

MISSING LINKS OF miRNA REGULATION AND TRAIL;

Missing Links Of miRNA regulation and TRAIL mediated signaling in endometrial cancer: do we have enough understanding

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Endometrial cancer is multifactorial disease. Genetic and mechanistic diversity creates challenges for therapy. Interestingly, high-throughput technologies, including the analyses of apoptotic pathway have considerably enhanced our current understanding of dysregulated protein network in endometrial cancer.

It is now clear that cancer proteome is exceptionally multifaceted because of regulation of gene network by downstream effectors of signaling cascades. Apoptotic response in endometrial cancer cells is impaired because of interconnectivity of proteins into complexes and signaling networks that are highly divergent in time and space.

Insights from TRAIL mediated signaling research are catalyzing new lines of study that could not only explain molecular mechanisms of disease but also highlight opportunities for therapeutic interventions.

Following features are highlighted;

- miRNA subsets are regulated by downstream effectors of signaling cascades.
- miRNAs regulate tumor suppressor and oncogenes in endometrial cancer cells.
- Various approaches which show promise in restoring apoptosis in endometrial cancer cells.

Increasingly it is being realized that main regulators of microRNAs biogenesis are misrepresented in endometrial cancer. These are accountable for altered microRNAome in endometrial cancer cells. Transiently transfecting miR-34b in endometrial cancer cells

resulted in inhibition of cell growth, migration and most notably invasion. miR-200c negatively regulated BRD7 and facilitated entry of β -catenin in the nucleus to stimulate the expression of cyclinD1 and c-myc¹.

Emerging evidence suggests that miRNA expression is also regulated by progesterone. In line with this approach, a recent study indicated that cells treated with medroxyprogesterone acetate had upregulated miR-625*, -21, -142-5p, and 146b-5p by more than 400%, whereas miR-633, -29c, -29*, and -193b were decreased by 50%².

Targeted inhibition of metadherin (MTDH) in endometrial cancer cells resulted in an increase of sensitivity of cancer cells to TRAIL-induced apoptosis³. Similarly, Kinase suppressor of Ras 1 (KSR1), death-associated protein kinase (DAPK) and casein kinase (CK2) abrogation sensitized resistant endometrial cell lines to both TRAIL- and Fas-induced apoptosis^{4,5,6}.

DAPK silencing notably increased the secretion of TRAIL protein from the cells⁷. The multikinase inhibitor Sorafenib sensitized endometrial cancer cells to TRAIL by inhibiting FLICE-Inhibitory Protein (FLIP)⁸. It has been convincingly revealed that DcR1 expression occurred in a subset of EC and contributed to resistance to TRAIL-induced apoptosis⁹.

It has been convincingly revealed that estrogen metabolite 2-methoxyoestradiol alone or in combination with TRAIL mediates apoptosis in cancerous cells¹⁰.

We do not have well developed understanding of different tumor suppressors, oncogenes, activating mutations and loss of function of genes of endometrial cancer patients of our local population moreover valid predictive biomarkers for stratification of therapy are not available at present. Future studies should converge on dismantling disease associated genes and post-transcriptional processing of the genes. Without detailed and comprehensive knowledge of endometrial cancer biology and genes that predispose individuals to cancer identification of high-risk population will be difficult.

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