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Review article

Chromatin methylation and cardiovascular aging

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ABSTRACT

DNA and histone methylation are well characterized epigenetic marks that are altered during the aging process. In aged cells and tissues, DNA cytosine tagging by methylation undergoes the so-called "epigenetic drift", in parallel with a change in the methylated histone profile. Despite the large body of knowledge regarding age-dependent epigenetic changes, there are few reports related to this topic in the cardiovascular field. This review summarizes age-dependent changes in DNA and histone methylation with a specific focus on age-related cardiovascular diseases (CVDs).

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1. Introduction

Epigenetic alterations have been included among the nine hallmarks of aging [1] and, in the past few years, it has become increasingly evident that aging and epigenetics constitute an indivisible binomial. Indeed, most of the variability observed in the organ function of the elderly may be explained by changes in tissue-specific epigenetic landscapes, together with genetic susceptibility and environmental cues. An epigenetic trait "is a stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence" [2]. This definition, however, is, somehow, incomplete as the term epigenetics also refers to the rapid modification of chromatin structure occurring in

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response to defined stimuli. Stability and, at the same time, the reversible nature of epigenetic modifications account for the heritability and adaptation to external signals of cellular gene expression programs, respectively, in the presence of a common genetic make-up. These two features make epigenetic mechanisms an extraordinary tool to control cell identity and ability to answer to both physiological and pathological stimuli. Histone modifications, DNA methylation and non-coding RNA activity represent the fundamental epigenetic mechanisms controlling chromatin architecture. A recent effort to expand the current view of epigenetic mechanisms has been attempted with the introduction of signaling categories which ultimately lead to the establishment of a stable epigenetic phenotype. According to this suggestion, the "epigenator" is the first signal, basically an environmental hit, which is converted in an intracellular pathway. The latter activates an "epigenetic initiator" (i.e. transcription factors, non-coding RNAs), responsible for seeking the target chromatin domain, whose structure is, thereafter, modified and preserved by an "epigenetic maintainer", that is a chromatin remodeling machinery [2]. Thus, alterations of these epigenetic modules, which occur over time, are responsible, at least in part, for the decline in the cellular homeostatic capacity and ability to face age-related physiological changes [3].

The cardiovascular system does not escape these phenomena; epigenetic alterations accumulate in aged vascular cells and are typical of cardiovascular diseases (CVDs) [4]. Nevertheless, recent evidences support the idea that developmental processes before birth, when epigenetic mechanisms establish cell fate [5], contribute to age-dependent CVD. To enforce the concept of a "fetal programming of cardiovascular disease hypothesis" [6,7], it has been recently reported that apparently healthy children conceived by assisted reproductive technologies (ART), which alter the epigenetic scenario of the embryo [8], suffer from systemic endothelial dysfunction, the first step of the atherosclerotic process [9]. Studies in mice have demonstrated that this vascular dysfunction is chromatin-based [10]. Thus, the clinical manifestation of CVD late in the lifetime is only the endpoint of a complex process in which environment, lifestyle, diseases, genes and epigenetics play specific and interconnected roles.

The detailed description of epigenetic mechanisms, marks and machineries has been the object of extensive reviews [11–14].

Here we discuss the impact of DNA and histone methylation during aging and in aged cardiovascular cells in particular, as the human methylome is, intriguingly, mainly altered during the aging process.

2. DNA methylation and demethylation

Methylated cytosine in the context of CpG dyads (meCpG) is a "true" epigenetic mark, as it is stable, although this is not a dogma (see below), and transmitted through cell generations through mitotic and meiotic divisions. The methyl groups, protruding into the major groove of DNA and changing its biophysical characteristics, inhibit the recognition of DNA by some proteins and allow the binding of others, impacting gene transcription [15]. DNA methyltransferases (DNMTs) are the catalysts of the reaction. Three enzymes are known in mammals: DNMT1, DNMT3a, and DNMT3b. The latter two DNMTs are served by their cofactor DNMT3L which is catalytically inactive [16]. Another member of the family, DNMT2, harboring sequence similarity to the others, has different functions and can methylate also RNA molecules [17,18]. The "maintenance" enzyme DNMT1 fully methylates the hemimethylated DNA resulting from DNA replication, while the "de novo" DNA methyltransferases, DNMT3a and b, preferentially methylate naked DNA [16,19] (Fig. 1, left panel). The methyl group induces transcriptional repression by the binding of other proteins which usually load repressive remodeling complexes and compact chromatin structure [20,21]. Alternatively, DNMTs may be recruited onto specific chromatin domains, potentiating gene repression [22]. These evidences indicate a dynamic crosstalk between DNA and histone methylation (see below). Three families of methylated DNA binding proteins are known [23]. The first family is characterized by a DNA binding domain called Methylbinding Domain (MBD) and contains MBD1, MBD2, MBD4, and MeCP2 [15,23]. MBD2 and MeCP2 are capable of recruiting Histone Deacetylases (HDACs) to enhance gene repression [20,24]. Kaiso, ZBTB4, and ZBTB38 proteins constitute the second family [25,26]. They possess a zinc-finger domain and are bifunctional as they bind methylated and unmethylated DNA sequences. The third family comprises UHRF1 and UHRF2; they bind methylated DNA through their SET-and-RING-Finger-Associated (SRA) domain. They are molecular players during cell cycle [27] and linkers of DNA and histone methylation [28]. Basically, three classes of genes are repressed by DNA methylation: parentally imprinted genes, according to their maternal or paternal origin [29]; transposons and intergenic sequences [30,31]; and tissue specific genes [32]. meCpG has been considered an irreversible mark of gene silencing. This assumption is, however, obsolete, as several evidences have pointed out as dynamic waves of DNA methylation/de-methylation events have a positive transcriptional effects and play

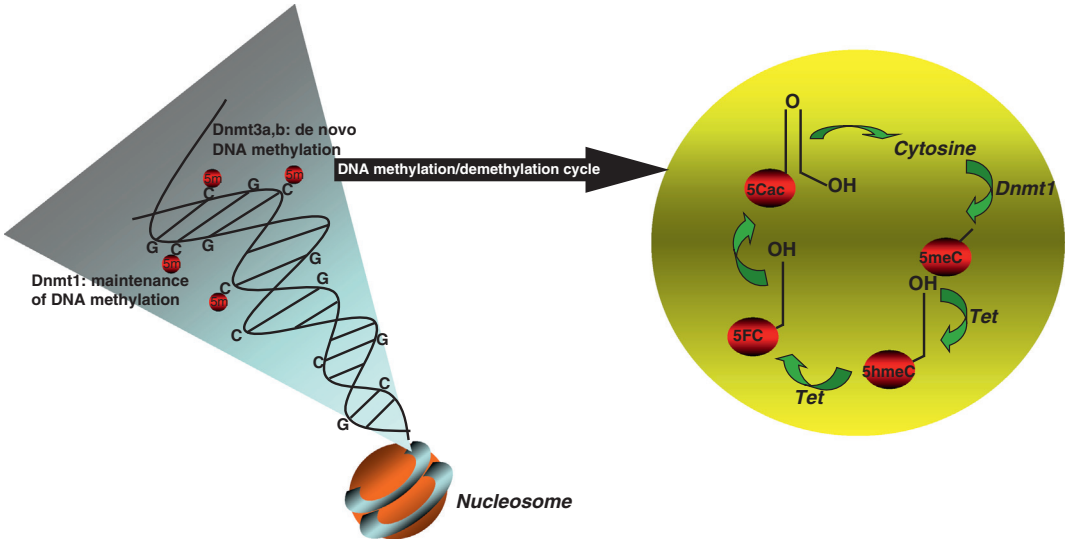

Fig. 1. Left. Schematic representation of a nucleosome – a histone octamer wrapped by 146 bp of DNA – bearing a DNA sequence containing a methylated CpG island. Right. DNA methylation/demethylation cycle. Tet family of enzymes including Tet1 and Tet2 and are believed to oxidize 5-meC to 5-hydroxymethyl- (5-hmeC), 5-formyl- (5-fC) and 5-carboxy- (5-caC) cytosine.

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