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# Cancer cell resistance to the death receptor targeted therapies

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Multiple clinical trials are ongoing to test the antitumor potential of the recombinant forms of human TNFα variants, Fas ligand (FasL), TNF-related apoptosis inducing ligand (TRAIL) and its receptor agonistic antibodies. These protein products act through their corresponding death receptors (DRs), including TNF receptor 1 (TNFR1), Fas/CD95, DR4 (TRAIL-R1) and/or DR5 (TRAIL-R2). Therefore, characterization of the expression levels and subcellular localization of individual DRs in cancer cells is important for predicting tumor response to the targeted therapies. We have made novel findings that some cancer cells are defective in expressing one or multiple DRs on cell surface, despite the total protein expression of the specific receptors. This deficiency is well correlated with cancer cell resistance to the targeted therapies. We provide evidence that suggest distinct mechanisms responsible for DR deficiency on surface membrane. In some cancer cells, DRs are found to undergo constitutively endocytosis and thus being trapped in intracellular compartments. Our recent data demonstrate an accumulation of autophagosomes in TRAIL-resistant cells, thereby downregulating DR4 and DR5 expression on cell surface. Further, pharmacological inhibition of endocytosis or autophagosome formation successfully restored DR expression on surface membrane and sensitized the cells to TRAIL induced apoptosis. These data could have implication in the development of biomarkers for predication of tumor response to the DR-targeted therapies and in the identification of novel molecular targets for combination drugs to overcome or bypass the resistance mechanisms.

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