

WORLD OF REPRODUCTIVE BIOLOGY

Channel to Implantation

An essential event for embryo implantation is the decidualization of the endometrial stroma in which underlying stromal cells enlarge and undergo other changes in preparation for pregnancy. In rodents, decidualization is prompted by the embryo, which releases the serine protease trypsin. Trypsin release leads the endometrial epithelial cells to produce prostaglandins, which mediate decidualization.

A study in *Nature Medicine* now fleshes out the unknown molecular events between trypsin release and production of prostaglandins. Ye Chun Ruan and Jing Hui Guo report that trypsin activates a sodium channel in the mother's cells, leading to upregulation of cyclooxygenase 2 a.k.a. Ptg2, the inducible form of the enzyme required for production of prostaglandins.

ENaC (epithelial sodium channel) is known to be activated by serine proteases in various tissues and is upregulated in the endometrium during the time of implantation. To examine the role of ENaC in implantation, the researchers first turned to cell culture experiments. They found that trypsin activates ENaC in mouse endometrial epithelial cells, leading to an influx of calcium, upregulation of Ptg2 via a calcium-activated transcription factor (CREB) and release of prostaglandins—all leading to the morphological changes in stromal cells that are characteristic of decidualization.

The researchers verified their findings in mice, showing—for instance—that knocking out ENaC activity in mice with an inhibitor or with siRNA affects embryo implantation.

In humans, decidualization occurs spontaneously during each menstrual cycle but may similarly involve ENaC. The researchers looked at the levels of ENaC in women undergoing in vitro fertilization (IVF), and found that ENaC expression is reduced in women with implantation failure, compared with women with successful pregnancies.

The researchers speculate that ovarian stimulation during IVF may affect ENaC expression, which is known to respond to ovarian hormones. Future studies will help establish whether changes in ENaC may contribute to the spontaneous miscarriage and implantation failure often seen during IVF.

— Charlotte Schubert

Ruan YC, Guo JH, Liu X, Zhang R, Tsang LL, Dong JD, Chen H, Yu MK, Jiang X, Zhang XH, Fok KL, Chung YW, Huang H, Zhou WL, Chan HC. Activation of the epithelial Na⁺ channel triggers prostaglandin E₂ release and production required for embryo implantation. *Nature Medicine* 2012; (in press). Published online ahead of print 24 June 2012; DOI: [10.1038/nm.2771](https://doi.org/10.1038/nm.2771)