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Overexpression of Reticulon 3 (RTN3) Enhances TRAIL-mediated Apoptosis via Up-Regulation of Death Receptor 5 (DR5) and Down-Regulation of c-FLIP

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Reticulons (RTNs) are a group of integral membrane proteins that have no homology to other known apoptosis-related domains. Herein, we found that RTN3 overexpressing Caki cells were sensitive to TRAIL-mediated apoptosis. RTN3-inducd down-regulation of c-FLIP was recovered by pancaspase inhibitor, z-VAD to basal levels in TRAIL-treated cells. The forced expression of c-FLIP attenuated the TRAIL-mediated apoptosis in RTN3 overexpressing cells. In addition, RTN3 overexpression provoked the enhanced protein levels in DR4 and DR5 as well as levels in DR5 surface protein but failed to detect increase in DR4 surface protein. RTN3-mediated enhancement of TRAIL-induced apoptosis was markedly blocked by the DR5/Fc chimera or DR5 siRNA, indicating that the sensitization by RTN3 was mainly mediated through interactions of TRAIL with its receptors, DR5. Overexpression of RTN3 also enhanced TNF-a and Fas-mediated apoptosis. Taken together, overexpression of RTN3 might increase DR5 surface protein and concomitantly more activated caspase-8 pathways, which caused the enhancement of TRAIL-mediated apoptosis.

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Cystamine Sensitizes Human Renal Cancer Cells to TRAIL-Mediated Apoptosis through c-FLIP Down-Regulation

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Cancer therapy traditionally combines cytotoxic agents, or inhibitors that suppressed enzyme activity. In this study, we investigated the combined effect of cystamine, a molecule that has been known to inhibit of transglutaminase 2 (TG2) activity, and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) on the activation of the apoptotic pathway in human renal cancer cells. We demonstrate for the firsttime cystamine selectively enhanced TRAIL-mediated apoptosis in Caki cells without any cytotoxicity in normal cells. Cystamine plus TRAIL-induced down-regulation of c-FLIP was recovered by pancaspase inhibitor, z-VAD to basal levels. The forced expressionof c-FLIP attenuated the cystamine and TRAIL-mediated apoptosis in Caki cells. Interestingly, high TG2 expressed cells were more sensitive to cystamine plus TRAIL-mediated apoptosis than low TG2 expressed cells. Ectopic expression of TG2 enhanced cystamine plus TRAIL-mediated apoptosis. Conversely, the knock down with TG2 siRNA showed decreased sensitivity to cystamine plus TRAIL in high-TG2 expressing cell line. These results implicate that the expression levels of TG2 modulates cystamine plus TRAIL-induced apoptosis. Taken together, the present studies suggest that cystamine may be an effective sensitizer of TRAIL-induced apoptosis in high-TG2 expressing cancer cells.