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Editorial

Introduction to the thematic review series on different levels of genetic regulation of cardiovascular disease

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This series of reviews is centered around the novel developments in gene regulation to better understand the underlying pathobiology of cardiovascular disease. The process of gene regulation in cardiovascular disease is complex and involves many regulatory mechanisms located at different systemic levels. In the traditional approach, a simple transcriptome signature based on gene expression analysis, in combination with a genome analysis including whole exome sequence or genome wide single nucleotide polymorphism (GWAS) analysis, was sufficient to explain basic gene regulation [1]. However, it is now well established that environmental factors greatly impact the cardiovascular outcome, suggesting the importance of additional pathways so far greatly ignored [2,3]. New improved technologies, together with more advanced mathematical modelling, allow for a more in depth analysis of detailed regulatory processes, including transcriptional control by histones and non-histone proteins and their impact on cardiovascular disease [4]. In the review series published in this issue of *Atherosclerosis*, we aim to provide an overview of the current knowledge in the field and open novel pathways for target identification of novel therapeutics.

The review by Constantino et al. [10] discusses the epigenetic processes, including DNA methylation, histone modifications and non-coding RNA, that participate in the dynamic interplay between different tissues and organs in patients at risk. In visceral and subcutaneous adipose tissue, this will partly underlie the transcription of genes implicated in inflammation, insulin resistance and lipo- and adipogenesis. In the vasculature, chromatin modifying enzymes are responsible for impaired nitric oxide availability and defective insulin signalling, which consequently results in reduced capillary recruitment and insulin delivery to tissues. Lastly, methylation status of certain genes is crucial for the polarization of immune cells, which influences adipose tissue inflammation and atherosclerosis. Whether this can be further translated into novel therapeutic targets remains to be investigated.

The review by Hoeksema and Glass [11] focuses on the epigenetic regulation of macrophages, which play an essential role in the underlying pathobiology of cardiovascular disease. Interestingly, macrophage behaviour and regulation are strongly tissue dependent, which will be discussed in great detail. Environmental signals play a major role in determining the macrophage phenotypes by regulation of transcription factors that activate regulatory elements, leading to tissue specific gene expression and thereby forming the macrophage phenotype. In line, monocytes and macrophages turn out to have a memory leading to long-lasting epigenetic changes at promoters and enhancers. Thus, the understanding of macrophage behaviour driven by different environmental and genetic factors will improve our insights into the disease process.

Next, Aavik and colleagues [12] discuss the implications of DNA methylation in the atherosclerotic plaque, with a focus on hypomethylation and hypermethylation processes. Atherosclerosis development is initiated at the sites of repeated injury at the endothelium, resulting in endothelium dysfunction. Consequently, regeneration of the endothelium is prevented, and gradual intima thickening further initiates the atherosclerotic process by enhancing lipid retention and inflammation [5,6]. Alterations in DNA methylation, which is an adaptive response to inflammation, occurs and further enhances the inflammatory state. Since atherosclerosis is an aging-related disease, understanding DNA methylation processes upon aging is essential, as DNA methylation is reversible and therefore may be a future target for treatment of atherosclerosis.

In their review, Zhang et al. [13] discuss the role of long intergenic noncoding RNAs in cardiovascular disease, which are increasingly recognized for their role in the pathobiology of atherosclerotic disease. However, due to the complex nature of the actions of lincRNAs, the current knowledge is limited. Additionally, the poor species conservation of lincRNAs complicates the investigations on the role in human biological processes. One of the best know examples underlining the difficulties is the study on the 9p21 locus, which has been associated with CVD risk in large GWAS studies [7–9]. The review highlights the current knowledge and offers some suggestion for future studies that will enable us to improve our understanding of lincRNA in the pathobiology of cardiovascular disease.

Finally, Nicorescu et al. [14] discuss the future of therapeutic options to interfere in epigenetic processes using specific inhibitors to improve atherosclerotic disease. In cancer, epigenetics is a major pharmacological target and epigenetic drugs are more and more frequently used. However, a number of issues have to be resolved. An

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overview is provided of all the new drugs that are currently under investigation.

With this review series, we hope to have provided an update on current standings of novel regulatory pathways that influence cardiovascular disease and that may give novel handles for innovative therapies.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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