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Review article

Life stress, glucocorticoid signaling, and the aging epigenome: Implications for aging-related diseases

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ABSTRACT

Life stress has been associated with accelerated cellular aging and increased risk for developing aging-related diseases; however, the underlying molecular mechanisms remain elusive. A highly relevant process that may underlie this association is epigenetic regulation. In this review, we build upon existing evidence to propose a model whereby exposure to life stress, in part via its effects on the hypothalamic-pituitary axis and the glucocorticoid signaling system, may alter the epigenetic landscape across the lifespan and, consequently, influence genomic regulation and function in ways that are conducive to the development of aging-related diseases. This model is supported by recent studies showing that life stressors and stress-related phenotypes can accelerate epigenetic aging, a measure that is based on DNA methylation prediction of chronological age and has been associated with several aging-related disease phenotypes. We discuss the implications of this model for the prevention and treatment of aging-related diseases, as well as the challenges and limitations of this line of research.

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1. Introduction

The increase in life expectancy over the last decades is a major accomplishment of modern medicine, but it has also led to a steep rise in the prevalence of aging-related diseases. Several of these diseases, including cardiovascular disease, cancer, and dementia, are now the leading causes of morbidity and mortality (Niccoli and Partridge, 2012), with enormous physical, emotional, and financial impact on individuals and societies. Studies further predictthat the number of older adults will more than double in the next two decades (Centers for Disease Control and Prevention, 2013; Office for National Statistics, 2012), suggesting that the impact of aging-related diseases will also continue to rise dramatically in the years to come.

Efforts to tackle aging-related diseases could substantially benefit by an improved, mechanistic understanding of modifiable risk factors that may accelerate the aging process and contribute to disease pathogenesis. In particular, a risk factor that is ubiquitous in modern societies is life stress. Higher levels of experienced or perceived life stress have been repeatedly associated with accelerated cellular aging as measured by telomere shortening. Specifically,

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telomere shortening has been observed with chronic caregiver stress (Epel et al., 2004; Litzelman et al., 2014), perceived stress (Parks et al., 2009; Puterman et al., 2010), intrauterine and early life stress (Entringer et al., 2011, 2013; Kananen et al., 2010; Savolainen et al., 2014), and work-related stress (Ahola et al., 2012); however, these relations have not been replicated in all populations studied (Jodczyk et al., 2014; Litzelman et al., 2014; Shalev et al., 2014). Furthermore, chronic and excessive stress as well as exposure to childhood trauma are independent risk factors for late-life neuropsychiatric disorders (Peavy et al., 2009; Tsolaki et al., 2009; Zannas et al., 2012), cardiovascular and cerebrovascular disease (Chandola et al., 2006; Eriksson et al., 2014; Everson-Rose et al., 2014; Hamer et al., 2012; Kaltsas et al., 2012; Rozanski et al., 1999; Suadicani et al., 2011), and certain types of tumors, such as breast cancer (Eskelinen and Ollonen, 2010; Michael et al., 2009), colon tumors (Wong et al., 2009), and cervical intraepithelial lesions (Pereira et al., 2003), though negative findings have been reported with breast and endometrial cancers (Kroenke et al., 2004; Nielsen et al., 2007, 2005). Despite this accumulating evidence for stress as an important factor shaping risk for aging-related disease, the underlying molecular mechanisms remain poorly understood.

An important mechanism to consider in the relation of life stress and aging-related phenotypes is epigenetic regulation, defined as processes that impact genomic regulation without changes in the underlying DNA sequence. Besides regulating cell differentiation (Hirabayashi and Gotoh, 2010), an important role of the epigenome is to function as a molecular interface between the genome and the environment that on one end is influenced by environmental exposures (Telese et al., 2013), including life stressors (Zannas and West, 2014), and on the other end shapes gene function and contributes to complex phenotypes, including aging-related diseases (Brunet and Berger, 2014). Epigenetic regulation encompasses a large and ever growing repertoire of processes such as DNA methylation, posttranslational histone modifications, noncoding RNAs, and three-dimensional changes in the conformation of chromatin. Since these molecular processes show substantial cell and tissue specificity, epigenetic modifications should ideally be examined in the tissue directly implicated in the phenotype of interest. However, select epigenetic signatures may show similar patterns across multiple tissues (Capra, 2015; Hannon et al., 2015; Horvath, 2013), suggesting that assessing these signatures in easily accessible tissues may hold promise as biomarkers for certain disease phenotypes.

Among epigenetic mechanisms, this article will largely focus on methylation of the 5′ cytosine of cytosine-guanine dinucleotides (CpG) of DNA, hereafter denoted as DNA methylation, which is the most studied modification in relation to aging and life stress in humans. The levels of DNA methylation can be dynamically regulated across the lifespan via the activity of DNA methyltransferases and enzymes involved in active demethylation (Telese et al., 2013). Profound changes in DNA methylation have been observed with increasing age and in several aging-related diseases. The vast majority of the studies to date have examined DNA methylation in whole blood (Bjornsson et al., 2008; Christensen et al., 2009; Florath et al., 2014; Heyn et al., 2012; Horvath, 2013; Horvath et al., 2012; Rakyan et al., 2010; Talens et al., 2012; Weidner et al., 2014), but some studies have also interrogated the brain and multiple other tissues (Christensen et al., 2009; Hernandez et al., 2011; Horvath, 2013). Furthermore, studies in human cohorts show that life stressors, especially early in development, can induce lasting changes in DNA methylation, both at specific candidate loci as well as on a genome-wide level (Boks et al., 2015; Brody et al., 2016a, 2016b; Klengel et al., 2013; McGowan et al., 2009; Non et al., 2014; Perroud et al., 2011; Yehuda et al., 2015; Zannas et al., 2015). The importance of stressors on shaping the epigenome has been corroborated by studies in rodents (Levine et al., 2012; Li et al., 2015; Murgatroyd et al., 2009; Schmauss et al., 2014; Schraut et al., 2014; Weaver et al., 2004, 2006).

Thus, it is plausible that stressors occurring throughout the lifetime could alter the epigenetic landscape and, consequently, influence genomic regulation and function in ways that are conducive to the development of aging-related disease phenotypes. In the following sections, we will provide a conceptual and mechanistic framework and discuss existing evidence supporting this model.

2. ‘Stressing’ the epigenome: focus on glucocorticoid signaling

Responses to stressors comprise a crosstalk of molecular, hormonal, neuronal, and behavioral processes. These multilevel adaptations are essential for coping with stressful challenges and maintaining organismic and cellular homeostasis. One of the primary effectors of the stress response is the hypothalamic-pituitary-adrenal (HPA) axis, which is centrally regulated by the hypothalamus, a region of the brain that sets this highly conserved axis into motion by signaling the anterior pituitary to secrete adrenocorticotropic hormone (ACTH) (Chrousos and Gold, 1992). ACTH then drives adrenal release of circulating glucocorticoids in the systemic circulation. Glucocorticoids primarily exert their actions in target tissues by activating two receptors, the mineralocorticoid receptor and the glucocorticoid receptor (GR). Various environmental stressors can exert lasting effects on the organism’s physiology and HPA axis via glucocorticoid signaling. In particular, certain stressor characteristics, including stressor duration, intensity, type, and context affect the function of the HPA axis and its ability to regulate glucocorticoid secretion (Tsigos and Chrousos, 2002). Dysregulation of the HPA axis can be programmed in an age- and sex-dependent manner, and these programming effects have been linked with susceptibility to psychiatric and age-related diseases in both human studies and animal models (Barha et al., 2011; Bourke and Neigh, 2011; de Kloet et al., 2006; Heim et al., 2008a, 2008b; Jankord et al., 2011).

Glucocorticoids can functionally impact essentially every tissue and body organ through activation of the GR. The GR acts as a transcription factor that regulates gene transcription by binding as a dimer to glucocorticoid response elements (GRE), i.e., conserved DNA regulatory elements in the regulatory regions of glucocorticoid-responsive target genes (Bamberger et al., 1996; McCabe et al., 2001), but also via GRE-independent interactions of the GR monomer with other transcription factors (Scheinman et al., 1995; Zannas and Chrousos, 2015). The GR-induced transcriptional regulation is characterized by high cellular and tissue specificity (Biddie et al., 2012). Notably, GRE binding has not only been shown to regulate gene transcription but to also induce lasting changes in DNA methylation, most notably demethylation, in CpGs located at or near GREs (Klengel et al., 2013; Thomassin et al., 2001; Wiench et al., 2011a, 2011b; Zannas et al., 2015). This GR-induced demethylation is rapid and dynamic, suggesting that it is driven by active demethylating mechanisms. Indeed, exposure to glucocorticoids may upregulate enzymes involved in active demethylation, such as the Tet family of 5-methylcytosine dioxygenases in neuronal tissue (Bose et al., 2015; Sawamura et al., 2015). Nonetheless, glucocorticoids have also been shown to decrease, in a dose-dependent manner, the expression of the gene encoding DNA methyltransferase 1 (DNMT1), the enzyme responsible for maintaining DNA methylation after cell division, in the mouse hippocampus (Yang et al., 2012). Overall, stressor and glucocorticoid-induced changes in DNA methylation represent a form of molecular memory thought to shape subsequent responses to glucocorticoids and stressors, thus contributing to stress-related phenotypes. Beyond changes