Summary

Atherosclerosis is an inflammatory disease that involves the arterial wall and is characterised by the progressive accumulation of lipids in the vessel wall. The first step is the internalisation of lipids (LDL) in the intima with endothelial activation which enhances the permeability of the endothelial layer and the expression of cytokines/chemokines and adhesion molecules. These events increase LDL particles accumulation in the extracellular matrix where they aggregate/fuse, are retained by proteoglycans and become targets for oxidative and enzymatic modifications. In turn, retained pro-atherogenic LDLs enhance selective leukocyte recruitment and attachment to the endothelial layer inducing their transmigration across the endothelium into the intima. While smooth muscle cell numbers decline with the severity of plaque progression, monocytes differentiate into macrophages, a process associated with the upregulation of pattern recognition receptors including scavenger receptors and Toll-like receptors leading to foam cell formation. Foam cells release growth factors, cytokines, metalloproteinases and reactive oxygen species all of which perpetuate and amplify the vascular remodelling process. In addition, macrophages release tissue factor that, upon plaque rupture, contributes to thrombus formation. Smooth muscle cells exposed in eroded lesions are also able to internalise LDL through LRP-1 receptors acquiring a pro-thrombotic phenotype and releasing tissue factor. Platelets recognise ligands in the ruptured or eroded atherosclerotic plaque, initiate platelet activation and aggregation leading to thrombosis and to the clinical manifestation of the atherothrombotic disease. Additionally, platelets contribute to the local inflammatory response and may also participate in progenitor cell recruitment.

Keywords
Atherosclerosis, thrombosis, inflammation

Update in lipids and inflammation

LDLs and endothelial dysfunction

Under physiological conditions, endothelial cells resist adhesion and aggregation of inflammatory cells and platelets, promote fibrinolysis and control the vascular tone. These anti-atherogenic properties are mainly driven by the endothelial nitric oxide synthase (eNOS) enzyme (1). Nitric oxide (NO) synthesis and release blocks the expression of nuclear-factor (NF) kappa B-regulated inflammatory molecules and adhesion molecules (ICAM-1, VCAM-1), prevents platelet activation and induces vasodilation. Continuous exposure of the endothelial layer to risk factors (hyperlipidaemia, hypertension, smoking, obesity, insulin resistance or inflammation) leads to endothelial cell activation and eventual eNOS impairment, the hallmark of endothelial dysfunction. We have reported that atherogenic concentrations of native-LDL (nLDL) and low concentrations of modified LDL (mLDL) suffice to decrease NO bioavailability either via a reduction of eNOS activity or via a decrease in mRNA and protein eNOS expression (2). Furthermore, oxLDL has been shown to impair acetylcholine-induced ENOS activation by displacement of eNOS and caveolin-1 (cav-1) to the intracellular compartment (3, 4). Other lipoprotein-related mechanisms that have been shown to mediate NO decrease include: a higher interaction between eNOS and cav-1 which retains eNOS in an inactive form; eNOS internalization and subsequent inactivation by a CD36-mediated depletion of cholesterol content in caveolae; higher plasmatic concentrations of ADMA (asymmetric dimethylarginine, an endogenous competitive NO synthase); eNOS uncoupling and the subsequent increase in superoxide anion; and vascular increase in reactive oxygen species (ROS) (5). Hence, increased plasma levels of LDL particles damage the endothelium favouring nLDL entry and accumulation within the arterial wall. In fact, arterial deposition of cholesterol has been shown to be directly proportional to the concentration of circulating plasma lipoproteins.
**LDL and extracellular matrix components: Interplay for LDL retention and modification**

Subendothelial retention and modification of LDL particles and subsequent accumulation of LDL-derived lipids in the intima are the central pathogenic event that promotes atherosclerotic lesion formation. These ApoB-rich lipoproteins display an increased affinity for extracellular matrix (ECM) components of the intima, such as proteoglycans. Chondroitin sulfate proteoglycans, such as versican, are the main structural proteoglycans of the ECM and are considered important atherogenic elements since they can strongly interact with, retain, and aggregate LDLs. The length and number of proteoglycan-related glycosaminoglycan chains as well as their degree of sulfation determine their capacity to retain LDL particles within the arterial intima. Once sequestered in this intimal microenvironment, lipoprotein-proteoglycan complexes are susceptible to modifications including aggregation/fusion, oxidation (via lipoxigenase, myeloperoxidase, free radicals, etc.) and enzymatic cleavage (via proteolytic, lipolytic and hydrolytic enzymes) rendering these LDL particles pro-atherogenic.

**Mononuclear cell recruitment and maturation to foam cells**

Modified LDL particles induce endothelial secretion of chemotactic substances and the expression of adhesion receptors including integrins and selectins that favour leukocyte (monocyte and T-cell) recruitment, adhesion, and transmigration into the arterial wall. Simultaneous expression of different chemotactic and adhesion molecules suggests an intensive activation of different genes probably activated through a common transcription factor (e.g. nuclear factor κB [NFκB]). For instance, the chemo-kine monocyte chemoattractant protein (MCP)-1/CCL2 interacts with monocyte receptor CCR2 recruiting the monocytes to the endothelial layer favouring their entry by diapedesis. Transmigration of monocytes preferably occurs in areas where the basal lamina is enriched with modified LDL particles and takes place mainly through the junctions between endothelial cells. Junction adhesion molecule (JAM)-A and -C have been shown to be involved in the control of vascular permeability and leukocyte transmigration across endothelial-cell surfaces.

A newly recognised component of the inflammatory response to high cholesterol levels is the selective recruitment of distinct monocyte subsets into the atherosclerotic lesion. Indeed, recent studies have documented monocyte heterogeneity in humans and mice. In humans, monocytes have been divided into two main subsets based on their expression of specific receptors including CD14 and CD16 (CD14⁺CD16⁻ and CD14⁺CD16⁺/CD14⁺⁺CD16⁺) i.e. CD14, and -C have been shown to be involved in the control of vascular permeability and leukocyte transmigration across endothelial-cell surfaces.

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In mice, monocyte subsets have been divided mainly based on Ly-6C receptor expression. Mice Ly-6C hi monocytes have been suggested to show a molecular agreement with human CD16+, whereas Ly-6Clo mice monocytes seem to show molecular relation with human CD16+. Although at present there are discrepancies relating to the function of human monocyte subsets, in mice it is currently believed that different monocyte subsets reflect developmental stages of atherosclerosis. As such, Ly-6C hi monocytes appear to attenuate inflammation, are less abundant in atherosclerotic lesions and promote angiogenesis, whereas Ly-6Clo monocytes have been suggested to be more abundant under inflammatory conditions and promote macrophage formation in the atherosclerotic plaque. Moreover, in the absence of inflammation, Ly-6C hi monocytes are thought to differentiate into Ly-6C lo monocytes, although Ly-6C hi to Ly-6C lo conversion is still under dispute.

In addition to macrophages, T-lymphocytes have been shown to contribute to atherogenesis in mouse models and, as monocytes, display heterogeneity of function with some subsets appearing to be proinflammatory (Th1 cells) while others appear to inhibit inflammation (Th2 cells and Treg). T-lymphocytes enter the intima by binding to VCAM-1 where they are activated by interferon-γ (IFN-γ) and start releasing inflammatory cytokines, such as CD40 ligand (CD40L).

Several studies also support the contribution of vascular dendritic cells (DCs) and mast cells on atherogenesis progression. In fact, their number is significantly elevated in atherosclerosis-prone arteries being mainly detected in the intima and adventitia of atherosclerotic vessels. Although the role of vascular DCs is poorly understood they are thought to show antigen to naïve T cells accelerating lymphocyte recruitment into the atherosclerotic vessel. As to mast cells, they orchestrate both the innate and acquired immunity via toll-like receptors (TLR) activation and the ensuing cytokine release.

Once monocytes reach the intimal space, colony-stimulating factor (CSF) induces monocytes to phenotypically transform into macrophages and begin the uptake of modified LDL particles. Macrophage-related receptors involved in the uptake of modified LDL are diverse, reflecting the variety of LDL modifications. Scavenger receptor class A (SRA)-1 and SRA-II, CD36, LOX-1, or CXCL16 have been involved in oxidised LDL internalisation, whereas we have demonstrated that LRP-1 (low-density lipoprotein receptor related protein-1) is mainly involved in the internalisation of aggregated LDLs in a process regulated by SREBP1 and SREBP2. Fc γ receptor has been shown to regulate the incorporation of LDL into immune complexes. In addition to the specific scavenger receptor-mediated uptake, a new mechanism of macrophage lipid accumulation has been described in which minimally oxidised LDL (mmLDL) and its active components, polyoxygencated cholesteryl ester hydroperoxides, are involved in endogenous activation of TLR-4 that through spleen tyrosine kinase (Syk) leads to macrophocytosis, a liquid-phase uptake mechanism leading to significant lipid accumulation in macrophages. TLRs are pattern recognition receptors initially described as responsive to numerous pathogen-associated molecular patterns.
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... molecules, that are now increasingly associated to respond to modified LDLs (26). In fact, besides TLR4 expression, TLR2 has also been found in endothelial cells and macrophages within human and mouse atherosclerotic lesions (27, 28).

Overwhelming lipid accumulation on macrophages leads to foam cell formation (which involves the ingestion and metabolism of lipoprotein-derived cholesterol). Intracellular cholesterol esters joined together into membrane-bound cytoplasmic lipid droplets gives cells the characteristic foamy appearance (29). Formed foam cells release cytokines, growth factors, MMP, ROS and tissue factor (TF) perpetuating the inflammatory response, inducing vascular remodelling and increasing plaque susceptibility to thrombus formation. The endoplasmic reticulum (ER) is involved in fatty-

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acid sterification of cholesterol. Among other functions ER preserves expression of chaperones and degrades unfolded proteins in the so-called unfolded protein response (UPR). However, under severe stress ER-UPR function is impaired leading to foam cell apoptotic death and plaque instability. (30)

With regards to TF, the proximity of TF and lipid-rich areas in advanced atherosclerotic lesions has established the link between LDL particles and TF cell expression. Along with macrophages, smooth muscle cells (SMCs) are another important source of TF in the vessel wall. We have shown that the interaction between LRP-1 and LDL aggregates induces TF expression in vascular smooth muscle cells (VSMC) and the release of microparticles enriched in active TF in a process that requires RhoA translocation to the cellular membrane (31, 32).

Effect of LDLs on VSMC migration

VSMCs in the media produce most of the main components of the ECM found in the arterial intima (proteoglycans, collagen, and elastin) as well as a large number of enzymes responsible for the equilibrium between ECM synthesis (lysyl oxidase) and degradation (metalloproteinases, plasminogen activators) during the atherogenic process. Under the effect of atherogenic stimuli, VSMCs undergo phenotypic changes. Thus, VSMCs with a non-proliferative contractile phenotype, typical in healthy arteries, transform into actively proliferative cells (synthetic phenotype), migrate attracted by chemotactic agents, and increase ECM synthesis. In fact, migration of VSMCs from the vascular media to the vascular intima is a key process in intimal thickening and vascular remodelling. Recent data indicate that circulating bone marrow cells and progenitor cells present in the adventitia may also be a potential source of SMCs in the intima (33).

Functional studies in genetically modified animals and cell culture studies have suggested that certain domains of the LDL-related receptors modulate VSMC migration. In fact, atherogenic concentrations of both native and modified LDL have been shown to significantly reduce the migratory capacity of human VSMCs. In this regard, we have recently shown, by proteomic approaches, that LDL particles affect the expression and phenotypic profile of different cytoskeleton-related proteins including the myosin light chain in both the essential and regulatory isoforms (34). Indeed, atherogenic concentrations of native or modified LDLs induce myosin regulatory light chain (MRLC) dephosphorylation, impairing a key event on the formation of actin-myosin complexes during cell migration and the dynamics of actin fibre formation. We have also observed that this process is regulated by proteins such as the chaperone heat shock protein (HSP)-27 (34).

High-density lipoproteins in atherothrombosis

Multiple epidemiological studies have provided robust evidence that high HDL-cholesterol levels reduce the risk of coronary events regardless of LDL levels. It is currently believed that most of the atheroprotective effects of HDLs stem from its capacity to remove cholesterol from the vasculature, and to deliver it to the liver for disposal in a process commonly referred to as reverse cholesterol transport (RCT). For an in-depth review of this topic please refer to Badimon et al. and Choi (35–37). However, during recent years, other features of HDL have been suggested to contribute to its overall anti-
atherothrombotic effects including anti-inflammatory, antioxidant, and antithrombotic effects as detailed in Figure 2.

New players in the regulation of the inflammatory response: epigenetics and microRNAs

Epigenetic regulation has been regarded as a plausible mechanism by which risk factors (diet, environment, lifestyle, etc) may contribute to the atherogenic inflammatory response. Recent studies have demonstrated a link between inflammation and epigenetics by linking global DNA hypermethylation in the inflammatory mononuclear cells with predisposition to and angiographic confirmation of atherosclerosis (38, 39). However, which genes are directly affected by DNA methylation still remains to be determined. On the other hand, the study of microRNAs (miRNAs), endogenous nucleotides that bind to mRNA and induce translation repression, has also rapidly emerged during the last few years. Recent findings have revealed a significant role for miRNAs in atherosclerosis and lipoprotein metabolism (40). At the moment, a large number of miRNAs have already been identified in regulatory mechanisms contributing to endothelial integrity, macrophage inflammatory response to atherogenic lipids, VSMC proliferation, and cholesterol synthesis. For instance, endothelial cell miR-126 has been shown to inhibit the tumour necrosis factor (TNF)-α-mediated expression of VCAM-1 suggesting an involvement in mononuclear cell transmigration to the intima (41). Moreover, in mice, endothelial-derived apoptotic bodies rich in miR-126 have shown to induce the expression of chemokine CXCL12 promoting the mobilisation and incorporation of Sca+ progenitor cells into the atherosclerotic plaque (42). On the other hand, endothelial overexpression of miR-92a has demonstrated to block angiogenesis and vessel formation both in vitro and in mice (43). Finally, miR-143 and miR-145 have been shown to play a crucial role in regulating VSMC phenotypes and controlling neointima formation (44). Yet, for most of the miRNAs the target they act upon has yet to be identified.

Update in atherothrombosis

Platelet adhesion/activation

The discontinuity of the endothelial surface is not a necessary prerequisite for functionally relevant interactions of platelets with vascular endothelial cells. For instance, platelets are activated by local haemodynamics in the atherosclerotic vessels. Indeed, high shear stress induce the exposure of platelet receptors and the triggering of the aggregation cascade (45). Recent data shows that GRP78, an ER-chaperon, is exposed in resting platelet membrane and is translocated to the cytosol after shear-induced platelet activation to permit platelet aggregation (46). In addition, the chronic exposure to risk factors also induces platelet interaction in the intimal but activated endothelial layer. Indeed, inflamed endothelial cells downregulate NO and PGII, and express molecules such as fibronectin, ICAM-1, P-selectin, E-selectin, integrin αvβ3, and von Willebrand factor (vWF) in their surface all of which promote platelet adhesion and activation (47). However, these stimuli induce a limited platelet deposition that mostly intervenes in the progression of atherosclerosis rather than in the ultimate thrombotic complications. In contrast, both endothelial denudation (erosion) and atherosclerotic plaque rupture expose components of the vascular matrix (e.g. different types of collagen, vWF, fibronectin, laminin, fibulin, and thrombospondin) to the bloodstream which triggers extensive platelet adhesion and activation that eventually leads to aggregation and thrombus formation (Figure 3).

At high shear rates platelet adhesion is mainly driven by the interaction of circulating vWF with exposed collagen (type I and type III collagen in the deepest vascular layers and type VI collagen in the subendothelial layers). vWF binding to collagen allows vWF interaction with platelet glycoprotein (GP)IIb receptors (GPllb/IX/V platelet complex; Figure 3). However, the high rate of dissociation between vWF and GPllb/IX/V indicates that these links cannot provide stable binding between platelets and the subendothelial matrix. Unlike GPllb/IX/V, the GPVI platelet receptor binds directly to collagen and induces an activation of other adhesion receptors such as GPllb/IIa and GPLa/IIa. Both GPllb/IIa and GPLa/IIa act in unison to promote a firm, stable, and irreversible bond between platelets and the vascular endothelium, by direct binding with collagen (integrin αIIβ1) or with the C1 domain of vWF (integrin αIIβ3).

A recent study has reported that C-reactive protein also induces platelet adhesion to endothelial cells under high shear conditions (47). In this regard, we have recently demonstrated that the monoclonic form of C-reactive protein exerts a significant effect on platelet adhesion (48). As such, native or circulating CRP does not affect platelet deposition whereas monomeric CRP displays a prothrombotic phenotype enhancing not only platelet deposition but also thrombus growth under arterial flow conditions (48). In addition, Eisenhardt et al. (49) have reported the capability of activated platelets to dissociate native CRP (pentameric) into monomeric CRP which may then be deposited in the atherosclerotic plaques.

At low shear rates, platelet adhesion mainly occurs through the collagen receptor that directly binds to the platelet receptor αIIβ1. To a lesser extent, fibronectin, laminin, vitronectin and thrombospondin also contribute to platelet adhesion by binding to GPIC-IIa, GP Ic-IIa, vitronectin receptors, and to GPIV, respectively.

Platelet aggregation

Besides platelet interaction with damaged-vascular components adenosine diphosphate (ADP) released by lysed erythrocytes at the site of injury, epinephrine, serotonin, and thrombin generated upon atherosclerotic plaque exposure of tissue factor favour the platelet activation and aggregation process (50). Once activated,
platelets undergo shape change, expose a procoagulant surface and release their granule contents which contain adhesion proteins (e.g. fibrinogen, fibronectin, VWF, thrombospondin, vitronectin, P-selectin, integrin αIIbβ3), growth factors (e.g. platelet-derived growth factor, transforming growth factor-β, epidermal growth factor, basic fibroblast growth factor), chemokines (e.g. PF-4, epithelial neutrophil-activating protein 78, macrophage inflammatory protein-1β), cytokines and cytokine-like factors (e.g. interleukin [IL]-1β, CD40 ligand, thromboglobulin-β), and coagulation factors (e.g. factor V, factor XI, plasminogen activator inhibitor type 1, plasminogen, protein S). These substances act in concert to mediate a wide range of functions including cell adhesion, activation, aggregation, chemotaxis, cell survival and proliferation, coagulation, and proteolysis. For in-depth details of platelet granule content please refer to Parise et al. (51). However, platelets are not only stores of several bioactive molecules but also generate lipid-derived mediators such as thromboxane A₂ (TXA₂) that once released into the bloodstream, bind to thromboxane receptors (TP receptors) present on the surface of adjacent platelets, circulating inflammatory cells and on atherosclerotic plaque components amplifying and perpetuating the overall atherothrombotic process. Indeed, TP receptor blockade has been shown to induce regression of vulnerable atherosclerotic plaques (52) as well as reduce the risk of thrombosis induced by vascular stenting (53). Regardless of the trigger, platelet aggregation is regulated in the final part of the pathway by activation of the platelet GPIIb/IIIa receptor. The heterodimer GPIIb/IIa receptor is the most abundant protein on the platelet surface. Activation of this receptor is calcium dependent and requires a conformational change in the two subunits such that a new binding domain is exposed. Fibrinogen (of plasma or platelet origin) is the main ligand for the GPIIb/IIIa receptor. The dimeric structure of fibrinogen allows it interaction with two platelets at the same time, thereby favouring platelet aggregation. Other ligands for GPIIb/IIA that participate, though to a lesser extent, in platelet aggregation are VWF, fibronectin, and vitronectin (Fig. 2). In the final phase of thrombus formation, fibrinogen is also converted to fibrin by thrombin, and this leads to stabilisation of the platelet aggregates. In addition, besides the recruitment of more platelets that encounter such a prothrombotic microenvironment, there is also recruitment of other blood cells including leukocytes and red blood cells (54, 55).

Cross-talk between platelets and the coagulation cascade

Platelet aggregation and activation of the coagulation cascade are complementary processes. As state above, strong evidence supports the concept that TF (56) expressed in atherosclerotic lesions is the principal non-fibrillar thrombogenic factor in the plaque’s lipid-rich core, that, by binding clotting FVII/VIIa, promotes local thrombin generation by initiating the extrinsic pathway of the coagulation cascade (57). However, in addition to TF, both dysfunctional endothelium and activated platelets also play an important role in further promoting the coagulation cascade and the subsequent production of fibrin. Indeed, activated platelets externalize phosphatidylserine becoming a substrate for coagulation cofactor/enzyme complexes VIIa/Xa and Va/Xa triggering the activation of the intrinsic coagulation pathway (58). Coagulation fac-
Platelets as important players in inflammatory cell recruitment

Activated platelets, through the release of chemokines, cytokines, and a number of immunomodulatory ligands, self-amplify the platelet activation process, contribute to endothelial activation, mediate the inflammatory response and exert immunomodulatory activity (59). Indeed, activated platelets have a large arsenal of mediators to boost inflammatory responses that interact with both leukocytes and endothelial cells promoting atherogenesis and further complications (Fig. 1). Platelet factor 4 (PF4; CXCL4), CD40 ligand (CD40L, CD154), and IL-1β are some of the key molecules released upon platelet activation that contribute to endothelial inflammation. Activated and adherent platelets also provide an ideal environment for the attachment of leukocytes by the expression of P-selectin, GPIbα, JAM-3, among other products (60). P-selectin mediates the binding of platelets to P-selectin glycoprotein ligand-1 (PSGL-1) on neutrophils and monocytes, forming the subsequent platelet-leukocyte aggregates (Figs. 1, 3). Yet, endothelial cells and platelets also bind to one another via this interaction, although in this case, endothelial cells expose P-selectin that binds to platelet PSGL-1 receptors. Activated platelets can also deposit chemokines (e.g., RANTES, PF4) onto endothelial cells during transient interactions thereby promoting further monocyte recruitment and arrest (Figs. 1, 2) (61). In this regard, studies have implicated JAM-A and GPIb/IIa in endothelial deposition of chemokines by activated platelets. In addition, recent reports suggest that platelets may also be important for the adaptive immune response since platelets, via CD40L, may induce dendritic cell maturation and B-cell isotype switching.

Novel insights into platelet function

Activated platelets appear to be the common thread that links inflammation, thrombosis and atherogenesis. During the last years, novel characteristics of platelets have been unveiled. For instance, platelets, despite the lack of nucleus, have demonstrated the ability to synthesise proteins de novo by a mechanism called signal-dependent pre-mRNA splicing (62). Such protein synthesis has been shown to alter functional events relevant to thrombosis and inflammation including an increase in platelet-leukocyte interaction via de novo synthesis of IL-1β (63), clot retraction via Bcl-3 (B-cell lymphoma 3) (64), and also recover cyclooxygenase (COX)-1 synthesis upon COX-1 inhibition by aspirin treatment (65). On the other hand, Mason et al. (66) have recently shown that platelets also possess an intrinsic program for anucleated cell death that controls platelet survival and dictate their life span. In this regard, pro-survival Bcl-x(L) constrains the pro-death activity of Bak to maintain platelet survival, but as Bcl-x(L) degrades, aged platelets are primed for cell death. In addition, several recent studies have shown that platelets, via chemokine release, are capable of interacting with and mediating the recruitment of circulating stem or progenitor cells (Fig. 1) (67). For instance, platelets secrete stromal cell-derived factor (SDF)1α and chemokine CXCL12 (a ligand for CXC chemokine receptor 4; CXCR4), which enhance the recruitment of progenitor cells. Hence, by attracting CXCR4-expressing cells, platelets may promote vessel repair and the formation of neointima (68, 69). Similarly, chemokine receptor CXCR2 has shown to play a pivotal role in endothelial progenitor cells homing to the sites of endothelial injury facilitating endothelial recovery (70). In line with these platelet-derived proangiogenic effects studies in mice have supported the capacity of platelet-derived microparticles, small vesicles released from activated platelets, to enhance the vasoregenerative potential of angiogenic early outgrowth cells after vascular injury (71).

Apart from SDF1α, platelets have been shown to attract EPCs homing to sites of injury by secreting epithelial-derived neutrophil-activating protein-78 (ENA-78 or CXCL5) and platelet basic protein/neutrophil activating peptide (PBP/NAP-2 or CXC7). (72) Additionally, it has been demonstrated that the functional relevance of interactions between platelets or platelet-derived factors is not only restricted to the recruitment of circulating stem/progenitor cells but they may also influence important progenitor cell functions such as migration or differentiation (73). In fact, recent data has established platelets capacity to induce progenitor cells differentiation into foam cells via CD36 and macrophage scavenger receptor A (SR-A) (74).

Concluding remarks

In this review, we have demonstrated how the rich complexity of interactions that underlie the process of atherothrombosis is gradually unravelling through understanding of the myriad of functions of the different cell types involved and the characteristics of
the extracellular molecules with which they interact. The role of LDL in atherogenesis is well established but much more has been learnt recently about how LDL drives the vascular inflammation that characterises this process, including characterisation of monocyte/macrophage and VSMC behaviour and the molecules that influence this. Whilst the role of platelet in the thrombotic consequences of atherosclerotic plaque rupture or erosion is obvious, the engagement of platelets in the vascular inflammation underlying atherosclerosis is more complex and new aspects of the role of platelets continue to emerge. This evolving science offers the exciting prospect of identifying novel therapeutic targets beyond LDL cholesterol that can lead to more effective therapies for managing atherothrombosis in the future.

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Conflict of interest
None declared.

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