Insight

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Myeloid IL-10 receptor signalling as pro-atherogenic factor modulating cholesterol homeostasis

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Interleukin-10 (IL-10) is a prototypical anti-inflammatory cytokine mainly produced by monocytes/macrophages and T lymphocytes. Although generally described as anti-atherogenic, IL-10 seems to have more complex functions in atherosclerosis, e.g. when produced by different T-cell or B-cell subsets (1–3). Furthermore, it enhances the lipid accumulation in oxLDL-stimulated macrophages through partial inhibition of oxLDL-induced apoptosis (4). However, IL-10 exerts these effects within the atherosclerotic lesion by modulation of the limited inflammatory reaction and can thus locally regulate matrix metalloproteinase, synthesis of tissue factor and production of thrombin, but also macrophage polarization. Whereas anti-inflammatory M2 macrophages express large amounts of IL-10 and are more susceptible to foam cell formation, pro-inflammatory M1 macrophages express low levels of IL-10. In addition, IL-10 can drive the conversion of M1 macrophages towards M2 macrophages. On the other hand, lipid uptake during foam cell formation represents a critical step in atherogenesis. In this regard, IL-10 was found to influence cellular lipid metabolism by facilitating both cholesterol uptake and efflux. Cholesterol uptake could be considered as athero-protective, as it removes oxLDL from the blood flow (5).

In this issue of Thrombosis and Haemostasis, Stöger et al. (6) have demonstrated that the suppression of IL-10R1 in myeloid cells attenuates atherogenesis in LDLR−/− mice and improves hypercholesterolaemia by shifting intestinal cholesterol fluxes. Given that the most abundant inflammatory cell type in plaques and foam cell formation are macrophages, the effects of IL-10 on myeloid cells are of particular interest. Under high-cholesterol diet, irradiated-mice reconstituted with myeloid IL-10R1-deficient bone marrow have significant smaller atherosclerotic lesion sizes and reduced CD68⁺ cell accumulation in the aortic arch. Although the distribution, polarisation and frequency of T cells, B cells and macrophages were not investigated, IL-10 seems to have diverse cell-specific effects in atherogenesis. Overall, IL-10 prevents the differentiation of monocytes to dendritic cells, while promoting their maturation to M2 macrophages and stimulating endocytosis (7), thereby leading to foam cell formation. Beyond this context, the authors demonstrated that myeloid IL-10R1 deficiency modulates cholesterol homeostasis by enhancing efflux of non-biliary cholesterol and reducing its intestinal absorption. This novel mechanism may provide an additional explanation for pro-atherogenic effects of IL-10 on foam cell formation through stimulation of oxLDL uptake, as well as for its antiapoptotic mechanisms (4). In addition, this calls for a reconsideration of myeloid cells as target cells of IL-10 for atheroprotection.

Although significant progress has been achieved towards understanding cholesterol homeostasis and foam cell formation, the functions of cytokines in these processes are still unclear. Defining these functions and particularly unraveling the modulation of endocytosis and exocytosis of modified cholesterol by cytokines may shed light on new fields of investigation, as well as provide additional therapeutic targets.

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Conflicts of interest

None declared.

References