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TGF-β'S INDUCE SMAD-DEPENDENT SIGNALING AND APOPTOSIS IN HUMAN ENDOMETRIAL AND ENDOMETRIOTIC CELLS

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The transforming growth factor-β (TGF-β) superfamily play a prominent role in various cellular processes. TGF-βs are highly expressed in the peritoneal fluid of patients with endometriosis, as well as in endometriotic sites. Thus, TGF-βs might be involved in biological processes leading to endometriosis. This study aimed to analyse the effects of TGF-β1 or TGF-β2 on cell numbers, on apoptosis and signal transduction in endometrial and endometriotic cells *in vitro*.

Immortalized human endometrial stromal (T-HESC), epithelial (HES), endometriotic stromal (22B) and epithelial (12ZVK) cell lines were used. Cells were treated with or without TGF-β1 or TGF-β2, respectively, and the cell numbers were counted. By using specific inhibitors targeting TGF-β signaling, Smad and apoptotic pathways were studied.

Our results showed that: (1) TGF-β1 or TGF-β2 significantly decreased cell numbers of all cell lines at high initial cell numbers. The decrease in cell numbers of endometrial cells was higher (T-HESC=61%, HES=29%) compared to endometriotic cells (22B=24%, 12ZVK=21%). (2) A TβRI inhibitor completely blocked the TGF-β-induced reduction in cell numbers. A Smad3 inhibitor partly blocked it, suggesting that the Smad pathway is the main pathway of TGF-β signaling in endometrial and endometriotic cells. Additionally, TGF-β1 or TGF-β2 reduced the cell numbers of both endometrial and endometriotic cells through apoptosis via the mitochondrial pathway. This effect was Smad-dependent. In addition, TβRI inhibitor completely blocked TGF-β induced PAI-1 secretion.

In conclusion, TGF-β1 or TGF-β2 reduced cell numbers by stimulating apoptosis and PAI-1 production, because we recently found that bioactive PAI-1 reduced cell adhesion to the extracellular matrix. Since the TGF-βs dramatically increased secretion of PAI-1, thus may play an important role in the pathogenesis of endometriosis. The Smad pathway is the main pathway of TGF-β signaling in endometrial and endometriotic cells. TGF-βs induces apoptosis via the mitochondrial pathway in endometrial and endometriotic cells.