Introduction

Impact of Nutritional Epigenomics on Disease Risk and Prevention: Introduction

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This special issue of the *Journal of Nutrigenetics and Nutrigenomics* covers an emerging topic that has been implicated in disease risk and prevention: nutritional epigenomics. Although the impact of epigenetics has been addressed for the last 3 decades in cancer research, only in recent years has interest surfaced in other fields, including cardiovascular and neurodegenerative diseases, obesity, diabetes and nutrition. Many definitions have been proposed for epigenetics in the literature, but most often epigenetics refers to heritable changes in gene expression that are not accompanied by alterations in DNA sequence [1]. Although there is some debate on which processes fall into this definition, DNA methylation, histone posttranslational modifications and more recently microRNAs are considered the main epigenetic phenomena. Methylation of cytosines, acetylation and methylation of lysine residues in histone proteins and microRNAs influence chromatin architecture and thus gene expression. They are involved in many biological processes including DNA-protein interactions, suppression of transposable element mobility, cellular differentiation, embryogenesis, X-chromosome inactivation and genomic imprinting. Accumulating evidence shows that these epigenetic processes can be influenced by nutritional components. For example, folate and vitamin B₁₂ participate in the 1-carbon metabolism and are necessary for chromatin methylation reactions. Furthermore, several bioactive food components have been shown to modulate the activity of enzymes that integrate the epigenetic machinery, including DNA methyltransferases and histone deacetylases and acetyltransferases. Thus, nutritional modulation of epigenetic processes adds a further layer of complexity to gene-nutrient interactions and should be considered for the definition of strategies for health promotion and disease prevention. Because epigenetic marks are potentially reversible and are implicated in the pathogenesis of diverse non-communicable diseases representing major public health problems in both developed and developing countries, the epigenome becomes an attractive target for

nutritional intervention. This special issue presents four papers that address the impact of nutritional epigenomics on disease risk and prevention.

The first paper by Lillycrop and Burdge provides an overview of the effects of nutrition during early life on the epigenetic regulation of transcription and implications for human diseases. The authors emphasize the importance of early-life environment, particularly nutrition, as a key determinant of disease risk in adult life and highlight the altered epigenetic regulation as the underlying mechanism of this developmental programming. By inducing permanent changes in gene expression in the embryo through altered epigenetic regulation of genes, nutrition could lead to altered susceptibility to diseases such as obesity, diabetes and hypertension. Because DNA methylation patterns are largely set during in utero life and early postnatal life, these early phases of development represent sensitive windows of susceptibility to environmental factors. According to the authors, both under- and overnutrition are implicated in the developmental origins of non-communicable diseases. They conclude that understanding the influence of nutrition and other environmental cues on the epigenome is critical for both the identification of individuals at risk and the definition of intervention strategies for the control of non-communicable diseases.

In the second paper by Zaina and Lund, epigenetics is discussed as a potential tool to understand diet-related cardiovascular risks. According to the authors, epigenetics is critical for the understanding of how cardiovascular risk factors interact with the genome by establishing a proatherogenic transcriptional program that – if corrected or reversed – could influence disease development. Animal and human data are presented showing that similarly to cancer and senescent tissue, global DNA hypomethylation is a hallmark of the advanced atherosclerotic lesion. Because vitamins and other dietary components may act as epigenome modifiers, the long-term health implications of dietary supplements on gene expression in an individual's lifetime or even through mother-to-progeny effects poses a complex question from a public health perspective. They further reinforce the need for integrating epigenetic information in genetic analysis in order to characterize functional interactions between genetic variants, epigenome and gene expression that may explain in a more comprehensive way variability in cardiovascular disease risk.

In the third paper, Ong et al. discuss the epigenome as a promising target for cancer prevention with bioactive food components. They briefly present an overview of epigenetic abnormalities as an underlying mechanism of aberrant gene expression implicated in the carcinogenic process from its initial stages. The authors then present data on the influence of bioactive food components with anticancer potential on epigenetic processes, with emphasis on DNA methylation and histone oncomodifications. Examples of such bioactive compounds include methyl donor nutrients, polyphenols, selenium, retinoids, fatty acids, isothiocyanates and allyl compounds. By interfering with epigenetic processes, these dietary compounds could influence transcriptional programs and affect several cellular processes. They further discuss the fetal origins of cancer hypothesis and highlight the importance of epigenetic programming by nutritional interventions during early life. According to the authors, the necessary dose and timing of interventions using bioactive food components to attain cancer-preventive epigenetic effects, as well as duration and specificity of epigenetic modulation by these dietary agents represent important topics that should be further investigated.

The importance of polymorphisms in 1-carbon metabolism and epigenetics in the context of folate-related pathologies is reviewed by Stover in the fourth paper. It focuses on the relationships among folate-mediated 1-carbon metabolism, chromatin methylation and human diseases, and the role of gene-nutrient interactions in modifying epigenetic processes. An overview of folate-mediated 1-carbon metabolism is initially presented. The association of folate-related diseases (cancer, cardiovascular disease and neural tube defects) with this

complex metabolic network that generates and transfers 1-carbons for the de novo synthesis of nucleotide synthesis and chromatin methylation reactions is then discussed. Animal and human data are presented showing the influence of 1-carbon metabolism-associated nutrients, including folate, methionine, vitamin B₁₂ and choline, on the cellular methylation potential and chromatin methylation. The role of genetic variants in this metabolic network and their impact on 1-carbon metabolism, epigenetic processes and human disease is then further reviewed. According to the author, although the exact mechanisms underlying the gene-nutrient interactions implicated in folate-associated pathologies are not clear, impairments in DNA synthesis and repair, and/or changes in chromatin methylation that alter genome expression and stability are assumed to be involved.

Based on what has been presented and discussed in the minireview articles presented in this issue, there is accumulating evidence showing the importance of disturbances in the epigenome mediated by environmental factors, including nutrition, for the development of several non-communicable diseases. Because of its plasticity, especially during development, the epigenome offers a promising molecular target for dietary interventions aiming at reducing the risk for these public health problems. For this to happen, it will be necessary to consider a life course approach probably starting early in life. It is important to keep in mind that nutritional epigenomics, as a specific dimension of nutritional genomics, is at its infancy, and many challenges and opportunities lie ahead. Thus, for the field to advance it is imperative to adopt a more epigenomic approach, focusing on the global analysis of epigenetic changes across the entire genome. Human nutritional epigenomic studies are also clearly needed. It is anticipated that by introducing an epigenomic perspective in gene-nutrient interaction studies, new insights will be gained into the complex relationship between genes, diet and disease risk.

Reference

- 1 Callinan PA, Feinberg AP: The emerging science of epigenomics. *Hum Mol Genet* 2006;15:R95–R101.