Original Research Article

**Constitutive activity of Erk1/2 and NF-κB protects human endometrial stromal cells from death receptor-mediated apoptosis**

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**Abstract**

Apoptosis in the human endometrium plays an essential role for endometrial receptivity and early implantation. A dysbalance of pro- and anti-apoptotic events in the secretory endometrium seems to be involved in implantation disorders and consecutive pregnancy complications. However, little is known about the mechanisms regulating apoptosis-sensitivity in the human endometrium. Therefore this study was performed to identify molecular mechanisms underlying the resistance toward apoptosis in human endometrial stromal cells (ESCs). Human ESCs were isolated from hysterectomy specimens and used as undifferentiated cells or after decidualization in vitro. Cells were incubated with an activating anti-Fas antibody, tumor-necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), TNF-α and inhibitors of protein- and RNA-syntheses, a caspase-inhibitor and inhibitors of extracellular signal regulated kinase (Erk)1/2, nuclear factor (NF)-κB and Akt. Apoptosis was measured by flow cytometric detection of hypodiploid nuclei. Caspase-activity was detected by luminescent assays. Several pro- and anti-apoptotic molecules and the activation of Erk1/2, NF-κB and Akt were analyzed by in-cell Western assays or flow cytometry. Inhibition of protein- and RNA-syntheses differentially sensitized human ESCs for death receptor-mediated apoptosis in a caspase-dependent manner, based on the up-regulation of the death receptors Fas and TRAIL-R2. The constitutive activity of Erk1/2 and NF-κB could be identified as a reason for the apoptosis-resistance of human ESCs. These results suggest the pro-survival signaling pathways Erk1/2 and NF-κB as key regulators of the sensitivity of human ESCs for death receptor-mediated apoptosis. The modulation of these pathways might play an important role in the physiology of implantation.

**Keywords**

Apoptosis; Death receptor; Endometrium; Erk1/2; NF-κB