METABOLIC CHANGES IN VANDETANIB AND ROSMANTUZUMAB-TREATED HUMAN ENDOMETRIAL AND ENDOMETRIOTIC STROMAL CELLS

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Endometriosis is a chronic inflammatory disease affecting about 1 in 10 women of reproductive age. Symptoms vary from pelvic pain and fatigue to nausea, depression, with severe cases causing infertility and organ adhesions. Currently, treatment for endometriosis is limited to hormonal therapy and surgical interventions. Hormonal therapy has side effects such as a reduction in bone density and is not suitable for every patient, while surgical methods are often invasive and not effective in preventing lesion regrowth [1].

New treatment strategies, including targeted pharmacological drugs, regenerative stem-cell therapy, immunotherapies, epigenetic and gene-based treatments, are being investigated [2]. To date, few studies have identified potential biomarkers and therapeutic targets for the disease. One recent analysis identified several potential markers and possible drug targets, including RSPO3 and EPHB4 proteins, which are important in lesion growth and angiogenesis, and it was proposed that the inhibition of these proteins could suppress lesion growth [3]. Rosmantuzumab and vandetanib are known inhibitors of RSPO3 and EPHB4, respectively, and the therapeutic potential of these drugs for endometriosis treatment remains unexplored.

Vandetanib modulates cellular metabolism through the inhibition of mTOR/HIF1α pathway. *In vitro* studies have shown that this inhibition leads to decreased GLUT1 and GLUT4 expression, resulting in reduced glucose uptake, thereby suppressing aerobic glycolysis [4]. Vandetanib has also been shown to reduce tumor glycolytic metabolism *in vivo*, as evidenced by decreased glucose uptake on 18F-FDG PET imaging [5]. RSPO3 enhances the Wnt/β-catenin pathway, which upregulates PDK1 and promotes glycolysis while suppressing oxidative phosphorylation [6]. Based on these mechanisms, we hypothesize that inhibiting EPHB4 with vandetanib and RSPO3 with rosmantuzumab will reduce glycolytic capacity and cell viability.

In this study, we aimed to determine the effects of rosmantuzumab and vandetanib treatments on cell viability (XTT assay), mitochondrial function, ATP production rate, glycolytic rate (Seahorse metabolic assays, Agilent), and gene expression (RT-qPCR) in both healthy endometrial and endometriotic stromal cells.

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