BASIC SCIENCE

Improving the treatment of atherosclerosis by linking anti-inflammatory and lipid modulating strategies

Alma Zernecke, 1 Christian Weber2,3

Atherosclerotic vascular disease manifests as a progressive narrowing of the vessel wall, and underlies coronary artery disease (CAD) and cerebrovascular disease. With consequences such as myocardial infarction and stroke, atherosclerosis remains the most frequent cause of death in the western world. While a strong heritable component is undisputed, the molecular inflammatory and immune mechanisms in the evolution of the disease are still not fully understood. By using both animal models of disease (foremost genetically manipulated mice) as well as human tissue, and more recently by employing unbiased approaches to discover genetic loci predisposing to disease development, investigators have revealed a complex picture of multilayered cellular processes and molecular mechanisms. Here we highlight the current view on atherosclerosis and provide an updated account of the critical factors involved in disease development, as illustrated by various prototypic examples.

In brief, the response-to-injury hypothesis of Russell Ross introduced the notion that monocyte–endothelial interactions give rise to foam cells and growth factor induced smooth muscle cell (SMC) proliferation, triggering lesion formation.1 Our understanding of the atherogenic process has been considerably refined by the appreciation of subendothelial ApoB lipoprotein retention containing low density lipoprotein (LDL) in the vessel wall under conditions of elevated concentrations of circulating cholesterol. This may predominantly occur at predilection sites with disturbed flow; for example, at branch points of vessels, where increased endothelial turnover and structural changes in elastins and proteoglycans occur, which permit subendothelial accumulation of LDL. In the intima, LDL particles are prone to modifications by reactive oxygen species or enzymes such as myeloperoxidase or lipoxygenases released from inflammatory cells. These oxidised lipids (oxLDL) further trigger the expression of adhesion molecules which contribute to intimal leucocyte recruitment. While early ‘fatty streak’ lesions mostly comprise lipid laden, monocyte derived, macrophage-like foam cells, the continued accumulation of different leucocyte subsets, their apoptotic cell death, together with the collection of debris and cholesterol crystals in the vessel wall, leads to the formation of a necrotic core. Collagen and SMCs can form a fibrous cap covering the lesion.

Classical risk factors for atherosclerosis include hypertension (which can increase arterial wall tension and lead to disturbed repair processes), the pressor hormone angiotensin II system (which can alter endothelial function, smoking, diabetes), and cholesterol metabolism. Clinical manifestations arise when flow limiting stenoses occur that cause tissue ischaemia, or when thrombi form that either result in emboli or lead to the occlusion of the vessel. One of the conundrums that remains to be elucidated is the fact that thrombotic events frequently are not observed at the sites of the most severe arterial narrowing, but occur as a consequence of a thinning of the fibrous cap, for example, by inflammatory proteases or when being replaced with infiltrating inflammatory cells. The identification and diagnosis of such processes will therefore be a major objective in future research.2 3

LIPID TRIGGERED INFLAMMATION IN ATEROGENESIS

An intriguing recent finding is the presence of small cholesterol crystals in human and mouse atherosclerotic lesions. These crystals appear to be associated with lesional macrophages, accumulate in subendothelial and necrotic areas, and promote atherogenesis by activating the NLRP3 inflammasome, a pattern recognition receptor platform mediating interleukin 1β (IL1β) secretion via caspase-1, and neutrophil recruitment.4 Whether these crystals precede monocyte recruitment or are formed within macrophages, and what their functional role is in atherogenesis, remain to be fully elucidated (box 1).

The formation and accumulation of foam cells within the vessel wall is thought to be a key event in atherosclerosis. The uptake of cholesterol entails an array of disadvantageous signalling pathways: differentiating macrophages upregulate scavenger receptors (such as SR-A/B and CD36) that mediate the majority of modified LDL uptake. Their genetic deletion, however, does not affect foam cell or

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Box 1 Atherosclerotic vascular disease: a lipid driven, inflammatory disease

- Macrophage scavenger receptors cooperate with toll-like receptors to respond to lipids to drive inflammation and atherogenesis.
- Cholesterol can cause endoplasmic reticulum stress (‘lipotoxic ER stress’) that leads to macrophage apoptosis and plaque necrosis.
- Cholesterol crystals associated with lesional macrophages accumulate in necrotic areas and promote atherogenesis by activating the NLRP3 inflammasome and recruiting neutrophils.
- Cholesterol-rich lipid rafts in the cell membrane can enhance cytokine receptor signalling driving myeloproliferation; cholesterol efflux from these rafts to high density lipoprotein (HDL) protects against atherosclerosis.
- Oxidised low density lipoprotein (LDL) can be hydrolysed by lipoprotein associated phospholipase A2 to generate proinflammatory mediators, such as lysophosphatidylcholine (LPC) or its derivate lysophosphatidic acid (LPA) that drive inflammatory gene expression.

lesion formation, but leads to a reduction in the expression of inflammatory genes and macrophage apoptosis. Interestingly, CD36 cooperates with the toll-like receptor 4 (TLR4) and TLR6 in the inflammatory response of macrophages to atherogenic oxLDL. Sequestered CD36 induces an intracellular CD36-TLR4-TLR6 heteromerisation, which activates NF-kB (nuclear factor κ-light-chain-enhancer of activated B cells) and chemokine expression, and is similarly seen in proatherogenic TLR4 activation. The importance of TLR mediated signalling in atherosclerosis is further accentuated by a reduction in atherosclerosis in mice, with a genetic deletion of TLR2, TLR4 or the TLR signalling adaptor MyD88.

Intracellular free cholesterol can also cause an induction of endoplasmic reticulum (ER) stress; this may at least be mediated by the combined signalling of CD36 with TLR2-TLR6, and promote oxidative burst and macrophage apoptosis. The importance of lipotoxic ER stress in atherogenesis is further highlighted by findings showing that mice with a somatic deficiency in the ER stress effector CHOP display a reduction in macrophage apoptosis and plaque necrosis. Similarly, blocking fatty acid binding protein-4 (aP2) function reduces macrophage apoptosis and atherogenesis by limiting lipotoxic ER stress and reactivation of the de novo lipogenesis and lipid desaturation.

Cholesterol is also integrated into cellular membrane lipid rafts. Defective cholesterol efflux due to deficiency of the ABC transporters ABCA1 and ABCG1 can enhance cholesterol-rich raft formation in haematopoietic stem cells, increasing surface expression of the common IL3 and granulocyte macrophage colony stimulating factor (GM-CSF) receptor β subunit and its downstream signalling, resulting in an enhanced myeloproliferation. Accordingly, mice with ABCA1 and ABCG1 deficient bone marrow showed accelerated atherosclerosis. Myeloproliferation and atherosclerosis could be reversed by promoting cellular cholesterol efflux to high density lipoprotein (HDL), as in ApoA-1-transgenic mice with increased HDL concentrations.5

Importantly, the inverse relationship between HDL and leucocytosis/atherogenesis confirms human correlation studies. However, HDL not only effects reverse cholesterol transport, and transfers cholesterol from peripheral tissue to the liver for excretion, it has also been shown to exert anti-inflammatory actions. However, HDL is a heterogeneous particle with different contents of lipids and proteins, and clinical assays for HDL do not reflect this. Thus, the mere increase in HDL concentrations may not necessarily confer clinical benefit.

Interestingly, a high expression of the lipoprotein associated phospholipase A2 (Lp-PLA2), which can be deployed in the intima bound to LDL but is also synthesised by inflammatory cells, can be detected in human vulnerable atherosclerotic lesions. An increased Lp-PLA2 activity correlates with pro-atherogenic lipids and cardiovascular risk in humans. Lp-PLA2 primarily hydrolyses oxidised phospholipids in LDL to generate proinflammatory mediators such as lysophosphatidylcholine (LPC) and oxidised non-esterified fatty acids. Selective inhibition of Lp-PLA2 with darapladib reduces development of complex CAD in swine, limiting LPC content, lesions with an unstable phenotype and inflammatory gene expression. The LPC derivative lysophosphatidic acid (LPA), which is increased in plaques and serum in hypercholesterolaemia, has similarly been implicated in atherogenesis—for example, by mediating the activation of and interactions between endothelial cells, monocytes and platelets, and promoting macrophage accumulation and lesion progression in atherosclerosis-prone mice.6

**CYTOKINES AND CHEMOKINES IN ATHEROSCLEROSIS**

A number of pro- and anti-inflammatory cytokines controlling leucocyte recruitment and cell functions determine lesion growth. Among the cytokines upregulated within atherosclerotic lesions, macrophage migration inhibitory factor (MIF) can be detected in endothelial cells and macrophages in response to oxLDL. MIF is critically involved in a number of processes, such as endothelial cell activation, monocyte recruitment, foam cell formation, SMC migration and extracellular matrix destabilisation, exerting pro-inflammatory and proatherogenic functions. The importance of MIF during atheroprosession was strikingly demonstrated in studies using an MIF specific antibody that afforded true regression of established atherosclerosis (box 2).6

As another example, type I interferons (IFNs) have been implicated in atherogenesis. Treatment of atherosclerosis prone mice with IFNβ increases lesion size, whereas myeloid deficiency of IFNAR1, the receptor for type I IFNs, attenuates atherosclerosis, macrophage accumulation and necrotic core formation. These effects are at least in part mediated by the upregulation of CCL5 production.
**Box 2 Cytokines and chemokines in atherosclerosis: functions in cell recruitment and beyond**

- Inflammatory cytokines, such as macrophage migration inhibitory factor (MIF) and type I interferons, and co-stimulatory molecules can critically promote inflammation and atherogenesis.
- Signature combinations of chemokines and their heteromers act in a spatial-temporal manner to recruit leucocyte subsets via specific chemokine receptors, e.g., CCL5/CXCL4 via CCR5.
- Chemokines in addition control post-recruitment cell homeostasis, e.g., CX3CL1/CX3CR1 drives monocyte survival; the chemokine CCL17 restricts the maintenance of Tregs.

...limited late stage plaque formation and monocyte infiltration in the aortic root. In contrast, mouse CXCR3 deficiency primarily delayed early atherosclerosis by attenuating recruitment of T helper 1 (Th1) T cells. The lack of the CCL5 receptor CCR5 in somatic or blood cells reduced plaque formation in mice at later stages, upregulated systemic IL10 and downregulated interferon γ (IFNγ), reflecting an attenuated Th1-type response. From the functions of chemokines in recruitment, the absence of CX3CR1 or CX3CL1 has been shown to reduce Ly6C<sup>+</sup> blood monocyte concentrations under steady state and inflammatory conditions, which could be rescued by expression of anti-apoptotic Bcl2, indicating that this axis confers essential survival signals. Enforced survival of monocytes, plaque phagocytes and foam cells restored atherogenesis in Cx3cr1<sup>-/-</sup> mice, emphasising the homeostatic functions of this axis in atherosclerosis. Conversely, deficiency or antibody blockade of DC derived CCL17 in hyperlipidaemic mice reduced atheroprogession by expanding T<sub>reg</sub> cells, whereas CCL17 expression in DCs restricted T<sub>reg</sub> cell maintenance to promote atherosclerosis, identifying CCL17 as a central regulator of T<sub>reg</sub> cell homeostasis.

**LEUCOCYTES INVOLVED IN Atherosogenesis**

**Monocytes/macrophages**

While monocytes/macrophages predominate the inflammatory cell infiltrate in atherosclerosis and have been discussed in detail elsewhere, new cellular players have recently been uncovered in recent years, with hitherto underappreciated cell populations emerging as contributors to disease development. In addition, the important role of different subtypes of activated macrophages has become evident in diet induced obesity and atherosclerosis, where the activation state of resident and newly recruited macrophages may shift from an alternatively activated M2 phenotype (polarised through IL4/IL13) to a classical pro-inflammatory M1 phenotype (responding to IFNγ) to exacerbate disease.

**Neutrophils**

Polymorphonuclear leucocytes (neutrophils) have been detected in aortic fatty streak lesions of primates and correlate with the incidence and severity of CAD, and have been localised to human and mouse atherosclerotic lesions. Convincing evidence for a proatherogenic role of neutrophils has recently been disclosed in the initial phase of atherosclerosis in mice. It was furthermore demonstrated that hyperlipidaemia triggers neutrophilia by stimulating granulopoiesis and bone marrow egress. Moreover, a disturbed lipid balance facilitates their recruitment to lesions, as shown in bone marrow ABC transporter deficient mice, which showed pronounced neutrophil infiltration upon peripheral inflammatory signals. Neutrophils can subsequently promote monocyte recruitment. Furthermore, a link between neutrophils and coagulation has been provided by...
evidence that neutrophil serine proteases along with externalised nucleosomes promote intravascular thrombus growth in vivo by enhancing tissue factor and factor XII dependent coagulation through proteolysis of the tissue factor pathway inhibitor. The continued presence of neutrophils in advanced plaques may thus contribute to large vessel thrombosis as a trigger for myocardial infarction and stroke.8

Dendritic cells
DCs are another cell population gaining recent attention in regard to their role in atherosclerosis. This cell population constitutes a heterogeneous group that includes several distinct subsets defined by surface marker expression profiles. A DC based network is detectable in the intima of healthy human arteries and in the aorta of mice, mainly localised to atherosclerosis prone regions. Resident intimal CD11c+ DCs accumulate lipids and may be the first cells to form foam-like cells in the intima within days of hyperlipidaemia. However, although DCs are bona fide antigen presenting cells, they share phenotypic and functional features with macrophages. A distinction between macrophages and DCs thus remains controversial and confounded by their plasticity. Notably, a prolonged DC lifespan by human Bcl2 expression resulted in increased conventional DC numbers and reduced plasma cholesterol concentrations, whereas short term depletion of DCs in Apoe−/− mice increased hypercholesterolaemia. This implicates conventional DCs in cholesterol homeostasis and atherogenic effects.

Mature DCs further accumulate during atherosclerosis and cluster with T cells in the shoulder and rupture prone plaque regions. Moreover, aortic CD11c+ DCs have been shown to trigger antigen specific T cell proliferation. By sensing atherogenic danger signals and antigen internalisation, DCs may be ideally positioned at the crossroads of innate and adaptive immunity and may be instrumental in orchestrating a switch from tolerance to adaptive immunity activation.14 Recently, distinct DC subsets with opposing functions have been discovered. In advanced plaques, CCL17 expression by mature DCs restricts Treg cell expansion and sustains atherosclerosis, identifying the control of Treg cell homeostasis as an effector mechanism of CCL17+ DCs in atherogenesis.11 In contrast, aortic CD103+ DCs are associated with the protection of atherosclerosis and the maintenance of Treg.15

T cells
Atherosclerotic plaques feature a clonal expansion of memory effector T cells, indicating antigen specific reactions, and can also confer lesion formation upon reconstitutive transfer. The importance of antigen specific immune responses in atherogenesis is widely acknowledged. Moreover, activation of CD8+ T cells against an SMC expressed artificial antigen exacerbates atherosclerosis in hyperlipidaemic mice. Ldlr−/− mice deficient in the major T1,1 differentiating transcription factor T-bet show a reduced lesion size, indicating that atheroprotection is driven by a T1,1-type response and its signature cytokines IFNγ, IL12, and IL18. Conversely, numerous studies have established atheroprotective effects mediated by Treg cell subsets and their products transforming growth factor β (TGFβ) and IL10. In contrast, data for T1,2 and T1,17 cells are less conclusive and partially contradictory.

B cells
Bone marrow B cell deficiency or splenectomy aggravates atherosclerosis in mice, whereas splenic B cell transfer mediates protection in splenectomised recipients. Accordingly, deficiency in bone marrow IL5, a cytokine that expands natural B1 cells, increases atherosclerosis and reduces oxLDL reactive immunoglobulin M (IgM) values. Although oxLDL specific IgG titres correlate with CAD, oxLDL specific IgM titres are associated with atheroprotection, which—like regression—can be conferred by recombinant antibodies to oxLDL in mice. Notably, depletion of conventional B2 cells ameliorates atherosclerosis, whereas transfer of B2 but not B1 cells promotes atherosclerosis, confirming subset specific effects.

MicroRNAs in atherogenesis
miRNAs (miRNAs) that post-transcriptionally regulate gene expression may in addition add another dimension in the regulation of cell differentiation and functions. In addition, miRNAs have emerged as important post-transcriptional regulators of lipid metabolism, and represent a new class of targets for therapeutic intervention. Recently, miRNA-33a and b (miR-33a/b) were discovered as key regulators of metabolic programmes including cholesterol and fatty acid homeostasis. These intronic microRNAs are embedded in the sterol response element binding protein genes, which code for transcription factors that coordinate cholesterol and fatty acid synthesis. By repressing a variety of genes involved in cholesterol export and fatty acid oxidation, miR-33a/b boost cellular sterol efficiency in bone marrow IL5, a cytokine that expands natural B1 cells, increases atherosclerosis and reduces oxLDL reactive immunoglobulin M (IgM) values. Although oxLDL specific IgG titres correlate with CAD, oxLDL specific IgM titres are associated with atheroprotection, which—like regression—can be conferred by recombinant antibodies to oxLDL in mice. Notably, depletion of conventional B2 cells ameliorates atherosclerosis, whereas transfer of B2 but not B1 cells promotes atherosclerosis, confirming subset specific effects.

The analysis of miRNA expression patterns in arterial lesions and atherosclerotic plaques has revealed fundamental changes in the miR signature comprising many different miRs. Moreover, single miRNAs have been pinpointed to exert a significant impact on neointimal lesion formation, for example, miR-143 and miR-145, and studies addressing the function of miRNAs in the development of atherosclerosis are ongoing.15 Recent miRNA profiling studies further revealed that circulating concentrations of vascular derived microRNAs, including miR-126, were reduced in individuals with CAD.5 Interestingly, miR-126 or miR-126 carrying endothelial apoptotic bodies have been identified as being atheroprotective in mice, promoting CXCR4 dependent mobilisation and
lesional incorporation of angiogenic progenitor cells. By repressing RGS16, miR-126 unleashes autoregulatory CXCR4 signalling and increases endothelial production of CXCL12, a mediator of stem cell mobilisation and homing.\(^{18}\) The recruitment of such circulating (or locally residing) cytokine releasing progenitor cells may support endothelial regeneration or modulate inflammation, but may contribute to neovascularisation in advanced plaque stages.\(^{8}\) These findings support the development of microRNA antagonists as potential therapeutic agents for the treatment of dyslipidaemia, atherosclerosis, and related metabolic disease.

### MICROBIOTIC FLORA IN THE GUT

The intestinal microbiotic flora performs essential functions in nutrient processing and assists host immune responses, but it has also been linked to metabolic and immune disorders, prompting studies of its relation to human disease. A recent metabolomics approach identified the dietary lipid phosphatidylcholine and its metabolites choline, betaine, and trimethylamine N-oxide (TMAO) as risk factors for cardiovascular disease. In mice, a choline-rich diet increased TMAO values and risk factors for cardiovascular disease. In mice, a choline-rich diet increased TMAO values and atherosclerosis, depending on gut flora activity, as shown by broad spectrum antibiotic treatment. Although earlier antibiotic trials failed to reduce event rates in humans with CAD, specific targeting of bacterial species responsible for choline metabolism using selective antibiotics or probiotics might have therapeutic value for cardiovascular disease.\(^{19}\)

Detailed analysis of the relations between gut microbiota, host metabolism, and atherosclerosis may allow for subtle microbiota manipulation as a new way to modulate lipid metabolism and treat CAD.

### THERAPEUTIC OPTIONS AGAINST Atherosclerosis

The high incidence of atherosclerosis related cardiovascular disease and CAD imposes an enormous burden on healthcare systems. The established therapeutics against atherosclerosis are largely focused on alleviating hypertension and hyperlipidaemia or controlling haemostasis to prevent thrombotic complications (table 1).\(^{2,20}\)

Treatment with statins for secondary prevention in patients with CAD can result in a pronounced risk reduction, which correlates with lowering of LDL cholesterol. Statins exert a pleiotropy of anti-inflammatory actions, improve endothelial function and reduce plaque lipids and thrombogenicity, thereby limiting atheroprogression and increasing plaque stability. Aggressive lipid lowering by high dose atorvastatin decreases high sensitivity C reactive protein (hs-CRP) serum concentrations and causes regression of atheromas. This clinical benefit is extended to primary prevention in patients with LDL cholesterol concentrations <130 mg/dl (<3.4 mmol/l) but elevated hs-CRP where rosuvastatin significantly reduces major cardiovascular event rates, with reductions in both LDL cholesterol and hsCRP indicating successful treatment. In acute coronary syndrome (ACS), aggressive statin treatment also lowered the incidence of primary end points including myocardial infarction, with the most substantial benefit in patients with declines in both LDL cholesterol and CRP. In statin treated patients with low HDL cholesterol, extended release of nicotinic acid (niacin) may shift the lipid...

### Table 1  Atherosclerosis therapy

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<th>Compound or method</th>
<th>Mechanism</th>
<th>Status or effect</th>
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<td><strong>Established therapies</strong></td>
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<td></td>
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<tr>
<td>Statins, eg, atorvastatin, rosuvastatin</td>
<td>Inhibit cholesterol synthesis; anti-inflammatory</td>
<td>Primary and secondary prevention</td>
</tr>
<tr>
<td>Nicotinic acid (niacin)</td>
<td>Inhibits fat breakdown and increases high density lipoprotein (HDL) cholesterol; anti-inflammatory</td>
<td>Secondary prevention</td>
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<tr>
<td>Aspirin, clopidogrel, prasugrel, ticagrelor</td>
<td>Inhibit platelet aggregation</td>
<td>Secondary prevention</td>
</tr>
<tr>
<td>β-blockers, renin–angiotensin system inhibitors</td>
<td>Antihypertensive</td>
<td>Secondary prevention</td>
</tr>
<tr>
<td><strong>Emerging therapeutic approaches</strong></td>
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<td></td>
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<td>HDL mimetics, eg, apoA1-Milano</td>
<td>Promote cholesterol efflux; anti-inflammatory</td>
<td>Clinical phase 1/2</td>
</tr>
<tr>
<td>Darapladib (Lp-PLA2 inhibitor)</td>
<td>Decreases atherogenic lipid production</td>
<td>Clinical phase 3</td>
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<tr>
<td>Anakinra</td>
<td>IL1 receptor antagonist</td>
<td>Clinical phase 2</td>
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<tr>
<td>Canakinumab</td>
<td>Blocking IL1β antibody</td>
<td>Clinical phase 3 (CANTOS)</td>
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<tr>
<td>Methotrexate</td>
<td>Immunosuppressive</td>
<td>Clinical phase 3 (CIRT)</td>
</tr>
<tr>
<td>Thiazolidinediones (PPAR (peroxisome proliferator activated receptor) agonists)</td>
<td>Anti-inflammatory</td>
<td>Increased risk of heart failure and myocardial infarction</td>
</tr>
<tr>
<td>CETP (cholesterol ester transfer protein) inhibitors, eg, anacetrapib</td>
<td>Inhibit cholesterol transport from HDL to low density lipoprotein (LDL)</td>
<td>Torcetrapib raised blood pressure</td>
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<tr>
<td><strong>Novel experimental strategies</strong></td>
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<td>Maraviroc</td>
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<td>MLN1202</td>
<td>Blocking CCR2 antibody</td>
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<td>CT-2009</td>
<td>Inhibits CCL5-CXCL4 and atherosclerosis in mice</td>
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<td>Blocking macrophage migration inhibitory factor (MIF) receptor binding</td>
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<td>Blocking the CD40-TRAF6 interaction</td>
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<td>Immunisation CCL17 inhibition</td>
<td>Protective antibodies and Treg expansion, inhibits atherosclerosis in mice</td>
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developed to complement existing ones or to combine multiple biomarkers in an integrated approach to monitor such new therapies.

Contributors Both AZ and CW wrote the paper.

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Provenance and peer review Commissioned; externally peer reviewed.

REFERENCES

- This is a landmark review article setting the stage for the new millennium of atherosclerosis research.
- This review article provides a comprehensive overview on current concepts of the pathogenesis, and surveys established and novel therapeutic options in atherosclerosis.
- This articles opens a new perspective for linking lipid deposition in the form of cholesterol crystals and initiation of inflammatory signalling and cell recruitment in atherosclerosis.
- This article provides important insights into the anti-inflammatory regulation of haematopoietic cell proliferation by components of the reverse cholesterol transport.
- This study demonstrates an important post-recruitment function of chemokines derived from a dendritic cell subset in suppressing atheroprotective immune cell maintenance.
   - This recently published metabolomic approach identified an interesting and possibly targetable relation between gut microbiota, host metabolism and atherosclerosis.

   - This position paper provides an excellent and comprehensive overview on therapeutic options for treating atherosclerosis and stabilising vulnerable plaques.
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