

microRNA Response Elements-Regulated TRAIL Expression: Control of Micro Steering Wheels During the Journey from Bench-Top to the Bedside

TNF-related apoptosis-inducing ligand (TRAIL) is a well acknowledged member of TNF family. Detailed structural studies have verified that TRAIL is a type II transmembrane cytokine and has been shown to selectively trigger apoptosis in various cancer cells by interacting with its death receptors DR4 and DR5. In-vitro, and in various in-vivo tumor xenograft models, TRAIL has shown considerably enhanced single-agent antitumor activity and worked synergistically in resistant cancer cells treated with chemotherapeutic drugs and natural agents. In this editorial I will provide an overview of the TRAIL related gene therapy and how three recently published articles have opened new horizons for differential expression of TRAIL using previously existing knowledge about dysregulated miRNAs in cancer cells.

Rapidly accumulating evidence has started to shed light on the fact that a gene therapy using vectors for TRAIL has a promising potential and the efficacy has been tested in rodent models of different cancers. Consistent with similar strategy, telomerase reverse transcriptase promoter triggered expression of TRAIL had previously been suggested to be effective in inducing apoptosis in pancreatic tumor cells Katz et al, 2003. Consequent studies focused on similar techniques in different cancer cells including CD20 promoter controlled expression of TRAIL gene in B-non-Hodgkin lymphoma Yuan et al, 2013. Increasingly sophisticated biotechnological methodologies revealed that Herpesvirus saimiri based vector was designed in which TRAIL was under control of α -survivin promoter. Colorectal cancer cells transfected with TRAIL carrying vector demonstrated notably enhanced apoptosis in cancer cells Turrell et al, 2012. On a similar note another oncolytic adenovirus ZD55 was re-equipped with TRAIL and Smac gene and was noted to be potent in substantially reducing xenograft hepatoma Wang et al, 2012. Recombinant adeno-associated virus (rAAV) has been persuasively used as a carrier of TRAIL gene in cancer cells. Transfection of rAAV was reported to be effective in efficiently decreasing breast carcinoma in nude mice Zheng et al, 2012. Likewise, another study highlighted further improved rAAV by loading it with TRAIL gene and siRNA against Bcl-2. This technique was more effective in inducing apoptosis in non-small cell lung cancer cells Zhang et al, 2012. It has lately been seen that oncolytic adenovirus (p55-hTERT-HRE-TRAIL) induced apoptosis in MDA-MB-231 breast cancer cells Zhu et al, 2013. Circumstantial studies provide sufficient experimental evidence that Mesenchymal stem cells (MSCs) have emerged as a potential cell therapy carrier for TRAIL into tumor sites. Nanotechnological advances have revolutionized the strategies for delivery of TRAIL gene into target site and it has been shown that a non-viral vector generated by linkage of β -cyclodextrin and polyethylenimine has been used to introduce TRAIL into MSCs. MSCs-TRAIL were later introduced into lung metastases bearing C57BL/6 mice and displayed remarkable regression of tumor load Hu et al, 2012.

It is becoming progressively more understandable that there is a rapidly increasing trend of evaluating the efficiency of approaches particularly, insertion of the complementary sequences for miRNAs selectively suppressed in cancer cells into the expression cassette could enhance the expression of gene of interest in tumor cells. Increasingly it is being realized that miRNA response elements (MREs) regulated TRAIL delivery may be effective in different cancer cells. In accordance with this concept, TRAIL delivery mediated by adenoviral vectors was tested in glioma cells having remarkably reduced expression of miR-124, miR-128, miR-146b and miR-218. In-vitro assays indicated that TRAIL was highly expressed in glioma cells and apoptosis was noted in cells reconstituted with TRAIL expression vector Bo et al, 2013. There are some other exciting pieces of evidence which further substantiate the efficacy of MRE regulated TRAIL expression in different cancer cells. Bladder cancer cells were transfected with recombinant adenovirus with TRAIL expression regulated by MREs. Bladder cancer cells had reduced expression of miR-1, miR-133 and miR-218. Selective expression of TRAIL in bladder cancer cells deficient in expression of these miRNAs resulted in notably enhanced apoptosis in cancer cells Zhao et al, 2013. Another contemporary study provides appealing evidence of selective expression of TRAIL in uveal melanoma cells. These cells had downregulated expression of miR-34a, miR-137 and miR-182. Insertion of miRNA response elements (MREs) of miR-34a, miR-137 and miR-182 to regulate expression of TRAIL differentially in normal and cancer cells was effective Liu et al, 2013.

It is encouraging that there is a rapidly increasing interest in translating the knowledge obtained through in-vitro assays and simultaneous evaluation of efficacy in preclinical models. Gene therapy related to TRAIL in cancer cells, using viral and non-viral vectors has progressed incredibly however it needs to be seen which approach will be helpful in getting a step closer to clinical trials, keeping in view the lesser off-target effects.

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