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Current Opinion

Eutopic or Ectopic Pregnancy: A Competition between Signals Derived from the Endometrium and the Fallopian Tube for Blastocyst Implantation

Z. Jia-rong [a], L. Shuang-di [a], W. Xiao-ping [b,*]

[a] Department of Obstetrics and Gynecology, Shanghai Jiao Tong University Affiliated First People's Hospital, Shanghai, China
[b] Shanghai International Peace Maternity and Child Health Hospital, 910 Hengshan Road, Shanghai 200030, China

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ABSTRACT

Embryo retention in the fallopian tube is thought to lead to ectopic pregnancy, which is a significant cause of morbidity. This pathological condition does not occur in laboratory rodents. Moreover, incidences of tubal pregnancy after assisted reproduction (ART) are continuously increasing. What are the factors that need to be considered responsible for this condition? Ectopic pregnancies occur because of conflicting signals to the blastocyst from the two epithelia (uterine and fallopian). The signals consist of cytokines, chemokines and adhesion molecules that mediate both blastocyst adhesion to the uterine (and fallopian) epithelium and leukocyte adhesion to the vascular endothelium and, presumably, the fallopian epithelium. Chronic inflammation in the fallopian tube caused by infections or misplacements of the blastocyst (in the case of ART) can alter expression (upregulate) of the signals emanating from the fallopian tube and thereby can compete with the uterine (normal) site of implantation. That is, in ectopic pregnancy, a blastocyst may receive stronger signals from the tubal epithelia, migrate to the fallopian tube, and be implanted at that site.

1. Introduction

An ectopic pregnancy occurs when a fertilized ovum is implanted outside the intrauterine cavity. In more than 95% of all ectopic pregnancies, the fertilized ovum is implanted in the fallopian tubes. The human fallopian tube is the site for oocyte pickup, fertilization, early embryonic stem cell proliferation, and embryo transport. However, the factors responsible for ectopic implantation of the fertilized ovum are not completely understood. In humans, the primary cause of tubal implantation is thought to be an impairment of tubal transport of gametes, which often results from a chronic inflammatory disease. Theoretically, neither fertilization nor embryo transfer involves the fallopian tubes directly. Assisted reproductive technology (ART) might reduce the risk of ectopic pregnancy. However, a large number of ectopic pregnancies have been reported after assisted reproduction; their incidence ranged from 2.2% to 8.6% of all the clinical pregnancies recorded in 1990–1992, compared to the estimated rate of 2.0% for the general US population [1]. Ectopic pregnancy is a paradoxical condition since a tubal ectopic pregnancy results when the transport of an embryo is passively delayed in the oviduct. It is necessary to understand the molecular etiology of tubal ectopic pregnancy. Does the embryo actively migrate to the final implantation site as leukocytes are guided to the inflammatory response site?

2. Embryonic implantation and leukocyte migration: different processes with similar mechanisms

Leukocyte subsets are recruited from the blood to the sites of inflammation via a multi-step process that involves distinct adhesive interactions and activation steps. Initially, marginated leukocytes are tethered to the endothelium via microvillous processes and then undergo rapid activation that leads to the upregulation of integrins and allows the leukocytes to adhere firmly to the endothelium. Adherent leukocytes subsequently migrate across the endothelium and localize to distinct microenvironmental sites on the basis of the signals received from multiple chemoattractant sources [2]. Similarly, embryonic implantation of the free-floating blastocysts involves different steps—apposition, attachment, and invasion—leading to an effective interaction between the blastocyst and maternal endometrium, which is essential for mammalian reproduction [3,4].

L-Selectin is constitutively expressed on lymphocytes and plays an essential role in lymphocyte homing [5]. In the lymph nodes, lymphocytes adhere to endothelial cells in high endothelial venules (HEVs). This adhesion is mediated by the binding of L-selectin on lymphocytes to its carbohydrate ligand on HEVs. When lymphocytes pass through HEVs, they experience sheer stress and roll on

* Corresponding author. Tel.: +86 21 63831956.
E-mail address: xiaopingw1961@126.com (W. Xiao-ping).

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the HEVs. The rolling allows lymphocytes to be stimulated by cytokines, which are concentrated on the endothelial surface of the HEVs. This phenomenon induces integrin activation, which mediates stronger adhesion of lymphocytes, thereby leading to lymphocyte extravasation.

In order to identify the molecules involved in the initial step of embryo implantation, Genbacev et al. [6] applied the principles of vascular biology. They demonstrated that L-selectin is expressed by human blastocysts to initiate interactions with the uterine lining. Carbohydrate ligands that bind L-selectin are localized on the luminal epithelium at the time of implantation, and the expression of L-selectin in blastocysts is significantly increased after implantation. The authors next investigated the physiological importance of the interaction between L-selectin and its oligosaccharide ligands. They coated polystyrene latex beads with an oligosaccharide that binds to L-selectin and observed that the beads bound avidly to trophoblast cells in the villous tissue of the human placenta when the shear stress was the same as that of the uterus. The shear stress exerted by blood flow is known to be necessary for optimal L-selectin-mediated adhesion of leukocytes to the vascular endothelium. These findings suggest that the interaction between L-selectin expressed by trophoblast cells and its oligosaccharide ligands expressed by the hormonally primed uterus may constitute the initial step in the implantation process [7].

Leukocyte adhesion is mediated by the interactions of members of the integrin family (lymphocyte function-associated antigen (LFA-1; $\alpha L\beta 2$), Mac-1 ($\alpha M\beta 2$), very late antigen-4 (VLA-4; $\alpha 4\beta 1$), and lymphocyte-Payer's patch adhesion molecule-1 (LPAM-1; $\alpha 4\beta 7$)) with the members of the immunoglobulin family (intracellular adhesion molecules 1 and 2 (ICAM-1 and ICAM-2), vascular cell adhesion molecule-1 (VCAM-1), and mucosal addressin cell adhesion molecule-1 (MAdCAM-1)) [8]. Chemokines or proinflammatory cytokines induce the activation of leukocyte integrins in situ; integrin-dependent signals and polarization of the cell are also required for this activation [9].

During embryo apposition, chemokines are the first group of molecules that are produced locally by the endometrium. An array of different types of chemokines is expressed and produced in the human endometrium at the time of implantation. Chemokines such as interleukin 8 (IL-8), RANTES, or monocyte chemoattractant protein (MCP)-1 are secreted locally either by the endometrium during the implantation window or by the human blastocyst during the apposition phase. These chemokines might act as signals for receptor polarization and activation of endometrial adhesion molecules. In addition, immunoreactive CCR2B (MCP-1 receptor) and CCR5 (RANTES receptor) are localized on the human blastocyst. Furthermore, the human blastocyst induces the expression and polarization of CXCR1 (IL-8 receptor), CXCR4 (SDF-1α receptor), and CCR5 in the endometrial epithelial cells [4]. In humans, adhesion of the embryo to the endometrium occurs in a specific polarized manner. The blastocyst becomes more adhesive at the pole where the inner cell mass (ICM) is situated. Embryo adhesion/polarization is a critical step in implantation.

Finally, the embryonic trophoblast becomes invasive, penetrates the basal membrane, and invades the stroma up to the uterine vessel by the activation of different metalloproteinases such as MMP9 and MMP2.

3. A blastocyst may not roll but may float into the fallopian tube during tubal ectopic implantation

A previous study indicated that the initial attachment of an embryo to the endometrium depends on the binding of L-selectin expressed by the blastocyst to the oligosaccharide-based ligands expressed by the endometrium [6]. However, the expression of L-selectin ligands was observed to be less in oocyte donors than in the controls on day 19 of the menstrual cycle in the luminal epithelium and from day 19 to day 24 of the menstrual cycle in the glandular epithelium, which corresponds to the time of the implantation window [10]. A number of studies have shown that alteration in the endometrium during ovulation induction may be detrimental to the receptivity of the endometrium [11,12]. It may be speculated that high levels of estradiol (E2) adversely affect the expression of endometrial L-selectin ligands during the implantation window [13]. In fact, these factors prevent the blastocyst from rolling on the tube wall and instead let it float into the tube with the luminal fluid during ovulation induction; this could further explain why tubal ectopic pregnancy is more commonly observed in women who have conceived with ART.

4. Trophinin: abnormal interactions prior to adhesion of the blastocyst in tubal pregnancy

It is well documented that the blastocyst and maternal epithelial cells interact with each other prior to blastocyst adhesion [3]. Given that episialin (MUC1) is downregulated at the blastocyst attachment site [14] and the pinopodes represent the adhesive epithelial site for implantation, direct adhesion between the trophectoderm cells and epithelial cells may be mediated by a molecule other than L-selectin. Trophinin is a homophilic cell adhesion molecule mediating the initial step of blastocyst adhesion to endometrial epithelia in humans. In the human uterus, trophinin expression is upregulated during early secretory phase or timing for "the implantation window". However, overall expression of trophinin in the uterus is low. Immunohistochemical screening of biopsy specimens from human endometrial tissues showed in rare incidences very strong trophinin expression by endometrial surface epithelia in a narrowly restricted region of about 100 μm. Furthermore, trophinin was barely detectable in intact fallopian tubes from women with in utero pregnancies or without pregnancies [15]. Analysis of ectopic pregnancies, it was observed that both embryonic and maternal cells express trophinin at the ectopic implantation sites. In contrast, tubal epithelia distant from the implantation site do not express trophinin. It may be speculated that an embryonic factor acting locally on the maternal epithelia may induce the expression of trophinin. It has been observed that when a fallopian tube explant was incubated with human chorionic gonadotropin (hCG), the levels of trophinin mRNA were elevated. Therefore, it is likely that hCG secreted by the blastocyst induces the expression of the trophinin gene in adjacent maternal cells. Although there has been no report of the differences in the expression patterns of trophinin in the endometrium and the tubal epithelia in tubal pregnancy, the above mentioned results strongly suggest that trophinin may be highly expressed in the tubal epithelia; thus, trophinin and hCG together play a unique role in the pathogenesis of ectopic pregnancies [15,16]. Interestingly, tubal pregnancy does not occur in rodents [17]. In addition, the incidence of ectopic pregnancies in nonhuman primates is extremely low [18], suggesting that a unique mechanism is involved in ectopic pregnancy in humans. Suzuki found that the expression pattern and in vivo function of trophinin in humans were significantly different from those in mice [19–21]. In humans, trophinin is strongly expressed in trophoblasts in the placenta during the early stage of pregnancy; however, in mice, it is not expressed in trophoblastic cells during and after implantation. It is also known that the gene encoding the β subunit of hCG or CGβ in humans is significantly different from that in nonhuman primates. These findings are consistent with the hypothesis that CGβ and trophinin are uniquely involved in embryo implantation in humans, and hence ectopic pregnancies only occur in humans.