Maturitas 74 (2013) 130–136

Contents lists available at SciVerse ScienceDirect

Maturitas

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

Review

Epigenetics and aging

Patrizia D'Aquila, Giuseppina Rose, Dina Bellizzi, Giuseppe Passarino*

Department of Cell Biology, University of Calabria, 87036 Rende, Italy

ARTICLE INFO

Article history:
Received 5 November 2012
Accepted 11 November 2012

Keywords:
Epigenetics
Aging
Age-related diseases
Mitochondrial DNA

ABSTRACT

Over the past two decades, a growing interest on the research of the biological basis of human longevity has emerged, in order to clarify the intricacy of biological and environmental factors affecting (together with stochastic factors) the quality and the rate of human aging. These researches have outlined a complex scenario in which epigenetic marks, such as DNA methylation and numerous histone modifications, are emerging as important factors of the overall variation in life expectancy. In fact, epigenetic marks, that are responsible of the establishment of specific expression programs and of genome stability, represent a "drawbridge" across genetic, environmental and stochastic factors.

In this review we provide an overview on the current knowledge and the general features of the epigenetic modifications characterizing the aging process.

Contents

1. Introduction

Aging is a process of slow and gradual deterioration of the functional capacities that makes the individual particularly susceptible to environmental challenges and more prone to a variety of illnesses, and leads to a dramatic reduction of the individual survival probability and, ultimately, to death [1,2]. Aging affects all organisms, but lifespan is species-specific; in addition, among and within populations, a noticeable inter-individual variability exists with respect to the rate and the quality of aging. This heterogeneity results from a complex interaction of genetic, environmental and stochastic factors [3]. The continuous changes that occur during the process of aging can be observed not only in the individual's anatomy and physiology, but also at cellular and molecular levels. In fact, numerous studies revealed that an extensive remodeling of gene-expression profiles, driving physiological and/or pathological changes in different tissues, takes place with aging [4].

In disentangling the molecular basis of the above changes, exciting revelations have emerged by a branch of research known as "aging epigenetics".

Epigenetics refers to the study of mitotically and, in some cases, meiotically hereditable changes of a phenotype that tightly regulate the cell-type specific expression of genetic information without affecting the DNA sequence [5]. Epigenetic patterns are established

* Corresponding author. Tel.: +39 0984492932; fax: +39 0984492911.
E-mail address: g.passarino@unical.it (G. Passarino).

0378-5122/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.maturitas.2012.11.005

at pre-conceptional and gestational level. In fact, both paternal and maternal exposure to environmental factors during gametogenesis or gestation has been demonstrated to be responsible of the offspring's epigenome [6]. On the other hand, during the early stages of life, the inherited epigenetic status undergoes several changes to ensure an appropriate process of cell development and differentiation. Non-random mechanisms such as environmental stimuli or stochastic errors are able to induce changes in epigenetic profiles at both early and late life stages, being in most cases responsible for many processes occurring during the lifespan, including development, differentiation, stress response, and pathological conditions [7]. Although the epigenetic role in the above processes has been extensively investigated, little is yet known about the relationship between epigenetics and aging.

In this review we will focus on the correlation with aging of the best known epigenetic marks, such as DNA methylation and post-translational modifications of histones, that occur overtime in higher organisms and cooperate in chromatin remodeling, leading to a dynamic regulation of gene expression. We will also highlight the role of mitochondria in modulating the above modifications.

2. DNA methylation and aging

2.1. General features of DNA methylation

DNA methylation is a covalent biochemical modification consisting in the addition of a methyl group to the aromatic ring of cytosine (5-mC) predominantly located 5′ to a guanosine (CpG) [8]. This process prevalently involves CpGs located into intergenic and intronic CpG-poor regions as well as in repetitive sequences, most of which derived from transposable elements, thus hindering the event of amplification and new insertion in the genome [9]. Unmethylated CpG dinucleotides are, instead, concentrated in CpG-rich regions, termed CpG islands (CGIs), sequences of about 1 kb in length and with a CG content greater than 55%, that are mostly associated to the promoter regions and to the first exons of almost 60% of genes, including most housekeeping genes and half of all tissue-specific genes [10,11]. Conversely, Maunakea et al. revealed also the presence of methylated CGIs within intra- and intergenic regions, that are likely to be involved in a fine regulation of alternative transcripts, as emerged by the cell type specific expression of SHANK3 [12].

Different biological functions, such as development and differentiation, genomic imprinting, X chromosome inactivation and parasitic DNA suppression are mediated by DNA methylation, as it influences chromatin structure and, thus, inducing gene silencing. This process takes place either inhibiting the transcription factor binding to DNA target sequences or facilitating the recruitment of methyl-binding proteins [13,14].

DNA methylation has also been rarely reported to occur asymmetrically outside the CpG context (non-CpG methylation). This methylation, so far reported in plants, has been described more recently occurring in mammal embrional stem cells and in promoter regions of different genes, although its biological significance is unknown [15,16].

DNA methylation takes places after DNA replication and is mediated by a family of DNA methyltransferases (DNMTs) that includes *DNMT1*, *DNMT3A*, *DNMT3B* and *DNMT3L* [17,18]. These enzymes transfer a methyl group from S-adenosyl-L-methionine (SAM) to deoxycytosine, producing 5-methylcytosine and S-adenosylhomocysteine. DNA methylation patterns are also determined by DNA demethylases, that operate: (i) by preventing DNMT1 accessibility to newly replicated DNA strands; (ii) by recruiting enzymes belonging to the mismatch-repair pathways; (iii) through processes initiated by DNMT3A and DNMT3B themselves [19]. In this context, recent evidence demonstrated the capacity of the Ten-11 translocation family proteins (TET1-3) to oxidize 5-mC to 5-hydroxymethyl-cytosine (5-hmC) [20,21]. Despite 5-hmC is commonly considered an intermediate of the demethylation process of 5mC residues, both for its lowest levels in the genome and its short half-life, this species is emerging to be another epigenetic marker (the "sixth base"), having important roles in epigenetic reprogramming and regulation of tissue-specific gene expression [22,23].

2.2. DNA methylation and aging

DNA methylation patterns are not fixed; during various stages of mammalian development they are reprogrammed to ensure the normal mammalian embryogenesis and cell differentiation. Therefore, the above patterns can change during lifetimes in response to several stimuli from the external and internal environment. These stimuli are able to induce loss or gain of DNA methylation that can be propagated during cell division and sometimes transmitted across generations, resulting in permanent maintenance of the acquired phenotype [24].

Starting from the pioneering studies of Berdyshev and Vanyushin, several epigenetic alterations are now increasingly recognized as part of aging and aging-related diseases [25–28]. For instance, a complex relation between epigenetic control and X-linked or imprinted genes occurs in aging. In particular, it was demonstrated an age-reduction in DNA methylation of the inactive X chromosome, particularly in the myeloid cell lineage of peripheral blood cells [29]. As a result, a positive correlation between age and degree of somatic X chromosome inactivation (XCI) skewing was observed as well as in cancer, autoimmune disorders and other diseases [30,31].

In disentangling the role of epigenetics in human aging, a significant contribution has been provided by studies in which global and gene-specific methylation levels were assessed in mono- (MZ) and dizygotic (DZ) twins, mainly in order to elucidate the phenotypic divergence of MZ over time with respect to their susceptibility to diseases or other phenotypes [32,33]. Two independent works reported that lower epigenetic differences occur between MZ than DZ twins. In addition, although MZ twins are epigenetically indistinguishable during the early years of life, older individuals exhibited significant tissue-specific differences in their overall content and genomic distribution of 5-methylcytosines, affecting global gene-expression [34,35]. Moreover, Wong et al., through a gene-specific longitudinal study, found that epigenetic differences between MZ twins already occur during the course of childhood development, thus suggesting that environmental factors in the early stage of life can establish long-lasting epigenetic changes [36].

The relationship between the epigenetic changes and aging was also confirmed by observation of time-dependent changes in global DNA methylation levels in Icelandic unrelated individuals and in three-generation families from Utah [37]. The finding of familial clustering of methylation supports the idea that the DNA methylation stability is genetically determined.

Taken together, the above evidence demonstrate that in lifetime the epigenome can be regulated by genetic, stochastic (due to random epimutations) or systematic (in response to environmental changes) factors.

A gradual loss of total methylcytosine content with age occurs in most vertebrate tissues including humans [38]. This hypomethylation predominantly affects non island-CpGs and interspersed repetitive sequences (IRSs), such as Alu and human endogenous retrovirus K (HERV-K), through different age-dependent mechanisms [39–41]. More recently, Heyn et al. corroborated and extended the above findings demonstrating that the age-associated hypomethylation is present in all genomic compartments,