Embryonic Implantation Regulation Through Uterine Gene Networks

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Embryonic implantation take place at the stage of hatched blastocyst. The events of implantation includes 1) apposition of the blastocyst to the uterine luminal epithelium, 2) adhesion to the epithelium, 3) penetration through the epithelium and basal lamina and 4) invasion into the stromal vasculature. In rodents and human, the attached blastocyst starts to invade the endometrial stroma and induces the decidual response. The attachment and invasion of the blastocyst are strictly regulated through communication between embryo and uterus. The advent of microarray technology has begun to elucidate the global gene changes that allow implantation in the mouse and the human, and gene targeting experiments in the mouse have resolved the uterine function of many genes. From the classical studies, it is well established that the steroid hormone progesterone (P) and estrogen (E) are a critical regulator of embryo implantation and maintenance of pregnancy. P acting through the nuclear progesterone receptors (PRs) regulates the expression of specific gene networks that in turn control the extensive cell proliferation, differentiation, and remodeling that occur in various uterine cell types during the progressive phases of implantation. E also regulate gene expression like P in the uterus during implantation. To know the regulatory mechanisms of the embryonic implantation we tried to identify the genes which are regulated by P or E in the pregnant uterus. To identify the P-regulated pathways that underlie the implantation process in the mouse, RU 486, a well-characterized PR antagonist that binds to the receptor and blocks its gene regulatory function was employed. To identify the E regulated genes which are expressed at the time of implantation delayed-implantation was employed. We performed messenger RNA (mRNA) profiling in the peri-implantation uterus using oligonucleotide microarrays to analyze changes in mRNA levels in response to RU 486 or E. This analysis provided, for the first time, a comprehensive profile of PR-regulated gene networks with potential roles during implantation. Our study identified a variety of novel PR-regulated molecules, such as growth factors, protease inhibitors, metabolic enzymes, peptide hormones, transcription factors, immune response molecules, cytoskeletal proteins, and cell adhesion molecules, that are potential mediators of P action in the peri-implantation mouse uterus. Some of the candidate genes which may be regulated by estrogen also identified. Using several molecular methodologies and experimental models, we could explore networks of some genes during implantation. The suppressions of these genes expressions by chemicals or overexpressed or ablated genes, showed defects in the embryonic implantation. These evidences showed that the embryonic implantation regulated through the complex uterine gene networks. As can seen from

the well-characterized known factors, these experimental models can facilitate identification of factors necessary in human implantation and other species.