Published in final edited form as:
Exp Gerontol. 2011 May ; 46(5): 317–319. doi:10.1016/j.exger.2010.09.001.

For the Special Issue: Aging studies in *Drosophila melanogaster*

Blanka Rogina
Department of Genetics and Developmental Biology, School of Medicine, University of Connecticut Health Center, 263 Farmington, CT 06030-6403, Unites States

Blanka Rogina: Rogina@neuron.uchc.edu

Keywords

Drosophila melanogaster; Aging; Model system

Following the success of the Special issue of Experimental Gerontology on "The nematode *Caenorhabditis elegans* in aging research", this issue is dedicated to aging studies in *Drosophila melanogaster*. This issue comes at an auspicious time since 2010 marks 100 years of *Drosophila* research. In 1910 Thomas Hunt Morgan published a paper identifying the *white* gene entitled "Sex limited inheritance in *Drosophila*" (Morgan, 1910). Since then *Drosophila* has had a remarkable history of breakthroughs relevant to higher organisms and biology in general. Morgan's paper marks the beginning of an era of groundbreaking research centered in his "Fly room" at Columbia, ultimately yielding the chromosome theory of inheritance and a Nobel Prize for Morgan in 1933. One of Morgans' students, Hermann J. Muller, was awarded the Nobel price in 1946 for his work on X-ray mutagenesis and the discovery of the connection between radiation and lethal mutation in *Drosophila*. In 1995 Edward B. Lewis, Eric F. Wieshaus and Christiane Nuesslein-Volhard shared the Nobel Prize for discovering key developmental processes in the fly and the genes that control these processes (Lewis, 1978, Jurgens, et al., 1984). Analogous genes were found to play significant roles in the early development of mammals, illustrating unsuspected parallels between *Drosophila* and mammals. For instance, similar phenotypic characteristics mark developmental stages in *Drosophila* and mammals. The era of genomic scale biology has revealed many pathway conserved between *Drosophila* and mammals. It is likely there will be conservation of the aging process across these species, an argument more fully discussed throughout this issue.

Remarkably, the first use of *Drosophila* as a model to study aging dates from 1916, when Loeb and Northrop studied the effects of temperature and food on fly longevity (Loeb and Northrop, 1916, 1917). They showed that the longevity of flies as poikilothermic organisms depends on the temperature of the environment. Interestingly they also examined the effects of starvation and sugar concentration on fly longevity. Pearl's studies in the 1920s demonstrate that the longevity of flies is hereditable (Pearl and Parker, 1921, 1922). Genetic background was reported to have effects on fly longevity in 1970 (Clark and Gould, 1970). In 1948 Gardner screened drugs for an effect on longevity using *Drosophila* as the model system, and obtained extended life spans with biotin, pyridoxine and pantothenic acid

(Gardner, 1948a, b). The effect of reproduction on aging has been a topic of study since the fifties when J. Maynard Smith studied the effect of changing reproductive status on fly longevity (Smith, 1958). The interplay between reproduction and longevity has continued to be an area of interest and is covered in the review by Thomas Flatt. The plasticity of fly longevity was revealed by selection experiments performed in the 80s, which showed that longevity could be considerably extended when female flies were selected for late-life fertility (Rose and Charlesworth, 1980, 1981, Luckinbill et al., 1984, Luckinbill and Clare, 1985). Michael Rose reviews the history of laboratory-based evolution experiments and the use of different genomic technologies to study the genetics of longevity in *Drosophila*, examples being single-nucleotide polymorphism (SNP), quantitative trait locus characterization, genome-wide characterization and next-generation resequencing.

The use of *Drosophila* in aging research has many advantages. Flies have a relatively short life span compared to other model organisms - at 25°C fruit flies live about 2 months. Flies are easy to maintain and relatively inexpensive, making it practical to have hundreds in a single longevity experiment. Most cells in *Drosophila* are post-mitotic, with the exception of some gut cells and the gonads, allowing researchers to study a continuously aging organism and avoid any influence of newly dividing cells (Bozuck, 1972). Several environmental manipulations affect fly longevity such as temperature, reproductive status, dietary content of the food or addition of drugs. Sophisticated genetic and molecular tools commonly used in *Drosophila* allow for any gene of interest to be removed or overexpressed in a specific tissue at a specific time during adult life. The UAS-GAL4 system, and particularly the gene switch system, allows overexpression in a tissue and time-dependent manner using specific transgenic flies. Use of RNAi libraries make it possible to test any gene for the effects of mRNA down-regulation on a specific phenotype such as longevity. Additionally, a number of stocks with altered gene expression are available in several Stock Centers (Bloomington Drosophila Stock Center, Vienna Drosophila RNAi Center, The Exelixis Collection at the Harvard Medical School). All of these tools are supported by the availability of the complete nuclear and mitochondrial genome sequences.

Drosophila and mammals show similar age-related declines in functional and behavioral performance, underscoring the fundamental conservation of the aging process. Michael Grotewiel reviews examples of these similarities such as declines in locomotion, learning abilities, sensory function, sleep-like behavior, and others. Studies of behavioral and functional decline are important for several reasons, as they allow us to determine whether such pathologies are caused by declines in tissues such as the nervous system or musculature, and they provide additional biomarkers of aging besides death. Furthermore, these studies allow determination of the role of specific genes or interventions in age-related pathologies. Similarly to other species flies suffer an age-associated accumulation of oxidative damage to proteins, DNA and mitochondria, and deterioration in specific tissues. For instance, age-associated changes in fly heart physiology and function, such as decreased response to stress or increased arrhythmias and dysfunction are similar to changes found in the human heart and can be used to determine the role of specific genes in the aging heart. The Bodmer group reviews the use of flies to study cardiac aging and current knowledge of the molecular mechanisms underlying age-associated changes in the fly heart.

Interest in mitochondria has been growing over the last several years, stimulated by exciting research linking oxidative stress, calorie restriction, energy homeostasis, apoptosis, some human degenerative diseases and age-associated changes in mitochondrial physiology. An overview of the role of mitochondria in the determination of *Drosophila* longevity is covered in the review from the Walker laboratory. *Drosophila* can be also used as a model to study neurodegenerative diseases. Gabrielle Boulianne reviews one such application, the

use of *Drosophila* to study Alzheimer's disease (AD) and in particular genes such as β-Amyloid Precursor Protein (APP), presenilin, and tau.

The role of stem cells in maintaining tissue homeostasis has become a thriving area of research. Leanne Jones reviews *Drosophila* studies of age-associated changes in germline and midgut stem cells and the role of longevity pathways in mediating these changes.

Several reviews in this issue discuss how environmental manipulations affect fly longevity. Eric Le Boug reviews the effects of hormesis / mild stresses on fly longevity, stress resistance and locomotion. However, the hormetic effects are not universal and depend on the stressors, gender and genotype of the flies. The Jasper group reviews the role of the Jun-N-terminal Kinase (JNK) signaling pathway in sensing and responding to environmental and intrinsic stressors. Low-levels of JNK activation may mediate hormesis and its beneficial effect on longevity, while long-term activation negatively affects longevity. JNK, the transcriptional factor FOXO and the heat shock transcriptional factor (HSF) mediate the transcription of heat shock protein (hsp) genes in response to acute (proteotoxic) stresses such as heat, oxidative stress, toxins and bacterial infections. John Tower reviews the role of hsps in aging, stress resistance and maintenance of protein homeostasis.

Dietary restriction without malnutrition extends longevity in a variety species including *Drosophila*. Marc Tatar covers the complex issues associated with the dietary content of the food, such as the effects of specific nutrients on reproduction and longevity in flies. Tatar also reviews the potential role of several genes in mediating the effects of dietary restriction.

Michael Klass reported the discovery of *C. elegans* longevity mutants in 1983 (Klass, 1983). This work was continued by Friedman and Johnson, who in 1988 mapped the first single mutation with a longevity extension phenotype to the age-1 gene (Friedman and Johnson, 1988). A single gene mutation extending fly longevity was discovered in the Benzer laboratory in the late nineties (Lin et al., 1998). Since then a number of *Drosophila* genes have been shown to affect longevity when mutated (Rogina et a., 2000, Clancy et al., 2001, Tatar et al., 2001, reviewed in Kenyon 2010). Several reviews illustrate the diverse genetic and molecular pathways associated with longevity extension in flies. The Kapahi group reviews the nutrient sensing Tor signaling pathway, which has been extensively examined for its central role in a variety of processes such as growth, development, metabolism, protein synthesis and longevity in several species. The Partridge group reviews the complex roles of insuling/IgF and Tor signaling pathways and their interactions. The role of dSir2 in fly longevity and calorie restriction is reviewed by Rogina and colleagues. The authors also review evidences linking dSir2 to Rpd3 and p53.

Drosophila and its close relative the Mediterranean fruit fly have been used in large demographic studies. Groundbreaking work by Vaupel and collaborators in the mid nineties revealed a previously unknown decline in late life mortality rates (Carey et al., 1992, Curtsinger et al., 1992). In this issue, James Carey reviews the biodemography of Mediterranean fruit flies brought from the wild.

The humble fruit fly has played a remarkable role in many groundbreaking discoveries. The *Drosophila* research community has provided enormous contributions to our understanding of genetics and developmental biology. I hope that this issue illustrates the great promise of *Drosophila* research for the study of aging and its already abundant contribution to knowledge of the mechanisms underlying aging. It has become evident that aging is a well-orchestrated, complex process regulated by overlapping pathways and networks. *Drosophila* longevity research holds extended promise for a fruitful future of groundbreaking discoveries.

I would like to thank Thomas Johnson, the Editor in chief of Experimental Gerontology, for his invitation to be the Editor of this Special Issue. It was my privilege and honor to do it, and my only regret is that more laboratories could not be included. For that I sincerely apologize. Some areas of aging research in *Drosophila* are missing from this issue, but as is inevitably the case not all of the laboratories contacted were able to contribute reviews. Brendan Daly, the Journal Manager, helped greatly with my Editorial work and his efforts are very much appreciated. I also would like to acknowledge all contributors and reviewers who participated in this special issue.

Acknowledgments

I thank my former mentor Stephen L. Helfand for introducing me to *Drosophila* and aging research and for his continuous support, collaboration and friendship. I am grateful to my long time technician Suzanne Kowalski for her excellent help. In addition I want to thank current and former members of my laboratory: Vijay Parashar, Graham Garber, Ryan Rogers and Tahereh Ziafazeli, as well as my collaborators Joseph Jack, Stewart Frankel and Robert Reenan for their continuous contributions and support. This work was supported by grant from the National Institute on Health RO1AG023088.

REFERENCES

Bozuck N. DNA synthesis in the absence of somatic cell division associated with ageing in *Drosophila subobscura*. Exp. Gerontol. 1972; 7:147–156. [PubMed: 5047811]

Carey JR, Liedo P, Orzco D, Vaupel JW. Slowing of mortality rates at older ages in large medfly cohorts. Science. 1992; 258:457–561. [PubMed: 1411540]

Clancy DJ, Gems D, Harshman LG, Oldham S, Stocker H, Hafen E, Leevers SJ, Partridge L. Extension of life-span by loss of CHICO, a Drosophila insulin receptor substrate protein. Science. 2001; 292:104–106. [PubMed: 11292874]

Clark AM, Gould AB. Genetic control of adult life span in *Drosophila melanogaster*. Exp. Gerontol. 1970; 5:157–162. [PubMed: 5451261]

Curtsinger JW, Fukui HH, Townsend DR, Vaupel JW. Demography of genotypes: failure of the limited life-span paradigm in Drosophila Melanogaster. Science. 1992; 258:461–463. [PubMed: 1411541]

Friedman DB, Johnson TE. A mutation in the age-1 gene in *Caenorhabditis elegans* lengthens life and reduces hermaphrodite fertility. Genetics. 1988; 118:75–86. [PubMed: 8608934]

Gardner TS. The use of Drosophila Melanogaster as a screening agent for longevity factors; panthothenic acid as a longevity factor in royal jelly. J. Gerontol. 1948a; 3:1–8. [PubMed: 18856647]

Gardner TS. The use of Drosophila Melanogaster as a screening agent for longevity factors II. The effects of biotin, pyridoxine, sodium yeast nucleate, and pantothenic acid on the life span of the fruit fly. J. Gerontol. 1948b; 3:9–13. [PubMed: 18856648]

Jurgens G, Wieschaus E, Nusslein-Volhard C, Kluding H. Mutations affecting the pattern of the larvae cuticle in Drosophila Melanogaster. Rouxs. Arch. Dev. Biol. 1984; 193:296–307.

Kenyon C. The genetics of ageing. Nature. 2010; 464:504–512. [PubMed: 20336132]

Klass MR. A method for the isolation of longevity mutants in the nematode Caenorhabditis elegans and initial results. Mech. Ageing Dev. 1983; 22:279–286. [PubMed: 6632998]

Lewis EB. A gene complex controlling segmentation *in Drosophila*. Nature. 1978; 276:565–570. [PubMed: 103000]

Lin YJ, Seroude L, Benzer S. Extended life-span and stress resistance in the Drosophila mutant methuselah. Science. 1998; 282:943–946. [PubMed: 9794765]

Loeb J, Northrop JH. Is there a temperature coefficient for the duration of life? Proc. Acad. Sci USA. 1916; 8:456–457.

Loeb J, Nortrop JH. What determined the duration of life in metazoa? Proc. Acad. Sci USA. 1917; 5:382–386.

Luckinbill L, Arking R, Clare MJ, Cirocco WC, Buck S. Selection for delayed senescence in *Drosophila melanogaster*. Evolution. 1984; 38:996–1003.

Luckinbill L, Clare M. Selection for life span in *Drosophila melanogaster*. Heredity. 1985; 55:9–18. [PubMed: 3930429]

Morgan TH. Sex limited inheritance in *Drosophila*. Science. 1910; 32:2216–2218.

Pearl R, Parker SL. Experimental studies on the duration of life. I. Introductory discussion of the duration of life in Drosophila. Amer. Nat. 1921; 60:481–509.

Pearl R, Parker SL. Experimental studies on the duration of life. II. Hereditary differences in duration of life in line-bread strains of *Drosophila*. Amer. Nat. 1922; 56:174.

Rose M, Charlesworth B. A test of evolutionary theories of senescence. Nature. 1980; 287:141–142. 1980. [PubMed: 6776406]

Rose MR, Charlesworth B. Genetics of life history in *Drosophila melanogaster*. II. Exploratory selection experiments. Genetics. 1981; 97:187–196. [PubMed: 6790341]

Rogina B, Reenan RA, Nielsen S, Helfand SL. Extended life-span conferred by cotransporter gene mutation in Drosophila. Science. 2000; 290:2137–2140. [PubMed: 11118146]

Smith JM. The effect of temperature and egg-laying on the longevity of *Drosophila subobscura*. J. Exp. Biol. 1958; 35:832–842.

Tatar M, Kopelman A, Epstein D, Tu MP, Yin CM, Garofalo RS. A mutant Drosophila insulin receptor homolog that extends life-span and impairs neuroendocrine function. Science. 2001; 292:107–110. [PubMed: 11292875]