Introduction to special issue on implantation

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Implantation is essential for survival of all mammalian species. Surprisingly, normal human reproduction is an inefficient process with only 22.8% of conceptive matings resulting in live birth [1]. Lack of successful implantation is estimated to account for 75% of conceptions that are lost [2]. Thus, implantation of the blastocyst into the uterine endometrium is the pivotal event for establishing a successful human pregnancy.

Failure of implantation is the most common cause of lack of successful reproduction, and affects approximately 10% of couples compared to 2–4% suffering recurrent spontaneous abortions. Many infertile couples must eventually seek the option of in vitro fertilization (IVF) and embryo transfer (ET), and here, implantation failure has been referred to as the last barrier in assisted reproductive technologies [3]. In view of the low efficiency of human implantation, this special issue has been put together to

consider what is currently understood about the mechanisms underlying success and failure.

The first manuscript in this issue by Rinehart [4] addresses the question “what is recurrent implantation failure after IVF/ET.” Successful implantation requires the coordinate development of a blastocyst competent to implant and an endometrium receptive to its implantation. A variety of molecules, produced by the embryo as well as maternal tissue participates in the “cross-talk” between the implantation blastocyst and the endometrium. Unsuccessful implantation can be the consequence of abnormalities within the blastocyst or the endometrium.

Preparation for implantation in the human begins at fertilization with ensuing growth of the early embryo. Beginning as a single cell, the fertilized egg rapidly divides and eventually the trophoctoderm invades in a controlled and orderly fashion interacting first with the epithelial and later the stromal and endothelial components of the endometrium. The earliest events of implantation occur within a narrow time frame and are dictated by the state of endometrial development. In humans, the embryo enters the uterine cavity at 72 to 96 h after fertilization in the oviduct. In a normal menstrual cycle, endometrial growth begins 2 to 3 weeks earlier in response to increasing serum estrogen arising from developing ovarian follicles. With ovulation the endometrium undergoes secretory transformation in response to rising progesterone and peptide hormones from the newly formed corpus luteum. Early in the secretory phase, the endometrial lining appears to represent a barrier to implantation. Embryos at this stage are capable of implanting almost anywhere in the body except the endometrium as evidenced by the occurrence of ectopic pregnancies. Thus, although embryos possess an innate capacity for invasion, the endometrium can both facilitate and limit the process.

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Endometrial receptivity is usually achieved between cycle days 20 to 24 of a 28 day cycle and is characterized by the acquisition of a number of protein markers which have been used to identify a “window of implantation” during which time the embryo apposes, attaches and then invades into the endometrium. This cycle-dependent expression of molecules is the consequence of the embryo-endometrial dialogue. Among the molecules involved in embryo implantation is human chorionic gonadotropin (hCG), a hormone secreted from trophoblasts. The article by Afshar et al. [5] describes the role of hCG and Notch 1 in implantation. HCG reaches the maternal ovary through blood circulation and stimulates the corpus luteum to produce progesterone, which in turn is transferred to the uterus to maintain embryo implantation through its interaction with progesterone receptor.

Interaction between the trophoblasts and the endometrium is accomplished through a series of chemokines and cytokines, whose are mediated locally by specific receptors. Both pleiotrophy and redundancy exist within cytokine families, and several different cytokines often exert similar and overlapping functions on certain cells. The cytokine receptors also often display redundancy and utilize different signal transduction pathways. These receptor/ligand interactions contribute to regulation of the expression and functional activity of adhesion molecules such as L-selectin outlined by Foulk et al. [6]. After hatching, the blastocyst expresses a protein known as L-selectin. At the same time the uterine epithelium becomes enriched with carbohydrates. L-selectin normally binds briefly to such carbohydrates resulting in a continual sticking and unsticking interplay between the protein and carbohydrates slowing down the embryo’s progress along the uterine wall until it comes to rest. A wide array of cytokines are expressed within the uterus both by the embryo and maternal tissues, and may play a role in implantation [7]. It is not surprising, given the importance of implantation to the survival of the species and the remarkable redundancy of the cytokine network, there is not a lack of a single cytokine or its receptor that is associated with implantation failure as discussed in a future contribution to the new Immunology Updates series [8].

As the embryo implants, it may stimulate immunotolerance so as not to be rejected by maternal immune cells. A major player in the induction of immunotolerance appears to be soluble HLA G (sHLA G) as presented in the manuscript by Roussev and Coulam [9]. HLA-G may also

play a role in enhancing embryo development. Based on current data, sHLA-G in IVF culture supernatants may be a better option than Prenatal Embryo Selection (embryo biopsy and karyotyping to select only normal karyotype embryos for transfer). The controversy concerning the latter technique will be discussed in a future issue of the journal.

Once the embryo has completely implanted into the endometrium, it must induce its own blood supply in order to receive sufficient nutrients to continue to grow. The process of angiogenesis is described by Torry et al. [10]. This is currently an area of great interest given the role of uterine NK cells (CD56^{Bright}) that are associated with successful implantation and modulation of maternal vascular development during reproduction [11].

It is hoped that an understanding the processes involved in implantation will eventually provide insight for better diagnosis and treatment of recurrent implantation failure that continues to frustrate infertile couples, and physicians trying to help them achieve their dreams.

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