Review

Uterine receptivity and implantation: The regulation and action of insulin-like growth factor binding protein-1 (IGFBP-1), HOXA10 and forkhead transcription factor-1 (FOXO-1) in the baboon endometrium

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Abstract

In primates, the phase of the menstrual cycle when the uterus becomes receptive is initially dependent on estrogen and progesterone. Further morphological and biochemical changes are induced as a result of biochemical signals between the embryo and the maternal endometrium. Blastocyst implantation in the baboon usually occurs between 8 and 10 days post ovulation and is similar to that described for the rhesus macaque. In the baboon, when chorionic gonadotropin is infused in a manner that mimics blastocyst transit, this has physiological effects on the three major cell types in the uterine endometrium. The luminal epithelium undergoes endoreplication and distinct epithelial plaques are evident. The glandular epithelium responds by inducing transcriptional and post-translational modifications in the major secretory product, glycodelin. The stromal fibroblasts initiate their differentiation process into a decidual phenotype and are characterized by the expression of actin filaments. Decidualization, is the major change that occurs in the primate endometrium after conception. During this process the fibroblast-like stromal cells change morphologically into polygonal cells and express specific decidual proteins. Studies in the baboon demonstrated that insulin-like growth factor binding protein-1 (IGFBP-1) gene expression is a conceptus-mediated response. Subsequent studies *in vitro* established that IGFBP-1 is transcriptionally regulated by FOXO1 and HOXA10 which together upregulate the IGFBP-1 promoter activity. A baboon endometriosis model was utilized to determine if the changes observed during uterine receptivity in normally cycling animals were compromised. The data suggests that in animals with disease, markers of uterine receptivity are not appropriately expressed in the eutopic endometrium. It is possible that these differences influence the fertility of the animals with disease and the baboon could be used as a primate model to study the causes of infertility as a result of endometriosis.

Background

The dialogue that occurs between the preimplantation embryo and the uterus is one of true elegance. Although the precise molecules and events involved remain unclear, it is well known that the initiation of pregnancy requires a precisely timed synchrony between endometrial develop-

ment and the implanting blastocyst. In primates, at the appropriate phase of the menstrual cycle, the uterus becomes "receptive" and enables the blastocyst to attach. This "receptive window" is initially dependent on estrogen and progesterone. Further morphological and biochemical changes are induced within the uterus by signals from the developing embryo and following trophoblast invasion.

Uterine receptivity and implantation in the baboon can be categorized into three distinct phases. Phase I is regulated by estrogen and progesterone and is evident between days 8 and 10 post-ovulation (PO) of the normal menstrual cycle. Morphologically it is characterized by the presence of columnar epithelium with microvilli and an increase in stromal cells proliferation [1]. At the biochemical level, there is a loss of estrogen receptor (ERα) and progesterone receptor (PR) in the luminal epithelium [2] together with a marked reduction of the polymorphic mucin, Muc-1 expression [3]. Coincident with the decrease in Muc-1 staining, there is an increase in smooth muscle myosin II (SMM II) expression in the luminal and glandular epithelium [4] and the appearance of pinopod-like structures on the surface epithelium, similar to those reported in the human [5]. The second phase of uterine receptivity is induced by blastocyst 'signals' superimposed on the estrogen/progesterone-primed receptive endometrium. This phase is associated with functional and morphological changes in the endometrium that are distinct from those observed at a comparable time of a nonpregnant cycle (i.e. phase I of uterine receptivity). Phase III of uterine receptivity is initiated following blastocyst attachment and implantation. A universal response is the significant increase in the permeability of the subepithelial capillaries surrounding the blastocyst [6,7]. In primates the morphological changes associated with implantation have been extensively studied and elegantly reviewed by Enders [8]. In general, together with glandular hypertrophy, stromal cell decidualization is initiated and is accompanied by increased extracellular matrix (ECM) accumulation.

In this review, a brief summary of the studies in the baboon that demonstrate the modulation of the uterus by embryonic signals (Phase II) is given. The molecular regulation of stromal cell differentiation (Phase III) will be the focus of this review and the aberration of uterine receptivity in baboons with endometriosis will be discussed.

Influence of embryonic signals on uterine receptivity – phase II

Several lines of evidence demonstrate that embryo-derived factors directly or indirectly influence endometrial receptivity and implantation in primates. Studies in the rhesus monkey indicate that endometrial physiology

during the midluteal phase in the presence of the conceptus is discernibly different from that in the nonfecund midluteal phase [9]. An early maternal response to pregnancy in the luminal epithelium of primates is the formation of the epithelial plaque [10]. This response is characterized by hypertrophy of the surface epithelium and cells in the neck glands that round up and form acinar clusters [11,12]. In the baboon, chorionic gonadotropin (CG), when infused in a manner that mimics blastocyst transit, has physiological effects on the three major cell types in the uterine endometrium (i.e. luminal and glandular epithelium and stromal fibroblasts [13]). The effects of CG on glandular transformation and stromal cell differentiation are direct, and occur independent of the ovary [13]. The glandular response to CG infusion is characterized by a marked increase in transcriptional and post-translational modulation of glycodelin [13]. Synthesis of glycodelin by the glandular epithelium parallels the rise and later decline of CG in the peripheral circulation [14]. The primary effect of CG on stromal fibroblasts is the induction of α-smooth muscle actin (αSMA; 13, 15). It has been hypothesized that the induction of αSMA in stromal fibroblasts occurs as a consequence of the binding of integrins on the stromal cell membranes (that are also induced in response to CG) to secreted ECM proteins [16]. The interaction between integrins and the ECM induces changes in the actin cytoskeleton that are thought to be critical for signal transduction [17,18].

Decidualization – phase III

One of the fundamental requirements for the successful establishment and maintenance of pregnancy in the primate is the decidualization of the endometrium. Decidualization is defined as the differentiation of the fibroblast-like mesenchymal cells in the endometrium to a decidual cell which is morphologically and biochemically distinct [19]. The decidualized cell biochemically expresses new proteins such as prolactin and insulin-like growth factor binding protein-1 (IGFBP-1; 1).

In the human, regardless of whether implantation occurs, stromal edema is observed on day 23 of the menstrual cycle and is followed 3 to 4 days later by a predecidual reaction which begins around the spiral arteries and spreads through the upper two-thirds of the endometrium [20]. If implantation occurs, the reaction is intensified and becomes the decidua of pregnancy. In contrast, the baboon does not undergo a predecidual reaction during the menstrual cycle [12,21]. However, following implantation, the stromal fibroblasts undergo extensive modification to form the decidua in the baboon (11,12, 22). Turner [23] and Bryce and Teacher [24] first suggested that decidualization is regulated by the trophoblast. In vivo data clearly demonstrate that decidualization in the baboon, based on IGF-I receptor, IGFBP-1 and prolactin

expression, is a conceptus-induced phenomenon, first evident at the implantation site between days 18 and 25 of pregnancy [25,26]. Treatment of endometrial stromal cells in cell culture with estrogen and progesterone, which can decidualize human stromal cells, is insufficient to fully decidualize stromal cells isolated from the baboon endometrium. An additional factor, i.e. dibutyryladenosine 3':5' cyclic monophosphate (dbcAMP) is required, suggesting that a conceptus-mediated factor involving cAMP-mediated pathways is important in the baboon [27].

Although there are many studies that have defined the morphological and biochemical end points of a decidual cell [12,28], the sequence of cellular and molecular events associated with the transformation of a stromal fibroblast to a secretory decidual cell has yet to be elucidated. IGFBP-1 is not only a marker for decidualization but also a paracrine/autocrine factor which is intimately involved in the sequence of events leading from implantation to normal fetal outcome. By studying the factors which regulate IGFBP-1 gene expression, a general sense of the types of changes that occur during the process of decidualization can be obtained.

IGFBP-1 gene regulation

Many studies have demonstrated the regulation of the IGFBP-1 gene in both the liver and the endometrium. Multiple factors contribute to the regulation of IGFBP-1 gene expression, including insulin, glucocorticoids, progesterone, cytokines and hypoxia [29-32]. In the decidualized human endometrium, progesterone induces IGFBP-1 synthesis perhaps via a glucocorticoid response element [33]. Further modulation of its expression in vitro is mediated by cAMP [34]. Many of the important cis-regulatory elements are located within 500 bp of the transcription start site. [35]. The hepatocyte nuclear factor 1 (HNF1) binding region, insulin response element (IRE), gluococorticoid response element (GRE) and TATA element are highly conserved among the human, rat and mouse IGFBP-1 promoters, suggesting a crucial, evolutionarily conserved role for these gene promoter regions in its regulation. In the recent years, there has been great interest in the regulation of IGFBP-1 by FOXO1, a member of the FOXO sub-family of forkhead/winged-helix family of transcription factors in liver-derived cells [36-39]. The DNA-binding domain of FOXO1 is comprised of three tightly packed alpha helical domains and a C-terminal basic region [40]. It is the third helix (H3) that establishes DNA base contacts within the major groove of its recognition sequence. The IGFBP-1 promoter contains an FOXO1 binding site (GCAAAACAA) in the IRE of the human IGFBP-1 promoter.

FOXO1 is expressed in the baboon endometrium and is upregulated during the luteal phase of the menstrual cycle which intensifies during pregnancy [35]. Furthermore, FOXO1 can upregulate the IGFBP-1 promoter in endometrial stromal cells [35]. Studies have shown FOXO1 to physically associate with additional nuclear transcription factors and cause repression or transactivation of genes. FOXO1 can interact with the estrogen receptor, retinoic acid receptor, and thyroid hormone receptor causing either repressive or activating effects on nuclear receptor mediated genes [41,42]. FOXO1 can also associate with and function cooperatively with CCAAT/enhancer-binding protein (C/EBP) beta to cause a significant upregulation of the decidual prolactin promoter in response to cAMP agonists [43]. FOXO1 can physically associate with HOXA10, another nuclear transcription factor which then acts cooperatively to increase the IGFBP-1 promoter activity [35].

HOXA10 is one member of the homeobox (HOX) gene family. Homeobox genes are involved in the genetic control of development, in particular in the specification of the body plan, pattern formation, the determination of cell fate, and several other basic developmental processes (reviewed in 44). Proteins in the homeobox gene family contain a unique homeodomain that is a 61 amino acid residue polypeptide which represents the DNA-binding domain of the proteins.

HOX proteins can regulate genes in adult tissues. Hoxa5 [45] and HOXA10 [46] stimulate the p53 promoter in breast cancer cells and promote the expression of the progesterone receptor [47]. Other targets of HOXA10 regulation include beta 3 integrin [48] and empty spiracles homolog 2(EMX2) [49]. In the developing reproductive tract, four genes of the HOXA cluster (HOXA9, HOXA10, HOXA11, and HOXA13) are expressed [50]. HOXA10 is expressed in the developing uterus, specifically in the endometrial glands and stroma of the endometrium where its expression is dependent on the stage of the menstrual cycle, dramatically increasing at the time of implantation [50-52]. HOXA10 deficient mice exhibit uterine factor infertility due to implantation defects. Specifically, decidualization of the endometrium is severely compromised during blastocyst implantation [53]. The role of HOX genes on IGFBP-1 regulation has been demonstrated for the first time using transgenic mice over-expressing HOXA5. These mice exhibit a 12-fold increase of IGFBP-1 expression in the liver and undergo growth arrest during weeks two and three of postnatal development, resulting in proportionate dwarfism [54]. HOXA10 has a modest effect on IGFBP-1 promoter activity, but when FOXO1 is present, promoter activity is upregulated in a cooperative manner [35]. For this to occur, binding of FOXO1 to the IRE is required.

Studies have suggested that HOX family members interact with cofactors such as PBX, the mammalian homolog of *Drosophila* extradenticle [55-57]. It is believed that interactions with PBX cofactors may contribute to the regulatory control and refinement of HOX protein function. Given that there is a high proportion of presumptive HOX binding sites on any given promoter and the affinity of HOX proteins for nonspecific sites is relatively strong, it is not unreasonable to assume a need for cofactors for site-specific recognition. It is possible that there are multiple potential HOXA10 binding sites on the IGFBP-1 promoter. Whether these binding sites are functional may depend on the availability of FOXO1 to interact with HOXA10 and assist in its recruitment to the IGFBP-1 promoter. It is possible that HOXA10 stabilizes FOXO1 DNA binding and in turn modulates specificity of HOX DNA binding.

The cooperative action of FOXO1 and HOXA10 is highly intriguing with great potential implications. Not only are FOXO1 and HOX transcription factors expressed in numerous tissues and cell types, these two transcription factors have independently been shown to be critical regulators of genes. The possibility that FOXO1 and HOX proteins, by associating with one another can regulate genes more powerfully and specifically than by themselves, is extremely provocative.

The repertoire of gene expression during conceptus-induced decidualization is very different from a non-pregnant endometrium. When critical genes are aberrantly expressed during the decidualization process or even during the window of implantation, this could result in the failure of the blastocyst to implant or inadequate implantation. Studies have demonstrated that the eutopic endometrium of women with endometriosis expresses an aberrant pattern of genes and several markers of uterine receptivity are abnormally or not expressed [58].

Uterine receptivity in endometriosis
Women and baboons with endometriosis have a lowered fecundity [59,60]. Endometriosis, which is characterized by the presence of a functional endometrium outside of the uterine cavity, is a condition that affects five million American women. The etiology of endometriosis is unclear; however, the most widely accepted hypothesis for its development is retrograde menstruation, where fragments of menstrual endometrium are refluxed through the fallopian tubes into the peritoneal cavity [61]. The baboon has been used as a model to understand this disease. Intraperitoneal autotransplantation of menstrual endometrium in the baboon results in experimental endometriosis, supporting Sampson's theory of retrograde menstruation. This method of induction resulted in red raised and reddish-blue implants to scared lesions

with powder-black appearance that were macroscopically similar to those seen in women with spontaneous endometriosis [62]. There is also evidence that the baboon can spontaneously develop endometriosis: however, it is unclear whether this is truly a spontaneous condition or whether it is induced by repetitive surgical manipulation [63].

Glycodelin, αSMA, and αvβ3, which have been previously characterized as markers of uterine receptivity, are absent from eutopic endometrium during the window of implantation in baboons and humans with endometriosis [59,64]. The lack of induction of glycodelin and αSMA is seen at early stages of endometriosis in the baboon. An understanding of the mechanisms by which the expression of these genes is controlled may elucidate the reasons for implantation failure in women with endometriosis.

In recent years, studies have shown that the gene expression profile in the endometrium of women with endometriosis is aberrant [58,65-68]. HOXA10 downregulated in the endometrium of women with endometriosis [69]. Since transcription factors activate or repress genes, it is possible that the aberration lies in the expression or function of transcription factors. We collected preliminary data showing that in stromal cells isolated from the endometrium of baboons with endometriosis, FOXO1 and HOXA10 had a minimal effect on the IGFBP-1 promoter. Interestingly, the cooperative effect of FOXO1 and HOXA10 was also repressed. These cells were isolated from baboons with endometriosis that have been considered to be subfertile. These intriguing data suggest that the cells from animals with endometriosis are different from those of normal baboons. One can speculate that if the cooperative action of FOXO1 and HOXA10 does not occur in these cells, the upregulation of IGFBP-1 to necessary levels may not occur, which may somehow be associated with the infertile status of the animal. Furthermore, if the cooperative action of FOXO1 and HOXA10 does not occur, other relevant gene expression may also be inadequate. To date, it is unclear why certain genes are downregulated or abnormally expressed in endometriosis. Determining the mechanisms responsible for the dysregulation of genes will give us a better understanding of the potential causes of infertility associated with endometriosis.

Conclusions
The use of the baboon as an animal model to study uterine receptivity and implantation has been invaluable. Much information on the morphological, biochemical and molecular events that occur during early pregnancy has been generated. There is direct evidence of endometrial modulation by local infusion of CG demonstrating that embryonic signals directly act on the endometrium in

primates. The implanted embryo promotes decidualization of the endometrium which is essential for the establishment of pregnancy and potential transcription factors within the endometrium that may play a role in this process have been identified. With the use of these experimental paradigms, it has been shown that endometriosis affects uterine receptivity in the baboon. Elucidating the cellular and molecular events associated with uterine receptivity and implantation will have significant implications in understanding the fundamental causes of implantation failure and subsequent infertility.

Acknowledgements

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