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Review

Foam cell formation: A new target for fighting atherosclerosis and cardiovascular disease

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ABSTRACT

During atherosclerosis, the gradual accumulation of lipids into the subendothelial space of damaged arteries results in several lipid modification processes followed by macrophage uptake in the arterial wall. The way in which these modified lipoproteins are dealt with determines the likelihood of cholesterol accumulation within the monocyte-derived macrophage and thus its transformation into the foam cell that makes up the characteristic fatty streak observed in the early stages of atherosclerosis. The unique expression of chemokine receptors and cellular adhesion molecules expressed on the cell surface of monocytes points to a particular extravasation route that they can take to gain entry into atherosclerotic site, in order to undergo differentiation into the phagocytic macrophage. Indeed several GWAS and animal studies have identified key genes and proteins required for monocyte recruitment as well cholesterol handling involving lipid uptake, cholesterol esterification and cholesterol efflux. A re-examination of the previously accepted paradigm of macrophage foam cell origin has been called into question by recent studies demonstrating shared expression of scavenger receptors, cholesterol transporters and pro-inflammatory cytokine release by alternative cell types present in the neointima, namely; endothelial cells, vascular smooth muscle cells and stem/progenitor cells. Thus, therapeutic targets aimed at a more heterogeneous foam cell population with shared functions, such as enhanced protease activity, and signalling pathways, mediated by non-coding RNA molecules, may provide greater therapeutic outcome in patients. Finally, studies targeting each aspect of foam cell formation and death using both genetic knock down and pharmacological inhibition have provided researchers with a clearer understanding of the cellular processes at play, as well as helped researchers to identify key molecular targets, which may hold significant therapeutic potential in the future.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide, and accounts for 45% of all deaths in Europe (*European Cardiovascular Disease Statistics 2017*). It encompasses a wide range of pathologies including coronary artery disease, cerebrovascular disease and deep vein thrombosis. Typically, the initial trigger leading to the onset of these conditions is characterised by the steady accumulation of lipids, immune cells and later fibrous tissue to the inner lining of arterial walls experiencing turbulent blood flow and high sheer stress. Increased intimal thickening may eventually lead to reduced or complete occlusion of blood flow to vital organs such as the heart and brain, resulting in myocardial infarction (MI) or stroke [1], respectively. One of the key processes responsible for the development of atherosclerosis is the formation and accumulation of foam cells within the lipid-rich subendothelial space of the affected artery. Monocytes attracted to the area will differentiate into tissue macrophages capable of taking up modified lipoproteins in an attempt to clear the neointima of hazardous material [2]. Lipid metabolism by macrophages is marked by three different processes; cholesterol uptake, esterification and efflux. Unfortunately, dysregulation of these lipid metabolic pathways results in the formation of lipid dense macrophages, termed 'foam cells'. Over the course of atherosclerosis these cells will accumulate within the arterial lining and a characteristic 'fatty streak' will be apparent along the arterial wall in early atherosclerotic lesions [3]. As foam cells inhabit this space, they begin to carry out a number of pro-atherogenic functions, including the release of matrix degrading enzymes, leading to a greater likelihood of plaque rupture and consequently blood vessel occlusion.

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As such, a significant amount of research has been carried out to understand key processes occurring within the arterial intima including monocyte/macrophage differentiation, cholesterol metabolism as well as non-myeloid cell contributions to the foam cell population. Moreover, pharmacological interference of foam cell protease activity and non-coding RNA (ncRNA) function has been investigated for their therapeutic potential. Information gleaned from genome wide association studies (GWAS), genetic animal models and pharmacological inhibition studies, in both humans and mice, have been instrumental in our quest to determine the best candidate for the prevention of foam cell formation during atherosclerosis.

Since the first description of plaque formation within the aortic walls of rabbits, by Ignatowski in 1908, many scientists have attempted to characterise the atherosclerotic process using mice, pigs, and non-human primates [4]. The description by Cookson in 1970 of 'the macrophage foam cell' as 'an extremely active phagocyte which rapidly achieves a large size', has paved the way for intense investigations into the processes responsible for its formation. Moreover, its eventual demise within the atherosclerotic lesion has also been of great interest within the scientific community, as upon degeneration it 'forms a considerable portion of the gruel core of older plaques' [5]. The plethora of studies, describing the processes and mechanisms at play, leading to the life and death of the foam cell have been of immeasurable benefit to the wider field of cardiovascular medicine, not only by informing future pharmacological treatments but also current clinical practice. As such, this Review will attempt to provide an up-to-date account of foam cell formation and death within the atherosclerotic lesion, in order to understand where future therapeutic strategies may lead in our quest to halt the damaging consequences of atherosclerosis in CVD.

2. GWAS findings relating to foam cell formation in atherosclerosis

GWAS have been used within the medical sciences since 2007, as the development of DNA sequencing and the further improvement of such techniques allowed those studying complex diseases to see genotype to phenotype similarities for the first time. This has enabled observation of countless interactions between proteins and disease that would otherwise not have been identified. In the instance of atherosclerosis, cellular and protein interactions have been looked into with varied success. As the underlying pathology involves a number of different processes, including low-density lipoprotein (LDL) accumulation, inflammatory signalling and foam cell formation [6], a number of genetic polymorphisms have been identified as possible candidates for future therapeutic intervention.

Since elevated blood lipid and lipoprotein levels are a coronary risk factor for CVD and the formation of foam cells requires LDL cholesterol uptake by macrophages following their retention and oxidation within the vascular wall, it is not surprising that multiple loci associated with lipid synthesis and metabolism have been at the forefront of GWAS studies since its inception [7]. Lipoprotein A has been identified by a number of studies, associated with an increased risk of atherosclerosis and coronary artery disease [8]. Similarly, loci for the LDL receptor (LDLR) and proprotein convertase subtilisin/kexin 9 (PCSK9), involved in the degradation of LDLR [9] were reported to have strong associations for CAD in the large CARDIoGRAM study [10].

The LDLR related protein 6 (LRP6) gene locus on chromosome 12p13 has also been identified as a regulator of the atherosclerotic phenotype [11], with variants in the gene showing relation to increased levels of plasma LDL and CVD. These traits may be due to the locus' role within the Wnt signalling pathway which influences not only vascular development but also glucose and lipid metabolism [12]. The same finding was reproduced and identified LRP6 and myocyte enhancer factor 2A as additional associated genes in further studies [13]. Non-coding variants on chromosome 1p13 have also been identified and shown to enhance liver-specific expression of Sortilin1, which, when replicated in mice, led to marked changes in total plasma cholesterol and LDL-C levels [14]. Conversely, individuals carrying the genetic polymorphisms for ATP-binding cassette (ABC) transporters G8 (ABCG8) gene, which works in concert with ABCG5 to inhibit dietary absorption of cholesterol and promote efflux back into the gut lumen, show a 24% reduction in cholesterol uptake, pointing to a novel mechanism through which hyperlipidemic blood profiles may be lowered in future [15]. Similarly, GWAS studies have shown a decreased risk of coronary heart disease (CHD) in carriers of ApoE alleles ε2, associated with lower plasma cholesterol levels, whereas carriers with the ε4 polymorphism genotype, have an increased risk of CHD with higher circulating cholesterol levels [16, 17].

Finally, whilst many loci identified through GWAS are associated with lipid synthesis and uptake, several additional loci associated with CAD and MI have been identified that are not involved in modulating circulating levels of LDL cholesterol but rather alternative processes required for foam cell formation. For instance, the locus for C-X-C motif chemokine 12 (CXCL12) has been identified in several GWAS studies associated with CAD and MI [18]. Indeed, elevated plasma levels of CXCL12 are detected in patients with acute coronary syndromes (ACS). Moreover, an important role for CXCL12 in monocyte to macrophage differentiation has been elucidated [18, 19], thus providing additional insight into novel disease pathways, as well as highlighting future clinical biomarkers for CAD. Beyond specific mutations with known function in the pathological process, there have also been discoveries of variance in loci with unknown function at the time of their discovery. Some of these are highly significant, such as the K469E and G241R mutations in the Intercellular Adhesion Molecule 1 (ICAM-1) gene which are associated with an increased risk of ischemic heart disease and MI [20]. Consequently, we are able to see the influence genetics has within the pathological process of atherosclerosis. As discussed, there are clear associations between both genetic mutations detected within GWAS studies and development of atherosclerosis. A lot of work has been focused on the findings from broad GWAS studies to identify the significance of some variants and whether this could lead to novel therapeutic approaches to treating the condition. Since several of the aforementioned GWAS findings point to specific alterations at the genetic level that are responsible for key processes involved in foam cell formation, such as monocyte/macrophage recruitment and cholesterol metabolism, it stands to reason that future randomised clinical trials (RCT) may benefit from using foam cell formation as a further clinical endpoint to access the efficacy of future treatments.

3. Strategies targeting monocyte/macrophage differentiation and phenotypes to prevent foam cell formation and atherosclerosis

3.1. Monocyte recruitment

Atherosclerosis involves the steady accumulation of lipoproteins, bearing cholesterol, in arteries at sites of endothelial disturbance. Once there, these lipoproteins will undergo a series of enzymatic and non-enzymatic modifications, including oxidation of LDLs [21], resulting in the aggregation and fusion of vast amounts of oxidised LDL (oxLDL) in these regions [22]. Monocytes, responding to monocyte chemoattractant protein-1 (MCP-1) [23] released by damaged endothelial cells, migrate to these sites and attempt to remove oxLDL present, which if left unchallenged, induces cellular apoptosis and inflicts DNA damage through reactive oxygen species (ROS) release [24, 25].

Several other cytokines and chemokines regulate the influx of monocytes and are associated with atherosclerotic disease progression including IL-8, chemokine (C-C motif) ligands 3, 4 and 5 (CCL3, CCL4 and CCL5) [26–28]. Indeed single nucleotide polymorphisms (SNPs), rs1746048 and rs501120, at chromosome 10q11, upstream of the gene encoding inflammatory chemokine CXCL12, have been identified as coronary artery disease (CAD) risk alleles, pointing to the disturbance

Table 1
Monocyte/macrophage surface markers and inhibitions.

Species	Cell surface marker	Ligand	Inhibition/Deletion studies	Ref.
Mouse	**CCR2**	MCP-1	siRNA-mediated nanoparticle CCR2 gene silencing reduces inflammatory monocyte ($Ly6C^{high}$) accumulation in atherosclerotic plaques	[56]
Mouse/Human	**CCR5**	CCL3 (MIP-1α) CCL4 (MIP-1β) CCL5 (RANTES)	Pharmacological inhibition with CCR5 antagonist, maraviroc, reduces inflammatory cell recruitment in $ApoE^{-/-}$ mice	[57, 58]
Mouse/Human	**CD43**	(*in vitro*) ICAM-1, E-selectin, MHC class I	Anti-CD43 monoclonal antibody, L11, inhibits monocyte to endothelial cell interactions and prevents enhanced monocyte adhesion in atheroprone regions in rabbits fed high cholesterol diet.	[59–63]
Mouse/Human	**CD14**	Lipopolysaccharide (LPS)	siRNA-mediated CD14 knock down blocked LPS-induced oxLDL uptake in bone marrow-derived primary macrophages	[64]
Mouse/Human	**CD16**	IgG1, IgG2c, IgG2b	CD16 (FcRIII) knock down reduces arterial lesion formation in $LDL^{-/-}$ mice fed a high fat western diet, as a result of increased IL-10 levels due to an expansion in the CD4 T cell population	[65]

of a regulatory region upstream of this particular chemokine that leads to an increased CAD risk [29]. Studies demonstrating hypocholesteraemia-induced monocytosis in mice, have offered numerous chemoattractants as potential targets for preventing monocyte recruitment, including combined cytokine inhibition for CCL2, CXCR1 and CCR5 as well as macrophage colony-stimulating factor (M-CSF) [30], whereby genetic inactivation of genes encoding these chemoattractants results in smaller and less advanced atherosclerotic lesions in $ApoE^{-/-}$ mice [31, 32]. Further study also showed that increased cell survival, continued cell proliferation, and impaired Ly-$6C^{hi}$ to Ly-$6C^{lo}$ conversion are the underlying mechanisms of hypercholesterolemia-associated monocytosis [33]. Therapies targeting specific chemokine signalling pathways may help to limit monocytes from accessing the subendothelial space and providing a continual source of macrophages for foam cell formation [34]. For instance, in a murine model of atherosclerosis, treatment with the antagonist for CXCR3 (CXC chemokine receptor 3), NBI-74330, reduced atherosclerotic lesion size in mice [35]. Using a thioglycollate-induced peritonitis model of inflammation, the authors observed a decline in leukocyte migration, most notably macrophage and T cell recruitment following treatment with the CXCR3 antagonist. Using the same animal model, treatment with a variant of the chemokine, CCL5, led to reduced monocyte rolling and arrest, and therefore monocyte migration to the subendothelial space [36]. It is worth noting that in both studies, interference of chemokine signalling affected multiple inflammatory processes in the atheroma such as increased VSMC recruitment, as well as reduced secretion of pro-inflammatory cytokines and matrix metalloproteinases (MMPs). Whilst reduced monocyte migration may be partly responsible for the overall reduction in atherosclerosis lesion size, these chemokines are not monocyte-specific [26, 37] and therefore may be acting on alternate processes, independently of the monocyte population. Moreover, compensatory upregulation of other chemokines [38] and/or chemokine receptors on alternative cell types [39] provide new routes for monocyte extravasation and consequently impede efforts to identify key, monocyte-specific chemokines that may be targeted therapeutically in order prevent monocyte migration.

Furthermore, in order for monocytes to travel into the subendothelial space and undergo differentiation into macrophages, and eventually foam cells, they also require a distinct set of cell surface proteins to enable their transmigration. Firstly, expression of selectin proteins on both the monocyte and endothelial cell surface enables the monocytes to tether and roll along the surface of the endothelial layer. The interaction between integrins with fucosylated and sialyted carbohydrates, expressed across both cell surfaces, followed by chemokine-driven integrin activation leads to adherence of the monocyte to the endothelial cell surface via cellular adhesion molecules (CAMs) allowing them to begin migration [40]. Animal studies have shown successful reduction in atherosclerosis development in $LDR^{-/-}$ mice, either through knock down of VCAM-1 [41] or through pharmacological inhibition with the natural antioxidant AGI-1067 [42]. Unfortunately, these findings have not translated well into humans, as seen with the Aggressive Reduction of Inflammation Stops Events (ARISE) study whereby administration of AGI-1067 to patients with acute coronary syndrome showed no improvement in primary endpoints such as cardiovascular death, MI, stroke, or coronary revascularisation [43]. Similarly several other VCAM-1 inhibitors have also been considered including HUN-7293 [44] and CAM741 [45, 46]. While targeting monocyte recruitment, through inhibition of cytokines, has shown some degree of success, it is clear that current CAM inhibition methods are not effective, and hence do not offer a plausible means of reducing foam cell formation in atherosclerosis. Moreover, differences in monocyte classification, differentiation and lipid uptake between macrophages of different species, in the isolation of the laboratory versus *in situ*, compounds our efforts to halt the process of monocyte recruitment at sites of foam cell formation [47–50].

3.2. Monocyte classification

The linear view of macrophage-foam cell origin describes the differentiation of a precursor, bone-marrow derived monocyte which, having travelled through the blood, homes to the arterial wall and differentiates into tissue macrophages [51, 52] or alternatively, dendritic cells [53, 54]. Two dichotomous monocyte subpopulations were first described in mice [47], namely the classical 'tissue-resident' monocyte (Gr1/$Ly6C^{high}$) and the non-classical 'blood-resident' monocyte (Gr1/$Ly6C^{lo}$). The classical monocyte population is distinguished by $CX3CR1^{lo}$, $CCR2^{+}$, $CCR5^{hi}$, $CD43^{lo}$ expression on their cell surface, whilst the non-classical monocyte is characterised by $CX3CR1^{hi}$, $CCR2^{-}$, $CCR5^{lo}$, $CD43^{high}$ cell surface expression. Similarly, human monocytes are described using a different set of cell surface receptors, with classical monocytes expressing $CD14^{++}$ $CD16^{-}$, and non-classical monocytes expressing $CD14^{+}CD16^{++}$. Several of these cell surface markers have been silenced or knocked down in mice to determine their atheroprotective potential, as listed in Table 1.

Of interest, classical monocytes, which are usually characterised by low CXCR3 expression, require its expression to navigate successfully into the plaque, alongside chemokine receptors such as CCR5 and CCR2, whereby CCR2 appears to play a dual role in regulating both monocyte exit from bone marrow as well as monocyte entry into plaques. Non-classical monocytes, on the other hand, require CCR5 expression, which is consequently upregulated in atheroprone regions of murine arteries [55].

Whilst the number of 'non-classical' monocytes in the circulation is correlated with plaque lesion size, it is the 'classical' or 'inflammatory' monocytes that are recruited to these sites at a much greater rate [30, 55]. Indeed, in a hypercholesterolemia-associated monocytosis murine model, $Ly6^{hi}$ monocytes levels were found to be substantially elevated with fewer conversions into the $Ly6^{lo}$ population, and instead had undergone rapid trans-activated endothelium migration and differentiation into lesional macrophages [33]. Atherosclerosis, however, can only

be maximally inhibited when the entry of $Ly6^{hi}$ and $Ly6^{lo}$ monocytes is simultaneously blocked [55], highlighting the need to target both in atherogenesis.

Monocyte classification studies have since highlighted the existence of a third 'intermediate' subpopulation of monocytes existing at much lower frequency in mice ($Gr1^{high}$,$CD43^{high}$) and in humans ($CD14^{++}CD16^{+}$) [66, 67]. Whilst some studies have revealed an angiogenic role for these cells [68, 69], others argue that this subpopulation simply represents cells in a transient state undergoing differentiation from their developmental precursor, the 'classical' monocyte into a 'non-classical' monocyte [70, 71]. As more research is carried out on 'intermediate' $CD14^{++}CD16^{+}$ monocytes, clinical findings reveal higher rates of cardiovascular events and death in patients with higher circulating numbers of this monocyte subtype [72, 73], and a faster inflammatory response compared to the classical and non-classical monocyte [74], suggesting these intermediate cells possess a unique set of proatherogenic properties and represent a monocyte subtype in their own right [75].

3.3. Macrophage phenotypes

Once monocytes enter the subendothelial space they respond to their microenvironment by differentiating into macrophages and dendritic cells, due to high levels of M-CSF and granulocyte/macrophage colony stimulating factor (GM-CSF), respectively. Enlargement of their cytoplasm and increased expression of CD68 are characteristic of monocytes undergoing macrophage differentiation [40]. Like their precursors, macrophages fall into a number of different categories based on their cell surface expression as well as their functional role within the plaque. These 'macrophage phenotypes' were originally described to reflect the T helper cell classification system with M1 'pro-inflammatory' macrophages corresponding to Th1 helper cells, and M2 'anti-inflammatory' macrophages corresponding to Th2 helper cells, with further subdivisions of the M2 family [76]. M1 macrophages can be 'classically' activated with interferon γ (IFNγ), tumor necrosis factor α (TNFα) and/or lipopolysaccharide (LPS) [77]. They have been largely studied *in vitro* and secrete pro-inflammatory cytokines; interleukin-6 (IL-6), IL-1β and TNF-α, as well as nitric oxide (NO) and reactive oxygen species (ROS) [78]. M2 macrophages, are 'alternatively' activated with IL-4 and IL-13 cytokines [79], and are considered to be mainly involved in promoting angiogenesis and tissue repair [80]. Expectedly, transcriptomics and immunohistochemistry analysis of macrophage subset dynamics in successive stages of human atherogenesis showed that M1 and M2 macrophage phenotype markers were overexpressed in human ruptured plaques compared to their adjacent stable control segments. Importantly, M1 macrophages appeared to localise in the rupture-prone shoulder region of unstable plaques taken from patients undergoing endarterectomies, whereas M2 macrophages are numerous in stable plaques and appear to congregate in the adventitia and reside at sites of neovascularisation in advanced atherosclerotic plaques [40, 81]. Indeed overexpression of the signal transducer and activator of transcription 6 (STAT6) in macrophages was shown to promote plaque stabilization by inducing M2 macrophage conversions as well as antagonizing ox-LDL-induced cell apoptosis and lipid deposition in macrophages in $ApoE^{-/-}$ mice [82].

Neither M1 nor M2 macrophages have been identified as the specific precursor to foam cell formation [81], although several studies have shown that M2 macrophages are more susceptible to foam cell formation and exhibit similar pro-inflammatory responses [83–85]. Indeed, activation of a member of the peroxisome proliferator-activated receptor (PPAR) family, PPARγ, an important regulator of lipid uptake by macrophages, was apparent in both M2 macrophages and foam cells, highlighting an overlap in signaling pathways between the two macrophage phenotypes. Nevertheless, whole transcriptome sequencing has revealed a more pro-fibrotic phenotype for murine foam cells exhibiting dendritic-like, antigen presenting properties [86] (Fig. 1).

4. Strategies targeting cholesterol handling and metabolism in macrophages to prevent foam cell formation and atherosclerosis

The trinity of cholesterol handling consists of lipid uptake, cholesterol esterification and cholesterol efflux from the macrophage. Individually, each process will determine the rate of cholesterol accumulation within the cell. As such, studies have shown greater efficacy at slowing down the rate of foam cell formation by targeting more than one process at a time [87], highlighting the existence of compensatory mechanisms within the cell, as well as crosstalk between transporters and enzymes responsible for regulating cholesterol metabolism mediated by several key signaling pathways.

4.1. Macrophage lipid uptake and scavenger receptors

Investigations into scavenger receptor (SR) function began in the 1979 by Brown and Goldstein [88, 89], who showed faster uptake of modified LDLs by macrophages compared to native LDL. Since then, the characterisation of 8 different classes of extracellular receptors [90], capable of recognising and binding to modified lipoproteins for degradation and storage in the cell, now termed 'scavenger receptors', have been identified [91–93]. Several regulators of SR function have been identified within the cell, including MEKK-2 [94], MAP kinases [94, 95] and STAT1 [96]. Whilst lipid uptake appears to be the main SR role responsible for foam cell formation and will be the focus of SR function in this Review, these receptors are multifunctional and have been shown to regulate several inflammatory processes as well. For instance, following oxLDL treatment, CD36 expression-induced toll like receptor (TLR)-4/TLR-6 complex assembly leads directly to NFκB activation, resulting in ROS production and chemokine release [97]. Moreover, reduced cytokine production in macrophages deficient in CD36, has also been observed [98]. Additionally, evidence also suggests a role for SR-As in monocyte migration and adhesion, two key factors responsible for macrophage recruitment and foam cell formation [99]. For a more extensive review on SR biology and function we recommend the reader refers to the following Reviews by Kzhyshkowska et al. (2012) and Greaves and Gordon (2009) [100].

Macrophages internalise modified lipoproteins in the subendothelial space by expressing a unique set of scavenger receptors (SRs), each capable of taking up different forms of modified lipoprotein. For instance, members of the SR-A class, SR-AI and SR-AII are expressed by tissue macrophages and have a strong affinity for acetylated LDL and extensively oxidised LDL [101].There is still some debate as to whether these receptors play a proatherogenic role particularly with regards to foam cell formation. Whilst some studies have shown a reduction in atherosclerotic development in mice following inhibition of SR-A [102, 103], other studies claim the opposite effect. Disruption of exon 4 in the MSR-1 gene, which gives rise to both SR-AI and SR-AII trimeric receptors through alternative splicing, significantly reduced atherosclerotic lesion size in the aortic sinus in the $MSR\text{-}1^{-/-}$ $ApoE^{-/-}$ mice, due to decreased LDL uptake by macrophages in one study [104]. Similar observations were found in $LDLR^{-/-}$ mice [105, 106] but not ApoE3-Leiden mice [107], where an increase in lesion size was observed. This was attributed to a difference in diet used in the study, as well as the, albeit limited, presence of ApoE in their ApoE3-Leiden mouse model which, the authors of study claim, reveals a protective rather than contributory role for SR-A in atherogenesis. Moreover, SR-A gene manipulation studies have shown an unexpected reduction in atherosclerosis development in both $ApoE^{-/-}$ and $LDL^{-/-}$ mice, further confounding our efforts to understand the role of SR-As in foam cell formation [106, 108, 109]. Studies examining another key scavenger receptor in foam cell formation, namely CD36, have largely been carried out in $ApoE^{-/-}$ mice [110–113], and offer similarly perplexing results, with particularly marked differences between genders. Male $CD36^{-/-}ApoE^{-/-}$ double knock out mice ($CD36^{-/-}$ $ApoE^{-/-}$) have significantly smaller atherosclerotic lesions in the

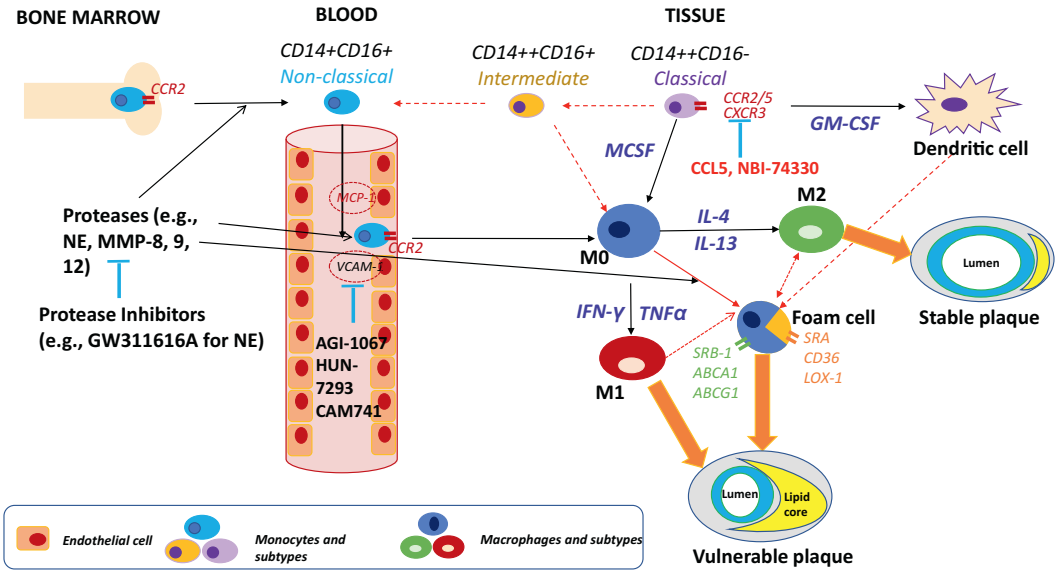

Fig. 1. Strategies targeting monocyte/macrophage differentiation and phenotypes to prevent foam cell formation and atherosclerosis. Current understanding of monocyte/macrophage differentiation and phenotypes, and relevant key molecules for therapeutic targeting was depicted in this schematic illustration. The process of foam cell formation involves the expression of specific chemokine receptors and chemoattractant proteins (red) for monocyte extravasation; cytokines for macrophage differentiation and polarisation (blue), and lipid scavenger receptors (green) and transport carriers (orange) for cholesterol uptake and efflux. Continuous arrows denote the direction of monocyte/macrophage movement and polarisation. Discontinuous arrows denote possible movement and polarisation. Selected key molecules as a therapeutic drug target that has been reported in pre-clinical or clinical studies were also presented here. M0, M1 and M2 indicate uncommitted, M1 and M2 polarized macrophages, respectively; MMP indicates matrix metalloproteinase; RANTES, regulated on activation, normal T cell expressed and secreted; NBI-74330, CXCR3 antagonist; AGI-1067, antioxidant and anti-inflammatory compound; HUN-7293 and CAM741, VCAM-1 inhibitors. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

aortic sinus compared to ApoE$^{-/-}$ single knock out male mice on chow and proatherogenic, Western Diets [112]. However, the same observation could not be made in female CD36$^{-/-}$ApoE$^{-/-}$ mice, who showed no change in aortic sinus lesion size. Conversely, Moore et al. 2005 saw a significant increase in atherosclerotic lesions size in the aortic sinus of male but not female CD36$^{-/-}$·ApoE$^{-/-}$ mice fed a high fat/high cholesterol diet compared to control mice, despite the observed reductions in peritoneal macrophage foam cell numbers [110].

Finally, a third scavenger receptor, lectin-like oxLDL receptor-1 (LOX-1), is upregulated in macrophages and VSMCs isolated from advanced atherosclerotic plaques in humans [114]. Following pro-inflammatory cytokine treatment, macrophages and VSMCs express LOX-1 *in vitro* [115]. Moreover, *in vivo* studies have demonstrated that overexpression of LOX-1 in ApoE$^{-/-}$ mice results in an accelerated atherosclerotic pathology [116], while LOX-1$^{-/-}$LDLR$^{-/-}$ mice developed smaller atherosclerotic lesions sizes on a high fat diet [117] compared to controls, confirming a pro-atherogenic role for this SR in foam cell formation. However, it is worth noting that these investigations were concerned with endothelial LOX-1 expression and as a result, refer to endothelial contributions to atherosclerotic processes. While this does not necessarily exclude foam cell formation, endothelial involvement in atherogenesis is diverse and LOX-1-mediated effects are not strictly limited to lipid uptake [118]. Thus, more studies need to be carried out to understand macrophage-specific LOX-1 expression and whether pharmacological inhibition alone would suffice to prevent lipid uptake by macrophages.

In light of conflicting evidence regarding roles of SRs in foam cell formation, several limitations are apparent when it comes to the study of SRs in macrophages. Firstly, since these studies deal with SRs in isolation, the importance of reciprocal upregulation of other SRs cannot be underestimated [102]. Secondly, each SR has a distinctive affinity for different types of modified LDLs and this must be taken into consideration for *in vitro* investigations [101]. Moreover, uptake of modified lipoproteins by macrophages is not strictly limited to receptor-mediated pathways, but also occurs through alternative routes, such as phagocytosis and pinocytosis [101, 119–121]. Finally, as mentioned previously, expression of all three SRs is not limited to macrophages, but also aortic endothelial cells (ECs) [122] and vascular smooth muscle cells (VSMCs) [123], each of which has shown foam cell potential, and highlights a crucial caveat required when deducing a role for SRs in foam cell formation, from knock down studies where SR deletion is not macrophage-specific. The contributions of other cell types to foam cell formation will be addressed later in this Review.

The competing theories claiming SRs as either pro-atherogenic or anti-atherogenic, highlight not only the difficulty in studying these receptors, but also reveal a complex network involved in the regulation of lipid metabolism that begins with, but is not limited to, lipid uptake. This particular aspect of lipid processing has by no means been fully elucidated, and requires further investigation to understand the true role of each receptor and lipid uptake mechanism involved, to determine whether they can be harnessed to attenuate the rate at which macrophages transition into foam cells.

4.2. Cholesterol esterification

Following cellular uptake, modified lipoproteins are carried to the intracellular lysosomes to be hydrolysed into free cholesterol (FC) and fatty acids. The accumulation of FC in the cell requires another process of re-esterification by the enzyme acylcholesterol transferase 1 (ACAT-1), which allows excess FC to be stored as cholesterol esters (CE) in cytoplasmic lipid droplets budding off the endoplasmic reticulum [87]. Unfortunately, studies attempting to inhibit foam cell formation by targeting ACAT-1 have not been successful. Knock down of ACAT-1 in ApoE$^{-/-}$ and LDLR$^{-/-}$ mice showed no change in atherosclerosis lesion development but instead a rapid onset of dermal xanthoma formation and FC crystal deposits in the brain of these mice, highlighting a novel role for this enzyme in skin and brain cholesterol metabolism [124]. Moreover, pharmacological inhibition of ACAT-1 led to an increase in foam cell formation in murine and rabbit models of atherosclerosis [125], casting doubts on efforts to reduce foam cell formation

via the ACAT-1 route. For cholesterol efflux, CEs must undergo hydrolysis back into FCs by neutral CE hydrolases, such as neutral cholesterol ester hydrolase 1 (Nceh1) and hormone sensitive lipase (LIPE). Unsurprisingly, a study investigating genetic ablation of both enzymes showed an increase in CE accumulation, alongside a decline in cholesterol efflux, from macrophages exposed to acLDL. Moreover, the authors of this study showed an additive effect when both genes were knocked out in macrophages (Nceh1$^{-/-}$LIPE$^{-/-}$), as shown by a 70% increase in CE accumulation compared to controls [126]. The opposite was observed with overexpression of Nceh1, but only when ACAT-1 was downregulated at the same time [127], revealing the need for a multi-targetted approach when it comes to interference of cholesterol storage.

4.3. Cholesterol efflux

The third and final stage of cholesterol metabolism in macrophages is cholesterol efflux, which is mainly mediated by several transporters whose expression relies heavily on the activation of key transcription factors, PPAR and liver X receptor α (LXLRα). PPAR and LXR pathways will be briefly discussed in this Section, for a more in-depth discussion please refer to the following Reviews [128, 129]. ATP-binding cassette transporter 1 (ABCA1), ATP-binding cassette sub-family G member-1 (ABCG1) and SR-B1 mediate the active transport of cholesterol and phospholipids out of the macrophage, for removal by Apolipoprotein A1 (ApoA1) and high density lipoproteins (HDL), as part of reverse cholesterol transport (RCT) system, preventing excessive intracellular cholesterol accumulation, and consequently foam cell formation [130]. Many studies have been carried out investigating the individual transporters but similar to cholesterol uptake, other routes, including passive diffusion, are available for cholesterol movement out of the cell across the cellular membrane [131]. Studies modulating the expression of these transporters have unearthed a confusing relationship with the regards to RCT. Genetic ablation of both ABCA1 and SR-B1 simultaneously resulted in enhanced foam cell accumulation but with no atherosclerotic lesion development [132]. Whereas, overexpression of ABCA1 led to an increase in proatherogenic lipoprotein accumulation with enlarged aortic atherosclerotic lesions [133]. Conversely, knock down studies determined a promotive role for ABCG1 in atherogenesis LDLR$^{-/-}$ mice, which resulted in smaller atherosclerotic lesion sizes [134, 135]. However, further investigations revealed a temporal role for this transporter, with knock down of ABCG1 in early atherogenesis accelerating disease progression but slowing late stage development in LDLR$^{-/-}$ mice [136]. This effect was attributed to the increased incidence of apoptosis that occurs as a result of ABCG1 deficiency [137]. Finally, studies investigating SR-B1 have also generated mixed results, with one suggesting a promotive role for SR-B1 in early atherogenesis, but a protective role in later stages in LDLR$^{-/-}$ mice [138]. However, whilst SR-B1 knock down led to accelerated atherosclerosis in ApoE$^{-/-}$mice [139], RNA-interference of SR-B1 resulted in reduced atherosclerosis in rabbits [140], highlighting a discrepancy across species and experimental techniques.

The expression of the aforementioned cholesterol exporters is largely considered to be under the regulation of the PPAR/LXR signalling axis (Fig. 2). Indeed, atherosclerosis development in LDLR$^{-/-}$ mice treated with PPARα and PPARγ agonists, was reduced due to increased expression of ABCG1 and enhanced HDL-mediated cholesterol efflux, as well as LXR-mediated upregulation of ABCA1, providing a potential therapeutic target to promote cholesterol efflux and reduce foam cell formation. On the other hand, PPARβ did not show any changes to atherosclerotic development in these mice, despite the fact that activation of PPARβ/δ has been shown to increase SR-A1 and CD36 expression and therefore lipid uptake in macrophages [141, 142].The differences between PPAR subtypes must be stressed with regards to studying cholesterol metabolism. Of interest, studies conducted on human macrophages showed that LXLR and ABCA1 expression is reduced in M2 macrophages, and consequently, cholesterol efflux is prevented in M2 macrophages, possibly revealing how foam cells materialise from M2 macrophages [143].

Of note, PPARs are also able to regulate inflammatory processes through inhibition of MCP-1, required for monocyte recruitment [144], with one study demonstrating downregulation of its receptor, CCR2, in monocytes treated with glitazone, a PPAR agonist, currently used in the treatment of type II diabetes [145]. Similarly, PPAR agonists have also shown successful suppression of pro-inflammatory cytokines both in animal models of atherosclerosis and in human clinical trials [146]. Studies investigating these two nuclear receptors have shown they are not only capable of transcriptionally regulating genes involved in lipid metabolism and trafficking, but also in some cases, provide a protective role against foam cell formation, either by promoting expression of lipid transporters, or by preventing immune cell recruitment, marking these as a highly attractive therapeutic targets for regulating foam cell formation.

5. Strategies targeting foam cell apoptosis, secondary necrosis and efferocytosis in macrophages to prevent atherosclerosis

The formation of a foam cell, via oxLDL uptake, initiates various apoptotic pathways leading to its demise within the lesion [147]. Numerous studies have shown that oxLDL can trigger activation of the caspase cascade via the mitochondrial apoptotic pathway [148–150], proteasomal dysfunction [151] as well as sustained cytosolic calcium accumulation [152, 153], resulting in activation of degradative enzymes and toxic cell injury. Thus, attempts to slow foam cell death may provide potential therapeutic strategies for slowing atherosclerosis progression [154]. Interestingly, genetic inhibition of the proapoptotic protein, Bax, in macrophages led to reduced apoptosis in LDL$^{-/-}$ mice but with accelerated atherosclerosis [155]. Similarly, knock down of the *a*poptosis inhibitor expressed by macrophages, AIM, resulted in accelerated apoptotic death of macrophages with an overall decrease in atherosclerotic lesion size, revealing a proatherogenic effect of inhibiting apoptosis in early atherogenic lesions [156]. Conversely, enhanced apoptosis via Bcl-2 deficiency resulted in greater plaque necrosis in advanced atherosclerotic lesions of female ApoE$^{-/-}$ mice [157]. Thus, these studies highlight a time-dependent outcome when targeting cell apoptosis pathways for atherosclerosis treatment. Moreover, defective clearance of these 'post-apoptotic' foam cells, said to be undergoing 'secondary necrosis' [158, 159], has long been considered the defining feature of necrotic core formation and a major cause of enhanced inflammation within the region [160, 161]. Of note, uptake of apoptotic cells but not necrotic cells was shown to alleviate cholesterol loading in neighbouring 'healthy' macrophages, via extracellular phosphatidylserine (PS) expression during uptake, resulting in increased ABCA1 expression and thus cholesterol efflux [162]. Thus, clearance of apoptotic cells prior to undergoing necrosis, may prove beneficial for preventing the development of 'vulnerable plaques' [163]. Several attempts have been made to promote apoptotic macrophage efferocytosis, by activating nuclear receptor signalling pathways using LXR ligands [164, 165], glucocorticoids [166, 167], and activating PPARγ pathways [168]. Thus, whilst a multitude of therapeutic options are being considered for promoting apoptotic cell clearance, strategies aiming to prevent cellular apoptosis are met with more consideration to ensure only advanced atherosclerotic lesions are targeted [169].

6. Other strategies to inhibit foam cell formation and function to prevent atherosclerosis

As discussed previously, several different pharmacological agents have been tried and tested to determine their use as inhibitors of foam cell formation and enhancers of foam cell clearance. These have involved inhibiting processes that lead up to the formation of the foam

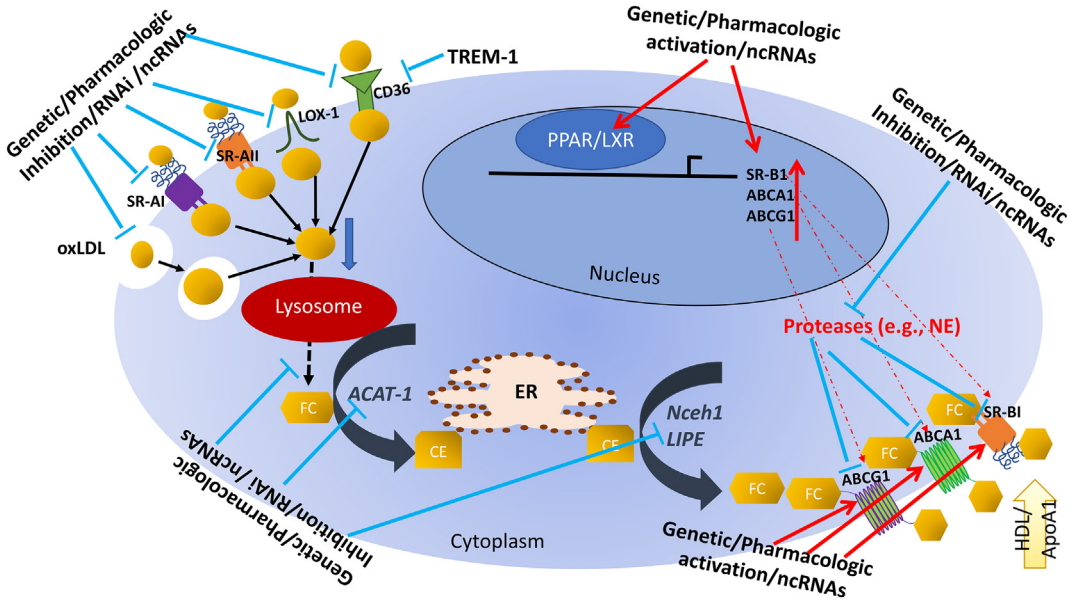

Fig. 2. Illustration summarising cholesterol metabolism within the macrophage and possible genetic/pharmacologic strategies targeting cholesterol metabolism in macrophage. Oxidised LDL (oxLDL) can be taken up by transporters; SRA-I/II, CD36 and LOX-1 or phagocytosis/pinocytosis, and converted to free cholesterol (FC) by lysosomal degradation. FC is stored at the endoplasmic reticulum as cholesterol esters (CE) generated by ACAT-1 enzyme. CE can then be converted back into FC by nCEH enzyme for reverse cholesterol transport via proteins ABCG1, ABCA1 and SRB-1, under the regulation of the PPAR/LXY signalling axis. Potential strategies (e.g., genetic/pharmacologic, RNA interference and/or non-coding RNAs) could be utilised to inhibit cholesterol uptake and esterification or promote cholesterol efflux, respectively, to control foam cell formation and prevent atherosclerosis. ncRNAs and RNAi indicate non-coding RNAs and RNA interference, respectively.

cell, including cholesterol accumulation within the macrophage, as well as recruitment of the macrophage or a macrophage-like cell to the neointima, as well as regulating apoptosis and clearance to offset the development of a necrotic core within the lesion. Some studies have shown great success by targeting both facets of foam cell formation simultaneously. For example, pharmacological inhibition of the triggering receptor expressed on myeloid cells (TREM-1) was found to reduce lipid uptake, by downregulating CD36 expression, and monocyte recruitment to atherosclerotic lesions resulted in a 60% reduction in atherosclerotic lesion size [170]. More recently, several other treatment strategies have been investigated for their use in preventing foam cell formation using statin therapy, as well as foam cell function using protease inhibition and non-coding RNA signalling to reveal novel signalling pathways which may provide clinicians with even more scope for targeting foam cell formation during atherosclerosis (Table 2).

6.1. Modulating macrophage function and foam cell formation using statins

Besides their primary use as inhibitors of cholesterol synthesis via the HMGCoA reductase pathway [171], it has long been accepted that statins exert many pleiotropic effects in patients with cardiovascular disease including but not limited to, improved endothelial function through eNOS activation [172, 173], reduced oxidative stress [174, 175] and enhanced plaque stability [176]. In addition to which, statin treatment has been shown to disrupt key processes required for foam cell formation by disrupting pro-inflammatory pathways and dysregulated cholesterol handling within macrophages [177, 178].

Evidence for anti-inflammatory actions of statins are numerous, including hypercholesterolemia-associated Ly-6C^{hi} monocytosis with statin administration in atherosclerotic mice [33], and the clinical phenomenon of rebound inflammation following statin withdrawal in patients with acute coronary syndromes [179]. Moreover, the JUPITER trial proved an important anti-inflammatory role for statins, independent of lipid control, by revealing a marked decrease in the levels of the inflammatory biomarker C-reactive protein (CRP), an important predictor of cardiovascular events, in normolipidaemic patients with elevated CRP levels [180].

Similarly, fluvastatin treatment has been shown to reduce macrophage accumulation in carotid arteries of hypercholesteraemic rabbits, without affecting cholesterol levels [181]. Studies revealing statin-mediated downregulation of cellular adhesion molecules [182, 183] and integrins [184], as well upregulation of chemokine receptors responsible for promoting macrophage emigration, such as CCR7 [185], reveal a number of ways in which statins reduce macrophage accumulation and, by potential default, foam cell formation in the atherosclerotic plaque.

Importantly, statin treatment not only reduces LDL available for oxidative modifications, responsible for triggering SR expression, but also targets a number of signalling pathways involved in cholesterol uptake and efflux through PPAR [186] and RhoA/ROCK signalling pathways [187, 188]. In addition to which, statins have also been shown to promote macrophage efferocytosis by deactivating Rho GTPases responsible for preventing uptake of apoptotic cells by macrophages [189, 190]. However, statins' inhibitory effect on Rho and Ras GTPases, resulting in SR-A downregulation, is reversible with the addition of mevalonate metabolites [191], otherwise generated through the HMGCoA reductase pathway, reinforcing their original mechanism of inhibition. It is clear from these studies, predominantly conducted in mice, that statin therapy can have far-reaching consequences on foam cell formation. Thus, these drugs should continue to be investigated in humans to provide further insight into the molecular processes occurring within the macrophage, specifically with regards to foam cell formation, accumulation and death within the atherosclerotic plaque.

6.2. Modulating macrophage function and foam cell formation by matrix metalloproteinase inhibition

Once macrophages have established themselves as foam cells within the ever-growing atherosclerotic plaque, they begin to take on a profibrotic phenotype by releasing higher levels of chemokines and proteases. For instance, release of matrix metalloproteinase-8 (MMP-8) promotes monocyte recruitment and macrophage M2 polarisation, by degrading a sequestering protein of TGF-β, fibromodulin, thereby increasing TGF-β bioavailability in the surrounding media [192].

Table 2
Possible targets for inhibition of foam cells and prevention of atherosclerosis.

Drugs/targets	Experimental model	Signal pathway/substrate/target gene	Outcome	Possible therapeutic strategies	Ref
I. Statins					
Fluvastatin	Carotid injury-induced lesion in male rabbits on cholesterolrich diet-	Reduced tissue factor expression	Reduced macrophage infiltration No effect on plasma cholesterol levels, nor macrophage proliferation or apoptosis	Administration to patients post-vascular injury to aid recovery and slow intimal hyperplasia	[181]
Rosuvastatin	Transplant-based mouse model of atherosclerosis regression	Increased CCR7 expression	Enhanced macrophage emigration from plaques	Administration to patients with pre-existing early atherosclerotic plaques prior to the macrophage apoptosis and development of necrotic core	[185]
Atorvastatin		Decrease in MCP-1	Decrease in atherosclerosis		
Cortistatin	$ApoE^{-/-}$ mice on western diet	Decreased selectin and ICAM-1 expression on endothelium	Impaired macrophage migration	Administration to patients with ongoing vascular disease to prevent new or recurring neointima formation	[186]
		Increased PPAR-γ- induced ABCA1 expression	Reduced foam cell formation		
		Enhanced cholesterol efflux	Decreased plaque formation		
disease to prevent new or recurring neointima formation	THP-1-derived macrophages treated with acetylated LDL and cholesterol	Decreased RhoA and increased PPARγ and LXR –mediated ABCA1 and ABCG1 expression	Enhanced cholesterol efflux Reduced foam cell formation	Administration to patients with ongoing vascular disease to prevent new or recurring neointima formation	[188]
Lovastatin	THP-1-derived macrophages	Decreased SR-A expression, reversible with addition of mevalonate metabolites	No recorded effects on foam cell formation	Possible added benefit of current lovastatin treatment in hyperlipidemic patients	[191]
II. MMPs					
MMP-1 *(Interstitial collagenase)*	Macrophage-specific overexpression of MMP-1 in $ApoE^{-/-}$ mice	Diminished content of fibrillar collagen	Reduced atherosclerotic lesion size High MMP-1 expression also associated with foam cells in shoulder regions of vulnerable plaques [220] and increased incidence of MI [221]	Administration of therapeutic MMP-1 monoclonal antibody, or Target delivery of MMP-1 specific inhibitor to atherosclerotic lesion	[222]
MMP-2 *(Gelatinase A)*	Carotid artery ligation in MMP2 knock-out mice	Matrigel	Attenuated SMC migration Reduced lesion size	Administration of therapeutic MMP-2 monoclonal antibody, or Target delivery of MMP-2 specific inhibitor to atherosclerotic lesion	[223]
MMP-3 *(Stromelysin-1)*	MMP-3 knock out in $ApoE^{-/-}$ mice	fibrillar collagen, elastic lamina	Increased macrophage/foam cell accumulation Increased lesion size but reduced aneurysm formation	The activity and level of MMP3 should be fine balanced; its activation may represent a beneficial effect for atherosclerotic plaque, but harmful for aneurysm	[202, 224]
MMP-7 *(Matrilysin)*	MMP-7 knock out in $ApoE^{-/-}$ mice	Unknown	Increased VSMC population No effect on plaque growth or stability	No clear benefit	[202]
MMP-8 *(Collagenase 2)*	MMP8 knock out in $ApoE^{-/-}$ mice	Angiotensin I (Ang I) to Ang II; Reduced VCAM-1 expression in endothelium	Reduced macrophage accumulation & leukocyte migration	Administration of therapeutic MMP-8 monoclonal antibody, or Target delivery of MMP-8 specific inhibitor to atherosclerotic lesion	[192, 199, 225–227] [198]
		ADAM10/E-Cadgerin Ang II/PECAM-1	Reduced stem cell recruitment to plaque Decreased angiogenesis		
		ADAM10/N-Cadherin	Reduced VSMC migration & proliferation		
		Fibromodulin/ TGF-β activation	Promotes macrophage differentiation and M2 macrophage polarization Reduced lesion size Increased carotid MMP-8 plaque levels are associated with an unstable plaque phenotype, and high MMP-8 levels in the carotid plaque are associated with the occurrence of systemic cardiovascular outcome during follow-up.	Administration to patients undergoing carotid endarterectomy (CEA) to prevent new or recurring systemic cardiovascular events	

(*continued on next page*)

Table 2 (*continued*)

Drugs/targets	Experimental model	Signal pathway/substrate/target gene	Outcome	Possible therapeutic strategies	Ref
MMP-9 *(Gelatinase B)*	MMP9$^{-/-}$knock out in ApoE$^{-/-}$ mice		Increased macrophage accumulation, accelerated lesion growth	Not clear	[202]
		Collagen	Reduced macrophage and collagen content, decreased lesion size		
MMP-12	MMP12$^{-/-}$knock out in ApoE$^{-/-}$ mice		Decreased lesion size and reduced buried fibrous layers	No clear benefit	[202]
		Elastin	Reduced elastin degradation, No change in lesion growth, macrophage or collagen content		
MMP-13 *(Collagenase 3)*	MMP13$^{-/-}$ knock out in ApoE$^{-/-}$ mice	Interstitial collagen	No change in lesion growth, macrophage or VSMC content	No clear benefit	[228]
MMP-14	MMP14$^{-/-}$→LDLR$^{-/-}$ mice		No change in lesion growth, macrophage or VSMC content	No clear benefit	[229]
III. Neutrophil elastase	NE$^{-/-}$ApoE$^{-/-}$ mice & NE pharmacological inhibition (GW311616A)	ABCA1 transporter	Enhanced cholesterol efflux Decreased foam cell formation Reduced lesion size	Administration of therapeutic NE monoclonal antibody, or Target delivery of NE specific inhibitor (e.g., GW311616A) to atherosclerotic lesion	[203]
IV. Non-coding RNAs					
miR-33	miR33 overexpression	ABCA1 downregulation	Reduced cholesterol efflux Foam cell formation in mouse and human macrophages	Targeted inhibition of both miR-155 and miR-33	[204, 205]
miR-486	miR486 mimic/inhibitor transfection	histone acetyltransferase-1 (HAT-1)/ ABCA1	Modulating cholesterol efflux and foam cell formation in THP-1 cell macrophages	Treatment with miR486 inhibitor to promote reverse cholesterol transport	[206]
miR-27a/b	miR27a/b mimic	ABCA1 3'UTR mediated downregulation LPL ACAT-1	Reduced conversion of 'cholesterol ester to free cholesterol' & decrease in cholesterol uptake by THP-1-derived foam cells	Treatment with miR27a/b mimic to prevent cholesterol uptake and conversion of macrophages into foam cells	[213]
miR-590	miR-590 mimic	LPL 3'UTR mediated downregulation	Reduced foam cell formation and pro-inflammatory cytokine release in THP-1-derived foam cells	Treatment with miR-590 mimic to promote anti-inflammatory effects and lipid accumulation in macrophages	[214]
miR134	miR134 mimic	ANGPTL4 UTR' mediated downregulation	Increased LPL activity Increased lipid accumulation	Targeted inhibition of raised miR134 levels in atherosclerotic macrophages to prevent lipid accumulation	[215]
DYNLRB2-2 (lincRNA)	LincRNA *DYNLRB2-2* overexpression	GRP119/ABCA1; Increased ABCA1 expression	Increased cholesterol and phospholipid efflux in THP-1 macrophages	Targeted suppression of macrophage specific *LincRNA- DYNLRB2-2* or downstream GRP119 to inhibit foam cell formation	[218]
RP5-833A20.1 (lincRNA)	LincRNA *RP5-833A20.1* overexpression	Negative regulation of NFIA gene by inducing miR-382-5p expression	Increased oxLDL uptake Decreased cholesterol efflux Promotes THP-1-derived foam cell formation	Treatment with LincRNA *RP5-833A20.1 or miR-382-5p inhibitor to* prevent lipid accumulation in macrophages	[219]

Meanwhile, macrophages release cathepsin K to degrade collagen type 1 in the fibrous cap [193]. In combination, these actions promote monocyte and macrophage recruitment, as well as plaque instability, leading to greater lesion development and higher risk of plaque rupture. As a result, the accumulation of these pro-fibrotic foam cells exacerbates conditions within the atheroma, resulting in a higher risk of myocardial infarctions and stroke [194]. Thus, studies have been carried out to understand the impact of protease inhibition on atherosclerosis progression. For instance, protease inhibitors used in the treatment of HIV, have been investigated for their role in promoting atherosclerosis in patients, at the same time as reducing viral load [195]. Antiretroviral drugs and protease inhibitors, amprenavir, indinavir, and ritonavir, were found to promote foam cell formation, by increasing CD36 expression in macrophages, resulting in enhanced intracellular cholesteryl ester accumulation [196]. On the other hand, inhibition of MMPs released from foam cells presents a viable means for reducing the likelihood of adverse cardiovascular events. It has been well-established that MMPs have the ability to degrade extracellular matrix (ECM) proteins such as collagen and fibronectin within the fibrous cap [197], and thereby promote plaque destabilisation and rupture. MMPs therefore stand as a useful target. For instance, a pro-atherosclerotic role for MMP8 has been demonstrated in humans, where elevated carotid MMP8 plaque levels are associated with an unstable plaque phenotype [198]. Moreover, MMP8 deficient ApoE$^{-/-}$ mice (MMP8$^{-/-}$ApoE$^{-/-}$) have reduced leukocyte/monocyte recruitment, decreased lesion macrophage, and lower blood pressure as a result of reduced angiotensin I cleavage and conversion to the vasoconstrictor, angiotensin II [199]. Several MMPs are also required for migration and proliferation of VSMCs, the primary source of collagen synthesis, and are thus likely to determine the resilience and integrity of the fibrous cap [200]. Thus, it is important to discern which MMPs promote plaque stabilisation and which promote plaque rupture. Whilst MMP-12 deficiency appears to protect against elastin degradation, MMP-9 deficiency also appears to inhibit macrophage and collagen content in atherosclerotic lesions located in the descending aorta of ApoE$^{-/-}$ mice, implying that MMP-12 and MMP-9 promote plaque instability, with MMP-9 also playing a role in macrophage infiltration [201]. Another study, however, found that MMP-9 deficiency promotes atherosclerotic lesion growth in brachiocephalic arteries of ApoE$^{-/-}$ mice, with an observed increase in macrophage content, and decrease in VSMC content. On the other hand, MMP-12 deficiency appeared to reduce lesion size in this study, with a marked decrease in macrophage number but a greater VSMC count, in line with the previous study [202]. Despite the use of a similar murine ApoE$^{-/-}$ genetic background, contradictory evidence for the role of MMP-9, but not MMP-12, in atherosclerosis could be due to the different atherosclerotic lesion locations and differences in mouse gender.

Finally, a more recent study has looked at the role of neutrophil elastase (NE), a serine protease with proteolytic activity in ECM, which appears to play a vital role in foam cell formation by promoting ABCA1 degradation, thereby preventing cholesterol efflux from macrophages. Both genetic ablation and pharmacological inhibition of this protease leads to increased ABCA1 protein levels, resulting in less lipid loading in macrophages and reduced atherosclerotic lesion formation [203]. Due to NE's specific expression in atherosclerotic lesions, NE may serve as a novel biomarker for atherosclerosis. Alternatively, the administration of an oral NE-selective inhibitor may prevent lipid accumulation within macrophages at developing lesion sites at a molecular level and delay cardiovascular disease onset.

6.3. Non-coding RNAs in foam cell formation

Several studies have attempted to identify key non-coding RNA molecules capable of changing the course of atherosclerosis progression at the level of the foam cell. Upregulation of microRNAs (miRNAs), miR-155 and miR-33, have been identified as vital to the transition of macrophages towards a foam cell fate following *Mycobacterium tuberculosis* infection. Upregulation of miR-155 and miR-33 causes ABCA1 downregulation, preventing cholesterol efflux from the cell, resulting in higher levels of intracellular cholesterol available for the tuberculosis-inducing bacteria [204, 205]. Similarly, in THP-1 monocyte-derived foam cells, miR-486 inhibits ABCA1 expression by binding to the histone acetyl transferase 1 (HAT-1) 3'UTR sequence, preventing cholesterol efflux, a process that was reversed by treatment with a miR-486 inhibitor [206]. Whilst a large number of miRNAs regulate cholesterol efflux by modulating ABCA1 expression [207–212], miRNAs with multiple targets may prove more useful for preventing foam cell formation. For instance, the highly conserved miRNAs, miR-27a and miR-27b target not only ABCA1 by directly binding to its 3'UTR sequence, but also lipoprotein lipase (LPL) and ACAT-1 in THP-1, RAW 264.7 and HepG2 cells. As a result, total cholesterol content was not observed but rather a reduction in the 'cholesterol ester to free cholesterol' ratio, as well as an overall decrease in cholesterol uptake, suggestive of a compensatory mechanism, orchestrated by miR-27a/b to alleviate cholesterol loading on the cell [213]. miRNAs targeting lipoprotein lipase (LPL) can, either directly or indirectly, control cellular uptake and hydrolysis of lipoproteins within the subendothelial space. miR-590 reduces LPL activity by directly targeting the 3'UTR of LPL mRNA [214], while miR134 promotes LPL expression via suppression of angiopoietin-like 4, an anti-atherosclerotic protein released by macrophages [215]. Equally, other miRNAs are upregulated following uptake of oxLDLs into macrophages, and attempt to promote cholesterol efflux by upregulating cholesterol transporters, ABCA1 and ABCG1, through targeting of adiponectin receptor 2 (AdipoR2) [216].

Several long non-coding RNAs (lncRNA) have also been put forward as potential players in foam cell formation, with particular regard to cellular lipid metabolism [217]. The long intergenic *DYNLRB2-2* lncRNA (*lincRNA- DYNLRB2-2)* has been shown to promote ABCA1-mediated cholesterol efflux [218]. Whilst another lncRNA *RP5-833A20.1* has been shown to interact with miRNA-382-5p to suppress the transcription factor, nuclear factor I A (NFIA), resulting in a decline in ABCA1 and ABCG1 proteins and an increase in SRA-I, CD36 and NFκB, resulting in greater intracellular cholesterol accumulation and higher inflammatory cytokine release[219].

As evidenced by the studies above, there exists an abundance of pro-atherogenic and atheroprotective non-coding RNAs involved in regulating foam cell formation within the macrophage. Therefore, non-coding RNAs present a multitude of molecular targets to use for fine-tuning macrophages within atherosclerotic lesions. Unfortunately, extensive *in vivo* investigations are lacking and therefore, as of yet, it is unclear whether non-coding RNAs will provide the therapeutic advantage researchers are seeking from these untranslated RNA molecules.

7. Strategies targeting the alternative cellular origins of foam cells to inhibit foam cell formation and prevent atherosclerosis

So far, inhibition of foam cell formation has largely been centred on monocytes and macrophage derivatives. However, alternative cell types present in the artery wall, such as ECs and VSMCs, as well as stem/progenitor cells (SPCs) have been shown to exhibit foam cell like properties and behaviour within the ever-growing neointima in atherosclerosis in both humans [230] and mice [231] (Fig. 3).

7.1. VSMC derived foam cells

Analogous to the original foam cell, non-macrophage derived foam cells employ similar strategies to engulf and process modified lipoproteins in the surrounding lipid-rich environment. Indeed, VSMCs have been shown to express ACAT-1 in response to oxLDL exposure in a TLR-4 dependent manner [232] and enhanced NFkB activity [233].

Whereas previously, dedifferentiated VSMCs that have migrated

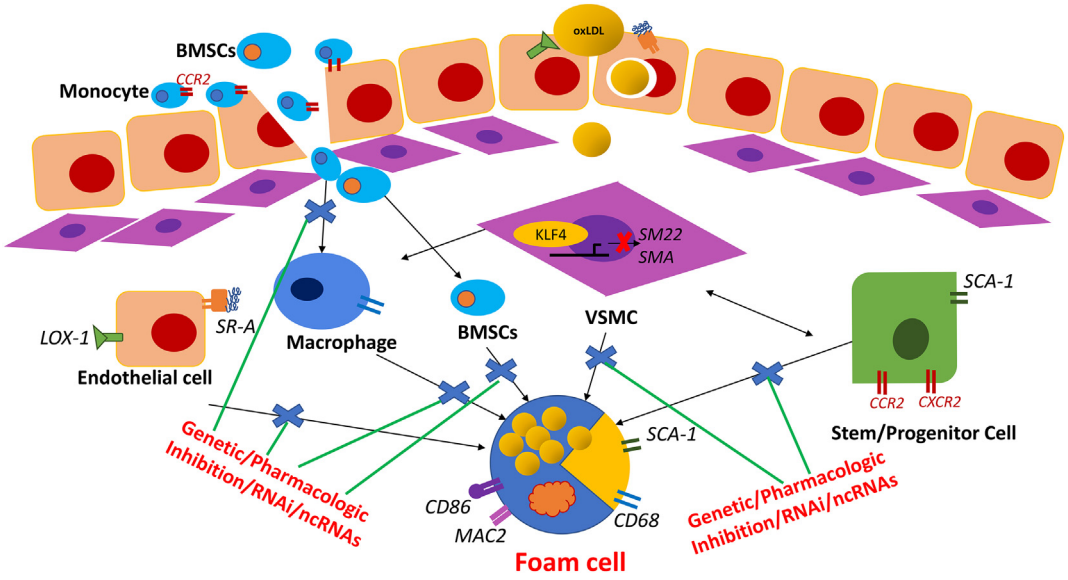

Fig. 3. Alternative cellular origins of foam cells. Multi-cellular origins of foam cells have been recently identified, including endothelial cells (EC), macrophages, vascular smooth muscle cells (VSMCs), bone marrow mesenchymal stem cells (BMSCs) and vascular stem/progenitor cells (SPCs), are illustrated in this schematic diagram. Whilst ECs express several lipid uptake receptors, VSMCs can undergo foam cell formation under KFL4 regulation either by direct differentiation or through a SPC type present in the adventitia. Several endothelial, VSMC and SPC cell surface markers have been identified on the surface of foam cells providing evidence of a non-myeloid foam cell origin. Potential strategies (e.g., genetic/pharmacologic, RNA interference and/or non-coding RNAs) could be utilised to manipulate the cell transformation (or trans-differentiation) to control foam cell formation and prevent atherosclerosis. KLF4 indicates Kruppel Like Factor 4; SCA-1, stem cell antigen-1; SM22, smooth muscle 22 alpha; SMA, smooth muscle alpha-actin.

into the subintimal space of atherosclerotic lesions were only thought to provide structural integrity to the fibrous cap, due to their plasticity, VSMCs are able to carry out a number of functions within the lipid core including cholesterol uptake [234]. In fact, VSMCs have been shown to contribute to over 50% of foam cell populations in human atherosclerotic lesions, and exhibit much lower expression of the cholesterol exporter, ABCA1 compared to macrophage-derived foam cells [235]. Moreover, when responding to the pro-inflammatory cytokines released by ECs and macrophages, mature VSMCs begin to adopt a 'macrophage-like' phenotype expressing scavenger receptors with decreased VSMC gene expression [236]. Using SM22-driven inducible Cre lineage tracing VSMCs and their progenies in ApoE$^{-/-}$ mice, a large number of VSMC-derived cells in intimal regions of atherosclerotic plaques were shown to express macrophage markers, CD68 (54%) and Mac2 (62%), as well as oxLDL (81%), providing direct evidence that these cells undergo transdifferentiation into macrophage-like, lipid-rich cells during atherosclerosis [237]. Similarly, in human coronary artery lesions, 18% of CD68+ cells were shown to be positive for a VSMC-specific epigenetic signature that remains in VSMC-derived cells long after VSMC genes expression has been switched off [238]. This study also identified a key regulator in the VSMC transdifferentiation process, namely Kruppel-like factor 4 (KLF-4). VSMC-specific knock down of KLF-4 prevented suppression of VSMC genes resulting in fewer macrophage-like cell conversions, marked reductions in proliferation and apoptosis of VSMC cells and the formation of a thicker fibrous cap. Molecular manipulation of this specific transcription factor provides compelling evidence for a VSMC-specific approach to tackling foam cell accumulation in the atherosclerotic plaque.

7.2. Stem/progenitor cell (SPC) contribution

SPCs have been identified as another source of foam cells within the advanced atherosclerotic plaque. Several studies have described a role for resident SPCs in the adventitia of atheroprone arteries following acute vascular injury, with a particular role in contributing to the neointimal VSMC populations. Thus, it stands to reason that these cells should be investigated for their role in a more chronic, low grade form of arterial disease such as atherosclerosis. Chen et al. 2013 found that explanted adventitial SPCs, expressing stem cell antigen-1 (Sca-1+), contributed to 30% of neointimal VSMC populations in a model of vein graft atherosclerosis in ApoE$^{-/-}$ mice, and this led to a large increase in neointimal size which consisted predominantly of foam cells [239]. Migration of these Sca-1^{+}, vascular SPCs into the neointima was shown to be actively induced by binding of chemokines derived from 'synthetic' VSMCs, CCL2 (chemokine (C-C motif) ligand 2) and CXCL1 (chemokine (C-X-C motif) ligand 1) to their respective receptors expressed on vascular SPCs. Of interest, knock down of CCL2 reduced vascular SPC migration into the neointima, and consequently neointimal lesion size, highlighting one way in which VSMC populations may be prevented from further aggravating atherosclerosis [240]. However, this last finding was carried out in a wire-injury model and therefore may not attest to foam cell-specific contributions in the neointima. To add to the VSMC story, a more recent lineage tracing study has highlighted the existence of a subpopulation of VSMCs which can differentiate back into adventitial, Sca-1^{+} cells, which in turn are capable of contributing to several cell types including macrophages [241]. The generation of VSMC-derived Sca-1^{+} cells was dependant on KLF4 induction, reaffirming the role for this transcription factor in directing VSMC generation over other cell types. Since a high VSMC to macrophage ratio within the atheroma is associated with greater plaque stability and consequently a lower risk of plaque rupture [39], forced induction of KLF-4 may be key in mediating a phenotypic shift away from the macrophage/foam cells towards a more atheroprotective VSMC and/or adventitial vascular progenitor cell phenotype.

Questions arising from this last study have led to a quandary regarding the origin of VSMCs within the arterial wall and thus highlight the existence of a far more dynamic network of cell-to-cell interactions and transdifferentiation than previously thought (Fig. 3).

Another local stem cell population, resident in the adventitia, has been identified as a 'macrophage progenitor' cell population. Expression of these Sca-1^{+}CD45^{+} cells was increased in hyperlipidaemic ApoE$^{-/-}$ and LDLR$^{-/-}$ mice. After 12 weeks on a Western diet, Sca-1^{+}CD45^{+} cells were found distributed transmurally, compared to mice fed a chow diet where Sca-1^{+}CD45^{+} cells were present

mainly within the adventitia. Further investigations into the function and activities of Sca-1$^+$CD45$^+$ cells during atherosclerosis, particularly at neointimal sites, will help to decipher the overall contributions of the adventitia to foam cell populations [242].

Interestingly, circulating bone marrow mesenchymal stem cells (BMSCs) can also contribute to VSMC populations, and these can then converted into foam cells following exposure to oxLDL [243]. These bone marrow derived-foam cells showed stronger migratory ability compared to VSMC-derived foam cells, highlighting an added advantage for these cells in establishing a prominent colony within the neointimal layers of the atherosclerotic plaque [244].

7.3. Endothelial-derived foam cells

Finally, less research has been carried out on endothelial-derived foam cells, however, there is evidence to suggest that over time, these cells are capable of upregulating SRs in response to the gradual accumulation of modified lipoproteins in the subendothelial space. For instance LOX-1 and to a lesser extent, CD36 and SR-A1, upregulation was found to be crucial at mediating uptake of human carbamylated LDL, a product of urea-derived cyanate LDL modifications, whose levels are elevated in patients with chronic kidney disease and are associated with greater risk of atherosclerosis and cardiovascular disease [245].

Another *in vitro* study showed that human ECs exposed to serum from hyperlipidaemic patients not only led to an increase in expression of cellular adhesion molecules, VCAM-1 and VLA-1, but also increased ox-LDL accumulation within the cell which appeared to increase heat shock protein 70 (Hsp70) levels, whose anti-apoptotic and anti-oxidant properties aid in its cytoprotective role under cellular stress [245]. Additional studies reveal human CD34+ progenitor cells capable of differentiating into foam cells *in vitro*, attenuated by PPARα and PPARγ agonists [230]. More research in humans is needed, however, to determine the relative contributions of neointimal cells to the foam cell population and whether cell-specific targeting warrants further investigation, which may lead to improved outcomes for patients with atherosclerosis.

With several studies providing strong evidence that VSMC-derived foam cells are less able to cope with lipid-loading, compared to their myeloid-derived macrophage counterparts, it is feasible to consider that perhaps the VSMC is a more significant player in foam cell formation. The challenge now stands in ascertaining the relevant contribution of each cell type responsible for contributing to foam cell formation during atherosclerosis, and reviewing whether work carried out in earlier studies of foam cell formation reflected the true cellular activities within the atheroma. Where alleged macrophage activity was once held solely responsible for the appearance of large stretches of foam cells, resulting in fatty streak formation along the length of atherogenic arteries, now more and more cell types have been found exhibiting similar behaviour and have added to the list of foam cell suspects (Fig. 3). As a result, more sophisticated molecular-based approaches may be required to truly eliminate foam cell populations in the atherosclerotic plaque.

8. Future perspectives/conclusion

Foam cell formation marks the beginning of several architectural changes occurring within the blood vessel wall that, if left unchecked, will eventually lead to vessel narrowing or complete occlusion resulting in tissue hypoxia and necrosis. Depending on the location of this event, the damage inflicted on tissues downstream of the occlusion may be irreversible, and result in a severely reduced quality of life, or even death. As discussed in this Review, foam cell formation is problematic not only in isolation, by contributing to the development of a pro-inflammatory, lipid-dense core of apoptosing cells, but it also promotes other pro-atherogenic processes, such as immune cell recruitment and protease activity, which further aggravate the situation by increasing the likelihood of plaque rupture. Several GWAS studies have identified key genes in CVD patients, associated with processes required for foam cell accumulation, such as increased circulating LDL cholesterol levels and monocyte recruitment, which in turn has sped up the search for effective therapeutic targets. The identification of key cytokines, CAMs, key molecules (or signal pathways) controlling cholesterol metabolism in macrophages, proteases and ncRNAs have provided an abundance of possibilities for targeting foam cell formation, however, each with its own set of limitations. Moreover, contradictory findings in foam cell formation and inhibition from studies carried out in animals, especially mice, have highlighted the need to design a standard mouse model for use across all studies and remove the variability that arises due to differences in genetic mouse models (i.e. ApoE$^{-/-}$ vs. LDLR$^{-/-}$ vs. ApoE-Leiden), gender, study duration and diet. Moreover, the discrepancies in atherosclerosis development between humans and murine models must be taken into consideration, namely differences in topography of arterial lesions, fibrous cap formation and rupture, as well as chronology of cellular recruitment, as early accumulation of macrophages within the murine subintima only occurs following adaptive intimal thickening in humans [4, 246]. Deciding which combination of study parameters provides a more accurate representation of foam cell formation in humans, could constitute a Review in itself, and several groups have covered this topic in the past [101, 247]. Finally, determining the significance of foam cell formation at various stages of atherosclerosis will factor into deciding when foam cell specific-treatments should be administered to patients, as well as identifying the relative contributions of different cell types to the foam cell population. Recognising that foam cell formation is a multi-cellular process and inhibition requires a multi-faceted approach, appears to be the overwhelming consensus derived from the current literature, however, as with most multi-target based approaches, the risk of off-target effects is increased. Thus, the success of this approach will depend on the outcome of clinical trials involved in assessing macrophage activity, particularly in CVD patients receiving therapies targeting foam cell biology. Results from early clinical trials showed a promising outcome as evidenced by reduced inflammation [248] and decreased macrophage cell content [249] within atherosclerotic lesions in patients receiving a short-term treatment with high-dose statin. However, findings from the Goal of Oxidized LDL and Activated Macrophage Inhibition by Exposure to a Recombinant Antibody trial (GLACIER—NCT01258907) have been disappointing [250]. Despite the inconsistent information gleaned from previous trials, findings from ongoing studies (e.g., NCT02576288) specifically pertaining to foam cell interference would be greatly welcomed by clinicians and researchers aiming to optimise and improve CVD treatments. Based on the plethora of targets available for foam cell intervention, we await the outcome of the ongoing and future clinical trials with great interest.

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