Ageing Research Reviews 12 (2013) 8–21

Contents lists available at SciVerse ScienceDirect

Ageing Research Reviews

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

Review

The mouse as a model organism in aging research: Usefulness, pitfalls and possibilities

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ARTICLE INFO

Article history:
Received 20 October 2011
Received in revised form 20 March 2012
Accepted 30 March 2012
Available online 17 April 2012

Keywords:
Aging
Mouse models
Genetic linkage
Caloric restriction
Compounds
Genetic modifications

ABSTRACT

The mouse has become the favorite mammalian model. Among the many reasons for this privileged position of mice is their genetic proximity to humans, the possibilities of genetically manipulating their genomes and the availability of many tools, mutants and inbred strains. Also in the field of aging, mice have become very robust and reliable research tools. Since laboratory mice have a life expectancy of only a few years, genetic approaches and other strategies for intervening in aging can be tested by examining their effects on life span and aging parameters during the relatively short period of, for example, a PhD project. Moreover, experiments on mice with an extended life span as well as on mice demonstrating signs of (segmental) premature aging, together with genetic mapping strategies, have provided novel insights into the fundamental processes that drive aging. Finally, the results of studies on caloric restriction and pharmacological anti-aging treatments in mice have a high degree of relevance to humans. In this paper, we review a number of recent genetic mapping studies that have yielded novel insights into the aging process. We discuss the value of the mouse as a model for testing interventions in aging, such as caloric restriction, and we critically discuss mouse strains with an extended or a shortened life span as models of aging.

1. Introduction

Aging is characterized by an increasing mortality rate with age after maturation, progressive changes in the biochemical composition of tissues, decrease in physiological capacity with age, reduced ability to respond adaptively to environmental stimuli with age and increased vulnerability to disease (Troen, 2003). Aging is caused by complex interactions between biological changes and environmental and/or social factors. Factors such as the quality and extent of healthcare throughout life, diet and genetic constitution, and habits such as smoking, alcohol consumption and physical activity affect the speed of biological aging and complicate the study of the biology of aging in human populations.

Using humans as subjects in aging research is complicated by many ethical issues, the long natural life span, environmental influences, and various other limiting factors. Therefore, various animal models have been developed to study the fundamental biology of aging. Animal models used to investigate the genetic and physiological basis of aging and age-related diseases should try to mimic the biological changes that occur with age while controlling for intrinsic and extrinsic influences. Genetic background, diet, environment and health status can be strictly controlled in many model organisms. Lower organisms, such as worms and fruit flies, have obvious advantages and have been very useful in the study of certain aging-related genes, but many researchers are convinced that mammalian model organisms are indispensible to understand human aging. Although primates might be ideal in that respect, there are ethical issues and, moreover, most primates have a long life span. Mammals that have a shorter life span yet are good models and can be genetically modified are found among the rodents. Although mice differ from humans in a number of aspects, they are quite similar to humans in much of their physiology and cellular functions, and to a lesser degree, even in their anatomy. The musculoskeletal, immune, endocrine and digestive systems of mice and humans are similar in both function and architecture. Cardiac function and age-related changes in the liver have been modeled in mice. While the mouse brain is less complex than the human brain, at the cellular level there are many similarities between the mouse and human nervous systems. Mice provide good models for testing potential therapeutics by combining the value of a mammalian system with a low-cost test subject, short life span and facility of genetic manipulation (Hasty and Vijg, 2004). Indeed, longitudinal

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http://dx.doi.org/10.1016/j.arr.2012.03.010

studies are easy to conduct on mice because of their short life span, and mouse tissues can be analyzed at all stages of the aging process (Nadon, 2004).

Despite the advantages of mouse models of aging, there are some important age-related differences between mice and humans. In contrast to humans, mice have long telomeres and high telomerase activity in many organs. They can synthesize vitamin C but humans cannot (Gershoff, 1993). Availability of vitamins is of great importance because vitamins can influence certain aging processes. Also, aging mice do not demonstrate all the typical age-related diseases seen in humans, *e.g.*, cardiovascular disease and Alzheimer's disease. Cardiovascular diseases in general, and particularly atherosclerotic disorders, are the main causes of illness, disability and death in humans worldwide (Roger et al., 2011). To study the involvement of cardiovascular disease in aging in mice, ApoE-knock-out mice were generated and fed a high fat western diet (Zhang et al., 1992). As they aged, they developed fatty streaks and fibroproliferative lesions, which made these mice a powerful model and a widely accepted tool in cardiovascular research. Moreover, though mice do show decreases in cognition and memory that parallel changes seen in much of the aged human population (Jucker et al., 1994), they do not develop Alzheimer's disease. Nevertheless, it is possible to study Alzheimer's disease in the context of aging by transgenic expression of mutated forms of human β-amyloid precursor protein or altered secretases that result in the formation of β-amyloid plaques in mice (Spires and Hyman, 2005).

In this review, we discuss the usefulness, pitfalls and possibilities of using mice with normal, extended or shortened lifespan in aging research and examine if whether genetic modifications or interventions altering life span in mice have similar effects in humans.

2. Normal, healthy aging of the mouse

Mice housed under privileged pathogen-free conditions, fed a balanced diet and kept away from natural predators live only a fraction of the life span of a human being. Differences in metabolism and body size are probably related to differences in life span, but other important factors must exist because the life spans of size-matched species can differ substantially. For example, rats live about 3 years whereas squirrels live up to 25 years (de Haan and Williams, 2005). The main causes of these differences in life span are likely genetic differences caused by selection under different environmental conditions (de Haan and Williams, 2005).

The difference in life span between different rodent species makes rodents suitable for studying connections between certain parameters and longevity. For example, Seluanov et al. studied telomerase activity in 15 rodent species with diverse life spans and body masses (Seluanov et al., 2007). Most rodents showed high telomerase activity in multiple somatic tissues. Surprisingly, the longest living rodents, the naked mole rat and the Eastern gray squirrel, had the highest telomerase activity. On the other hand, the largest rodents, the beaver and the capybara, had almost no telomerase activity.

The ongoing whole genome sequencing of species or strains with comparable body size but different life spans is expected to provide some basic answers. This is exemplified by a study in which the genomes of randomly mutagenized yeast strains were sequenced (Timmermann et al., 2010). In that study, a new dominant peroxiredoxin allele was identified as a cause of oxidant resistance and premature aging. Although full genome sequencing of different rodents will be very useful, other types of investigations must be considered, such as focusing on epigenetics and aging.

2.1. Inbred mouse strains

One good way to study the aging process is to monitor different parameters in inbred mice during their life span. Many inbred mouse strains of different ages are available from conventional breeding centers. But some principles should be kept in mind when using these mice in aging research. First, animals should be healthy, free of pathogens and disease, and have no signs of tumors or lesions to ensure that aging and not disease is being studied. This implies that mice at the very end of their life should be eliminated from the study to reduce the influence of diseases. It is also important to use mice that have already reached maturity to avoid observation of maturation rather than aging effects. Studying a particular trait in only two age groups is very risky because it would not be clear whether a difference in a trait is due to aging, maturation or age-associated pathologies. Increasing the number of age groups can reduce the risk of misinterpreting data. Also, it is advised to perform longitudinal studies when possible and to measure the trait at as many time-points as possible without interfering in the normal aging process (Miller and Nadon, 2000).

Some strains of mice live longer than others. The Jackson Aging Center carried out an in-depth life span study of 31 genetically diverse inbred mouse strains housed in specific pathogen-free conditions. Many reports are expected from this study, but an initial report showed that survival curves vary considerably between strains and that median life spans range from 251 to 964 days. Moreover, plasma IGF-1 levels were inversely correlated with median life span. In humans, high plasma IGF-1 levels were associated with increased mortality but the influence on life span has not been studied (Andreassen et al., 2009; Chisalita et al., 2011). This relationship supports the hypothesized key role of the IGF-1 pathway in regulating longevity in mice and humans and indicates that common genetic mechanisms might exist for regulating IGF-1 levels and life span (Yuan et al., 2009). Thus, identifying the genetic regulation of IGF-1 levels could help to elucidate the genetic regulation of aging. Leduc et al. used two approaches: Quantitative Trait Loci (QTL) analysis after crosses between two inbred strains with different IGF-1 plasma levels, and Haplotype Association Mapping (HAM) analysis using 28 inbred strains from the study discussed above (Leduc et al., 2010; Yuan et al., 2009). For the first approach, MRL females with high IGF-1 levels were crossed with SM males with low IGF-1 levels. (MRL × SM) F1 mice were then intercrossed to produce 136 females and 235 male F2 mice. The IGF-1 levels of F2 mice were normally distributed. The QTL analysis of IGF-1 levels of these F2 mice detected four QTLs on chromosomes 9, 10, 15 and 17. The most significant locus was the QTL on chromosome 10, which contains the *Igf1* gene. Plasma IGF-1 levels, measured in 28 domesticated inbred strains at the age of six months as discussed above (available online http://phenome.jax.org), were used to perform HAM analyses, which resemble genome-wide association studies in humans. These analyses revealed a major QTL on chromosome 10 overlapping the QTL identified in the F2 mice (Leduc et al., 2010). When The Jackson Aging Center reports more results, QTL analysis on parameters other than IGF-1, *e.g.* TOR signaling, can be done to reveal important longevity pathways, which can then be studied more directly in humans. Genetic studies focusing on the growth hormone/IGF-1 pathway and aging have already been performed, and they will be discussed in part three of this review.

2.2. Recombinant inbred mouse strains

The genetic basis for the difference in life span between different mouse strains can be investigated by genetic linkage studies or by using recombinant inbred strains of mice. These strains have been produced by repeated brother-sister mating, starting with two genetically distinct parents, each belonging to a certain inbred