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Life Extension

Lessons from Drosophila

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Preface

Human life expectancy has nearly doubled over the last 100 years due, in part, to a wide range of novel medical technologies and treatments. The trend toward increased life expectancy in the developed countries is accompanied by the increased number of people surviving to an advanced age and having different chronic age-associated pathologies. This trend leads to the need to understand the genetic and physiological mechanisms underlying aging processes and particularly those that promote healthy aging. Moreover, in recent years, substantial evidence has emerged supporting the possibility of the radical human life extension, primarily due to the rapid development of genetic and stem cell-based technologies.

In the development of such technologies, several insect models may provide useful starting points prior to animal and human studies. The use of insect models seems particularly reasonable since, despite the large phylogenetic distance between insects and mammals, some metabolic processes and signaling pathways were shown to play an evolutionarily conserved role in aging across various insect and mammal species. Among them, the insulin/insulin growth factor signaling pathway, histone deacetylases, and genes involved in oxidative stress all exert evolutionarily conserved effects on aging and life span in a wide range of model organisms. These data suggest that aging itself is an evolutionarily conserved process and not simply an inevitable deterioration of biological systems. The high degree of conservation between diverse species in the genetic pathways that regulate longevity suggests that work in model organisms can expand the theoretical knowledge of aging, yield valuable insight into the molecular and cellular processes that underlie aging process, and perhaps provide new therapeutic targets for the treatment of age-related disorders.

Among the widespread model organisms, the fruit fly, *Drosophila melanogaster*, is likely one of the most appropriate model organisms to study biological mechanisms of aging due to its relatively short life span (60–80 days), convenient husbandry, and well-studied genetics. The *Drosophila* genome was one of the first to be sequenced. It has powerful systems for gene knockout and targeted mutagenesis. The 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. Furthermore, almost all cells in adult insects are postmitotic except a few cells in the malpighian tubules, gut, and gonads. Therefore, the age-related decline in cellular functions may be examined without interference from newly dividing cells. Certainly, 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 between flies and humans. In the last years, *Drosophila* models have been developed for a large variety of aging-related processes and diseases.

The goal of this book is to provide the reader with an overview of current research concerned with the use of the *Drosophila* experimental model as a tool for unraveling the genetic, molecular, and physiological mechanisms underlying the aging process and to search for life-extending remedies. This research field is currently a hot topic in biomedicine. Thereby, the present book, which is a collective work of the world's leading researchers in the field of biogerontology, may be of interest to a wide audience, ranging from academic researchers to the general public.

Finally, the editors would like to thank Prof. Suresh I.S. Rattan, the "Healthy Ageing and Longevity" book series editor, for his kind support and wise advices. We would also like to thank Oksana Zabuga for the valuable help in preparing the book manuscript.

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Part I
Genetic Regulation of Longevity

Chapter 1
Neuronal Genes and Developmental Neuronal Pathways in *Drosophila* Life Span Control

Elena Pasyukova, Alexander Symonenko, Natalia Roshina, Mikhail Trostnikov, Ekaterina Veselkina and Olga Rybina

Abstract The nervous system has long been suggested as a key tissue that defines life span. The identity of neuronal cell types is established during development and maintained throughout adulthood due to the expression of specific neuronal genes coding for ion channels, neurotransmitters and neuropeptides, G-protein-coupled receptors, motor proteins, recognition and adhesion molecules. In this paper, we review data on the role of neuronal genes in *Drosophila melanogaster* life span control. Several pathways responsible for life span regulation are also important for the development of the nervous system. Genes involved in insulin-like, Target of Rapamycin, Janus Kinase/Signal Transducer and Activator of Transcription and cell polarity pathways, a number of global regulators and transcription factors play key roles both in aging and longevity control and in shaping the nervous system as a network of specialized neuronal cells in early development. Is their impact on life span related, at least partially, to their developmental functions or is it explained by other pleiotropic influences later in life? In this paper, we address this question based on the published data and our own findings.

Keywords Nervous system · Neuronal genes · *Drosophila* · Life span · Transcription factors

1.1 Introduction

The nervous system has long been suggested as a key tissue that defines life span. The numerous and diverse interactions between the nervous system and life span are reciprocal and intimately linked. On the one hand, via different types of sensory neurons and a wide variety of environmental cues, the nervous system

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receives complex information from the environment and further processes, integrates and transforms it into various physiological outputs that have a major impact on life span; on the other hand, aging also affects the functional state of the nervous system and is associated with the development of age-associated neurodegenerative diseases.

The impact of the nervous system on *Drosophila* life span was initially indicated by accumulating data on the genetic control of life span. Primarily, overexpression of many genes only in the nervous system of transgenic flies resulted in an increase in life span (see, for example, Parkes et al. 1999; Seong et al. 2001; Ruan et al. 2002; Wang et al. 2003; Morrow et al. 2004; Bauer et al. 2005a, b; Orr et al. 2003; Fridell et al. 2005, 2009; Liao et al. 2008; Martínez-Azorín et al. 2008; Simonsen et al. 2008; Lee et al. 2009; Alic et al. 2011; Plyusnina et al. 2011; Rana et al. 2013). Multiple molecular and genetic mechanisms for the impact of the nervous system on aging and longevity were reported (for review, see Broughton and Partridge 2009; Alcedo et al. 2013). These include insulin-like signaling; stress-sensing pathways; antioxidative response mechanisms, reactive oxygen species (ROS) signaling and mitochondrial homeostasis; molecular chaperones, autophagy, lysosomal degradation; etc. Despite this progress, little is known whether genes that control specific functions of neuronal cells affect normal life span. Indeed, the abovementioned aging pathways are not specifically neuronal and function in several other tissues such as fat body, muscles, gonads, etc. (see, for example, Giannakou et al. 2004; Kapahi et al. 2004; Flatt et al. 2008; Biteau et al. 2010; Demontis and Perrimon 2010; Stenesen et al. 2013).

The identity of neuronal cell types is established during development and maintained throughout adulthood. In addition to housekeeping genes, a differentiated neuron is thought to express combinations of genes that define its functional properties (Hobert 2011). These genes code for: (1) ion channels (Potassium channels, Calcium channels, ligand-gated ion channels, etc.); (2) neurotransmitters and neuropeptides (their synthesis, transport, reuptake, and degradation); (3) G-protein-coupled receptors; (4) motor proteins and their associated complexes (kinesin, dynein and myosin motors); (5) recognition and adhesion molecules (immunoglobulin superfamily, cadherins, neurexins superfamily) and some others. Collectively such genes will be further referred to as neuronal genes, even though we fully realize that this term is conditional, given the pleiotropic nature of most genes. In this paper, we review data on the role of neuronal genes in *Drosophila melanogaster* life span control.

Several pathways responsible for life span regulation are also important for the development of the nervous system. Genes involved in Insulin/Insulin Receptor (InR), Target of Rapamycin (TOR), Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) and cell polarity pathways, a number of global regulators and transcription factors play key roles both in aging and longevity control and in shaping the nervous system as a network of specialized neuronal cells in early development (Table 1.1). Even though, according to the definition given above, these genes can not be regarded as neuronal genes, they exemplify another embodiment of the relationship between the nervous system and longevity. Is their

Table 1.1 Neuronal genes and developmental neuronal pathways in life span control

Gene and pathway	Protein	Function in the nervous system	Stage	References	Function in life span control	References
Shaker (*Sh*); **cAMP/PKA pathway?**	Alpha subunit of a voltage-dependent potassium channel	Synaptic activity	Larvae	Papazian et al. (1987), Budnik et al. (1990), Ueda and Wu (2006)	Mutation: decreased activity decreases LS	Trout and Kaplan (1970), Rogina and Helfand (1995)
Hyperkinetic (*Hk*); **cAMP/PKA pathway?**	Beta subunit of a voltage-dependent potassium channel	Synaptic activity	Larvae	Budnik et al. (1990), Wilson et al. (1998)	Mutation: decreased activity decreases LS	Trout and Kaplan (1970), Rogina and Helfand (1995)
Rutabaga (*rut*); **cAMP/PKA pathway**	Adenylyl cyclase	Learning and memory	Adults	McGuire et al. (2003)	Mutation decreases LS	Tong et al. (2007)
		Synaptic activity	Larvae	Renger et al. (2000), Baines (2004)		
Dunc (*dnc*); **cAMP/PKA pathway**	cAMP phosphordiesterase	Learning and memory	Adults	Dudai et al. (1976), Byers et al. (1981)	Mutation restores LS of NF1 mutants	Tong et al. (2007)
		Synaptic activity	Larvae	Renger et al. (2000), Zhong and Wu (2004)		
cAMP-dependent protein kinase 1 (*PKA-C1*); **cAMP/PKA pathway**	Catalytic subunit of cAMP-dependent protein kinase A (PKA)	Learning and memory	Adults	Drain et al. (1991), Skoulakis et al. (1993), Yamazaki et al. (2007), Gervas et al. (2010)	Mutation does not affect LS	Yamazaki et al. (2007)
		Synaptic activity	Larvae	Baines (2004)	Ubiquitously increased activity (mouse PKA) restores LS of *NF1* mutants	Tong et al. (2007)
Neurofibromin 1 (*NF1*); **cAMP/PKA pathway**	Ras GTPase activator	Learning and memory	Adults	Buchanan et al. (2000), Buchanan and Davis (2010)	Mutation decreases LS	Tong et al. (2007)
		Synaptic growth, synaptic activity	Larvae	Tsai et al. (2012)		

(continued)

Table 1.1 (continued)

Gene and pathway	Protein	Function in the nervous system	Stage	References	Function in life span control	References
Maleless (*mle*)	ATP-dependent double-stranded RNA helicase	Synaptic activity (via RNA editing of the Na^+ channel gene *paralytic*)	Larvae	Reenan et al. (2000), Zhong and Wu (2004)	Gain-of-function mutation: increased activity decreases LS	Reenan and Rogina (2008)
Paralytic (*para*)	Major voltage-gated sodium channel	Synaptic activity	Larvae	Reenan et al. (2000)	Increased dosage of *para* restores LF of mle mutants	Reenan and Rogina (2008)
Insulin-like peptide 2 (*Ilp2*); InR/TOR pathway	Insulin-like peptide	Insulin signaling	Larvae, adults	Grönke et al. (2010)	p53 dominant negative mutation: decreased activity increases LS	Bauer et al. (2005a, b, 2007, 2010)
					Loss-of-function mutation: decreased activity increases LS	Grönke et al. (2010)
					UCP3 overexpression: increased activity decreases LS	Humphrey et al. (2009)
					See other data and references in the text	
Insulin-like peptide 3 (*Ilp3*); InR/TOR pathway	Insulin-like peptide	Insulin signaling	Larvae, adults	Grönke et al. (2010)	mUCP1 or hUCP2 overexpression: decreased activity increases LS	Fridell et al. (2009)
					DR: decreased activity increases LS	Grönke et al. (2010)

(continued)

Table 1.1 (continued)

Gene and pathway	Protein	Function in the nervous system	Stage	References	Function in life span control	References
Insulin-like peptide 5 (*Ilp5*); InR/TOR pathway	Insulin-like peptide	Insulin signaling	Larvae, adults	Grönke et al. (2010)	DR: decreased activity increases LS	Min et al. (2008)
Catecholamines up (*catsup*)	Negative regulator of tyrosine hydroxylase activity	Neurotransmitter synthesis	Adults	Stathakis et al. (1999)	Mutational variation is associated with LS	Carbone et al. (2006), Roshina and Pasyukova (2007)
Dopa decarboxylase (*Ddc*)	Dopa decarboxylase	Neurotransmitter synthesis	Adults	Livingstone and Tempel (1983), Stathakis et al. (1995)	Mutational and molecular variation is associated with LS	De Luca et al. (2003)
Odorant receptor co-receptor (*Orco*)	Odorant receptor co-receptor protein	Sensory perception of smell	Adults	Mukunda et al. (2014)	Loss-of-function mutation: decreased activity increases LS	Libert et al. (2007)
Gustatory receptor 63a (*Gr63a*)	Gustatory receptor	Detection of carbon dioxide	Adults	Kwon et al. (2007)	Loss-of-function mutation: decreased activity increases LS	Poon et al. (2010)
Metabotropic GABA-B receptor subtype 2 (*GABA-B-R2*)	Metabotropic GABA-B receptor subtype 2 subunit	Synaptic activity, olfactory behavior	Adults	Root et al. (2008)	RNAi knockdown: decreased activity decreases LS	Enell et al. (2010)
Cyclin-dependent kinase 5 (*Cdk5*)	Cyclin-dependent kinase 5 (Cdk5)	Axon guidance	Embryo	Connell-Crowley et al. (2000), Connell-Crowley et al. (2007)	*p35* null mutation: decrease in activity decreases LS	Connell-Crowley et al. (2007)
p35	Cdk5 activating subunit	Synaptic growth	Larvae	Kissler et al. (2009)		

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