

Insights from Mechanism Involved in Uterine Receptivity for Blastocyst Implantation in Mouse

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Introduction

Human reproduction is a very complex process and now a days it is not very efficient because of various environmental chemicals, smoking and diet factors affecting the fertility [1]. Early pregnancy loss in humans often occurs due to defects before, during or immediately after implantation, is a worldwide social and economic concern. In majority of cases, spontaneous abortion occur at the time of blastocyst implantation due to inappropriate uterine environment results diminished uterine receptivity or delayed implantation [2]. This unwanted failure of pregnancy causes emotional and psychological stress in women which emerges another clinical problem-the problem of infertility. Many underlying causes of human infertility have been overcome by *in vitro* fertilization and embryo transfer technique. The ultimate goal of understanding implantation at a molecular level is to improve the diagnosis and treatment of infertility.

Normal fertility involves production and maturation of male and female germ cells by the gonads, fertilization of the oocyte by spermatozoa and implantation in the uterus. The implantation of the healthy blastocyst into the maternal receptive uterus is a very crucial step in mammalian reproduction for successful pregnancy and it involves an intricate succession of genetic and cellular interactions, all of which must be executed within an optimal time frame. The fertilized egg undergoes specific cell divisions to form a blastocyst. These developmental events are synchronized with the proliferation and differentiation of specific uterine cell types, primarily under the direction of ovarian hormone like Progesterone (P_4) and Estrogen (E_2). These hormones make the uterus conductive (receptive) to accept a blastocyst for implantation. A reciprocal interaction between the blastocyst and receptive uterus is essential for blastocyst implantation.

Window of Implantation

Successful implantation is the end result of complex molecular interactions between the hormonally primed uterus and activated blastocyst. Synchronized development of the embryo to blastocyst stage and differentiation of the uterus to the receptive state are essential to this process [3]. Therefore successful implantation is depended on the following two factors: 1) blastocyst activation and 2) receptivity of the uterus.

Blastocyst activation: For successful implantation to occur in the receptive uterus, the blastocyst must also attain implantation competency, a process termed blastocyst activation. Mechanism that enables the blastocyst to activate includes catecholestrogens, a class of estrogen metabolite, which is produced from primary estrogen in the uterus [4-5]. Blastocyst activation by catecholestrogen involves COX2 derived prostaglandins (PGs) and cAMP [4]. Another lipid signaling molecule that target blastocyst is an endocannabinoid anandamide which activates G-Protein coupled cannabinoid receptors CB1 and CB2.

Receptivity of the uterus: Uterine receptivity is defined as the state during the period when the uterine environment is conductive

to support blastocyst growth, attachment and subsequent events of implantation [6-8]. In humans, the window of uterine receptivity is considered to be between cycle days 20 and 24 [9]. In the rat and mouse, uterine receptivity occurs only for a limited period during pregnancy or pseudo pregnancy. In these species, uterine receptivity divided into neutral, receptive and non-receptive or refractory phase [7,10-11]. The uterus becomes receptive only on D4 and becomes refractory on D5. The neutral phase is achieved when the uterus is exposed to P_4 only. Molecular signals that render the uterus receptive and orders the two-way interactions between blastocyst and uterus to initiate the process of implantation still remain ill defined. However a numerous molecules including growth factors, cytokines, prostaglandins (PGs) mainly PGE2 and PGI2, histamine, platelet activating factor and various other molecules have been implicated in this process [8,12-13]. Latest report suggest the important role of Kruppel like- factor 5 (KLF5), a zinc factor containing transcription factor and *Msx1*/*Msx2* genes which play critical role in uterine receptivity and blastocyst implantation [14-15].

Still there is a need to better understand about the molecular mechanism involved in blastocyst implantation and uterine receptivity which will be helpful to improve pregnancy rates in women via development of new drugs to treat infertility with impaired uterine receptivity.

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