CURRENT OPINION

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

*Norbert Gerdes[a,b], Holger Winkels[a,b], and Christian Weber[a]*

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 proinflammatory 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

[a]Institute for Cardiovascular Prevention (IPEK), Ludwig-Maximilians University (LMU), Munich, Germany and [b]Department of Medical Biochemistry, Academic Medical Center (AMC), University of Amsterdam, Amsterdam, the Netherlands

Correspondence to Norbert Gerdes, Institute for Cardiovascular Prevention, Ludwig-Maximilians University, Pettenkoferstr, 9, 80336 Munich, Germany. Tel: +49 89 5160 4672; e-mail: norbert.gerdes@med.uni-muenchen.de

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

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## FURTHER RECOMMENDED READING

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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.

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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.