Dendritic cells in atherosclerosis: Functions in immune regulation and beyond

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Summary
Chronic inflammation drives the development of atherosclerosis. Dendritic cells (DCs) are known as central mediators of adaptive immune responses and the development of immunological memory and tolerance. DCs are present in non-diseased arteries, and accumulate within atherosclerotic lesions where they can be localised in close vicinity to T cells. Recent work has revealed important functions of DCs in regulating immune mechanisms in atherogenesis, and vaccination strategies using DCs have been explored for treatment of disease. However, in line with a phenotypical and functional overlap with plaque macrophages vascular DCs were also identified to engulf lipids, thus contributing to lipid burden in the vessel wall and initiation of lesion growth. Furthermore, a function of DCs in regulating cholesterol homeostasis has been revealed. Finally, phenotypically distinct plasmacytoid dendritic cells (pDCs) have been identified within atherosclerotic lesions. This review will dissect the multifaceted contribution of DCs and pDCs to the initiation and progression of atherosclerosis and the experimental approaches utilising DCs in therapeutic vaccination strategies.

Keywords
Atherosclerosis, inflammation, dendritic cells

Introduction
Atherosclerotic vascular disease remains the number one cause of death and morbidity in the Western world (1–4). It is now established that atherosclerosis is a chronic inflammatory disease of the vessel wall. Initially characterised by endothelial-cell dysfunction and activation under conditions of hyperlipidaemia and systemic inflammation, the sustained adhesion of leukocytes to the endothelium and increased permeability for plasma lipid components such as low-density lipoprotein (LDL), subsequently promotes lesion development. The recruitment of monocytes, which accumulate cell-activating oxidised LDL (oxLDL) and other lipids, and their transformation into foam cells leads to formation of early fatty-streak lesions in the intima. Continued growth of the lipid core, recruitment of inflammatory cells, secretion of cytokines and growth factors, apoptosis of plaque cells and the formation of a necrotic core, leads to fibroproliferative progression of the plaque and stenosis of the arterial lumen. Secretion of matrix proteases and cytokines can trigger thinning of the fibrous cap which covers the core, ultimately leading to plaque erosion or rupture, triggering thrombus formation and occlusion of the artery (1–5).

Although macrophages constitute the largest cell population, other immune cell subsets, namely dendritic cells (DCs) and T cells, can be found within atherosclerotic lesions and seem to participate in immune responses during atherogenesis (3, 4, 6–8). DCs constitute a heterogeneous family of cells with distinct phenotype and function. In humans, DC subtypes have been segregated based on location (e.g. in blood, in lymphoid or peripheral tissue), source (e.g. monocyte- or CD34-derived) and phenotype. In mice, subtypes include conventional DCs (cDCs) that are subdivided into migratory and lymphoid-tissue-resident subtypes and based on their expression of CD11c in mice (9–12). However, the distinction between macrophages and the heterogeneous family of DCs is controversial and complicated by their plasticity. While highly migratory cDCs are considered to develop from precursors of DCs arising from common DC precursors, monocytes which exit the blood and enter tissues under inflammatory conditions, can give rise to macrophages and DCs that share many of the phenotypic features and functions of prototypic DCs, making it impossible to clearly define macrophages and DCs as separate entities (13, 14). Therefore, DCs here will be defined by their expression of pan-DC markers (such as CD11c in mice) and their capacity to present antigens to prime adaptive immune responses. This review will summarise the current state of knowledge regarding the contribution of DCs to atherosclerosis (Fig. 1).
Localisation of DCs in the arterial vessel wall

Increased numbers of DCs have been observed in atherosclerotic lesions in mouse models of atherosclerosis (15–17). Similarly, numbers of mature blood-derived DCs and their precursors are increased in advanced human plaques, compared with early lesions, and are arrayed in clusters with T cells primarily localising to the exposed shoulder and rupture-prone regions of the plaque (18–20). Interestingly, patients with angina pectoris and acute myocardial infarction have reduced circulating blood-derived DC precursors (21), and blood-derived DCs and plasmacytoid DCs are diminished in patients with angiographically documented coronary artery disease (22, 23), possibly due to their increased recruitment to plaques.

However, a network of DCs can already be detected in the arterial intima of healthy young individuals (24). Similarly, in mice immunofocal microscopy revealed the abundant accumulation of CD11c+ intimal DCs (that frequently co-stained for CD68) in regions which are predisposed to atherosclerosis, while in contrast CD68+ macrophages could frequently be detected throughout the adventitia with only sparse numbers of CD11c+ cells in this location (25). Employing CD11c-EYFP reporter mice, 0.25–0.5% of aortic cells were shown to express EYFP and were localised primarily to the intima below the endothelium in an immature state, with dendritic processes penetrating between endothelial cells into the lumen, and to a lesser extent in the adventitia (26). EYFP-expressing cells were also abundant in the root of the aorta and cardiac valves with focal accumulations, i.e. in the lesser curvature of the aortic arch (26). This may be in line with topographic variations in endothelial cells in atherosclerosis-prone regions with disturbed flow leading to their inflammatory activation and adhesion molecule expression; a process which occurs even in mice with normal plasma lipoproteins (25, 27). Flow cytometric analyses of C57BL/6 as well as Apoe−/− aortae revealed the presence of CD11c+ DCs in normal/non-inflamed aortae primarily in the adventitia (15).

Origin of vascular DCs

DCs accumulate in the intima of atherosclerosis-susceptible regions through the participation of VCAM-1 and CX4CR1 during low-grade chronic inflammation, as lower numbers of DCs accumulate in Vcam−/− and Cx4cr1−/− mice (17, 25). This recruitment is considered to occur primarily from bone marrow-derived monocytes via the blood stream (25). DCs might predominantly differentiate from Ly6C+ monocytes that act as precursors for inflammatory DCs (28) and CX4CR1-dependently patrol arterial vessels, primed for recruitment during early immune responses (29). The finding that lower numbers of intimal arterial CX4CR1+ DCs correlate with decreased atherosclerosis in Cx4cr1−/− mice supports this view (17, 30). In addition, blood monocytes, in particular of the Ly6C− subtype, express CD11c during severe hypercholesterolemia, which contributes to their arrest to endothelium and the accumulation of CD11c+ monocytes/macrophages in the intima and the development of atherosclerosis (31). However, both Ly6Chigh and Ly6C− monocytes share the capacity to differentiate into DCs in vivo (28, 32), and BrdU-labelling studies demonstrated a preferential recruitment of Ly6Chigh monocytes into the intima, likely giving rise to CD11b+ vascular DCs (27, 28, 33, 34). Conversely, GM-CSF was shown to regulate lesional DC content (35), with GM-CSF being a key regulator of intimal proliferation of DCs within lesions independent of monocyte recruitment (34). GM-CSF deficiency, however, had differing effects on atherosclerosis in Ldlr−/− versus Apeo−/− mice (34, 36). In addition, some of the DCs in nascent plaques express 33D1+, a marker found on only some DC subtypes and expressed by non-monocyte derived splenic DCs (26, 34, 37). Hence, the overall relationship of DCs with the monocyte lineage, widely accepted as precursors of macrophages, and the heterogeneity and origin of vascular DCs remain to be conclusively defined.

Functions of DCs in atherosclerosis

DC accumulation in regions prone to atherosclerosis clearly suggests that their recruitment accounts for an initial inflammatory or immune activation. Lipoproteins deposited in the arterial wall may constitute stimuli or display antigens that participate in such early immune activation. After only a few days of high-fat-diet feeding, lipids are deposited in the lesser curvature of the aorta and are detected primarily within lipid-loaded CD11c+ DCs in Ldlr−/− mice (38). Upon depletion of vascular DCs using a strain of mice that expresses diphtheria toxin receptor (DTR) under the control of the CD11c promoter, lipid accumulation was substantially reduced, indicating that vascular DCs are important in regulating the early accumulation of lipids during the earliest stages of plaque formation (38). This may occur via pinocytosis and/or internalisation of lipoproteins deposited in the vessel wall by scavenger receptors, or the capturing of lipoproteins directly from the circulation through dendrites extending into the artery lumen (27).

Lipoproteins trapped in the vessel wall are prone to oxidation modifications caused by enzymatic attack of myeloperoxidases, lipoxigenases or by reactive oxygen species during inflammation and atherosclerosis. These modifications generate a spectrum of LDL particles that have undergone a variety of physiochemical changes (39). These differing forms of LDL present within the plaque (or circulation) may have varying effects on DC differentiation and function e.g. both native LDL and oxLDL induce maturation markers of DCs (HLA-DR and CD86), whereas oxLDL increases expression of CD40, CD83, CCR7 and interleukin (IL)-6 release and DC-induced T-cell proliferation. Higher concentrations of highly oxidised LDL, however, induce apoptosis (40, 41). Moreover, oxLDL has been found to induce the upregulation of scavenger-receptors on DCs (42), which may contribute to dendritic foam cell formation in the vasculature, a characteristic previously ascribed solely to macrophages. Lipoproteins may in addition also effect the differentiation of macrophages into DCs, as indicated by the upregulation of CD11c on macrophages treated...
Figure 1: DC functions in atherosclerosis. A network of DCs can be detected in the arterial intima, with dendritic processes penetrating between endothelial cells into the lumen. DCs accumulate in atherosclerosis-susceptible regions through VCAM-1 and CX3CR1. DCs may differentiate from Ly6C<sup>hi</sup> monocytes that CX3CR1-dependently patrol arterial vessels, but can also differentiate form Ly6C<sup>lo</sup> monocytes, which seem to be preferentially recruited. Intimal proliferation of DCs within lesions can be regulated by GM-CSF. Lipoproteins deposited in the arterial wall accumulate within lipid-loaded CD11c<sup>+</sup> DCs contributing to early plaque formation. DCs, possibly via lipoprotein uptake and clearance from the circulation, can control cholesterol homeostasis. DCs control T-cell activation in the aorta and influence T helper cell responses, with lipoproteins being able to contribute to DC maturation and activation. T cells and B cells can be detected in the adventitia and vascular-associated lymphoid tissue even in non-inflamed aortae, and pathological immune activation can lead to the formation of adventitial lymphoid-like tissue. DCs and T cells may migrate from the inflamed vessel to secondary lymphatic tissue (possibly requiring CCR7) but may also (re-)enter the vessel. Plaque DCs express the CCR7 ligands CCL19/CCL21, and CCL17, which may function to recruit T cells to lesions. In addition, DC-derived CCL17 restrains regulatory T-cell homeostasis. Phenotypically distinct pDCs secrete large amounts of type I IFNs in response to TLR7 and TLR9 stimulation and act as inflammatory amplifiers. IFN-α release in the plaque controls CD4 T-cell cytotoxic effector functions and elicits pro-inflammatory DC activation.

with LDL or oxLDL, and of DC genes upon exposure to oxLDL and minimally-modified LDL (but not native LDL) (43). Notably, dyslipidaemia can inhibit DC migration into lymph nodes leading to their peripheral sequestration (44), further indicating that DCs may participate in the local initiation of vascular inflammation.

Several lines of evidence further support the notion that DCs modulate atherosclerosis. Short-term depletion of DCs using CD11c-DTR Apoe<sup>−/−</sup> mice reconstituted with CD11c-DTR bone marrow and continuously depleted of DCs over 12 weeks, displayed an increase in free plasma cholesterol and aggravated lesion formation which was, however, identified to primarily stem from an enhanced apoptosis of CD11c<sup>+</sup> plaque macrophages (46). In mice expressing hBcl2–2 under the control of the CD11c promoter to enhance the lifespan of cDCs, an expanded DC population was achieved, and high cDC numbers were accompanied by a decrease in plasma cholesterol levels. However, this was also associated with an enhanced T-cell activation and Th1- and Th17-cytokine expression.
profile, and elevated levels of IgG2c auto-antibodies directed against oxidation-specific epitopes in both DC-hBcl-2 Apoe−/− mice and chimeric Ldlr−/− mice reconstituted with DC-hBcl-2 bone marrow (45). T-cell activation and Th1-polarisation were antagonised by the cholesterol-lowering effects in these mouse models, balancing each other out and resulting in unaffected atherosclerotic lesion burden (45). Besides effects on lipid homeostasis, accumulating evidence supports that DCs control immune processes in atherosclerosis.

In a model system of bioengineered arteries, lipopolysaccharide-activated adventitial cDCs stimulate autologous CD4+ T cells to produce interferon (IFN)-γ and infiltrate the model arterial wall, breaking T-cell tolerance to self-antigens and initiating vascular inflammation (47). Indeed, in vitro, vascular CD11c+ DCs sorted from the aorta in principle bear the capacity to induce antigen-specific proliferation of T cells (16, 26) and in vivo, aortic DCs can take up intravenously injected OVA-1 from the blood stream and after isolation induce antigen-specific OT-1 T-cell proliferation (26). Moreover, the adoptive transfer of OVA-loaded bone marrow derived DCs (BMDCs) induces a profound proliferation of TCR-specific lymphocytes in the adventitia of OT-1 Rag-2−/− mice, providing evidence that T cells residing within the aorta can be activated by antigen-presenting cells (15).

The presence of antigen-specific and clonally expanded T cells with strong reactivity for modified or native lipoproteins in early plaques from patients further indicates that interactions between DCs and T cells can result in immune priming at these sites with lipid derivatives serving as antigens (3, 39, 48). Moreover, an oligoclonal expansion of T cells can be found in the vessel wall (49), indicating that priming of T cells or re-encounter of antigen may also occur locally at sites of inflammation. Notably, endogenous disease-specific antigen presentation and T-cell activation seem to play an important role in atherosclerosis. Ldlr−/− mice lacking the invariant chain (CD74) of MHC-II are protected from atherogenesis, mediated by reduced T-cell activation in atheromata (50).

During hypercholesterolaemia CD11c+ DCs were shown to fully retain the capacity to prime native CD4+ T cells (51). CD8α− (but not CD8α+) cDCs were impaired in their Toll-like receptor-induced production of pro-inflammatory cytokines and expression of co-stimulatory molecules in dyslipidaemia, with oxLDL being the key active component responsible for this effect. Decreased CD8α+ DC activation profoundly influenced T helper (Th) cell responses, leading to impaired Th1 and enhanced Th2 responses (52). This may support the observation that Th1 cells predominate in moderate hypercholesterolaemia, whereas severe hypercholesterolaemia causes a Th2-cell bias (53).

It has become clear that T-cell subpopulations with a specific signature of pro- or anti-inflammatory cytokines control the atherogenic process (54–60). In particular, also regulatory T cells (Tregs), which suppress activation of the immune system, have been characterised as powerful inhibitors of atherosclerosis (57, 61). We have recently identified that the accumulation of a subset of CCL17-expressing cDCs in the aorta of Apoe−/− mice during lesion growth was associated with T-cell recruitment but a reduction in Treg accumulation in atherosclerotic lesions and a restrained regulatory T-cell homeostasis in lymph nodes, contributing to atherosclerotic lesion formation (16). Together, these findings may imply that different DC subsets may exert distinct and stage-specific functions during plaque evolution.

**Local versus systemic immune regulation**

It remains to be determined whether immune responses are initiated and sustained in the vascular wall or in secondary lymphatic tissue. DCs, T cells and B cells can be detected in vascular-associated lymphoid tissue even in normal/non-infamed aortae, suggesting that the immune system may also be modulated in the vessel wall. In addition, pathological immune activation during lesion growth leads to the formation of adventitial lymphoid-like tissue (15, 62). However, DCs might also migrate from the vessel wall to secondary lymphatic tissue where they can interact with other immune cells after peripheral activation and/or be exposed to circulating lipids and antigens in lymph nodes. Clearly, DC populations in lymphatic tissue largely exceed numbers of vessel wall-associated DCs, and lymph nodes and spleen also contain oxLDL-reactive T cells (3, 44). Although the egress of immune cells from the aortic wall seems to be minimal during progressive disease, emigration of cells from tissue is considered to be a hallmark of DCs (63). The first evidence for the molecular mechanisms of ex-migration from plaque tissue was obtained during a plaque regression study, where atherosclerotic lesions from Apoe−/− mice were transplanted into wild-type recipients (and therefore a regression-inducing environment) (64). In these mice, CCR7 expression was upregulated and required for the emigration of CD68+ cells, and a reduction in foam cell content was seen in regressing plaques (64). However, in a slower and more physiological model of macrophage removal and plaque regression, achieved by treating Apoe−/− mice with viral vectors encoding apoE, CCR7 was not required for macrophage accumulation in plaques and in fact involved no or minimal induction of macrophage egression. Moreover, atherosclerotic plaque size was not significantly reduced but tended to be smaller in Ccr7−/− Apoe−/− mice compared to Apoe−/− mice with an unaltered content of CD68+ macrophages (65). Conversely, a protection from atherosclerosis and a reduction in lesional MOMA-2+ macrophage content was observed in Ccr7−/− Ldlr−/− mice. In this study it was shown that CD11c+ cells and T cells accumulated in the atherosclerotic aortic root of Ccr7−/− Ldlr−/− mice, whereas their numbers were decreased in secondary lymphoid organs, consistent with an impaired migration of CCR7-deficient CD11c+ DCs and T cells to these sites (66). In addition, adaptively transferred Ccr7−/− T cells showed a reduced migration into the inflamed aorta and failed to promote atherosclerosis. These findings suggest that local priming processes seem to be unable to generate and maintain an adaptive immune response, and that the trafficking of T cells and DCs, such as their egress from inflamed tissue into the draining lymph node and their (re)-entry into inflamed tissue, is essential for the generation of an immune response promoting atherosclerotic plaque development (66).
In accordance, a number of studies have previously demonstrated that the accumulation of activated T cells within atherosclerotic lesions, e.g. via CXCRR3, CXCRR6 or in response to MIF, was associated with enhanced plaque growth (67, 68). Given the expression of the CCR7 ligands CCL19/CCL21 by plaque DCs (20), and the role of CCL17-expressing DCs in the accumulation of T cells in atherosclerotic lesions (16), these studies furthermore indicate that DCs, by recruiting or retaining T cells in the inflamed vessel wall, may contribute to atherosclerotic lesion growth.

**DCs in vaccination approaches**

Due to their ability to regulate T- and B-cell responses, DCs have also been explored as adjuvants in vaccination strategies. *Ex vivo* loading of DCs with antigen or the targeting of DC receptors for delivery of antigen have been shown to result in specific humoral and cellular responses and bear promise in the potential treatment of carcinomas (69, 70). The understanding that T and B cells and their immune responses critically control atherosclerosis suggests that atheroprotective vaccination may constitute a feasible approach for disease modulation. Initially, immunisation of rabbits and mice with oxidised LDL was shown to result in a protection from atherosclerosis (71). However, oxLDL is a complex particle and a number of additional antigens have been identified, among them oxidised epitopes and peptide fragments generated by the proteolytic degradation and modulation of apoB-100, as well as heat-shock protein 60, with protective effects of specific antibodies (39, 71). Furthermore, circulating antibodies and T cells reactive to native LDL have also been identified (39). However, the effects of antibodies to oxLDL or other epitopes of modified lipoproteins remain controversial – IgG autoantibodies are thought to be either protective or atherogenic, whereas IgM autoantibodies might protect against atherosclerosis (72).

Seminal work has shown that in principle, immune responses elicited by transferred antigen-loaded DCs directed towards artificial antigens presented by arterial SMCs aggravate atherosclerosis (73), linking immune-mediated arterial inflammation and cholesterol-induced atherosclerosis. DC-based vaccination studies in native and diet-induced atherosclerosis employing *ex vivo* generated and antigen pulsed BMDCs have yielded different outcomes. Habets et al. repetitively injected BMDCs matured with LPS and simultaneously pulsed with copper-oxidised LDL intravenously into *Ldlr*-/- mice prior to the initiation of a high-fat diet. This resulted in a significant reduction in plaque formation in the carotid artery after perivascular collar placement, however, although there was no alteration in lesion size in the aortic root after seven weeks, plaques had a more stable phenotype (74). This was also associated with an induction of both IgG1 and IgG2a directed against oxLDL, when compared with mice injected with unpulsed DCs (74). Hjerpe et al. subcutaneously administered *ApoE*<sup>-/-</sup> BMDCs simultaneously pulsed with LPS and MDA-LDL or KLH-DCs into *ApoE*<sup>-/-</sup> mice at frequent intervals during lesion formation. After 17 weeks, lesion size in the aortic root was significantly increased and accompanied by elevated circulating anti-MDA-LDL IgG1, IgG2a and IgG2b antibodies (75). Hermansson et al. repeatedly injected mice expressing the full-length human ApoB100 in the liver and humanised hyperlipidaemic lipoprotein profiles (hub100<sup>0%/Ldlr</sup>-/- mice), with a single injection of LPS-matured BMDCs incubated with IL-10 and ApoB100, prior to the initiation of a high-fat diet. After 10 weeks of diet, ‘tolerogenic’ IL-10-exposed DCs decreased lesion area in the descending thoracic aorta, which was associated with the generation of antigen-specific regulatory T cells (Tregs) and decreased cellular but not humoral immunity toward ApoB100 (76). These seemingly contradictory studies may indicate that local concentrations of IL-10 (and possibly other mediators) determine the outcome of DC-transfer experiments. In particular, the choice of mouse model and diet may influence the DC-phenotype, reflecting altered Th-cell balance and increased IL-10 levels with increasing hypercholesterolaemia (53, 76). Tolerogenic DC therapy may so far constitute a feasible approach to prevent systemic inflammation. However, treatment of patients with full-grown lesions and ongoing disease in the clinical setting may be more challenging and additional studies in mice with established atherosclerosis are warranted.

**pDCs in atherosclerosis**

pDCs constitute a phenotypically distinct DC subtype known to secrete large amounts of type I IFNs in response to TLR7 and TLR9 stimulation (77). Also pDCs are found in carotid artery plaques, primarily in the shoulder region, where they cluster with myeloid DCs (78–80). In atherosclerotic tissue, IFN-α transcripts were shown to correlate with plaque instability and TNF-α expression (78, 81) and it was demonstrated that IFN-α release in the plaque controls CD4 T-cell cytotoxic effector functions by stimulating naive CD4<sup>+</sup> T cells to produce IFN-γ and to express TRAIL (TNF-related apoptosis-inducing ligand) in an antigen-independent manner, enabling them to kill vascular SMCs (81). In addition, pDCs may act as inflammatory amplifiers, as plaque DCs respond to IFN-α by producing markedly higher amounts of pro-inflammatory mediators, such as cytokines and MMP-9 (78). The responsiveness of pDCs to viruses or bacterial infections may provide a link between atherosclerosis and chronic infection burdens and possibly also inflammatory activation of vulnerable plaques in response to acute infections (81). However, also nucleotides released from necrotic or apoptotic cells in plaques may be prone to bind TLR7 or TLR9 and to induce IFN-α production by pDCs in the presence of antimicrobial peptides released from inflammatory cells (82). Conversely, pDCs can also exert tolerogenic functions, as shown in a vascularised graft model, in which pDC depletion or prevention of pDC lymph-node homing inhibited regulatory T-cell differentiation and tolerance induction, whereas adoptive transfer of tolerised alloantigen-presenting pDCs induced regulatory T-cell development and prolonged graft survival (83). Thus, the role of this DC subtype in atherosclerosis remains to be conclusively explored.
Concluding remarks

Given the remarkable role of immunity in atherosclerosis, the targeting of its cellular constituents appears to harbor the possibility for new therapeutic approaches to attenuate the disease process. However, atherosclerosis is not a homogenous entity but occurs with different characteristics at different locations of the vascular tree and encompasses distinct pathogenetic mechanisms, e.g. in stable versus unstable and acute disease. Moreover, the mechanisms of atherogenesis under conditions of severe metabolic disorders, such as familial hyperlipidaemia or as in Apoe<sup>−/−</sup> or Ldlr<sup>−/−</sup>-mice, may markedly differ from more clinically common settings of mild metabolic disorders.

Monocytes have been appreciated as central players in atherosclerosis. Given that some vascular DCs represent their progeny, it will be important to further understand the mechanisms of their recruitment and the signaling cues involved in their differentiation. In addition, precursors of lesional DCs not derived from monocytes remain to be defined. Vascular DCs contribute to plaque burden by accumulating lipids and by controlling cholesterol metabolism by yet unknown processes. In addition, DCs may promote local antigen contact, T-cell instruction in the vessel wall and function to recruit T cells, but may also egress from lesions (►Fig. 1). However, T-cell responses affecting plaque growth seem to be primarily systemically modulated by DCs within lymphoid organs. Further studies will be required to determine at which stage of lesion progression or degree of hyperlipidaemia such mechanisms would amount to pro-atherogenic or atheroprotective effects, and how this may modulate pro-inflammatory versus tolerogenic DC functions. Notably, DC-based vaccination strategies would amount to pro-atherogenic or atheroprotective mechanisms during the stage of lesion progression or degree of hyperlipidaemia such as in Apoe<sup>−/−</sup> or Ldlr<sup>−/−</sup>-mice, may markedly differ from more clinically common settings of mild metabolic disorders.

Conflict of interest

None declared.

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