Ahn YS. Pyrrolidine dithiocarbamate and zinc inhibit proteasome-dependent proteolysis.

許重義
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Abstract

Proteasomes play important roles in a variety of cellular processes such as cell cycle progression, signal transduction and immune responses. Proteasome activity is important in maintaining rapid turnover of short-lived proteins, as well as preventing accumulation of misfolded or damaged proteins. Alteration in ubiquitin-proteasome function may be detrimental to its crucial role in maintaining cellular homeostasis. Here, we have found that treatment of pyrrolidine dithiocarbamate (PDTC), a zinc ionophore, resulted in the accumulation of several proteasome substrates including p53 and p21 in HeLa cells. The PDTC effect was due to an extended half-life of these proteins through the mobilization of zinc. PDTC and/or zinc also increased fluorescence intensity of UbG76V-GFP fusion protein that is degraded rapidly by the ubiquitin-proteasome system. Treatment of cells with zinc induced formation of ubiquitinated inclusions in the centrosome, a histological marker of proteasome inhibition. Western blotting showed zinc-induced increase in laddering bands of polyubiquitin-conjugated proteins. In vitro study, zinc inhibited the ubiquitin-independent proteasomal degradations of p21 and a-synuclein. These results suggest that zinc may modulate cell functions through its action on the turnover of proteins that are susceptible to proteasome-dependent proteolysis.