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Drosophila melanogaster: A Promising System for Neurobiology Research

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Last century has witnessed the emergence of *Drosophila melanogaster* as a premier experimental model organism and its exceptional contribution in field of genetics, developmental biology, behavioural studies, stem cell research and modelling of various fatal human neurodegenerative disorders. *Drosophila*, as a model organism not only confers the power of genetics on the manipulator but also offers several additional advantages that make it an attractive choice for use in widespread facets of the scientific genre. The large-scale genetic mutagenesis screens have made elucidation of genes involved in human disease pathways relatively rapid and less cumbersome. Moreover, completion of the *Drosophila* genome sequencing paved ways for a comparative genomic analysis approach, which has elucidated that 70% of human diseases causing genes have *Drosophila* homologues [1-4]. In addition, conservation of important biochemical and developmental pathways between noticeably distant fruit flies and humans further encouraged the scientific community to utilize *Drosophila* as a model organism to study the insights of human disease development and to design novel therapeutic strategies.

Human neurodegenerative diseases represent a group of illnesses which develop due to progressive degeneration of neuronal cells in distinct parts of brain [5]. Majority of such neurodegenerative diseases exhibit a common feature of an increased number of CAG nucleotide triplet repeats in their protein coding sequence which results in abnormally long polyglutamine [poly (Q)] tract in the encoded proteins [6]. Therefore, the diseases wherein the instigating protein encompasses such abnormal numbers of repeats are known as polyglutamine or poly (Q) diseases. Increased numbers of polyglutamine repeats exhibit germ line instability and tend to increase further with successive generations [7].

Extra glutamine residues in a mutated protein could acquire toxic properties through a variety of ways such as irregular protein folding, altered sub cellular localization and abnormal interactions with other cellular proteins [8]. Extended poly (Q) containing proteins often aggregate together to form nuclear inclusion bodies (IBs) and exert a dominant effect by interacting with other key cellular proteins such as transcription factors, molecular chaperons, proteasome subunits, cytoskeletal components etc., and sequester them in nuclear inclusion bodies [9-16]. The toxic effects of insoluble protein aggregates are therefore; exaggerate by the functional depletion of other normal cellular proteins owing to their sequestration by inclusion bodies. Although the exact mechanism of aggregate formation is still enigmatic, however, it is believed to be triggered by an altered beta pleated sheet-enriched structure of polyglutamine region which arises due to its abnormal length and facilitate aberrant clumping of these proteins with each other and also with other surrounding proteins [17]. Interestingly, additive role of normal repeat-length polyglutamine peptides in accelerating aggregation, nucleation and cytotoxicity of expanded polyglutamine proteins has also been reported [18]. Progressively, increasing loads of nuclear inclusions bodies lead to neuronal dysfunction and finally degeneration. Intriguingly, although the mutated protein displays a widespread expression in all types of tissues, however, disease manifestation is restricted only to the nervous system.

Human neurodegenerative disorders could be classified as per the location of protein aggregate formation. For instance, cytosolic aggregation pattern in case of Parkinson's disease where the α-synuclein forms insoluble fibrils called Lewy bodies; nuclear aggregation of mutated Ataxins and Huntingtin proteins in cases of Spinocerebellar ataxia type 1 (SCA1) and Huntington's disease respectively [19-21], accumulation of neuroserpin inclusion bodies in endoplasmic reticulum (ER) in case of familial encephalopathy, and extracellular spaces in case of Alzheimer's disease where beta amyloid and hyper phosphorylated tau proteins form major components of the senile plaques and neurofibrillary tangles respectively [6,9]. In addition to the aggregate formation, all these neurodegenerative disorders also share common features of late onset disease manifestation and progressive dynamic nature [22].

Several fatal human autosomal dominant neurodegenerative disorders such as Huntington's disease, Spinocerebellar ataxia, Parkinson's disease etc. have been successfully modelled and extensively studied in *D. melanogaster* [6,9]. The most common approach undertaken to express human disease genes in *Drosophila* involve two-component GAL4/UAS system [23]. This system is based on the fact that yeast GAL4 transcriptional activator binds to the Upstream Activating Sequence (UAS) enhancer element in order to drive expression of the gene present immediately downstream of UAS [23]. Tissue specific ectopic expression of any desired transgenes could be achieved by adopting the above strategy. *Drosophila* compound eyes have emerged as an excellent organ for modelling the human neurodegenerative diseases and to perform their in-depth cellular and molecular analysis. It provides an exceptional opportunity to study the disease progression through the entire life span of *Drosophila*, since a functional eye is not essential for viability. It was exquisitely demonstrated that the expression of truncated/full length protein of interest with 75 or 120 glutamines repeats result in length-dependent degeneration of photoreceptor neurons of adult *Drosophila* eyes which gradually depreciate with aging [24,25].

Following the initial success of human neurodegenerative disease modelling in *Drosophila*, attempts were made to model a verity of diseases using various mutagenesis/ transgenic approaches. Subsequently, this approach has emerged as valuable tool to decipher in-depths of human disease pathogenicity and to screen for genetic/ chemical modifiers and to design novel remedial strategies [6,9,24].

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Many of such disease models are readily available in several *Drosophila* stock centres. Indeed, *Drosophila* disease models have been used comprehensively to generate significant information regarding disease pathogenicity, identification of novel genetic modifiers and chemical compounds [26-28]. A large number of genetic modifiers have already been identified in case of Huntington's disease alone, which could be categorized in several sub-groups as per their functional characteristics [6,9].

Taken together, *Drosophila* provides a powerful system to study the various aspects of human neurodegenerative diseases. However, given an excellent model and the wealth of tools available to study modified phenotypes of flies, the precise mechanism that causes disease toxicity still stands as a question mark. Therefore, genetic studies should be focussed on unravelling the molecular nature of the neurotoxic species for each disease type, and to decode the key neuronal functions which are being affected by the accumulation of toxic proteins. Moreover, in view of the conserved disease pathology in *Drosophila* and human, there is an urgent need to develop parallel comprehensive study plans for not only to decipher the mechanistic details of the disease pathogenicity but also to perform large scale screening for the candidate molecules and genetic modifiers to appraise their potential as the suppressor of disease phenotypes. Subsequently, the identified genes/molecules could be verified for their effects and reproducibility in higher model systems. The fruit fly has, thus, proved its worth in the field of neurobiology research and will continue to contribute significantly towards novel discoveries prove to be as fruitful as its name.

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