Cytokine 122 (2019) 154819

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

Inflammation in atherosclerosis: A key role for cytokines

Accumulating evidence makes it clear that inflammation is an essential contributor to atherosclerotic lesion formation and subsequent progression, as well as instability and eventually, lesion regression [1–4]. Broadly anti-inflammatory interventions using methotrexate and colchicine were successful in the past [5,6]. The publication of a large study demonstrating successful specific anti-cytokine intervention in high-risk patients with this disease [7] enforces the concept of an anti-inflammatory therapeutic route in atherosclerosis and encourages the exploration of individual pathways.

This special issue of "Cytokine" contains a selection of timely review articles and original papers addressing cytokine regulation and their effector functions with specific attention to their role in cardiovascular diseases with an emphasis on atherosclerosis. The purpose of this issue is thus to assemble current knowledge, introduce potential new molecular targets and signaling pathways and point out the "hot topics" requiring further investigation.

Ray and Autieri undertake a broad view on regulatory mechanisms of both pro- and anti-inflammatory cytokines in atherosclerosis, with a special focus on TNFα and mechanisms regulating cytokine expression, specifically mRNA stability. Atherosclerosis outcome studies in animals with modified mRNA binding proteins, possibly in different vascular cell types, are eagerly awaited. An original research paper included in this issue by Ursu and colleagues addresses the role TRAF6 that is required for TNFα signal transduction in myocarditis caused by Cocksackievirus B3 infection. The authors found that infection increased TRAF6 expression, the functional consequences of which remain to be determined.

IL-1 is the topic of the review by Pfeiler and colleagues. Biologic properties of IL-1, its cytokine family members and the inflammasome as well as experimental work on their function in atherosclerosis and results of observational and interventional studies in humans are covered. This is especially timely as anti-IL-1β therapy was successful in a large controlled CANTOS trial, which the authors also discuss in their paper [7].

Platelets, well known for their role in thrombus formation, also store significant amounts of preformed cytokines. Bakogiannis and colleagues review the evidence for functional roles of platelet-derived cytokines in atherosclerosis. CXCL4 and its family members, CXCL5 and CXCL12 (SDF-1) act on multiple cell types, such as vascular endothelium and leukocytes including monocytes and monocyte-derived macrophages. CXCL4 even induces a specific macrophage phenotype that in reviewed in detail by Domschke and Gleissner in this issue. Beyond this, the authors give an account of the current knowledge on the role of CXCL4 chemokine in human atherosclerosis.

Function of macrophages and other myeloid cells is central in atherosclerotic plaque development and progression, as myeloid-derived cytokines regulate much of plaque structure, as well as functional processes ongoing in the plaque, including the adaptive immune responses. Van der Heijden and colleagues address the role of IL-12 and IL-12 cytokine family members in atherosclerosis, giving a detailed summary of both *in vitro* and *in vivo* animal model studies and clinical observations on IL-6, IL-12, IL-27 and IL-35 expression and function. Grufman and colleagues performed longitudinal studies on a cohort of 524 patients with acute coronary syndrome and found that elevated IL-27 levels correlated with cardiovascular events and death even after correction for multiple common risk factors. They discuss whether the possible role of IL-27 is directly pro-atherosclerotic or rather a dysfunctional repair attempt.

As a IL-12 cytokine member, IL-27 inhibits IL-17 production while related IL-23 promotes it. Nordlohne and von Vietinghoff cover the current literature on IL-17 in atherosclerosis and discuss IL-17 expression modification in disease that may promote its expression. This includes tryptophan metabolites that are more and more appreciated as significant modifiers of the immune response. This field is revised comprehensively in the paper by Baumgartner and colleagues. Their review addresses the underlying biochemical pathways and complex pro- and anti-inflammatory functions exerted by each metabolite as well as gaps in knowledge especially regarding the final metabolite NAD.

IL-35 is a newly identified immunoregulatory cytokine that shares subunits with both IL-12 and IL-27. Li and colleagues present a thought-provoking review on IL-35, indicating that while its role in atherosclerosis beyond mere expression in the plaque is presently unknown, the foundation to study IL-35 is there. That seems to be especially important given the anti-inflammatory function of IL-35 in other diseases.

Increased myelopoiesis is a hallmark of atherogenesis and expression of various colony stimulating factors (CSF) essential for myelopoiesis is promoted by various above-mentioned cytokines, including IL-17. Singhal and Subramanian in depth review the current data on CSFs in atherosclerosis, including G-CSF, M-CSF, GM-CSF with decisive impact on macrophage functions and their cytokine secretion, connecting to the TNFα, IL-1 and IL-12 work reported above. The authors reference previous studies in detail as well as identify key gaps in existing knowledge. Given the frequent therapeutic use of CSF factors in other diseases (especially G-CSF), a better mechanistic understanding of what these factors can do in possible promotion of atherosclerosis is urgently needed.

In addition to summarizing the data on established factors of atherosclerosis, several papers in this issue address potential new cytokines with complex pro- and anti-inflammatory action and their unusual interaction partners. Farokzadian and colleagues introduce S100A12, a cytokine and a CD36 binding protein with yet unknown function in atherosclerosis. Given both cytokine functions and direct interaction with a major lipid uptake protein, the authors discuss its

https://doi.org/10.1016/j.cyto.2019.154819

Available online 22 August 2019

regulation and binding partners. McCurdy et al. address the function of IL-37 in atherosclerosis. The anti-inflammatory functions of this cytokine are exerted via both intra- and extracellular binding partners resulting in multiple putative disease-modifying mechanisms.

With this collection, we hope to provide the readers helpful summaries of knowledge and stimulate further research in inflammation and atherosclerosis.

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