Inflammatory mechanisms

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Traditional concepts of the pathogenesis of acute coronary syndromes have changed over the last few years. In particular it has been demonstrated that high-risk lesions are not necessarily angiographically severe. Rather, unstable high risk lesions are the ones composed of large lipid cores and thin fibrous caps. It is now widely accepted that plaque instability is related to the development of inflammation within the intima. A consequence of this is that stabilization of lesions provides a new therapeutic target. Furthermore, there is growing evidence that statins may stabilize lesions by altering the inflammatory response. A brief overview of these developments and their impact on clinical practice is presented.

The process of atherosclerosis was considered for many years to merely represent a relentless, accumulation of lipids within the artery wall. However, over the last two decades, major developments in the field of vascular biology have made it clear that atherosclerotic lesions are in fact a series of highly specific, dynamic, cellular and molecular responses that are essentially inflammatory in nature. Indeed, the earliest lesion of atherosclerosis, the fatty streak, is a pure inflammatory lesion, consisting only of T lymphocytes and monocyte-derived macrophages. A brief overview of these developments and their impact on clinical practice is presented below.

Endothelial cell dysfunction

The original response-to-injury hypothesis put forward by Russell Ross and his colleagues postulated that endothelial denudation and injury were the first steps in the atherosclerotic process. This was based on observations in which removal of endothelium by mechanical means dramatically enhanced the ability of a high lipid diet to induce atherosclerosis in animal models. However, subsequent observations in humans and animal models in the late 1970s seemed to indicate that the endothelium overlying atherosclerotic lesions was anatomically intact. These apparently inconsistent observations were rationalized by Gimbrone who proposed the concept of ‘endothelial dysfunction’. This acknowledged the importance of an intact, normally functioning endothelium in protecting against atherosclerosis but emphasized functional abnormalities of the endothelium in the setting of...
atherosclerosis. Ludmer and colleagues provided the first clinical evidence of endothelial dysfunction as an important component of coronary atherosclerosis. They demonstrated that the muscarinic cholinergic agonist acetylcholine, was able to vasodilate angiographically normal coronary arteries but produced paradoxical vasoconstriction in segments with either minimal angiographic disease or severe stenosis. These abnormalities of vasomotor tone were assumed to reflect underlying endothelial dysfunction because of Furchgott’s classical observations on endothelium-dependent vasorelaxation. He had elegantly demonstrated an in vitro organ bath system in which preconstricted arterial rings would relax in response to muscarinic cholinergic agonists only if endothelial cells were present. Removal of the endothelium by any means abolished the vasorelaxation which was mediated by an undefined endothelium derived relaxing factor (EDRF). EDRF was subsequently shown to be, in large part, nitric oxide (NO). NO diffuses to the underlying vascular smooth muscle cells and stimulates the second messenger cGMP to cause relaxation. Ludmer’s observations of abnormal vasomotor control in atherosclerotic vessels were, therefore, assumed to indicate abnormalities of NO production by the overlying endothelium.

It is now thought that the earliest detectable physiological manifestation of atherosclerosis is reduced production or bioavailability of NO in response to pharmacological or haemodynamic stimuli. This phenomenon is even observed in children with hypercholesterolaemia. Other causes of this endothelial dysfunction include free radicals caused by cigarette smoking, hypertension, diabetes mellitus, elevated plasma homocysteine levels and infectious micro-organisms such as Chlamydia pneumoniae. Indeed, virtually every atherosclerotic risk factor is associated with endothelial dysfunction.

The above data are consistent with the idea that the primary event in atherogenesis is endothelial dysfunction. The endothelium can be damaged by a variety of means, leading to dysfunction and subendothelial lipid accumulation (due to increased permeability of the endothelium to plasma lipoproteins). In this situation, the normal homeostatic features of the endothelium break down. It becomes more adhesive to inflammatory cells and platelets, and it loses its anticoagulant properties. This is associated with reduced bioavailability of NO. Importantly, drugs that have been shown to improve the outcome of vascular disease – including statins and angiotensin converting enzyme inhibitors – have been shown to improve endothelial function.

**Oxidative stress**

The initiating mechanisms leading to endothelial dysfunction have been the focus of a great deal of research activity. One of the major developments in
vascular biology over the last 20 years has been the understanding of the importance of oxidation mechanisms in mediating pathophysiological responses in the arterial wall and endothelial dysfunction. In particular, the role of oxidised low density lipoprotein (LDL) has been intensively investigated. LDL appears to be a major cause of injury to the endothelium\(^9\). Moreover, increased permeability of the endothelium to plasma lipoproteins are amongst the earliest detectable changes of the atherosclerotic process. LDL particles trapped in the arterial wall can undergo progressive oxidation leading to internalization by macrophages by means of the scavenger receptors on the surface of these cells. The original observation which stimulated much of this work was that mononuclear cells in culture were unable to take up freshly isolated LDL to form lipid-rich foam cells, but that exposure of the LDL to cultured endothelial cells modified the lipoprotein so that it was taken up by monocyte/macrophages to form foam cells\(^{10}\). The modification of LDL that allowed recognition and uptake was oxidation, and oxidised LDL was found to have multiple biological and pro-inflammatory properties\(^{11}\). From observations such as these, it has become apparent that an extracellular oxidation mechanism is fundamentally important in the pathogenesis of atherosclerosis and endothelial dysfunction\(^{12}\).

The importance of oxidative stress has been emphasized by a number of studies, which have provided compelling evidence that atherosclerosis is associated with enhanced production of oxygen free radicals at a time when NO production is continuing but endothelium dependent relaxation is impaired\(^{12}\). From these observations, it has been concluded that NO is being degraded and inactivated in the setting of atherosclerosis by reactive oxygen species. NO is itself an effective antioxidant and is produced from arginine by the enzyme NO synthase (NOS). NOS is a highly regulated enzyme whose activity is probably reduced in advanced atherosclerosis. Endothelial NOS is up-regulated by HMG-CoA inhibitors and this effect may be responsible for some of their clinical efficacy through enhancement of the antioxidant status of the arterial wall. Paradoxically, NO can, under certain circumstances, become highly pro-oxidant. High levels of NO – which can be produced by a different NOS isoform in macrophages/foam cells as well as by endothelial NOS – can combine with high concentrations of oxygen free radicals to form peroxynitrite. Peroxynitrite is a highly reactive pro-oxidant capable of changing protein functions and contributing to the vascular dysfunction in atherosclerosis.

**Inflammatory cells and the atherosclerotic plaque**

As early as the 1950s, investigators were aware of the presence of inflammatory cells within atherosclerotic lesions, but this was not really
appreciated until many decades later. Postmortem studies of infarct related lesions in coronary arteries demonstrated a localized inflammatory response manifested by accumulation of mononuclear cells. The mechanism by which these inflammatory cells are attracted into the arterial wall became an important focus of investigation. Important clues are provided by in vitro experiments that demonstrate the expression of leukocyte adhesion molecules on the surface of endothelial cells after cytokine stimulation. Similar observations have been made in the arteries of rabbits after several days of cholesterol feeding. Monocyte adhesion has been observed at arterial branch points and regions of low flow or disturbed flow that are known to be sites of predilection for the development of atherosclerotic lesions. In some areas, the mononuclear cells were seen to have entered into the arterial wall and were located just beneath the overlying endothelial cells. On the endothelial cell surface there was evidence of expression of a new protein that was found to be the rabbit equivalent of human vascular cell adhesion molecule-1 (VCAM-1), which by interaction with its ligand VLA-4 causes adhesion of monocytes and T cells to endothelial cells. Therefore, VCAM-1 is the prototype of a set of molecules that are up-regulated during the very earliest stages of atherosclerosis and are involved in recruiting inflammatory cells into atherosclerotic lesions. Indeed, mice deficient in similar molecules such as intercellular adhesion molecule 1 (ICAM 1) and P selectin develop smaller lesions with less lipid and fewer inflammatory cells than control mice fed a high lipid diet. Interestingly, Marui et al have demonstrated that oxygen-derived radicals are involved in the intracellular signalling events controlling VCAM-1 gene expression. They have shown that the VCAM-1 gene is regulated by a reduction/oxidation-dependent activation of the transcription factor NF-κB. Moreover, a number of intracellularly active antioxidants inhibit VCAM-1 expression in vitro in cultured endothelial cells and in hypercholesterolaemic animals. In these animals, fatty streak and foam cell formation has been inhibited by antioxidants, even in the presence of very high plasma cholesterol levels, suggesting that antioxidants may inhibit atherosclerosis by mechanisms other than the inhibition of LDL oxidation.

As previously mentioned, small accumulations of subendothelial lipid (particularly oxidised LDL) appear in the arterial wall at the very earliest stages of atherosclerosis. It is unclear to what extent this is a result of endothelial dysfunction and to what extent it causes it. Regardless of which process occurred first, oxidised LDL is a highly inflammatory substance leading to increased expression of selectins and adhesion molecules and also expression of chemokines, in particular monocyte chemo-attractant protein-1 (MCP-1). Chemokines are pro-inflammatory cytokines that lead to leukocyte chemo-attraction and activation. The importance of chemokines is highlighted by the
observation that mice lacking MCP-1 develop much smaller atherosclerotic lesions than those expressing MCP-1. Inflammatory cells which have been 'attracted' in this way from the circulation migrate into the subendothelial space where, under the influence of local chemokines, they become activated. The monocytes develop into macrophages expressing the scavenger receptor necessary to ingest oxidised LDL to form foam cells. Removal of modified LDL is a critical part of the initial protective role of macrophages in the inflammatory response and minimizes the effects of modified LDL on endothelial and vascular smooth muscle cells. Unfortunately, the inflammatory response itself can lead to significant effects on lipoprotein movement into the arterial wall. Specifically, mediators of inflammation such as tumour necrosis factor-α (TNF-α), interleukin-1 and macrophage colony stimulating factor increase binding of LDL to endothelium and vascular smooth muscle cells and increase transcription of the LDL receptor. Thus a vicious cycle is set up by the presence of modified lipids in the arterial wall that leads to inflammation which itself causes further modification of lipoproteins that in turn leads to further inflammation and so on.

Vascular smooth muscle cells and the atherosclerotic plaque

As described above, inflammatory reactions in the subendothelial space result in the production of a large number of cytokines and inflammatory mediators. Many of these are chemo-attractant for the underlying medial VSMCs resulting in their migration into the intima where they form a fibrous cap over the lipid and inflammatory core. In the original response to injury hypothesis, this migration of VSMCs into the intima was seen as the initiating event in the development of a plaque and was thought of as being harmful by causing plaque growth and narrowing of the lumen. However, recent developments in the understanding of the cellular biology of VSMCs have led to a fundamental reversal of views on their effects in the atherosclerotic plaque. Medial VSMCs contain a substantial amount of contractile proteins, which allows them to maintain vascular tone. This contractile phenotype is partly maintained by extracellular signals in the VSMC environment. When VSMCs are taken out of this environment and placed in culture, they undergo a phenotypic change characterized by reduced production of contractile proteins and increased production of synthetic organelles. Interestingly, recent studies have shown a remarkable similarity between the gene expression pattern of intimal VSMCs in atherosclerosis and those in early developing blood vessels. This has led to the hypothesis that intimal VSMCs may be acting in a reparative role. This reparative/synthetic phenotype is associated with
the expression of proteinases which break down the underlying basement membrane to allow migration into the site of injury. They produce growth factors that facilitate their proliferation at the site of injury and they produce a range of matrix proteins such as collagens and elastin that may be used to repair injured tissues. It now seems that the expression of these genes is fundamental to the formation of the fibrous cap over the lipid core of atherosclerotic plaques. This role of the VSMC is a critical defence mechanism against the progression of atherosclerosis because it separates the highly thrombogenic lipid core from circulating platelets and the proteins of the coagulation cascade. In addition, it confers structural stability to the plaque. The VSMC is in fact the only cell capable of synthesizing the cap and is, therefore, pivotal in maintaining plaque stability.

**Plaque stability**

Atherosclerotic lesions can manifest themselves clinically by steady growth leading to a gradual restriction in blood flow such that nutrient supply cannot meet demand as in chronic angina pectoris. The growth of the plaque is gradual and is related to apoptotic death of macrophage foam cells and their incorporation into an enlarging necrotic lipid-laden core as well as the migration of medial VSMCs in response to inflammatory stimuli within the plaque. Alternatively, if the lesion either ruptures or erodes, there is exposure of the thrombogenic lipid core. This results in rapid platelet accumulation, fibrin deposition and thrombosis, leading to the acute coronary syndromes.

Over recent years, it has become apparent that some plaques are inherently more prone to rupture and complications than others of equal size. Careful post mortem pathological studies have described several characteristics that seem to be predictive of the risk of rupture in individual lesions. Vulnerable plaques tend to have thin fibrous caps, a high ratio of inflammatory cells to VSMCs in the fibrous cap, a lipid core that occupies more than 50% of the volume of the plaque and a high tissue factor content. The most important of these is the cellular composition of the fibrous cap. Plaques with a heavy inflammatory cell infiltrate and relatively few VSMCs are at highest risk of rupturing. It is thought that the balance of power between the repairing effects of VSMCs and the destructive effects of the inflammatory cells determines fibrous cap integrity and, therefore, plaque stability.

Inflammatory cells can weaken and destroy the fibrous cap through a number of mechanisms. Firstly, activated T-lymphocytes can produce pro-inflammatory cytokines such as interferon-γ (INF-γ), that directly inhibit VSMC proliferation and almost completely shut down collagen
The result of this is that VSMCs in the vicinity of activated T-lymphocytes are unable to lay down or repair extracellular matrix effectively. Secondly, macrophage derived inflammatory cytokines such as interleukin-1β, TNF-α as well as INF-γ from T lymphocytes are cytotoxic to VSMCs in a synergistic fashion, leading to a reduction in cell numbers through apoptosis. Thirdly, work from our laboratory has shown that activated macrophages can induce VSMC apoptosis by direct cell–cell contact. Fourthly, and perhaps most importantly, macrophages produce a number of matrix metalloproteinases (MMPs) that are capable of degrading matrix components of the fibrous cap by proteolytic cleavage. MMP production appears to be up-regulated by inflammatory mediators such as TNF-α. Furthermore, for reasons that are not entirely clear, VSMCs from mature atherosclerotic plaques appear to have a reduced proliferative ability and an enhanced susceptibility to apoptosis. Thus, the inflammatory process which is central to atherosclerosis can lead to the destruction of intimal VSMCs and the structural framework of the plaque, leading to plaque instability and rupture. It is extremely important to realize that these features are often present in small, angiographically and haemodynamically insignificant atherosclerotic plaques that are clinically silent. In other words, plaque composition is much more important that plaque size in determining the propensity to rupture. Atherosclerotic plaques can cause acute coronary syndromes either through rupture or endothelial cell erosion. Following plaque rupture, there is immediate exposure of the highly thrombogenic extracellular matrix of the cap as well as the tissue factor-rich lipid core to platelets and proteins of the coagulation cascade. This leads to platelet aggregation, activation and clot formation. Less commonly, erosion of the endothelial cells overlying the fibrous cap may occur which can also lead to the build-up of platelet-rich thrombi. Endothelial erosion seems to account for about 30% of acute coronary syndromes, but seems to be more common in women. Both forms of plaque destruction lead to platelet binding, aggregation and activation. This in turn leads to fibrin deposition and activation of the clotting cascade resulting in thrombus formation. However, thrombus extension and vessel occlusion are not inevitable consequences of this process. In a recent clinical study, up to 70% of plaques causing high grade stenosis were found to contain histological evidence of previous plaque rupture and subsequent repair in the absence of vessel occlusion or clinical events. This is particularly likely to occur if high flow through the vessel prevents accumulation of occlusive thrombus. Platelet-rich thrombi contain many chemokines and mitogens, in particular platelet derived growth factor, thrombin and transforming factor β, which can induce migration and proliferation of VSMCs from the underlying media. This, therefore, helps drive formation of a new fibrous cap, thereby increasing the size of the lesion.
Since this process occurs rapidly, there is presumably little opportunity for adaptive remodelling of the artery and the healed lesion may now impede flow sufficiently to cause ischaemic symptoms. A major clinical implication of this is that, potentially, pharmacological inhibition of these repeated episodes of plaque rupture would be expected to reduce progression of atherosclerotic lesions. This also explains and re-iterates the importance of antiplatelet drugs in the treatment of atherosclerosis.

Thus atheromatous plaques may enlarge either gradually or in a sudden stepwise fashion. Gradual growth is through continued lipid deposition, macrophage apoptosis, and VSMC migration from the media. In contrast, the stepwise growth is due to repeated, often silent episodes of plaque rupture or erosion with secondary VSMC driven migration and repair (Fig. 1).

**Infection**

One of the most interesting developments in recent years has been the hypothesis that infectious agents may play a role in atherosclerosis, either through a direct pro-inflammatory effect in the vessel wall or through a less specific, long distance pro-inflammatory effect. \( \text{C. pneumoniae} \) probably remains the most plausible candidate pathogen. It is found within plaques, reaches high concentrations within macrophages and is rarely found in normal arteries. Furthermore, a high titre
(>1:1024) of C. pneumoniae is twice as frequent among cases than controls; and a high titre positive serology is associated with an odds ratio of 4 for cardiovascular events within 2 years. However, several prospective studies have failed to confirm these results. Therefore, although evidence for a link between viral and bacterial infections and atherosclerosis grows, a direct causal link remains tantalizingly out of reach. Studies have produced inconsistent results regarding the precise identity of the pathogens involved. It is not certain which organisms are culprits and which are innocent bystanders. Considerable interest was raised by the publication of a small British pilot study showing that short courses of azithromycin reduced coronary events. However, in the subsequent ACADEMIC trial no reduction in cardiovascular events was seen in 2 years after a more reasonable 3 months of antibiotic treatment. The results of two, large, on-going randomized, controlled trials of anti-chlamydia antibiotics (WIZARD and ACES) may give a more definitive answer. Although, the known anti-inflammatory effects of macrolide antibiotics, independent of their antibacterial effects, might cloud the issue.

Clinical implications of recent scientific advances

Risk factor evaluation

The realization that atherosclerosis is essentially an inflammatory condition has prompted a great deal of research into identification of measurable biochemical markers of plaque inflammation. The presumption being that perhaps some of the multitudes of inflammatory mediators discussed above may be measurable in blood and reflect the degree of plaque inflammatory activity and, therefore, in some way relate to plaque instability. Some of these markers probably reflect the degree of plaque macrophage activation. Circulating levels of serum amyloid A (SAA), C-reactive protein (CRP) and TNF-α all correlate with risk of coronary events, but they are non-specific and may simply reflect inflammation or infection elsewhere in the body. The development of a highly sensitive assay to measure CRP (hs-CRP) has allowed the measurement of CRP levels below those of the routine assay. This was used in the Physicians’ Health Study which revealed a strong correlation between CRP and the risk of myocardial infarction and stroke. Furthermore, the subjects with the highest CRP levels (but still within the conventional normal range) derived most benefit from prophylactic aspirin. The recently reported Women’s Health Study showed that women in the highest quartile of hs-CRP had a cardiovascular risk 4.4 times women in the lowest quartile. The recent CARE study, which was designed to look at the effects of pravastatin in
post-myocardial infarction patients with a moderately raised cholesterol, confirmed the association between vascular risk and CRP levels. Moreover, it also showed that even though the CRP level rose over 5 years in the placebo group, it fell in association with vascular event risk in the treatment group. Interestingly, this reduction was not correlated with the magnitude of the decrease in serum lipids in the treatment group.

Proteolysis of cell surface molecules such as ICAM-1, VCAM-1, E-selectin and P-selectin (which are up-regulated during atherosclerotic inflammation) may provide more specific markers of vascular risk than the general markers described above. In one study, Ridker and colleagues showed that soluble ICAM-1 levels were independently predictive of the risk of cardiovascular events in apparently healthy men, with levels in the highest quartile conferring an increased risk of 80% compared with those in the lowest quartile. Although soluble ICAM-1 levels were strongly correlated with CRP levels, adjustment for CRP levels did not substantially decrease the relative risk associated with an elevated level of ICAM-1. This finding suggests that levels of soluble adhesion molecules may provide predictive information that is additive to the information provided by levels of general inflammatory markers.

What are the implications of the finding of multiple serum-based inflammatory markers that are predictive of the risk of cardiovascular events? It is now generally agreed that although evaluation of traditional factors produces reasonably accurate estimates of population risk, it fails to predict 40–50% of the variation in the absolute risk of an event in individual patients. Therefore, the addition of other factors that would increase the predictive ability would also probably improve the accuracy of decisions regarding the use of proven therapies for prevention. When Ridker made a comparison of the usefulness of various serum based markers, he found that the effects of inflammatory markers and those of lipids were obviously additive with respect to the ability to predict cardiovascular risk. Therefore, the argument has been made that the measurement of highly validated inflammatory markers such as CRP in selected patients may increase the clinical accuracy of assessments of cardiovascular risk. However, at the time of writing, more work is required before the levels of soluble, vascular specific, adhesion molecules such as ICAM-1 may be used for clinical risk assessment.

Imaging

The realization that plaque composition is far more important than plaque size has important implications for the practice of clinical cardiology. The mainstay of much of clinical practice is the angiogram. However, angiography can only detect lesions which impinge significantly
on the lumen. It provides little or no information on plaque composition. Since it is plaque composition which determines the risk of rupture, it follows that angiography is a poor predictor of clinical events. Therefore, two lesions of equivalent size, one of which is stable and the other unstable, may look identical angiographically. Furthermore, as far back as the 1980s, it was known that arteries can accommodate large atherosclerotic plaques, without reducing lumen size, by ‘remodelling’. This is a process in which the artery expands as the plaque increases in size. Therefore, large atherosclerotic plaques can be clinically silent and sometimes angiographically invisible. Falk and colleagues have convincingly demonstrated that most lesions which lead to myocardial infarction are due to rupture of plaques which cause less than 50% stenosis on angiography. These observations emphasize the importance of developing newer and more useful diagnostic tools than angiography for the identification of unstable atherosclerotic plaques. One such approach has been the detection of coronary artery calcification using electron beam computed tomography (EBCT) since calcium apatite crystals are an intimate component of the plaque as early as the fatty streak stage. A positive correlation has been shown between coronary calcium score, as measured by EBCT, and subsequent clinical events in patients with known coronary artery disease. However, the extent to which this predicts coronary events independently of traditional risk factors – particularly in asymptomatic patients – needs further study. The National Institutes of Health funded multi-ethnic study of atherosclerosis (MESA) will provide some of these data over the next decade.

Over the next few years, developments in magnetic resonance imaging (MRI) and radionucleotide-based techniques, especially positron emission tomography (PET), may allow non-invasive imaging of plaque composition. Presently, MRI can differentiate some plaque components in animal models and human vessels. However, image resolution and movement artefact remain obstacles to the use of MRI in coronary vessels. Furthermore, although MRI might provide fine anatomical detail, it seems unlikely that it will be able to provide information on plaque inflammatory activity. In contrast, PET provides very little anatomical detail but offers the potential of measuring and monitoring plaque inflammatory cell activity. Fuster and colleagues have demonstrated positive PET images of atherosclerotic plaques in cholesterol-fed rabbits using fluorinated deoxyglucose (a glucose substrate which is taken up by cells through the glucose transporter in proportion to their metabolic activity). This has been presumed to reflect inflammatory cell activity. Preliminary work in our laboratory has suggested that this technique may be applicable in human arteries.

Statins

Angiographic studies have shown that statins reduce the incidence of new lesion formation and produce significant, but haemodynamically
negligible improvements in lumen diameter\textsuperscript{31}. In contrast to these somewhat disappointing angiographic results, several large outcome studies, both in primary and secondary prevention of vascular events, have shown an impressive and consistent reduction (30–40\%) in clinical events among patients receiving statins\textsuperscript{32,33}. The only plausible explanation seems to be that statins are reducing new lesion formation and preventing rupture of pre-existing plaques. In other words, statins stabilize plaques. It is likely that most of this effect is directly due to lipid lowering because all lipid lowering studies have shown a reduction in cardiovascular events. However, statins do have a number of other biological properties that may influence plaque stability and inflammation. For example, statins have been shown to exert direct effects on endothelial cell function, inflammatory cell activity, VSMC proliferation, platelet aggregation and thrombus formation. The best evidence for the beneficial effects of statins independent of lipid lowering comes from the laboratory of Libby\textsuperscript{34}. In this important study, monkeys were fed an atherogenic diet for 2 years so that they all developed atherosclerosis. The monkeys were then put on lipid lowering diets for a further 2 years and subdivided into two groups, one of which received pravastatin. The diet was adjusted so that each group had similar cholesterol levels. At the end of the study both groups had similar sized lesions but, compared with the untreated group, the pravastatin treated group had better endothelial function, and their atherosclerotic lesions contained fewer macrophages, less calcification and fewer new vessels, implying greater stability. More recent studies by Aikawa\textsuperscript{35} and Crisby\textsuperscript{36} strongly support the notion that statins act by reducing plaque inflammation.

Conclusions

Atherosclerosis is a dynamic process in which the risk of plaque rupture and therefore outcome is determined by the balance between destructive inflammatory cell activity and the reparative effects of VSMCs. This balance can be modified beneficially by medical therapy, particularly with statins. Understanding the cellular events involved offers exciting therapeutic and diagnostic opportunities for the future. Possible therapeutic targets include adhesion molecules, MMPs, infectious pathogens, inflammatory cytokines and their receptors. Given the potential importance of oxidative stress in the pathogenesis of atherosclerosis, there are many theoretical reasons for believing that antioxidants might be beneficial. Unfortunately, results from recent clinical trials have been inconsistent and further work is required to resolve this issue. Stimulation of VSMC repair is also a potential therapeutic aim. This
is currently achieved – rather crudely – with balloon angioplasty, which stimulates a vigorous VSMC response to create a matrix-rich neointima. Although this may lead to restenosis, the resulting lesion rarely, if ever, precipitates an acute coronary syndrome, even when the original target lesion was unstable. In the future, utilization of modulators of VSMC proliferation and matrix production may lead to new therapies aimed at strengthening the protective fibrous cap.

Key points for clinical practice

- High-risk lesions are not necessarily angiographically severe
- Unstable, high risk lesions, are the ones composed of large lipid cores and thin fibrous caps
- Plaque instability is related to the development of inflammation
- Statins may stabilize lesions by altering the inflammatory response

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