Review

### Use of *Drosophila* as a model organism in medicine

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The fruit fly *Drosophila* has been an extensively important system for investigating various aspects in life science including medicinal sciences. This fly *Drosophila* is richly contributed to our understanding the aging pattern, neurodegenerative diseases and its use as a model organism in future, especially in the field of medicine. The utility of the *Drosophila* resides in two resources: its small genome which resembles more or less human genome for various diseases, and its powerful genetic tools as a model system. Here we provide a review of the genetics of diseases and medicinal system, where *Drosophila* can be used in the research field.

Keywords: Drosophila, Ayurveda, Neurodegenerative diseases.

### INTRODUCTION

Actually, there was a time when non-mammals were thought to be non ideal materials to study biomedical science, due to their phylogenically too distant from humans. However, presently there are some nonmammals which are not only convenient materials but are also there is a similarity in pharmacological and physiological properties common to humans. Thus, in several such non-mammals, the fruit fly Drosophila is one among them which stands very close to man. The fruit fly Drosophila was introduced as a model organism at the beginning of the 20<sup>th</sup> century. Probably around 1901 in the context of genetics, but soon become a running horse in biological research. Its main attributes were then the same as they are now; rapid generation time, short life cycle, and life span, larval stages, ease and robustness and low maintenance of culturing. This species D. melanogaster large numbers of homologous genes with mammals, 13,601 with humans (Adams et al., 2000) these have been analyzed to identify sequences related to those causing human diseases. It has large numbers of induced and spontaneous mutations with a few chromosomes in a small genome. These facts make Drosophila melanogaster particularly study of the genetics of disease, degeneration, and aging processes, since results should yield insights into what to seek in

humans (Reiter et al., 2001). Today, the fruit fly *Drosophila* is one of the most intensively studied organisms in biology and serves as a model system for investigations of many developmental and cellular processes, biochemistry, physiology, embryology, but also in pharmacology and bio-medical sciences common to higher eukaryotes, including man. This review is focused on the use of *Drosophila* models in the field of medicine.

### Concept of aging in Drosophila

Maintaining the vitality of youth and preserving quality of life has long been a quest of civilized man. Drosophila is excellent organism favored for human-related aging research. For instant, the human Xist gene and the analogous Drosophila Sxl gene both control sex determination and may both be involved in regulating life span according to Tower (2006). This suggests that any means of systematically influencing aging is worth studying for possible sex- dependence. Partridge (2008) showed that research findings in Drosophila *melanogaster* can throw light on probable happenings in human aging processes. The same above author also argued Dietary restriction (DR) is well recognized to extend *D.melanogaster* lifespan; DR effects are greater in females. But DR can also produce conflicting results different species and with complex interaction with

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pathology. Normal lifespan is about 40 days in males and females (Priyadarshini et al., 2010). *Drosophila* longevity genes with human homologous have been identified, as have their single gene mutations extending lifespan. Selection of all such genes results in the "Methuselah" fly with a greatly extended life span (Lin et al., 1998). Life span extension has been demonstrated by two other genes in *Drosophila* that may operate through mechanism related to *IIS* and dietary restricted *rpd3* and *Sir2*. Reduction in levels of the histone deactlase *rpd3* extends life span, but not under dietary restriction, suggesting a common mechanism between these two process. (Rogina et al., 2002). This shows the activity of the gene *rpd3* play very important role in extending the life span.

Identification of specific genes that regulate life span in D. melanogaster has been achieved by two processes: 1. Quantitative trait locus (QTL) analysis in which genetic elements affecting natural variation in longevity have position specific been mapped to along the chromosomes. This QTL analysis mapping has identified a substantial number of specific genes that affect longevity and even more genic regions that contain unexplained candidate loci. This approach identifies aging loci by localizing differences in longevity between natural strains to chromosomal regions, either flanked by known molecular markers. 2. Mutational analysis is another type where manipulation of gene or pathway function has demonstrated life span extension genes which are involved in stress response and the association between stress and life span has motivated the identification of many genes according to Paaby and Schmidt 2008, 2009. The hypothesis that reactive oxygen species (ROS) cause aging led to tests for life span extension by increasing activity of genes that promote antioxidant defenses (Paaby and Schmidt, 2008). The over expression of both catalase (Cat) and superoxide dis mutase have demonstrated increased organismal longevity (Harmon, 1981; Parkes et al., 1998). The diaphase is also one of the life stages which can increase the length of the life span. Like many insects D. melanogaster is also capable of expressing a form of diapause, a neuroendrocrine mediated physiological syndrome that results in reproductive guiescence and organismal persistence over long periods of suboptimal conditions (Orr and Sohal, 1994). In Drosophila, phenotypic variation shows significant variation in lifespan within and among natural population. This is also true in the case between the populations and correlation of the longevity between the longitude and altitude. The Isofemale lines derived from high latitude populations from the United States east coast show longer lifespan than lines from low latitude populations, and lines along this gradient shows relationship between the longevity and other phenotypic traits. This shows the variation of the environmental factors which can have some impact on the genes of life span.

# *Drosophila* powerful model for neurodegenerative disease

Why use animal models? Animal models are in important aid to study pathogenic mechanisms and therapeutic strategies in human diseases through the use of an animal model. For example, the straital dopamine deficiency was associated with symptoms of Parkinson disease (PD) and Levodopa (dihydroxyphenylalanine or L-DOPA) was first used to compensate for striatal dopamine loss, L-DOPA therapy still remains the gold standard of treatment of PD according to Feany and Bender (2000) and Ranjita et al. (2002). At the same time prolonged use of L-DOPA however, commonly results in depilating involuntary movement (dyskinesia), confounding the usefulness of the drug. Moreover, the pathogenesis of PD is not well understood to this day. Therefore, it is very important to develop animal models for understand the pathogensis of PD and discovering new therapeutics to treat PD.

As noted, animal models may be useful for studying pathogenic mechanisms, for testina therapeutic strategies, or both. As such, *Drosophila* is a ideal model for the neuronal cell biology and disease. The mitochondrial encephalomyopathies are a diverse set of disorders that includes neuropathy, ataxia, retinitis pigmentosa, famial bilateral striatal necrosis and maternally inherited Leigh syndrome. These diseases are characterized by tissue degeneration and neurological as well as muscular dysfunction. The Palladino laboratory Pittsburgh presented their work on an endogenous mitochondrial genome mutation in *mtATP6*, which encodes an essential subunit of the complex V ATP synthase. In Drosophila, mtATP6 mutants display a shortened life span, Progressive degeneration of the adult flight muscles, and neural dysfunction. Furthermore, these flies have mitochondrial dysfunction, reduced ATP production, and extraordinary mitochondrial ultrastructural changes. The characterization of a missence mutation in the fly, similar to those that produce human disease, demonstrated many phenotypes directly related to human disease symptoms suggesting the fly will be a wonderful model insect to examine these diseases.

Recent work has focused by Clark et al (2006) and Park et al (2006) on the mitochondrial contribution to disease pathology in several neurodegenerative disorders including Parkinson's disease (PD). Ming Guo (UCLA from Los Angeles) presented work from her on *Drosophila* homologs of the PD associated Loci *PTENinduced kinase-1* (*pink1*, *parkin park6*). Greene et al (2003) and Pesah et al (2004) showed the pink1 protein has a mitochondria and mutations at this locus produce male sterility, myopathy, mitochondrial structural defects, and sensitivity to oxidative stress. With the connection of the function parkin mutants have similar phenotypic effects as those observed in pink1 flies. Ming Guo also showed that the expression of the human pink1 gene in pink1 mutant flies rescues the pink1 mutant phenotypes, suggesting that human and fly pink1 is functionally conserved. This work on the fly model of these two genes indicates that there are important non-dopamine dependent disease mechanism involved in PD progression.

Along with these defects in mitochondrial function, Parkinson's is also characterized by the presence of Lewy Bodies and thus is connected to a set of Neurodegenerative disorders, Such as Alzheimer's and Huntington's referred to as Proteopathies due to the accumulation of toxic intracellular protein aggregates. The presence of these inclusions has led to work focused on the cellular systems that are charged with the degradation of protein, specifically the ubiquitinproteasome system and macroautophagy. These works is taken from the Taylor lab. In addition, the work presented by the Taylor lab support autophagy as a target of interest in the development of pharmaceutical therapies for a diverse group of human disease from cancer to devastating neurodegenerative disease such as spinobulbar muscular atrophy using fly model.

The hereditary spastic paraplegies (HSP) are a large group of neurodegenerative disorders found together by a common disease phenotype of progressive weakness of the lower extremities due to retrograde axonal degeneration. Twenty-nine loci have been identified in humans that produce symptoms associated with HSP. These loci can produce protein form of HSP that affects that affects only motor axons which leads into axonal degeneration. There are reports from the Tear Lab (Kings College, London, UK) where they had developed fly as a model for the juvenile onset form of Batten disease. A part from this the four characterized genes (spastin, kinesin, family member 5A, atlastin and heat shock protein 60) that are associated with an autosomaldominant pure HSP (AD-HSP) have homologs in the Drosophila model system. AD-HSP produces spasticity and walking difficulties due to the degeneration of corticospinal tract axons. The spastin protein is an AAA ATPase that is associated with microtubules and has microtubule cleaving activity. Approximately 40% of human AD-HSP mutations are found in the SPG4 genes which encodes *spastin*. Previous work has demonstrated that null mutations in the Drosophila spastin ((Spas) SPG4 gene) homolog recapitulate the motor defects associated with AD-HSP along with defects in synaptic structure and function reported by Sherwood, 2000 and Trotta et al. 2004. Further more the Sherwood lab focusing on the Spas function through several genetic approaches in the fly. First they demonstrated that both wild type fly and human Spas proteins rescue the null function and further indicating the *Drosophila* phenotypes showing the evolutionary conservation of protein function shows the capability of the fly. The same group is also working on the Drosophila to explore an interesting transmodification effect in compound heterozygote patients with AD-HSP using *Gal4/UAS* of *Drosophila*.

Drosophila has been the common organism for genetic studies in eukaryotes. These studies provide the basis of much of our conceptual understanding of functional aspects of eukaryotic genetics, including chromosomal mechanics and behavior genetic linkage, sex determination. This fly has a wealth of mutants and special chromosomes that have been endowed with visible and molecular markers and other properties which can manipulate the gene. Using these molecular markers one can study the visible and lethal phenotype this can be study for number of generations. The other transposon- based methods for manipulating genes have also been developed all made possible the P-transposon can be integrated into the chromosomes. These types of techniques allow experts to create the genetically modified and stable transgenic system in Drosophila.

#### Drosophila as a model Mosquito

The host-pathogen interactions should be studied using the relevant infectious agent in its native host. From a biologist's view, however, the mosquito is not an ideal experimental organism. This is due to rearing and culturing the mosquite is complex than Drosophila particularly, for example, female Anopheles which require blood for breeding. There are two views for using the Drosophila as a model mosquito. The first is to use the fruit fly to identify interesting genes than to study these during the course of an infection in a disease vector. For example, the sequencing of expressed sequence tags in the mosquito Anopheles gambiae revealed some potentially interesting genes on the basis of their similarity to genes known to be involved in the Drosophila immune system. The second view to using *Drosophila* in vector biology research is to study host-pathogen interactions by directly infecting flies with the parasite of interest. This work benefits from the large collection of genetic mutants, the simplicity of phenotypic screens in the fly and the sequence of the *Drosophila* genome this is reported by Schneider and Shahabuddin (2000). These genetic studies have the use of allowing the insect to reveal what is important in host-interactions. Drosophila can be used directly as a model insect to study aspects of malarial transmission (Schneider, 2000). Today, scientist have found that plasmodium gallinaceum, an avian plasmodia, is not infectious when fed to Drosophila but it can infect the fly when it is injected to the haemocoel. This shows in haemocoel the parasite develops from an ookinete into an infective sporozoite but does not seem to enter the salivary glands. The parasite is rapidly cleared after injection into the haemolymph. It seems that this clearance is due to the cellular-immune response of the fruit fly. These studies reflect Drosophila is also good model to study immune response system.

# *Drosophila* for Chinese and Ayurvedic medicine system

Traditional Chinese medicine is also known as TCM, traditional medicine practices originating in China. Although a common part of medical care throughout East Asia, from long back, is considered an alternative medicine system in most of the Western world. Modern TCM was systematized in the 1950s under the people's Republic of China and Mao Zedong. Prior to this, Chinese medicine was mainly practiced within family systems.

There have been various ancient medicine systems like Avurveda, Chinese medicines and others. The Chinese system of medicine is one that has stood the test of time and is still one of the best medicinal systems. There are various reasons for the use of Chinese system of medicine even today. The herbal medicine system in the Chinese medicine uses the various naturally occurring plants to be used as medicines to heal certain diseases. Other than the herbal therapy that is used, the Acupuncture is a well known method of Chinese medicine, where the small pins are used to prick in areas where the problem may be present. The Chinese medicine has cures for many of the diseases with the acupuncture system. The main reason for the use of this system of medicine is that it is based on natural cures. The herbs, animal products and other aspects of the treatment are those that do not cause any toxicity in the body. The modern system of health medicine has been using various toxic drugs to treat diseases. "The reductionist approach to treating multiple side effects triggered by cancer chemotherapy or complicated disease may not be sufficient. Rigorous studies of the biology of traditional herbal medicines, which target multiple sites with multiple chemicals, could lead to the development of future medicines," said Cheng Scientist from Yale University. There are therapies such as Auriculotherapy, Chinese food therapy; Chinese herbal medicines which can clinically tested using Drosophila as a model right now.

Avurveda is another old Asia's traditional systems of medicine which restores high levels of health as curing disease. Its name implies "knowledge of life and life span "implies an ability to prolong life by restoring health and reversing tendencies to aging. In Ayurveda, rasayana is common and well known therapy meant for physical, mental and spiritual conditions. This type of therapy forms the seventh of eight subdivisions of Aryuveda's earliest extant text of Charaka Samhita noted in Charaka Samhita Sutrasthana (2000a). The main concept of this rasayana is for health promotion. By the time of Charka, rasayana health-promoting, herbal formulae were already well developed, indicating clinical observation and practice over centuries, if not millennia. But now, it had gone to formulation. Shustruta also describes rasayanas as "reversing naturally occurring senility" and so

"preventing death" further indicating that rasayanas are considered "special herbal formulations" for health care.

Valiathan (2006) has recognized the opportunity to create" Ayurvedic Biology". His vision is to produce an evidence base for Ayurveda, should include clinical rasayana evaluations. He has since been quoted by Mashelkar (2010) as saying that rasayanas should be tested on animal models. Mashelkar emphasized his personal dream to see *D. melanogaster*, the well known fruit fly used for such tests. Drosophila constitutes a suitable system for testing myriad hypotheses in Ayurveda (Adams et al., 2000). There are some reports where some of the rasayana play very important role to increase the longevity in Drosophila melanogaster (Priyadarshini, 2010). Study conducted by Jafari et al., 2008 showed that Rosa damasecene decreases the mortality in adult Drosophila. From the above reference today, Drosophila slowly occupying the area of research in field of Avurveda too.

#### CONCLUSION

The fruit fly *Drosophila melanogaster* has the longest history of any model organism and extensively used organism in various branch of biology. This powerful fruit fly biological system is utilized to address fundamental questions concerning neurological disorders, due to similarities in genome between man and *Drosophila*. *Drosophila* offers great experimental advantages in cell and molecular biology. Etiologies and pathogenesis underlying number of monogenic neurological disorders including familial Parkinson, Alzheimer's disease or ataxia have been success replicated in Drosophila system, when causative mutations of those disorder were transgenically introduced or loss of function mutations were made.

There are many aspects of Drosophila biology and physiology waiting to be explored by genetics and the new genomic approaches. We expect the future of Drosophila research to turn increasingly to questions beyond the cellular level to questions of physiology maintenance and regeneration of whole organs. For example, some human renal disorder and colon cancer are associated with defects in genes involved in the fluid, electrolyte transport *Drosophila* orthologs of these genes found in the genomic sequence should spur studies of the physiology of insect colon and malphigian tubules which serves as kidney in Drosophila. This fruit fly will be the fruitful model for testing many herbs and plant products which are unknown to world for curing many unknown diseases. Lastly, one as to agree that Drosophila genome sequence and Human genome sequence opened new era for the biological research. The future is bright for Drosophila and the many human diseases that are studied in this beautiful wealthy model organism. As can be seen from the work highlighted at

the maggot meeting and neuronal circuit behavior meeting organized by EMBO at NCBS, Bangalore, the genetics of the fly will continued to provide important clues to the molecules which is responsible for many human diseases.

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