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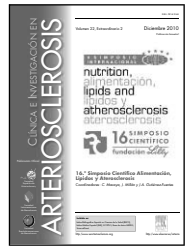

16.º SIMPOSIO CIENTÍFICO ALIMENTACIÓN, LÍPIDOS Y ATEROSCLEROSIS

Epigenetics and atherosclerosis

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Epigenetic mechanisms regulate chromosomal organization and gene expression by affecting DNA methylation and via modifications of histones surrounding chromatin[1]. Epigenetic changes are reversible leaving the genetic code unaltered. Thus, epigenetic regulation affects fenotype and it is currently clear that a certain physiological fenotype is not solely defined by the DNA sequence present in the genome. Epigenetic regulation of gene expression could explain some rapid changes in risk factors and disease profiles over the last few decades, which are difficult to explain based on DNA mutations or alterations in genomic sequence. For example, rapid increase in the incidence of cardiovascular diseases since 1950's and their decline during the last 2-3 decades could be at least partially affected by epigenetic regulation caused by dietary and other environmental factors.

Contribution of epigenetic mechanisms to cardiovascular diseases remains still poorly understood. Hypermethylation of genomic DNA has been found in human atherosclerotic lesions[2] and methylation changes occur at the promoter level of several important genes involved in the pathogenesis of atherosclerosis, such as extracellular superoxide dismutase, estrogen receptor-α, endothelial nitric oxide synthase and 15-lipoxygenase[3]. However, no clear data is currently available about histone modifications in atherosclerotic lesions. RNAi mechanisms may also contribute to the epigenetic regulation of vascular cells[4]. Thus, therapies directed towards modification of the epigenetic status of vascular cells might provide new tools for the treatment and prevention of atherosclerosis-related cardiovascular diseases.

Atherosclerosis is a chronic inflammatory disease of large- and medium-sized arteries which is characterized by accumulation of cholesterol, proliferation of arterial smooth muscle cells and accumulation of extracellular matrix components. Monocyte macrophages and T-cells play an important role in this process together with endothelial dysfunction[5]. It is obvious that unfavorable changes in dietary lipids and smoking contribute to the changes seen in atherosclerosis-related diseases over the last decades. However, it is plausible that epigenetic changes may also contribute to atherogenesis. Atherosclerosis involves proliferation of smooth muscle cells and some dietary components can affect methylation machinery which has an effect on proliferation[6].

As an example, dietary modification can have marked effects on epigenetic modifications of genome. Folate and methionine deficiency can lead to altered imprinting of insulin-like growth factor 2[7]. About 10%of human population may be affected by hyperhomocysteinemia and elevated plasma total homocysteine is associated with increased risk of coronary heart disease and stroke[8]. Homocysteine is metabolized to methionine after activation to S-adenosylmethionine, which is known to act as a methyl donor. Recent evidence suggests that pathogenetic role of hyperhomocysteinemia in vascular diseases might be mediated at least partly via adenosylhomocysteine accumulation and DNA methylation[9] which could affect lipid metabolism or oxidative stress status of vascular cells. Elevated homocysteine also decreases the bioavailability of nitric oxide[10].

In human somatic cells, approximately 1%of all cytosines appear to be methylated. This corresponds to 70%-90%of all cytosines in CpG dinucleotides, which are present in the 5' regulatory areas of genes and in the intronic and repetitive areas of several genes. Usually, CpG dinucleotides are unmethylated in the promoter areas, whereas they are often methylated in intronic and repetitive DNA elements[11]. It is interesting to note that increased methylation of

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estrogen receptor-α promoter has been detected in atheromas[12]. Also, promoter of an important antioxidative enzyme in arterial wall, extracellular superoxide dismutase, is methylated in atherosclerotic lesions, but is not methylated in normal arterial wall[2].

Methylation and acetylation of lysine residues in histone proteins appear to be other important mechanisms for epigenetic regulation of gene expression. Rapid changes in methylation and acetylation of histone proteins regulating the status of chromatin can also be targets for specific drugs, which are currently tested in phase II-III clinical trials for cancer therapy. It is possible that dysregulation of histone code caused by epigenetic changes could be normalized with drug therapy, thus generating new targets for drug development in cardiovascular diseases.

Conclusion

Epigenetic changes have been detected in atherosclerotic lesions, these changes may contribute to the pathogenesis of atherosclerosis and modify properties and gene expression in lesion cells. Treatments directed towards modification of epigenetic changes in vascular cells may provide new possibilities for the treatment of cardiovascular diseases.

Conflict of interest

The author declares he has not any conflict of interest.

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