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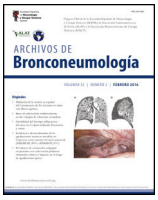

Editorial

New Biomarkers for Smoking: Epigenetic Changes☆

Nuevos biomarcadores en tabaquismo: modificaciones epigenéticas

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The key role of genetic variations in nicotine dependence and the risk of developing tobacco-related diseases are both well known. Smoking is a complex, multifactorial disease involving both genetic and environmental factors.[1] In recent years, numerous studies have revealed a significant genetic influence in various aspects of the behavior of smokers. Genes that influence an individual's response to nicotine, including nicotine metabolizers or receptors, and genes associated with addictive behavior in the smoker, due to the effects of nicotine on serotonergic, dopaminergic, and noradrenergic neurotransmitter pathways in the brain, have been described. However, the complex relationship between genetic and environmental factors is still largely unknown.[2,3] Individual susceptibility to these effects cannot be fully explained by the data obtained from variations in the DNA sequence.

In recent years, more evidence has emerged on the influence of smoking on epigenetic mechanisms that alter gene expression, such as DNA methylation, histone modification, and chromatin restructuring.[4] Methylation in specific CpG islands in the promoter region of various genes is the most common epigenetic modification in human DNA and a critical mechanism in the regulation of gene expression and adaptation to environmental stress. Changes in the DNA methylation pattern play an important role in the development of various diseases, such as cancer or psychiatric disorders; however, very few studies have analyzed the methylation pattern and its association with addiction to various substances.[4]

It is important when discussing epigenetic modifications in the DNA of smokers to differentiate between 2 processes; on the one hand, the association between altered DNA methylation and nicotine dependence as a cause of tobacco use, and on the other, epigenetic changes reflecting exposure to nicotine.[5,6] In the past decade, several studies of global methylation have found changes in the methylation status of various genes, such as those that encode the enzymes monoamine oxidase A and B, catechol-O-methyltransferase, aryl hydrocarbon receptor repressor (AHRR), which are related to the consumption of tobacco or are responsible for nicotine dependence.[7–9]

Both the monoamine oxidase enzymes and catechol-O-methyltransferase play a key role by modulating monoaminergic neurotransmission via the catabolism of dopamine, epinephrine, norepinephrine, and other related neurotransmitters.[10] The hypermethylation of specific sites on these genes has been associated with reduced expression, reduced activity and, therefore, greater exposure to dopamine in the brain, increasing the reward obtained after smoking the cigarette and the risk of dependence.[8] The results of these studies coincide with current knowledge about the role of these genes in nicotine dependence obtained from the analysis of genetic polymorphisms that affect gene function.

The main changes in DNA methylation as a response to tobacco consumption have been described in the xenobiotic response pathway, regulated by the AHRR gene.[7,11] A number of large-scale genomic studies reveal differences in AHRR methylation between smokers and non-smokers. Epigenetic modifications in AHRR have also been found to reflect intensity in tobacco consumption, and are reversible after giving up smoking; this appears to be an extremely sensitive and specific marker of this compound.[12–14]

Several authors have now proposed a potentially more specific use for epigenetic analysis in the field of smoking, namely, the analysis of the AHRR methylation pattern as a measure of the clinical status of the smoker (smoking habit study or monitoring during treatment for addiction), a method that shows increased sensitivity and specificity compared to other markers. One of the barriers to improving smoking prevention strategies and the effectiveness of smoking cessation treatments is our reluctance to use objective methods, such as the analysis of nicotine metabolites in various samples or in exhaled CO, to quantify tobacco use; instead, other less precise measurements, such as self-reported tobacco use, continue to be widely used in certain populations.[15] The analysis of AHRR methylation has advantages over the traditional markers mentioned above, both by widening the detection window (CO should be analyzed within 3–4 h of smoking the last cigarette), and by increasing specificity, since nicotine metabolite values can be affected by the use of substitute products that contain this compound. However, the use of AHRR methylation analysis in the treatment of smokers also has limitations. Given that studies have shown that AHRR methylation status is reversible after quitting smoking, we need to ascertain how much time would be needed to recover normality. This is a key factor in a correct assessment of the degree of smoking cessation using this marker, but no complete data have been published to date. It is known that AHRR methylation changes are more closely associated with average daily consumption in the preceding year than

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with shorter periods of time.[12] We would need to assume that epigenetic changes have a long-term, rather than short-term regulatory role. In addition, more extensive longitudinal studies in different populations would be needed to address this issue more precisely.

DNA methylation analysis has been proposed as a very interesting tool that provides information on exposure to tobacco in the context of the prevention and cessation of tobacco use. However, the best way of integrating it into the current system of prevention and treatment of smoking remains to be seen. Moreover, an understanding of changes in DNA methylation produced by tobacco consumption in a given setting would provide an comprehensive picture that could clarify the development of complex diseases such as cancer, and lead to the design of potential therapies.

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