CMLS, Cell. Mol. Life Sci. 62 (2005) 320–343
1420-682X/05/030320-24
DOI 10.1007/s00018-004-4297-y

CMLS Cellular and Molecular Life Sciences

Review

The role of insulin and IGF-1 signaling in longevity

M. Katic and C. R. Kahn*

Joslin Diabetes Center and Department of Medicine Harvard Medical School, One Joslin Place, Boston, Massachusetts 02215 (USA), e-mail: c.ronald.kahn@joslin.harvard.edu

Received 8 July 2004; received after revision 25 August 2004; accepted 17 September 2004

Abstract. There are many theories of aging and parameters that influence lifespan, including genetic instability, telomerase activity and oxidative stress. The role of caloric restriction, metabolism and insulin and insulin-like growth factor-1 signaling in the process of aging is especially well conserved throughout evolution. These latter factors interact with each other, the former factors and histone deacetylases of the SIR family in a complex interaction to influence lifespan.

Key words. Aging; lifespan; genetic instability; telomerase; oxidative stress; superoxide dismutase; oxidants; antioxidants; reactive oxygen species; gluthatione; thioredoxin metabolism; calorie restriction; insulin; IGF-1; growth hormone; signaling; Sir; FOXO; p66; klotho; animal models; *S. cerevisiae*; *C. elegans*; *D. melanogaster*; mouse; knockout; human; syndrome; Ames Dwarf; Snell Dwarf; FIRKO.

Introduction

What is aging? Why do we age? Why do some species live longer than the others? Do genes determine lifespan? What is the role of metabolism on longevity? These are some of the questions that have intrigued biologists for ages.

Social scientists have raised other considerations: Do we want to live longer? And if so, how much longer? Is increasing longevity good for survival of the species, since natural/energy resources (water, food etc.) are limited? Will artificially prolonged lifespan alter natural evolutionary processes? How do we balance quality of life with quantity of life?

These two perspectives of aging and longevity are certainly connected, but are also distinct. One is the biology of aging and lifespan and the other is the social and evolutionary forces that may interact with the biology. In this review, we will focus on the biology of aging, and try to answer some of the first group of questions. We will focus especially on the role of metabolism and insulin and insulin-like growth factor-1 (IGF-1) signaling in this process.

What is aging?

Aging is a progressive loss of physiological functions that increases the probability of death. This decline in function occurs both within individual cells and within the organism as a whole. Life expectancy (or average lifespan) depends highly on both the biology of aging and the life circumstances of the organism. Evolutionarily speaking, very few organisms or animals were allowed to age, since mortality from starvation, predators, infection, diseases or environmental stresses often resulted in death before the biology of aging could play a role. Even human aging has become common in only the past few centuries. Two hundred years ago average lifespan was about 24 years due to high infant mortality, poor hygiene and inability to treat infectious disease [1, 2]. Now, with the development of good principles of hygiene, a wide range of effective

* Corresponding author.

medicines and relatively abundant food, the average lifespan in many developed countries is 80 or more years [3, 4]. With this increase in lifespan, causes of death have also changed, with infectious diseases and trauma being replaced by cardiovascular disease, cancer, diabetes mellitus and diseases of the elderly such as Parkinson's and Alzheimer's diseases. Interestingly, it appears that maximum lifespan (longevity) has not changed dramatically and seems to rest at about 120 years [5]. Thus, although the number of centenarians has increased, maximum human lifespan has not.

Theories of aging

There are several theories of aging [6] that point to four broad physiological processes important for longevity: genetic stability, telomere shortening, stress resistance and metabolic control.

Genetic stability: accumulation of genetic errors

One of the classic theories of aging is based on the role of accumulation of genetic errors. It has been recognized for many years that ionizing radiation causes DNA damage that can lead to early aging in mice [7–9]. Conversely, resistance to ultraviolet radiation is associated with increased lifespan in yeast [10]. Somatic mutations and chromosomal abnormalities, such as translocations and aneuploidy, are increased in cells isolated from old individuals compared to young individuals, presumably as a result of such DNA damage [11, 12].

In addition, dysregulation of DNA repair, cell cycle and integrity of extracellular matrix are found in cells isolated from old people and individuals with some premature aging syndromes [13–16]. Patients with Werner's syndrome who have mutations in the *WRN* gene, which encodes a helicase needed for DNA repair, show early signs of aging and have decreased lifespan [17, 18]. Patients with Cockayne syndrome have mutations in genes responsible for DNA repair and reduced lifespan [19]. Patients with ataxia telangiectasia who lack the ATM gene, a gene product required for detecting DNA damage and initiating repair response, also die young [20]. *ATM* kinase is activated by insulin and has a wide role in signal transduction and cell growth as well as in sensing redox homeostasis [21]. Thus, individuals with ATM mutations are also predisposed to cancer [22]. Children with Hutchinson-Gilford progeria syndrome show signs of aging very early and often die in their teens [23]. This disease is caused by mutations in the gene for lamin (*LMNA*). Although not proven to be directly involved in genetic stability, this is an intermediate filament protein that stabilizes the inner membrane of the nuclear envelope [24, 25]. Interestingly, mutations in this same gene are also associated with lipoatrophic diabetes [26–30]. DNA repair rates appear to correlate positively with lifespan among mammals. Furthermore, the DNA repair rate positively correlates with body size, which itself correlates with lifespan [31]. Accumulation of genetic errors also causes cancer, so it is not surprising that incidence of cancer increases with age.

In addition to mutations of nuclear DNA, point mutations and deletions of mitochondrial DNA (mtDNA) accumulate in a variety of tissues during aging in humans [32], monkeys [33] and rodents [34]. They cause a mosaic pattern of respiratory chain deficiency in tissues such as heart [35], skeletal muscle [36] and brain [37]. Mice that express a proofreading-deficient version of the nucleus-encoded catalytic subunit of mtDNA polymerase develop mtDNA mutator phenotype with an increased level of point mutations and deletions [38]. This is associated with reduced lifespan and premature onset of aging-related phenotypes, such as weight loss, reduced subcutaneous fat, alopecia (hair loss), kyphosis (curvature of the spine), osteoporosis, anaemia, reduced fertility and heart enlargement [38]. This provides a causative link between mtDNA mutations and aging phenotypes in mammals.

Telomere shortening: a 'biological clock'

Telomeres are the termini of linear eukaryotic chromosomes. They are involved in stabilizing the integrity of the ends of chromosomes [39], inhibiting the aberrant fusions and rearrangements that occur on broken chromosomes, and aiding the completion of duplication. During each cell cycle telomeric repeats (TTAGGG) are lost because DNA polymerase is unable to replicate the 3′ end of linear DNA completely, leaving a G-strand overhang. In germ cells and carcinomas, telomeric repeats are maintained by ribonucleoprotein telomerase that is capable of elongating telomeres de *novo* [40]. However, in the absence of telomerase activity, telomeres shorten with each cell division, reflecting the age of the cell lineage [41–43]. Many studies in a variety of tissues from mammals and other vertebrates have shown a gradual decrease of telomere length with age [43–46] and with doubling time in cell culture [41]. In addition, a positive correlation between telomere shortening and maximum lifespan has been shown in birds and mammals [47–49], suggesting that regulation of telomere length is not only associated with cellular replicative lifespan, but also with lifespan of the whole organism.

Genome size (DNA quantity per cell) is also positively correlated with longevity in birds [50] and in fishes [51]. However, how genome size can affect an organism's phenotype and longevity remains unclear.

In yeast, one of the manifestations of aging is a loss of transcriptional silencing of genes located in the heterochromatic region near telomeres and at the silent mat-