REVIEW

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Characteristics of plaque lipid-associated macrophages and their possible roles in the pathogenesis of atherosclerosis

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Purpose of review
Recent findings from single-cell transcriptomic studies prompted us to revisit the role of plaque foamy macrophages in the pathogenesis of atherosclerosis. In this review, we compared the gene expression profile of plaque foamy macrophages with those of other disease-associated macrophages and discussed their functions in the pathogenesis of atherosclerosis.

Recent findings
To understand the phenotypes of macrophages in atherosclerotic aorta, many research groups performed single-cell RNA sequencing analysis and found that there are distinct phenotypic differences among intimal foamy, nonfoamy and adventitial macrophages. Especially, the plaque foamy macrophages express triggering receptor expressed on myeloid cells 2 (TREM2), a key common feature of disease-associated macrophages in Alzheimer's disease, obesity, cirrhosis and nonalcoholic steatohepatitis. These TREM2^{+} macrophages seem to be protective against chronic inflammation.

Summary
As the gene expression profile of plaque foamy macrophages is highly comparable to that of lipid-associated macrophages from obesity, we named the plaque foamy macrophages as plaque lipid-associated macrophages (PLAMs). PLAMs have a high level of gene expression related to phago/endocytosis, lysosome, lipid metabolism and oxidative phosphorylation. Considering the protective function of lipid-associated macrophages against adipose tissue inflammation, PLAMs may suppress atherosclerotic inflammation by removing modified lipids and cell debris in the plaque.

Keywords
atherosclerosis, macrophage, plaque lipid, TREM2

INTRODUCTION

Atherosclerosis is a chronic inflammatory cardiovascular disease. Over the last three decades, the number of cardiovascular disease cases worldwide has nearly doubled, from 271 million cases to 523 million [1], demanding precise risk assessment tools and novel therapeutic regimens. Macrophages are well known primary myeloid cells that accumulate lipids in the cytosol, leading to a foamy appearance of atherosclerotic plaques [2]. Previously, foamy macrophages were assumed to be the pathogenic cell types that drive atherosclerotic inflammation. However, we demonstrated that foamy macrophages in atherosclerotic aorta highly express triggering receptor expressed on myeloid cells 2 (TREM2) and are less inflammatory but possess more homeostatic phenotypes [3]. A recent meta-analysis also recapitulated that foamy macrophages are not inflammatory, but nonfoamy and interferon-inducible macrophages express pro-inflammatory genes. In this review, we summarized the macrophage populations in normal and atherosclerotic aortas and compared the aortic foamy macrophages with disease-associated macrophages expressing TREM2 in other inflammatory tissues. In particular, we named the intimal foamy macrophages as plaque

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KEY POINTS

- PLAMs express a high level of TREM2, a common feature of disease-associated macrophages.
- PLAMs and LAMs have shared a common feature of homeostatic gene expressions.
- PLAMs may suppress atherosclerotic inflammation by eliminating apoptotic cell debris and modified lipids.

lipid-associated macrophages (PLAMs); this was based on their similarity of gene expression profiles compared with lipid-associated macrophages (LAMs) recruited in adipose tissue during obesity [4▪▪]. Finally, we discussed the possible role of PLAMs in the pathogenesis of atherosclerosis.

REDEFINING THE CHARACTERISTICS OF INTIMAL MACROPHAGES ASSOCIATED WITH PLAQUE LIPIDS

In the steady state, aortic macrophages mostly reside in the adventitia, and a small number of macrophages accumulate in atherosclerosis-prone areas [5–7]. Intimal macrophages residing in atherosclerotic-prone areas are responsible for initial foamy macrophages but are soon replaced by macrophages derived from blood monocytes [7]. During the initial stage of atherosclerosis, plaque macrophages originate mostly from blood monocytes, while some originate from extramedullary monocytosis [8]. The infiltration of monocytes depends on the expression of C-C chemokine receptor type 2 (CCR2), CCR5 and CX3CR1 [9,10] and various adhesion molecules on endothelial cells [11]. The recruited intimal macrophages take up modified lipids, mostly oxidized LDL, and have a foamy appearance. Macrophages in atherosclerotic plaques can be affected by various microenvironmental factors, including modified lipoproteins, inflammatory cytokines, cell debris and cholesterol crystals, leading to various cellular phenotypes. For example, the accumulation of lipids can activate liver X receptor (LXR) target genes and suppress sterol regulatory element-binding protein (SREBP) target genes, leading to fatty acid metabolism reprogramming and inflammatory gene suppression [12,13]. In contrast, increased free cholesterol and cholesterol crystals induce NLRP3-dependent activation of macrophages [14–16]. Thus, it is important to examine the macrophage populations in atherosclerotic plaques, the primary site for atherosclerotic inflammation, to understand the pathogenesis of atherosclerosis and develop novel therapeutic immune targets.

Previously, to characterize the phenotype of plaque foamy macrophages, a direct analysis of lesional macrophages using laser capture microdissection [17] or an analysis of foamy macrophages in sponges surgically inserted into the subcutaneous area of hyperlipidemic mice, which showed enhanced gene expression that is related to growth, proliferation and cholesterol metabolism (e.g. *Abca1*, *Pparγ*, *Rxra*, *Rxrb* and *Srebp1*), was performed [18]. Single-cell RNA sequencing (scRNA-seq) analysis has broadened our understanding of the phenotypic changes in immune and nonimmune cells during disease progression. As scRNA-seq has been well established, many research groups have performed unbiased transcriptome analysis of immune cells from mouse and human atherosclerotic aortas at the single-cell level (Rahman *et al.* [19], Winkels *et al.* [20], Cochain *et al.* [21], Kim *et al.* [3], Lin *et al.* [22] and Fernandez *et al.* [23]). The meta-analysis of available single-cell transcriptome datasets showed the common macrophage populations in the atherosclerotic aorta and the distinct phenotypic differences among adventitial resident, intimal nonfoamy and foamy macrophages [24]. These single-cell analyses revealed that intimal foamy macrophages are less inflammatory than nonfoamy macrophages and express many homeostatic genes related to cholesterol transport, fatty acid metabolism, phagocytosis, endocytosis and protein metabolism compared with their nonfoamy counterparts [3,25▪]. Interestingly, foamy macrophages in atherosclerotic plaques highly express TREM2, a typical membrane receptor commonly expressed in recently reported disease-associated macrophages in various inflammatory tissues, including the brain (damage-associated microglia, DAMs), adipose tissue (lipid-associated macrophages, LAMs) and liver [scar-associated macrophages, SAMs and nonalcoholic steatohepatitis (NASH)-associated macrophages, NAMs] (Table 1) [3,4▪▪,21–23,26–32].

EMERGING ROLE OF TREM2^{+} MACROPHAGES IN INFLAMMATORY DISEASES

TREM2 is a transmembrane receptor of the immunoglobulin superfamily expressed in the immune cells of various tissues [33▪▪]. TREM2 interacts with various molecules, including lipids, apolipoproteins, lipopolysaccharides, dextran sulfate, DNAs and phospholipids [34–37]. TREM2 activates Syk or PI3K via the formation of heterodimers with DAP12 (TYROBP) or DAP10, respectively [38]. It also regulates cell survival via the mTOR or β-catenin pathways [39–42]. Furthermore, TREM2 enhances phagocytosis, leading to suppression of secondary

Table 1. Characteristics of Trem2^{hi} macrophages in various diseased organs

Tissue	Aorta	Adipose tissue	Brain	Liver
Disease	Atherosclerosis	Obesity	Alzheimer's disease	Cirrhosis Nonalcoholic steatohepatitis (NASH)
Trem2^{hi} macrophages	Plaque lipid-associated Macrophages (PLAMs)	Adipose tissue lipid-associated macrophages (LAMs)	Disease-associated microglia (DAMs)	NASH-associated macrophages (NAMs) Scar-associated macrophages (SAMs)
References (Mouse)	Cochain *et al.* [21] Kim *et al.* [3] Lin *et al.* [22]	Jaitin *et al.* [4▪▪]	Keren-Shaul *et al.* [26]	Xiong *et al.* [29] Seidman *et al.* [30▪▪]
References (Human)	Fernandez *et al.* [23]	Jaitin *et al.* [4▪▪]	Hasselmann *et al.* [27] Thrupp *et al.* [28]	Ramachandran *et al.* [31] Govaere *et al.* [32]
Location	PLAMs are in atherosclerotic plaques and not present in normal aorta	LAMs surround apoptotic adipocytes (crown-like structures) and are not present in a normal adipose tissue	DAMs surround amyloid beta plaques and are not present in normal brain cortex	The cells are present in hepatic sinusoids (NAMs) or collagen-rich areas (SAMs) They are not present in normal liver
Cell origin	Blood monocytes	Blood monocytes	Homeostatic microglia	KC-N: from healthy Kupffer cells KN-RM: from blood monocytes
Cell distinction	PLAMs are distinct from adventitia macrophages and intimal nonfoamy macrophages	LAMs are distinct from monocytes and tissue-resident macrophages	DAMs are distinct from monocytes and perivascular macrophages	SAMs and NAMs are distinct from healthy Kupffer cells and blood monocytes
Representative enriched genes (mouse)	*Abca1, Abcg1, Cd36, Cd63, Cd9, Ctsb/d/l/z, Fabp4/5, Hvcn1, Itgax, Lgals3, Lipa, Mertk, Msr1, Npc1, Nr1h3, Spp1, Trem2*	*C1qa, Cd36, Cd68, Cd9, Ctsb, Ctsl, Fabp4, Fabp5, Lagls1/3, Lipa, Lpl, Trem2*	*Apoe, Axl, Cd36, Cd9, Csf1, Cst7, Ctsb/d, Hexb, Itgax, Lpl, Lyz2, Spp1, Timp2, Trem2, Tyrobp*	KC-N: *Aif1, Apoc1, Apoe, C1qb, Ccl24, Cd5l, Clec1b, Clec4f, Clec4n, Ctsd, Ear2, Fabp7, Folr2, Igf1, Il18bp, Lpl, Mmp12, Pltp, Trem2, Wfdc17* KN-RM: *Apoe, Bcl2a1b, Cd207, Cd63, Cd74, Cd9, Clec4b1, Cx3cr1, Cxcl14, Fabp5, Gpnmb, H2-Aa, H2-Eb1, H2-M2, Mmp12, Ms4a7, Pf4, Trem2*
Relatively low expressed genes	*Il1b, Nlrp3, Mgl2* (vs. intima nonfoamy macrophages)	*Ccr2, Il1b, Ly6c2, Lyz2, S100a10* (Loss from monocytes)	*Ccr5, Cx3cr1, Pyry12/13, Txnip, Tmem119, Selplg* (vs. homeostatic microglia)	*Cd163, C6* (vs. healthy Kupffer cells) *Mgl2* (vs. Ly6C^{lo} RM) *Runx1/2/3* (vs. blood Ly6C^{hi} monocytes)
Enriched pathways	Cholesterol metabolism Lysosome Oxidative phosphorylation Proteasome PPAR signalling	Intracellular metabolism Lysosome Oxidative phosphorylation Phagosome PPAR signalling Sphingolipid metabolism	Endocytosis Lysosome Phagocytosis Regulation of immune response Response to wounding	Endocytosis Lipid catabolism Lysosome MHCII presentation ROS metabolic process Tissue remodelling

KC-N, Kupffer cells in nonalcoholic steatohepatitis; KN-RM, recruited macrophages occupying the Kupffer cell niche; MHCII, major histocompatibility complex II; PPAR, peroxisome proliferator-activated receptor; RM, recruited macrophages; ROS, reactive oxygen species.

necrosis and pro-inflammatory danger signals, and eventually attenuates the inflammatory response [43–45]. Activation of the TREM2 signalling pathway attenuates toll-like receptor (TLR) and the production of TLR-associated cytokines in macrophages and dendritic cells [43,45,46]. Although the exact mechanisms responsible for TREM2 expression remain to be elucidated, it appears that TREM2 is induced in macrophages in a lipid-rich tissue environment with chronic inflammatory conditions and plays a key role in sensing and processing disease-associated microenvironments. TREM2$^+$ macrophages are present in lipid-rich, hypoxic and chronic inflammatory conditions, including atherosclerosis, obesity, Alzheimer's disease, cirrhosis and NASH. They contain lipid droplets or amyloid beta originating from the surrounding injured tissues, suggesting that they are involved in the clearance of injured cells and debris, leading to the resolution of inflammation. As expected, the decrease in TREM2 expression impairs the phagocytosis of apoptotic cells, cellular debris and lipoproteins in microglia, suggesting the protective function of DAMs against Alzheimer's disease [36,47]. NAMs are markedly increased in NASH, which is induced by a high-fat diet [29,30▪▪]. The loss of TREM2 exacerbates hepatic lipid accumulation and inflammation [48], suggesting a protective function of NAMs against hepatic injury triggered by lipid overload. Collectively, TREM2$^+$ macrophages appear to be protective against chronic inflammation. However, the exact function of TREM2$^+$ macrophages in chronic inflammation should be elucidated using a conditional loss-of-function approach.

COMMON FEATURES OF TWO TYPES OF LIPID-ASSOCIATED MACROPHAGES IN CASES OF OBESITY AND ATHEROSCLEROSIS

Obesity and atherosclerosis have common features of disease progression. Both diseases are induced by an imbalance in energy intake and expenditure, leading to hyperlipidaemia and chronic inflammation in various tissues. Obesity is strongly associated with adipose tissue inflammation, leading to insulin resistance and type 2 diabetes mellitus [49]. Macrophages are crucial effector cells involved in obesity-induced adipose inflammation and insulin resistance [50]. The Ido Amit group described a novel and highly conserved TREM2$^+$ macrophages, named LAMs, in the adipose tissue during obesity [4▪▪]. LAMs possess lipid droplets and express the lipid receptor TREM2 and lipid metabolism-related genes residing in crown-like structures surrounding adipocytes of obese mice. However, they are not present in the normal state. Previously, we demonstrated that PLAMs also show enhanced expression of TREM2 and other lipid metabolism-related genes. Therefore, we compared the gene expression profiles of LAMs and PLAMs. These two macrophages showed highly conserved gene expressions, including *Lipa*, *Ctsl*, *Fabp4*, *Fabp5*, *Lgals3*, *Cd9* and *Cd36*. Next, we defined the enriched genes in LAMs ($n = 65$, log2FC >2.5, vs. normal adipose tissue macrophages) and analysed their expressions in our scRNA-seq data from atherosclerotic aortas. We found that the enriched genes in LAMs were highly correlated with those enriched in PLAMs (Fig. 1). In particular, these two LAMs share a common feature of gene expression related to phagocytosis, endocytosis, lysosomes, lipid metabolism, peroxisome proliferator-activated receptor gamma and oxidative phosphorylation (Fig. 1). These results suggest that LAMs present in cases of obesity and atherosclerosis have similar functions in a lipid-enriched inflammatory milieu.

POSSIBLE ROLE OF PLAQUE LIPID-ASSOCIATED MACROPHAGES IN THE PATHOGENESIS OF ATHEROSCLEROSIS

In a previous study, *Trem2*$^{-/-}$ mice showed increased adipose hypertrophy, insulin resistance and hyperlipidaemia. Mice transplanted with *Trem2*$^{-/-}$ bone marrow also showed the same phenotypes, suggesting that TREM2 expressing LAMs may be responsible for the protective effect of TREM2 against metabolic inflammation [4▪▪]. Considering the similarities in the gene expressions between LAMs and PLAMs, PLAMs can be expected to suppress plaque inflammation by eliminating apoptotic cell debris and modified lipids. Indeed, myeloid LXR deficiency accelerated atherosclerosis and decreased the number of plaque TREM2$^+$ foamy macrophages, that is PLAMs, with decreased expression of TREM2 downstream genes related to cholesterol transport and metabolism, whereas inflammatory gene expressions were increased in nonfoamy and foamy macrophages [51▪▪]. These results suggest that PLAMs may increase the expression of genes related to lipid metabolism via a collaborative interaction between TREM2 and LXR to cope with the lipid-rich atherosclerotic milieu.

CONCLUSION

The phenotypes and functions of macrophages in various disease settings have been widely investigated using single-cell transcriptome analysis, and the heterogeneity and function of macrophages in atherosclerosis have been elucidated. PLAMs commonly express genes related to phagocytosis, lysosomal

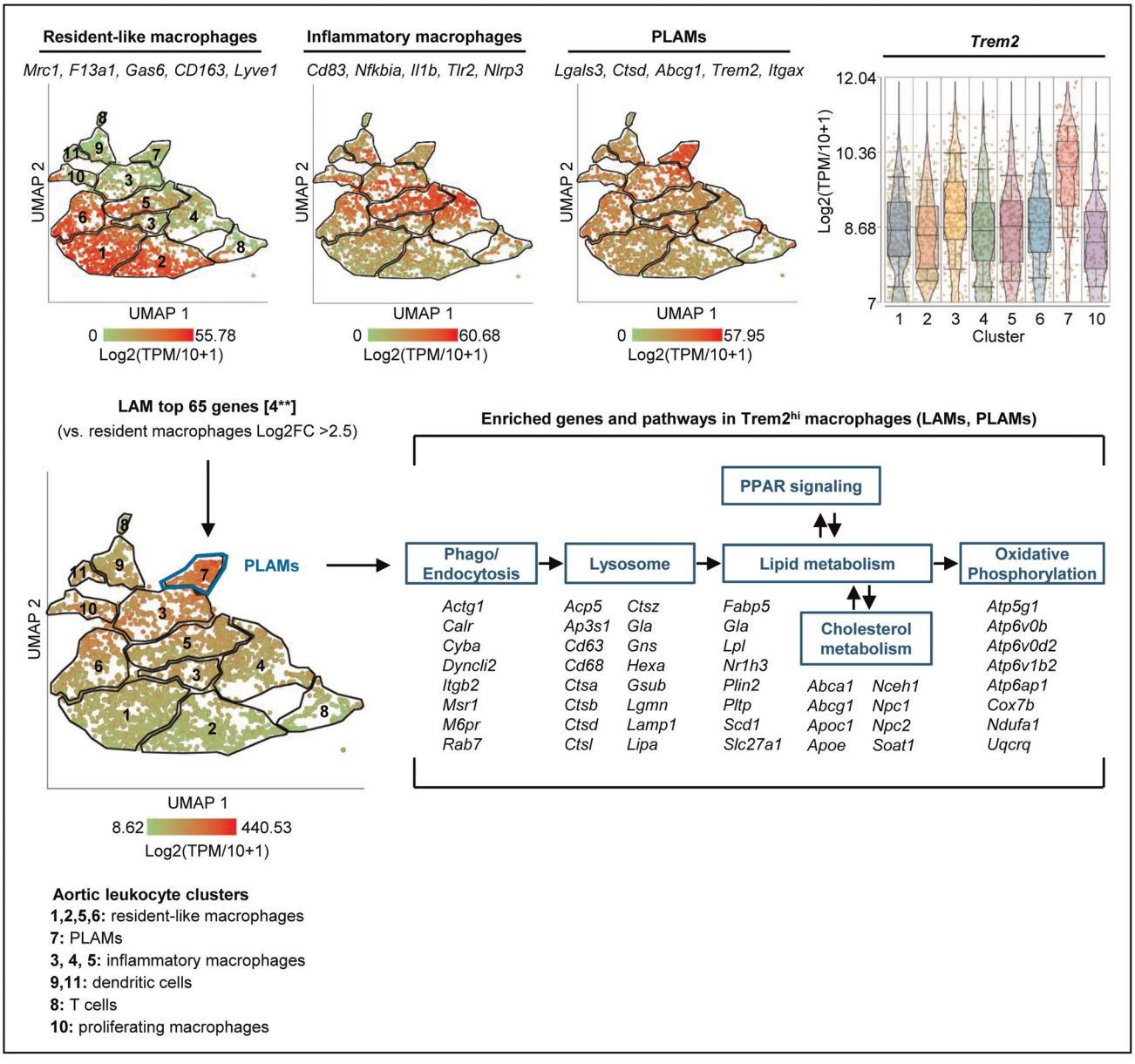

FIGURE 1. Enriched genes and pathways in Trem2^{hi} macrophages present in cases of atherosclerosis and obesity. Top: single-cell RNA sequencing data from Kim *et al.* [3] are re-visualized using UMAP clustering. Bottom: The top 65 LAM genes from Jaitin *et al.* [4▪▪] are highly upregulated in PLAMs (Cluster 7). FC, fold change; LAM, lipid-associated macrophages; PLAM, plaque LAM; PPAR, peroxisome proliferator-activated receptor; UMAP, Uniform manifold approximation and projection.

activity and lipid metabolism and are expected to play a role in maintaining homeostasis in response to tissue injury. However, to understand the exact function of PLAMs and develop novel therapeutic regimens, extensive and comprehensive studies are required. For example, whether PLAMs originate from initial inflammatory macrophages or from a specific population of monocytes/macrophages and how macrophages gain the PLAM phenotype in atherosclerotic plaques need to be determined. Moreover, the exact function of TREM2 in the pathogenesis of atherosclerosis remains unclear. A conditional loss-of-function approach using macrophages is required to understand the exact role of PLAMs in the pathogenesis of atherosclerosis.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Roth GA, Mensah GA, Johnson CO, *et al.* Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: update from the GBD 2019 Study. J Am Coll Cardiol 2020; 76:2982–3021.
2. Tabas I, Bornfeldt KE. Macrophage phenotype and function in different stages of atherosclerosis. Circ Res 2016; 118:653–667.
3. Kim K, Shim D, Lee JS, *et al.* Transcriptome analysis reveals nonfoamy rather than foamy plaque macrophages are proinflammatory in atherosclerotic murine models. Circ Res 2018; 123:1127–1142.
4. ■■ Jaitin DA, Adlung L, Thaiss CA, *et al.* Lipid-associated macrophages control metabolic homeostasis in a Trem2-dependent manner. Cell 2019; 178:686–698; e614.

This study reported Trem2-expressing LAMs from obese adipose tissue in mice and humans. Trem2 deficiency resulted in the absence of LAMs and increased adipose tissue hypertrophy, systemic hypercholesteremia and glucose intolerance.

5. Jongstra-Bilen J, Haidari M, Zhu SN, *et al.* Low-grade chronic inflammation in regions of the normal mouse arterial intima predisposed to atherosclerosis. J Exp Med 2006; 203:2073–2083.
6. Ensan S, Li A, Besla R, *et al.* Self-renewing resident arterial macrophages arise from embryonic CX3CR1(+) precursors and circulating monocytes immediately after birth. Nat Immunol 2016; 17:159–168.
7. Williams JW, Zaitsev K, Kim KW, *et al.* Limited proliferation capacity of aortic intima resident macrophages requires monocyte recruitment for atherosclerotic plaque progression. Nat Immunol 2020; 21:1194–1204.
8. Robbins CS, Chudnovskiy A, Rauch PJ, *et al.* Extramedullary hematopoiesis generates Ly-6C(high) monocytes that infiltrate atherosclerotic lesions. Circulation 2012; 125:364–374.
9. Swirski FK, Libby P, Aikawa E, *et al.* Ly-6Chi monocytes dominate hypercholesterolemia-associated monocytosis and give rise to macrophages in atheromata. J Clin Invest 2007; 117:195–205.
10. Tacke F, Alvarez D, Kaplan TJ, *et al.* Monocyte subsets differentially employ CCR2, CCR5, and CX3CR1 to accumulate within atherosclerotic plaques. J Clin Invest 2007; 117:185–194.
11. Gerhardt T, Ley K. Monocyte trafficking across the vessel wall. Cardiovasc Res 2015; 107:321–330.
12. Spann NJ, Garmire LX, McDonald JG, *et al.* Regulated accumulation of desmosterol integrates macrophage lipid metabolism and inflammatory responses. Cell 2012; 151:138–152.
13. Zhang X, McDonald JG, Aryal B, *et al.* Desmosterol suppresses macrophage inflammasome activation and protects against vascular inflammation and atherosclerosis. Proc Natl Acad Sci U S A 2021; 118:e2107682118.
14. Duewell P, Kono H, Rayner KJ, *et al.* NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature 2010; 464:1357–1361.
15. Sheedy FJ, Grebe A, Rayner KJ, *et al.* CD36 coordinates NLRP3 inflammasome activation by facilitating intracellular nucleation of soluble ligands into particulate ligands in sterile inflammation. Nat Immunol 2013; 14:812–820.
16. Nahrendorf M, Swirski FK. Neutrophil-macrophage communication in inflammation and atherosclerosis. Science 2015; 349:237–238.
17. Feig JE, Fisher EA. Laser capture microdissection for analysis of macrophage gene expression from atherosclerotic lesions. Methods Mol Biol 2013; 1027:123–135.
18. Thomas AC, Eijgelaar WJ, Daemen MJ, Newby AC. Foam cell formation in vivo converts macrophages to a pro-fibrotic phenotype. PLoS One 2015; 10:e0128163.
19. Rahman K, Vengrenyuk Y, Ramsey SA, *et al.* Inflammatory Ly6Chi monocytes and their conversion to M2 macrophages drive atherosclerosis regression. J Clin Invest 2017; 127:2904–2915.
20. Winkels H, Ehinger E, Vassallo M, *et al.* Atlas of the immune cell repertoire in mouse atherosclerosis defined by single-cell RNA-sequencing and mass cytometry. Circ Res 2018; 122:1675–1688.
21. Cochain C, Vafadarnejad E, Arampatzi P, *et al.* Single-Cell RNA-Seq reveals the transcriptional landscape and heterogeneity of aortic macrophages in murine atherosclerosis. Circ Res 2018; 122:1661–1674.
22. Lin JD, Nishi H, Poles J, *et al.* Single-cell analysis of fate-mapped macrophages reveals heterogeneity, including stem-like properties, during atherosclerosis progression and regression. JCI Insight 2019; 4:e124574.
23. Fernandez DM, Rahman AH, Fernandez NF, *et al.* Single-cell immune landscape of human atherosclerotic plaques. Nat Med 2019; 25:1576–1588.
24. Zernecke A, Winkels H, Cochain C, *et al.* Meta-analysis of leukocyte diversity in atherosclerotic mouse aortas. Circ Res 2020; 127:402–426.
25. ■ Li C, Qu L, Matz AJ, *et al.* AtheroSpectrum reveals novel macrophage foam cell gene signatures associated with atherosclerotic cardiovascular disease risk. Circulation 2022; 145:206–218.

This study is a meta-analysis study using new algorithms (AtheroSpectrum) to identify the standard features and contributing factors of macrophages affecting the cause of atherosclerosis in mouse models and human patients.

26. Keren-Shaul H, Spinrad A, Weiner A, *et al.* A unique microglia type associated with restricting development of Alzheimer's disease. Cell 2017; 169:1276–1290; e1217.
27. Hasselmann J, Coburn MA, England W, *et al.* Development of a chimeric model to study and manipulate human microglia in vivo. Neuron 2019; 103:1016–1033; e1010.
28. Thrupp N, Sala Frigerio C, Wolfs L, *et al.* Single-nucleus RNA-Seq is not suitable for detection of microglial activation genes in humans. Cell Rep 2020; 32:108189.
29. Xiong X, Kuang H, Ansari S, *et al.* Landscape of intercellular crosstalk in healthy and NASH liver revealed by single-cell secretome gene analysis. Mol Cell 2019; 75:644–660; e645.
30. ■■ Seidman JS, Troutman TD, Sakai M, *et al.* Niche-specific reprogramming of epigenetic landscapes drives myeloid cell diversity in nonalcoholic steatohepatitis. Immunity 2020; 52:1057–1074; e1057.

In this study, Seidman *et al.* [30■■] analysed the phenotypic changes of liver myeloid cells in the NASH mouse model. They used CHIP-seq and ATAC-seq to investigate in the transcription factors and gene expression patterns of myeloid cells in NASH. These findings suggest that the LXR-RXR pathway is involved in the induction of TREM2-expressing macrophages.

31. Ramachandran P, Dobie R, Wilson-Kanamori JR, *et al.* Resolving the fibrotic niche of human liver cirrhosis at single-cell level. Nature 2019; 575:512–518.
32. Govaere O, Cockell S, Tiniakos D, *et al.* Transcriptomic profiling across the nonalcoholic fatty liver disease spectrum reveals gene signatures for steatohepatitis and fibrosis. Sci Transl Med 2020; 12:eaba4448.
33. ■■ Deczkowska A, Weiner A, Amit I. The physiology, pathology, and potential therapeutic applications of the TREM2 signaling pathway. Cell 2020; 181:1207–1217.

This review study summarized the of TREM2 and its therapeutic application. This study is helpful to obtain the current understanding about the function of TREM2 and its perspectives on therapeutic application.

34. Bailey CC, DeVaux LB, Farzan M. The triggering receptor expressed on myeloid cells 2 binds apolipoprotein E. J Biol Chem 2015; 290:26033–26042.
35. Atagi Y, Liu CC, Painter MM, *et al.* Apolipoprotein E is a ligand for triggering receptor expressed on myeloid cells 2 (TREM2). J Biol Chem 2015; 290:26043–26050.
36. Yeh FL, Wang Y, Tom I, *et al.* TREM2 binds to apolipoproteins, including APOE and CLU/APOJ, and thereby facilitates uptake of amyloid-beta by microglia. Neuron 2016; 91:328–340.
37. Wang Y, Cella M, Mallinson K, *et al.* TREM2 lipid sensing sustains the microglial response in an Alzheimer's disease model. Cell 2015; 160:1061–1071.
38. Peng Q, Malhotra S, Torchia JA, *et al.* TREM2- and DAP12-dependent activation of PI3K requires DAP10 and is inhibited by SHIP1. Sci Signal 2010; 3:ra38.
39. Wu K, Byers DE, Jin X, *et al.* TREM-2 promotes macrophage survival and lung disease after respiratory viral infection. J Exp Med 2015; 212:681–697.
40. Ulland TK, Song WM, Huang SC, *et al.* TREM2 maintains microglial metabolic fitness in Alzheimer's disease. Cell 2017; 170:649–663; e613.
41. Otero K, Turnbull IR, Poliani PL, *et al.* Macrophage colony-stimulating factor induces the proliferation and survival of macrophages via a pathway involving DAP12 and beta-catenin. Nat Immunol 2009; 10:734–743.
42. Otero K, Shinohara M, Zhao H, *et al.* TREM2 and beta-catenin regulate bone homeostasis by controlling the rate of osteoclastogenesis. J Immunol 2012; 188:2612–2621.
43. Hamerman JA, Jarjoura JR, Humphrey MB, *et al.* Cutting edge: inhibition of TLR and FcR responses in macrophages by triggering receptor expressed on myeloid cells (TREM)-2 and DAP12. J Immunol 2006; 177:2051–2055.
44. Turnbull IR, Gilfillan S, Cella M, *et al.* Cutting edge: TREM-2 attenuates macrophage activation. J Immunol 2006; 177:3520–3524.
45. Ito H, Hamerman JA. TREM-2, triggering receptor expressed on myeloid cell-2, negatively regulates TLR responses in dendritic cells. Eur J Immunol 2012; 42:176–185.
46. Gao X, Dong Y, Liu Z, Niu B. Silencing of triggering receptor expressed on myeloid cells-2 enhances the inflammatory responses of alveolar macrophages to lipopolysaccharide. Mol Med Rep 2013; 7:921–926.
47. Takahashi K, Rochford CD, Neumann H. Clearance of apoptotic neurons without inflammation by microglial triggering receptor expressed on myeloid cells-2. J Exp Med 2005; 201:647–657.
48. Hou J, Zhang J, Cui P, *et al.* TREM2 sustains macrophage-hepatocyte metabolic coordination in nonalcoholic fatty liver disease and sepsis. J Clin Invest 2021; 131:e135197.
49. Hotamisligil GS. Inflammation and metabolic disorders. Nature 2006; 444:860–867.
50. McNelis JC, Olefsky JM. Macrophages, immunity, and metabolic disease. Immunity 2014; 41:36–48.
51. ■■ Endo-Umeda K, Kim E, Thomas DG, *et al.* Myeloid LXR (Liver X Receptor) deficiency induces inflammatory gene expression in foamy macrophages and accelerates atherosclerosis. Arterioscler Thromb Vasc Biol 2022; 42:719–731.

This study demonstrated that LXR activation is important to induce the Trem2 gene expression programme leading to suppression of inflammation in the foamy macrophages of atherosclerotic plaques.