## Review Article

# Delineating the prime mover action of progesterone for endometrial receptivity in primates

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**Progesterone is essential for endometrial receptivity in primates. It is now evident that embryo-derived signal influences implantation stage endometrium under progesterone dominance, and collectively results in endometrial receptivity to implanting blastocyst. Previously, a few studies were performed using global gene profiling based on microarray technology to identify changes in gene expression between early luteal phase and mid luteal phase endometrium, however, the issue of combinatorial regulation by progesterone-dependent regulation and by embryo-derived signal on transcripts profiles during endometrial differentiation toward receptivity for blastocyst implantation in primates has not been addressed. The present review summarizes a few issues, specifically that of transforming growth factor β-tumour necrosis factor α (TGFβ-TNFα) pathways and signal transducer and activator of transcription (STAT) signalling system related to luteal phase progesterone action on endometrial receptivity in terms of its transcriptomic expression using a potent antiprogestin (mifepristone) in conception cycles of the rhesus monkey as a non-human primate model.**

**Key words** Endometrium - mifepristone - receptivity - Rhesus monkey - transcriptomics

## Introduction

Progesterone is essential for endometrial receptivity and pregnancy maintenance in the human and non-human primates[1-5]. As shown in Table I, there are a few reports on the molecular characteristics of the 'window' of implantation in which high density cDNA microarray screening was performed for global gene profiling to essentially identify changes in gene expression between early luteal (pre-receptive) and mid luteal (receptive) phases in primate and human endometrium to elucidate steroidal regulation of endometrial physiology towards receptivity[6-14]. There

are two studies describing the differential display of genomic expression in human endometrium in response to high affinity progesterone antagonist (mifepristone) during the period of progesterone dominance *in vitro* and *in vivo*[10,14]. However, it is now clearly evident that a dialogue between embryo and endometrium under progesterone dominance results in complex interaction of genomic expressions that collectively manifests endometrial receptivity to an implanting blastocyst[15-17]. The potential effect of human chorionic gondotropin (hCG), a putative preimplantation stage embryo-derived signal on transcript profiles in implantation

| Reference | Subject (No. of gene targets) | Experimental design (sample size) |
|---|---|---|
| Kao *et al*[6] | Normally cycling human (~12,000) | Differential array analysis between late proliferative phase, cycle days 8-10 (n=4) and mid secretory phase LH 8-10 (n=7) |
| Carson *et al*[7] | Fertile human (~12,000) | Differential array analysis between early luteal LH 2-4 (n=3) and mid luteal LH 7-9 (n=3) phases |
| Borthwick *et al*[8] | Normally cycling human (~60,000) | Differential array analysis between proliferative phase, cycle days 9-11 (n=5) and secretory phase LH 6-8 (n=5) |
| Riesewijk *et al*[9] | Normally cycling (~12,000) human | Differential array analysis between paired samples (n=5) collected during pre-receptive LH 2 and receptive LH 7 phases |
| Catalano *et al*[10] | Human endometrial explant culture (1000) | Differential array analysis between mid-secretory phase (n=5) endometrial explants treated with $10^{-9}$ M estradiol plus $10^{-7}$ M medroxy-progesterone acetate and $10^{-9}$ M estradiol $10^{-7}$ M medroxy- progesterone acetate plus $10^{-6}$ M RU486 |
| Ace and Okuliz[11] | Ovariect-omized hormone simulated rhesus monkey (~12,000) | Differential array analysis of normal proliferative, day 13 (n=3) and mid secretory days 21(n=3) and day 23 (n=3) endometrial samples |
| Talbi *et al*[12] | Normally cycling human (~55000) | Differential array analysis of samples collected during mid-late proliferative (n=5), early (n=3), mid (n=8) and late (n=6) secretory phases of cycle |
| Sherwin *et al*[13] | Adult female baboons (custom made; 8000) | Differential array analysis of LH+10 samples with either no treatment (control; n=2) or rhCG (1.25 IU/h) treatment (n=2) during days 5-10 after ovulation |
| Catalano *et al*[14] | Normally cycling human (custom made;16000) | Differential array analysis of LH+8 endometrial samples with no treatment (control; n=15) and with mifepristone (200 mg) treatment at either 6 h (n=5) or 24 h (n=4) |

**Table I.** Summary of differential expression studies in endometrial receptivity

LH, luteinizing hormone

stage baboon endometrium has been demonstrated[13]. All of the above-mentioned studies, except two[10,13] adopted an inductive approach based on genome wide expression arrays. We, on the contrary, delineated the transcripts profile during endometrial differentiation for 'receptivity' under the dual control of steroidal regulation and embryo-derived signal using a deductive approach[18]. To this effect, we have compared transcript profiles for known 409 genes between 'receptive', and mifepristone-induced desynchronized 'non-receptive' stage monkey endometrial samples from mated, potential conception cycles, using cDNA arrays containing sequence-verified clones known to be important in endometrial function[18]. In the present review, we discuss a few issues related to luteal phase progesterone action on endometrial receptivity using mifepristone as a potent antiprogestin in terms of its transcriptomic expression in fecund cycles of rhesus monkeys as a non-human primate model. The significance of transforming growth factor β-tumour necrosis factor α (TGFβ-TNFα) pathways and signal transducer and activator of transcription (STAT) signaling system under the receptivity-hostility paradigm of endometrial preparation for blastocyst implantation has been specifically addressed.

## Transcriptomics of receptive endometrium of conception cycle

A large number of gene products (31 out of 54) showed changes within five fold, while relatively less (23) number of genes showed more than five fold changes in both days 4 (10 out of 26 gene products) and 6 (13 out of 28 gene products) post-ovulation endometrium[18]. Further analysis revealed a total of 26 genes (20 increased and 6 decreased) on day four, and 28 genes (25 increased and 3 decreased) on day 6 after fertilization displayed significant differential expression in endometrium as a result of mifepristone treatment on day 2 after ovulation in proven fertile cycles[18]. The relative abundance of transcripts of nine gene products (*Jun B*, *KDR*, Leptin receptor, matrix metalloprotease 9 (*MMP 9*), ribosomal protein s7 (*Rsp7*), ribosomal protein s9 (*Rsp9*), *STAT3*, *Tastin*, TGF beta1) was higher in endometrial samples on both days 4 and 6 after ovulation following mifepristone treatment as compared to control samples and these showed progressive increase between days 4 and 6 after ovulation in mifepristone treated group. A set of another twelve gene products showed changes following mifepristone treatment only in day 4 samples; ten of these (α1-anti-trypsin, Bystin, Follistatin-like1,

3β-HSD, Integrin-α, Keratan sulphotransferase1, matrix metalloprotease 3 (*MMP3*), *STAT-PIASγ*, Tissue factor/Thromplastin and Wnt inhibitor factor were increased and two of these [erythroblastic leukemia viral oncogene B (ErB3) and Prolactin receptor]

showed decreased expression. Similarly, a different set of fourteen gene products showed changes only in day 6 samples, twelve of these (*CD44*, cyclooxygenase 1 (*COX1*), *DLX4*, E74-like factor 1 (*ELF1*), interlukin 6 (*IL6*), *JAK1*, *JUN*, *MIF*, *MMP10*, *PGFR*, Thioredoxin,

| Table II. Functional clustering of progesterone regulated genes in implantation stage endometrium | |
|---|---|
| Category of genes | Gene name (GenBank ID) |
| Homeobox genes | Distal loss homeobox 4 (NM_138281)<br>Enigma (BC067806) |
| Transcription associated genes | *c-jun* (NM_002228)<br>*Jun B*[7,8] (M29039)<br>Elongation factor 1α (AF321836)<br>Ribosomal protein S7 (BC061901)<br>Ribosomal protein S9 ((U14971)<br>*WIF*[12] (AY358344) |
| Cytokine genes | Colony stimulating factor 1 (NM_000757)<br>Interleukin 6[13] (X04602)<br>*TGF β1*[6-9,11,12] (X02812)<br>Tumour necrosis factor α (X02910) |
| Receptor genes | Kinase domain receptor (NM_002253)<br>Leptin receptor (U43168)<br>PGF receptor[7] (L24470)<br>Prolactin receptor[7,12] (S78505) |
| Signaling genes | *JAK-1*[10] (M35203)<br>*STAT3* (L29277)<br>*STAT-PIASγ* (AF077952)<br>*Ras p21* (BC007353) |
| Enzyme genes | *3β HSD* (M27137)<br>Cyclooxygenase 1 (HSU63846)<br>*ErbB3* (NM_00198)<br>17,20 desmolase (U14953)<br>Keratan sulphotransferase1 (AF19990)<br>Presenilin 1 (AF458103) |
| Adhesion genes | Bystin (L36720)<br>*CD 44* (M59040)<br>Integrin α6 ((X53586)<br>Mucin 1[12] (NM_182741)<br>Tastin (U04810) |
| Mediator genes | α1 anti-trypsin[8,9] (K01396)<br>Follistatin-like1[14] (M19481)<br>*MIFα* (NM_002415)<br>*MMP3*[8,10,11](X05232)<br>*MMP9*(J05070)<br>*MMP10*[14] (X07820)<br>Thioredoxin (J04026)<br>Tissue factor (Thromboplastin) (NM_001993)<br>Uteroferrin (M30284)<br>Uteroglobin[11] ((X59875) |

References are shown for the gene products that were identified in earlier transcriptomic studies
*Source*: Refs 6-14, 18

*TNFα,*) were increased and two (17, 20-desmolase, *MUC1*) were decreased following mifepristone treatment[18].

## New leads in transcriptomics of receptive endometrium

Table II shows the common gene products appeared to be regulated by progesterone in previous reports including our study[6-14,18]. Table II also shows a new group of 28 gene products that were affected in implantation stage endometrium following early luteal phase administration of anti-progestin mifepristone[18] and those were not reported to be affected by progesterone in earlier array-based studies using the model of comparative study between pre-receptive and receptive stage endometrium[6-14]. We have validated our cDNA array based data for nine gene products using TaqMan validation; of the nine gene products, seven (*CD 44*, *CSF-1*, *DLX4*, Enigma, *KDR*, Leptin receptor, and *MIF*) appeared to be novel candidates, while two (*MUC1* and Uteroglobin) have been reported earlier[11,12]. While previous reports indicated that *wnt*-associated pathways were involved in progesterone action on endometrial differentiation[12], changes in transcripts profiles of homeobox genes like distal less homeobox 4 *(DLX4)* and enigma, as well as, of transcription and translation related gene products like *JunB*, *c-Jun*, *Elf1*, and ribosomal proteins in implantation stage endometrium following mifepristone treatment[18] have not been reported earlier. It is assumed that endometrial receptivity in the primate is associated with categorical reprogramming in endometrial transcriptomics as observed in human endometrial fibroblasts *in vitro*[19], human placental villous cytotrophoblasts *in vitro*[20], and mouse decidual cells[21]. Thus, the elucidation of the time course pattern of endometrial receptivity associated transcriptomic networks will be beneficial to clinical sciences for improvising strategies to assist the establishment of pregnancy.

## Functional correlates

*General*: The results of our study in the rhesus monkey[18] have substantiated earlier reports indicating that endometrial cyclooxygenase, prostaglandin receptor, matrix metalloproteinases, tissue necrosis factor, prolactin receptor and mucin are regulated in mid-luteal phase endometrium by progesterone[22-33]. On the other hand, it is notable that relative abundance of transcripts for colony stimulating factor 1 (*CSF1*), interleukin 6 (*IL-6*), leptin receptor, and kinase insert domain receptor *(KDR)* were actually up-regulated in response to mifepristone treatment,

contrary to the expected changes based on earlier reports[34-40]. Collectively, the Enrichment Analysis by Process Maps and Process Networks using Metacore platform (GeneGo, St. Joseph, MI, USA) revealed that the group of 40 genes showing differential expression in endometrium regulated by progesterone action computed upon cell cycle, differentiation and development, immune response and inflammation. Of the all the 40 genes that showed differential expression on inhibition of progesterone action in implantation stage endometrium, two gene products, namely *TGFβ1* and *STAT3*, appear intriguing for disparate reasons as discussed below.

*TGFβ*: Transforming growth factor beta (TGFβ) has reportedly been observed in a good number of genome-wide expression array studies[6-8, 11,12] to be involved in the process of luteal phase endometrial differentiation under progesterone dominance. *TGFβ* denotes a family of structurally related, dimeric protein that controls proliferation, apoptosis, cellular differentiation, angiogenesis, tissue remodelling and repair, immune responses and other functions depending on cell types, physiological states and its concentration and availability of its receptors[41,42]. Our observation of increased *TGFβ1* expression along with higher expression *MMPs* and *TNF* in mifepristone treated endometrium corroborates well with the earlier reports that *(i)* progesterone mediates a balance of *MMPs* and *TNF* in endometrium involving paracrine action of *TGFβ*[43-45] and thus it plays an important role in the process of endometrial receptivity and blastocyst implantation[46,47], and *(ii)* a very high level of *TGFβ* may suppress progestational maturation of endometrium[48-50]. Furthermore, we have observed that the protein expression for these mediators was higher in anti-progestin (mifepristone) treated monkey endometrium as compared to control endometrium. Thus, it appears that higher expression of *TNFα* and *TGFβ* may mediate endometrial hostility in mifepristone treated fecund cycle through a putative model function as shown in the Figure.

*STAT3 signaling*: STAT3 activation in endometrium was reportedly associated with endometrial receptivity to implantation in rodents[51-53]. Furthermore, Janus Kinase 1 (*JAK1*) at the transcript level in human luteal phase endometrial explant cultures following mifepristone administration was reduced and immunopositve protein levels of *JAK1* was higher in stroma and luminal epithelium of luteal phase endometrium as compared to other stages of menstrual cycle[10]. Thus, the observed relative higher abundance of transcripts
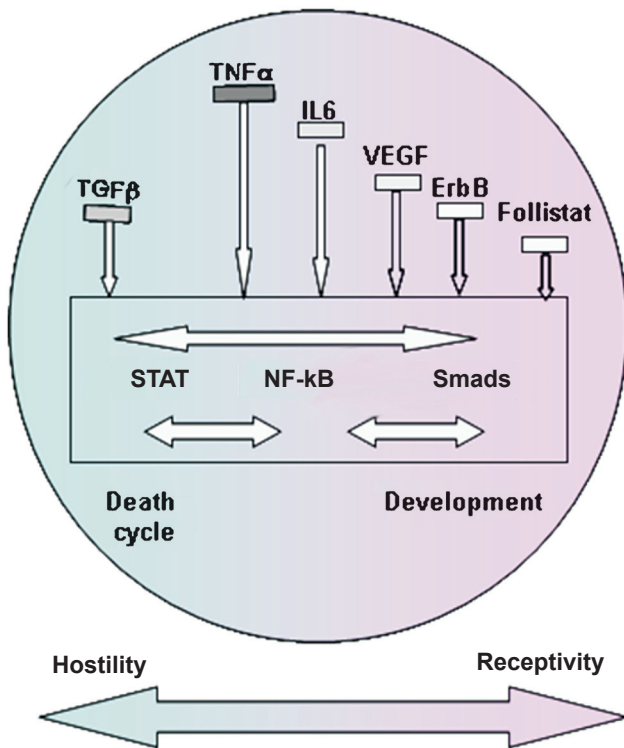
**Fig.** A putative model based on enriched pathways analysis of transcriptomic profiles highlighting the basic seed genes operative in the progesterone-dominant implantation stage endometrium regulating endometrial receptivity (development) and hostility (death cycle). ErbB, erythroblastic leukemia viral oncogene B; Follistat, follistatin; IL6, interleukin 6; NF-kB, nuclear factor kappa-light chain enhancer of activated B cells; Smads, homologs of both the *Drosophilla* protein, MAD and the *C. elegans* protein SMA; STAT, signal transducer and activator of transcription; TGFβ, transforming growth factor beta; TNFα, tumour necrosis factor alpha; VEFG, vascular endothelial growth factor.

for *JAK1* and *STAT3* in anti-progestin (mifepristone) treated endometrium in our study[18] appears counter-intuitive. To further examine this issue, we investigated immunohistochemically the protein products expression of activated *STAT3* in endometrial samples collected on days 4 and 6 after fertilization with and without mifepristone treatment. The immunopositive signals for *JAK1* and phosphorylated STAT 3 (*pSTAT3*) were consistently and markedly higher in epithelial compartment and were depressed in stromal and vascular compartments on days 4 and 6 after ovulation, while mifepristone treatment resulted in higher pSTAT3 in the vascular compartment[18]. Although the mechanism and function of increased expression of pSTAT3 in vascular compartment following mifepristone treatment are unclear, it is likely that inflammatory changes are triggered in luteal phase endometrium

by mifepristone induced vasocentric *JAK1-STAT3* pathway[54,55], thereby rendering endometrial hostility to blastocyst implantation. This observation corroborated well with earlier observation that early luteal phase administration of mifepristone resulted in significant changes in mid-lueal phase endometrial vascular physiology associated with phenotypic hostility of endometrium towards blastocyst implantation[56].

In conclusion, we propose that TGFβ-TNFα pathways and STAT signaling system are important effectors in mediating the combinatorial regulation of luteal phase progesterone action on endometrial receptivity in fecund cycle.

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