Abstract

Thesis Title: **Role of TRB3 in Neuronal Cell Death in Alzheimer's Disease Model**

Neurodegeneration is one of the pathognomonic features in Alzheimer's disease (AD). Among several death modalities, autophagy and apoptosis play important roles in the death of neurons. The general mechanism which governs these two phenomena mutually is still not understood fully. Amyloid beta (Aβ) induced neuron death is considered pivotal in the pathogenesis of AD. This study aims to understand the complex mechanism by which Aβ1-42 induces neuronal death in AD. Unravelling these mechanisms may prove to be pivotal for development of therapeutics for AD. We report that Tribbles3 (Trib3/TRB3 a mammalian ortholog of the Drosophila Trib3), is upregulated in neurons, both *in vivo* and *in vitro* upon Aβ treatment. Increased levels of Trib3 inhibit the activity of Akt by interacting with it. As a result, FoxO1, a member of Fork-head box transcription factors that is negatively regulated by Akt, gets activated, translocates to the nucleus, and induces an apoptotic gene Bim. Conversely, FoxO1 also binds with Trib3 and enhances its expression upon Aβ insult. This establishes a feed forward loop between Trib3 and FoxO1 in Aβ-treated neurons. On the other hand, our investigations reveal that upon Aβ insult, Trib3 also leads to induction of autophagy via the Akt/m-TOR/ULK1 pathway. Further downstream this leads to the augmentation of autophagosome formation as confirmed by presence of LC3-II and reduced autophagy flux as evident by increase in p62 levels. Thus, we find that Trib3 is required for autophagosome formation and impaired autophagy flux. Most importantly, silencing endogenous Trib3 strongly protects neurons from Aβ insult. We find that inhibition of autophagy leads to better survival of neuronal cells upon Aβ treatment. Further studies into the cross talk between autophagy and apoptosis reveals that autophagy induced Beclin1 is cleaved by active caspases which may thwart further autophagy and induces apoptosis. Moreover downregulating Beclin1 leads to increased survival of neurons treated with Aβ. Our results suggest that a self-amplifying feed-forward loop among Trib3, Akt and FoxO1 in Aβ-treated neurons leads to induction of both apoptosis and autophagy that culminates in neuron death. Thus, Trib3 may serve as potential therapeutic target for AD.

duly attested
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09.08.2017