ELSEVIER

Ageing Research Reviews
4 (2005) 55–65

ageing
research
reviews

www.elsevier.com/locate/arr

Review

Lessons learned from gene expression profile studies of aging and caloric restriction

Sang-Kyu Park, Tomas A. Prolla*

Department of Genetics and Medical Genetics, University of Wisconsin, 5302B Genetics building, 445 Henry Mall, Madison, WI 53706, USA

Received 26 August 2004; accepted 9 September 2004

Abstract

To examine molecular events associated with aging and its retardation by caloric restriction (CR), we have employed high-density oligonucleotide microarrays to define transcriptional patterns in mouse tissues, including skeletal muscle, brain, heart, and adipose. Aging results in a differential gene expression pattern specific to each tissue, and most alterations can be completely or partially prevented by CR. Transcriptional patterns of tissues from calorie-restricted animals suggest that CR retards the aging process by reducing endogenous damage and by inducing metabolic shifts associated with specific transcriptional profiles. These studies demonstrate that DNA microarrays can be used in aging research to generate panels of hundreds of transcriptional biomarkers, providing a new tool to measure biological age on a tissue-specific basis and to evaluate interventions designed to mimic the effects of CR.

Keywords: Aging; CR; Microarray; Mouse

1. Introduction

The molecular basis of aging is poorly understood, in part because we lack a large number of molecular markers of aging that can be used to measure the aging process in specific tissues. Survival curves, which are useful in assaying aging rates in short-lived organisms, such as *Drosophila* and *Caenorhabditis elegans*, are less practical in longer lived, complex organisms such as mammals. The increasing probability of death with age in mammals is due to a number of factors, including neoplasia, sepsis, and organ-specific

* Corresponding author. Tel.: +1 608 265 5204; fax: +1 608 262 2976.
E-mail address: taprolla@wisc.edu (T.A. Prolla).

1568-1637/$ – see front matter
doi:10.1016/j.arr.2004.09.003

failure. Given the long mammalian lifespan, measuring the aging process on an organ-specific basis in mammals through a panel of molecular markers is appropriate for evaluating interventions. In order to gain a better understanding of general aspects of aging, we are currently using DNA microarray analysis to study caloric restriction (CR) as a model system of aging retardation in mammals. We have characterized the gene expression profile associated with the aging process and CR in several organs, including skeletal muscle (Kayo et al., 2001; Lee et al., 1999), brain (Lee et al., 2000a), heart (Lee et al., 2002), and adipose tissue (Higami et al., 2004). These studies have shown the feasibility and utility of gene expression profiling to identify basic aspects of aging and its retardation by CR.

2. The gene expression profile of aging and CR in mouse skeletal muscle

Skeletal muscle is primarily composed of long-lived, high oxygen-consuming post-mitotic cells, a feature shared with other critical aging targets such as heart and brain. Loss of muscle mass (sarcopenia) and associated motor dysfunction is a leading cause of frailty and disability in older persons (Dutta and Hadley, 1995). At the histological level, aging of gastrocnemius muscle of mice is characterized by muscle cell atrophy, variations in size of muscle fibers, presence of lipofuscin deposits, collagen deposition, and mitochondrial abnormalities (Ludatscher et al., 1983).

Our comparison of gene expression patterns from gastrocnemius muscle from 5- and 30-month old male C57BL/6 mice revealed that aging is associated with alterations at the mRNA level, which may reflect changes in gene expression, mRNA stability or both (Lee et al., 1999). Aging in mouse skeletal muscle is characterized by increases in expression of genes involved in stress responses. Several transcriptional alterations in aging muscle suggest a decline in mitochondrial function or turnover, supporting the concept that mitochondrial dysfunction plays a central role in aging of this tissue. Additionally, a metabolic deficit is suggested by a decrease in the expression of genes involved in glycolysis, glycogen metabolism, and the glycerophosphate shunt. Aging was also characterized by large reductions in the expression of biosynthetic enzymes and a concerted decrease in the expression of genes involved in protein turnover such as 20S proteasome subunit, the 26S proteasome component TBP1, ubiquitin-thiolesterase, and Unp ubiquitin-specific protease. Remarkably, age-related changes in gene expression were significantly and broadly attenuated by CR. Of the four major gene classes that displayed consistent age-associated alterations (i.e. stress response, biosynthesis, protein metabolism, and energy metabolism), 84% were either completely or partially suppressed by CR. A global view of alterations in gene expression in CR mice suggests a metabolic reprogramming characterized by a transcriptional shift towards energy metabolism, increased biosynthesis, and protein turnover (Table 1). CR was also associated with a reduction in expression of inducible genes involved in stress responses and/or DNA repair. Because many DNA repair genes are likely to be inducible, our gene expression observations are in agreement with the observed reduction in oxidative damage to DNA in caloric restricted rodents (Sohal and Weindruch, 1996).