Molecular Aspects of Medicine 54 (2017) 28–36

Contents lists available at ScienceDirect

Molecular Aspects of Medicine

journal homepage: www.elsevier.com/locate/mam

Review

One-carbon metabolism and epigenetics

Simonetta Friso [a, *], Silvia Udali [a], Domenica De Santis [a], Sang-Woon Choi [b, c]

[a] Department of Medicine, University of Verona School of Medicine, Verona, Italy
[b] Tufts University School of Nutrition Science and Policy, Boston, MA, USA
[c] Chaum Life Center, CHA University, Seoul, South Korea

ARTICLE INFO

Article history:
Received 18 November 2016
Accepted 18 November 2016
Available online 19 November 2016

Keywords:
One-carbon metabolism
Folate
Choline
Epigenetics
DNA methylation
Histone modifications

ABSTRACT

The function of one-carbon metabolism is that of regulating the provision of methyl groups for biological methylation reactions including that of DNA and histone proteins. Methylation at specific sites into the DNA sequence and at histone tails are among the major epigenetic feature of mammalian genome for the regulation of gene expression.

The enzymes within one-carbon metabolism are dependent from a number of vitamins or nutrients that serve either as co-factors or methyl acceptors or donors among which folate, vitamin B12, vitamin B6, betaine, choline and methionine have a major role. Several evidences show that there is a strict interrelationship between one-carbon metabolism nutrients and epigenetic phenomena.

Epigenetics is closely involved in gene transcriptional regulation through modifications super-imposed to the nucleotide sequence of DNA, such as DNA methylation, through chromatin remodeling systems that involves post-translational modifications of histones or through non-coding RNAs-based mechanisms. The epigenetic features of the genome are potentially modifiable by the action of several environmental factors among which nutrients cover a special place and interest considering their potential of influencing regulatory pathways at a molecular level by specific nutritional intervention and eventually influence disease prevention and outcomes. The present review will focus on the link between one-carbon nutrients and epigenetic phenomena based on the current knowledge from findings in cell culture, animal models and human studies.

Contents

1. Introduction

Epigenetic mechanisms are key phenomena for gene expression regulation that are independent from structural DNA sequence. They refer to chromatin remodeling systems, post-translational histone modifications, non-coding RNAs function and DNA

Abbreviations: THF, tetrahydrofolate; MAT, methionine adenosyltransferase; GNMT, glycine N-methyltransferase; SAdoHcy, S-adenosylhomocysteine; SAHH, S-adenosylhomocysteine hydrolase.

* Corresponding author. Department of Medicine, University of Verona School of Medicine, Policlinico "G.B. Rossi", P.le L.A. Scuro, 10, 37134 Verona, Italy.
E-mail address: simonetta.friso@univr.it (S. Friso).

http://dx.doi.org/10.1016/j.mam.2016.11.007
0098-2997/

methylation, the latter being the most studied epigenetic mechanism in mammalian cells. Biological methylation including that of DNA relies on methyl groups availability through the function of methyl donors and acceptors within one-carbon metabolism. In the present review the focus is on the role of one-carbon nutrients, i.e. folate, vitamin B12, choline, betaine and other vitamins, on the main epigenetic features of DNA with the scope of highlighting the link between nutritional factors and gene expression regulation through epigenetics. The modulation of epigenetic phenomena by nutritional factors opens up toward fascinating issues, from a deeper understanding of the pathophysiology of diseases to address novel ways for disease prevention or acquisition of better outcomes.

1.1. Epigenetic mechanisms

Epigenetic mechanisms refers to the complex of heritable states that regulate gene expression, and result from modifications in chromatin structure, at histone tails site and over-imposed at nucleotide series that occurs without alterations in the DNA sequence (Mizzen and Allis, 1998; Wolffe and Matzke, 1999; Robertson and Wolffe, 2000; Bird, 2007). Since they are modalities through which gene expression is modulated they greatly influence the development of several human diseases including cancer and cardiovascular illnesses (Friso et al., 2012; Heyn and Esteller, 2012; Udali et al., 2013) (Fig. 1). Moreover, differently from the genetic modalities of gene expression related to the decoding of the DNA sequence, epigenetic phenomena are potentially reversible and influenced by environmental factors, therefore, there is a growing interest in the understanding of epigenetically-determined regulation of gene expression by the different environmental exposure including that of nutrients (Friso and Choi, 2002; Choi and Friso, 2010; Tammen et al., 2013).

DNA methylation is the most studied epigenetic feature of DNA in higher eukaryote cells (Bird, 2002). It consists in the transfer of a methyl group (-CH3) to the 5'position of a cytosine at the CpG dinucleotide residues, it is catalyzed by the concert action of several DNA methyltransferases (DNMTs) and regulates gene expression patterns by altering chromatin structures (Fig. 1). Nutrients and bioactive food compounds can alter global and gene-specific promoter DNA methylation by affecting the function of DNA methyltransferases or the provision of methyl groups. Nutrients may, therefore, modulate gene expression by changing the chromosomal integrity and influence the health conditions from early development all through the progression towards aging processes (Kim

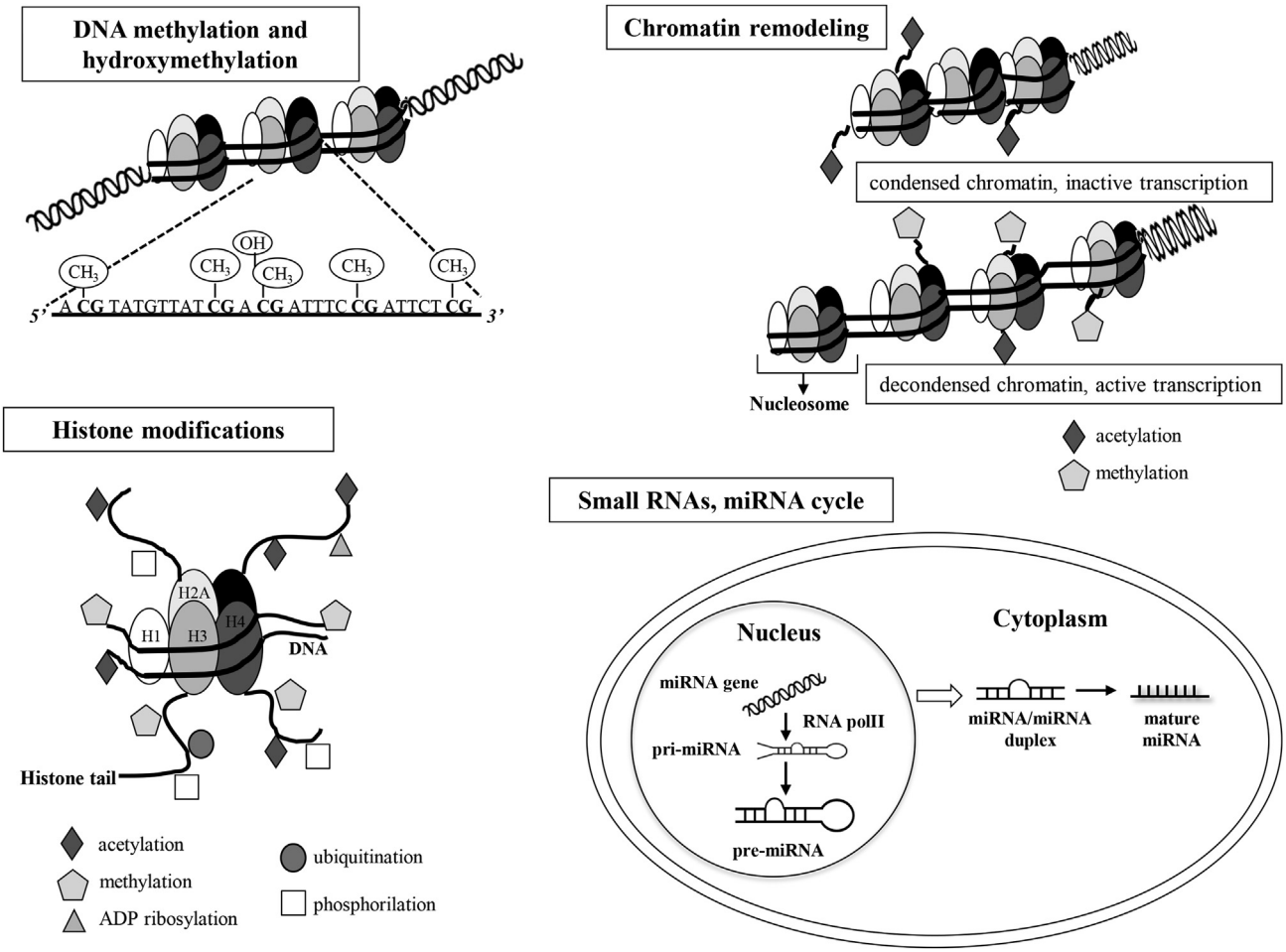

Fig. 1. Overview of the epigenetic mechanisms. Epigenetic mechanisms comprise all those phenomena that influence chromatin structure and gene expression without modifying the sequence of the DNA. DNA methylation and hydroxymethylation are modifications that pertain a single base of the DNA, *i.e.* the cytosine (*upper left panel in the Figure*). While DNA methylation has been extensively studied and its effects on gene expression demonstrated in relation to several genes, DNA hydroxymetilation has been recently described and the mechanisms of regulation have not been fully elucidated. Histone modifications (*bottom left panel*) are the modification of the aminoacids in the histone tails that can be acetylated, methylated, ADP-ribosylated, ubiquitinated, and phosphorylated. The modifications of specific residues of the histones, in particular through acetylation and methylation, determine conformational changes in the chromatin, a phenomenon known as Chromatin remodeling (*upper right panel*). The small non coding RNAs, and in particular microRNAs (miRNAs), have been recently recognized as epigenetic mechanisms for its capacity to modulate the expression of specific genes. The miRNAs are encoded by miRNA genes and the transcripts are then modified in the cytosol to produce the mature miRNAs that regulate specific target mRNAs (*bottom right panel in the Figure*).