Transcriptional Signatures of Aging

R. Stegeman [1] **and V.M. Weake** [1,2]

*1 - **Department of Biochemistry,** Purdue University, West Lafayette, IN 47907, USA*
*2 - **Purdue University Center for Cancer Research,** West Lafayette, IN 47907, USA*

***Correspondence to V.M. Weake:** Department of Biochemistry, Purdue University, West Lafayette, IN 47907, USA.*
vweake@purdue.edu
http://dx.doi.org/10.1016/j.jmb.2017.06.019
Edited by M. Yaniv

Abstract

Genome-wide studies of aging have identified subsets of genes that show age-related changes in expression. Although the types of genes that are age regulated vary among different tissues and organisms, some patterns emerge from these large data sets. First, aging is associated with a broad induction of stress response pathways, although the specific genes and pathways involved differ depending on cell type and species. In contrast, a wide variety of functional classes of genes are downregulated with age, often including tissue-specific genes. Although the upregulation of age-regulated genes is likely to be governed by stress-responsive transcription factors, questions remain as to why particular genes are susceptible to age-related transcriptional decline. Here, we discuss recent findings showing that splicing is misregulated with age. While defects in splicing could lead to changes in protein isoform levels, they could also impact gene expression through nonsense-mediated decay of intron-retained transcripts. The discovery that splicing is misregulated with age suggests that other aspects of gene expression, such as transcription elongation, termination, and polyadenylation, must also be considered as potential mechanisms for age-related changes in transcript levels. Moreover, the considerable variation between genome-wide aging expression studies indicates that there is a critical need to analyze the transcriptional signatures of aging in single-cell types rather than whole tissues. Since age-associated decreases in gene expression could contribute to a progressive decline in cellular function, understanding the mechanisms that determine the aging transcriptome provides a potential target to extend healthy cellular lifespan.

Introduction

Aging is associated with increased mortality, progressive physiological decline, and increased risk of human pathologies such as cancer, heart disease, and neurodegenerative disease [1]. The progressive decline in physiological function of an organism is generally referred to as *senescence* [2], while the term *cellular senescence* specifically refers to the proliferative arrest observed in cells grown in culture after a finite number of divisions, also known as the Hayflick limit [3]. The rate and progression of senescence are influenced both by the chronological age of the organism and by genetic and environmental factors. Dynamic changes in gene expression occur during aging and are influenced by environmental stimuli and genetic factors. The transcriptome of a cell reflects both transcription and RNA processing events such as splicing and polyadenylation. Here, we broadly define transcriptional signatures of aging as the set of processed transcripts that are differentially expressed during chronological aging following completion of development.

The molecular changes that occur during senescence have been categorized into nine hallmarks of aging [1]. One such hallmark of aging is depletion of stem cell reserves, resulting in part from cellular senescence due to telomere attrition [1,4]. Other hallmarks of aging include genomic instability, mitochondrial dysfunction, epigenetic alterations, altered intracellular communication, deregulated nutrient sensing, and loss of proteostasis [1]. These molecular

hallmarks of aging both impact and are influenced by transcriptional changes. The transcriptional signatures of aging have been identified for a number of species in different cell types and tissues, with remarkably little overlap [5–8]. While individually these studies have identified potential biomarkers for aging, they also raise the question as to the long-term effect of cumulative changes in expression of multiple genes within a cell: Are these transcriptional changes protective or detrimental? Identifying the mechanisms that lead to age-associated transcriptional changes could provide potential targets for therapies to delay the onset of age-associated diseases by enhancing protective responses and suppressing detrimental changes. However, the low correlation in transcriptional signatures of aging observed in different studies provides a challenge to identifying such mechanisms.

There are different models for aging that have implications for the potential mechanisms that could lead to age-associated transcriptional changes [9]. Evolutionary theories of aging for species that reproduce repeatedly throughout their lifespan seek to explain longevity in terms of natural selection on the level of the organism rather than the cell. These aging theories can be broadly categorized as programmed or passive [9]. The concept of aging as a genetically programmed trait, framed in evolutionary terms, is based on the idea that aging is beneficial for the species as a whole [10]. Removing older individuals could benefit the population by preventing overcrowding and increasing the rate of evolution [9]. While this model is widely disputed [9], it is clear that aging can be regulated since mutations in genes such as *daf-2* or *daf-16*, encoding the IGF-1 receptor and FOXO, respectively, can extend lifespan in worms (*Caenorhabditis elegans*) [11]. Moreover, there are clear correlations between genetic loci, such as *APOE*, *FOXO3, 5q33.3*, and *ACE*, and longevity [11–20]. While these genes clearly modulate lifespan, their association with longevity does not necessarily imply that lifespan itself is under selection pressure. Arguing against this idea is the observation that the force of natural selection decreases with age [21]. Since animals are vulnerable to predation or disease, an animal's potential to produce future offspring declines with age, resulting in decreasing natural selection pressure with chronological age [21]. This decreasing natural selection pressure during aging forms the basis of the three major passive theories of aging that each seek to explain aging at the organismal level.

The passive theories for aging center around the concept that aging could have evolved by sacrificing late survival for early reproduction [22]. In these models, diverting resources toward growth and reproduction enhances fitness at the cost of maintaining cellular function [2,22,23]. These theories suggest that tissues within an organism and individual cells within those tissues age because they lack either the resources or mechanisms to fully maintain long-term cellular function. The first of these theories, the *disposable soma theory*, states that an organism balances growth and reproduction with preventing cellular damage by diverting resources toward growth and reproduction, thus enhancing fitness at the cost of maintaining cellular function [22,23]. The second *antagonistic pleiotropy theory* proposes that some genes that are important at the early stages of the life of an organism reduce fitness later during life [2]. The third *mutation accumulation theory* proposes that age-associated deleterious mutations would be weakly selected against, resulting in their accumulation in a species over evolutionary time [21]. All three of these theories describe how aging could have evolved by sacrificing late survival for early reproduction [22]. These concepts fit with the idea that aging is a balance between damage and repair [11,24], with organisms distributing energy expenditure between maintaining function and producing offspring. Genetic or environmental factors that shift this balance can alter aging.

In this review, we compare aging transcriptome studies to obtain insight into the mechanisms that could be involved in age-associated changes in gene expression. We focus on those studies examining chronological aging, rather than longevity per se, in healthy wild-type animals. We identify common classes of genes that are misregulated with age across different species, tissues, and cell types. We highlight new studies describing a pervasive role for splicing and RNA processing in aging. In addition, we describe potential mechanisms, consistent with the passive theories of aging, to describe how specific aspects of transcription and RNA processing could be particularly vulnerable to aging.

Global *versus* local changes in gene expression

The failure to maintain proper cellular homeostasis with age might be expected to result in a global deregulation of gene expression. An early study implicating gene expression changes as a major component of aging found a decrease in the amount of processed mRNA in the cytoplasm of aged rat liver cells, consistent with a global decrease in gene expression [25]. However, later studies in a variety of cell types and organisms indicated that relatively few genes show age-related changes in transcript levels. In contrast to a global deregulation of gene expression with age, only 4% of genes show age-related changes in expression in either human brain or kidney tissue, or in monkey (*Macaca mulatta)* skeletal muscle [26–29]. Moreover, fewer than 2% of genes show altered expression profiles with age in human skin, Achilles tendon, blood leukocytes, and retina, or rodent brain, skeletal muscle, liver, and heart tissue [6,30–39]. Furthermore, no more than 4% of mouse genes have age-associated changes in