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TRAIL-based therapeutics in osteosarcoma: involvement of bone tumor microenvironment in TRAIL resistance

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Osteosarcoma (OS) is the most common pediatric bone tumor. OS patients have not seen major therapeutic advances these last thirty years and the survival rate of 70 % at five years for a localized tumor still falls to around 20 % in the case of a metastatic tumor or resistance to chemotherapy. The pro-apoptotic cytokine TNF-Related Apoptosis Inducing Ligand (TRAIL) can selectively kill tumor cells representing a promising therapeutic approach for patients at high risk. However, therapeutic use of TRAIL in OS patients seems limited since several OS cell lines showed high resistance towards TRAIL sensitivity.

In vitro and in vivo studies identified several molecular mechanisms involved in TRAIL resistance in OS that could be targeted for subsequent therapeutic strategies. Different levels of TRAIL regulation signaling pathways have been explored: death (DR4 and DR5) and decoy (DcR1, DcR2, Osteoprotegerin) receptor expression, involvement of inhibitory proteins of apoptosis (c-FLIP, IAP1/2), activation of TRAIL-induced surviving, migration or invasion pathways (NF-kB, MAPK, PI3K/Akt...).

We hypothesized that the bone micro-environment may provide a favorable niche for TRAIL resistance due in particular to hypoxia, inflammation or acidic extracellular pH. Therapeutic perspectives are linked to the possibility to overcome TRAIL resistance by combining drugs targeting the bone micro-environment with TRAIL or death receptor agonist antibodies. Therefore, this area might be targeted by new re-sensitizing agents. For example, zoledronic acid already used as an antiresorptive agent in OS, shows a sensitizing effect to TRAIL by inhibition of IAPs in in vitro synergy studies. However the transition of these observations to nude mouse models reveals that zoledronic acid is not sufficient to overcome TRAIL resistance mechanisms, largely because of the induction of the TRAIL non-canonical pathway in OS cells which overrides the pro-apoptotic canonical pathway. Activation of this second signaling pathway leads to increased tumor cell proliferation, survival, migration and invasion. It is more importantly observed in vivo and may be linked to the particular bone tumor micro-environment observed in OS. We propose that a combinatory therapy based on a selective TRAIL activating apoptosis pathway (APG880) associated with zoledronic acid may overcome TRAIL resistance of OS models.