Abstract

Proteins, being the key components of living cells, are required to be regularly synthesized and folded into their native conformation for their proper functioning. However, under stress conditions or synthesis errors there is always a risk of protein misfolding and aggregation that may ultimately lead to cellular toxicity or occurrence of diseases. In order to cope up and eliminate those unwanted entities, healthy cells employ proteostasis mechanisms, which include the chaperone machinery, the ubiquitin proteasome system and the autophagy pathway. Sometimes, these mechanisms are unable to accomplish the task of misfolded proteins clearance causing disruption of state of cellular proteostasis or protein homeostasis. This may ultimately lead to activation of cell death mechanisms for removal of those abnormal cells. Interestingly, the strategy of inducing cell death mechanism by inhibiting proteasome function has been found to have therapeutic significance.

The proposed research work was carried to characterize molecules that have the property to interfere with proteasome functions and to understand the mechanisms associated with the proteasome inhibition induced apoptosis. Nonsteroidal anti-inflammatory drugs, are class of drugs that are used for their ability to reduce pain, fever and inflammation by acting on cyclooxygenases enzymes. However, various epidemiological studies have demonstrated their anti-proliferative and pro-apoptotic effects. Here, it was observed that treatment of cells with diclofenac or indomethacin induces proteasomal malfunction and mitochondrial abnormalities, prompting up key apoptotic events. The findings improve the existing understanding of Nonsteroidal anti-inflammatory drugs mediated anti-proliferative effects in cells and suggest possible beneficial insights of Nonsteroidal anti-inflammatory drugs induced apoptosis in anti-proliferative strategies development.

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