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REPRODUCTIVE ENDOCRINOLOGY

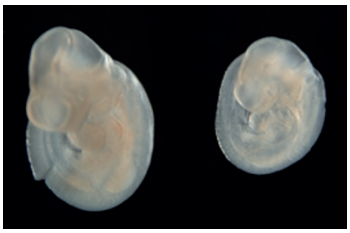
BMPR-2 signalling is essential for maintenance of pregnancy

Bone morphogenetic protein (BMP) signalling via the uterine bone morphogenetic protein receptor type 2 (BMPR-2) is essential for the development of the embryo after implantation and the maintenance of pregnancy, show findings in mice.

BMP-2, a member of the transforming growth factor β (TGF-β) superfamily is a pivotal regulator of uterine function; female mice that lack BMP-2 are infertile owing to defects in uterine decidualization—the changes that occur in the endometrium in response to progesterone during pregnancy. BMP ligands mediate their effects by signalling through different serine–threonine kinase receptors; currently three type I and three type II receptors, including BMPR-2, are known. Their uterine functions, however, remain unclear.

The group of Martin Matzuk (Baylor College of Medicine, Houston, TX, USA) was interested in defining the key receptor signalling pathways downstream of BMP-2 and other uterine-expressed BMP ligands. "It is impossible to define fertility in a test tube," says Matzuk. "Thus, we had to rely on using an *in vivo* approach. The TGF-β superfamily signalling pathways are highly conserved, and BMPR-2 is >98% identical between mice and humans." To overcome the embryonic lethality of *BMPR2* knockout mice and define the roles of BMPR-2 in the female reproductive system, Matzuk and his team generated mice that lack BMPR-2 in the preovulatory ovarian follicle and the uterine epithelium and stroma.

Surprisingly, deletion of BMPR-2 in the preovulatory ovarian follicle did not cause defects in ovulation. Moreover, despite the essential roles of BMP-2 in implantation, the absence of BMPR-2 resulted in normal implantation and early embryogenesis. "These findings suggest redundant functions of the three known type II receptors in BMP-2 signalling in implantation," explains Matzuk. Absence of uterine BMPR-2 led to midgestation abnormalities in decidualization that resulted in abnormal vascular development, trophoblast defects and a deficiency of uterine natural killer cells, which indicates that BMPR-2-mediated signalling regulates a number of key pathways in uterine vascular development.



Disrupted uterine BMPR-2 signalling (right) affects embryo development. Courtesy of T. Nagashima, Keio University, Japan.

Furthermore, the mouse model generated by Matzuk and co-workers mimics intrauterine growth retardation—embryos from pregnant BMPR-2 conditional knockout mice are visibly smaller than those from control mice—and placental abruption. Thus, the BMPR-2 conditional knockout mouse may potentially be exploited as a model for studies on the diagnosis and treatment of these disorders. "We believe such studies will help to develop new BMP-mediated therapies to treat these important maternal diseases by targeting the specific genes and pathways involved in these clinical conditions," concludes Matzuk.

Linda Koch

Original article Nagashima, T. *et al.* BMPR2 is required for postimplantation uterine function and pregnancy maintenance. *J. Clin. Invest.* doi:10.1172/JCI65710