Abstract

With the increase in life expectancy neurodegenerative diseases like Alzheimer's disease (AD) and Parkinson's disease (PD) are on the rise. While neurodegeneration has been studied in the context of various pathological conditions, not much is known on the molecular mechanisms that cause/regulate axonal retraction during aging. Identification of key targets that delay the process of neuronal death before they reach the 'point of no return' may enhance their longevity and prevent subsequent disease pathology.

SARM1 (Sterile alpha and TIR motif-containing 1 protein) is a key molecule that plays a pivotal role in axonal death. To study the role of endogenous SARM1 we established a cellular model of neurodegeneration in SH-SY5Y cells by treatment with the mitochondrial complex I inhibitor rotenone. We showed that rotenone induced neuronal death through SARM1 activation that was accompanied by increased inflammation, deregulation of electron transport chain (ETC) complex genes and defective autophagy. To study age-associated neurodegeneration, we established a drosophila model of aging for the study of age-dependent vulnerability to rotenone, a pesticide that has been implicated in sporadic cases of PD. Our results showed that age plays a major role in the increased susceptibility to rotenone that is accompanied by decreased lifespan, severe locomotor deficits, and loss of dopaminergic neurons. Rotenone exposure results in the SARM1 induction that is accompanied by an increased inflammatory response and independent of ROS generation. Thus, this study aims to provide a detailed mechanistic insight into the regulation of neuronal homeostasis by SARM1 and its implication in age-associated neurodegeneration.