MicroRNA-145 replacement as a therapeutic tool to Improve TRAIL therapy

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Pancreatic cancer (PanCa) is a third leading cause of cancer related deaths in US. Unlike other cancers, PanCa is highly resistant to TNF-related apoptosis-inducing ligand (TRAIL) that emerges as one of the most-promising therapy in clinical trials. Our group has previously identified microRNA-145 (miR-145) is downregulated in PanCa, the restoration of which inhibits tumor growth and enhances gemcitabine sensitivity. In this study, we have observed that miR-145 restoration in PanCa cells renders them sensitive to TRAIL treatment. Therefore, we have engineered unique superparamagnetic nanoparticles (SPs) for co-delivering miR-145 and TRAIL in PanCa for improving their therapeutic response to TRAIL. The results in this study demonstrate that acquired resistance to TRAIL in PanCa cells can overcome with the replacement of lost levels of miR-145 expression. Our SP nanoparticles were engineered to co-deliver miR-145 and TRAIL to PanCa cells, which resulted in simultaneous restoration of miR-145 and inhibition of acquired resistance to TRAIL. Combined actions of miR-145 and TRAIL markedly improve TRAIL-induced apoptotic effects in PanCa cells through the activation of an extrinsic apoptosis pathway pathway as indicated by activation of DR5, FLIP, FADD and enhanced expression of caspase-8/3. The co-delivery of miR-145 and TRAIL using SP nanoparticles inhibited tumorigenic characteristics of PanCa cells, which include proliferation, invasion, migration and clonogenicity. The results were reciprocated and got further confirmed with the inhibition of tumorsphere formation and *in vivo* tumorigencity in xenograft mice. Immunohistochemical staining of excised tumor tissues demonstrate an activation of death receptor pathway and subsequent expression of apoptotic markers. The study provides novel insights on two facades-how resistance of cancer cells to TRAIL-based pro-apoptotic therapies can be tackled, and how efficient intracellular delivery of TRAIL can be achieved. Our results suggest that acquired resistance to TRAIL can be overcome by co-delivery of miR-145 and pEGFP-TRAIL using SP nanoparticles.