Atherogenesis and inflammation

From cellular mediators to regulatory mechanisms of inflammation in atherosclerosis

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Atherosclerotic vascular disease remains the main cause of morbidity and mortality worldwide, especially in industrialized countries. Impressive and permanently growing research of the recent past has partially changed and further extended our understanding about this broad disease. So far, atherosclerosis results not solely from imbalanced lipid metabolism with lipoprotein retention in the arterial wall and subsequent migration and proliferation of smooth muscle cells but still represents a very complex immune-inflammatory syndrome (1, 2). The atherosclerosis field is so immense that attempts to meticulously explain each pathophysiological aspect in detail will be futile. The role of well-established risk factors, endothelial and vascular smooth muscle cells, monocytes, foam cells, platelets and innate versus adaptive immunity have been extensively studied and discussed up to now. However, novel aspects on monocyte heterogeneity, macrophage polarization and less appreciated leukocyte subsets such as neutrophils, mast cells and dendritic cells become progressively evident in lesion formation, growth and destabilization (1–4). Beyond this cellular level, several inflammatory mediators participate in all stages of atherosclerosis. For example, chemokines and their receptors or even combined interactions amplify the atherogenic recruitment of immune cells to the injured vascular wall (2, 5). On the other site, microparticles and microRNAs have been recognized as further subcellular fine tuners of endothelial regeneration, neointimal hyperplasia and angiogenesis (6, 7).

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The present theme issue contains six review articles written by experts in the field of cardiovascular immunobiology. These works successfully update recent knowledge on inflammatory mechanisms in atherogenesis by including consistent data from basic research, experimental animal models and clinical studies. In particular, central aspects about immune and endothelial cells, platelet chemokines, metabolic pathways and microRNAs are considered in detail.

Hristov and **Heine** compare and critically discuss the phenotype and function of human and mouse monocyte subsets by highlighting their sequential, subset-specific recruitment in experimental atherosclerosis next to potential prognostic and therapeutic relevance for clinical setting (8). **Wezel et al.** rather focus on the role of mast cells and mast cell derived mediators in destabilization of advanced plaques (9). **Hartwig et al.** update in condensed form emerging details on the impact of neutrophils during early inflammatory responses in the arterial wall as well as during plaque progression and destabilization (10). **Polyzos** and **Ketelhuth** address the direct and indirect roles of the kynurenine pathway in modulation of cardiovascular risk factors, vascular inflammation and atherosclerosis (11). **Duchene** and **von Hundelshausen** further concentrate on atherothrombosis by supplementing the effects of pro-inflammatory chemokines secreted upon platelet activation (12). Finally, **Natarelli** and **Schober** describe the microRNA dependent modulation of vascular wound healing and envisage the development of novel microRNA targeting therapeutic interventions (13).

Collectively, these comprehensive reviews clearly confirm that atherosclerosic has gained broad acceptance as chronic in-

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flammatory disease. Controlling of local arterial inflammation, endothelial resistance, immune cell infiltration and platelet activation next to manipulation of metabolic pathways and microRNA signalling could help to develop novel, more powerful clinical therapeutics. In this regard, accumulating evidence from basic research and experimental animal models as summarized in the above articles suggest plausible candidates of interest such as chemokine receptor antagonists and microRNA mimics or inhibitors. This pioneering drug development requires however stringent evaluation of effectiveness which has to rely on surrogate markers. Although a variety of cellular, soluble, imaging or functional parameters are available, their predictability remains partially limited. Therefore, new biomarkers should be developed to complement existing ones and rather multiple biomarker panels should be combined in an integrated approach to reach higher predictive potential.

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