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Short Notes

Epigenetics and Atherosclerosis – Challenges and Potential

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Atherosclerosis is a pathogenic process characterized by accumulation of lipids and immune cells in the arterial wall. As the lesion develops, the lumen is narrowed and the plaque can rupture, leading to acute, potentially lethal events, such as myocardial infarction or ischemic stroke. Atherosclerosis is the main cause of cardiovascular disease (CVD), which is the number one killer in the world [1,2]. Increased knowledge of the underlying mechanisms of atherosclerotic plaque progression can improve prevention and treatment, and increase life quality and life expectancy world wide. Epigenetics refers to heritable changes to the genome, which do not affect the DNA code itself. The modifications are reversible, allowing environmental factors to affect gene expression throughout life. Epigenetic modulation is an important regulatory mechanism in the cell, however is also involved in development of disease, especially studied in cancers. The current literature also suggests an important role for epigenetic regulation in development of atherosclerosis [3-6]. This paper will discuss the potential of and challenges related to this growing field of research.

Epigenetic mechanisms

Epigenetic modulation occurs through chemical modification of the DNA strand or of DNA associated proteins. The most studied epigenetic mechanism is DNA methylation. DNA methyltransferases (DNMTs) transfer a methyl group from the methyl donor S - adenosylmethionine (SAM) to the 5' position of a cytosine forming 5 -methylcytosine. This is a frequent event, mostly occurring in CpG dinucleotides. DNMT1 is responsible for maintaining methylation during cell division, while DNMT3A and DNMT3B are *de novo* methyltransferases, producing new DNA methylation marks. In promoter regions, DNA methylation stimulates recruitment of proteins that block transcription, turning gene expression off. Histon modification is another mechanism of epigenetic regulation where the N - terminal histon tails undergo post - translational modification such as acetylation, methylation and phosphorylation. Acetylation and phosphorylation change the ionic charge of the histon protein, altering its interaction with the DNA strand. Methylation on the other hand, regulates transcription through recruitment of chromatin factors, which affect chromatin packing. The effect on gene expression is dependent on which and how the histon are modified, and also histon - histon interaction. There is close interrelation between DNA methylation and histon modification, and also the transcription of miRNAs, a third epigenetic mechanism which can regulate gene expression by binding to complementary mRNAs or by modulating chromatin [3,7].

Epigenetics in atherosclerosis

Several central aspects of atherosclerosis are regulated by epigenetic mechanisms and vice versa, such as inflammation, lipid metabolism, oxidative stress and vascular cell function [4,5,6]. Oxidative stress is a common feature of atherosclerotic plaques, and the oxidizing agent H_20_2 is shown to regulate DNMT1 function and DNA methylation [8]. Further, smooth muscle cell function is regulated by both DNA methylation and histon modification [9]. With regard to inflammation, hypomethylation of the toll - like receptor (TLR) 2 promoter is associated with an increased inflammatory response [10], and DNMT3b is upregulated by saturated fat in macrophages, stimulating M1 polarization [11]. These are only a few examples suggesting epigenetics as a key mechanism regulating the pathological processes involved in atherosclerotic plaque development. Supporting this, studies have shown epigenetic alterations in patients with atherosclerosis; however there are some discrepancies between results. While one study showed increased DNA methylation in human atherosclerotic plaques compared to adjacent normal tissue [12], another study showed reduced DNA methylation in atherosclerotic plaques compared to healthy arteries [13]. Moreover, studies examining global methylation patterns in blood in relation to CVD risk have also shown contradictory results [4]. In a more detailed study, Greißel et al., examined DNA and histon methylation in blood and atherosclerotic plaques from patients. DNA methylation of the repetitive sequences LINE1 and SATα, as a measure of global DNA methylation, was decreased in plaques compared to healthy vessels, and was further decreased in advanced lesions. This was accompanied with reduced DNA methylation in serum from the patients compared to controls, but not in peripheral blood cells; suggesting the plaque as source of the circulating hypomethylated DNA. They further found cell and plaque - stage specific alterations in histon methylation patterns, implying that epigenetic regulation is important in plaque progression [14]. This study illustrates the importance of investigating different stages of disease, as well as different cells and compartments to get a complete picture of the epigenetic signature.

Therapeutic potential

Epigenetic modification is altered by lifestyle factors such as diet and smoking, which are known risk factors for CVD. Further, epigenetic modification is, as mentioned, involved in relevant pathogenic processes such as inflammation, and altered in patients with atherosclerotic disease. This gives therapeutic opportunities in modulating disease risk, as well as targeting established disease through epigenetic mechanisms. Epigenetics may also explain why individuals with similar genetics and risk factors respond differently to treatment and increased knowledge of these mechanisms may open up for more personalized medicine.

In addition to the possibility of new therapeutic strategies, already established treatments, such as statins, are thought to work at least in part through epigenetics mechanisms [15]. Studying how these affect epigenetic mechanisms can help identity new specific targets for treatment. Inhibitors of histondeacetylases (HDACs) have immune modulatory effects, and have shown therapeutic potential in many different diseases [16], and possibly also atherosclerosis. Epigenetic pathways are involved in macrophage activation [17], and targeting macrophage polarization to modulate development of atherosclerosis is of great therapeutic interest. Van den Bossche et al., have shown that inhibition of HDAC3 in murine macrophages skewed the cells towards an athero protective phenotype [18]. The therapeutic potential of this is further supported by HCDA3 deletion in myeloid cells resulting in more stable plaques in LDLR -/- mice. Moreover, HDCA3 expression was upregulated in ruptured compared to stable human plaques [19]. This supports epigenetic regulation as an important mechanism in plaque progression and as a possible target to prevent disease development. Contradictory however, blocking of HDAC3 in endothelial cells of ApoE-/- mice led to endothelial cell death and increased atherosclerosis [20]; underscoring the significance of cell specificity for these mechanisms.

Challenges and needs

Humans have great diversity in their genetic code, and the environment which they are exposed to; and both of these factors regulate the epigenome. Also, as epigenetic modifications are both heritable and reversible, study design and comparison of results are challenging. For analysis of epigenetic patterns, a cross - sectional design is often used, and proving causality is therefore difficult. As an example, epigenetic patterns change naturally with aging, and separating the cause and the consequences regarding age - related diseases, such as atherosclerosis, is problematic. The markers and methods used to detect global methylation are also shown to affect the results, and standardized protocols should be developed. Furthermore, transcriptional outcome depends on the localization of epigenetic modification, and global analyses provide an oversimplified picture. A combination of global maps and promotor specific approaches is warranted.

Increased understanding of epigenetic regulation in health and disease will provide answers to some of the major challenges with regard to therapeutic interventions, such as specificity and the risk of off - target effects. Studies combining epigenome and transcriptome analysis from *in vitro* experiments, animal models and clinical data are needed to get a full picture of this complex regulatory system.

The possibility that lies in epigenetic research is huge, and the aspects which complicates analysis, interpretation and application, are also what gives epigenetics its great potential. A new area of atherosclerotic research is emerging, and epigenetics should be appreciated as a key to better understand the pathogenesis of atherosclerosis, as well as a tool to develop new strategies to combat the disease. The job, however, is to figure out how.

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