Immunotherapy for Atherosclerosis—Novel Concepts

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Despite considerable progress in its management and therapy, cardiovascular disease remains the major cause of death in the Western world.[1] The causal factor driving most of these conditions is atherosclerosis. To develop more effective strategies for the prevention and treatment of arterial disease, a better understanding of the pathogenesis and progression of atherosclerosis is crucial. A group of outstanding basic and clinical scientists from different research campuses in Munich, Germany, has joined forces in a unique multidisciplinary network entitled Collaborative Research Center (CRC) 1123 "Atherosclerosis—Mechanisms and Networks of Novel Therapeutic Targets." The long-standing goal of the CRC 1123 is to provide an in-depth mechanistic understanding of molecular networks in atherogenesis, progression and atherothrombosis. This theme issue presents some of the novel immunotherapeutic targets that are currently studied by the CRC 1123 network as potential future treatment for atherosclerosis in a collection of five review articles.

To start with, Kaltner and Gabius highlight the relevance of cell surface glycans, which are recognized by specific receptors called lectins, as biological signals for haemostasis, platelet functionality and inflammation.[2] For example, the circulatory lifespan of platelets is shortened during systemic bacterial infection due to the activity of bacterial sialidases on cell surface glycans. Desialylated platelets can be removed from the circulation by specific hepatic lectin receptors, which is also a relevant mechanism during sepsis to limit the severity of disseminated intravascular coagulation.[3] The variability of the glycan structures composed of sugars and glycosidic bonds on the cell surface binding to a large network of lectin receptors may translate into very fine-tuned intracellular effects. Initially widely ignored, it is increasingly recognized that the carbohydrate structures represent specific 'codes' with biological specificity that are defined by the variability of their sugars and linkage position. On the receptor side, the growing network of lectins involved in the biological processes of platelet activation and inflammation comprises selectins and many other C-type lectins, galectins and siglecs.[2]

The following two reviews[4,5] discuss the emerging family of atypical chemokines (ACKs). Macrophage migration-inhibitory factor (MIF) is an inflammatory cytokine that is classified as ACK, because it exhibits chemotactic activity and binds to classical chemokine receptors CXCR2 and CXCR4, but lacks the typical chemokine-fold and conserved N-terminal cysteines of classical chemokines.[4] MIF is upregulated in human atherosclerotic lesions and promotes atherogenic leukocyte recruitment and lesional inflammation in experimental models via CXCR2 and CXCR4 as well as CD74 (also known as human leukocyte antigen class II histocompatibility antigen gamma chain).[4] Although inhibitors of MIF signalling are already in clinical development for specific conditions such as metastatic colorectal cancer,[6] the possible therapeutic targeting of MIF in cardiovascular disease is challenging due to stage-dependent differential effects. Other ACKs bind to ACK receptors (ACKRs), which in contrast to the well-known classical CC- and CXC-type chemokines, do not elicit a G-protein-dependent signalling response upon binding to their cognate receptors.[5] While the implication and therapeutic targeting of classical chemokine receptors in cardiovascular disease has been extensively studied during the last two decades, the pathophysiological roles of ACKRs in this context is still poorly understood. In view of developing more efficient therapeutic drugs for cardiovascular disease, ACKRs are of particular interest as they are major regulators of chemokine availability and

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signalling. Despite their inability to bind G proteins, ACKRs can internalize, scavenge, transport or present chemokines and thus regulate the bioavailability of chemokines and thereby chemokine signalling via classical receptors.[5]

In the next contribution, Van Avondt et al provide an update on growing experimental evidence for a causal relationship between neutrophil extracellular traps (NETs) and atherothrombosis.[7] NETs have been linked to acute coronary events, including ST elevation myocardial infarction in humans, as well as plaque formation and superficial erosion in experimental models. The strategies used to clarify the pathophysiological role of NETs and mechanisms triggering NET release in atherosclerosis and thrombosis involve DNase injection or transgenic mouse models that fail to induce NETs. Although it is tempting to suggest that interfering with NET formation may result in multiple beneficial effects in cardiovascular disease patients, more research is needed to better understand the molecular mechanisms of NET activation as well as their detrimental and possibly beneficial functions in acute and chronic cardiovascular conditions.

The last review article[8] adds metabolic disorders such as obesity as additional complication in cardiovascular disease, which is a common co-morbidity that has risen dramatically over the last four decades.[9] Overactive endocannabinoid signalling is a common feature of obesity and atherosclerosis, which involves an up-regulation of endogenous lipid mediators (endocannabinoids) derived from membrane phospholipids that bind to central and peripheral cannabinoid receptors. Enhanced endocannabinoid signalling affects atherosclerosis by modulating vascular inflammation, leukocyte recruitment and cholesterol metabolism. In addition, enhanced CB1 signalling promotes metabolic disorders such as obesity and dyslipidaemia, which further promotes the chronic inflammatory state underlying atherosclerosis.[8]

In summary, this theme issue highlights some emerging regulators and their interactions in the complex pathogenesis of atherosclerosis, which deserve further attention. The recent findings of the CANTOS trial have clearly proven that inflammation is a key driver of atherosclerosis and that targeting inflammation improves cardiovascular disease outcomes.[10] Nevertheless, innovative anti-inflammatory therapies are warranted that more efficiently reduce cardiovascular disease and mortality, while limiting side effects such as enhanced susceptibility to infection. Among the potential targets presented in the five review articles, interfering with chemokine signalling may be most promising and advanced. In light of the positive CANTOS outcome, the CRC 1123 will continue its mission to provide an in-depth mechanistic understanding of the molecular networks underlying atherogenesis to identify novel therapeutic targets. To this end, we will extend the scope of the theme issue series in a subsequent second part to therapeutic targeting of platelets in atherothrombosis, highlighting novel Bruton's tyrosine kinase inhibitors, to targeting mononuclear phagocytes, for example, focusing on regulatory effects of long non-coding ribonucleic acids (RNAs) and micro-RNAs, and to exploring novel imaging modalities for therapeutic translation.

Conflict of Interest
None declared.

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