Therapeutic Utility of EC359 for Targeting LIFR Signaling in Type II Endometrial Cancer

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Topic: Endometrial

Objectives

Endometrial cancer is the most common gynecologic malignancy in women. Of the two histological subtypes of endometrial cancer described, Type II tumors are biologically more aggressive and convey a less favorable prognosis when compared to Type I tumors. Novel therapeutics for treatment of Type II endometrial cancer are needed. Leukemia Inhibitory Factor Receptor (LIFR) and its ligand, LIF, play a critical role in cancer progression, metastasis, stem cell maintenance, and therapy resistance. Our recent studies revealed high levels of LIF and its receptor LIFR are associated with poor survival in endometrial cancer patients. We evaluated the efficacy of EC359, a novel small molecule inhibitor of the LIF receptor, against Type II Endometrial cancer cells.

Methods

Primary and established cell lines were utilized in this study. Established cell lines were purchased from the American Type Culture Collection (ATCC CRL-1622). All primary samples were collected through the UT Health San Antonio tumor registry under IRB approval. The recently developed LIFR inhibitor, EC359, was used to elucidate the therapeutic utility of targeting the LIF/LIFR pathway in Type II endometrial cancer. In vitro activity was tested using MTT, colony formation, invasion, and apoptosis assays. Mechanistic studies were conducted using Western blot, reporter gene assays, and RT-qPCR analysis. Patient-derived xenograft (PDX) models were used for preclinical evaluation and toxicity.

Results

Treatment of established and primary endometrial cancer cells with the LIFR inhibitor EC359 significantly reduced cell viability, long-term cell survival, invasion, and promoted apoptosis. Treatment with EC359 attenuated the activation of LIF/LIFR driven pathways including STAT3, mTOR, and AKT. EC359 significantly reduced tumor progression in patient derived xenograft model.

Conclusions

These data support EC359 as a potential novel small molecule therapeutic for treatment of Type II Endometrial cancer.