MicroRNA-155 and macrophages: a fatty liaison

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This editorial refers to ‘Elevated microRNA-155 promotes foam cell formation by targeting HBP1 in atherosclerosis’ by F.-J. Tian et al., pp. 100–110, this issue.

The inflammatory activation of lipid-loaded macrophages in the arterial intima plays a major role in the pathogenesis of atherosclerosis.¹ The unrestricted uptake of oxidatively modified low-density lipoprotein (oxLDL) via scavenger receptors results in the storage of cholesterol esters in lipid droplets in macrophages due to the limited efflux of free cholesterol.¹ However, free cholesterol can accumulate in the membrane of the endoplasmic reticulum (ER), which triggers ER stress and inflammatory activation. Moreover, cholesterol crystals may form and induce the activation of the NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome and IL-1β production.² Nevertheless, it is still incompletely understood how cholesterol accumulation triggers inflammation in macrophages.

A distinct subset of small non-coding RNAs (miRNAs), including miR-155 and miR-146, regulates the inflammatory signalling pathways in macrophages by translational repression or degradation of their target mRNAs.³ Activation of various Toll-like receptors (TLR) induces miR-155 expression via myeloid differentiation primary response gene (MyD88)- or toll-interleukin-1 receptor (TIR) domain-containing adapter-inducing IFN-β-dependent signalling, probably through NF-κB activation.⁴ Moreover, mildly oxidized LDL, which can bind to TLR4, in combination with IFN-γ induces the expression of miR-155 in macrophages.⁵ However, the findings regarding the effects of highly oxidized LDL on miR-155 expression are controversial.⁶

The functions of miRNAs are highly cell type- and context-dependent and can be altered by changes in the expression of competing endogenous targets.⁶,⁷ In macrophages, miR-155 suppresses negative regulators of inflammatory cytokine signalling, such as suppressor of cytokine signalling 1 (SOCS1), Src homology 2 domain-containing inositol-5-phosphatase-1 (SHIP-1), or B cell lymphoma 6 (BCL6), and thereby promotes the release of inflammatory mediators.⁸ In contrast, miR-155 can reduce the secretion of cytokines, such as IL-6 and TNF-α, in oxLDL-stimulated macrophages by inhibition of mitogen-activated protein kinase (MAPK) pathways.⁹ Therefore, the role of miR-155 in the inflammatory activation of macrophage-derived foam cells is currently unclear.

In the current issue of the study of Cardiovascular Research, Tian et al.¹⁰ provide novel evidence for a dual role of miR-155 in inflammatory macrophage activation and foam cell formation by targeting the transcriptional repressor HMG box-transcriptional protein 1 (HBP1). They found that oxLDL increases miR-155 expression in murine macrophages and thereby promotes foam cell formation and the generation of reactive oxygen species (ROS). This effect of miR-155 is due to suppression of HBP-1, which negatively regulates macrophage migration inhibitory factor (MIF) and p47phox (Figure 1). MIF is known to increase the uptake of oxLDL by macrophages and the foam cell formation in vascular lesions.¹¹ Therefore, Tian et al. suggest that miR-155-mediated suppression of HBP1 increases foam cell formation through MIF. Moreover, the findings of Tian et al. indicate that de-repression of p47phox causes the miR-155-induced ROS production in macrophages. Notably, miR-155 also affects the expression of several other miRNAs, for instance, through targeting C/EBP, in oxLDL-treated macrophages, which may be implicated in the observed effect of miR-155.¹²

Negative regulators of miR-155 expression, such as Akt1, control the inflammatory activation of macrophages, and targeting of Akt1 by miR-342-5p induces miR-155 expression and promotes atherosclerosis.⁷ Therefore, identifying transcriptional repressors of miR-155 may be important to design novel miRNA-based therapeutic strategies to combat atherosclerosis. Tian et al. demonstrate that YY1 is a novel transcriptional repressor of miR-155 in macrophages, which recruits HDAC2/4 to the miR-155 promoter and both synergistically down-regulate miR-155. Interestingly, oxLDL decreases the activity of HDAC and may thus be implicated in the up-regulation of miR-155 by oxLDL, indicating that enhancing HDAC activity may limit inflammatory macrophage activation and foam cell formation by regulating miR-155.

The authors performed elegant in vivo studies to determine the effect of pharmacological miR-155 inhibition on atherosclerosis in Apoe⁻/⁻ mice with extreme hypercholesterolaemia induced by a cholesterol content of 1.25% in the diet. In this atherosclerosis model, advanced lesions develop within the 11-week feeding programme. This treatment with miR-155 antagonists substantially reduced lesion formation, lesional macrophage content, and the production of lesional TNF-α and IL-6, although the expression level of miR-155 was only reduced by 50% in macrophages. Moreover, Tian et al. found that inhibition of miR-155 up-regulated the expression of HPB1 in the atherosclerotic arteries, suggesting that targeting of HPB1 by miR-155 may promote lesion formation. In line with these results, previous reports showed that deficiency of miR-155 in bone marrow limits the formation of advanced atherosclerotic lesions in Apoe⁻/⁻ mice due to the derepression of Bcl6.⁵,¹³ In contrast, in a model with less advanced atherosclerotic

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lesions using Ldr−/− mice, the lack of miR-155−/− expression in bone marrow cells increased lesion formation after 10 weeks of a high-fat diet (HFD) feeding.14 One explanation for these controversial results may be that miR-155 in macrophages has different effects in early and advanced atherosclerotic lesions. In addition, blocking miR-155 with an antisense oligonucleotide as used by Tian et al. does not affect the expression of the sister strand of miR-155, miR-155*, which has opposite effects compared with miR-155 in dendritic cells. Therefore, the study by Tian et al. clearly demonstrates the role of miR-155 on atherosclerosis independent of possible effects of miR-155*. However, additional studies are required to dissect the pro- and anti-atherogenic roles of miR-155 to assess the therapeutic potential of miR-155 inhibition against atherosclerosis.8

In this regard, Tian et al. also addressed the possible translation of their findings in the mouse model into the human system. Although miR-155 levels in the circulation of patients with cardiovascular disease are reduced,15 Tian et al. found that the miR-155 expression in monocytes is up-regulated and its target HBP1 is reduced. These data indicate that miR-155 may have similar effects in human myeloid cells as in mouse macrophages and thus, inhibition of miR-155 may be a feasible therapy against atherosclerosis.

Conflicts of interest: none declared.

References