

## **Knockdown of MTDH increases drug sensitivity to HDAC inhibitor and TRAIL combination treatment in endometrial cancer cells**

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Understanding the molecular mechanisms of chemoresistance is vital to design therapies to restore chemosensitivity. In particular, metadherin (MTDH) has been demonstrated to have a critical role in chemoresistance. Over-expression of MTDH has recently been correlated with poor clinical outcomes in breast cancer, neuroblastoma, hepatocellular carcinoma and prostate cancer. In endometrial cancer patients, lymph node metastasis and increase of mortality were significantly associated with chromosome 8q22-q23 copy number gains, which is where MTDH is localized. However, it is unclear how MTDH overexpression mechanistically contributes to endometrial cancer development, progression, or response to therapy. In this present study, we detected overexpression of MTDH in endometrial cancer tissues compared to normal endometrium. Studies in endometrial cancer cell lines indicate that MTDH depletion enhanced sensitivity to chemotherapy agents as well as cell death induced by a combinatorial treatment of histone

deacetylase (HDAC) inhibitor and tumor necrosis factor-alpha-related apoptosis-inducing ligand (TRAIL). TRAIL promotes death of cancerous cells of the human reproductive tract, and HDAC inhibitors, such as LBH 589 used in this study, have been shown to increase sensitivity of cancer cells to TRAIL-induced apoptosis. Inhibition of PI3K/AKT survival pathway such as PDK1 and AKT phosphorylation, increased degradation of anti-apoptosis protein XIAP, and increased expression of pro-apoptosis protein Bim and cleaved active isoforms of caspase 8 and caspase 3 were all observed during cell death induced by TRAIL and LBH 589 combination treatment in MTDH depleted endometrial cancer cells. However, in cancer cells with MTDH overexpression, TRAIL/LBH 589 treatment had no effect on these pro-survival factors. Interestingly, MTDH was also found to be involved in G2/M checkpoint regulation. Treatment of MTDH-depleted cells with TRAIL and LBH589 resulted in an increased number of cells arrested in G2/M compared to cells with MTDH

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overexpression. Using microarray technology, 57 genes with greater than two-fold gene expression alteration were identified after MTDH depletion, including Calbindin 1 and Galectin 1, which may contribute to MTDH-mediated drug resistance. Therefore, MTDH mediates drug resistance by regulating expression of genes required

for the control of apoptosis and cell cycle. These findings indicate that sensitivity to chemotherapy agents and combination treatment with HDAC inhibitor and TRAIL can be restored by manipulating MTDH, and hence depletion of MTDH is a potentially novel avenue for effective cancer therapy.