Molecular and Cellular Endocrinology 455 (2017) 33–40

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

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

Epigenetic mechanisms underlying lifespan and age-related effects of dietary restriction and the ketogenic diet

Cesar L. Moreno [a], Charles V. Mobbs [b, *]

[a] Department of Neurology, 1470 Madison Ave., 9-119, New York, NY 10029, USA
[b] Departments of Neuroscience, Endocrinology, and Geriatrics, Icahn School of Medicine at Mount Sinai, 1470 Madison Ave., 9-119, New York, NY 10029, USA

ARTICLE INFO

Article history:
Received 22 June 2016
Received in revised form
18 November 2016
Accepted 19 November 2016
Available online 22 November 2016

Keywords:
Histone acetylation
Creb-binding protein
Cbp
Sirtuin
HDAC inhibitor
Beta-hydroxybutyrylation
Dietary restriction
Ketogenic diet
Aging
Caloric restriction

ABSTRACT

Aging constitutes the central risk factor for major diseases including many forms of cancer, neurodegeneration, and cardiovascular diseases. The aging process is characterized by both global and tissue-specific changes in gene expression across taxonomically diverse species. While aging has historically been thought to entail cell-autonomous, even stochastic changes, recent evidence suggests that modulation of this process can be hierarchal, wherein manipulations of nutrient-sensing neurons (e.g., in the hypothalamus) produce peripheral effects that may modulate the aging process itself. The most robust intervention extending lifespan, plausibly impinging on the aging process, involves different modalities of dietary restriction (DR). Lifespan extension by DR is associated with broad protection against diseases (natural and engineered). Here we review potential epigenetic processes that may link lifespan to age-related diseases, particularly in the context of DR and (other) ketogenic diets, focusing on brain and hypothalamic mechanisms.

1. Introduction

According to the U.S. department of Health and Human services, the elderly population in the United States, as defined as 65 years or older, numbers 44.7 million and is expected to more than double by 2060. This population is also burdened by costly and chronic age-related diseases including Type-2 diabetes (21%), heart disease (31%), and Alzheimer's Disease (11%) (Hebert et al., 2013a). During aging bodily functions begin to decline leading to age-related diseases, making the aging process a major risk factor for a broad spectrum of disorders. Thus understanding what drives the aging process, and what links age to disease, is a major focus of translational research.

Several genetic and biochemical "hallmarks of aging" have been proposed to reflect processes driving aging (López-Otín et al., 2013). Many of these manifest as age-related changes in gene expression, which generally depend on tissue type (Lee et al., 1999; Park et al., 2009; Kayo et al., 2001; Swindell, 2009). Altered gene expression could be the result of genomic instability as a consequence of accumulated genetic damage (Moskalev et al., 2013), loss of DNA integrity (Hoeijmakers, 2009), and/or impaired nutrient sensing (López-Otín et al., 2013). Changes in gene expression could also be due to epigenetic mechanisms, including changes in chromatin modification or DNA methylation. These potential mechanisms are highly linked, making it difficult to assess cause and effect. For example, genetic and epigenetic mechanisms influence cellular processes like proteostasis, and vice versa. Nevertheless, targeting epigenetic mechanisms is a promising therapeutic approach to delay, prevent, or even reverse age-related diseases and impairments, since interventions influencing aging, such as dietary restriction (DR), may act in part through epigenetic modifications.

Here we outline evidence that the aging process and age-related diseases are modulated by epigenetic mechanisms, using observations from DR studies as a framework to understand these complex processes. Furthermore, because some protective effects of DR lead to increased levels of blood ketones, and these are also

* Corresponding author.
E-mail address: charles.mobbs@mssm.edu (C.V. Mobbs).

http://dx.doi.org/10.1016/j.mce.2016.11.013
0303-7207/

produced by ketogenic diets, we discuss potentially common epigenetic pathways mediating these effects (Maalouf et al., 2009). In particular, we focus in the hypothalamus because (1) neurons are (chronologically and phylogenetically) among the oldest cells in the body (Esiri, 2007; Spalding et al., 2005); and (2) nutrient-sensing neurons, in mammals largely confined to the hypothalamus, mediate many effects DR, including neuroendocrine and autonomic responses (Bishop and Guarente, 2007; Broughton et al., 2010; Dacks et al., 2013).

2. Aging influences global epigenetic characteristics

Aging not only influences gene expression but also related epigenetic characteristics. Aging can influence the genomic environment through effects on nuclear architecture (e.g. lamins) (Dechat et al., 2008), telomere shortening (Armanios et al., 2009; Hewitt et al., 2012), DNA methylation, and chromatin (through acetylation, methylation, and many other histone modifications) (Sun and Yi, 2015). Many of these changes correlate with age, and importantly interventions in epigenetic processes can accelerate or delay markers of aging, lifespan, and age-related diseases.

Lamins are nuclear scaffolding proteins that facilitate nuclear stability in part by regulating chromatin structure (Dechat et al., 2008). There are two types of lamins in animal cells: Types A and B. A-type (in the form of prelamin A) accumulates in aging human vascular tissue (Ragnauth et al., 2010), of particular interest mutations in A-type result in progerioid syndromes including Hutchinson-Gilford (Gruenbaum et al., 2005). Conversely, lamin Type B levels decline during cell senescence (Shimi et al., 2011), but less is known about its role in the aging process in vivo. Telomere shortening has been proposed to mediate the limitation on replicative potential in mitotic non-cancerous cells (the “Hayflick limit”), providing a potentially tractable target by enhancing telomerase, whose activity maintains telomere length but decreases dramatically in normal differentiated (but not in germline and cancer) cells (Hayflick, 1965). Inactivating mutations that affect telomerase activity produce some evidence of accelerated aging (Vulliamy et al., 2001). Telomere length in human blood cells decreases with age and is associated with increased age-associated mortality (Cawthon et al., 2003). In mice, reducing telomere length results in progerioid syndromes (Armanios et al., 2009) and intervening in these models by reactivating telomerase can reverse neurodegeneration and other systemic degenerative phenotypes (Jaskelioff et al., 2011). Further supporting a causal role for telomere maintenance in protective effects from aging, over-expression of telomerase reverse transcriptase, a component of telomerase, increases median lifespan in a cancer-resistant mouse model (Tomás-Loba et al., 2008). Finally, dietary restriction (discussed below) further maintains telomere length in cancer-resistant and wild-type mouse models (Vera et al., 2013). Interestingly, telomere function appears to have a synergistic relationship with progerin (the mutant form of lamin in Hutchinson-Gilford progeria syndrome), wherein progressive telomere damage increases progerin levels in normal human fibroblasts (Cao et al., 2011). It remains to be established if dietary interventions can also prevent progerin accumulation.

DNA methylation is another potential epigenetic mechanism impinging upon the aging process. DNA methylation was formerly thought to reduce gene transcription, especially during differentiation, but more recent studies have indicated that correlations between DNA methylation and gene expression levels are weak (Steegenga et al., 2014). Early studies suggested that global DNA methylation decreases with age (Romanov and Vanyushin, 1981). However, more recent studies using more precise methods have revealed complex patterns of methylation during aging, in which DNA methylation of some genes (or near regulatory sequences) increases with age. These complex patterns are nevertheless highly predictive of chronological age in humans in both cross-sectional and longitudinal studies (Florath et al., 2014). Furthermore, DNA methylation patterns are associated with age-related diseases including cancer (Issa et al., 1994), Type 2 diabetes (de Mello et al., 2014), and Alzheimer's disease (Fuso et al., 2005; Tohgi et al., 1999). Nevertheless, there is no published study demonstrating that manipulating DNA methylation patterns results in increased lifespan, although DR does influence DNA methylation in a similarly complex pattern (Ions et al., 2013). Although speculative, it is likely that DR influences methylation in the epigenome. For example, hypoglycemia (Fowler, 1993; Zhu and Krnjevic, 1993) and exercise (Dworak et al., 2007) increase adenosine in brain tissue, and elevation of this nucleotide has been shown to reduce DNA methylation levels (Williams-Karnesky et al., 2013). Similarly, ketogenic diets (further discussed below) have also been shown to elevate adenosine levels in the brain (Masino et al., 2009) supporting that there are common demethylation targets which respond to both diets.

Numerous effects on chromatin have been associated with aging, and targeting these modifications may modulate lifespan and protect against disease. Briefly, chromatin includes the association of DNA with histone proteins, in which H2A, H2B, H3 and H4 shape the core of the nucleosomes, whereas H1 and H5 serve as linker proteins. The residues in these proteins, particularly in the tail of histones H3 and H4, can be reversibly altered through several modifications that include acetylation, methylation, phosphorylation, ubiquination, and, more recently reported and of particular interest for the present review, beta-Hydroxybutyrylation (Xie et al., 2016). Some of these modifications are influenced by age and may impact lifespan. For example, H3K4 tri-methylation increases with age in *C. elegans* and preventing this modification increases lifespan (Greer et al., 2010), an observation corroborated in flies (Li et al., 2010). Furthermore, in a comparison of human prefrontal cortex of 11 individuals ranging from 0.5 to 69 years of age, H3K4 tri-methylation was reported to increase with age (Cheung et al., 2010). Conversely, H3K27 trimethylation decreases with age in *C. elegans*, and potentially influences lifespan since decreasing the H3K27 histone demethylase, UTX-1, was reported to increase lifespan (Maures et al., 2011; Jin et al., 2011). Interestingly, these effects are dependent on IGF-1 signaling pathways, which appear to share common mechanisms in some, though not all, modes of DR in C. elegans (Jin et al., 2011). H4K20 tri-methylation increases with age in the rat liver (Sarg et al., 2002), a pattern accentuated in human cells from Hutchinson-Gilford Progeria Syndrome (HGPS) patients (Shumaker et al., 2006).

Acetylation is one of the best studied histone modifications within the context of aging research. Histone acetylation and deacetylation are generally thought to result in euchromatin (transcriptional activation) and heterochromatin (transcriptional repression) states, respectively (Kouzarides, 2007; Li et al., 2007). Histones are acetylated by histone acetylases (HATs), and deacetylated by histone deactylases (HDACs). HDAC inhibition (leading to increased histone acetylation) is protective in a wide variety of age-related disease models (Jia et al., 2012; Mielcarek et al., 2011; Guan et al., 2009; Advani et al., 2011), and several HDAC inhibitors are approved for use in human diseases such as cancer. HDAC inhibition can even extend lifespan (described in more detail below) (Zhang et al., 2009). Of particular interest, mouse models of progeria exhibit reduced acetylation of H4K16, and HDAC inhibitors rescue this molecular profile while ameliorating age-related phenotypes (Krishnan et al., 2011). Furthermore, H4K16 acetylation increases with age in yeast where it appears to reduce cell span (Dang et al., 2009). On the other hand, substantial evidence suggest