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Concepts in the use of TRAIL/Apo2L: an emerging biotherapy for myeloma and other neoplasias.

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TNF-related apoptosis inducing ligand/Apo2 ligand (TRAIL/Apo2L) is a member of the TNF superfamily of death ligands that selectively induces apoptosis in tumour cells of diverse origins. In this report, we have reviewed recent studies examining TRAIL/Apo2L-induced apoptosis in multiple myeloma (MM), a B-cell malignancy which, in spite of its initial sensitivity to steroids, cytotoxic and high-dose chemotherapy, remains incurable. Recently, we demonstrated that TRAIL/Apo2L induces apoptosis of steroid- and chemotherapy-sensitive and resistant MM cell lines. Moreover, TRAIL/Apo2L selectively induced apoptosis of patient MM tumour cells while sparing non-malignant bone marrow and peripheral blood mononuclear cells. In addition, TRAIL/Apo2L inhibited the growth of human plasmacytomas xenografted into mice. Importantly, TRAIL/Apo2L-induced apoptosis was unaffected by IL-6, a potent growth and survival factor for MM cells which, as we and others have previously shown, blocks various pro-apoptotic signals including Fas ligand, which like TRAIL/Apo2L is also a member of the TNF family of ligands. In view of the potential clinical application of TRAIL/Apo2L to the treatment of MM, we have attempted to discern intracellular mechanisms of action and resistance for TRAIL/Apo2L in MM, along with strategies to increase sensitivity and overcome resistance of MM cells to TRAIL/Apo2L. These studies demonstrated that doxorubicin, an agent which is commonly used to treat MM patients, upregulated the expression of the DR5 death-signalling TRAIL receptor and synergistically enhanced the pro-apoptotic effect of TRAIL on MM cells. Moreover, NF-kappaB inhibitors such as SN50 (a cell permeable inhibitor of NF-kappaB nuclear translocation) as well as the proteasome inhibitor PS-341, which is currently in Phase II clinical trials, also enhanced the pro-apoptotic activity of TRAIL/Apo2L in MM cells. Lastly, TRAIL/Apo2L-induced apoptosis in MM cells was dependent on caspase-8 activation and inhibited by the caspase regulatory proteins FLIP and cIAP2. These studies provide a framework for the use of TRAIL/Apo2L as a single agent or as part of combination therapy for the treatment of MM.