Title: Cathepsin inhibition : Novel cancer therapy adjuvant

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Abstract

Cancer cell lysosomes are less stable than normal lysosomes. Cathepsins, which are lysosomal proteases, have important roles in cancer. Enhanced cathepsin activity out of the cell is linked to tumor growth, whereas such activity inside the cell is linked to tumor growth inhibition. Here, we tested whether inhibition of cathepsin S could sensitize TRAIL-mediated apoptosis. Inhibitor of cathepsin S (Z-FL-COCHO;ZFL) markedly induced apoptosis in TRAIL-treated human renal, breast, and glioma cells. In contrast, the combined treatment with ZFL and TRAIL had no effect on normal cells. ZFL induced down-regulation of c-FLIP, and over-expression of c-FLIP blocked apoptosis induced by ZFL plus TRAIL. Moreover, ZFL induced Cbl expression, which is E3 ligase of c-FLIP, in a p53-dependent manner and knock-down of Cbl markedly prevented c-FLIP down-regulation and apoptosis in ZFL plus TRAIL-treated cells. Furthermore, ZFL down-regulated Bcl-2 expression at the transcriptional levels in a p53-dependent manner, and over-expression of Bcl-2 also markedly blocked apoptosis induced by combined treatment with ZFL and TRAIL. Interestingly, ZFL induced p53 mRNA and protein expression via production of mitochondrial reactive oxygen species (ROS). We also showed that down-regulation of cathepsin S by siRNA sensitized TRAIL-mediated apoptosis. Furthermore, we confirmed in tissue of patient with human clear

cell renal cell carcinoma using immunohistochemistry analysis. Patients with higher cathepsin S levels had higher expression of Bcl-2 and c-FLIP compared to the lower ones ($p < 0.014$, $p < 0.061$, respectively). Thus, inhibition of cathepsin S enables TRAIL-induced apoptosis through p53-dependent down-regulation of Bcl-2 expression and Cbl-mediated c-FLIP expression in human cancer cells.

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