Role of Circadian Clock Components in Apoptosis and Tauopathy in Drosophila

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Role of Circadian Clock Components in Apoptosis and Tauopathy in Drosophila

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Research Abstract

PROJECT SUMMARY In humans, it is clear that reduced function of the circadian clock is associated with increased incidence of neurodegeneration (e.g., Alzheimer’s Disease; AD). While it has been hypothesized that circadian dysfunction and neurodegeneration may be linked, the mechanism for these proposed links remains uncertain. My lab has evidence that the

circadian clock components in Drosophila regulate sensitivity to cell death and neurodegeneration pathways after prolonged exposure to light. The doubletime protein kinase (DBT), which phosphorylates key circadian clock proteins to control their daily accumulation, is the common link. In various genotypes with reduced DBT kinase activity, the DRONC caspase, which cleaves various target proteins to initiate cell death pathways, becomes activated and cleaves tau protein, which is associated with enhanced degeneration in a fly eye model for tauopathy. DBT interacts with two other circadian proteins recently discovered by my lab (SPAG and BDBT) to maintain inhibition of DRONC activation. In turn, SPAG may interact with heat shock protein 90 (HSP90) and tau to reduce tauopathies. Furthermore, activation of the DRONC caspase occurs more broadly in cells that do not express the transgenes knocking down DBT activity and is signaled by the circadian neuropeptide PDF. These findings lead us to propose a mechanism in which the circadian component DBT kinase phosphorylates DRONC caspase to inhibit its activation and DRONC- dependent tau cleavage, which can lead to tauopathy. The inhibition of cell death seems to require phosphorylation of DBT. The work proposed will test this mechanism and map out the biological consequences in the fly model. Aim 1. Determine the biochemical pathway of DBT-dependent caspase activation and tau interactions. Specifically, my lab will investigate whether DBT kinase directly phosphorylates the DRONC caspase to inhibit its cleavage, and whether cell cell-death inducing stimuli like UV stimulate autophosphorylation of DBT, dissociation of SPAG cochaperone and BDBT FKBP from DBT and cleavage of DRONC. The capacity of BDBT cochaperone to regulate activation of DRONC kinase will be investigated in novel bdbt CRISPR mutants, and the nature of SPAG cochaperone interactions with HSP90 and tau will be assessed. Aim 2. Determine whether tau cleavage in the fly eye in response to reduced DBT activity leads to typical tauopathy features that contribute to enhanced neurodegeneration, or whether the effect of reduced DBT is mediated independently of tau via cell death (caspase-directed) pathways. We will try to induce eye degeneration by expressing these proteins only in the adult fly instead of throughout eye development in order to more accurately mimic age-dependent neurodegeneration. We will determine the extent to which cell death pathways are induced in the fly eye by DBT kinase reductions and the extent to which various aspects of tauopathy are downstream consequences (e.g., tau phosphorylation, NFT formation, and mitochondrial and cell cycle dysfunction). Also, the capacity of cleaved tau to produce tauopathy downstream of DBT kinase reductions will be tested, and the role of DRONC caspase activation in the neurodegeneration will be assessed by antagonizing DRONC with RNAi or potentiating it with nonphosphorylatable forms of DRONC. Aim 3. Determine the mechanisms for the interaction between DBT-mediated caspase activation and aging, light and the circadian rhythm PDF signaling pathway. We have found that light induces caspases in the optic lobes after 7 hrs of exposure, independent of circadian time, in our flies with reduced DBT activity in the circadian cells of the brain. The effect involves signaling by the circadian PDF neuropeptide and can occur in cells that do not express the transgenes reducing DBT kinase activity. We will determine the importance of circadian and visual photoreceptors for this process, and whether wild type flies produce tauopathy as a consequence of aging. The cells in which the DRONC caspase activation occurs will be determined, and whether the PDF neuropeptide receptor produces an increase in DBT kinase phosphorylation and a decrease in DBT levels in the cells. Finally, it will be determined whether the caspase activation we observe affects a previously observed light-dependent neuronal remodeling process in the optic lobes.

Further information available at:

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