The "escape" of transposons in drosophila models of central nervous system diseases: An integrated overview.

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Abstract

Transposable elements are repetitive sequences widely present in eukaryotic genomes, embedded in the heterochromatin-the tightly condensed chromatin-which prevents their transposition. The unscheduled transcription of transposons and its harmful consequences have been proven to play a role in neuron degeneration. Drosophila models are crucial to unveiling this role and the mechanisms triggering transposon activity. Specifically, abnormal heterochromatin relaxation, which is also observed in Alzheimer's disease, has been found as the key event leading to transposon "escape" in the brain. This review recapitulates the main efforts towards demonstrating the role of transposons in neurodegeneration focusing on drosophila models, and offers an integrated overview of common and specific molecular mechanisms useful for identifying new therapeutic targets.

Keywords: Drosophila, Transposons, Neurodegeneration.

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Introduction

The heterochromatin of *Drosophila melanogaster* corresponds to one third of the whole genome and it is concentrated in the telomeric and pericentromeric regions [1,2]. The Transposable Elements (TEs) are known to be major structural components of drosophila heterochromatin, which also includes other peculiar repetitive sequences, such as stellate and suppressor of stellate, as well as some coding genes and satellite repeats [3-5]. More recently, assembly and mapping of the repetitive sequences of drosophila heterochromatin were generated. In addition, complete sequencing of euchromatic genomic regions of *Drosophila melanogaster* has provided the sequence and insertion sites for the repetitive elements in the drosophila euchromatin [6-9].

The Structural and Mechanistic Features of Transposons in Drosophila

The embedding of transposable elements into heterochromatin ensures their transcriptional silencing and avoids their movement [10]. Transposable elements are mainly repressed by H3K9 di/tri-methylation, the epigenetic hallmark for HP1 (Heterochromatin Protein 1). SU (VAR) 3–9 encodes a histone methyl transferase which selectively methylates histone H3 at lysine 9 (H3K9) ensuring HP1 binding, spreading and chromatin condensation [11,12]. In fact, the constitutive heterochromatin or "green chromatin" that is marked by SU (VAR) 3-9, HP1, and enriched of H3K9me2 histone mark, contains closely packed DNA that is transcriptionally repressed. Mapping studies revealed multiple binding of HP1 to TEs [13-15].

In addition to transcriptional silencing, transposable elements undergo a post-transcriptional silencing mediated by Argonaute proteins and specific classes of small non coding RNAs [16]. In drosophila germ cells, the Argonaute proteins Ago3, piwi and aubergine and the small non coding RNAs piRNAs are the key players in the post-transcriptional transposons silencing [17]. In drosophila somatic cells, including neurons, Argonaute protein Ago2 and ribonuclease Dicer2, in concert with the small RNAs endo siRNAs, silence transposable elements by degrading their transcripts [18].

The unscheduled activity of transposons has dangerous effects for the cell as a result of different genome alterations. The new insertion of transposons can cause not only gene mutations, but also changes in global transcript levels in cells, by providing promoters or altering chromatin state [19].

Studies conducted in drosophila unveiled a de-regulation of transposons due to gene mutations responsible of human nervous system diseases. This review offers an integrated vision of these recent studies related to transposons activation in altered conditions of the brain [20].

Transposable Elements are Dysregulated in Heads of Transgenic Drosophila Expressing Human Mutant Tau

Alzheimer's disease is an age-related degenerative neurological disorder that affects the brain [21]. The main hallmarks identifying Alzheimer's brain include the extracellular presence of aggregates of amyloid A peptide and the tau neurofibrillary tangles in neuronal cell bodies or neurites. Tau is a microtubule-associated protein, which stabilizes neuronal microtubules and, thus, ensures their functions. In Alzheimer's disease tau is abnormally hyper-phosphorylated, affecting its ability to bind microtubules which consequently disassemble [22-24].

Transgenic drosophila, expressing mutant form of human tau, shows age-related and progressive neurodegeneration in

specific brain regions without the accumulation of neurofibrillary tangles. RNAseq and qPCR analyses revealed the activation of multiple transposons in human tau transgenic drosophila heads. The dysregulation of transposable elements has been related to heterochromatin decondensation. In addition, the Piwi protein and piRNAs depletions were observed in tau transgenic drosophila, identifying a Piwi-mediated mechanism causing transposons activation. Double stranded RNAs derived from transcriptional release of transposons contribute to an inflammation state in neurons.

The evidence from drosophila models is in agreement with TE activation highlighted in brains of tau transgenic mice and in brains from deceased individuals with Alzheimer's disease. In tau transgenic drosophila, heterochromatin relaxation is linked to nuclear lamin dysfunction. Mechanistically, Tau stabilizes the actin filaments that in turn cause the reduction and disorganization of the nuclear lamin in neurons [25].

Pin1-Mediated Mechanism Underlies Heterochromatin Maintenance and Transposons Control in Drosophila Brain

In the cell nucleus, heterochromatin is mainly located at the nuclear periphery and it is tightly associated to the nuclear lamin in the LADs (Lamina-Associated Domains).

The nuclear lamin is a network of A- and B-type lamins, intermediate filamentous proteins coating the inner nuclear membrane, that interact with multiple proteins such as Barrier to Autointegration Factor (BAF), LAP proteins, Lamin B Receptor (LBR) or Emerin. Proteins of the LINC complex such as Nesprins and Sun proteins connect nuclear lamin and cytoskeletal components across the nuclear envelope. Nuclear lamin has a crucial role in maintaining chromatin organization, and nucleus shape under mechanical intra- and extracellular forces. Cells from individuals with a Lamin A mutation present a loss of heterochromatin, causing Hutchinson Gilford Progeria Syndrome [26-28].

Studies in drosophila, confirmed in mice and human, have provided advancement towards understanding the molecular mechanisms underlying the relationship between mechanical cues, nuclear lamina and heterochromatin organization, by attributing a key role to the prolyl-isomerase Pin1.

Mechanistically, in the fly brain Pin1 maintains lamin B structure in a phosphorylation-dependent manner ensuring HP1a binding and stability. Loss of Pin1 decreases HP1a stability and causes heterochromatin relaxation and transposons dysregulation. These experiments demonstrated the fundamental role of Pin1 in controlling transposons, preserving neuron survival and cognitive functions [29]. The action of Pin1 is specifically essential during mechanical stress, preventing nuclear shape deformation and heterochromatin relaxation in these stressful conditions. Interestingly, the reduction of Pin1 takes place in Alzheimer affected brains and has an effect in the maintenance of the nuclear envelope structure and heterochromatin condensation [30,31].

Transposable Elements are Dysregulated in Drosophila Model of Huntington Disease

Huntington Disease (HD) patients present an array of motor, cognitive and behavioural deficits. The disease is caused by the expansion of a CAG trinucleotide repeat in HTT gene that encodes the protein huntingtin. The mutant huntingtin protein has a long polyglutamine sequence and results toxic to neurons. The feature of the disease is a progressive loss of spiny neurons of the striatum [32,33].

In larval and adult brains from transgenic drosophila expressing human mutant huntingtin, the global heterochromatin relaxation drives the deregulation of transposons. Regarding the transposable element GYPSY_I, the increase of RNA expression level correlates with a higher number of genomic insertion sites in HD fly brains than in controls [34]. However, other studies need to be performed to establish the potential role of transposons in huntington disease. In a recent study, the RNA and protein levels of the transposon Line1 have been investigated in a mouse model of HD. The Line1 RNA expression level decreases in HD, but the expression of Orf1 and Orf2 doesn't correlate with RNA levels and it increases in specific regions of the brain and at specific age [35-39].

Discussion

Unscheduled transcription of transposons causes harmful effects in neurons, leading to neurodegeneration. Interestingly, the use of inhibitors of the retro-transcriptase in drosophila models had rescued neurodegeneration effects from cellular to phenotypic level. The relaxation of the heterochromatin structure appears the principal and common event at the base of transposon transcriptional release (Figure 1). However, the mechanisms that lead to chromatin decondensation are different as revised in this review [40-43].

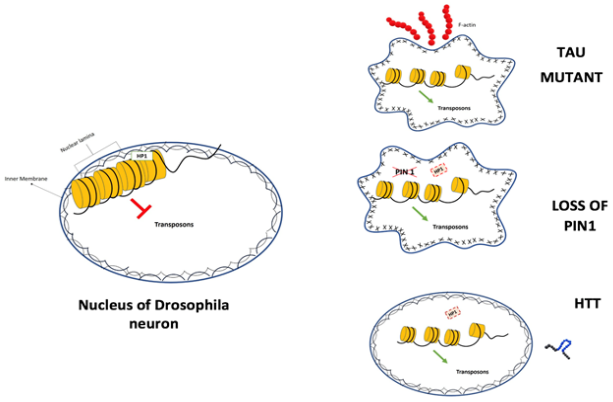

Figure 1. *Schematic overview of heterochromatin relaxation and transposons activation in different genetic background of drosophila neurons.*

Conclusion

The “transposons” escape in neurons is emerging as a mechanism that contributes to neurodegenerative processes. Therefore, the genetic and molecular dissection of the mechanisms underlying the transposon activation in neurons and in age-dependent manner is crucial to unlock therapeutic targets.

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