Abstract

Cellular protein quality control mechanisms always present a continuous and rigorous check over all intracellular proteins before they can participate in various physiological processes with the help of cellular proteolytic pathways like autophagy and ubiquitin-proteasome system (UPS). E3 ubiquitin ligases are a major component of UPS and play a crucial role in diseases like cancer and neurodegeneration. The UPS employs a few E3 ubiquitin ligases for the intracellular degradation of cyclin-dependent kinase inhibitor 1B/ p27 kip1 that tightly controls cell cycle progression and may function as biomarkers in various cancers. The current study demonstrated that glycoprotein Gp78, a putative E3 ubiquitin ligase, is involved in the stabilization of intracellular levels of p27. Gp78 increases the accumulation of both phosphorylated and unphosphorylated forms of p27 in cells. Overall, it suggests a valuable multifactorial regulatory mechanism and linkage of p27 with UPS pathway and its components. Major neurodegenerative disorders are characterized by the formation of misfolded proteins aggregates inside or outside the cells. E3 ubiquitin ligases are associated with multiple neurobiological mechanisms and degradation of these aggregates. The present study found Myricetin, a natural molecule (flavonoid) as a modulator of E3 ubiquitin ligases, which can eliminate various misfolded proteins via modulating levels of Hsp70 chaperone and E3 ubiquitin ligase E6-AP. Results suggest that Myricetin treatment suppresses the aggregation of different aberrant proteins associated with neurodegeneration and reduce cytotoxicity. Thus, it provides a new mechanistic and therapeutic insight based on small molecule-mediated regulations of disturbed protein quality control mechanism, to maintain the state of proteostasis.

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