Atherosclerosis: cell biology and lipoproteins-focus on anti-inflammatory mechanisms as therapeutic options

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Atherosclerosis is a chronic inflammatory reaction of the arterial wall characterized by the infiltration of inflammatory cells into the nascent atherosclerotic lesions leading to its growth and eventual destabilization [1,2].

Transforming growth factor beta (TGFβ), an anti-inflammatory cytokine, is centrally involved in balancing the immune response in atherosclerosis [3–5]. Recently, Lievens *et al.* [6▪▪] reported that abrogation of TGFβ signaling in dendritic cells leads to a two-fold increase in lesion size and acceleration of plaque inflammation. Furthermore, this overexpression of dominant-inactive TGFβ receptor in $CD11c^{+}$ cells increased cytokine production and T-cell content in the plaque. *In vitro*, dendritic cells deficient in TGFβ signaling displayed a profound inflammatory phenotype promoting T-cell activation, proliferation, and differentiation into effector cells, thus providing a mechanistic link to the changes observed in the vasculature. Taken together, this study suggests a potential therapeutic approach in which dendritic cell-specific promotion of TGF signaling may dampen atherosclerosis without the detrimental profibrotic and neoplastic complications caused by systemic TGFR activation. Regulatory T cells (Tregs) are increasingly recognized as potent atheroprotective players [7]. Interestingly, TGFβ plays a dual role in Tregs, as it regulates their differentiation and function but also is secreted as one of the most potent effector cytokines. Treg numbers and function were modulated in the atherosclerosis models either by direct adoptive transfer or by indirect measures such as vaccination [8]. Treg function is also mediated by indoleamine 2,3-dioxygenase (IDO) and IDO-catalyzed tryptophan metabolism [9]. The tryptophan metabolite 3-hydroxyanthranilic acid (3-HAA) inhibits inflammation in different experimental autoimmune disease models by repressing pro-inflammatory T cells and increasing the percentage of Tregs [10]. Zhang *et al.* [11▪▪] now show that 3-HAA reduced atherosclerotic lesion formation in hyperlipidemic mice. Interestingly, 3-HAA treatment also reduced plasma lipid levels, indicating beneficial action on both the inflammatory and the lipid-metabolic component of atherosclerosis [12].

Interleukin (IL)-13 is an anti-inflammatory cytokine acting predominantly on monocytic cells. Cardilo-Reis *et al.* [13▪] reported that administration of IL-13 increases collagen and reduces macrophage content within murine atherosclerotic lesions yielding a stable plaque phenotype. In addition, IL-13 promoted an alternatively activated macrophage phenotype. *In vitro*, these macrophages show enhanced oxLDL uptake but differentiate to a lesser extent into foam cells compensated by enhanced cholesterol efflux. *Vice versa*, atherosclerosis is exacerbated in mice reconstituted with bone marrow deficient in IL-13.

MicroRNAs (miRNAs) are small, noncoding, regulatory, short RNA molecules that modify gene expression by targeting messenger RNA (mRNA) for degradation or repressing their translation [14▪]. Circulating miRNAs correlate with cardiovascular risk and clinical manifestations such as myocardial infarction. Recently, Nazari-Jahantigh *et al.* [15▪▪] discovered the involvement of miRNA-155 in the progression of atherosclerosis by influencing macrophage subsets. Increased expression of miRNA-155 was observed following partial carotid ligation and in bone marrow-derived and M1-polarized macrophages. Furthermore, miRNA-155 promoted BCL6-mediated transcription of CCL2, a chemokine

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that attracts leukocytes to infiltrate into the atherosclerotic plaque.

Taken together, these experimental studies detailing the anti-inflammatory mechanisms may lead to the development of targeted interventions without affecting systemic function or host defense.

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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. Weber C, Noels H. Atherosclerosis: current pathogenesis and therapeutic options. Nat Med 2011; 17:1410–1422.
2. Weber C, Zernecke A, Libby P. The multifaceted contributions of leukocyte subsets to atherosclerosis: lessons from mouse models. Nat Rev Immunol 2008; 8:802–815.
3. Lutgens E, Daemen MJ. Transforming growth factor-beta: a local or systemic mediator of plaque stability? Circ Res 2001; 89:853–855.
4. Robertson AK, Rudling M, Zhou X, *et al.* Disruption of TGF-beta signaling in T cells accelerates atherosclerosis. J Clin Invest 2003; 112:1342–1350.
5. Mallat Z, Gojova A, Brun V, *et al.* Induction of a regulatory T cell type 1 response reduces the development of atherosclerosis in apolipoprotein E-knockout mice. Circulation 2003; 108:1232–1237.
6. ■■ Lievens D, Habets KL, Robertson AK, *et al.* Abrogated transforming growth factor beta receptor II (TGFbetaRII) signalling in dendritic cells promotes immune reactivity of T cells resulting in enhanced atherosclerosis. Eur Heart J 2012 [Epub ahead of print].

This study details the crucial role of TGFβ signaling in dendritic cells in vascular inflammation and atherosclerosis.

7. Ait-Oufella H, Salomon BL, Potteaux S, *et al.* Natural regulatory T cells control the development of atherosclerosis in mice. Nat Med 2006; 12:178–180.
8. Klingenberg R, Lebens M, Hermansson A, *et al.* Intranasal immunization with an apolipoprotein B-100 fusion protein induces antigen-specific regulatory T cells and reduces atherosclerosis. Arterioscler Thromb Vasc Biol 2010; 30:946–952.
9. Grohmann U, Bronte V. Control of immune response by amino acid metabolism. Immunol Rev 2010; 236:243–264.
10. Platten M, Ho PP, Youssef S, *et al.* Treatment of autoimmune neuroinflammation with a synthetic tryptophan metabolite. Science 2005; 310:850–855.
11. ■■ Zhang L, Ovchinnikova O, Jonsson A, *et al.* The tryptophan metabolite 3-hydroxyanthranilic acid lowers plasma lipids and decreases atherosclerosis in hypercholesterolaemic mice. Eur Heart J 2012; 33:2025–2034.

This study shows that treatment with the tryptophan metabolite 3-HAA reduces atherosclerosis and modulates local and systemic inflammatory responses. Furthermore, 3-HAA inhibited the uptake of oxLDL by macrophages and decreased plasma lipid levels offering several therapeutic benefits.

12. Klingenberg R, Gerdes N, Badeau RM, *et al.* Depletion of FOXP3+ regulatory T cells promotes hypercholesterolemia and atherosclerosis. J Clin Investig 2013; in press.
13. ■ Cardilo-Reis L, Gruber S, Schreier SM, *et al.* Interleukin-13 protects from atherosclerosis and modulates plaque composition by skewing the macrophage phenotype. EMBO Mol Med 2012; 4:1072–1086.

Exogenous IL-13 promotes more fibrotic and less inflammatory atherosclerotic lesions accompanied by the induction of alternatively activated (M2) macrophages. Conversely, deficiency of IL-13 results in accelerated atherosclerosis in hyperlipidemic mice, implicating IL-13 as a potential therapeutic tool.

14. ■ Weber C, Schober A, Zernecke A. MicroRNAs in arterial remodelling, inflammation and atherosclerosis. Curr Drug Targets 2010; 11:950–956.

This study reviews the role of miRs in arterial remodelling and atherosclerosis and describes the potential roles of miRs in vascular biology by modulating the differentiation and functions of immune cells.

15. ■■ Nazari-Jahantigh M, Wei Y, Noels H, *et al.* MicroRNA-155 promotes atherosclerosis by repressing Bcl6 in macrophages. J Clin Investig 2012; 122:4190–4202.

This study reports enhanced expression of Mir155 in atherosclerosis and shows that leukocyte-specific deficiency thereof represses plaque size and inflammatory status likely by inhibiting the proinflammatory transcription factor Bcl6.

FURTHER RECOMMENDED READING

Dinh TN, Kyaw TS, Kanellakis P, *et al.* Cytokine therapy with interleukin-2/
■ antiinterleukin-2 monoclonal antibody complexes expands $CD4^{+}CD25^{+}$ $Foxp3^{+}$ regulatory T cells and attenuates development and progression of atherosclerosis. Circulation 2012; 126:1256–1266.

This study shows that treatment of hyperlipidemic mice with IL-2/anti-IL-2 complexes attenuates atherosclerosis via selective Tregs expansion, suggesting this as an attractive approach for treating atherosclerosis.

Soehnlein O, Drechsler M, Döring Y, *et al.* Sequential contribution of chemokine
■ receptor axes to the prominent proatherogenic function of classical monocytes. EMBO Mol Med (in press).

This study details the mechanisms of monocyte trafficking and its regulation during atherosclerosis.

Dutta P, Courties G, Wei Y, *et al.* Myocardial infarction accelerates atherosclerosis.
■ Nature 2012; 487:325–329.

This study demonstrates that the systemic inflammatory response to ischemic injury persistently aggravates atherosclerosis though neuroimmunologically mediated monocytosis.