—Review—

The inflammatory process and successful implantation

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Abstract: Implantation is essential for successful reproduction. In humans, uterine receptivity is restricted to the mid-secretory phase, days 19 to 24 of the menstrual cycle; and this period is called the window of implantation (WOI). Large populations of decidual leukocytes infiltrate the implantation site, and the levels of cytokines, prostaglandins (PGs), and leukocytes are up-regulated in the endometrium during implantation. Implantation is like a local wound healing process which is characterized by a strong Th1, pro-inflammatory response in which high levels of pro-inflammatory cytokines such as IL-6, LIF, IL-8, and TNFα are involved. In addition, cyclooxygenase (COX)-2 expression increases between days 2 to 5, suggesting that PGs are necessary for the process of stromal cell decidualization in early pregnancy. Recently, it was reported that endometrial biopsies taken during spontaneous cycles that preceding IVF treatment improved the rate of implantation, clinical pregnancies, and live births in patients with recurrent implantation failure. These results suggest an ininflammatory environment is not adequately induced in some IVF patients with recurrent implantation failure in the absence of local injury provoked by biopsy treatment, further suggesting that uterine receptivity is mediated by the expression of molecules associated with a pro-inflammatory process.

Key words: Implantation, Immune system, Inflammation

Introduction

Implantation and is necessary for successful reproduction occurs in a receptive uterus. In humans, uterine receptivity is restricted to the mid-secretory phase, days 19 to 24 of the menstrual cycle. This period of endometrial receptivity is called the window of implantation (WOI). During WOI, fibroblast-like endometrial stromal cells transform into large rounded decidual cells [1], and large apical protrusions (pinopodes) and microvilli on the luminal epithelium appear [2]. Simultaneously, alterations in the expression of different cytokines, growth factors, transcription factors, prostaglandins, and adhesion molecules take place [3]. Imbalance in any of these protein levels may lead to pathological conditions and subsequent reproductive failures. On the other hand, the involvement of the immune system serves to provide protection from invading organisms, and this system appears to be crucial for successful implantation and maintenance of pregnancy [4]. This review discusses the inflammatory events in implantation and their roles in the reproductive system.

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Implantation

The implantation process is divided into three steps; (1) apposition - initial contact of the blastocyst to the uterine wall; (2) adhesion - increased physical contract between the blastocyst and uterine epithelium; and (3) invasion - penetration and invasion of syncytiotrophoblast and cytotrophoblasts into the endometrium, inner third of the myometrium, and uterine vasculature. The levels of cytokines, prostaglandins, and leukocytes are up-regulated in the human endometrium during implantation [5]. Gradually increasing levels of chemokines and cytokines, produced by endometrial cells, guide the blastocyst to the implantation site allowing its interaction with the uterine lining. Trophoblast cells penetrate into the epithelial and stromal cells, during invasion. The endometrial tissue is repaired and remodeled by the growing placenta. In humans, this local wound healing-like process is characterized by a strong Th1, pro-inflammatory response in which high levels of pro-inflammatory cytokines such as IL-6, LIF, IL-8, and TNFα are involved [6, 7]. These cytokines and chemokines recruit immune cells to the decidua and

Table 1. Proportions of immune cells at the implantation site in early pregnancy

Immune cells		population (%)
Uterine specific natural killer cells		65–70
Macrophages Dendritic cells	antigen-presenting cells	10–20
Regulatory T cells		
NKT cells		
γδT cells		

large populations of human decidual leukocytes infiltrate the implantation site (Table 1). Among these recruited decidual leukocytes, 65–70% are uterine-specific natural killer (uNK) cells and 10–20% are antigen-presenting cells (APC) such as macrophages and dendritic cells [8]. Human decidual NK cells have been shown to play an important role in spiral artery remodeling and trophoblast invasion [9]. On the other hand, regulatory T cells have been shown to be important for fetus-specific immune tolerance in mice [10]. Decidual granular lymphocytes, called decidual NK cells, have been shown to exhibit a specific and distinct surface receptor repertoire allowing regulation by MHC class I molecules and non-MHC molecules that differ from those recognized by NK cells in the periphery [11]. Immune cells simultaneously exhibiting characteristics of NK cells and T cells, have been reported in the periphery and within the human endometrium and decidua [12, 13]. NKT cells have a phenotype suggesting they have an innate immune function and NKT cells at the implantation site are mediated by fetally expressed MHC class I or class I-like products derived from the paternal genome in mice [14]. Additionally, in mice, NKT cells secreting large amounts of interleukin (IL)-4 form the Th2-dominant milieu necessary for successful pregnancy [15].

Uterine dendritic cells (uDCs) are essential for decidual formation and may affect the angiogenic response by inhibiting blood vessel maturation in mice [16]. These cells form the initial contact with external antigens, controlling the antigen specific adaptive immune response. Macrophages are the second largest decidual leukocyte population in early pregnancy, and may be involved in implantation. They are natural candidates for contributing to tissue remodeling at the feto-maternal interface, given their pleiotropic functions in virtually all organ systems. Tissue remodeling involves transforming the spiral arterioles of the decidua into high-capacitance, low-resistance vessels and replacing the endothelium of these vessels with trophoblasts that have migrated from the placenta and invaded the decidua (they are termed extravillous trophoblasts in humans, to distinguish them from the trophoblast subtypes that constitute the villous tree of the placenta proper) as well reviewed by Erlebacher [17]. Decidual macrophages exhibit a predominantly immunosuppressive phenotype, designated M2 polarization, that is characterized by increased IL-10 production and indoleamine 2,3-dioxygenase activity. Before embryo attachment, these decidual macrophages produce leukocyte factor and IL-1β, which may help the endometrium become receptive to implantation by regulation of the surface glycan structure of epithelial cells in humans [18].

These noticeable roles of pathogen sensors and immune effector cells suggest they have a central role in the inflammatory responses to decidual or placental infection. As their function is elucidated, the biology of decidual macrophages represents an open area of research with major implications for human health.

Deletion of either macrophages, NK cells or dendritic cells (DC) has harmful effects in humans and mice [19–23]. In addition, Collins *et al.* demonstrated that uDC association with T cell responses to the fetal 'allograft' starkly contrast with their prominent role in organ transplant rejection in mice [24]. Dominant IL-10 and TGF-beta mRNA expression has been observed in γδT cells of human early pregnancy decidua and that suggests they have an immune-regulatory potential [25]. These cells play an important role in changing the Th1, pro-inflammatory environment, into the Th2, anti-inflammatory environment during the later stages of pregnancy in human [26].

These findings give further support to the idea that the fetal–maternal immune interaction is more complex than that in transplant allograft. They suggest the presence of immune cells at the implantation site is not associated with a response to the 'foreign' fetus but to facilitate and protect the pregnancy. Moreover, the immune system at the implantation site is not suppressed. On the contrary, it is active, functional and carefully controlled theTh2 anti-inflammatory response starting after implantation having a critical role in the continuation of pregnancy.

Endometrial Th1 Inflammatory Response and Successful Implantation

The remodeling of the female reproductive tract after menstruation is similar to that of injured tissue repair, involving inflammatory activity balanced with vascular, connective tissue, and epithelial cell remodeling in humans [27]. In guinea-pigs, injury induced by scratching of the progestational uterus provokes a rapid growth of endometrial cells, which are identical to the decidual cells

of pregnancy [28]. In rat model, decidualization in the progestational uterus was induced by trauma, such as the intrauterine injection of oil [29]. These observations suggest there is a positive association between uterine mechanical manipulation and pregnancy outcome in human patients. It has been reported that endometrial biopsies taken during the spontaneous cycles that precede the IVF treatment more than doubled the rate of implantation, clinical pregnancies, and live births [30, 31]. These studies demonstrate the beneficial effect of local endometrial injury on IVF success. Unfortunately, there is no evidence based on a controlled clinical study with a large sample size that endometrial biopsy increases the implantation rate in IVF patients. Nevertheless, endometrial biopsy may have the potential to increase the implantation rate in IVF patients.

Prior biopsy treatment in the proliferative phase induced the production of larger amounts of macrophages/dendritic cells, and elevated inflammatory cytokines, tumor necrosis factor-α (TNF-α), growth regulated oncogene-α (GRO-α), interleukin-15 (IL-15), macrophage inflammatory protein 1B (MIB-1B), and osteopontin (OPN). A positive correlation was observed between the level of macrophages/dendritic cells, MIP-1B, expression, and TNF-α expression and the pregnancy outcome in humans [32]. A biopsy-induced inflammatory response may facilitate the preparation of the endometrium for implantation. Macrophages and dendritic cells which are present in human endometrium have been shown to play a role in decidualization and implantation. Elevated amounts of macrophages and dendritic cells after biopsy treatment may be recruited by MIP-1B and GRO-α, or be differentiated from the monocytes that were stimulated to migrate to the site of injury by these cytokines. Macrophages and dendritic cells have the potential to secrete many cytokines/chemokines and enzymes that are related to tissue remodeling and angiogenesis [33, 34]. These secreted chemicals may act as mediators of immune cells that potentially target the luminal epithelium, thus contributing to the acquisition of endometrial receptivity in humans [7]. On the basis of these findings, local injury induced by endometrial biopsy seems to promote inflammatory responses. Pro-inflammatory cytokines such as TNF-α, produced by the wounded endometrium, increase the secretion of other cytokines/chemokines which, in turn, recruit macrophages and dendritic cells to the site of implantation in humans [35]. The local environment at the implantation site may be pro-inflammatory in humans, but the inflammatory milieu may not be adequately induced in some IVF patients with recurrent implantation failure in the absence of local injury provoked by the biopsy treatment, and this may explain the beneficial effects of endometrial injury on implantation and pregnancy success in patients undergoing assisted reproductive technology [36]. Accordingly, it is considered that uterine receptivity is mediated by the expression of molecules associated with inflammation.

Thrombotic/inflammatory processes are often observed at the maternal-fetal interface as the final pathological event in many cases of recurrent pregnancy loss (RPL). Both inherited and acquired thrombophilic conditions have been reported to be associated with RPL [37]. Thrombophilia and cellular immune abnormalities were present in more than half of recurrent pregnancy loss cases (72.4% and 63.3%, respectively), and in both known and unknown etiologies of RPL with comparable prevalence. The type 1 inflammatory immune response enhances the coagulation pathways, and the presence of inherited or acquired thrombophilia accentuates inflammation-induced thrombotic pathology at the maternal-fetal interface. Treatment based on a thorough evaluation of the underlying etiology including cellular immunity and thrombophilia may lead to a significantly improved live birth rate in women with RPL [38] (Fig. 1).

The Role of Prostaglandins at the Site of Implantation

Prostaglandins are produced from arachidonic acid which is released from the membrane phospholipids by phospholipase A2 enzyme in rats [39]. Arachidonic acid is converted into PGH_2 by PG-endoperoxide synthase (PTGS), also known as cyclooxygenase (COX). There are two isoforms of COX. One is the constitutively expressed enzyme (COX-1), and the other is the inducible enzyme (COX-2) [40]. PGH_2 is rapidly converted into various other prostanoids by specific terminal PG syntheses. The latter include PGE synthase (PGES), PGIS, PGDS, PGFS, and thromboxane synthase (TXS) that forms PGE_2, PGI_2, PGD_2, $PGF_2\alpha$, and TXA_2 from PGH_2.

After blastocyst attachment, vascular permeability increases and stromal edema appears in rats [41]. Alterations in vascular permeability are followed by a progressive increase in angiogenesis in mice [42].These changes in vascular permeability and angiogenesis at the time of implantation are induced by differential expression of proangiogenic factor in the uterus, as well as vascular endothelial growth factor (VEGF) and its receptor in rats [43]. VEGF accompanied with angiopoietin (Ang)-1, and Ang-2 induce angiogenesis during decidualization.

PGs and platelet-activating factor (PAF) are important paracrine factors involved in the increase in vascular per-

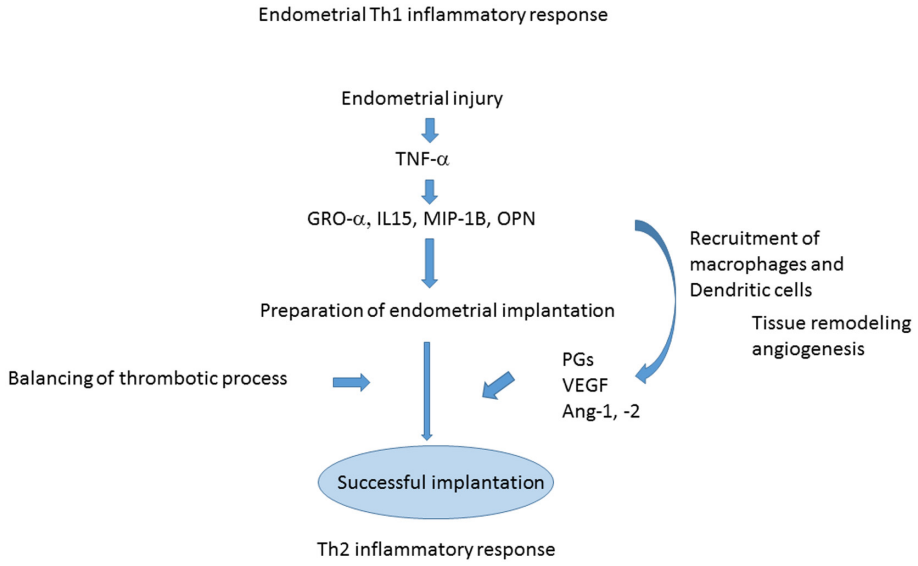

Fig. 1 The endometrial Th1 inflammatory response; TNF-α, tumor necrosis factor-α; GRO-α, growth-regulated oncogene-a; IL15, Interleukin-15; MIP-1B, macrophage inflammatory protein 1B; PGs, prostaglandins; VEGF, vascular endothelial growth factor; Ang-1, -2, angiopoietin-1, -2

meability at the site of embryo implantation in humans [44]. Interaction between PAF and its receptor results in a rapid release of nitric oxide (NO), a potent vasodilator, increases VEGF expression, and activates focal adhesion kinase, FAKpp125 in humans [45]. PGE_2 is more effective than prostacyclin (PGI_2), PPAR-γ, and retinoic acid (RXRA) at increasing in endometrial vascular permeability in rats [46]. PGE_2 mediates sex-steroid effects on VEGF and angiopoietin expression leading to increases in vascular permeability and angiogenesis during implantation. In the rat, the activity of nitric oxide synthase (NOS), an enzyme responsible for NO production, which was reported to be highest at embryo implantation [47], was inhibited by PGE_2 [48]. PGE_2 could be involved in the control of the extent of vascular permeability induced by NO, since $PGF_2\alpha$ was found to cause an acute increase in blood flow to the corpus luteum by stimulating the activity of epithelial nitric oxide synthase (eNOS) in bovine [49].

Prostacyclin (PGI_2) is a potent vasodilator, and has been reported to play a role in the increase in vascular permeability at the implantation site. Prostacyclin binds to IP in glandular epithelial cells, resulting in rapid activation of extracellular signal-regulated kinase (ERK) 1/2 as well as inducing the expression of proangiogenic genes, basic fibroblast growth factor (bFGF), and Ang-1 and Ang-2, via cross talk with the epidermal growth factor receptor (EGF-R) in humans [50].

Decidual cells have been reported to synthesize and secrete PGs and express PG receptors in humans [51, 52]. Upregulation of COX-1, COX-2, cPGES, and mPGES expression in humans [53, 54], and upregulation of AKR1B1, a highly functioning PGF synthase responsible for PGF2a production, all indicate an increase in PG synthesis [55]. In addition, COX-2 expression increases between days 2 to 5, suggesting that PGs are necessary for the process of stromal cell decidualization in early pregnancy in rats [56]. The increase in the expression of EP2 and PPAR-γ in mouse decidual cells means PGs are involved in implantation in mice [57]. The involvement of PGs in progesterone-induced decidualization has been reported. COX-2 was reported to regulate the expression of Snail transcription repressor in mice [58]. Dysregulation of EGF and COX-2 expression in the mouse uteri during the peri-implantation period, which is associated with a high plasma progesterone level resulted in implantation failure [59].

Concluding Remarks

PGs have been reported to play roles in the increase in vascular permeability, stromal decidualization, blastocyst growth and development, leukocyte recruitment, trophoblast invasion, and extracellular matrix remodeling during implantation. Inappropriate levels of PG synthases will lead to implantation failure. Embryo implantation is

associated with an active Th1 inflammatory response, while Th2-humoral inflammation is required for pregnancy maintenance. Local injury induced by endometrial biopsy may improve uterine receptivity by eliciting an inflammatory reaction in patients with recurrent implantation failure. Thus, successful implantation may well be a controlled inflammatory process.

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