Focus on Implantation

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A fundamental role of procreation is to sustain life by diversifying and passing on a superior genetic repertoire to offspring. Fostering an offspring within the womb is an enduring task, demanding safeguarded regulatory systems at multiple critical steps. In 1947, Corner wrote, '...the uterine chamber is actually a less favorable place for early embryos than say, the anterior chamber of the eye, except when the hormones of the ovary act upon it and change it to a place of superior efficiency for its new functions.' Subsequently, it was realized that pregnancy results from the culmination of an intimate relationship between the developing embryo and the differentiating uterus. Although conceptually accepted, the nature of the two-way interaction between the blastocyst and the uterus is still a challenging question. Embryo–uterine interactions leading to implantation are only initiated when the embryo reaches the blastocyst stage and gains implantation-competency, and the uterus, through steroid hormone-dependent changes, attains the receptive stage. The underlying mechanisms that coordinate blastocyst development to implantation-competency with uterine receptivity are not yet fully understood. Furthermore, dys-regulated events prior to, during or immediately after implantation are often the cause of poor pregnancy rates in eutherians. Therefore, unraveling the clues to preimplantation embryo development and implantation in the uterus has been a challenge to reproductive biologists with a mission of curing and improving infertility, ensuring birth of quality offspring and/or developing novel contraceptive approaches.

Although a wealth of knowledge regarding the roles of growth factors, cytokines, homeotic genes, transcription factors and lipid mediators in implantation has been generated, their hierarchical blueprint in directing uterine and embryonic functions during implantation remains to be deciphered. Defining the molecular landscape during the critical time of implantation necessitates well thought out experimental designs with both embryonic and uterine contributions. This objective is not easily achievable in humans due to experimental difficulties and ethical restrictions on research with human embryos. Therefore,

animal models are necessary for studying embryo–uterine interactions during implantation.

In this Focus issue, the authors present a variety of model systems ranging from small animals, e.g. rodents, to large ones such as sheep, not only to investigate the key steps and molecules involved in each species' implantation process, but also to define the common events between species. Lee & DeMayo (2004) describe how the implantation process and related signaling pathways, including that of growth factors and cytokines, vary in different species. On the other hand, Spencer *et al.* (2004) concentrate predominantly on large animals identifying critical endometrial proteins and describing the regulation of these proteins by progesterone and/or interferon τ . They discuss multiple approaches including the use of a gland knockout ewe model in an attempt to show the intricacies of the implantation process in large animals.

Another important aspect of the implantation process common to many species is the process and regulation of embryonic diapause (also referred to as delayed implantation). This process has evolved as a strategy to ensure the proper implantation timing of a species depending on environmental conditions, conducive to the survival of the offspring. Regulation of delayed implantation varies widely between species, ranging from hormonal changes, e.g. during lactation or those related to seasonal variation or photoperiod, to nutritional changes. This model of delayed implantation provides a powerful tool to study various aspects of the regulation of embryo–uterine cross-talk during implantation because of the known timing involved in this process. Lopes *et al.* (2004) present physiological, endocrinological and molecular aspects of diapause and how this process is regulated in various species. It is hoped that these review articles will provoke further research with the aim of increasing success in livestock reproduction and improved management of fertility in women.

Although the mechanics and cellular architecture of the implantation process varies, certain basic features are common to many species. For example, implantation occurs at the blastocyst stage and there is a

defined 'window' of uterine receptivity for implantation. A reciprocal interaction between the blastocyst and the uterus is essential for implantation and a localized increase in uterine vascular permeability occurs at the site of the blastocyst during the attachment reaction. Identification and characterization of signaling pathways in these steps should collectively reveal a unifying scheme relevant to understanding the mechanism of human implantation.

References

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