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A high TRAIL-receptor clustering is able to overcome TRAIL resistance in pediatric bone sarcoma models

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Osteosarcoma (OS) and Ewing's sarcoma (EWS) are the two most common pediatric bone tumors which mostly arise in children and adolescents. OS and EWS 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 a resistance to chemotherapy. The pro-apoptotic cytokine TNF-Related Apoptosis Inducing Ligand (TRAIL) can selectively kill tumor cells and could therefore represent a promising therapeutic approach for patients at high risk. However, the transfer to clinics seems limited because several OS and EWS cell lines show resistance towards TRAIL sensitivity in vitro.

In vitro and in vivo approaches allow us to identify several molecular mechanisms involved in TRAIL resistance in these particular pathologies: death receptor (DR4 and DR5) and decoy receptors (DcR1, DcR2, Osteoprotegerin) expression, involvement of inhibitory proteins of apoptosis (cFLIP; IAP1/2)...

Even if OS and EWS exhibit similar clinical features, these pathologies differ in response to TRAIL pro-apoptotic effects: the involvement of death receptor expression profile was clearly demonstrated in EWS with a very strong correlation between DR4 expression and TRAIL sensitivity, whereas OS cell lines are highly resistant to TRAIL independently of death/decoy receptor balance. In addition, a TRAIL-receptor agonist antibody (AMG655) induces MAPK pathway activation in OS cell lines, showing even a protumoral effect in vivo in a OS xenograft model. Accumulated evidences over the last years indicate that TRAIL, besides its well documented pro-apoptotic effects can also induce the activation of another signaling pathway involving NF-kB, MAPK, PI3K/Akt via binding to the same receptors, but leading to increased tumor cell proliferation, survival, migration and invasion. The key regulator of this kinase network is the RIPK1 protein which binds FADD and leads to the formation of a secondary signaling complex (Complex II) composed by TRADD, TRAF2 and RIPK1. We hypothesize that an efficient TRAIL-receptors clustering could raise resistance of tumor cells and trigger apoptosis instead of proliferation. To this aim, two different approaches were used: trimeric TRAIL presentation at the surface of carrier Mesenchymal Stem Cells (MSC) stably transfected with full length human TRAIL and a novel TRAIL-receptor agonist able to bind 6 receptors (APG880). We validate in vitro that coculture of tumor cells with MSC-TRAIL or use of APG880 can induce apoptosis even in initial resistant cell lines. In vivo, intratumoral injection of untransfected MSC accelerate tumor development in both EWS and OS models, whereas MSC-TRAIL inhibit tumor progression in EWS models but not in OS models. For these models, APG880 may represent a good compromise between the induction of receptor clustering and the lack of pro-proliferative effect of MSC by themselves.