



Review

Of mice and humans *through the looking glass*: “reflections” on epigenetics of lipid metabolismRaffaella Longo, Alessandra Ferrari¹, Monica Zocchi, Maurizio Crestani*

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ABSTRACT

Over the past decade, epigenetics has emerged as a new layer of regulation of gene expression. Several investigations demonstrated that nutrition and lifestyle regulate lipid metabolism by influencing epigenomic remodeling. Studies on animal models highlighted the role of epigenome modifiers in specific metabolic contexts and established clear links between dysregulation of epigenetic mechanisms and metabolic dysfunction. The relevance of findings in animal models has been translated to humans, as epigenome-wide association studies (EWAS) deeply investigated the relationship between lifestyle and epigenetics in human populations. In this review, we will provide an outlook of recent studies addressing the link between epigenetics and lipid metabolism, by comparing results obtained in animal models and in human subjects.

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1. Introduction

All the living organisms constantly communicate with the environment. Both unicellular organisms and cells within a multicellular organism must be ready to adapt to several perturbations occurring in the external world (Turner, 2009). The capacity to rapidly sense,

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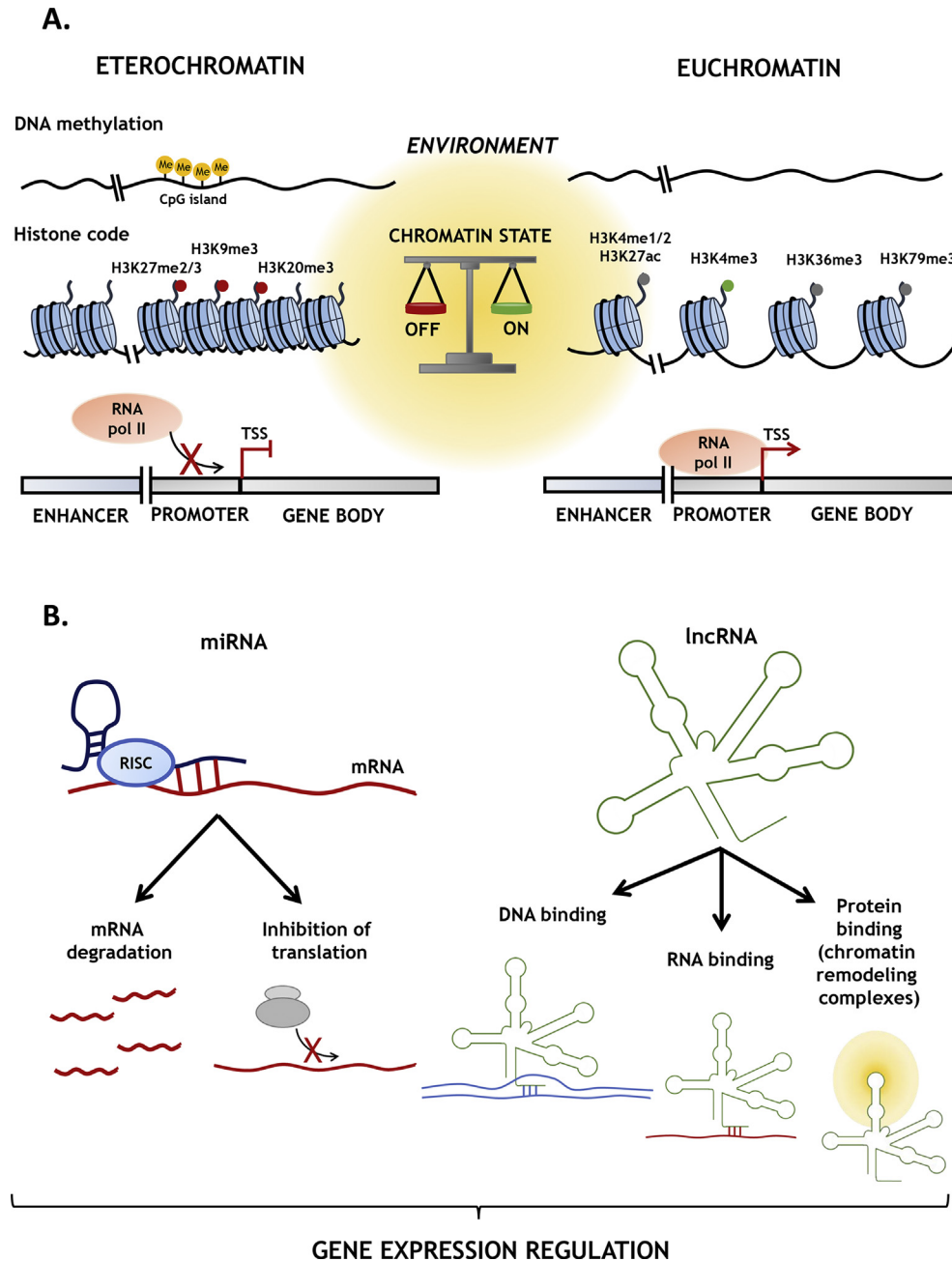


Fig. 1. Epigenetic mechanisms regulating genome function. (A) Environment influences chromatin state. Nutrients, life style and environmental stressors act as modulators of the epigenetic machinery, thus regulating the accessibility of DNA to transcription factors and RNA polymerase II, and establishing peculiar patterns of gene expression that are the results of a balance between activating and inhibiting DNA and histone modifications. (B) Furthermore, non-coding RNAs (*ncRNAs*), such as microRNAs (*miRNA* - 18–25 nt) and long non-coding RNAs (*lncRNAs* > 200 nt), influence gene expression at the level of transcription or translation through the interaction with DNA and mRNA, and play a role in chromatin regulation by interacting with chromatin remodeling enzymes or transcription factors.

integrate signals and elaborate a response is a signature of the plasticity and the robustness of a biological system (Kitano, 2007). All the external stimuli and the environmental changes influence the cell behavior through the activation of specific cellular programs, resulting in rapid and stable alterations in gene expression. The epigenetic machinery plays an important role in the establishment of peculiar patterns of gene expression and hence in the regulation of physiological responses. Epigenetics include all the mechanisms that heritably change the transcriptome by modifying chromatin structure without variations in the DNA sequence (Fig. 1A). These mechanisms make DNA locally more packaged or accessible to transcriptional factors and RNA polymerases (i.e. eu-

heterochromatin respectively). For this reason, chromatin is much more than a neutral system for packaging and condensing genomic DNA, but it is a highly dynamic platform that can be modified at different levels. The combination of different chromatin modifications constitutes the epigenetic code.

1.1. DNA methylation

The first layer of the epigenetic landscape architecture is DNA methylation: this covalent modification occurs at cytosine residues located at 5' of guanine residues ("CpG islands") and is mediated by DNA methyltransferase enzymes (Dnmt). In general, an exclusivity

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