Promising Epitranscriptomic Targets for Novel Breast Cancer Therapies: The Effects of TRAIL on m6A RNA Modification

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Apoptosis is a key mechanism in many cancer therapies and can be induced through the interaction of death receptors with specific ligands. Among these, TNF-alpha and TRAIL are widely studied. TRAIL stands out in literature with its ability to selectively trigger cancer cell death. Apoptosis is regulated by apoptotic RNAs and proteins, so RNA modifications like m6A regulate apoptosis. m6A's abundance in cell is dependent on the abundance of m6A writer proteins (METTL3, RBM15, WTAP). m6A's effect on TRAIL- and TNF-alpha-induced apoptosis in MDA-MB-231 cells is unexplored. We analyzed METTL3, RBM15, and WTAP protein levels in TRAIL- and TNF-alpha+CHX-treated MDA-MB-231 cells via Western Blot. According to the literature, while m6A writers decrease in TNF-alpha/cisplatin-treated HeLa cells, our results showed decreased m6A in TNF-alpha-treated MDA-MB-231 but increased levels with TRAIL. TRAIL is discovered to induce apoptosis of cancer cells by increasing the genome-wide m6A methlation profile, but with other anticancer agents mentioned in literature m6A levels decrease . With this discovered feature of TRAIL m6A regulators could potentially be targeted to enhance TRAIL sensitivity or apoptosis. To detect the amount of apoptotic RNAs and RNAs encoding m6A regulatory proteins, RNA-seq data in the GSE82047 dataset was analyzed. Under TRAIL treatment MCL-1, BCL-W, Bid, and Bak are potentially implicated in the mechanism of breast cancer resistance to TRAIL ligand. RBM15, YTHDF2, YTHDF3, IGF2BP3, ALKBH5 and FTO are identified as promising targets in breast cancer for treatments that aim to enhance m6A methylation. Targeting TRAIL induced apoptotic pathway holds potential for novel breast cancer treatments though RNA methylation.

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