Sarkar et al., Cell Dev Biol 2012, 1:5
DOI: 10.4172/2168-9296.1000e112

Cell & Developmental Biology
ISSN: 2168-9296

Editorial Open Access

Flying with Flies: Decoding Human Neurodegenerative Disorders in *Drosophila*

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Keywords: Neurodegeneration; Poly(Q); Tauopathy; Disease model; *Drosophila*

Human neurodegenerative diseases are traumatic illnesses characterized by progressive loss of neurons in specific areas of brain resulting locomotor imbalance, resting tremor, abnormal gait, dementia and defects in cognitive thinking [1]. This group of disorders exhibit highly comparable manifestation of symptoms, majority of which are adult onset and do not manifest during early stages of life. Thus, prevalence of most neurodegenerative disorders increased drastically since average life expectancy of world population extends into the eight decade [2]. Some of the neurodegenerative diseases affecting large number of population are Huntington's disease (HD), Dentatorubral-Pallidoluysian Atrophy (DRPLA), Spinal and Bulbar Muscular Atrophy (SBMA), Spinocerebellar Ataxia (SCA), Alzheimer's and Parkinson's diseases etc. [1].Most of these diseases are dominantly inherited and are passed from generation to generation. Interestingly, although majority of the neurodegenerative diseases exhibit overlapping clinical manifestations, some very specific symptoms are prevalent in different diseases which are primarily due to variances in part of brain affected; basal ganglia in Huntington's disease, cortical region in Alzheimer's disease and dopaminergic neuron in substantia nigra in case of Parkinson's disease [3].

Over a century after the first clinical characterization of Huntington's disease; human neurodegenerative diseases have been vigorously investigated and debated. Limitations and ethical issues associated with human genetic research often made it difficult to analyze genes and operating cellular/ molecular pathways in greater details, and subsequently, finding of remedial measures and drug discovery. Advancement and breakthroughs in contemporary biological sciences have made it possible to identify genes and to decipher underlying molecular mechanisms causing the pathogenic effects and cellular toxicity, however, several questions are remained to be answered. It is increasingly clear now that along with the intracellular or extracellular accumulation of misfolded protein aggregates, a wide array of defects in cellular dynamics also aggravate the pathogenic effects of these diseases, such as altered transcription, compromised quality control mechanism, abnormal axonal transport system, aberration in cellular detoxification pathway and modification in signal transduction [1].

To obtain the insight of pathogenic mechanisms of neurodegenerative diseases, *in-vitro* and *in-vivo* model systems have been developed following identification of mutation(s) in familial equivalents [4-6]. Attempts have been made to model human neurodegenerative disorders in a wide variety of model systems such as bacteria (*Escherichia coli*), plants (*Arabidopsis thaliana*), nematodes (*Caenorhabditis elegans*), insects (*Drosophila melanogaster*), fish (zebra fish, *Danio rerio*), rodents (mouse, *Mus musculus*), non-human primates (rhesus monkey, *Macaca mulatta*) and cell lines [6]. This strategy has emerged as an ultimate device to decipher in-depths of the pathogenic mechanism of these fatal illnesses and subsequent development of remedial strategies. Although no disease model is perfect and concomitantly all of them are important as per their distinctiveness; the fruit fly *Drosophila melanogaster* has appeared as most promising system for such studies [7-9]. *Drosophila* offers rapid genetic analysis with a generation time much faster than mice and other mammalian models. Intriguingly, *Drosophila* central nervous system functions on the same essential principles as their mammalian counterpart and are capable of demonstrating several complex behaviours such as learning and memory [9-11]. Therefore, it has been extensively utilized not only to study the biological functions of genes associated to neurodegenerative disorders and to determine the mechanisms by which mutations lead to neuronal dysfunction but also for behavioural studies, genetic modifier screening and drug discovery [5,12]. Above all, it has also been found that about 75% of disease-related genes in humans have their functional orthologs in *Drosophila* with conserved functional domains exhibiting 80 to 90% or higher level of similarity [13].

Targeted expression of disease genes in *Drosophila* has become possible through a highly acclaimed gene drive system; the UAS/Gal4 system [14]. Several amendments and improvements in this system have further refined the cell type and temporal expression specificity [15]. Several *Drosophila* transgenics representing various human neurodegenerative disorders such as Alzheimer's, Parkinson's, Huntington's and SCA-3 diseases etc. have been developed [6]. Expression of disease gene could be ectopically modulated in desired tissues to study their influence on disease pathogenicity. Predominantly, the compound eyes are used to read out the phenotypes since it makes minimum impact on viability or fertility of fly (Figure 1), and in turn could be easily scored and utilized for genetic suppressor and drug screening [5,9,16]. Studies on these *Drosophila* human disease models have made valuable contributions to our understanding of the molecular, genetic and cellular aspects of neurodegeneration from genes to brain and behaviour [16].

Genome wide modifier screenings in *Drosophila* models have facilitated identification of several genetic factors, signalling pathways which could potentially suppress (directly or indirectly) the progression of neurodegeneration and cellular toxicity, hence increases the chances of survivability [5]. Majority of the modifier genes could be grouped as per their functional characteristics, such as protein quality control/ folding, transcriptional regulation, apoptosis, axonal transport, translational control and many others [17]. It is also interesting to note that list of genetic modifiers includes several non-coding genes. Some of the common modifiers of poly (Q) induced neurodegenerative disorders are *Hsp70*, *DIAP1*, *P35*, *CBP*, *Sumo*, *Hsf1*, *Akt1*, *hsrω* etc.

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Received August 21, 2012; **Accepted** August 21, 2012; **Published** August 23, 2012

Citation: Sarkar S, Singh MD, Yadav R, Chanu SI (2012) Flying with Flies: Decoding Human Neurodegenerative Disorders in *Drosophila*. Cell Dev Biol 1:e112. doi:10.4172/2168-9296.1000e112

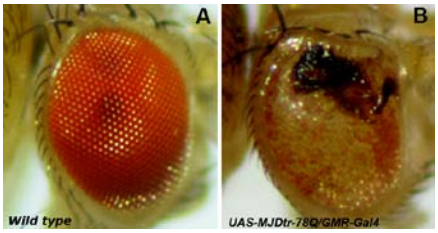

Figure 1: Human poly(Q) induced degeneration in *Drosophila* eye (A) wild type eye without phenotype looks normal (B) Targeted expression of *MJDtr-Q78* induces severe cellular degeneration (black patches) and de-pigmentation of eye.

[16,17]. In this context it is important to note that only a few modifier genes have been found to function as a "common modifier" among various neurodegenerative disorders [18]. Similarly, modifier capacity of certain genes is even limited to a specific cell or tissue type [18]. For instance, there are a few common modifiers for poly(Q) aggregation and tauopathy, of which majorly of the genes are directly involved in regulation of cell death pathways such as *DIPA1*, *DIAP2* and *P35* [19]. On the contrary, the common modifiers of poly(Q) diseases such as *Hsp70*, *Hsp40*, histone acetyltransferases and ubiquitin proteasome system are not found to suppress the pathogenic effects of tauopathy [20]. Moreover, modulation of *Hsp40* has been demonstrated to further aggravate tau induced cellular toxicity [18]. Consistently, the phosphatases (the c-Jun N-terminal Kinase, stress-activated protein kinase subfamily) and kinases (MAPK superfamily) which function as potential modifiers in tauopathy, do not make any significant difference in poly(Q) models [20,21]. In this context it is important to consider that although majority of the neurodegenerative disorders develop overlapping clinical features; their pathogenic mechanisms and affected tissues are rather divergent. poly(Q) diseases like SCA-3 and Huntington's are triggered by expansion of CAG repeats and aggregation of misfolded proteins known as inclusion bodies [22], Alzheimer's disease is caused by aggregation of hyper-phosphorylated tau protein by phosphatases and kinases [23]. Phosphorylated tau has reduced binding affinity for microtubules which leads to improper axonal transport system [19,24,25]. Formation of inclusion bodies in poly(Q) diseases encourage abnormal binding to other endogenous proteins and deplete their cellular level and most of the modifier proteins act by replenishing the required protein in cells [26]; whereas, modifiers of tauopathies usually involves genes altering the level of phosphorylation of proteins [25]. Therefore, it appears that increasing the level of protein through maintaining protein turnover either by induced folding or increasing the transcriptional activity is requisite method for mitigating the poly(Q) induced toxicity and cell death. On the other hand, maintaining the level of proper transport system appears to be more important in tauopathies. Therefore, consequences of a modifier gene activity in a given disease background seems to be reliant on the underlying pathogenic mechanism and not to the phenotypic manifestations of the disorders. Recent findings in our laboratory also substantiate the above phenomenon in which a novel poly(Q) suppressor has been found to further amplify the cellular toxicity in tauopathy and other disease conditions (M. Dhruba Singh and Surajit Sarkar, unpublished). Subsequently, it appears that although genome wide transcription modulation could be a promising method to minimise poly(Q) induced neurodegenerative disorders, yet, it could be equally deleterious in cases of tauopathies. Therefore, though the phenomenon of neuronal loss is a common feature in these broad ranges of disorders; hunt for a true "universal modifier" could be a herculean task.

Taken together, a wide variety of *Drosophila* neurodegenerative disease models have significantly improved our understanding of disease pathogenesis. They will continue to play central roles for years to come in not only deciphering exciting insights of these excruciating disorders but would also facilitate in designing of novel therapeutic approaches.

Acknowledgements

Research work in laboratory is supported by grants from the Department of Biotechnology (DBT), Government of India, New Delhi; DU/DST-PURSE scheme and Delhi University R & D fund to SS.

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