2. Rationale and Aims of Thesis

Alzheimer's Disease (AD) is a progressive neurodegenerative disease that causes memory loss and cognitive impairments due to massive loss of synapses and neurons. Extensive research has been continuing over the past three decades with the sole aim to identify effective treatment for AD. It is a multifactorial disease; hence an approach encompassing several avenues must be applied to elucidate its severity. Application of biochemistry, molecular biology as well as transgenic modeling has been able to elaborate on the molecular mechanism of the disease. Yet, involvement of several other arenas like chemistry, radiology and systems biology is essential to provide information on the novel biomarkers for this disease. Recently, scientists have had to face failure in the Phase III clinical trials, based on their approach of reducing Aβ and its aggregation. Therefore extensive research is needed to understand the best target and hence embark on the therapeutic strategy to be able to provide effective means to treat this devastating disease.

Though much has been unraveled regarding the mechanism of neuron death in neurodegeneration yet a lot still remains to be elucidated. A number of pro-apoptotic molecules have been identified that play pivotal roles in neuron death, however, these molecules are not indispensable since deletion of these molecules provides only partial protection from death. This indicates the presence of other molecules which may play important roles in neuron death. Most of the molecules identified have role in apoptotic death of neurons as apoptosis is one of the major death pathways for degenerating neurons. Though recent reports suggest the activity of several other death paradigms and their contribution in neuron death, their exact roles is still unclear. Therefore it is possible that there are molecules involved in one or more death pathways responsible for neuron death in neurodegeneration. Trib3, in this context proves to be an interesting molecule as it is involved in both autophagy and apoptosis. Hence a detailed study of the activities of Trib3 might prove to be beneficial in the quest for the identification of novel targets for therapeutic intervention in AD.

The present work is an attempt to understand the role of Trib3, a pseudokinase, in neuronal cell death using models of AD.

Chapter I

In the first part, we intended to look into the role and regulation of Trib3 in causing apoptotic death of neurons in a model of AD. We also aimed to check the mechanism by which Trib3 regulated FoxO and Bim in this death pathway. We also sought to check the presence of feed forward loop between Trib3 and FoxO.

Chapter II

In the second part, we intended to check the role and regulation of Trib3 in autophagic death of neurons in a model of AD. We also intended to look into the mechanism of this regulation and identify its downstream targets. Most importantly, we wanted to check whether overexpression of Trib3 was sufficient to cause neuron death.

Chapter III

In the last part of the study, we tried to unravel the crosstalk between autophagy and apoptosis at the molecular level. We checked the role of Beclin1 in this crosstalk mechanism. We further studied the involvement of caspases in cleaving Beclin1. Further we checked the translocation of the cleaved beclin1 fragment to the mitochondria, as it is a crucial event in mediating the crosstalk between the two phenomena. Finally, we intended to establish the role of Trib3 in orchestrating death of neurons by a dual mechanism, autophagy and apoptosis in a model of AD.