

Generation of new proteins and removal of damaged or old polypeptides is an uninterrupted mechanism essential for a healthy cellular environment. Impairment in the removal of misfolded proteins can disturb proteostasis; such toxic aggregation of misfolded proteins can act as a preliminary causative agent for neurodegenerative disorders and imperfect aging. Therefore, removal of such abnormal aggregates can ensure the re-establishment of proteostasis; the ubiquitin-proteasome system (UPS) actively participates in the specific clearance of aberrantly folded clients with the help of complex proteasome machinery. The critical challenge is to design effective protein quality control (PQC) based molecular tactics that could potentially eliminate aggregation-prone protein load from the cell. E3 ubiquitin ligases impart ability for identifying unique critical misfolded protein clients for targeting them towards proteasomal degradation. Several neurodegenerative and neurodevelopmental disorders are known to have compromised functioning of specific protein quality control E3 ubiquitin ligases.

The work presented here involves use of Itraconazole and Resveratrol to improve critical protein quality control functions of the cell in order to improve the removal of toxic abnormal protein aggregates thus, increasing cellular resistance towards proteotoxic stress mechanisms. The results demonstrate specific potentials of Itraconazole to enhance proteasome activity for increasing the clearance of various model and neurodegeneration causative abnormal proteins. Furthermore, Resveratrol exposure was found to significantly enhance the LRSAM1 E3 ubiquitin ligase, found mutated during spongiform neurodegeneration, levels in the cell. The expression levels of LRSAM1 were also found to influence the proteasome chymotrypsin-like and post-glutamyl peptidyl-hydrolase like functions. Resveratrol being a plant based stilbenoid compound was able to stop the occurrence of toxic proteinaceous species in the cell. The present work implicates the potential of improving protein quality control as significant therapeutic measure against several protein aggregation-based disorders. Moreover, specific potentials of upregulating proteasome and quality control E3 ubiquitin ligase functions by Itraconazole and plant derived Resveratrol can help to increase cellular cytoprotection.

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