Abstract

Proteostasis is an essential process ensuring the optimal functioning of proteins and cellular homeostasis, involving maintenance of synthesis of proteins, their folding, and degradation by cellular protein quality control (PQC). Failure of PQC machinery, including chaperones and the ubiquitin-proteasome system (UPS), can lead to protein misfolding and disturbed cellular proteostasis. The consequent misfolded protein accumulation can form the basis of neurodegeneration onset and largely represents imperfect aging. Understanding how cells rejuvenate deregulated PQC mechanisms to maintain proteostasis and prevent the aggregation of normal proteins by misfolded inclusions is a major challenge. The present work demonstrates that lanosterol, an intermediate in cholesterol synthesis pathway, enhances proteasome proteolytic activity, thereby supporting the PQC mechanisms for eliminating intracellular aberrant proteins. Moreover, lanosterol exposure promotes the clearance of both bona fide proteins and toxic proteins linked with neurodegenerative diseases.

In contrast, many cancer cell types have higher proteasomal expression as well as activity than normal cells. Designing of novel proteasome inhibitors and targeting proteasome machinery for therapeutic purposes emerged as a promising molecular strategy for restricting the cancer cell proliferation. Valproate, an approved drug for treating seizures, is a class I histone deacetylases (HDACs) inhibitor and an attractive chemotherapeutic agent for targeting cancer. Few reports suggest that valproate can suppress cell growth and cell differentiation and is linked with anti-tumor activity. However, valproate-associated anti-tumoral function and intracellular signaling cascade-mediated anti-cellular proliferation activities are still not completely known. This current study indicates that treatment of valproate inhibits proteasome activities and also aggravates the accumulation of expanded polyglutamine proteins and other proteasomal substrates. Moreover, inhibition of proteasome by valproate also induced mitochondrial dysfunction and apoptosis. Overall, our finding elucidates the potential of valproate as a proteasome inhibitor, which can be beneficial in combination with other anti-tumor agents for more effective therapeutic interventions.

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