

Review



Cite this article: Siriwardena D, Boroviak TE.

2022 Evolutionary divergence of embryo implantation in primates. *Phil. Trans. R. Soc. B* **377**: 20210256.

<https://doi.org/10.1098/rstb.2021.0256>

Received: 4 April 2022

Accepted: 8 August 2022

One contribution of 18 to a theme issue 'Extraembryonic tissues: exploring concepts, definitions and functions across the animal kingdom'.

Subject Areas:

developmental biology

Keywords:

primate, embryo implantation, human development, trophoblast, primate embryo

Authors for correspondence:

Dylan Siriwardena

e-mail: dks30@cam.ac.uk

Thorsten E. Boroviak

e-mail: teb45@cam.ac.uk

Evolutionary divergence of embryo implantation in primates

Dylan Siriwardena^{1,2,3} and Thorsten E. Boroviak^{1,2,3}

¹Department of Physiology, Development and Neuroscience, ²Centre for Trophoblast Research, University of Cambridge, Downing Site, Cambridge CB2 3EG, UK

³Wellcome Trust – Medical Research Council Stem Cell Institute, University of Cambridge, Jeffrey Cheah Biomedical Centre, Puddicombe Way, Cambridge CB2 0AW, UK

TEB, 0000-0001-8703-8949

Implantation of the conceptus into the uterus is absolutely essential for successful embryo development. In humans, our understanding of this process has remained rudimentary owing to the inaccessibility of early implantation stages. Non-human primates recapitulate many aspects of human embryo development and provide crucial insights into trophoblast development, uterine receptivity and embryo invasion. Moreover, primate species exhibit a variety of implantation strategies and differ in embryo invasion depths. This review examines conservation and divergence of the key processes required for embryo implantation in different primates and in comparison with the canonical rodent model. We discuss trophoblast compartmentalization, endometrial remodelling and embryo adhesion and invasion. Finally, we propose that studying the mechanism controlling invasion depth between different primate species may provide new insights and treatment strategies for placental disorders in humans.

This article is part of the theme issue 'Extraembryonic tissues: exploring concepts, definitions and functions across the animal kingdom'.

1. Introduction

Embryo implantation defects are a major cause of pregnancy failure in humans [1,2]. Implantation is mediated by trophoblast, the outer layer of the preimplantation embryo, which subsequently differentiates to form the fetal portion of the placenta. Errors in trophoblast development and invasion have been linked to numerous pregnancy complications, including miscarriage, pre-term labour, pre-eclampsia and placenta accreta spectrum disorders [3–5]. Complications can also persist after birth, with neurological or growth syndromes originating from defective placental development [6–8].

Human embryo implantation has remained elusive owing to the inaccessibility of early implantation stages. Most of our anatomical knowledge about this process has been sourced from classic histological sections of the Boyd and Carnegie collections [9,10] in tandem with preimplantation and, more recently, postimplantation *in vitro* embryo culture. However, preimplantation studies miss the crucial initial attachment of the embryo and *in vitro* postimplantation cultures lack the complex three-dimensional multicellular environment of the uterus. Therefore, our current understanding of early primate embryo implantation is largely derived from model organisms such as rodents (mouse and rat), New World monkeys (common marmoset (*Callithrix jacchus*)), Old World monkeys (rhesus macaque (*Macaca mulatta*), cynomolgus macaque (*Macaca fascicularis*) and baboon (*Papio* sp.)), lesser apes (agile gibbon (*Hylobates agilis*)) and great apes (chimpanzee (*Pan troglodytes*)).

Key transcriptional regulators of human trophoblast specification and development were first identified in mouse, including *Cdx2*, *Tead4* and *Gcm1* [11–16]. In both mice and humans, trophoblast formation and uterine receptivity regulate implantation via cyclic hormones and embryo–maternal

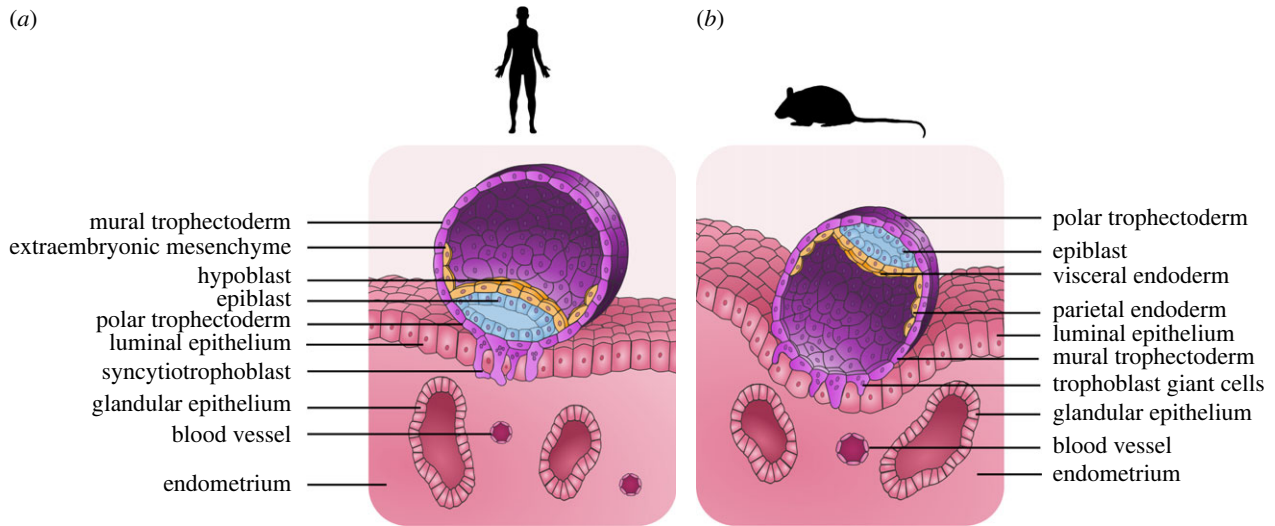


Figure 1. Early blastocyst adhesion and invasion in primate and mouse. Diagram depicting the different cell types during blastocyst implantation in human and mouse. (a) Polar trophoctoderm in human differentiates into syncytiotrophoblast, which invades into the luminal epithelium. (b) Mural trophoctoderm in mouse differentiates into trophoblast giant cells.

crosstalk [17–22]. However, primate implantation differs from rodent with regard to embryo orientation, the cell types mediating implantation, and the lineage potential of early trophoblast cells. Mouse blastocysts implant with the mural side of the embryo (the trophoctoderm compartment away from the inner cell mass (ICM)) and generate invasive multinucleated trophoblast giant cells [23] (figure 1). The polar side of the embryo (the trophoctoderm adjacent to the ICM) remains proliferative and forms extraembryonic ectoderm that expands and differentiates into the labyrinthine structure of the mouse placenta. By contrast, primate embryos first attach with the polar side, wherein polar trophoctoderm differentiates into multinucleated primary syncytiotrophoblast and proliferative cytotrophoblast. The invasive primary syncytiotrophoblast penetrates the basal lamina of the luminal epithelium and is essential for the formation of fluid-filled lacunae to facilitate histotrophic nutrition of the embryo [24–26].

In this review, we systematically compare trophoblast development and the early stages of embryo implantation in human and non-human primates. We discuss the steps leading up to implantation in both, the embryo and the uterus, the interactions between the conceptus and maternal tissues, as well as the initial stages of embryo attachment. Finally, we highlight how the evolutionary divergence between individual primate species can provide an avenue to elucidate trophoblast invasion, which will further our understanding of the pathophysiology of implantation and related pregnancy disorders.

2. Primates exhibit a wide range of implantation and placentation strategies

There is considerable variation in implantation type, invasion depth, maternal remodelling, and placentation between primates (table 1) [27]. Implantation type refers to the location of the embryo with regard to the uterine lining, and can be categorized as superficial, eccentric or interstitial (figure 2). In superficial implantation, the embryo remains within the uterine cavity (lemur, marmoset, baboon, rhesus macaque) and is often associated with shallow trophoblast invasion

[27]. With eccentric implantation (mouse, rat) the embryo partially embeds into the uterine tissues, leaving portions of the conceptus exposed to the uterine cavity. Interstitial implantation entails the embryo penetrating deep into the uterus and becoming fully engulfed in the endometrial tissue (lesser apes, great apes). Interestingly, interstitial implantation can be found in a variety of species, including guinea pigs, bats and humans. Owing to their large phylogenetic differences, it is likely the evolution of interstitial implantation evolved independently in these organisms [28].

Equally, the shape and organization of the placenta can vary considerably between primate species. Lemurs and lorises (*Strepsirhini*) develop a diffuse placenta that covers the entire surface of the uterine luminal epithelium and is invaginated with villi [29,30]. By contrast, ‘dry-nosed’ primates (*Haplorhini*) have a discoid placenta covering a smaller circular area [30]. Many New World and Old World monkeys form a bidiscoid structure with two circular placentae on opposing ends of the uterine cavity [27]. Lesser and great apes develop a single discoid placenta. Most primates give rise to villous placentae, wherein the functional units are chorionic villi, which are often organized into tree-shaped structures [30–32].

Further variation can be found in the number of tissue layers between the fetal and maternal circulation, which often correlates with invasion depth. Several species of lemur exhibit extremely shallow invasion and thus employ epitheliochorial or endotheliochorial placentation (table 1) [27]. In epitheliochorial placentation, the luminal epithelium is maintained throughout gestation [33]. Endotheliochorial placentation invades more deeply, breaching the luminal epithelium but retaining the maternal endothelial cells surrounding blood vessels [34,35]. Most primates, including New World, Old World and apes, invade even more deeply and undergo haemochorial placentation (humans, marmosets, rhesus macaques, baboons) [35–38]. Haemochorial placentation breaches both the luminal epithelium and endothelial cells, enabling fetal tissues to come into direct contact with maternal blood [35–38].

Studying the morphological, physiological and molecular features of placentation in different primate species can help

Table 1. Summary of implantation strategies in primates. Mens.: menstruation, Decid.: decidualization, BM: luminal basement membrane.

Common name	Sub-order, Family	Species	Primate group	Implantation and Placentation type	Interhaemal membrane	Pattern	Mens.	Decid.
slender loris	Strepsirrhini, Lorisidae	<i>Loris tardigradus</i>	lemurs and lorises, Strepsirrhini	superficial, diffuse	epitheliochorial, no BM breach	villous	N	at implantation
mouse lemur	Strepsirrhini, Cheirogaleidae	<i>Microcebus murinus</i>	lemurs and lorises, Strepsirrhini	superficial, diffuse and discoid	epitheliochorial and endotheliochorial, no BM breach	villous	N	at implantation
common marmoset	Haplorhini, Callitrichidae	<i>Callithrix jacchus</i>	New World monkeys, Ceboidea	superficial, bidiscoid	haemochorial, BM breach	villous	N	at implantation
rhesus macaque	Haplorhini, Cercopithecoidea	<i>Macaca mulatta</i>	Old World monkeys, Cercopithecoidea	superficial, bidiscoid	haemochorial, BM breach	villous	Y	at implantation
cynomolgus macaque	Haplorhini, Cercopithecoidea	<i>Macaca fascicularis</i>	Old World monkeys, Cercopithecoidea	superficial, bidiscoid	haemochorial, BM breach	villous	Y	at implantation
baboon	Haplorhini, Cercopithecoidea	<i>Papio</i> sp.	Old World monkeys, Cercopithecoidea	superficial, discoid	haemochorial, BM breach	villous	Y	at implantation
western gorilla	Haplorhini, Hominoidea	<i>Gorilla gorilla</i>	great apes, Hominoidea	interstitial, discoid	haemochorial, BM breach	villous	Y	pre-decidualization, small amount
chimpanzee	Haplorhini, Hominoidea	<i>Pan troglodytes</i>	great apes, Hominoidea	interstitial, discoid	haemochorial, BM breach	villous	Y	pre-decidualization
human	Haplorhini, Hominoidea	<i>Homo sapiens</i>	great apes, Hominoidea	interstitial, discoid	haemochorial, BM breach	villous	Y	pre-decidualization

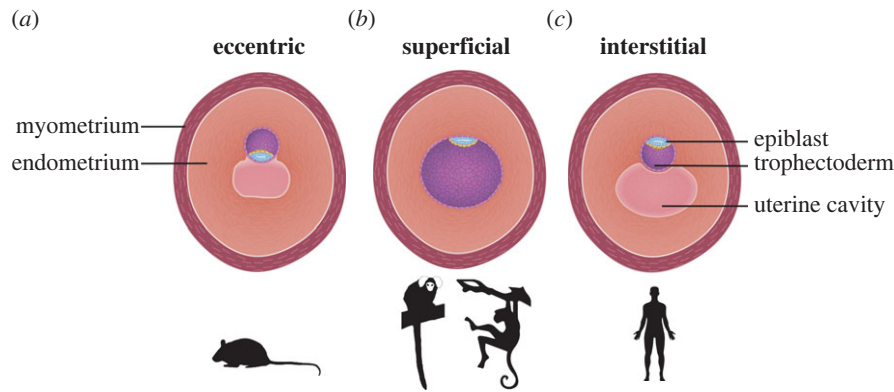


Figure 2. Types of implantation. Types of implantation strategies employed by mouse, marmoset, rhesus macaque and human. (a) Eccentric implantation: mouse. (b) Superficial implantation: marmoset, rhesus macaque, baboon and cynomolgus macaque. (c) Interstitial implantation: chimpanzee and human.

us to identify conserved processes applicable to all primates. Conversely, the differences in implantation and placentation might be used to dissect human-specific processes. Knowing the mechanisms controlling trophoblast invasion depth in primates of different implantation modes may inform new treatments for placental disorders resulting from either too shallow (pre-eclampsia) or too deep (placenta accrete spectrum) trophoblast invasion.

3. Trophoderm compartmentalization prepares the embryo for implantation

In primates, trophoblast is specified in the first lineage decision at the 16–32 cell stage. Inhibition of Hippo signalling in the outer blastomeres induces trophoderm specification, while the inner blastomeres are directed toward an ICM fate [12,39]. Trophoderm cells proliferate and cavitate to form the blastocyst. Subsequently, the trophoderm compartmentalizes into the polar trophoderm, adjacent to the ICM, and mural trophoderm on the opposite side, encompassing the blastocoel. At embryonic days 6–7, the human blastocyst hatches from the zona pellucida, and within the next 3–5 days implants into the luminal epithelium. Trophoderm mediates implantation in four stages: (i) trophoderm–uterine crosstalk, (ii) apposition, (iii) adhesion and (iv) primary invasion. The initial contact between the trophoderm and the luminal epithelium is established by signalling crosstalk. During apposition, the implantation site and embryo orientation are decided via loose connections between the trophoderm and the luminal epithelium. Adhesion occurs as the initial connections become tighter, enabling invasive trophoblast subtypes to push past the luminal epithelium and establish access to maternal histotrophic nutrition [25,26,40].

Trophoderm compartmentalization into polar and mural trophoderm is essential for proper implantation [41]. In mice, polar trophoderm is enriched for *Cdx2* and *Esrrb*, while transcripts for *Ascl2*, *Ndr1*, *Krt18*, *Tfap2c* localize towards the mural side [13,42,43]. Human blastocysts exhibit regionalized expression of FGFR1 and CCR7 in the polar trophoderm [44,45], and single-cell transcriptome profiling revealed co-expression of *GATA2*, *GATA3*, *CDX2* and *KRT18* in a subcluster of trophoderm [11,44]. Trophoderm subpopulations with increased levels of *CDX2* have also been observed in cynomolgus macaques and marmosets [46–48]; however, in the absence of spatial information, it is unclear

whether these cells truly represent polar trophoderm. A recent study revealed enrichment of *NR2F2* in polar trophoderm of human blastocysts [49], but *NR2F2* expression spread throughout the entire trophoderm within 2 days [49]. It is currently unclear whether this spread is specific to *NR2F2* alone, if polar trophoderm cells proliferate into the mural compartment, or if the polar phenotype is adopted by the entire trophoderm as it matures. Notably, in rhesus macaques and marmosets, the mural trophoderm implants at the opposite side of the uterine cavity (bidiscoid) after the initial polar implantation [38,46,50]. This mode of implantation would be in line with the hypothesis that the mural trophoderm gradually adopts a polar trophoderm phenotype in the implanting blastocyst.

Human and non-human primate embryo implantation is initiated at the polar end, as opposed to mouse, which implants at the mural side (figure 1). Microvilli, which appear at the late blastocyst stage, mediate the initial interactions between polar trophoderm and the luminal epithelium. [24,38]. In both rodents and primates, implanting trophoderm differentiates to form invasive cells that attach and penetrate the luminal epithelium (figure 1). In mouse, the mural trophoderm differentiates into multinucleated giant cells. In primates, the polar trophoderm gives rise to multinucleated cells during primary syncytiotrophoblast formation [51]. This is facilitated by the human luminal epithelium, which becomes more apoptotic [52] and secretes factors to promote primary syncytiotrophoblast in both mural and polar trophoderm [53].

Primary syncytiotrophoblast breaches the basal lamina of the luminal epithelium and invades the uterine lining, thus ensuring strong attachment to maternal tissues. It is important to note that primary syncytiotrophoblast differs from the secondary syncytiotrophoblast that covers the surface of villi in the human placenta, which can erode surrounding tissue but has little invasive character. While the exact timing of primary syncytium formation remains unclear, we know that primary syncytiotrophoblast forms in human embryo postimplantation *in vitro* cultures in the absence of maternal tissues [54–56]. In line with this observation, rhesus macaque and baboon-hatched blastocysts also establish binucleated cells, which are localized within the polar trophoderm [38,57]. Preimplantation trophoderm expresses fusion proteins, including *ERVV2*, which may poise trophoderm for primary syncytiotrophoblast differentiation even before embryo adhesion [55,56,58]. Further studies will be required to

determine how embryo adhesion controls and promotes primary syncytialization.

4. Maternal remodelling regulates uterine receptivity

The preparations for successful embryo implantation begin long before fertilization. Cycles of pituitary and ovarian hormones regulate periodic changes in uterine receptivity and therefore the 'window of implantation'.

The follicular, or proliferative, phase of the oestrus cycle promotes proliferation of uterine endometrium via high oestrogen and follicle-stimulating hormone levels [59–62]. During this phase, stromal cells proliferate and differentiate to expand the uterine lining [63]. This is followed by the luteal, or secretory, phase, where higher progesterone levels sustain the uterine endometrium for embryo implantation [59,61]. As progesterone levels decline, the uterine lining is either reabsorbed in rodents, strepsirrhines and some New World monkeys, including the marmoset, or shed in menstruation in humans, greater and lesser apes, Old World monkeys and some New World monkeys, including the tufted capuchin [64,65]. The importance of progesterone signalling is underlined by the fact that progesterone inhibitors effectively prevent embryo implantation in rodents and primates [19,66–68].

Progesterone induces decidualization of stromal cells in the endometrium. Decidualization refers to the transformation of stromal cells into larger, polyhedral decidual cells [69–72]. In chimpanzees, gorillas and humans, decidualization occurs before implantation [73], which has been linked to the evolution of interstitial implantation. In other primates, decidualization only occurs after implantation. Consequently, evolutionary analysis of decidualization prior to implantation represents an avenue to understand the requirements for human implantation [64].

In all primates, decidualization is sustained after embryo implantation and during trophoblast invasion [72,74–77]. Primary syncytiotrophoblast secretes chorionic gonadotropin (CG), which preserves the corpus luteum. This is of pivotal importance to sustaining high progesterone levels, which in turn prevents menstruation and loss of the implanted embryo [78]. The luminal epithelium further supports implantation by absorbing intrauterine fluid, thus promoting the narrowing of the uterine cavity [52,79]. Intrauterine volume is used as a contraindication of fertility in IVF procedures in humans [79].

Immune cells equally play a profound role in regulating uterine receptivity, decidualization and invasion. During the secretory phase, natural killer (NK) cells, dendritic cells, lymphocytes and macrophages are recruited to the uterine lining [71,72]. NK cells and macrophages are enriched at the implantation site in rhesus macaques [80], and decreases in NK cells at implantation sites have been associated with miscarriage in baboon [81]. In humans, reduced NK cell numbers and activity equally correlate with implantation failure [82,83]. The evolution of implantation has been linked to the development of anti-inflammatory mechanisms and decidualization [84,85], emphasizing the importance of studying the immune response and decidualization in non-human primates.

In most Old World and New World monkeys, including rhesus macaques, baboons and marmosets, the luminal and

glandular epithelia remodel to form large, glycogen-rich cells termed epithelial plaques [38,50,76]. Epithelial plaque formation radiates out from the implantation site and increases during the first 10 days of pregnancy [38,46,86]. In marmosets, the entire luminal epithelium remodels into epithelial plaques, including regions in the periphery of the embryonic compartment itself [46]. It has been suggested that epithelial plaques are similar to decidualized cells, but the precise role of epithelial plaques in uterine receptivity and implantation remains elusive.

5. Embryo–maternal crosstalk prior to embryo implantation

The trophoblast and luminal epithelium secrete a wide array of ligands preceding embryo implantation to adjust the outer layer of the blastocyst for adhesion and invasion (figure 3) [87–90]. Concomitantly, embryo secretions promote uterine receptivity and decidualization [91–93].

Heparin-binding EGF-like growth factor (HBEGF) is a member of the EGF protein family and binds several receptors including EGFR, ERBB2 and ERBB4 [94]. HBEGF is secreted by human endometrial epithelia and maximally expressed in the luteal (or secretory) phase of the oestrus cycle [95]. HBEGF binds to ERBB4, which is expressed in human trophoblast [95] and improves blastocyst development *in vitro* [96]. Human blastocyst culture experiments with HBEGF-coated slides showed increased adhesion of the embryos to the surface [97]. Moreover, EGFR and ERBB4 binding promotes syncytiotrophoblast formation [87–89]. In rhesus macaque, trophoblast motility and proliferation was increased in EGF-treated *in vitro* cultured embryos [88]. Collectively, this suggests that HBEGF signalling plays an important role in trophoblast development and priming the embryo for attachment and invasion.

Leukaemia inhibitory factor (LIF) is a cytokine from the interleukin (IL)6 family and an essential regulator of the early embryo and pluripotent stem cells [42,98–100]. LIF is essential for the establishment of a successful pregnancy in humans and rhesus macaques [101–103]. During implantation, LIF reinforces its own expression by upregulating other inflammatory agonists such as IL1, IL6 and TNF α in the endometrium [69,91,104]. Inflammatory cytokines, including IL1, induce CG expression in the human embryo [105] and integrin β 3 expression in endometrium [106]. Human CG both activates and inhibits LIF, through IL1 and IL6, respectively [92], suggesting dynamic regulation of LIF signalling via trophoblast–uterine crosstalk during implantation.

The human embryo resides in the uterine cavity for approximately 72 h prior to implantation [107]. It is tempting to speculate that mechanisms exist to prevent premature implantation. Mucins coat the apical surface of the luminal epithelium and have been suggested to inhibit implantation in both rodents and primates [108–112]. Mucins are large glycoproteins in mucosal barriers that are capable of steric receptor inhibition between the embryo and maternal tissues [113,114]. In mouse, Muc1 is globally reduced during the luteal phase [115]. Both, Muc1 knockout and the enzymatic removal of Muc1 increase embryo receptivity [110]. Primate MUC1 is upregulated in the luminal epithelium of the baboon and human uterus during the early luteal phase [116–118]. In the tufted capuchin, MUC1 coats the oviduct

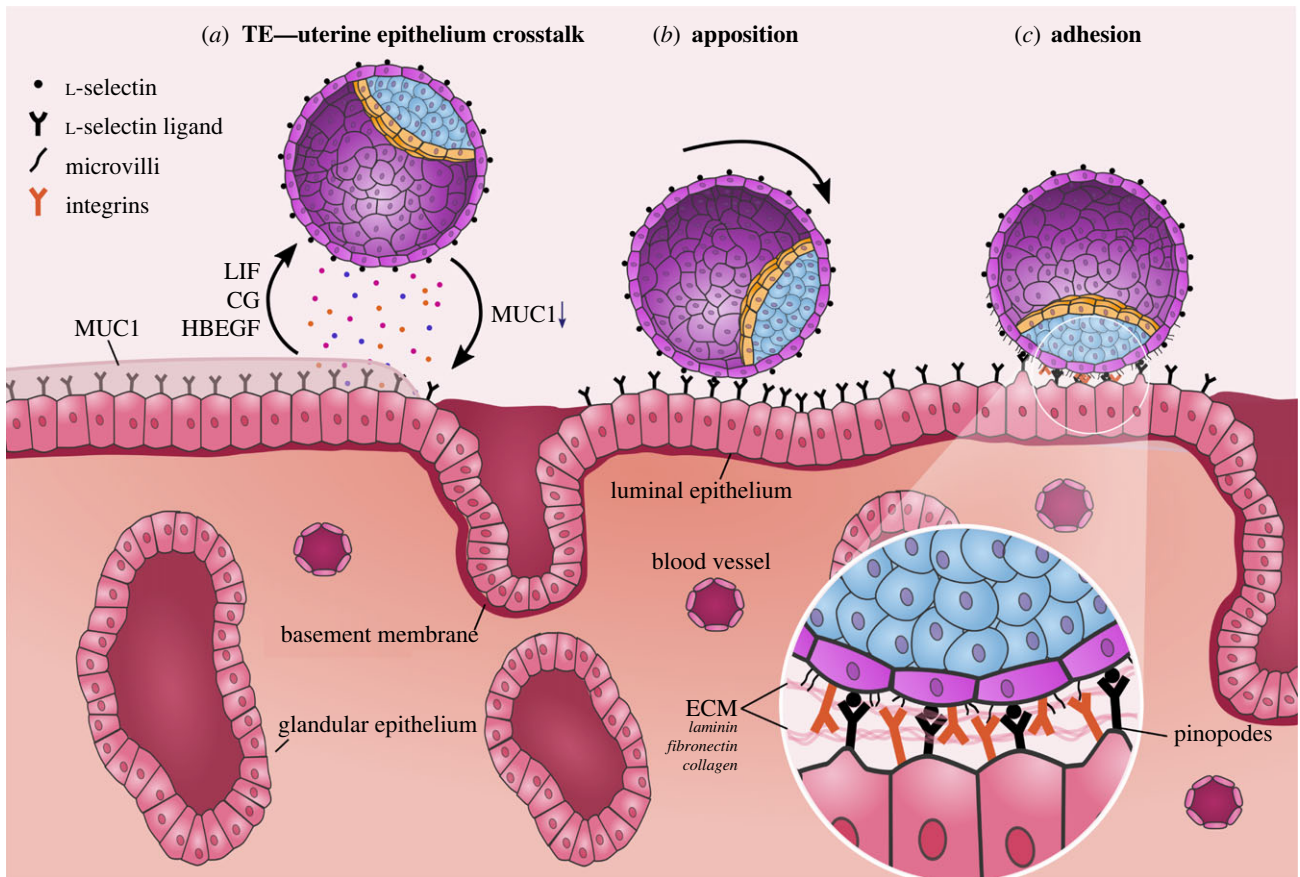


Figure 3. Apposition and adhesion of blastocyst to luminal epithelium. (a) Secreted ligands signal between the trophectoderm (TE) and luminal epithelium, down-regulating MUC1 in the luminal epithelium and exposing uterine ECM and adhesion proteins. (b) Transient interactions between L-selectin and L-selectin ligands slow embryo rolling and establishes initial adhesion. (c) Integrins on the TE and luminal epithelium bind to apically secreted ECM from both cell types.

but is reduced in the luminal epithelium, potentially indicating a role in preventing ectopic pregnancy [109]. Both rhesus macaque and baboons lose MUC1 in the entire luminal epithelium prior to trophoblast attachment [119]. Interestingly, the embryo itself seems to regulate the luminal epithelium in human, as blastocyst implantation assays *in vitro* showed local reduction of MUC1 in endometrial cultures around the embryo [118]. Nevertheless, future studies are required to functionally interrogate whether the luminal epithelium influences, or even determines, the prospective implantation site.

6. Transient interactions orient the embryo during apposition

Apposition refers to the initial interactions between the embryo and the endometrial lining of the uterus. In this process, transient connections between the trophectoderm and the luminal epithelium establish the final orientation of the implanting embryo (figure 3). In mouse, the first interactions occur between the mural side of elongated E4.5 embryos and both sides of the uterine cavity, essentially enclosing the embryo in an upright position [23]. It is postulated that the flattened mural trophectoderm becomes more adhesive and attaches to the luminal epithelium, which then bulges around the elongated E4.5 embryo to orient the embryo correctly [23]. However, in primates, the blastocyst does not undergo asymmetrical elongation, nor does the trophectoderm contact both uterine cavity walls simultaneously. Electron microscopy in rhesus macaque revealed interactions outside the polar trophectoderm that result in polar

orientation, with the ICM toward the endometrium [38]. This raises the question of how primate blastocysts orient correctly for implantation.

L-selectin (*SELL*) is a type-I transmembrane glycoprotein with well-established roles in circulating leucocytes [120]. L-selectin binds to a variety of ligands broadly grouped as sialylated and fucosylated carbohydrate molecules, which can be found on mucin-like glycoprotein membrane receptors [121]. Mouse *SELL* knockout embryos still implant, suggesting that these interactions are not essential for embryo adhesion [122]. In humans, L-selectin is expressed on trophoblast [123], while L-selectin ligands are expressed on the luminal epithelium during the luteal phase [124]. Interestingly, in leucocytes and neutrophils, L-selectin aids in their 'rolling action' in blood vessels [120,125], which bears resemblance to the rolling embryo [124,126]. This may suggest that selectins promote transient interactions to slow the embryo, allowing other embryo–uterine interactions to occur within the local area (figure 3).

Trophinin (*TRO*) is an apical membrane protein that has been implicated in mediating implantation [127–130]. In humans, trophinin is expressed by both maternal and trophoblast cells at the implantation site in normal and ectopic pregnancies [130–133]. Trophinin-binding induces EGF signalling in human trophoblast stem cells, which promotes syncytiotrophoblast formation [88]. The embryonic pole of the blastocyst is enriched for trophinin in the rhesus macaque [134], and *TRO* is lowly expressed in marmoset trophectoderm [46]. Therefore, trophinin-binding may assist in embryo orientation toward the polar trophectoderm by inducing the formation of invasive primary syncytium.

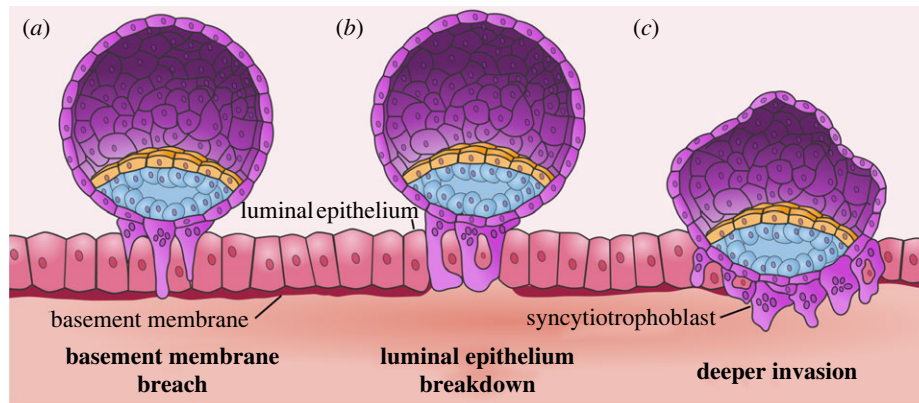


Figure 4. Initial invasion of luminal epithelium. Invasion of multinucleated syncytiotrophoblast past the luminal epithelium. (a) Syncytiotrophoblast projections push between uterine epithelia and breach the basement membrane. (b) Syncytiotrophoblast envelops the uterine epithelia. (c) Luminal epithelium is degraded as deeper invasion occurs.

7. Integrin-binding mediates stable adhesion

After apposition, stronger adhesions between the polar trophoderm and the luminal epithelium are established via integrin binding [135–137] (figure 3). Integrins are transmembrane receptors composed of α and β subunits that mediate cell–extracellular matrix (ECM) adhesion [138,139]. In mouse, human and baboon, α and β integrins are upregulated in both the luminal epithelium and TE during the luteal phase [137,140–144]. Integrin $\alpha 5\beta 3$, $\alpha 3\beta 3$, $\alpha 4\beta 6$ and $\alpha v\beta 5$ are expressed in the human luminal epithelium and have been suggested to play a role in blastocyst attachment [18,135,144–150]. Integrins bind a variety of ECM components, including fibronectin, vitronectin, laminin and collagen IV [151–153]. Laminin and collagen IV expression is increased at the implantation site and throughout the endometrium [144], while apical fibronectin increases in human and mouse blastocysts [154,155]. At implantation, both integrins of the implanting trophoderm and integrins of maternal luminal epithelium attach to apically presented ECM molecules. After attachment, integrin-binding remains important and promotes trophoblast invasion past the luminal epithelium in multiple species, including mouse, rhesus macaque, marmoset and human [139,150,156–158]. Collectively, the transient surface protein binding during apposition [159] is followed by more stable interactions via integrins on the polar trophoderm and luminal epithelium, both of which bind to apical ECM.

8. Primary syncytium breaks through the uterine lining

The initial embryo invasion process in primates consists of three main steps: (i) penetration of syncytium between luminal epithelium, (ii) breach of the uterine basal lamina, and (iii) breakdown of uterine epithelial cells (figure 4). Histological sections from implanting embryos in rhesus macaque, marmoset and baboon reveal multinucleated cells penetrating the luminal epithelium [38,57,76]. Cytoplasmic protrusions push between and surrounding epithelial cells during early implantation in rhesus macaque and baboon [37,38,57,76]. After projecting between the luminal epithelium, syncytiotrophoblast begins to break down the uterine basal lamina. Marmoset and rhesus macaque syncytium expresses matrix

metalloproteinases (MMPs), which aid in breaking down the basal lamina [46,160,161]. Syncytium projections in lemurs breach the basal lamina but do not envelop the luminal epithelium (figure 4) [37]. Consequently, the epitheliochorial mode of placentation found in lemurs provides an opportunity to identify specific regulators of luminal epithelium breaching. By contrast, during marmoset, rhesus macaque, and baboon embryo implantation, the luminal epithelium at the implantation site is broken down by a multinucleated syncytium that completely surrounds luminal epithelial cells and destroys them (figure 4). Interestingly, in sheep, binucleated cells invade and incorporate engulfed maternal epithelial cells [162,163]. It remains unclear whether similar luminal epithelium–syncytium fusions occur in primates [164] or if the maternal nuclei are broken down [165]. In mouse, the entire luminal epithelium undergoes apoptosis after implantation, including regions away from the implantation site [166,167]. By contrast to mouse, primates sustain a distinct layer of cells lining the uterine cavity [38,50,57].

Ultimately, the embryo is surrounded by maternal tissues. Human and chimpanzee embryos quickly become surrounded by the decidualized endometrium, almost appearing to move into the endometrium [10,168]. Human stromal cells migrate in response to trophoblast cells [169]. This suggests the intriguing possibility that the embryo is encapsulated by migratory stromal cells, rather than actively burrowing into the maternal tissues [170].

9. Differences in implantation and invasion depth between primate species as a platform to study trophoblast invasion

Primate species display considerable variation in embryo implantation and invasion depth (figure 5). In New World and Old World monkeys, which undergo superficial implantation, trophoblast invades to a lesser extent into the endometrium than in great apes, where the embryo implants interstitially [37]. Even among superficially implanting primates, the trophoblast invades to a variable degree. In marmoset, the trophoblast remains close to the uterine basal membrane and forms a thin layer of syncytiotrophoblast [24,46,50]. By contrast, primary syncytium invades substantially deeper into the maternal tissues in rhesus macaque and baboon [38,57,76].

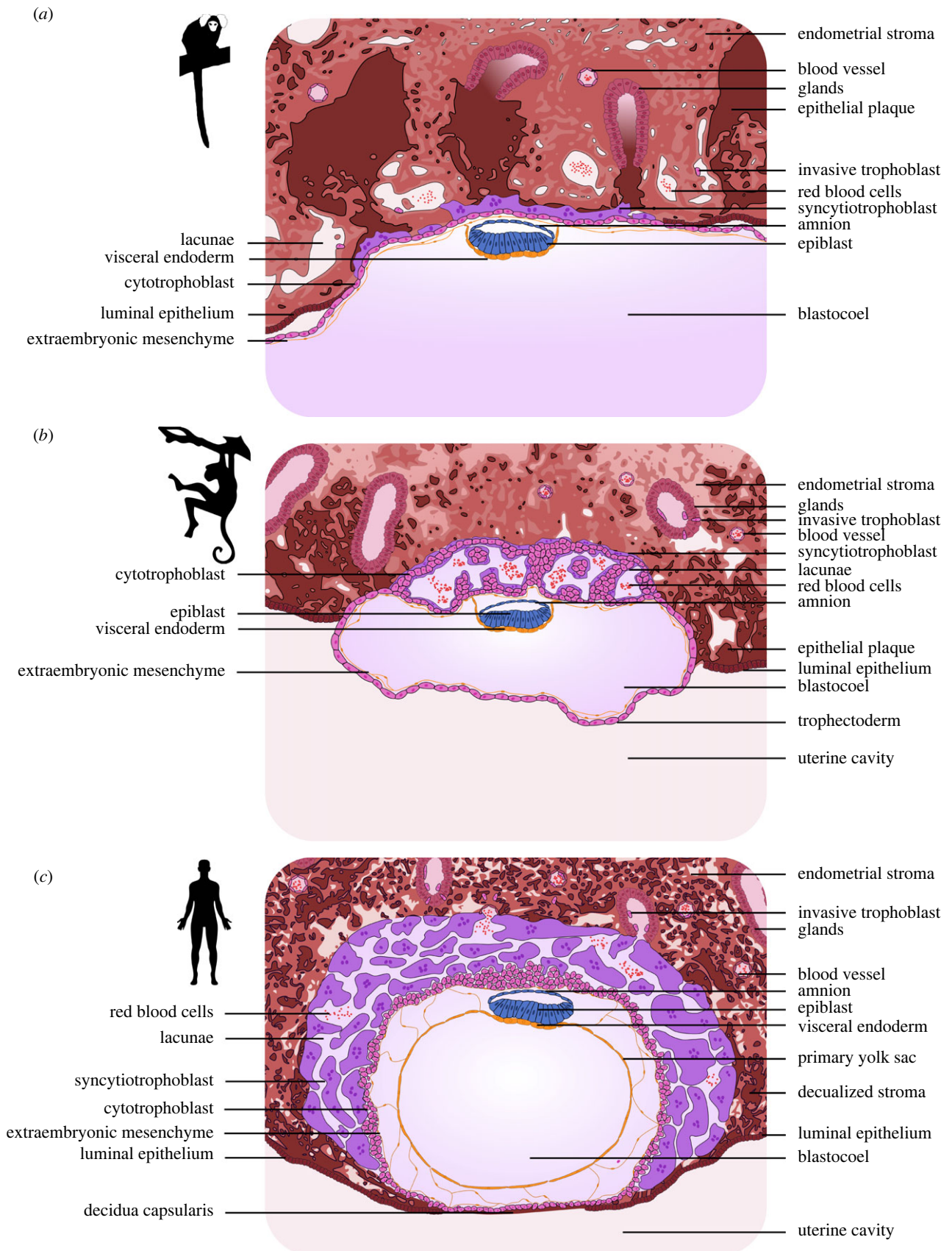


Figure 5. Implantation depth in primates at lacunar stage. Lacunar stage in (a) New World monkeys (marmoset), (b) Old World monkeys (rhesus macaque and baboon) and (c) great apes (human).

Cross-species analysis of trophoblasts from species with varying invasion depths could reveal important regulators of invasion. Indeed, there is significant overlap in placental genes associated with superficial implantation and placental disorders characterized by too shallow trophoblast invasion,

such as pre-eclampsia. Candidate regulators for increased invasion depth and pre-eclamptic placentae included *VGLL1*, *FLT1*, *CD97* and *EGLN3* [171]. *VGLL1* is expressed in human cytotrophoblast as well as invasive extravillous trophoblast [172], and *FLT1* is a *VEGF* receptor that promotes

extravillous trophoblast motility [173–175]. Thus, comparing the mechanisms of superficial implantation and invasion in postimplantation *in vivo* samples will provide promising candidates for functional studies to illuminate the pathophysiology of pre-eclampsia in the future.

Extravillous trophoblast is specified from cytotrophoblast shortly after embryo implantation and consists of highly migratory cells that rapidly invade the endometrium. Extravillous trophoblast cells play an important role in immune regulation, promote decidualization and modulate the maternal vasculature during early pregnancy [176,177]. In particular, extravillous trophoblast remodels the spiral arteries to protect early placental structures from high-pressure blood and to ensure proper perfusion of the developing placenta [2,178].

Rhesus macaque, baboon and marmoset, all of which undergo superficial implantation, vary greatly in extravillous trophoblast abundance and trophoblast invasion depth [27]. Marmosets generate minimal extravillous trophoblast, only surrounding arteries near the placental zone [24]. By contrast, both rhesus macaque and baboon exhibit deep extravillous trophoblast invasion [31,36]. In baboons, extravillous trophoblast surrounds spiral arteries as early as embryonic day 13 [31]. Human and chimpanzee spiral arteries undergo the most extensive remodelling [179]. Future cross-species analysis of the recently generated *in vivo* single-cell transcriptome datasets of postimplantation trophoblast in human, rhesus macaque and marmoset will facilitate the discovery of new regulators of extravillous trophoblast differentiation [46,48,58].

References

- Edmonds DK, Lindsay KS, Miller JF, Williamson E, Wood PJ. 1982 Early embryonic mortality in women. *Fertil. Steril.* **38**, 447–453. (doi:10.1016/S0015-0282(16)46579-9)
- Jauniaux E, Burton GJ. 2005 Pathophysiology of histological changes in early pregnancy loss. *Placenta* **26**, 114–123. (doi:10.1016/j.placenta.2004.05.011)
- Romero R, Kusanovic JP, Chaiworapongsa T, Hassan SS. 2011 Placental bed disorders in preterm labor, preterm PROM, spontaneous abortion and abruptio placentae. *Best Pract. Res. Clin. Obstet. Gynaecol.* **25**, 313–327. (doi:10.1016/j.bpobgyn.2011.02.006)
- Kadam L, Jain C, Kohan-Ghadr HR, Krawetz SA, Drewlo S, Armant DR. 2019 Endocervical trophoblast for interrogating the fetal genome and assessing pregnancy health at five weeks. *Eur. J. Med. Genet.* **62**, 103690. (doi:10.1016/j.ejmg.2019.103690)
- Norwitz ER. 2006 Defective implantation and placentation: laying the blueprint for pregnancy complications. *Reprod. Biomed. Online* **13**, 591–599. (doi:10.1016/S1472-6483(10)60649-9)
- Sun C, Groom KM, Oyston C, Chamley LW, Clark AR, James JL. 2020 The placenta in fetal growth restriction: what is going wrong? *Placenta* **96**, 10–18. (doi:10.1016/j.placenta.2020.05.003)
- Burkhardt T, Schäffer L, Schneider C, Zimmermann R, Kurmanavicius J. 2006 Reference values for the weight of freshly delivered term placentas and for placental weight–birth weight ratios. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **128**, 248–252. (doi:10.1016/j.ejogrb.2005.10.032)
- Bronson SL, Bale TL. 2016 The placenta as a mediator of stress effects on neurodevelopmental reprogramming. *Neuropsychopharmacology* **41**, 207–218. (doi:10.1038/npp.2015.231)
- Streeter G, O'Rahilly R, Müller F. 1942 *Carnegie collection*. Washington, DC: Carnegie Institute.
- Boyd J. 1950 *Boyd collection*. Cambridge, UK: University Cambridge.
- Blakeley P *et al.* 2015 Defining the three cell lineages of the human blastocyst by single-cell RNA-seq. *Development* **142**, 3151–3165. (doi:10.1242/dev.131235)
- Gerri C *et al.* 2020 Initiation of a conserved trophoctoderm program in human, cow and mouse embryos. *Nature* **587**, 443–447. (doi:10.1038/s41586-020-2759-x)
- Strumpf D, Mao CA, Yamanaka Y, Ralston A, Chawengsaksophak K, Beck F, Rossant J. 2005 Cdx2 is required for correct cell fate specification and differentiation of trophoctoderm in the mouse blastocyst. *Development* **132**, 2093–2102. (doi:10.1242/dev.01801)
- Ralston A, Rossant J. 2008 Cdx2 acts downstream of cell polarization to cell-autonomously promote trophoctoderm fate in the early mouse embryo. *Dev. Biol.* **313**, 614–629. (doi:10.1016/j.ydbio.2007.10.054)
- Chiu YH, Chen H. 2016 GATA3 inhibits GCM1 activity and trophoblast cell invasion. *Scient. Rep.* **6**, 21630. (doi:10.1038/srep21630)
- Baczyk D, Kibschull M, Mellstrom B, Levytska K, Rivas M, Drewlo S, Lye SJ, Naranjo JR, Kingdom JCP. 2013 DREAM mediated regulation of GCM1 in the human placental trophoblast. *PLoS ONE* **8**, e51837. (doi:10.1371/journal.pone.0051837)
- Xiong T, Zhao Y, Hu D, Meng J, Wang R, Yang X, Ai J, Qian K, Zhang H. 2012 Administration of calcitonin promotes blastocyst implantation in mice by up-regulating integrin $\beta 3$ expression in endometrial epithelial cells. *Hum. Reprod.* **27**, 3540–3551. (doi:10.1093/humrep/des330)
- Elnaggar A, Farag AH, Gaber ME, Hafeez MA, Ali MS, Atef AM. 2017 AlphaVBeta3 integrin expression within uterine endometrium in unexplained infertility: a prospective cohort study. *BMC Womens Health* **17**, 90. (doi:10.1186/s12905-017-0438-3)
- Lydon JP, DeMayo FJ, Funk CR, Mani SK, Hughes AR, Montgomery CA, Shyamala G, Conneely OM, O'Malley BW. 1995 Mice lacking progesterone receptor exhibit pleiotropic reproductive abnormalities. *Genes Dev.* **9**, 2266–2278. (doi:10.1101/gad.9.18.2266)
- Takeuchi M *et al.* 2017 Improvement of implantation potential in mouse blastocysts derived from IVF by combined treatment with prolactin, epidermal growth factor and 4-hydroxyestradiol. *Mol. Hum. Reprod.* **23**, 557–570. (doi:10.1093/molehr/gax035)

10. Conclusion

Trophoctoderm specification, embryo orientation, adhesion and invasion are all essential for proper embryo development. As early human implantation stages are not accessible, non-human primate models are imperative for our understanding of embryo implantation. The evolutionary divergence in implantation strategies among primate species presents an exciting opportunity to elucidate early trophoblast invasion by studying candidate regulator activities across primate species with varying invasion depth. The results from this research will be important to delineate the molecular mechanisms underlying pathophysiological changes in human placental development.

Data accessibility. This article has no additional data.

Authors' contributions. D.S.: conceptualization, visualization, writing—original draft; T.E.B.: conceptualization, writing—review and editing.

Both authors gave final approval for publication and agreed to be held accountable for the work performed herein.

Conflict of interest declaration. The authors declare no competing interests.

Funding. This research is generously supported by the Wellcome Trust (grant no. WT RG89228) and the Centre for Trophoblast Research. D.S. holds a Centre for Trophoblast Graduate Studentship and is supported by the Philosophical Society. T.E.B is a Wellcome Trust—Royal Society Sir Henry Dale Fellow.

Acknowledgements. We would like to thank Dr Gianluca Amadei, Professor Graham Burton and the members of the Boroviak laboratory for their enthusiasm and critical discussion of the manuscript.

21. Gellersen B, Brosens JJ. 2014 Cyclic decidualization of the human endometrium in reproductive health and failure. *Endocr Rev* **35**, 851–905. (doi:10.1210/er.2014-1045)
22. Charnock-Jones DS, Sharkey AM, Fenwick P, Smith SK. 1994 Leukaemia inhibitory factor mRNA concentration peaks in human endometrium at the time of implantation and the blastocyst contains mRNA for the receptor at this time. *J. Reprod. Fertil.* **101**, 421–426. (doi:10.1530/jrf.0.1010421)
23. Smith LJ. 1985 Embryonic axis orientation in the mouse and its correlation with blastocyst relationships to the uterus. II. Relationships from 4 1/4 to 9 1/2 days. *J. Embryol. Exp. Morphol.* **89**, 15–35.
24. Enders AC. 2000 Trophoblasts-uterine interactions in the first days of implantation: models for the study of implantation events in the human. *Semin. Reprod. Med.* **18**, 255–263. (doi:10.1055/s-2000-12563)
25. Burton GJ, Hempstock J, Jauniaux E. 2001 Nutrition of the human fetus during the first trimester—a review. *Placenta* **22**(Suppl.1), S70–S77. (doi:10.1053/plac.2001.0639)
26. Burton GJ, Watson AL, Hempstock J, Skepper JN, Jauniaux E. 2002 Uterine glands provide histiotrophic nutrition for the human fetus during the first trimester of pregnancy. *J. Clin. Endocrinol. Metab.* **87**, 2954–2959. (doi:10.1210/jcem.87.6.8563)
27. Mossman HW. 1987 *Vertebrate fetal membranes: comparative ontogeny and morphology, evolution, phylogenetic significance, basic functions, research opportunities*. New Brunswick, NJ: Rutgers University Press.
28. McGowen MR, Erez O, Romero R, Wildman DE. 2014 The evolution of embryo implantation. *Int. J. Dev. Biol.* **58**, 155. (doi:10.1387/ijdb.140020dw)
29. Turner W. 1876 On the placentation of the lemurs. *Phil. Trans. R. Soc. Lond.* **166**, 569–587. (doi:10.1098/rstl.1876.0022)
30. Carter AM, Pijnenborg R. 2011 Evolution of invasive placentation with special reference to non-human primates. *Best Pract. Res. Clin. Obstet. Gynaecol.* **25**, 249–257. (doi:10.1016/j.bpobgyn.2010.10.010)
31. Houston ML. 1969 The villous period of placentogenesis in the baboon (*Papio* sp.). *Am. J. Anat.* **126**, 1–15. (doi:10.1002/aja.1001260102)
32. Enders AC, King BF. 1991 Early stages of trophoblastic invasion of the maternal vascular system during implantation in the macaque and baboon. *Am. J. Anat.* **192**, 329–346. (doi:10.1002/aja.1001920403)
33. Carter AM, Enders AC. 2013 The evolution of epitheliochorial placentation. *Annu. Rev. Anim. Biosci.* **1**, 443–467. (doi:10.1146/annurev-animal-031412-103653)
34. Enders AC, Carter AM. 2012 The evolving placenta: convergent evolution of variations in the endotheliochorial relationship. *Placenta* **33**, 319–326. (doi:10.1016/j.placenta.2012.02.008)
35. Furukawa S, Kuroda Y, Sugiyama A. 2014 A comparison of the histological structure of the placenta in experimental animals. *J. Toxicol. Pathol.* **27**, 11. (doi:10.1293/tox.2013-0060)
36. Enders AC, Blankenship TN, Fazleabas AT, Jones CJP. 2001 Structure of anchoring villi and the trophoblastic shell in the human, baboon and macaque placenta. *Placenta* **22**, 284–303. (doi:10.1053/plac.2001.0626)
37. Carter AM, Enders AC, Pijnenborg R. 2015 The role of invasive trophoblast in implantation and placentation of primates. *Phil. Trans. R. Soc. B.* **370**, 20140070. (doi:10.1098/rstb.2014.0070)
38. Enders AC, Hendrickx AG, Schlafke S. 1983 Implantation in the rhesus monkey: initial penetration of endometrium. *Am. J. Anat.* **167**, 275–298. (doi:10.1002/aja.1001670302)
39. Nishioka N *et al.* 2009 The Hippo signaling pathway components Lats and Yap pattern Tead4 activity to distinguish mouse trophectoderm from inner cell mass. *Dev. Cell* **16**, 398–410. (doi:10.1016/j.devcel.2009.02.003)
40. O'Rahilly R, Müller F. 2010 Developmental stages in human embryos: revised and new measurements. *Cells Tissues Organs* **192**, 73–84. (doi:10.1159/000289817)
41. Kagawa H *et al.* 2021 Human blastoids model blastocyst development and implantation. *Nature* **601**, 600–605. (doi:10.1038/s41586-021-04267-8)
42. Niwa H, Ogawa K, Shimosato D, Adachi K. 2009 A parallel circuit of LIF signalling pathways maintains pluripotency of mouse ES cells. *Nature* **460**, 118–122. (doi:10.1038/nature08113)
43. Frias-Aldeguer J *et al.* 2020 Embryonic signals perpetuate polar-like trophoblast stem cells and pattern the blastocyst axis. *bioRxiv*, 510362. (doi:10.1101/510362)
44. Petropoulos S *et al.* 2016 Single-cell RNA-Seq reveals lineage and X chromosome dynamics in human preimplantation embryos. *Cell* **165**, 1012–1026. (doi:10.1016/j.cell.2016.03.023)
45. Niakan KK, Eggan K. 2013 Analysis of human embryos from zygote to blastocyst reveals distinct gene expression patterns relative to the mouse. *Dev. Biol.* **375**, 54–64. (doi:10.1016/j.ydbio.2012.12.008)
46. Bergmann S *et al.* 2022 Spatial embryo profiling of primate gastrulation. *Nature* **609**, 136–143. (doi:10.1038/s41586-022-04953-1)
47. Nakamura T, Yabuta Y, Okamoto I, Sasaki K, Iwatani C, Tsuchiya H, Saitou M. 2017 Single-cell transcriptome of early embryos and cultured embryonic stem cells of cynomolgus monkeys. *Scient. Data* **4**, 170067. (doi:10.1038/sdata.2017.67)
48. Ma H *et al.* 2019 *In vitro* culture of cynomolgus monkey embryos beyond early gastrulation. *Science* **366**, eaax7890. (doi:10.1126/science.aax7890)
49. Meistermann D *et al.* 2021 Integrated pseudotime analysis of human pre-implantation embryo single-cell transcriptomes reveals the dynamics of lineage specification. *Cell Stem Cell* **28**, 1625–1640.e6. (doi:10.1016/j.stem.2021.04.027)
50. Enders AC, Lopata A. 1999 Implantation in the marmoset monkey: expansion of the early implantation site. *Anat. Rec.* **256**, 279–299. (doi:10.1002/(SICI)1097-0185(19991101)256:3<279::AID-AR7>3.0.CO;2-0)
51. Lindenberg S, Hyttel P, Lenz S, Holmes PV 1986 Ultrastructure of the early human implantation *in vitro*. *Hum. Reprod.* **1**, 533–538. (doi:10.1093/oxfordjournals.humrep.a136469)
52. Brighton PJ *et al.* 2017 Clearance of senescent decidual cells by uterine natural killer cells in cycling human endometrium. *eLife* **6**, e31274. (doi:10.7554/eLife.31274)
53. Ruane PT *et al.* 2022 Trophoblast differentiation to invasive syncytiotrophoblast is promoted by endometrial epithelial cells during human embryo implantation. *Hum. Reprod.* **37**, 777–792. (doi:10.1093/humrep/deac008)
54. West RC *et al.* 2019 Dynamics of trophoblast differentiation in peri-implantation-stage human embryos. *Proc. Natl Acad. Sci. USA* **116**, 22 635–22 644. (doi:10.1073/pnas.1911362116)
55. Xiang L *et al.* 2020 A developmental landscape of 3D-cultured human pre-gastrulation embryos. *Nature* **577**, 537–542. (doi:10.1038/s41586-019-1875-y)
56. Zhou F *et al.* 2019 Reconstituting the transcriptome and DNA methylome landscapes of human implantation. *Nature* **572**, 660–664. (doi:10.1038/s41586-019-1500-0)
57. Enders AC, Lantz KC, Peterson PE, Hendrickx AG. 1997 From blastocyst to placenta: the morphology of implantation in the baboon. *Hum. Reprod. Update* **3**, 561–573. (doi:10.1093/humupd/3.6.561)
58. Chen Y, Siriwardena D, Penfold C, Pavlinek A, Boroviak TE. 2022 An integrated atlas of human placental development delineates essential regulators of trophoblast stem cells. *Development* **149**, dev200171. (doi:10.1242/dev.200171)
59. Mayor P, Pereira W, Nacher V, Navarro M, Monteiro FOB, El Bizri HR, Carretero A. 2019 Menstrual cycle in four New World primates: Poeppig's woolly monkey (*Lagothrix poeppigii*), red uakari (*Cacajao calvus*), large-headed capuchin (*Sapajus macrocephalus*) and nocturnal monkey (*Aotus nancymae*). *Theriogenology* **123**, 11–21. (doi:10.1016/j.theriogenology.2018.09.019)
60. Surveyor GA *et al.* 1995 Expression and steroid hormonal control of Muc-1 in the mouse uterus. *Endocrinology* **136**, 3639–3647. (doi:10.1210/endo.136.8.7628404)
61. De Ziegler D, Bergeron C, Cornel C, Medalie DA, Massai MR, Milgrom E, Frydman R, Bouchard P. 1992 Effects of luteal estradiol on the secretory transformation of human endometrium and plasma gonadotropins. *J. Clin. Endocrinol. Metab.* **74**, 322–331. (doi:10.1210/jcem.74.2.1730810)
62. Bergmann S, Schindler M, Munger C, Penfold CA, Boroviak TE. 2021 Building a stem cell-based primate uterus. *Commun. Biol.* **4**, 749. (doi:10.1038/s42003-021-02233-8)
63. Bromer JG, Aldad TS, Taylor HS. 2009 Defining the proliferative phase endometrial defect. *Fertil. Steril.* **91**, 698. (doi:10.1016/j.fertnstert.2007.12.066)
64. Emera D, Romero R, Wagner G. 2012 The evolution of menstruation: a new model for genetic assimilation. *Bioessays* **34**, 26. (doi:10.1002/bies.201100099)

65. Martin RD. 2007 The evolution of human reproduction: a primatological perspective. *Am. J. Phys. Anthropol.* **134**, 59–84. (doi:10.1002/ajpa.20734)
66. Ghosh D, Sengupta J. 1993 Anti-nidatory effect of a single, early post-ovulatory administration of mifepristone (RU 486) in the rhesus monkey. *Hum. Reprod.* **8**, 552–558. (doi:10.1093/oxfordjournals.humrep.a138094)
67. Gemzell-Danielsson K, Swahn ML, Svalander P, Bygdeman M. 1993 Early luteal phase treatment with mifepristone (RU 486) for fertility regulation. *Hum. Reprod.* **8**, 870–873. (doi:10.1093/oxfordjournals.humrep.a138157)
68. Mulac-Jericevic B, Mullinax RA, DeMayo FJ, Lydon JP, Conneely OM. 2000 Subgroup of reproductive functions of progesterone mediated by progesterone receptor-B isoform. *Science* **289**, 1751–1754. (doi:10.1126/science.289.5485.1751)
69. Salleh N, Giribabu N. 2014 Leukemia inhibitory factor: roles in embryo implantation and in nonhormonal contraception. *Scient. World J.* **2014**, 201514. (doi:10.1155/2014/201514)
70. Ashary N, Tiwari A, Modi D. 2018 Embryo implantation: war in times of love. *Endocrinology* **159**, 1188–1198. (doi:10.1210/en.2017-03082)
71. Vinketova K, Mourdjeva M, Oreshkova T. 2016 Human decidual stromal cells as a component of the implantation niche and a modulator of maternal immunity. *J. Pregnancy* **2016**, 8689436. (doi:10.1155/2016/8689436)
72. Okada H, Tsuzuki T, Murata H. 2018 Decidualization of the human endometrium. *Reprod. Med. Biol.* **17**, 220. (doi:10.1002/rmb2.12088)
73. Dollar JR, Graham CE, Reyes FI. 1982 Postovulatory predecidual development in the baboon, chimpanzee, and human. *Am. J. Primatol.* **3**, 307–313. (doi:10.1002/ajp.1350030130)
74. Atkins HM, Lombardini ED, Caudell DL, Appt SE, Dubois A, Cline JM. 2016 Decidualization of endometriosis in macaques. *Vet. Pathol.* **53**, 1252–1258. (doi:10.1177/0300985816646433)
75. Wetendorf M, DeMayo FJ. 2012 The progesterone receptor regulates implantation, decidualization, and glandular development via a complex paracrine signaling network. *Mol. Cell. Endocrinol.* **357**, 108–118. (doi:10.1016/j.mce.2011.10.028)
76. Enders AC. 1991 Structural responses of the primate endometrium to implantation. *Placenta* **12**, 309–325. (doi:10.1016/0143-4004(91)90340-L)
77. Afshar Y, Miele L, Fazleabas AT. 2012 Notch1 is regulated by chorionic gonadotropin and progesterone in endometrial stromal cells and modulates decidualization in primates. *Endocrinology* **153**, 2884–2896. (doi:10.1210/en.2011-2122)
78. Jones CJP, Fazleabas AT. 2001 Ultrastructure of epithelial plaque formation and stromal cell transformation by post-ovulatory chorionic gonadotrophin treatment in the baboon (*Papio anubis*). *Hum. Reprod.* **16**, 2680–2690. (doi:10.1093/humrep/16.12.2680)
79. Chien LW, Au HK, Xiao J, Tzeng CR. 2002 Fluid accumulation within the uterine cavity reduces pregnancy rates in women undergoing IVF. *Hum. Reprod.* **17**, 351–356. (doi:10.1093/humrep/17.2.351)
80. Slukvin II, Breburda EE, Golos TG. 2004 Dynamic changes in primate endometrial leukocyte populations: differential distribution of macrophages and natural killer cells at the rhesus monkey implantation site and in early pregnancy. *Placenta* **25**, 297–307. (doi:10.1016/j.placenta.2003.08.019)
81. Drury JA, Parkin KL, Coyne L, Giuliani E, Fazleabas AT, Hapangama DK. 2018 The dynamic changes in the number of uterine natural killer cells are specific to the eutopic but not to the ectopic endometrium in women and in a baboon model of endometriosis. *Reprod. Biol. Endocrinol.* **16**, 67. (doi:10.1186/s12958-018-0385-3)
82. Kong CS *et al.* 2021 Embryo biosensing by uterine natural killer cells determines endometrial fate decisions at implantation. *FASEB J.* **35**, e21336. (doi:10.1096/fj.202002217R)
83. Babayeva G, Purut YE, Giray B, Oltulu P, Alakus R, Çolakoglu MC. 2020 Endometrial CD56+ natural killer cells in women with recurrent implantation failure: an immunohistochemical study. *Turkish J. Obstet. Gynecol.* **17**, 236. (doi:10.4274/tjod.galenos.2020.90359)
84. Stadtmayer DJ, Wagner GP. 2020 Cooperative inflammation: the recruitment of inflammatory signaling in marsupial and eutherian pregnancy. *J. Reprod. Immunol.* **137**, 102626. (doi:10.1016/j.jri.2019.102626)
85. Chavan AR, Griffith OW, Stadtmayer DJ, Maziarsz J, Pavlicev M, Fishman R, Koren L, Romero R, Yeager M. 2021 Evolution of embryo implantation was enabled by the origin of decidual stromal cells in eutherian mammals. *Mol. Biol. Evol.* **38**, 1060. (doi:10.1093/molbev/msaa274)
86. De Rijk EPCT, Van Esch E. 2008 The macaque placenta—a mini-review. *Toxicol. Pathol.* **36**(Suppl.), 108S–118S. (doi:10.1177/0192623308326095)
87. Fang L, Gao Y, Wang Z, Li Y, Yan Y, Wu Z, Cheng JC, Sun YP. 2021 EGF stimulates human trophoblast cell invasion by downregulating ID3-mediated KISS1 expression. *Cell Commun. Signal.* **19**, 101. (doi:10.1186/s12964-021-00783-2)
88. Sugihara K *et al.* 2007 Trophoblast cell activation by trophinin ligation is implicated in human embryo implantation. *Proc. Natl Acad. Sci. USA* **104**, 3799–3804. (doi:10.1073/pnas.0611516104)
89. Kolahi KS, Valent AM, Thornburg KL. 2017 Cytotrophoblast, not syncytiotrophoblast, dominates glycolysis and oxidative phosphorylation in human term placenta. *Scient. Rep.* **7**, 42941. (doi:10.1038/srep42941)
90. Sawai K, Azuma C, Koyama M, Ito SI, Hashimoto K, Kimura T, Samejima Y, Nobunaga T, Saji F. 1995 Leukemia inhibitory factor (LIF) enhances trophoblast differentiation mediated by human chorionic gonadotropin (hCG). *Biochem. Biophys. Res. Commun.* **211**, 137–143. (doi:10.1006/bbrc.1995.1788)
91. Licht P, Fluhr H, Neuwinger J, Wallwiener D, Wildt L. 2007 Is human chorionic gonadotropin directly involved in the regulation of human implantation? *Mol. Cell. Endocrinol.* **269**, 85–92. (doi:10.1016/j.mce.2006.09.016)
92. d'Hauterive SP *et al.* 2004 Human chorionic gonadotropin and growth factors at the embryonic–endometrial interface control leukemia inhibitory factor (LIF) and interleukin 6 (IL-6) secretion by human endometrial epithelium. *Hum. Reprod.* **19**, 2633–2643. (doi:10.1093/humrep/deh450)
93. Chen Q, Zhang Y, Lu J, Wang Q, Wang S, Cao Y, Wang H, Duan E. 2009 Embryo–uterine cross-talk during implantation: the role of Wnt signaling. *Mol. Hum. Reprod.* **15**, 215–221. (doi:10.1093/molehr/gap009)
94. Iwamoto R *et al.* 2003 Heparin-binding EGF-like growth factor and ErbB signaling is essential for heart function. *Proc. Natl Acad. Sci. USA* **100**, 3221–3226. (doi:10.1073/pnas.0537588100)
95. Chobotova K, Spyropoulou I, Carver J, Manek S, Heath JK, Gullick WJ, Barlow DH, Sargent IL, Mardon HJ. 2002 Heparin-binding epidermal growth factor and its receptor ErbB4 mediate implantation of the human blastocyst. *Mech. Dev.* **119**, 137–144. (doi:10.1016/S0925-4773(02)00342-8)
96. Martin KL, Barlow DH, Sargent IL. 1998 Heparin-binding epidermal growth factor significantly improves human blastocyst development and hatching in serum-free medium. *Hum. Reprod.* **13**, 1645–1652. (doi:10.1093/humrep/13.6.1645)
97. Lim HJ, Dey SK. 2009 HB-EGF: a unique mediator of embryo–uterine interactions during implantation. *Exp. Cell Res.* **315**, 619. (doi:10.1016/j.yexcr.2008.07.025)
98. Mathieu ME, Saucourt C, Mournetas V, Gauthereau X, Thézé N, Praloran V, Thiébaud P, Bœuf H. 2012 LIF-dependent signaling: new pieces in the Lego. *Stem Cell Rev.* **8**, 1–15. (doi:10.1007/s12015-011-9261-7)
99. Chen H *et al.* 2015 Reinforcement of STAT3 activity reprogrammes human embryonic stem cells to naive-like pluripotency. *Nat. Commun.* **6**, 7095. (doi:10.1038/ncomms8095)
100. Smith AG, Hooper ML. 1987 Buffalo rat liver cells produce a diffusible activity which inhibits the differentiation of murine embryonal carcinoma and embryonic stem cells. *Dev. Biol.* **121**, 1–9. (doi:10.1016/0012-1606(87)90132-1)
101. Laird SM, Tuckerman EM, Dalton CF, Dunphy BC, Li TC, Zhang X. 1997 The production of leukaemia inhibitory factor by human endometrium: presence in uterine flushings and production by cells in culture. *Hum. Reprod.* **12**, 569–574. (doi:10.1093/humrep/12.3.569)
102. Lédée-Bataille N, Laprée-Delage G, Taupin JL, Dubanchet S, Frydman R, Chaouat G. 2002 Concentration of leukaemia inhibitory factor (LIF) in uterine flushing fluid is highly predictive of embryo implantation. *Hum. Reprod.* **17**, 213–218. (doi:10.1093/humrep/17.1.213)

103. Sengupta J, Lalitkumar PGL, Najwa AR, Ghosh D. 2006 Monoclonal anti-leukemia inhibitory factor antibody inhibits blastocyst implantation in the rhesus monkey. *Contraception* **74**, 419–425. (doi:10.1016/j.contraception.2006.05.070)
104. Mor G, Koga K. 2008 Macrophages and pregnancy. *Reprod. Sci.* **15**, 435–436. (doi:10.1177/1933719108317253)
105. Dimitriadis E, White CA, Jones RL, Salamonsen LA. 2005 Cytokines, chemokines and growth factors in endometrium related to implantation. *Hum. Reprod. Update* **11**, 613–630. (doi:10.1093/humupd/dmi023)
106. Gonzalez RR, Rueda BR, Ramos MP, Littell RD, Glasser S, Leavis PC. 2004 Leptin-induced increase in leukemia inhibitory factor and its receptor by human endometrium is partially mediated by interleukin 1 receptor signaling. *Endocrinology* **145**, 3850–3857. (doi:10.1210/en.2004-0383)
107. Sharma A, Kumar P. 2012 Understanding implantation window, a crucial phenomenon. *J. Hum. Reprod. Sci.* **5**, 2. (doi:10.4103/0974-1208.97777)
108. Aplin JD. 1997 Adhesion molecules in implantation. *Rev. Reprod.* **2**, 84–93. (doi:10.1530/ror.0.0020084)
109. Jones CJP, Ortiz ME, Croxatto HB, Manzur A, Slevin G, Aplin JD. 2001 Muc1 and glycan expression in the oviduct and endometrium of a New World monkey, *Cebus apella*. *Biol. Reprod.* **64**, 1535–1544. (doi:10.1095/biolreprod64.5.1535)
110. Desouza MM, Surveyor GA, Price RE, Julian J, Kardon R, Zhou X, Gendler S, Hilkens J, Carson DD. 1999 MUC1/episialin: a critical barrier in the female reproductive tract. *J. Reprod. Immunol.* **45**, 127–158. (doi:10.1016/S0165-0378(99)00046-7)
111. Refaat B, Simpson H, Britton E, Biswas J, Wells M, Aplin JD, Ledger W. 2012 Why does the fallopian tube fail in ectopic pregnancy? The role of activins, inducible nitric oxide synthase, and MUC1 in ectopic implantation. *Fertil. Steril* **97**, 1115–1123. (doi:10.1016/j.fertnstert.2012.02.035)
112. Gipson IK, Blalock T, Tisdale A, Spurr-Michaud S, Allcorn S, Stavreus-Evers A, Gemzell K. 2008 MUC16 is lost from the uterodome (pinopode) surface of the receptive human endometrium: *in vitro* evidence that MUC16 is a barrier to trophoblast adherence. *Biol. Reprod.* **78**, 134–142. (doi:10.1095/biolreprod.106.058347)
113. Dharmaraj N, Xiao H, Carson DD. 2021 Protein modifications | mucins in embryo implantation. *Encycl. Biol. Chem. III* **3**, 206–211. (doi:10.1016/B978-0-12-819460-7.00214-0)
114. Aplin JD. 1999 MUC-1 glycosylation in endometrium: possible roles of the apical glycocalyx at implantation. *Hum. Reprod.* **14**(Suppl. 2), 17–25. (doi:10.1093/humrep/14.suppl_2.17)
115. Chavez DJ, Anderson TL. 1985 The glycocalyx of the mouse uterine luminal epithelium during estrus, early pregnancy, the peri-implantation period, and delayed implantation. I. Acquisition of *Ricinus communis* binding sites during pregnancy. *Biol. Reprod.* **32**, 1135–1142. (doi:10.1095/biolreprod32.5.1135)
116. Hey NA, Graham RA, Seif MW, Aplin JD. 1994 The polymorphic epithelial mucin MUC1 in human endometrium is regulated with maximal expression in the implantation phase. *J. Clin. Endocrinol. Metab.* **78**, 337–342.
117. Aplin JD, Hey NA, Graham RA. 1998 Human endometrial MUC1 carries keratan sulfate: characteristic glycoforms in the luminal epithelium at receptivity. *Glycobiology* **8**, 269–276. (doi:10.1093/glycob/8.3.269)
118. Meseguer M, Aplin JD, Caballero-Campo P, O'Connor JE, Martín JC, Remohí J, Pellicer A, Simón C. 2001 Human endometrial mucin MUC1 is up-regulated by progesterone and down-regulated *in vitro* by the human blastocyst. *Biol. Reprod.* **64**, 590–601. (doi:10.1095/biolreprod64.2.590)
119. Julian JA, Enders AC, Fazleabas AT, Carson DD. 2005 Compartmental distinctions in uterine Muc-1 expression during early pregnancy in cynomolgus macaque (*Macaca fascicularis*) and baboon (*Papio anubis*). *Hum. Reprod.* **20**, 1493–1503. (doi:10.1093/humrep/deh801)
120. Ivetic A, Green HLH, Hart SJ. 2019 L-selectin: a major regulator of leukocyte adhesion, migration and signaling. *Front. Immunol.* **10**, 1068. (doi:10.3389/fimmu.2019.01068)
121. Gupta GS. 2012 L-selectin (CD62 L) and its ligands. In *Animal lectins: form, function and clinical applications*, pp. 553–574. Vienna, Austria: Springer.
122. Frenette PS, Wagner DD. 1997 Insights into selectin function from knockout mice. *Thromb. Haemost.* **78**, 60–64. (doi:10.1055/s-0038-1657501)
123. Yucha RW, Jost M, Rothstein D, Robertson N, Marcolongo MS. 2014 Quantifying the biomechanics of conception: L-selectin-mediated blastocyst implantation mechanics with engineered "trophospheres". *Tissue Engng A* **20**, 189–195. (doi:10.1089/ten.tea.2013.0067)
124. Genbacev OD *et al.* 2003 Trophoblast L-selectin-mediated adhesion at the maternal-fetal interface. *Science* **299**, 405–408. (doi:10.1126/science.1079546)
125. Tedder TF, Matsuyama T, Rothstein D, Schlossman SF, Morimoto C. 1990 Human antigen-specific memory T cells express the homing receptor (LAM-1) necessary for lymphocyte recirculation. *Eur. J. Immunol.* **20**, 1351–1355. (doi:10.1002/eji.1830200622)
126. Walcheck B *et al.* 1996 Neutrophil rolling altered by inhibition of L-selectin shedding *in vitro*. *Nature* **380**, 720–723. (doi:10.1038/380720a0)
127. Suzuki N, Zara J, Sato T, Ong E, Bakhiet N, Oshima RG, Watson KL, Fukuda MN. 1998 A cytoplasmic protein, bystin, interacts with trophinin, tastin, and cytokeratin and may be involved in trophinin-mediated cell adhesion between trophoblast and endometrial epithelial cells. *Proc. Natl Acad. Sci. USA* **95**, 5027–5032. (doi:10.1073/pnas.95.9.5027)
128. Suzuki N, Nadano D, Paria BC, Kupriyanov S, Sugihara K, Fukuda MN. 2000 Trophinin expression in the mouse uterus coincides with implantation and is hormonally regulated but not induced by implanting blastocysts. *Endocrinology* **141**, 4247–4254. (doi:10.1210/endo.141.11.7738)
129. Sugihara K, Kabir-Salmani M, Byrne J, Wolf DP, Lessey B, Iwashita M, Aoki D, Nakayama J, Fukuda MN. 2008 Induction of trophinin in human endometrial surface epithelia by CG β and IL-1 β . *FEBS Lett.* **582**, 197–202. (doi:10.1016/j.febslet.2007.12.001)
130. Fukuda MN, Sugihara K. 2008 An integrated view of L-selectin and trophinin function in human embryo implantation. *J. Obstet. Gynaecol. Res.* **34**, 129–136. (doi:10.1111/j.1447-0756.2008.00776.x)
131. Nakayama J *et al.* 2003 Implantation-dependent expression of trophinin by maternal fallopian tube epithelia during tubal pregnancies: possible role of human chorionic gonadotrophin on ectopic pregnancy. *Am. J. Pathol.* **163**, 2211–2219. (doi:10.1016/S0002-9440(10)63579-1)
132. Fukuda MN, Sato T, Nakayama J, Klier G, Mikami M, Aoki D, Nozawa S. 1995 Trophinin and tastin, a novel cell adhesion molecule complex with potential involvement in embryo implantation. *Genes Dev.* **9**, 1199–1210. (doi:10.1101/gad.9.10.1199)
133. Fukuda MN, Nozawa S. 1999 Trophinin, tastin, and bystin: a complex mediating unique attachment between trophoblastic and endometrial epithelial cells at their respective apical cell membranes. *Semin. Reprod. Endocrinol.* **17**, 229–234. (doi:10.1055/s-2007-1016230)
134. Carson DD, Bagchi I, Dey SK, Enders AC, Fazleabas AT, Lessey BA, Yoshinaga K. 2000 Embryo implantation. *Dev. Biol.* **223**, 217–237. (doi:10.1006/dbio.2000.9767)
135. Creus M, Ordi J, Fábregues F, Casamitjana R, Ferrer B, Coll E, Vanrell JA, Balasch J. 2002 α v β 3 Integrin expression and pinopod formation in normal and out-of-phase endometria of fertile and infertile women. *Hum. Reprod.* **17**, 2279–2286. (doi:10.1093/humrep/17.9.2279)
136. Taylor CV, Letarte M, Lye SJ. 1996 The expression of integrins and cadherins in normal human uterus and uterine leiomyomas. *Am. J. Obstet. Gynecol.* **175**, 411–419. (doi:10.1016/S0002-9378(96)70155-2)
137. Lessey BA, Damjanovich L, Coutifaris C, Castelbaum A, Albeida SM, Buck CA. 1992 Integrin adhesion molecules in the human endometrium. Correlation with the normal and abnormal menstrual cycle. *J. Clin. Invest.* **90**, 188–195. (doi:10.1172/JCI115835)
138. Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P. 2002 *Integrins*. New York, NY: Garland Science.
139. Burrows TD, King A, Loke YW. 1996 Trophoblast migration during human placental implantation. *Hum. Reprod. Update* **2**, 307–321. (doi:10.1093/humupd/2.4.307)
140. Kaneko Y, Day ML, Murphy CR. 2011 Integrin β 3 in rat blastocysts and epithelial cells is essential for implantation *in vitro*: studies with Ishikawa cells and small interfering RNA transfection. *Hum. Reprod.* **26**, 1665–1674. (doi:10.1093/humrep/der128)
141. Kaneko Y, Lecce L, Day ML, Murphy CR. 2011 β 1 and β 3 integrins disassemble from basal focal

- adhesions and $\beta 3$ integrin is later localised to the apical plasma membrane of rat uterine luminal epithelial cells at the time of implantation. *Reprod. Fertil. Dev.* **23**, 481–495. (doi:10.1071/RD10211)
142. Chen Y *et al.* 2006 Global analysis of differential luminal epithelial gene expression at mouse implantation sites. *J. Mol. Endocrinol.* **37**, 147–161. (doi:10.1677/jme.1.02009)
143. Govindasamy *Net al.* 2021 3D biomimetic platform reveals the first interactions of the embryo and the maternal blood vessels. *Dev. Cell.* **56**, 3276–3287.e8. (doi:10.1016/j.devcel.2021.01.014)
144. Fazleabas AT, Bell SC, Fleming S, Sun J, Lessey BA. 1997 Distribution of integrins and the extracellular matrix proteins in the baboon endometrium during the menstrual cycle and early pregnancy. *Biol. Reprod.* **56**, 348–356. (doi:10.1095/biolreprod56.2.348)
145. Van Mourik MSM, Macklon NS, Heijnen CJ. 2009 Embryonic implantation: cytokines, adhesion molecules, and immune cells in establishing an implantation environment. *J. Leukoc. Biol.* **85**, 4–19. (doi:10.1189/jlb.0708395)
146. Illera MJ, Lorenzo PL, Gui Y, Beyler SA, Apparao KBC, Lessey BA. 2003 A role for $\alpha_v\beta_3$ integrin during implantation in the rabbit model. *Biol. Reprod.* **68**, 766–771. (doi:10.1093/biolreprod/68.3.766)
147. Illera MJ, Cullinan E, Gui Y, Yuan L, Beyler SA, Lessey BA. 2000 Blockade of the $\alpha_v\beta_3$ integrin adversely affects implantation in the mouse. *Biol. Reprod.* **62**, 1285–1290. (doi:10.1095/biolreprod62.5.1285)
148. Yu M, Wang J, Liu S, Wang X, Yan Q. 2017 Novel function of pregnancy-associated plasma protein A: promotes endometrium receptivity by up-regulating *N*-fucosylation. *Scient. Rep.* **7**, 5315. (doi:10.1038/s41598-017-04735-0)
149. Nikzad H, Taherian AA, Akimoto Y, Iwashita M, Mahabadi JA, Salehi M, Nikzad M. 2013 $\alpha v\beta 3$ Integrin express on mid-luteal human endometrium: an immunogold and immunofluorescent staining study. *Anat. Sci. J.* **10**, 137–143.
150. Qin L, Wang YL, Bai SX, Ji SH, Qiu W, Tang S, Piao Y-S. 2003 Temporal and spatial expression of integrins and their extracellular matrix ligands at the maternal-fetal interface in the rhesus monkey during pregnancy. *Biol. Reprod.* **69**, 563–571. (doi:10.1095/biolreprod.103.015198)
151. Ieguchi K, Fujita M, Ma Z, Davari P, Taniguchi Y, Sekiguchi K, Wang B, Takada YK, Takada Y. 2010 Direct binding of the EGF-like domain of neuregulin-1 to integrins ($\alpha v\beta 3$ and $\alpha 6\beta 4$) is involved in neuregulin-1/ErbB signaling. *J. Biol. Chem.* **285**, 31 388–31 398. (doi:10.1074/jbc.M110.113878)
152. Fujita M, Takada YK, Takada Y. 2012 Integrins $\alpha v\beta 3$ and $\alpha 4\beta 1$ act as coreceptors for fractalkine, and the integrin-binding defective mutant of fractalkine is an antagonist of CX3CR1. *J. Immunol.* **189**, 5809–5819. (doi:10.4049/jimmunol.1200889)
153. Zeng BX, Fujiwara H, Sato Y, Nishioka Y, Yamada S, Yoshioka S, Ueda M, Higuchi T, Fujii S. 2007 Integrin $\alpha 5$ is involved in fibronectin-induced human extravillous trophoblast invasion. *J. Reprod. Immunol.* **73**, 1–10. (doi:10.1016/j.jri.2006.05.007)
154. Green CJ, Fraser ST, Day ML. 2015 Insulin-like growth factor 1 increases apical fibronectin in blastocysts to increase blastocyst attachment to endometrial epithelial cells *in vitro*. *Hum. Reprod.* **30**, 284–298. (doi:10.1093/humrep/deu0309)
155. Shimomura Y, Ando H, Furugori K, Kajiyama H, Suzuki M, Iwase A, Mizutani S, Kikkawa F. 2006 Possible involvement of crosstalk cell-adhesion mechanism by endometrial CD26/dipeptidyl peptidase IV and embryonal fibronectin in human blastocyst implantation. *Mol. Hum. Reprod.* **12**, 491–495. (doi:10.1093/molehr/gal019)
156. Thirkill TL, Hendren SR, Soghomonians A, Mariano NF, Barakat AI, Douglas GC. 2004 Regulation of trophoblast beta1-integrin expression by contact with endothelial cells. *Cell Commun. Signal.* **2**, 4. (doi:10.1186/1478-811X-2-4)
157. Zhang B, Horvath S. 2005 A general framework for weighted gene co-expression network analysis. *Stat. Appl. Genet. Mol. Biol.* **4**, 17. (doi:10.2202/1544-6115.1128)
158. Damsky CH, Librach C, Lim KH, Fitzgerald ML, McMaster MT, Janatpour M, Zhou Y, Logan SK, Fisher SJ. 1994 Integrin switching regulates normal trophoblast invasion. *Development* **120**, 3657–3666. (doi:10.1242/dev.120.12.3657)
159. Wang J, Armant DR. 2002 Integrin-mediated adhesion and signaling during blastocyst implantation. *Cells Tissues Organs* **172**, 190–201. (doi:10.1159/000066970)
160. Franek AD, Salamonsen LA, Lopata A. 1999 Marmoset monkey trophoblastic tissue growth and matrix metalloproteinase secretion in culture. *Reproduction* **117**, 107–114. (doi:10.1530/jrf.0.1170107)
161. Wang H, Li Q, Shao L, Zhu C. 2001 Expression of matrix metalloproteinase-2, -9, -14, and tissue inhibitors of metalloproteinase-1, -2, -3 in the endometrium and placenta of rhesus monkey (*Macaca mulatta*) during early pregnancy. *Biol. Reprod.* **65**, 31–40. (doi:10.1095/biolreprod65.1.31)
162. Seo H, Bazer FW, Burghardt RC, Johnson GA. 2019 Immunohistochemical examination of trophoblast syncytialization during early placentation in sheep. *Int. J. Mol. Sci.* **20**, 4530. (doi:10.3390/ijms20184530)
163. Wooding FBP. 1984 Role of binucleate cells in fetomaternal cell fusion at implantation in the sheep. *Am. J. Anat.* **170**, 233–250. (doi:10.1002/aja.1001700208)
164. Bazer FW, Wu G, Spencer TE, Johnson GA, Burghardt RC, Bayless K. 2010 Novel pathways for implantation and establishment and maintenance of pregnancy in mammals. *Mol. Hum. Reprod.* **16**, 135–152. (doi:10.1093/molehr/gap095)
165. Schlafke S, Enders AC. 1975 Cellular basis of interaction between trophoblast and uterus at implantation. *Biol. Reprod.* **12**, 41–65. (doi:10.1095/biolreprod12.1.41)
166. Tu Z *et al.* 2015 Uterine RAC1 via Pak1-ERM signaling directs normal luminal epithelial integrity conducive to on-time embryo implantation in mice. *Cell Death Differ.* **23**, 169–181. (doi:10.1038/cdd.2015.98)
167. Parr EL, Tung HN, Parr MB. 1987 Apoptosis as the mode of uterine epithelial cell death during embryo implantation in mice and rats. *Biol. Reprod.* **36**, 211–225. (doi:10.1095/biolreprod36.1.211)
168. Elder JH, Hartman CG, Heuser CA. 1938 A ten and one-half day chimpanzee embryo, "Yerkes A". *J. Am. Med. Assoc.* **111**, 1156–1159. (doi:10.1001/jama.1938.02790390012004)
169. Gellersen B, Reimann K, Samalecos A, Aupers S, Bamberger AM. 2010 Invasiveness of human endometrial stromal cells is promoted by decidualization and by trophoblast-derived signals. *Hum. Reprod.* **25**, 862–873. (doi:10.1093/humrep/dep468)
170. Rawlings TM *et al.* 2021 Modelling the impact of decidual senescence on embryo implantation in human endometrial assembloids. *eLife* **10**, e69603. (doi:10.7554/eLife.69603)
171. Elliot MG, Crespi BJ. 2015 Genetic recapitulation of human pre-eclampsia risk during convergent evolution of reduced placental invasiveness in eutherian mammals. *Phil. Trans. R. Soc. B* **370**, 20140069. (doi:10.1098/rstb.2014.0069)
172. Soncin F *et al.* 2018 Comparative analysis of mouse and human placentae across gestation reveals species-specific regulators of placental development. *Development* **145**, dev156273. (doi:10.1242/dev.156273)
173. Lash GE, Warren AY, Underwood S, Baker PN. 2003 Vascular endothelial growth factor is a chemoattractant for trophoblast cells. *Placenta* **24**, 549–556. (doi:10.1053/plac.2002.0923)
174. Lash GE, Cartwright JE, Whitley GSJ, Trew AJ, Baker PN. 1999 The effects of angiogenic growth factors on extravillous trophoblast invasion and motility. *Placenta* **20**, 661–667. (doi:10.1053/plac.1999.0427)
175. Xu S, Li J, Chen X, Liu B. 2020 *In vitro* study on the regulation of annexin IV and VEGF by hCG in the human endometrium. *Biochem. Res. Int.* **2020**, 8892930. (doi:10.1155/2020/8892930)
176. Liu Y *et al.* 2018 Single-cell RNA-seq reveals the diversity of trophoblast subtypes and patterns of differentiation in the human placenta. *Cell Res.* **28**, 819–832. (doi:10.1038/s41422-018-0066-y)
177. Burton GJ, Jauniaux E. 2017 The cytotrophoblastic shell and complications of pregnancy. *Placenta* **60**, 134–139. (doi:10.1016/j.placenta.2017.06.007)
178. Brosens I, Robertson WB, Dixon HG. 1967 The physiological response of the vessels of the placental bed to normal pregnancy. *J. Pathol. Bacteriol.* **93**, 569–579. (doi:10.1002/path.1700930218)
179. Pijnenborg R, Bland JM, Robertson WB, Dixon G, Brosens I. 1981 The pattern of interstitial trophoblastic invasion of the myometrium in early human pregnancy. *Placenta* **2**, 303–315. (doi:10.1016/S0143-4004(81)80027-6)