

Human implantation in view of dual regulation by endocrine immune systems

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Improvement of implantation rates is an imminent issue in ART as well as non-ART treatments of unexplained infertility. It has long been recognized that dual regulation by endocrine and immune systems of the mother and conceptus is immensely involved in implantation and subsequent advancement of pregnancy in mammalian species with invasive chemochorial placentation seen in humans and murines. In the present communication, the molecular and cellular mechanisms will be addressed in view of mutual interaction of the two regulatory systems at the trophoblast-endometrial interphase.

Unlike the described conventional staging with emphasis on endometrial receptivity, the entire implantation process can be divided into the following four stages phenomenologically. The first preparatory stage can be defined as gonadal steroids-dependent, embryo-independent period from ovulation to embryo attachment to endometrial epithelial cells (EEC). In this stage, endometrium differentiates to become receptive for embryo to implant, namely opening the implantation window, by priming action of progesterone (P) followed by preimplantation surge of estrogen (E). The second preimplantation stage is the stage of embryo-dependent further differentiation until attachment of embryo to EEC through cross-talk between trophoblasts and endometrium. During this stage maternal recognition of pregnancy is induced by endocrine and immune systems of the mother; thereby hCG may play a crucial role not only in activating menstrual corpus luteum to shift to pregnancy corpus luteum but also in sensitizing maternal immune system to embryonic antigens through macrophages at the systemic level. The third midimplantation stage from apoptosis of EEC to embryo invasion into endometrial stroma is characterized by a cascade of drastic changes in inflammatory reactions with recruitment of monocytes and granulocytes accompanied by enhancing immune responses of uterine NK and T cells with specialized phenotypes and functions respectively. In the final postimplantation stage from settlement of invading embryo and early placentation, inflammatory reactions subside with resultant tissue remodeling and immune responses reach stabilization with installation of active T cell tolerance which is characterized by predominant production of Th2-skewed cytokine production. With immunomodulatory actions of P Prostaglandins (PGs) and hCG on HLA, T and uNK functions directly or indirectly, an unique embryo-specific allotransplantation immunity is ultimately organized.

Decidua formation appears to take the most important part of this embryo-specific allotransplantation immune organization. Unlike therapeutic organ transplantation, the embryo-specific allotransplantation lacks direct vascular communication between mother and semi-allograft, but with supplemented with potential hormonal molecules which influence greatly on maternal immune system of Th1/Th2 paradigm and uNK cell activity. Thus implantation shall be deemed as the process of establishing embryo-specific allotransplantation immunity where decidua constitutes a functional and anatomical barrier intervening the two compartments for mutual survival so as to enable naturally occurring transplantation in a parabioc coexistence.