



# Healthy aging – insights from *Drosophila*

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Human life expectancy has nearly doubled in the past century due, in part, to social and economic development, and a wide range of new medical technologies and treatments. As the number of elderly increase it becomes of vital importance to understand what factors contribute to healthy aging. Human longevity is a complex process that is affected by both environmental and genetic factors and interactions between them. Unfortunately, it is currently difficult to identify the role of genetic components in human longevity. In contrast, model organisms such as *C. elegans*, *Drosophila*, and rodents have facilitated the search for specific genes that affect lifespan. Experimental evidence obtained from studies in model organisms suggests that mutations in a single gene may increase longevity and delay the onset of age-related symptoms including motor impairments, sexual and reproductive and immune dysfunction, cardiovascular disease, and cognitive decline. Furthermore, the high degree of conservation between diverse species in the genes and pathways that regulate longevity suggests that work in model organisms can both expand our theoretical knowledge of aging and perhaps provide new therapeutic targets for the treatment of age-related disorders.

**Keywords:** *Drosophila*, lifespan, aging, genetics, environment

## INTRODUCTION

Aging generally refers to the process of getting chronologically older and it is typically accompanied by senescence, the gradual loss of physiological functions. Both of these processes are to some degree, inevitable for all living organisms. Chronological aging is primarily predetermined by heredity, whereas senescence results from a complex interaction between environmental and genetic factors.

During the last century, advances in medical technology have significantly contributed to extension of human longevity. According to data from the United Nations, US Census Bureau, Statistical Office of the European Communities, and National Institute of Aging (NIA) there are several trends in global aging: (1) *The overall population is aging*. For the first time in history, people aged 65 and over will outnumber children under the age of 5. (2) *Life expectancy is increasing*. Most countries, including developing countries, show a steady increase in longevity over time. (3) *The number of oldest old is rising*. People aged 85 and over are now the fastest growing portion of many national populations. (4) *New economic challenges are emerging*. Population aging will have dramatic effects on social entitlement programs, labor supply, trade, and savings around the globe and may demand new fiscal approaches to accommodate a changing world (Doriansky et al., 2007). Altogether, these findings further emphasize the need to understand how to promote healthy aging rather than just extending lifespan.

Non-genetic factors such as nutrition, environmental quality, psychosocial factors, and lifestyle play an important role in healthy aging. However, experimental studies have indicated that the heritable component has a significant impact on the senescence of invertebrates and mammals and accounts for approximately 35%

of the variance in lifespan (see Finch and Tanzi, 1997; Finch and Ruvkun, 2001 for details). Over the past few decades and especially since the completion of the Human Genome Project, a great number of studies have been carried out aimed at identifying the genetic factors that affect human lifespan. Despite the wide range of approaches utilized to identify longevity genes in humans including, linkage analysis (Puca et al., 2001; Tan et al., 2004), candidate-gene association analysis (Park et al., 2009; Lopez et al., 2012), and longitudinal studies (Nybo et al., 2003; Soerensen et al., 2010), progress has been limited due to the fact that these methods can be experimentally intensive, time-consuming, and poorly replicated. In addition, it is very difficult to control for variations in environmental conditions. In contrast, it is easier to minimize the effect of environmental conditions, lifestyle, and genetic background in model organisms. Moreover, while studies of longevity in humans are limited to demographic observations of externally apparent symptoms, model organisms can be genetically manipulated and phenotypically characterized in much greater depth allowing theories of aging and age-related disease to be experimentally tested.

Model organisms have also revealed that diverse organisms may share common biological mechanisms regulating longevity (Guarente and Kenyon, 2000; Helfand and Rogina, 2003; Hekimi, 2006). For example, studies have shown that dietary restriction, without malnutrition, can extend lifespan, and delay the onset of age-related pathologies in a wide range of species including yeast, worms, flies, and mammals (Good and Tatar, 2001; Barger et al., 2003; Koubova and Guarente, 2003; Johnson, 2008; Mair and Dillin, 2008; Skinner and Lin, 2010). Similarly, several metabolic processes and signaling pathways have also been shown

to have an evolutionarily conserved role in aging. For example, the insulin/insulin growth factor (IGF) signaling pathway (Kenyon et al., 1993; Clancy et al., 2001; Tatar et al., 2001; Bluher et al., 2003), histone deacetylases such as rpd3/Sir2 (Kim et al., 1999; Tissenbaum and Guarente, 2001; Rogina et al., 2002), and genes involved in oxidative stress (Phillips et al., 1989; Sohal and Weindruch, 1996; Parkes et al., 1998; Honda and Honda, 1999; Migliaccio et al., 1999; Sun and Tower, 1999; Taub et al., 1999; Tower, 2000), all exert evolutionarily conserved effects on aging and lifespan in a wide range of model organisms. The extent of evolutionary conservation in both the outward signs of aging and the environmental and genetic factors that influence it, suggests that aging itself is an evolutionarily conserved process and not simply an inevitable deterioration of biological systems. As such, studies of both the effects and causes of aging in model organisms can yield valuable insight into the molecular and cellular processes that underlie aging in humans.

Various model systems, including yeast, *C. elegans*, and rodents have been used to study the processes regulating organismal longevity. *Drosophila* also has many advantages to studying the biology of aging. For example, flies represent an optimal compromise between physiological, genetic, and anatomical relevance to humans as well as genetic, physiological, behavioral, and demographic power (Boulianne, 2001; Reiter et al., 2001; Helfand and Rogina, 2003; Jafari et al., 2006; Iliadi and Boulianne, 2010). Fruit flies also have a number of strengths that specifically aid in studies of aging and longevity. For example, while the lifespan of flies is relatively short (60–80 days), flies still exhibit age-related decline in several behaviors (Grotewiel et al., 2005). Furthermore, the demarcation between development and adulthood is much clearer in insects than other model organisms (adulthood being defined as eclosion from the pupal case). Large brood sizes also make it possible to measure survival in large numbers of individuals within each experimental cohort in controlled environments and to test the functional consequences of senescence either longitudinally in individuals or as sampled from the aging population. Finally, since most cells in adult flies are postmitotic (except a few cells in the gut, malpighian tubules, and gonads), the age-related decline in cellular function can be examined without interference from newly dividing cells. In this review, we will discuss how studies in *Drosophila* can provide insight into the mechanisms regulating healthy aging.

## PHYSIOLOGY OF SENESCENCE

Aging is a universal process and all species studied show age-related functional declines. However, different species age at different rates likely due to different fitness strategies employed to survive and reproduce in a competitive environment. The rate of aging can also be quite variable between individuals of a given species. Furthermore, while all cells, tissues, and organs show a functional decline over time, not all tissues experience aging at the same rate. Some systems may change slowly, while others decline rapidly, and some may even show periods of increased function (Spiriduso et al., 2005). Despite the extensive variability both between species, and within individuals, several tissues exhibit physiological senescence in both invertebrates and mammals, including a decline in muscle strength (Nair, 2005; Augustin and Partridge, 2009; Demontis

and Perrimon, 2010), immune response (Hoffmann, 2003; Flajnik and Du Pasquier, 2004), stress resistance (Service et al., 1985; Rose, 1999; Murakami, 2006), reproduction (te Velde and Pearson, 2002; Novoseltsev et al., 2005; Tatar, 2010; Luo and Murphy, 2011), and cognition (Horiuchi and Saitoe, 2005; Grady, 2008).

## AGING, MUSCLE STRENGTH, AND LOCOMOTOR FUNCTION

Sarcopenia or loss of muscle mass and function, is perhaps one of the most marked problems associated with aging and has been described for both invertebrates and higher organisms (Fisher, 2004; Augustin and Partridge, 2009). At the cellular level, this disease reflects mitochondrial dysfunction, altered apoptotic and autophagic signaling, as well as trace metal dyshomeostasis (Marzetti et al., 2009). Morphologically, sarcopenia is characterized by a decrease in both the number and size of individual fibers (Larsson et al., 1978) and an increase in the extracellular space and deposition of protein aggregates within the interstitial matrix (Kim et al., 2008). Despite the fact that *Drosophila* and human muscles show essential differences in fiber type, innervation, and regeneration, they both exhibit age-related morphological and functional changes. For example, myofibrils of old flies display reduced sarcomere length, increased *in vivo* interfilament spacing, and increased lattice disorder, showing a loss of ultrastructural integrity and acute sarcopenia (Miller et al., 2008). Interestingly, heart muscle structure and cardiac performance are also progressively impaired with age in flies (Nishimura et al., 2011).

Additionally, recent studies in flies have indicated a role for the well-known longevity-regulating pathways in the coordination of muscle aging. For example, the activation of dFOXO and its target 4E-BP in muscle decelerates aging and reduces the age-related accumulation of protein aggregates, whereas *foxo* mutants accelerate loss of proteostasis (Demontis and Perrimon, 2010). RNAi-mediated knockdown of the mitochondrial superoxide dismutase 2 (SOD2) in muscle tissue decreases locomotion and shortens lifespan (Martin et al., 2009). Likewise, results from another study have shown that overexpression of p38 MAP kinase extends *Drosophila* lifespan in a MnSOD-dependent manner while inhibition leads to early lethality and accelerates age-related motor (muscle-restricted) dysfunction (Vrailas-Mortimer et al., 2011).

Behavioral locomotion assays can offer an accurate way of assessing changes in muscle function. In *Drosophila*, many studies have shown that motor functions are significantly reduced with aging (Le Bourg and Lints, 1984; Fernandez et al., 1999; Simon et al., 2006; Martinez et al., 2007; Rhodenizer et al., 2008). Among various available methods for the assessment of locomotor activity, the startle-induced climbing behavior (negative geotaxis) is a reliable and informative assay. Usually, in these experiments, flies are tapped down to the bottom of their test vial and the distance the flies climb up the vial within a particular period of time is measured. This assay measures a whole complex of different behaviors including the escape reflex in response to mechanical stress, negative geotaxis (an inner orienting response and movement in opposition to gravitational cues), climbing ability, and locomotor activity itself. All of these behaviors reflect the functional status of muscle and locomotor function to varying degrees. Interestingly, detailed studies have revealed that the age-related decline in performance does not depend on the density of animals in the

test vial or the housing conditions (Cook-Wiens and Grotewiel, 2002; Goddeeris et al., 2003) but rather is primarily due to an age-dependent decrease in locomotor speed (Rhodenizer et al., 2008) similar to that seen in humans, suggesting a conserved mechanism. The relative simplicity and reproducibility of these behavioral assays makes locomotor activity a useful biomarker for healthy aging.

### AGE-SPECIFIC IMMUNE RESPONSE

The aging of an organism is accompanied by weakening of both the acquired and innate immune response (immunosenescence) to a wide range of pathogens. This process is mainly characterized by a gradual depression of cellular function throughout the immune system that, not only decreases immune response, but can also provoke the development of autoimmune disorders (Prelog, 2006). The innate immune response represents the first line of defense, comprising multiple pathways and systems, which are functionally conserved in both vertebrates and invertebrates (Flajnik and Du Pasquier, 2004). In *Drosophila* an innate immune response consists of several general components including pathogen detection via receptors that activate the Toll or Imd (Immune deficiency) signaling pathways (De Gregorio et al., 2002), hormonal regulation by means of juvenile and 20-hydroxy-ecdysone hormones that antagonistically induce antimicrobial peptide genes (Flatt et al., 2008a), prophenoloxidase cascade resulting in melanization (encapsulation of pathogens) (Tang, 2009), and cellular events such as phagocytosis (Williams, 2007). In contrast, acquired or adaptive immunity is an antigen-specific response that lasts a very long time and can generate “immune memory” to protect an organism against re-exposure to the same antigens. This type of response has been described for vertebrates and represents the second line of defense that is initiated when the non-specific, innate immune response is unable to deal with an invading pathogen.

Several studies suggest that aging has a profound effect on the status of the immune system in insects. For example, reduced phenoloxidase activity was observed in aged bumblebees (Whitehorn et al., 2011) and crickets (Adamo, 2004). Adult scorpionflies show a dramatic decrease in phagocytic capacity with age, even though cell numbers remained fairly constant (Kurtz, 2002). To date, the majority of studies in *Drosophila* have focused on the analysis of genes that exhibit age-related transcriptional changes. Interestingly, the most striking genome-wide (Pletcher et al., 2002; Landis et al., 2004; Sarup et al., 2011) and body-wide (Seroude et al., 2002) age-related increase in expression was found for genes that are involved in the immune response. However, it is unclear why immune response genes are up-regulated during aging. One possible explanation is that organisms increase their expression of immune related genes in response to prolonged exposure to pathogens throughout their life. Alternatively, it may reflect the decline in functional capacity of innate immunity with age (Zerofsky et al., 2005; Ramsden et al., 2008; Sarup et al., 2011).

Studies such as these may be useful for identifying potential biomarkers of immunosenescence, although additional microarray and proteomic studies will be required to identify novel markers and validate genes/proteins previously shown to exhibit age-related expression changes following infection or in the absence of infection. Additional studies will also facilitate the development

of appropriate molecular biomarkers of immunosenescence and the possible discovery of a completely novel mechanism that does not involve any of the genes/pathways identified to date. Another approach is to use cellular immunity biomarkers such as hemocytes. In adult flies, hemocytes either freely float within the hemolymph or are sessile (Williams, 2007). They are primarily specialized for phagocytosis and encapsulation. In a recent study, Mackenzie et al. (2011) compared the numbers and activity of the circulating hemocytes in flies of different ages. They found that the hemocyte population, which is responsible for clearing microbes from the hemocoel, becomes less able to phagocytose microbes with age due to fewer cells with phagocytic activity. The number of circulating hemocytes in females also significantly declined with age. Given the similarity between plasmatocyte hemocytes in adult *Drosophila* and the monocyte lineage that gives rise to macrophages in vertebrates, coupled with the relative simplicity of these measurements, this method has the potential to be a valid way of monitoring healthy aging of the fly immune system. Furthermore, using techniques such as this to analyze age-specific survival and the ability to protect against, and clear infection, will improve our understanding of which components of the immune system are responsible for immunosenescence.

### AGING AND STRESS RESISTANCE

The rate of living theory is probably the oldest among theories of aging (Pearl, 1928). Pearl formulated his theory based on Rubner's observation of a negative relationship between metabolic rate, body size, and longevity. Pearl's theory postulated that the lifespan of an organism is related to its metabolic rate; such that individuals (within a given species) with a higher metabolic rate (high level of energy consumption) will have a shortened lifespan compared to individuals with a lower rate. Consistent with this theory, observations in *Drosophila melanogaster* and *Musca domestica*, showed that flies raised at lower ambient temperatures have a lower level of metabolic activity and much longer lifespan compared to flies raised at higher temperatures (Miquel et al., 1976; Sohal, 1986; Farmer and Sohal, 1987). The association between metabolic rate and lifespan was also supported by artificial selection experiments (Riha and Luckinbill, 1996; Arking et al., 2002). Although this theory is not universally accepted (Austad and Fischer, 1991; Speakman et al., 2004; Van Voorhies, 2004) it nevertheless formed the basis for a free radical theory of aging (Harman, 1956). According to Harman's theory, free radicals, produced as a by-product of oxidative phosphorylation can damage important biological molecules. Accumulation of this damage over time, accounts for the effects of aging and eventually leads to death. The reactive oxygen-containing species (ROS) can covalently modify biomolecules such as nucleic acids, proteins, and lipids and cause oxidative stress. The level of this stress is determined by the misbalance between the production of ROS on the one hand and the efficiency of the antioxidant defense and repair processes on the other hand. Several studies in *Drosophila* have shown that flies selected for extended longevity exhibit resistance to oxidative stress (Service et al., 1985; Arking et al., 1991). In healthy cells, resistance to oxidative stress is accomplished by means of a complex defense system consisting of both enzymatic and non-enzymatic components, the main role of which is to breakdown and/or to neutralize ROS. This

defense complex includes superoxide dismutases (Cu/Zn SOD and MnSOD), catalase (cat), and glutathione-peroxidase. Firstly, superoxide dismutases convert superoxide to hydrogen peroxide and then catalase and glutathione-peroxidase remove the hydrogen peroxide from the intracellular environment by converting it to water. It is thought that these defense mechanisms become less efficient with aging and in some disease conditions, and ROS damage accumulates within cells in the form of chromosomal aberrations, membrane destabilization, loss of essential protein function, and ATP depletion. In humans, damage caused by ROS is not only thought to contribute to the aging process but has also been linked to numerous neurodegenerative diseases such as Amyotrophic Lateral Sclerosis (Robberecht, 2000) and Alzheimer's disease (Smith et al., 2000).

Several selection experiments have shown that some long-lived *Drosophila* strains express higher than normal levels of SOD (Tyler et al., 1993; Dudas and Arking, 1995; Hari et al., 1998). Interestingly, reverse selection of the long-lived flies for short lifespan restores antioxidant gene expression to control levels (Arking et al., 2000). Studies of the effect of single gene mutations that affect the lifespan of flies may also serve as a confirmation of the relationship between aging and resistance to stress. For example, reduced expression of *methuselah* (encoding a G protein-coupled receptor), causes a significant increase in lifespan and resistance to a number of stresses including starvation, high temperature and paraquat (Lin et al., 1998). In contrast, mutations that affect genes involved in ROS defense such as SOD or catalase have a negative impact on lifespan and show hypersensitivity to a variety of agents that generate ROS including Cu<sup>2+</sup>, paraquat, ionizing radiation, and hyperoxia (Campbell et al., 1986; Mackay and Bewley, 1989; Phillips et al., 1989). The relationship between oxidative stress and lifespan has also been illustrated by overproducing ROS protective enzymes. Using an inducible expression system based on the FLP recombinase; Tower and colleagues found a positive effect of SOD overexpression on *Drosophila* lifespan (Sun and Tower, 1999; Tower, 2000). A similar effect was seen when human SOD was overexpressed in motorneurons (Parkes et al., 1998). Remarkably, the extension of lifespan did not change the overall metabolic rate of the flies, suggesting that the observed effect was due to increasing oxidative stress resistance. Lifespan was also extended by simultaneous overexpression of SOD and catalase (Orr and Sohal, 1994). Transgenic flies which overexpress these two tandem acting enzymes exhibited a one-third extension of lifespan as well as reduced oxidative damage and a delayed loss of locomotor activity.

Despite the above examples, it is unclear whether the activity of antioxidant enzymes is required to extend lifespan. For example, the activity of several antioxidant enzymes were essentially the same in *Drosophila* lines selected for long or short lifespan. Similarly, the glutathione content (Mockett et al., 2001), SOD allele frequency (Force et al., 1995), and the electrophoretic mobility of SOD enzymes (Luckinbill et al., 1989), were also similar in short and long-lived lines. Furthermore, other studies showed that transgenic manipulations of antioxidant enzyme expression had little or no effect on lifespan (Seto et al., 1990; Reveillaud et al., 1991; Orr and Sohal, 1992, 1993; Orr et al., 2003). These discrepancies may be explained by differences in genetic background, the level

of transgene expression, the experimental methodologies used and/or the lack of adequate controls. Overall, these studies suggest that antioxidant defense may not be essential for lifespan extension but rather play a primary role in healthy aging. Unfortunately, there are only a few studies that report the functional consequences of manipulating the levels of antioxidant enzymes in *Drosophila*. Nevertheless, several facts appear to indicate that antioxidant defense affects healthy aging. First, in those studies where behavioral analysis was reported, the increased or reduced/abolished antioxidant enzyme activity was associated with delayed or accelerated functional senescence, respectively (Orr and Sohal, 1994; Ruan et al., 2002; Piazza et al., 2009; Hirano et al., 2012). Second, increased antioxidant enzyme activity increases stress resistance while reduced/abolished activity has the opposite effect, in most studies (see Le Bourg, 2001b for details). Third, the positive effect of increased antioxidant expression on lifespan tends to be most apparent in short-lived genetic backgrounds. Using data from all published studies examining overexpression of antioxidant enzymes, Orr and Sohal (2003) found a clear negative correlation between lifespan extension with overexpression of the antioxidant enzymes and the lifespan of controls. It seems that when an organism is "genetically" under great stress, the enhancement of its antioxidative defense properties can have a beneficial (rescue) effect whereas, under optimal conditions including optimal (wild type) genetic background such enhancement is less effective or even ineffective. Finally, the progression and severity of many age-related pathologies and diseases can be increased or diminished through modulation of the expression of genes involved in oxidative defense. Salmon et al. (2010) summarized the data showing that healthspan rather than lifespan is strongly affected by antioxidant status. Altogether, the data suggests that resistance to oxidative stress can be used as an indicator of healthy aging.

#### AGING, SEXUAL BEHAVIOR, AND REPRODUCTION

From an evolutionary point of view, there is no doubt that a higher level of reproductive success positively contributes to total fitness (Ehrman and Parsons, 1981). At the same time, life history theory (antagonistic pleiotropy) proposes that higher levels of reproduction are negatively correlated with survival (Williams, 1957). This so-called "cost of reproduction" concept has been widely accepted and demonstrated in a number of experimental studies (see reviews; Rose and Bradley, 1998; Partridge et al., 2005; Flatt and Promislow, 2007; Tatar, 2010). For example, selection experiments in *Drosophila* have shown that direct selection for extended longevity decreases early reproduction (Zwaan et al., 1995), while selection for postponed reproduction leads to increased longevity (Rose, 1991; Partridge et al., 1999). Female flies sterilized by either irradiation or by the sterile *ovo<sup>D</sup>* mutation have reduced age-related mortality (Sgro and Partridge, 1999). However, several experiments have cast doubt on the relationship between lifespan and fecundity. Using *Drosophila* mutants that lack a proliferating germ line, Barnes et al. (2006) have shown that life-long germ line ablation reduced longevity in females and either had no effect, or gave rise to a slight extension of longevity in males. In a similar study, loss of germ cells late in development or in the adult extends lifespan and modulates components of insulin/insulin-like growth factor signaling in *Drosophila* (Flatt et al., 2008b) and

*C. elegans* (Arantes-Oliveira et al., 2002). Examination of lifespan in various mutant or transgenic animals, also argue against a direct cost of reproduction on lifespan. In *C. elegans*, mutations in the *age-1* and *daf-2* genes result in life extension, without changes in reproductive ability (Johnson et al., 1993; Gems et al., 1998). In *Drosophila*, females bearing mutations in either the insulin-like receptor gene (Tatar et al., 2001), or the insulin-receptor substrate *chico* (Clancy et al., 2001), show decreased fertility and increased lifespan consistent with the cost of reproduction theory. However, the extended longevity and reduced fecundity appear to be unrelated since in combination with the dominant sterile mutation *ovo<sup>D</sup>* (which blocks oogenesis and extends female lifespan), *chico* mutant flies do not live as long as either fertile *chico* heterozygotes or sterile homozygotes (Clancy et al., 2001). Interestingly, several long-lived lines, including *Indy* mutants (Marden et al., 2003), *ecdysone receptor* mutants (Simon et al., 2003), or flies overexpressing the transcription factor *dFOXO* in adult head fat body (Hwangbo et al., 2004), do not exhibit reduced fecundity and, in some cases, have even shown an increase for these traits. It has been demonstrated in a series of *Drosophila* behavioral experiments, that sexual behavior and mating itself may have a profound negative impact on lifespan. For example, males that were supplied daily with virgin females showed decreased lifespan (Partridge and Farquhar, 1981). In females, mating reduces lifespan (Fowler and Partridge, 1989), possibly as a result of the competitive reallocation of limited physiological resources for courtship and egg production (Partridge et al., 1987), or from toxic peptides transferred to females in male seminal fluid (Chapman et al., 1995). However, it is unclear whether all of these factors are relevant in nature. For example, most females in nature are fertilized. They actively reject male courtship in many different ways including decamping behavior (running away, jumping, and flying away from the courting male) that may lead to full loss of contact with the courting male. In addition, female egg production and egg-laying rates greatly depend on ecological context, such as weather and climatic conditions, food availability, and the presence of predators.

In humans, the relationship between longevity and reproduction have been addressed in numerous studies, however, the results have yielded even more conflicting conclusions. The majority of these studies were focused on validation of *The Disposable Soma Theory of Aging*. One of the basic principles Kirkwood's evolutionary theory is that aging occurs as a result of decreased investment of resources in somatic maintenance and repair, to allow for increased allocation of resources toward reproduction (Kirkwood, 1977). This theory was tested using historical data sets collected from the British aristocracy living from the eighth to the nineteenth century (Westendorp and Kirkwood, 1998). It was shown that both the longevity of women, living at least up to 50 years (i.e., after the end of their reproductive life) and the longevity of men were negatively correlated with fertility. Thus, the authors came to the conclusion that these results confirm the existence of a trade-off between longevity and fertility in humans. While this study had a large resonance in the scientific and public press, it has been severely criticized (Gavrilov and Gavrilova, 1999; Le Bourg, 2001a; Gavrilov and Gavrilov, 2005; Mitteldorf, 2010) primarily because of the quality of the database

and inadequate statistical approach. In another study, using data from 153 countries, a highly significant positive correlation was observed between lifespan and fecundity (Thomas et al., 2000). Also, in a more detailed genealogical analysis of British aristocrats, a significant correlation between human lifespan and fertility was found when the effects of health and of mortality selection during childbearing ages were considered (Doblhammer and Oeppen, 2003). There are many additional reports that indicate a positive (Muller et al., 2002; McArdle et al., 2006) or inconclusive association (Le Bourg et al., 1993; Lycett et al., 2000) between lifespan and fertility in humans (see also Gavrilova and Gavrilov, 2005 for historical review of the relevant studies). Le Bourg (2007), in his comprehensive review summarizes most of the available data and concludes that, at present, there is insufficient evidence to conclude that longevity requires limited resources to be invested in somatic maintenance, thus reducing the availability of resources for reproduction. In fact, as the author points out, even if a relationship between these variables does exist, it depends more on the population under study than on a general mechanism linking longevity and fertility.

Aging has a negative impact on sexual activity and reproductive function for both sexes. Age-related decline in these functions is caused by numerous physiological changes particularly in the neuroendocrine and reproductive systems. In women these changes are mainly manifested in the reduction in follicle number and ovarian function and, as a consequence, in reduced secretion of estrogens and progesterone (Djahanbakhch et al., 2007). In men, the progressive decline in sexual function is accompanied by changes in levels of testosterone and associated reproductive hormones (Murray and Meacham, 1993). There is a fundamental difference between reproductive senescence in men and women. Women, show an abrupt loss of reproductive potential that marks the end of their "reproductive life," while in men, reproductive function declines more gradually and does not involve an acute drop in fertility.

In contrast to humans, *Drosophila* females continue to produce primary oocytes from stem or progenitor cells throughout their life, reaching a maximum in young females and followed by a steady decline (Novoseltsev et al., 2005). The quality of eggs or level of fertilization is also affected by age (David et al., 1975). Interestingly, detailed analysis of female reproductive senescence revealed that *Drosophila* egg-laying and mortality rates were dependent on mating history (Rogina et al., 2007). Female reproductive life can be divided into three epochs: optimal, vulnerable, and declining terminal. The first epoch of adulthood is characterized by a high rate of egg-laying after mating and has a reversible effect on mortality. During the second epoch, mating does not induce increased egg-laying but does result in an irreversible increase in mortality. Finally, at the terminal stage, females exhibit sharp reductions in egg-laying regardless of their chronological age. Despite the differences between flies and humans as to the effect of age on reproductive behavior, there may be some parallels between the processes that occur in follicles of aging humans and in egg chambers of aged flies under oxidative stress (Tatar, 2010). Cumulative oxidative damage caused by free radicals was suggested to impair the viability of developing follicles in humans (Tatone et al., 2008). In *Drosophila*, overexpression

of the antioxidant enzyme SOD in germ line stem cells leads to increased numbers of these cells in aged females (Pan et al., 2007).

*Drosophila* males exhibit a peak of sexual activity up to 4 weeks. During this period they show a fairly constant performance in such traits as multiple mating, latency time, duration of copulation, and level of fertility. These characteristics decline in a manner that is similar to the age-dependent course of survivorship (Economos et al., 1979). Male reproductive success can be measured either under competitive or non-competitive mating conditions. Selection for delayed senescence increased the male reproductive success in both competitive and non-competitive conditions. This selection also resulted in significant increases in the ability to recover from exhaustive mating bouts (Service, 1993). Several components of male reproductive behavior show a clear age-dependent decline including the time to begin copulation, duration of copulation, and the proportion of females that were remated (Service, 1993). Moreover, males that had been subjected to selection for delayed senescence were superior to control males (rapid senescence) with regards to one of the components, sperm competition (sperm defense).

Overall, the peculiarities of *Drosophila* reproductive history allow us to conclude that fruit flies exhibit obvious senescence in reproductive functions. The progression of senescence can be monitored by measuring the age-related changes in sexual and reproductive behaviors. Delay in reproductive senescence may contribute to the general extension of lifespan, which is more important in healthy aging.

### SENESCENCE OF COGNITIVE FUNCTION

The gradual impairment of cognitive function is one of the main components of the normal aging process. Age-related decline in cognitive function may vary considerably between individuals and in the cognitive processes affected such as attention, memory, or decision-making. Progressive impairment of cognitive function is frequently associated with age-related degenerative brain disorders such as different types of dementia, including Alzheimer's and Huntington's disease, vascular and Parkinson's dementia, and Lewy body disease. These diseases are becoming more and more common amongst aged people across the globe and represent a growing clinical and social issue.

Attention is a key cognitive process that affects virtually all other cognitive functions. For example, it has been suggested that attentive processes may be involved in orientation, concentration, and filtration of distracting information (McDowd and Shaw, 2000). Older people usually have some difficulties with attention tasks that require dividing or switching of attention between multiple inputs (Verhaeghen and Cerella, 2002). An early symptom of Alzheimer's disease also involves problems with selective attention. Specifically, Alzheimer's patients exhibit a proportionally greater deficit in inhibitory and visual search tasks (Levinoff et al., 2004) as well as in tasks that require the inhibition of automatic cognitive ability (Perry et al., 2000).

Memory impairments are among the most commonly recognized cognitive changes in senescent humans. They arise from defects in the encoding, storage, and retrieval of information. In

general, these defects can be classified into several major groups: (1) "sensory memory" – retains information only long enough to operate on it (object recognition), and requires the contribution of different sensory inputs; (2) "working memory" also known as "short-term memory" – actively holds new information in the mind allowing temporal tasks such as reasoning and comprehension to be performed, and is required for further information processing; (3) "long-term memory" – where information can be essentially stored for a lifetime. Working memory is impaired in old age (Hertzog et al., 2003; Oberauer et al., 2003), however, the mechanisms underlying this impairment are still under debate. Loss of long-term memory in aged humans may be associated with a number of causes. First of all, there are several differences between the long-term memory defects observed during normal aging and those that are associated with some pathological conditions. In normal aging, the memory defects are mainly the result of inconsistent encoding and retrieval strategies, whereas pathologies such as Alzheimer's disease, are characterized by a selective and severe deterioration in the consolidation and storage of new information. In other words, in normal age-related memory loss, individuals may express a sense of frustration due to an inability to recall specific memories, while in Alzheimer's disease patients forget the memory entirely, including the context in which the memory was formed.

Evidence from a wide range of cross-sectional studies suggests that many of the individual differences in age-related cognitive function are associated with differences in sensory function such as hearing or sight. Moreover, when this variance in sensory function is statistically controlled, the differences in cognitive function disappear (Baltes and Lindenberger, 1997). Many cognitive processes such as problem solving, goal-directed behavior, and decision-making require the integration and processing of information from numerous primary inputs for its effective performance.

The study of learning and memory in fruit flies began in the laboratory of Seymour Benzer more than three decades ago. Using chemical mutagenesis approaches coupled with a reliable method designed to specifically induce learning and memory, several mutants were isolated (Quinn et al., 1974). Studies of these mutants have provided insight into the cellular and biochemical mechanisms underlying learning and different kinds of memory formation (Dubnau and Tully, 1998). Flies have multimodal sensory modalities that gather information about the external world and translate it by means of the nervous system into an appropriate behavioral response. In fact, flies possess a large number of sensory organs that result in the perception of taste, touch, smell, hearing, and vision (Stocker, 2004; Ebbs and Amrein, 2007; Gerber and Stocker, 2007; Kernan, 2007; Ting and Lee, 2007). Many studies clearly demonstrate that fruit flies are capable of both associative and non-associative learning and memory. For example, flies can learn to move toward odors previously associated with reward, or avoid an odor that has been paired with punishment (Tempel et al., 1983; Tully and Quinn, 1985). They can also learn to recognize different visual, tactile, and spatial cues (Wustmann and Heisenberg, 1997; Heisenberg et al., 2001). Interestingly, *Drosophila* males show a plasticity in courtship behavior, through a complex process that may include habituation, sensitization,



operant, and classical learning (Siegel and Hall, 1979; Kamyshev et al., 1999; Griffith and Ejima, 2009). Several recent studies have shown that flies may demonstrate attention-like (van Swinderen, 2007), goal-driven (Pick and Strauss, 2005), and decision-making behaviors (Zhang et al., 2007). To date, *Drosophila* has also been successfully used as a model system to reveal molecular, physiological, and behavioral mechanisms of several human neurodegenerative diseases, including Alzheimer's, Parkinson's, and Huntington's (Chan and Bonini, 2000; Lu, 2009; Bonner and Boulianne, 2011).

Similar to other organisms, *Drosophila* exhibit age-related reductions in learning ability and memory performance. In early studies, Le Bourg (1983) investigated the role of age on non-associative learning using a proboscis extension reflex (PER). This reflex represents a stereotyped response to the activation of chemoreceptors located on the foreleg tarsi by sucrose. Repeated application of sucrose caused habituation to the stimulus whereby the fly stopped extending its proboscis in response to application. In this study, flies did not show any age-related effect on habituation as measured either by the percentage of flies that were able to habituate or the number of training sessions required for habituation. Aged individual flies showed impairment in habituation, specifically in the speed of memory acquisition in this learning task (Fois et al., 1991). Decrease in learning performance was observed between 3 and 35 days, and reached a plateau after 35 days. In another paradigm, the conditioned suppression of PER, flies learned to associate sucrose stimulation with negative reinforcement (Brigui et al., 1990). Both middle-aged and old flies required more training to associate the positive and negative stimuli. Age-dependent effects on PER were also observed in a visual discrimination task. The acquisition of PER suppression was delayed in middle-aged and old flies (Fresquet and Medioni, 1993). Age-related memory impairment in flies was also observed using a Pavlovian olfactory avoidance paradigm (Tamura et al., 2003). In this paradigm, flies learn to associate an electric shock with an odor. Depending on the training regimen induced, memory may persist either for minutes (short-term memory), hours (short and middle-term memory), or even days (long-term memory). Flies exhibited a weak reduction in immediate memory performance (right after training) by about 10 days of age, which did not progress up to the age of 50. However, short-term memory was severely impaired in 20 day old flies and declined to a minimum up to the age of 50 days. Interestingly, aging has differential effects on distinct memory forms. For example, old and young flies perform comparably with respect to protein synthesis-independent anesthesia resistant memory, while the protein synthesis dependent long-term memory is completely abolished in old flies (Mery, 2007).

Several studies on *Drosophila* learning and memory mutants confirm that not all forms of memory are equally affected by age. For example, young *amnesiac* (middle-term memory mutant) flies show similar memory retention to aged wild type flies (Tamura et al., 2003). Expression of this gene does not decrease with age and its overexpression does not suppress age-related memory impairment in a wild type background (Saitoe et al., 2005). Another memory mutant, *DCO*, delays age-related memory impairment without altering lifespan and memory at early ages (Yamazaki et al.,

2007). Another method to induce and test learning and memory in flies is conditioned courtship suppression, where male flies learn to attenuate their courtship behavior after a negative experience of courting a fertilized female. This paradigm is based on natural sexual behavior and involves only natural stimuli such as visual and olfactory (pheromones) cues. Interestingly, 30-day-old wild type flies do not show a significant decrease in immediate or short-term memory with this assay, whereas mutants in the kynurenine pathway do (Savateeva et al., 1999). Thus, natural selection may favor the maintenance of some specific forms of memory in aged flies. Taken together, these studies demonstrate that *Drosophila* can be utilized to identify and characterize the effect of age and the role of single genes in learning and memory and provide insight into core mechanisms of cognitive senescence in many species including humans.

## CONCLUSION

It is well-known that advances in medicine and health care have significantly contributed to increased longevity in humans over the last 100 years. There is also a clear trend toward increased life expectancy including an increase in the numbers of people living to an advanced age and the number of people with chronic age-related diseases. These trends emphasize the need to understand the genetic and physiological factors underlying biological aging and particularly, those that promote healthy aging.

According to Arking (2003) there are three ways to extend lifespan: increasing early survival rate, increasing late survival rate, or delaying senescence. Remarkably, the first two do not affect basic aging processes. For example, the first one leads to a significant increase in mean but not maximum lifespan, while the second one leads to change in a maximum but not mean lifespan. Delayed senescence, in turn, leads to a significant increase in both the mean and maximum lifespan (Arking, 2005). This raises the question as to whether healthspan and delayed senescence are inter related. As stated above, while many genes have been shown to extend lifespan, these may have little or no ability to delay physiological senescence. In other words, the period of functional disability before death may increase despite the fact that the total duration of life is increased. Thus, the search for appropriate biomarkers applicable to monitor functional senescence is highly important with regards to healthy aging and age-related diseases.

Finally, it is likely that not all senescent physiological changes revealed in flies can be simply translated to humans. However, flies and humans often show very similar age-related physiological phenotypes suggesting that at least some of the basic biological properties and mechanisms that regulate longevity are conserved amongst species. Clearly, future studies focusing on mechanisms that promote healthy aging rather than lifespan extension could have significant impact on our elderly population and those suffering from age-related disorders.

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