

Focal adhesion kinase plays a dual role in TRAIL resistance and metastatic outgrowth of malignant melanoma

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Despite remarkable advances in therapeutic interventions, malignant melanoma (MM) remains a life-threatening disease. Following high initial response rates to targeted kinase inhibition metastases quickly acquire resistance and present with enhanced tumor progression and invasion, demanding for alternative treatment options. We show 2nd generation hexameric TRAIL receptor agonist IZI1551 (IZI) to effectively induce apoptosis in MM cells irrespective of the intrinsic BRAF/NRAS mutation status. Conditioning to the EC50 dose of IZI converted the phenotype of IZI-sensitive parental MM cells into a fast proliferating and invasive, IZI-resistant metastasis. Mechanistically, we identified focal adhesion kinase (FAK) to play a dual role in phenotype-switching. In the cytosol, activated FAK triggers survival pathways in a PI3K- and MAPK-dependent manner. In the nucleus, the FERM domain of FAK prevents activation of wtp53, as being expressed in the majority of MM, and consequently intrinsic apoptosis. Caspase-8-mediated cleavage of FAK as well as FAK knock down, and pharmacological inhibition respectively, reverted the metastatic phenotype-switch and restored IZI responsiveness. FAK inhibition also re-sensitized MM cells isolated from patient metastasis that had relapsed from targeted kinase inhibition to cell death, irrespective of the intrinsic BRAF/NRAS mutation status. Hence, FAK-inhibition alone or in combination with 2nd generation TRAIL-receptor agonists may be recommended for treatment of initially resistant and relapsed MM respectively.