Study identifies molecular key to healthy pregnancy

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Scientists have identified a crucial molecular key to healthy embryo implantation and pregnancy in a study that may offer new clues about the medical challenges of infertility/subfertility, abnormal placentation, and placenta previa.

Multi-institutional teams led by researchers at Cincinnati Children's Hospital Medical Center report their results in *Cell Reports* on July 17. The authors found that uterine expression of a gene called Wnt5a – a major signaling molecule in cell growth and movement in both embryo development and disease – is also critical to healthy embryo implantation in the uterus.

The scientists say that molecular signaling from Wnt5a – working in tandem with its co-receptors ROR1 and ROR2 in the uterus – causes uterine implantation chambers (crypts) in mice to form at regular intervals. The signaling also helps direct embryos to migrate in the proper direction as they settle into the womb. The authors show that disruption of appropriate uterine Wnt5a-ROR signaling leads to abnormal uterine luminal epithelial architecture, crypt formation, disorderly spacing of embryos and implantation. These adverse effects led to defective decidualization, placentation, and ultimately compromised pregnancy outcome.

"Proper implantation is important to healthy pregnancy, and it is not clearly understood what prompts embryos to move and implant within a uterine crypt with regular spacing," said Sudhansu K. Dey, PhD, senior investigator and director of Division of Reproductive Sciences, Cincinnati Children's Hospital Medical Center. "If something goes wrong at this stage, there could be adverse effects throughout the course of pregnancy – whether it is subfertility, infertility, restricted growth, miscarriage or preterm birth."

Although there are similarities and differences between mouse and human implantation, a role for Wnt5a-ROR signaling in embryo spacing could be clinically relevant, Dey said. This is because the embryo can sometimes implant close to or on the cervix (placenta previa), which can cause extensive bleeding and lead to increased mortality or morbidity for the mother and fetus. Aberrant embryo spacing may also contribute to complications in a multiple gestation pregnancy.

The current study is a continuation of the work Dey and his team published in 2011 in Developmental Cell. Also conducted in mice, this study showed two genes (Msx1 and Msx2 - which play integral roles in organ formation during fetal development) are also essential to direct the uterus to the receptive stage for successful embryo implantation. In that

study, Dey and colleagues found that Wnt5a signaling is disrupted when Msx is inactivated in the uterus. This suggests that Msx genes have a molecular relationship with Wnt5a. Subsequent studies by Dey and colleagues reported that Msx genes may be critical for successful implantation in other mammalian species.

Now that the researchers have identified Wnt5a and ROR as key regulators in embryo spacing and implantation, their next study focuses on the specific molecular and biochemical pathways (and related functions) regulated by Wnt5a-ROR signaling.

Provided by Cincinnati Children's Hospital Medical Center