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Mouse Models of Implantation: A Review on Molecular Signaling in Embryo-Uterine Interactions

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A considerable loss resulting from preimplantation embryonic death is common to many mammals and this is regarded as a natural selection process that directs superior embryos for implantation. In addition, defects in the events during and immediately after implantation often give rise to poor pregnancy rates in eutherian mammals. Therefore, a comprehensive understanding of preimplantation embryo development and implantation is a fundamental challenge in alleviating the problems of infertility or developing safe and useful contraceptive approaches. Successful implantation results from an intimate "two-way" interaction between the blastocyst and the uterus. During this interaction, a plethora of molecular interactions commences in a coordinated fashion marking the attachment phase. Molecular signals that render the uterus receptive for implantation and enable bi-directional communications between the uterus and the blastocyst are complex and yet to be clearly defined. Because it is not possible to use human embryos to study embryo-uterine interactions during implantation, the mouse fulfills this purpose and serves to provide a more mechanistic approach in defining the molecular basis of implantation. Physiological functions of specific factors can be examined more mechanistically by overexpression or targeted deletion of their genes in transgenic mice. Indeed, rapidly accumulating data using these approaches are helping us to generate novel concepts and ideas regarding implantation.

In this presentation, three knockout mouse models with distinctive reproductive phenotypes are discussed.

Firstly, *Hoxa-10*, a developmentally regulated transcription factor of *Hox* gene family, is expressed in the uterine stroma under the effect of progesterone. *Hoxa-10*(-/-) female mice show periimplantation failure due to defective decidualization, and the underlying mechanism of this phenotype is associated with reduced stromal cell proliferation. Secondly, Leukemia Inhibitory Factor (LIF) is known to be expressed in the uterine glands under estrogenic regulation. *LIF*(-/-) female mice exhibit complete failure of attachment reaction and blastocysts within their uteri stay dormant.

Our recent study revealed that LIF is also expressed in the stromal cells immediately surrounding the implanting blastocyst, and this expression is associated with the failure of attachment reaction in the absence of uterine LIF. Finally, *COX-2*(-/-) female mice show multiple reproductive failures including ovulation, fertilization, implantation, and decidualization. Using this model, we found that COX-2-generated prostacyclin plays a crucial role during implantation. Furthermore, a follow-up study on prostacyclin signaling during implantation will be discussed.