—Mini Review—

Angiogenesis and hormonal regulation on uterine receptivity for blastocyst implantation

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Abstract: Synchronization of embryonic development and differentiation of specific uterine cell types to a receptive state is essential for a successful pregnancy. The period of uterine receptivity for implantation is limited. Increased vascular permeability and angiogenesis are hallmarks of the implantation process. Although implantation involves the interaction of numerous signaling molecules, the hierarchical mechanisms that coordinate the embryo–uterine dialog remain poorly understood. This review highlights our knowledge about angiogenesis, uterine receptivity, and hormonal regulation for blastocyst implantation in the mouse. A better understanding of uterine biology during the peri-implantation period would facilitate the further development of reproductive technology.
Key words: Angiogenesis, Decidualization, Implantation, Steroid hormones, Uterus

Introduction

For a successful pregnancy, synchronization of embryonic development and differentiation of specific uterine cell types to a receptive state is essential [1, 2]. Under physiological conditions, angiogenesis, the process by which new blood vessels develop from pre-existing vessels, occurs primarily in the uterus and ovaries during the adult reproductive cycle and pregnancy [3]. Angiogenesis is a hallmark event during implantation and decidualization [4–7]. Indeed, increased vascular permeability and angiogenesis are crucial for successful implantation, decidualization, and placentation [4, 6, 7]. Numerous studies have provided evidence of the potential roles of estrogen (E_2) and progesterone (P_4) in these processes in various species [3, 8, 9]; thus, uterine angiogenesis controlled by angiogenic factors including vascular endothelial growth factor (VEGF) and its receptors has been studied. The present review of uterine angiogenesis during implantation and decidualization focuses on the molecular basis of angiogenic factors, steroid hormones, and prostaglandins for uterine receptivity in the mouse model.

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VEGF and their Receptors are Required in Uterine Angiogenesis

VEGF, originally discovered as a vascular permeability factor, is also a potent mitogen for endothelial cells and a key regulatory growth factor for vasculogenesis and angiogenesis [10]. Targeted disruption of even a single allele of the *Vegf* gene results in embryonic death *in utero* during mid-gestation, with aberrant blood vessel formation [11, 12]. Five human VEGF isoforms with 121, 145, 165, 189, and 206 amino acids are known, whereas three isoforms with 120, 164, and 188 amino acids have been identified in the mouse. These isoforms are generated from alternately spliced mRNAs from a single gene with eight exons [13]. Differential splicing of the *Vegf* gene transcript generates several VEGF isoforms in both humans and mice. $VEGF_{121}$ and $VEGF_{165}$ are the predominant isoforms in humans, whereas $VEGF_{120}$ and $VEGF_{164}$ are the most abundant isoforms in mice [8, 13]. In the mouse uterus, $VEGF_{164}$ is the predominant isoform, and mediates vascular changes and angiogenesis in the uterus during implantation and decidualization [8].

The effects of VEGF are primarily mediated by two tyrosine kinase receptors: VEGFR1 [fms-like tyrosine kinase 1 (Flt-1)] and VEGFR2 [fetal liver kinase 1 (Flk-1)/kinase insert domain-containing receptor (KDR)] [14–17]. Flk-1 is the major transducer of the VEGF signals that induce

chemotaxis, actin reorganization, and proliferation of endothelial cells [10, 18, 19]. In the mouse uterus, very low to undetectable expression levels of *Flk-1* are observed in the uterus during the first two days of pregnancy (day 1=vaginal plug) [8]. On days 3 and 4, *Flk-1* is distinctly expressed in cells in the stromal bed. The expression of *Flk-1* was evident in stromal cells close to, but not immediately surrounding, implanting blastocysts on day 5. On days 6–8, *Flk-1* mRNA accumulation occurred in cells at both the mesometrial and anti-mesometrial decidual beds. However, *Flk-1* expression was more intense at the mesometrial pole, the presumptive site of placentation and heightened angiogenesis. On day 8, some embryonic cells exhibited a marked accumulation of *Flk-1* mRNA. *Flk-1* mRNA is absent in the primary decidual zone (PDZ), which is avascular [8, 20]. Targeted deletion of the *Flk-1* gene in mice results in hematopoietic and endothelial cell developmental defects, leading to embryonic death by day 9.5 [21].

Although Flt-1 activation does not stimulate endothelial cell mitosis, targeted disruption of the *Flt-1* gene impairs endothelial cell assembly into blood vessels and is lethal to the embryo [22]. During peri-implantation in the mouse uterus, expression levels of *Flt-1*, as detected by northern blot hybridization and *in situ* hybridization, were lower than those of *Flk-1* [20].

Another multifunctional VEGF receptor is neuropilin-1 (Nrp1). Nrp1 was originally described as a neuronal transmembrane receptor that participates in axonal guidance in the developing nervous system [23, 24], and is a receptor for the collapsin/semaphorin family of proteins [25, 26]. *Nrp1* is expressed in human endothelial cells as a $VEGF_{165}$-specific receptor. When coexpressed in endothelial cells with Flk-1, Nrp1 enhances the binding of $VEGF_{165}$ to Flk-1, and increases $VEGF_{165}$-mediated chemotaxis more than Flk-1 alone [27]. Conversely, inhibition of $VEGF_{165}$ binding to Nrp1 inhibits its binding to Flk-1, as well as its mitogenic activity in endothelial cells [27]. *Nrp1*-deficient mice show peripheral nervous system abnormalities and die in mid-gestation due to vascular insufficiency of the yolk sac and developmental anomalies of the cardiovascular system [28]. The expression pattern of *Nrp1* mRNA is similar to that of *Flk-1* in the mouse uterus [8, 20]. However, it is interesting to note that *Nrp1* mRNA was observed to be more widely distributed than *Flk-1*, suggesting that Nrp1 is present in stromal cells other than endothelial cells [8].

Collectively, genes encoding murine VEGF isoforms and their receptors, Flk-1, Flt-1, and Nrp1, are differentially expressed in the mouse uterus in a spatiotemporal manner during implantation, and the predominant $VEGF_{164}$ isoform interacts with Flk-1 and Nrp1 [8, 9]. These results suggest that the VEGF system is involved in uterine vascular permeability and angiogenesis during implantation.

Angiopoietins and their Receptor Tie-2

The effects of VEGF are complemented and coordinated by another class of angiogenic factors, the angiopoietins [29]. VEGF acts during the early stages of vessel development [11, 12, 21], whereas angiopoietin-1 (Ang-1) acts later to promote angiogenic remodeling, including vessel maturation, stabilization, and leakiness [30–32]. In contrast to the agonistic functions of Ang-1, Ang-2 behaves as an antagonist. Thus, Ang-1 and Ang-2 are naturally occurring positive and negative regulators of angiogenesis, respectively. They interact with an endothelial cell-specific tyrosine kinase receptor Tie-2 [33]. Ang-2 has been shown to be required for postnatal angiogenic remodeling, and to participate in the development of lymphatic vasculature in collaboration with VEGF [34]. Ang-3, which is expressed in mice, appears to function as an antagonist to Ang-1 activation of Tie-2, in a fashion similar to Ang-2 [35]. Our previous study revealed that VEGF and its receptor Flk-1 are primarily important for uterine vascular permeability and angiogenesis before and during the attachment phase of implantation, whereas VEGF, together with the angiopoietins and their receptor Tie-2, direct angiogenesis during decidualization after implantation [36].

COX-2-derived Prostaglandins Participate in Uterine Angiogenesis during Implantation and Decidualization

Prostaglandins, because of their roles in angiogenesis, cell proliferation, and differentiation in other systems, are also likely to participate in uterine vascular permeability and angiogenesis during implantation and decidualization. Our previous study revealed genetic and molecular evidence that COX-2-derived prostaglandins participate in uterine angiogenesis during implantation and decidualization [36]. Thus, one cause of implantation and decidualization failure in *Cox-2*(−/−) mice is deregulated vascular events in the absence of COX-2. The attenuation of uterine angiogenesis in these mice is primarily due to defects in VEGF signaling, rather than the angiopoietin system. $Vegf_{164}$ expression is remarkably downregulated in stromal cells at the blastocyst site in *Cox-2*(−/−) mice. A prostacyclin (PGI_2) agonist, carbarprostacyclin (cPGI), functions as a ligand for peroxisome proliferator-activated receptor δ (PPARδ) and facilitates its heterodimerization

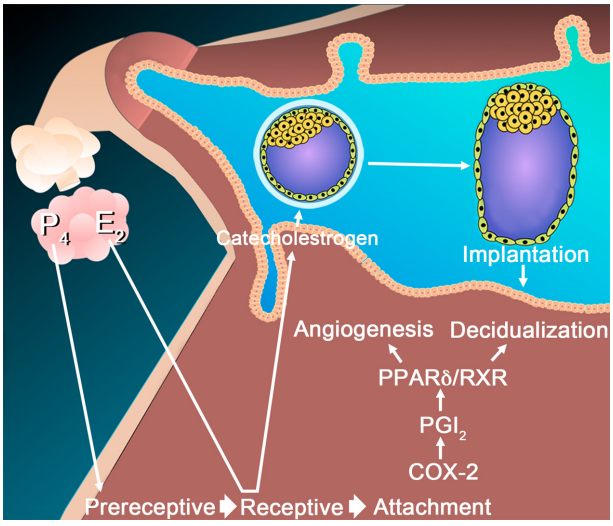

Fig. 1. Uterine receptivity and angiogenesis during implantation. Ovarian estrogen (E_2) and progesterone (P_4) are the primary effectors of the receptive state via a number of uterine factors, whereas the blastocysts gain an implantation-competent state through activation by uterine-derived catecholestrogen. During the attachment phase, sequential signaling events within the uterus lead to blastocyst implantation. Stromal cell decidualization follows the attachment phase. COX-2-derived prostaglandins participate in uterine angiogenesis during implantation and decidualization.

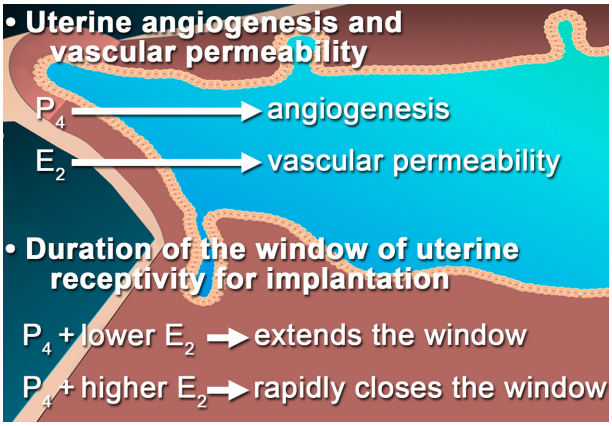

Fig. 2. Differential regulation of steroid hormones for vascular permeability, angiogenesis, and the duration of uterine receptivity. E_2 and P_4 have different effects *in vivo*: E_2 promotes uterine vascular permeability but profoundly inhibits angiogenesis, whereas P_4 stimulates angiogenesis with little effect on vascular permeability. The window of receptivity in the P_4-primed uterus changes in response to changing estrogen levels; a low threshold level of E_2 extends the window of uterine receptivity for implantation, while higher levels rapidly close this window, transforming the uterus into a refractory state.

with retinoid X receptor (RXR). cPGI (a more stable analog of PGI_2) together with the RXR agonist, 9-*cis*-retinoic acid (9-*cis*-RA), improves poor implantation in *Cox-2*(−/−) mice [36, 37]. Administration of cPGI and 9-*cis*-RA also restored the expression of *Vegf*, as well as the number of blood vessels, leading to improved implantation. These results suggest COX-2-derived prostaglandins influence uterine angiogenesis primarily via affecting the VEGF system during implantation (Fig. 1). In contrast, no significant difference was noted in the expression patterns of angiopoietins between the *Cox-2*(−/−) and wild-type mice, although the decidual response was depressed in *Cox-2*(−/−) mice. The expression pattern of *Tie-2* was also similar between the wild-type and *Cox-2*(−/−) uteri. Therefore, the angiopoietin signaling involved in uterine angiogenesis is distinct from that of the COX-2-derived prostaglandins. Collectively, these results provide evidence that COX-2-derived prostaglandins direct angiogenesis during implantation and decidualization by differentially regulating VEGF and angiopoietin signaling, whereas ovarian steroid hormones influence uterine vascular permeability and angiogenesis during the preimplantation period.

Differential Regulation of Steroid Hormones for Uterine Vascular Permeability and Angiogenesis

The expression of VEGF and its receptors in the uterus is affected by steroid hormones [20]. E_2 rapidly induces uterine vascular permeability and *Vegf* transcription via the nuclear estrogen receptor [20], and the *Vegf* gene contains E_2 response elements [38]. P_4 also upregulates uterine *Vegf* expression via activation of the nuclear progesterone receptor, but at a slower rate [38]. As E_2 rapidly stimulates uterine vascular permeability and *Vegf* expression, and because vascular permeability is considered a prerequisite for angiogenesis, it was widely believed that E_2 was a potent stimulator of uterine angiogenesis during normal reproductive processes *in vivo*. However, the evidence from molecular, genetic, physiological, and pharmacological studies has revealed that E_2 and P_4 have different effects *in vivo*; E_2 promotes uterine vascular permeability but profoundly inhibits angiogenesis, whereas P_4 stimulates angiogenesis with little effect on vascular permeability [39]. These effects of E_2 and P_4 are mediated by the differential spatiotemporal expression of proangiogenic factors in the uterus [39] (Fig. 2).

Differential Expression of Motin Family Members in the Uterus and their Hormonal Regulation

Angiomotin (Amot) is a vascular angiogenesis-related protein, which was initially identified as an angiogenesis inhibitor angiostatin-binding protein using a yeast two-hybrid screen [40, 41]. Amot can induce endothelial cell migration and tubule formation, and therefore, promotes angiogenesis [40, 42]. There are also two angiomotin-like proteins, Amotl1 and Amotl2. These three proteins belong to the motin family with a highly conserved coil-coil domain, PDZ binding domain, and glutamine-rich domain [41]. Amotl1 and Amotl2 also likely play important roles in cell migration and angiogenesis [43–46]. The expression patterns of motin family members vary during development. Our recent study revealed a spatiotemporal-dependent expression of *Amot*, *Amotl1*, and *Amotl2* in the mouse uterus during pre-implantation and post-implantation periods [47]. Specifically, ovarian steroid hormones regulate the differential expression of motins. The expression of *Amot* is induced by P_4 in stromal cells. Additionally, *Amotl1* expression is upregulated by both P_4 and E_2 in stromal cells. However, E_2 increases *Amotl1* expression for only a limited time, and after 12 h its expression diminishes. In contrast, P_4 regulates the expression of *Amotl2* in stromal cells while E_2 regulates its expression in luminal epithelial cells. Collectively, *Amot*, *Amotl1*, and *Amotl2* are differentially expressed in uterine cells during peri-implantation, and their expression is differentially regulated by P_4 and E_2.

Estrogen is a Critical Determinant that Specifies the Duration of the Window of Uterine Receptivity for Implantation

For successful pregnancies in mice, the “window” of uterine receptivity for implantation lasts for a limited time [4, 5, 48, 49]. At this stage, the uterine environment is capable of supporting blastocyst growth, attachment, and the subsequent events of implantation. The major hormones that specify uterine receptivity are the ovarian steroids P_4 and E_2. The pre-receptive uterus on day 3 of pregnancy becomes receptive on day 4, under the influence of rising P_4 and a small amount of ovarian E_2 secretion on the morning of day 4 of pregnancy [50]. In contrast, using the embryo transfer and P_4-treated delayed-implantation model mouse, it has been demonstrated that levels of E_2 within a very narrow range determine the duration of the uterine receptivity window. Although E_2 at different physiological concentrations can initiate implantation, the window of uterine receptivity remains open for an extended period at lower E_2 levels, but rapidly closes at higher levels [51] (Fig. 2). The uterine refractoriness that follows the receptive state at high E_2 levels is accompanied by the aberrant expression of implantation-related genes. Therefore, careful regulation of E_2 levels is an important factor for the improvement of female fertility in *in vitro* fertilization and embryo transfer programs.

Extended Uterine Receptivity for Blastocyst Implantation and Full-term Fetal Development in Mice with Vitrified–warmed Ovarian Tissue Autotransplantation

Our recent study demonstrated that vitrified-warmed ovarian tissue autotransplantation (VOAT) in estrus cycle-ceased ovariectomized mice restored fertility and achieved full-term fetal development of the transferred embryos, while less steroidogenesis in the corpus luteum was observed in VOAT mice [52]. Although VOAT mice, using our methods, possessed sufficient potential to support pregnancy and full-term development, steroidogenesis and blood vessel formation in the corpus luteum in VOAT mice were less prolific than in intact mice [52]. As described earlier, the window of uterine receptivity for blastocyst implantation in mice remains open for an extended period at lower E_2 levels [51]. Therefore, the implantation window may be prolonged in VOAT mice. To address this issue, we performed an embryo transfer into VOAT mice on day 5 of pseudopregnancy to examine whether the VOAT mice could support pregnancy and full-term fetal development. We also examined the uterine decidualization, ovarian steroidogenesis and blood vessel formation in the corpus luteum in VOAT mice. The rate of live birth pups from embryo transfer on day 5 of pseudopregnant VOAT mice was the same as that of VOAT mice with embryo transfer on day 4 of pseudopregnancy, while intact mice with embryo transfer on day 5 failed to support pregnancy [53]. Immunohistochemical analysis of the corpus luteum of day 8 pseudopregnant VOAT mice, with decidualization induced on day 5, exhibited less steroidogenesis and blood vessel formation than intact mice. In conclusion, uterine receptivity was extended in VOAT mice, and the lower levels of steroidogenesis and blood vessel formation in the transferred ovarian tissues may be associated with the extended uterine receptivity (Fig. 2).

Conclusion

Many important discoveries have been made in the

field of uterine receptivity; however, our knowledge of the complex events that occur during implantation is not enough to prevent infertility caused by implantation failure. This review article described the angiogenesis and uterine receptivity induced by key players such as VEGF and its receptors, angiopoietins, and the motin family. We also focused on the effect of COX-2 derived prostaglandins and hormonal regulations on angiogenesis and uterine receptivity. The extended uterine receptivity in VOAT mice was also described. These observations may help to elucidate the mechanisms behind the differentiation, proliferation, and angiogenesis of uterine cells that allow the establishment of pregnancy. However, further investigation is required to improve the success of implantation and pregnancy.

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