activity, and heightened amounts of proteolytic enzymes⁵⁵⁻⁵⁹. Therefore, inflammatory stimuli such as local immune reactions might activate macrophages, mast cells and T cells to release cytokines that inhibit cap formation and proteases that digest fibrous components of the cap (Fig. 1).

Much interest has focused on the collagenolytic action of matrix metalloproteinases and cysteine proteases in the plaque. A set of such enzymes are present in the human atherosclerotic plaque and has shown proteolytic activity in culprit lesions^{57, 60}. These findings have encouraged attempts at developing plaque-stabilizing therapies by targeting proteases. Several excellent reviews cover this interesting development in detail^{61, 62}.

A set of immune cytokines impacts powerfully on the fibrous cap (Fig. 1). Interferon-gamma, a proinflammatory, macrophage-activating cytokine produced by Th1-type T cells and NK cells, inhibits collagen fiber formation, causing plaques to adopt a vulnerable phenotype with reduced collagen content. This is due to a triple action of interferon-gamma, as it both inhibits smooth muscle differentiation²⁴, procollagen-I gene expression²³ and the collagen cross-linking enzyme, lysyl oxidase⁶³.

The action of Th1 cells is counterbalanced by Treg cells producing TGF-beta⁶⁴ (Fig. 1). This cytokine has a direct, fibrogenic action on smooth muscle cells and fibroblasts. In addition, it inhibits Th1 and macrophage activity, leading to reduced plaque inflammation. Treg also enhance the catabolism of very-low density lipoproteins, resulting in reduced plasma lipid levels.

A third type of T cells, the Th17 cell type, is involved in wound healing and exerts powerful fibrogenic activity⁶⁵. Th17 cells activated in the context of atherosclerosis promote the formation of thick collagen fibers that can withstand the mechanical assault on the plaque exerted by hemodynamic forces⁶⁶. This is

due to the capacity of the signature Th17 cytokine, IL-17A, to promote procollagen expression (Fig. 1).

In addition to reducing the capacity of the tissue to withstand mechanical strain, immune signals may also promote atherothrombosis by increasing the tendency to form platelet aggregates and clots (Fig. 1). The TNF/TNF receptor superfamily members, CD40 ligand (CD40L, CD154) and CD40, may have particular importance in this context. CD40L, typically expressed on activated T cells, ligates CD40 on cells of the macrophage lineage. This stimulation triggers expression of tissue factor as well as matrix metalloproteinase secretion⁶⁷. In addition, activated platelets also express CD40L⁶⁸ and endothelial cells exhibit its receptor CD40⁶⁹, allowing for multiple heterophilic interactions that may promote atherothrombosis^{70,71}.

Lipid mediators are at least as important as cytokines in the sequence of events leading to atherothrombosis (Fig. 1). The prothrombotic effect of thromboxane A2 released from platelets and the counterbalancing, antithrombotic effect of endothelium-derived prostaglandin I2 (PGI2, a.k.a. prostacyclin) is well known, crucial for vascular homeostasis, and the target of aspirin used in cardiovascular prevention^{72,73}. Other prostaglandins play different roles in the atherosclerotic artery wall. Thus, PGE2 produced by several cell types promotes vasodilation and macrophage activation but also increases expression of the antiinflammatory cytokine, IL-10⁷⁴.

The leukotriene pathway of lipid mediators also exerts powerful effects on atherosclerosis. Leukotriene B4 is a proinflammatory leukotriene expressed in plaques^{75,76}. Through its BLT1 receptor, it promotes plaque growth and enhances its inflammatory properties⁷⁷. It also increases vascular restenosis after endothelial injury⁷⁵. 5-lipoxygenase-activating protein (FLAP), a co-factor for the enzyme that converts arachidonic acid into the leukotriene pathway, is upregulated in plaques and promotes leukotriene(LT)B4 production⁷⁸. Genetic polymorphism in the FLAP encoding gene, ALOX5AP, was associated with cardiovascular disease in several genetic studies⁷⁹, although it did not turn out to be a major genetic risk factor in genome-wide association studies. However, this does not rule out a possible role for leukotriene signaling in cardiovascular

disease. As many patients with asthma are treated with leukotriene receptor blockers, long-term follow-up of these individuals permits an assessment of the importance of leukotriene signaling in cardiovascular disease⁸⁰. A population-based Swedish study of 7 million cases revealed that those treated with the leukotriene receptor blocker, montelukast had a 35% reduced risk of recurrent stroke and myocardial infarction⁸⁰.

Lipoxins and resolvins produced in the 12/15-lipoxygenase pathway counterbalance the proinflammatory effects of leukotrienes and may inhibit atherosclerosis and its clinical complications⁸¹. In line with this notion, targeting the lipoxin receptor FPR2/ALX by genetic abrogation leads to features of reduced plaque stability⁸². Further studies will be required to clarify the role of pro- and anti-inflammatory lipoxygenase products in atherosclerosis.

Clinical studies have associated ischemic atherothrombotic events such as MI and stroke with infections. Acute infections, via elicitation of systemic cytokines, may elicit an “echo” of inflammatory activation in the plaque, leading to bursts of proinflammatory, proteolytic, and prothrombotic activity, although we currently lack definitive evidence to confirm such a chain of events⁸³.

The lack of suitable animal models has hampered research on plaque disruption. Although under circumstances that should promote thrombosis on plaques in rodents, such experiments yielded a low incidence of thrombosis and lack of linear relationship between events and histopathological findings such as “buried caps”⁸⁴⁻⁸⁶. Such studies have not generally dealt with coronary arteries, rather the aorta or its large caliber branches. Yet, more recent work has described promising experimental preparations that may be more suitable for addressing mechanisms of plaque rupture⁸⁷. In genetically hypercholesterolemic mutant mice, several interventions can precipitate rupture of existing atherosclerotic plaques, for example virally-directed local overexpression of an active form of the MMP stromelysin, the long-term infusion of angiotensin II⁸⁸, placement of a cuff around the carotid artery⁸⁹, partial ligation of this artery⁹⁰ or increasing elastin fragmentation through a “knock-in” mutation in the fibrillin-1 gene⁹¹. Yet, none of these preparations induces standardized plaque ruptures at

a given time in a controlled manner. Instead, they increase the tendency for the plaque to rupture, and heal, spontaneously.

Signs of plaque rupture include intraplaque haemorrhage, fractured cap fibers, and multi-layered “buried” caps⁹². Enumeration of these signs by microscopy permits quantification of the phenomenon. Such methods have obvious limitations but may permit investigators to assess the effects of various treatments on the tendency for plaques to rupture. The contrived nature of these manipulations, however, limits the generalizability of such experiments. For example, a blocker of angiotensin II should limit disruptions produced by infusions of this mediator, and MMP inhibitors will reduce the consequences of stromelysin overexpression with no predictive value for the effects of these interventions on plaque rupture in humans.

Why does the endothelium erode?

Mechanisms instigating endothelial erosion have been unclear. However, recent studies point to a role for innate immunity in this process (Fig. 2). Endothelial cells overlying atherosclerotic lesions abundantly express the pattern recognition receptor, Toll-like receptor-2 (TLR2)¹¹. Ligation of this receptor results in endothelial apoptosis in a process accelerated by polymorphonuclear leukocytes, a cell type found at sites of fatal plaque erosion⁹³. TLR2 ligands include the extracellular molecule hyaluronan as well as components of Gram-positive bacteria⁹⁴, therefore endogenous as well as infectious factors may operate to promote atherothrombosis through this mechanism⁹³. Stressful events also associate with acute ischemic events. For example, the incidence of myocardial infarction often rises shortly after major sports events (particularly in males), and peaked after stressful events such as a major earthquake^{95, 96}. This association may result from acute changes in local hemodynamics of the atherosclerotic artery. Exposure of atherosclerotic mice to stressful stimuli led to endothelin-dependent vasoconstriction that preceded thrombosis and myocardial ischemia, possibly because the vasoconstrictive episode had caused endothelial erosion⁵⁶. Likewise, infusion of spasmogenic stimuli in MI-prone rabbits elicited occasional coronary artery thrombi resembling human superficial erosion⁹⁷.

How can plaques be stabilized?

Abundant experimental and some clinical data using MRI or intravascular imaging suggest that lipid lowering, and statin therapy in particular may alter plaque properties implicated in susceptibility to rupture. Several other approaches may stabilize plaques (Fig. 3). None of them have entered clinical trials on the indication to stabilize plaques, in part due to the difficulties in identifying vulnerable, ruptured, eroded and thrombosed lesions in the living patient. Current progress in in vivo imaging techniques might enable such trials in the future.

Conclusion

Atherosclerosis associates strongly with systemic risk factors (e.g. high LDL, hypertension, diabetes), yet the lesions distribute multifocally. Most plaques remain silent throughout life but certain individual lesions may provoke thrombotic complication and ischemia, resulting in life-threatening complications. The discovery of plaque rupture and endothelial erosion as two main causes of atherothrombosis helps us to understand why this very chronic condition manifest clinically in an episodic and unpredictable fashion. Further studies have clarified that inflammation, proteolysis, and reduced collagen fiber content predispose to plaque rupture, whereas endothelial erosion followed by neutrophil infiltration typically complicates lesions of a distinct morphology. Lack of animal preparations that develop disruption of atherosclerotic plaques has, however, hampered progress in mechanistic research on atherothrombosis. Similarly, limitations of non-invasive in vivo imaging of so called “vulnerable plaques” in humans has hampered clinical work in this domain. Recent progress in both these areas may address these issues and aid the development and evaluation of plaque-stabilizing therapies beyond lipid lowering in the forthcoming years. The many unanswered questions in this field provide ample opportunity for future research, and may yield avenues to improve patient outcomes.

References

1. Tabas I, Garcia-Cardena, G., Owens, G.K. Recent insights into the cellular biology of atherosclerosis. *J Cell Biol.* 2015;in press
2. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. *Nature.* 2011;473:317-325
3. Jonasson L, Holm J, Skalli O, Bondjers G, Hansson GK. Regional accumulations of t cells, macrophages, and smooth muscle cells in the human atherosclerotic plaque. *Arteriosclerosis.* 1986;6:131-138
4. Hansson GK, Holm J, Jonasson L. Detection of activated t lymphocytes in the human atherosclerotic plaque. *Am J Pathol.* 1989;135:169-175
5. Hansson GK, Hermansson A. The immune system in atherosclerosis. *Nat Immunol.* 2011;12:204-212
6. Libby P, Lichtman AH, Hansson GK. Immune effector mechanisms implicated in atherosclerosis: From mice to humans. *Immunity.* 2013;38:1092-1104
7. Libby P, Tabas I, Fredman G, Fisher EA. Inflammation and its resolution as determinants of acute coronary syndromes. *Circ Res.* 2014;114:1867-1879
8. Duewell P, Kono H, Rayner KJ, Sirois CM, Vladimer G, Bauernfeind FG, Abela GS, Franchi L, Nunez G, Schnurr M, Espevik T, Lien E, Fitzgerald KA, Rock KL, Moore KJ, Wright SD, Hornung V, Latz E. Nlrp3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. *Nature.* 2010;464:1357-1361
9. Libby P, Warner S, Friedman GB. Interleukin-1: A mitogen for human vascular smooth muscle cells that induces the release of growth-inhibitory prostanoids. *J Clin Invest.* 1988;81:487-498
10. Loppnow H, Libby P. Proliferating or interleukin 1-activated human vascular smooth muscle cells secrete copious interleukin 6. *J Clin Invest.* 1990;85:731-738
11. Edfeldt K, Swedenborg J, Hansson GK, Yan ZQ. Expression of toll-like receptors in human atherosclerotic lesions: A possible pathway for plaque activation. *Circulation.* 2002;105:1158-1161
12. Miller YI, Viriyakosol S, Worrall DS, Boullier A, Butler S, Witztum JL. Toll-like receptor 4-dependent and -independent cytokine secretion induced

- by minimally oxidized low-density lipoprotein in macrophages. *Arteriosclerosis, thrombosis, and vascular biology*. 2005;25:1213-1219
13. Miller YI, Choi SH, Wiesner P, Fang L, Harkewicz R, Hartvigsen K, Boullier A, Gonen A, Diehl CJ, Que X, Montano E, Shaw PX, Tsimikas S, Binder CJ, Witztum JL. Oxidation-specific epitopes are danger-associated molecular patterns recognized by pattern recognition receptors of innate immunity. *Circulation Research*. 2011;108:235-248
 14. Niessner A, Shin MS, Pryshchep O, Goronzy JJ, Chaikof EL, Weyand CM. Synergistic proinflammatory effects of the antiviral cytokine interferon-alpha and toll-like receptor 4 ligands in the atherosclerotic plaque. *Circulation*. 2007;116:2043-2052
 15. Saren P, Welgus HG, Kovanen PT. Tnf-alpha and il-1beta selectively induce expression of 92-kda gelatinase by human macrophages. *J Immunol*. 1996;157:4159-4165
 16. Branen L, Hovgaard L, Nitulescu M, Bengtsson E, Nilsson J, Jovinge S. Inhibition of tumor necrosis factor-alpha reduces atherosclerosis in apolipoprotein e knockout mice. *Arterioscler Thromb Vasc Biol*. 2004;24:2137-2142
 17. Bjorkbacka H, Kunjathoor VV, Moore KJ, Koehn S, Ordija CM, Lee MA, Means T, Halmen K, Luster AD, Golenbock DT, Freeman MW. Reduced atherosclerosis in myd88-null mice links elevated serum cholesterol levels to activation of innate immunity signaling pathways. *Nat Med*. 2004;10:416-421
 18. Michelsen KS, Wong MH, Shah PK, Zhang W, Yano J, Doherty TM, Akira S, Rajavashisth TB, Ardit M. Lack of toll-like receptor 4 or myeloid differentiation factor 88 reduces atherosclerosis and alters plaque phenotype in mice deficient in apolipoprotein e. *Proc Natl Acad Sci U S A*. 2004;101:10679-10684
 19. Hermansson A, Johansson DK, Ketelhuth DF, Andersson J, Zhou X, Hansson GK. Immunotherapy with tolerogenic apolipoprotein b-100-loaded dendritic cells attenuates atherosclerosis in hypercholesterolemic mice. *Circulation*. 2011;123:1083-1091
 20. Hermansson A, Ketelhuth DF, Strodthoff D, Wurm M, Hansson EM, Nicoletti A, Paulsson-Berne G, Hansson GK. Inhibition of t cell response to native low-density lipoprotein reduces atherosclerosis. *J Exp Med*. 2010;207:1081-1093
 21. Stemme S, Faber B, Holm J, Wiklund O, Witztum JL, Hansson GK. T lymphocytes from human atherosclerotic plaques recognize oxidized low density lipoprotein. *Proc Natl Acad Sci U S A*. 1995;92:3893-3897.
 22. Frostegard J, Ulfgren AK, Nyberg P, Hedin U, Swedenborg J, Andersson U, Hansson GK. Cytokine expression in advanced human atherosclerotic plaques: Dominance of pro-inflammatory (th1) and macrophage-stimulating cytokines. *Atherosclerosis*. 1999;145:33-43.

23. Amento EP, Ehsani N, Palmer H, Libby P. Cytokines and growth factors positively and negatively regulate interstitial collagen gene expression in human vascular smooth muscle cells. *Arterioscl Thromb*. 1991;11:1223-1230
24. Hansson GK, Hellstrand M, Rymo L, Rubbia L, Gabbiani G. Interferon gamma inhibits both proliferation and expression of differentiation-specific alpha-smooth muscle actin in arterial smooth muscle cells. *J Exp Med*. 1989;170:1595-1608.
25. Choi JH, Cheong C, Dandamudi DB, Park CG, Rodriguez A, Mehandru S, Velinzon K, Jung IH, Yoo JY, Oh GT, Steinman RM. Flt3 signaling-dependent dendritic cells protect against atherosclerosis. *Immunity*. 2011;35:819-831
26. Subramanian M, Thorp E, Hansson GK, Tabas I. Treg-mediated suppression of atherosclerosis requires myd88 signaling in dcs. *J Clin Invest*. 2013;123:179-188
27. Kaartinen M, Penttilä, A., Kovanen, P. T. Mast cells of two types differing in neutral protease composition in the human aortic intima. Demonstration of tryptase- and tryptase/chymase-containing mast cells in normal intimas, fatty streaks, and the shoulder region of atheromas. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 1994;14:966-972
28. Davies MJ, Thomas A. Thrombosis and acute coronary-artery lesions in sudden cardiac ischemic death. *N Engl J Med*. 1984;310:1137-1140
29. Farb A, Burke, A. P., Tang, A. L., Liang, Y., Mannan, P., Smialek, J., 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
30. Falk E, Nakano M, Bentzon JF, Finn AV, Virmani R. Update on acute coronary syndromes: The pathologists' view. *Eur Heart J*. 2013;34:719-728
31. Wilcox JN, Smith KM, Schwartz SM, 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
32. Hamsten A. Hemostatic function and coronary artery disease. *New England Journal of Medicine*. 1995;332:677-678
33. Virchow R. Der atheromatose prozess der arterien. *Wien Med Wochenschr*.6:825-828
34. Davies MJ, Thomas A. Plaque fissuring - the cause of acute myocardial infarction, sudden ischaemic death and crescendo angina. *Br Heart J*. 1985;53:363-373
35. Falk E, Shah, P., Fuster, V. Coronary plaque disruption. *Circulation*. 1995;92:657-671
36. Constantinides P. The role of arterial wall injury in atherogenesis and arterial thrombogenesis. *Zentralbl Allg Pathol*. 1989;135:517-530

37. 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, Serruys PW. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med.* 2011;364:226-235
38. Cheng JM, Garcia-Garcia HM, de Boer SP, Kardys I, Heo JH, Akkerhuis KM, Oemrawsingh RM, van Domburg RT, Ligthart J, Witberg KT, Regar E, Serruys PW, van Geuns RJ, Boersma E. In vivo detection of high-risk coronary plaques by radiofrequency intravascular ultrasound and cardiovascular outcome: Results of the atheroremo-ivus study. *Eur Heart J.* 2014;35:639-647
39. Yonetsu T, Kakuta T, Lee T, Takahashi K, Kawaguchi N, Yamamoto G, Koura K, Hishikari K, Iesaka Y, Fujiwara H, Isobe M. In vivo critical fibrous cap thickness for rupture-prone coronary plaques assessed by optical coherence tomography. *Eur Heart J.* 2011;32:1251-1259
40. Shah PK, Falk E, Badimon JJ, Fernandez OA, Mailhac A, Villareal LG, Fallon JT, Regnstrom J, Fuster V. Human monocyte-derived macrophages induce collagen breakdown in fibrous caps of atherosclerotic plaques. Potential role of matrix-degrading metalloproteinases and implications for plaque rupture. *Circulation.* 1995;92:1565-1569
41. Galis ZS, Sukhova GK, Lark MW, Libby P. Increased expression of matrix metalloproteinases and matrix degrading activity in vulnerable regions of human atherosclerotic plaques. *J Clin Invest.* 1994;94:2493-2503
42. Newby AC. Metalloproteinases and vulnerable atherosclerotic plaques. *Trends Cardiovasc Med.* 2007;17:253-258
43. Michel JB. Anoikis in the cardiovascular system: Known and unknown extracellular mediators. *Arterioscler Thromb Vasc Biol.* 2003;23:2146-2154
44. Liao X, Sluimer JC, Wang Y, Subramanian M, Brown K, Pattison JS, Robbins J, Martinez J, Tabas I. Macrophage autophagy plays a protective role in advanced atherosclerosis. *Cell Metab.* 2012;15:545-553
45. Myoishi M, Hao H, Minamino T, Watanabe K, Nishihira K, Hatakeyama K, Asada Y, Okada K, Ishibashi-Ueda H, Gabbiani G, Bochaton-Piallat ML, Mochizuki N, Kitakaze M. Increased endoplasmic reticulum stress in atherosclerotic plaques associated with acute coronary syndrome. *Circulation.* 2007;116:1226-1233
46. Thorp E, Li G, Seimon TA, Kuriakose G, Ron D, Tabas I. Reduced apoptosis and plaque necrosis in advanced atherosclerotic lesions of apoe^{-/-} and ldlr^{-/-} mice lacking chop. *Cell Metab.* 2009;9:474-481
47. Geng YJ, Libby P. Evidence for apoptosis in advanced human atheroma. Colocalization with interleukin-1 beta-converting enzyme. *Am J Pathol.* 1995;147:251-266

48. Schrijvers DM, De Meyer GR, Kockx MM, Herman AG, Martinet W. Phagocytosis of apoptotic cells by macrophages is impaired in atherosclerosis. *Arterioscler Thromb Vasc Biol.* 2005;25:1256-1261
49. Tabas I. Consequences and therapeutic implications of macrophage apoptosis in atherosclerosis: The importance of lesion stage and phagocytic efficiency. *Arterioscler Thromb Vasc Biol.* 2005;25:2255-2264
50. Thorp E, Cui D, Schrijvers DM, Kuriakose G, Tabas I. MERTK receptor mutation reduces efferocytosis efficiency and promotes apoptotic cell accumulation and plaque necrosis in atherosclerotic lesions of apoE^{-/-} mice. *Arterioscler Thromb Vasc Biol.* 2008;28:1421-1428
51. Ait-Oufella H, Poursmail V, Simon T, Blanc-Brude O, Kinugawa K, Merval R, Offenstadt G, Leseche G, Cohen PL, Tedgui A, Mallat Z. Defective mer receptor tyrosine kinase signaling in bone marrow cells promotes apoptotic cell accumulation and accelerates atherosclerosis. *Arterioscler Thromb Vasc Biol.* 2008;28:1429-1431
52. Serhan CN, Fredman G, Yang R, Karamnov S, Belayev LS, Bazan NG, Zhu M, Winkler JW, Petasis NA. Novel proresolving aspirin-triggered dHA pathway. *Chem Biol.* 2011;18:976-987
53. Fredman G, Kamaly N, Spolitu S, Milton J, Ghorpade D, Chiasson R, Kuriakose G, Perretti M, Farokhzad O, Tabas I. Targeted nanoparticles containing the proresolving peptide ac2-26 protect against advanced atherosclerosis in hypercholesterolemic mice. *Sci Transl Med.* 2015;7:275ra220
54. Lin J, Li H, Yang M, Ren J, Huang Z, Han F, Huang J, Ma J, Zhang D, Zhang Z, Wu J, Huang D, Qiao M, Jin G, Wu Q, Huang Y, Du J, Han J. A role of RIP3-mediated macrophage necrosis in atherosclerosis development. *Cell Rep.* 2013;3:200-210
55. van der Wal AC, Becker A E., van der Loos C. M., Das P. K. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. *Circulation.* 1994;89:36-44
56. Falk E, Shah P, Fuster V. Coronary plaque disruption. *Circulation.* 1995;92:657-671
57. Henney AM, Wakeley PR, Davies MJ, Foster K, Hembry R, Murphy G, Humphries S. Localization of stromelysin gene expression in atherosclerotic plaques by in situ hybridization. *Proc Natl Acad Sci U S A.* 1991;88:8154-8158
58. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. *Circ Res.* 2014;114:1852-1866
59. Kaartinen M, Penttila A., Kovanen P. T. Mast cells in rupture-prone areas of human coronary atheromas produce and store TNF- α . *Circulation.* 1996;11:2787-2792

60. Sukhova G, Shi, G.-P., Simon, D. I., Chapman, H. A., Libby, P. Expression of the elastolytic cathepsins s and k in human atheroma and regulation of their production in smooth muscle cells. *Journal of Clinical Investigation*. 1998;102:576-583
61. Newby AC. Proteinases and plaque rupture: Unblocking the road to translation. *Curr Opin Lipidol*. 2014;25:358-366
62. Ketelhuth DF, Back M. The role of matrix metalloproteinases in atherothrombosis. *Curr Atheroscler Rep*. 2011;13:162-169
63. Ovchinnikova O, Robertson AK, Wagsater D, Folco EJ, Hyry M, Myllyharju J, Eriksson P, Libby P, Hansson GK. T-cell activation leads to reduced collagen maturation in atherosclerotic plaques of apoe(-/-) mice. *Am J Pathol*. 2009;174:693-700
64. Klingenberg R, Gerdes N, Badeau RM, Gistera A, Strodthoff D, Ketelhuth DF, Lundberg AM, Rudling M, Nilsson SK, Olivecrona G, Zoller S, Lohmann C, Luscher TF, Jauhiainen M, Sparwasser T, Hansson GK. Depletion of foxp3+ regulatory t cells promotes hypercholesterolemia and atherosclerosis. *J Clin Invest*. 2013;123:1323-1334
65. MacLeod AS, Hemmers S, Garijo O, Chabod M, Mowen K, Witherden DA, Havran WL. Dendritic epidermal t cells regulate skin antimicrobial barrier function. *J Clin Invest*. 2013;123:4364-4374
66. Gistera A, Robertson AK, Andersson J, Ketelhuth DF, Ovchinnikova O, Nilsson SK, Lundberg AM, Li MO, Flavell RA, Hansson GK. Transforming growth factor-beta signaling in t cells promotes stabilization of atherosclerotic plaques through an interleukin-17-dependent pathway. *Sci Transl Med*. 2013;5:196ra100
67. Mach F, Schonbeck U, Bonnefoy JY, Pober JS, 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.
68. Henn V, Slupsky, J. R., Gräfe, M., Anagnostopoulos, I., Förster, R., Müller-Berghaus, G., Kroczeck, R. A. Cd40 ligand on activated platelets triggers an inflammatory reaction of endothelial cells. *Nature*. 1998;391:591-594
69. Mach F, Schonbeck, U., Sukhova, G. K., Bourcier, T., Bonnefoy, J. Y., Pober, J. S., Libby, P. Functional cd40 ligand is expressed on human vascular endothelial cells, smooth muscle cells, and macrophages - implications for cd40-cd40 ligand signaling in atherosclerosis. *Proceedings of the National Academy of Sciences of the United States of America*. 1997;94:1931-1936
70. Lievens D, Zerneck A, Seijkens T, Soehnlein O, Beckers L, Munnix IC, Wijnands E, Goossens P, van Kruchten R, Thevissen L, Boon L, Flavell RA, Noelle RJ, Gerdes N, Biessen EA, Daemen MJ, Heemskerk JW, Weber C, Lutgens E. Platelet cd40l mediates thrombotic and inflammatory processes in atherosclerosis. *Blood*. 2010;116:4317-4327

71. Wolf D, Hohmann JD, Wiedemann A, Bledzka K, Blankenbach H, Marchini T, Gutte K, Zeschky K, Bassler N, Hoppe N, Rodriguez AO, Herr N, Hilgendorf I, Stachon P, Willecke F, Duerschmied D, von zur Muhlen C, Soloviev DA, Zhang L, Bode C, Plow EF, Libby P, Peter K, Zirlik A. Binding of cd40l to mac-1's i-domain involves the eqlkkskkl motif and mediates leukocyte recruitment and atherosclerosis--but does not affect immunity and thrombosis in mice. *Circ Res*. 2011;109:1269-1279
72. Samuelsson B. Role of basic science in the development of new medicines: Examples from the eicosanoid field. *J Biol Chem*. 2012;287:10070-10080
73. Gabrielsen A, Qiu H, Back M, Hamberg M, Hemdahl AL, Agardh H, Folkersen L, Swedenborg J, Hedin U, Paulsson-Berne G, Haeggstrom JZ, Hansson GK. Thromboxane synthase expression and thromboxane a₂ production in the atherosclerotic lesion. *J Mol Med*. 2010;88:795-806
74. MacKenzie KF, Clark K, Naqvi S, McGuire VA, Noehren G, Kristariyanto Y, van den Bosch M, Mudaliar M, McCarthy PC, Pattison MJ, Pedrioli PG, Barton GJ, Toth R, Prescott A, Arthur JS. Pge(2) induces macrophage il-10 production and a regulatory-like phenotype via a protein kinase a-sik-crtc3 pathway. *J Immunol*. 2013;190:565-577
75. Back M, Bu DX, Branstrom R, Sheikine Y, Yan ZQ, Hansson GK. Leukotriene b₄ signaling through nf-kappab-dependent blt1 receptors on vascular smooth muscle cells in atherosclerosis and intimal hyperplasia. *Proc Natl Acad Sci U S A*. 2005;102:17501-17506
76. Qiu H, Gabrielsen A, Agardh HE, Wan M, Wetterholm A, Wong CH, Hedin U, Swedenborg J, Hansson GK, Samuelsson B, Paulsson-Berne G, Haeggstrom JZ. Expression of 5-lipoxygenase and leukotriene a₄ hydrolase in human atherosclerotic lesions correlates with symptoms of plaque instability. *Proc Natl Acad Sci U S A*. 2006;103:8161-8166
77. Heller EA, Liu E, Tager AM, Sinha S, Roberts JD, Koehn SL, Libby P, Aikawa ER, Chen JQ, Huang P, Freeman MW, Moore KJ, Luster AD, Gerszten RE. Inhibition of atherogenesis in blt1-deficient mice reveals a role for ltb₄ and blt1 in smooth muscle cell recruitment. *Circulation*. 2005;112:578-586
78. Back M, Sultan A, Ovchinnikova O, Hansson GK. 5-lipoxygenase-activating protein: A potential link between innate and adaptive immunity in atherosclerosis and adipose tissue inflammation. *Circulation Research*. 2007;100:946-949
79. Helgadóttir A, Manolescu A, Thorleifsson G, Gretarsdóttir S, Jonsdóttir H, Thorsteinsdóttir U, Samani NJ, Gudmundsson G, Grant SF, Thorgeirsson G, Sveinbjornsdóttir S, Valdimarsson EM, Matthiasson SE, Johannsson H, Gudmundsdóttir O, Gurney ME, Sainz J, Thorhallsdóttir M, Andresdóttir M, Frigge ML, Topol EJ, Kong A, Gudnason V, Hakonarson H, Gulcher JR, Stefansson K. The gene encoding 5-lipoxygenase activating protein

- confers risk of myocardial infarction and stroke. *Nat Genet.* 2004;36:233-239
80. Ingelsson E, Yin L, Back M. Nationwide cohort study of the leukotriene receptor antagonist montelukast and incident or recurrent cardiovascular disease. *J Allergy Clin Immunol.* 2012;129:702-707 e702
 81. Merched AJ, Ko K, Gotlinger KH, Serhan CN, Chan L. Atherosclerosis: Evidence for impairment of resolution of vascular inflammation governed by specific lipid mediators. *FASEB J.* 2008;22:3595-3606
 82. Petri MH, Laguna-Fernandez A, Gonzalez-Diez M, Paulsson-Berne G, Hansson GK, Back M. The role of the fpr2/alx receptor in atherosclerosis development and plaque stability. *Cardiovasc Res.* 2015;105:65-74
 83. Libby P, Egan, D., Skarlatos, S. Roles of infectious agents in atherosclerosis and restenosis. An assessment of the evidence and need for future research. *Circulation.* 1997;96:4095-4103
 84. Caligiuri G, Lévy, B., Pernow, J., Thorén, P., Hansson, G. K. Myocardial infarction mediated by endothelin receptor signaling in hypercholesterolemic mice. *Proceedings of the National Academy of Sciences of the United States of America.* 1999;96:6920-6924
 85. Johnson JL, Jackson CL. Atherosclerotic plaque rupture in the apolipoprotein e knockout mouse. *Atherosclerosis.* 2001;154:399-406
 86. Schwartz SM, Galis ZS, Rosenfeld ME, Falk E. Plaque rupture in humans and mice. *Arterioscler Thromb Vasc Biol.* 2007;27:705-713
 87. Matoba T, Sato K, Egashira K. Mouse models of plaque rupture. *Curr Opin Lipidol.* 2013;24:419-425
 88. Katsuki S, Matoba T, Nakashiro S, Sato K, Koga J, Nakano K, Nakano Y, Egusa S, Sunagawa K, Egashira K. Nanoparticle-mediated delivery of pitavastatin inhibits atherosclerotic plaque destabilization/rupture in mice by regulating the recruitment of inflammatory monocytes. *Circulation.* 2014;129:896-906
 89. Sasaki T, Kuzuya M, Nakamura K, Cheng XW, Shibata T, Sato K, Iguchi A. A simple method of plaque rupture induction in apolipoprotein e-deficient mice. *Arterioscler Thromb Vasc Biol.* 2006;26:1304-1309
 90. Chen YC, Bui AV, Diesch J, Manasseh R, Hausding C, Rivera J, Haviv I, Agrotis A, Htun NM, Jowett J, Hagemeyer CE, Hannan RD, Bobik A, Peter K. A novel mouse model of atherosclerotic plaque instability for drug testing and mechanistic/therapeutic discoveries using gene and microRNA expression profiling. *Circ Res.* 2013;113:252-265
 91. Van der Donckt C, Van Herck JL, Schrijvers DM, Vanhoutte G, Verhoye M, Blockx I, Van Der Linden A, Bauters D, Lijnen HR, Sluimer JC, Roth L, Van Hove CE, Franssen P, Knaapen MW, Hervent AS, De Keulenaer GW, Bult H, Martinet W, Herman AG, De Meyer GR. Elastin fragmentation in atherosclerotic mice leads to intraplaque neovascularization, plaque

- rupture, myocardial infarction, stroke, and sudden death. *Eur Heart J*. 2014
92. Williams H, Johnson JL, Carson KG, Jackson CL. Characteristics of intact and ruptured atherosclerotic plaques in brachiocephalic arteries of apolipoprotein e knockout mice. *Arterioscler Thromb Vasc Biol*. 2002;22:788-792
 93. Quillard T, Araujo HA, Franck G, Shvartz E, Sukhova G, Libby P. Tlr2 and neutrophils potentiate endothelial stress, apoptosis and detachment: Implications for superficial erosion. *Eur Heart J*. 2015; 36:1394-404.
 94. Lundberg AM, Hansson GK. Innate immune signals in atherosclerosis. *Clin Immunol*. 2010;134:5-24
 95. Carroll D, Ebrahim S, Tilling K, Macleod J, Smith GD. Admissions for myocardial infarction and world cup football: Database survey. *BMJ*. 2002;325:1439-1442
 96. Leeka J, Schwartz BG, Kloner RA. Sporting events affect spectators' cardiovascular mortality: It is not just a game. *Am J Med*. 2010;123:972-977
 97. Shiomi M, Ishida T, Kobayashi T, Nitta N, Sonoda A, Yamada S, Koike T, Kuniyoshi N, Murata K, Hirata K, Ito T, Libby P. Vasospasm of atherosclerotic coronary arteries precipitates acute ischemic myocardial damage in myocardial infarction-prone strain of the watanabe heritable hyperlipidemic rabbits. *Arterioscler Thromb Vasc Biol*. 2013;33:2518-2523.

Figure legends:

Figure 1. Mechanisms of plaque rupture.

Activated macrophages and Th1 cells produce metalloproteinases and cytokines that hamper the tensile strength of the collagen cap. Several proinflammatory cytokines including interferon- γ (IFN γ) and tumor necrosis factor (TNF), as well as CD40/CD40L cell surface receptors of the TNF superfamily promote an inflammatory state that enhance cell death and prothrombotic activity in the plaque. When the cap no longer can withstand the mechanical force of the blood pressure, superficial fissures are formed in the plaque. Exposure of the plaque's inner core with its thrombogenic material rapidly triggers platelet activation, humoral coagulation, and the formation of a thrombus that may either occlude the artery at the site of plaque rupture, or dissociate as an embolus and occlude the arterial lumen at a site downstream of the ruptured plaque.

Counteracting all these proinflammatory and tissue-destructive signals, subsets of macrophages and T cells produce anti-inflammatory molecules that counteract vascular inflammation and reduce the risk for plaque rupture and atherothrombosis. Among them, transforming growth factor- β (TGF- β) and interleukin-10 (IL-10) inhibit inflammation and immune cell activation. In addition, TGF- β has fibrogenic properties that it shares with IL-17A produced by Th17 cells. The resolution of plaque inflammation depends not only on anti-inflammatory signals but also on resolving mediators such as eicosanoids of the resolvins type and Annexin I, both of which ligate the FPR/ALX receptor.

EC, endothelial cell; SMC, smooth muscle cell; M Φ , macrophage; MMP, metalloproteinase; TXA₂, thromboxane A₂; PGI₂, prostaglandin I₂ (prostacyclin).

Figure 2. Mechanisms of plaque erosion.

Endothelial cells of atherosclerotic plaques commonly express Toll-like receptor -2 (TLR2) that can ligate both Gram-positive toxins (G⁺ toxins) of bacterial pathogens and hyaluronan released from the extracellular matrix. TLR2 ligation can trigger endothelial dysfunction with endoplasmic reticulum stress and apoptosis. Such reactions are further enhanced by neutrophil attack on the endothelium. As a result, endothelial cells may detach, exposing the

subendothelial matrix with its thrombogenic components. Activated neutrophils contribute to a prothrombotic state by releasing a set of proteases including neutrophil elastase and by forming neutrophil extracellular traps (NETs) that can damage endothelial cells, trap leukocytes, and enhance thrombosis. PAD4, Peptide arginine deaminase-4, a component of NETs.

Figure 3. Therapy targets for prevention of atherothrombosis.

Reduction of LDL (and other large lipoproteins) by lipid-lowering therapy, and prevention of LDL retention in the artery wall, both act to reduce cholesterol accumulation, an initiator of atherosclerosis. Stimulation of immunoregulatory mechanisms reduce vascular inflammation; they include administration of anti-inflammatory cytokines, enhancing Treg cells, and vaccination to elicit atheroprotective immunity. Mediators of resolution include resolvins-type eicosanoids, peptide mimetics of Annexin I, and other substances.

Figure 1.

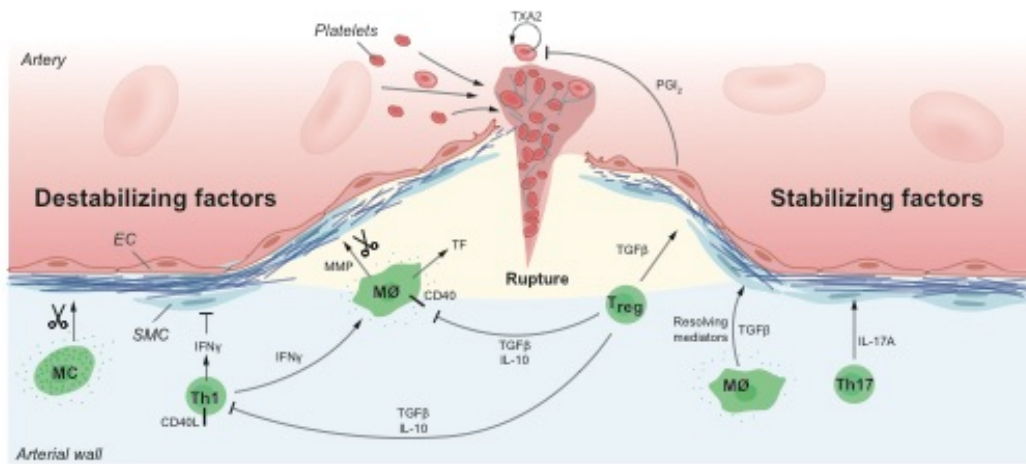


Figure 2.

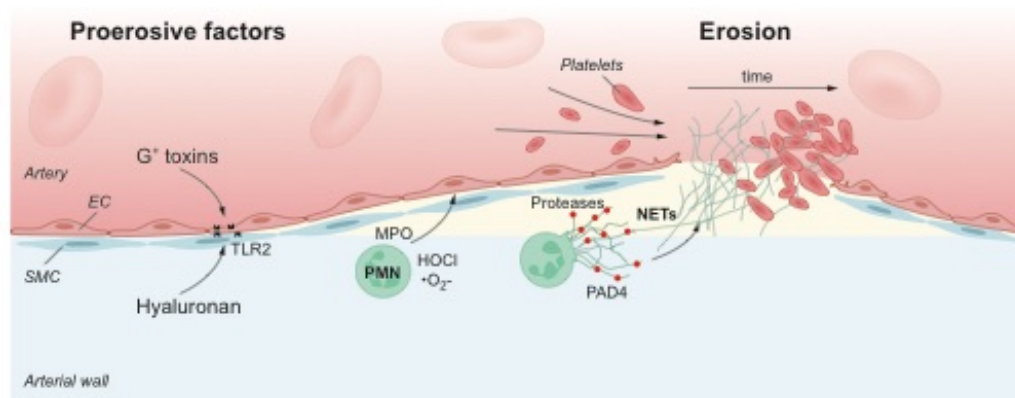


Figure 3.

