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The evolution of embryo implantation

MICHAEL R. MCGOWEN[1], OFFER EREZ[2], ROBERTO ROMERO[3,4,5] and DEREK E. WILDMAN*[,1,3,4,6]

[1]Center for Molecular Medicine and Genetics, Wayne State University School of Medicine, Detroit, MI, USA, [2]Department of Obstetrics and Gynecology, Soroka University Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel, [3]Perinatology Research Branch, Program for Perinatal Research and Obstetrics, Division of Intramural Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH, Bethesda, MD and Detroit, MI USA, [4]Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, MI, USA, [5]Department of Epidemiology and Biostatistics, Michigan State University, East Lansing, MI, USA and [6]Department of Obstetrics and Gynecology, Wayne State University School of Medicine, Detroit, MI, USA

ABSTRACT Embryo implantation varies widely in placental mammals. We review this variation in mammals with a special focus on two features: the depth of implantation and embryonic diapause. We discuss the two major types of implantation depth, superficial and interstitial, and map this character on a well-resolved molecular phylogenetic tree of placental mammals. We infer that relatively deep interstitial implantation has independently evolved at least eight times within placental mammals. Moreover, the superficial type of implantation represents the ancestral state for placental mammals. In addition, we review the genes involved in various phases of implantation, and suggest a future direction in investigating the molecular evolution of implantation-related genes.

KEY WORDS: *mammal, phylogeny, gene, implantation, superficial, interstitial*

Introduction

Embryonic implantation into the maternal endometrium/decidua is a key feature for successful mammalian pregnancy. Early pregnancy loss in humans is a broad concern as an estimated 15% of couples are infertile (Wang and Dey, 2006) and at least 40% of human pregnancies are lost before implantation (Edmonds *et al.*, 1982, Jauniaux and Burton, 2005). However, implantation varies across mammals and this variation may hold clues to treating infertility due to defective implantation. Tracing the evolution of reproductive features has the potential of unraveling reproductive disorders in humans by pinpointing reproductive model organisms and identifying where human-specific changes may have evolved (Crosley *et al.*, 2013, Hou *et al.*, 2009, Uddin *et al.*, 2008). This review examines the evolution of embryo implantation in mammals and sets out a research program for the future investigation of genes involved in implantation that may vary among species with different forms of trophoblast attachment and invasion.

Implantation in eutherian mammals is defined as the process by which the trophectoderm (i.e. the cells in the blastocyst that give rise to the placenta) of the developing blastocyst adheres to the endometrium of the uterus (Mossman, 1987). There are three phases of implantation: apposition, adhesion, and penetration (Schlafke and Enders, 1975). Apposition involves the establishment of physical contact between the trophectoderm of the blastocyst and the epithelial cells of the endometrium. Adhesion entails the process by which the blastocyst forms a stable connection with the uterus and cannot be readily detached. Finally, penetration is defined by the invasion of the endometrium by processes such as fusion, intrusion, or displacement of endometrial cells by the trophoectoderm (Schlafke and Enders, 1975).

Evolution of implantation depth

There are two major types of embryo implantation in eutherian mammals that can be distinguished by the degree of invasion of the blastocyst at the penetration stage. The most common is superficial attachment, in which there is little if any invasion of the trophectoderm into the endometrium, and the blastocyst is not wholly encapsulated by the endometrial extracellular matrix (Enders and King, 1991, Enders and Liu, 1991, Ramsey *et al.*, 1976, Salamonsen, 1999). The superficial type of attachment characterizes most of the studied species of mammals. Interstitial

Abbreviations used in this paper: AsymmMk, assymetrical Markov k-state 2 parameter; CG, chorionic gonadotropin; ECM, extracellular matrix; Mk1, Markov k-state 1 parameter; ML, maximum likelihood; MMP, matrix metalloproteinase; RIF, recurrent implantation failure.

***Address correspondence to:** Derek E. Wildman. Center for Molecular Medicine and Genetics, Wayne State University School of Medicine, 3240 Scott Hall, 540 E. Canfield Ave., Detroit, MI 48201, USA. Tel: +1-313-577-1253. Fax: +1-313-577-5218. E-mail: dwildman@wayne.edu

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attachment; however, involves the embedding and encasement of the blastocyst entirely within the uterine endometrium (Carson *et al.*, 2000, Norwitz *et al.*, 2001, Salamonsen, 1999). Interstitial implantation can be found in only four mammalian orders: Rodentia (rodents), Primates, Chiroptera (bats), and Eulipotyphyla (non-afrotherian insectivores) (Mossman, 1987). We note that the type of blastocyst attachment has not been characterized in the vast majority of mammalian species, but that at least one representative species has been characterized in most mammalian orders.

Due to the phylogenetic distribution of these orders within mammals, it is unlikely that interstitial attachment has originated only once. To determine the phylogenetic history of embryo implantation, we mapped this trait on a well-supported phylogenetic tree of placental mammals using maximum likelihood (ML) models in Mesquite 2.75 (Maddison and Maddison, 2011). Phylogenetic relationships and molecular dating estimates were taken from the amino acid tree of Meredith *et al.,* (2011), a recent comprehensive molecular phylogenetic study representing most mammal families. In many cases, we condensed genera from the same family into one taxon (i.e., *Rattus* and *Mus* = Muridae). Character states (superficial vs. interstitial implantation) for each species were taken from Mossman (1987) and Hayssen *et al.,* (1993). We used both the Mk1 (Markov k-state 1 parameter) and AsymmMk (Assymetrical Markov k-state 2 parameter) models, the second of which introduces asymmetry in the rate of change between the two character states. Using a likelihood ratio test with df=1, we rejected the AsymmMk (–lnL= 29.70786763), in favor of the slightly less parameter-rich Mk1 model (–lnL= 29.74966663); however, reconstruction barely differed between the two models.

From the ML reconstruction (Fig. 1), we can conclude that superficial attachment is ancestral for placental mammals. In addition, interstitial attachment has evolved separately at least eight times within placental mammals, at least three times within rodents, and at least twice within bats as well as eulipothyphlan insectivores. Humans and mouse, the two most extensively studied species, both have interstitial attachment, and evolved this attachment separately. The finding that the superficial type of implantation is ancestral for placental mammals stands in apparent contradiction to the previous observation that hemochorial placentation is also ancestral for placental mammals, and highlights the dynamic nature of developmental biology during the process of placentation. The only part of tree in which the probability of either superficial or interstitial implantation is P<0.95 is within yangochiropteran bats (see pie charts on nodes in Fig. 1). There is ~72% chance that interstitial implantation evolved separately in the Thyropteridae (*Thyroptera*) and Phyllostomidae (*Macrotus* + *Desmodus*), rather than a reversal back to superficial implanatation in the Noctilionidae (*Noctilio*).

What has lead to the repeated, although limited, evolution of this feature across the mammalian tree? This is unclear, as there are no features of the uterus or placenta that have a one to one correlation with depth of implantation; however, blastocyst size may be correlated. Blastocysts of species with interstitial attachment, such as human and mouse, tend to have smaller diameters than those with superficial attachment, presumably for the ease of penetration into the endometrium (Mossman, 1987). In some species with superficial attachment, such as ruminants, pigs, horses, and marsupials, elongation of the trophectoderm occurs before the apposition phase of implantation (Dey *et al.*, 2004, Spencer *et al.*, 2007), possibly due to the large surface area of placental attachment. It is unclear what the selective advantage is of interstitial attachment, although its ability to acquire rapid access to the maternal blood supply is noted (Mossman, 1987).

Embryonic diapause and delayed implantation

One other feature of implantation is its delay in many species, extending the total length of gestation. Delayed implantation (also known as embryonic diapause) has been identified in approximately 100 species of mammals (~70 eutherians and ~30 marsupials), from seven distinct orders, including Diprotodontia, Carnivora, Rodentia, Eulipotyphla, Chiroptera, Xenarthra, and Cetartiodactyla (Renfree and Shaw, 2000). At least in some species, delayed implantation is most likely correlated with the degree of seasonality of the environment. This is especially well documented in the Carnivora, where mustelids (weasels and relatives) and mephitids (skunks) living in temperate environments tend to retain delayed implantation (Ferguson *et al.*, 2006, Thom *et al.*, 2004), some delaying implantation for up to 11 months (McGowen *et al.*, 2013, Sandell, 1990). In other species with multiple litters per year, such as marsupials, rodents, and insectivores, delayed implantation occurs before the previous litter is weaned, and is likely an energy saving mechanism (Sandell, 1990). As with implantation depth, the phylogenetic distribution of species that undergo embryonic diapause is such that diapause likely evolved independently on multiple mammalian lineages.

Proteins involved in implantation

Researchers have identified multiple signaling molecules and proteins that are expressed in the blastocyst and the receptive endometrium before and during implantation that are critical for the establishment of pregnancy, especially in the well-studied mouse (Cha *et al.*, 2012, Dey *et al.*, 2004, Paria *et al.*, 2002, Wang and Dey, 2006). These include nuclear steroid hormone receptor genes such as estrogen and progesterone receptors (*ESR1*, *PGR*), other nuclear receptors (*PPARD*, *PPARG*), cytokines such as *LIF* (leukemia inhibitory factor) and *IL11* (interleukin 11), vasoactive factors such as *PTGS2* (prostaglandin-endoperoxide synthase 2), cannabinoid receptors (*CNR1*, *CNR2*), growth factors and their receptors (*HBEGF*, *EGFR*, *ERBB2*, *ERBB4*) and homeobox genes (*HOXA10*, *HOXA11*), among other genes (Table 1). Some of these genes are known to modulate the window of receptivity and attachment (*CB1*, *CB2*, *MSX1*, *MSX2*, *PLA2G4A*, *LPAR3*). For example, separate deletion of *PLA2G4A* and *LPAR3* in mouse causes the blastocyst to implant after the preferred window of receptivity, leading to complications at later stages of pregnancy, such as embryo crowding (Song *et al.*, 2002, Ye *et al.*, 2005). We propose that these genes are candidates for future research in the molecular evolution of delayed implantation, and sequencing these genes across a diverse array of mammals with and without delayed implantation would be beneficial for understanding implantation.

Many of the genes identified in the mouse also show expression in humans (Cha *et al.*, 2012). For example *IL11* has been identified as critical for implantation in humans as well as macaques (Dimitriadis *et al.*, 2003). *IL11* is expressed at the site of implantation and is related to the promotion of decidualization. However, many other genes have been implicated in uterine receptivity and implantation in humans that have not been noted in murids. Table 1 lists human genes implicated in uterine receptivity from microarray studies but

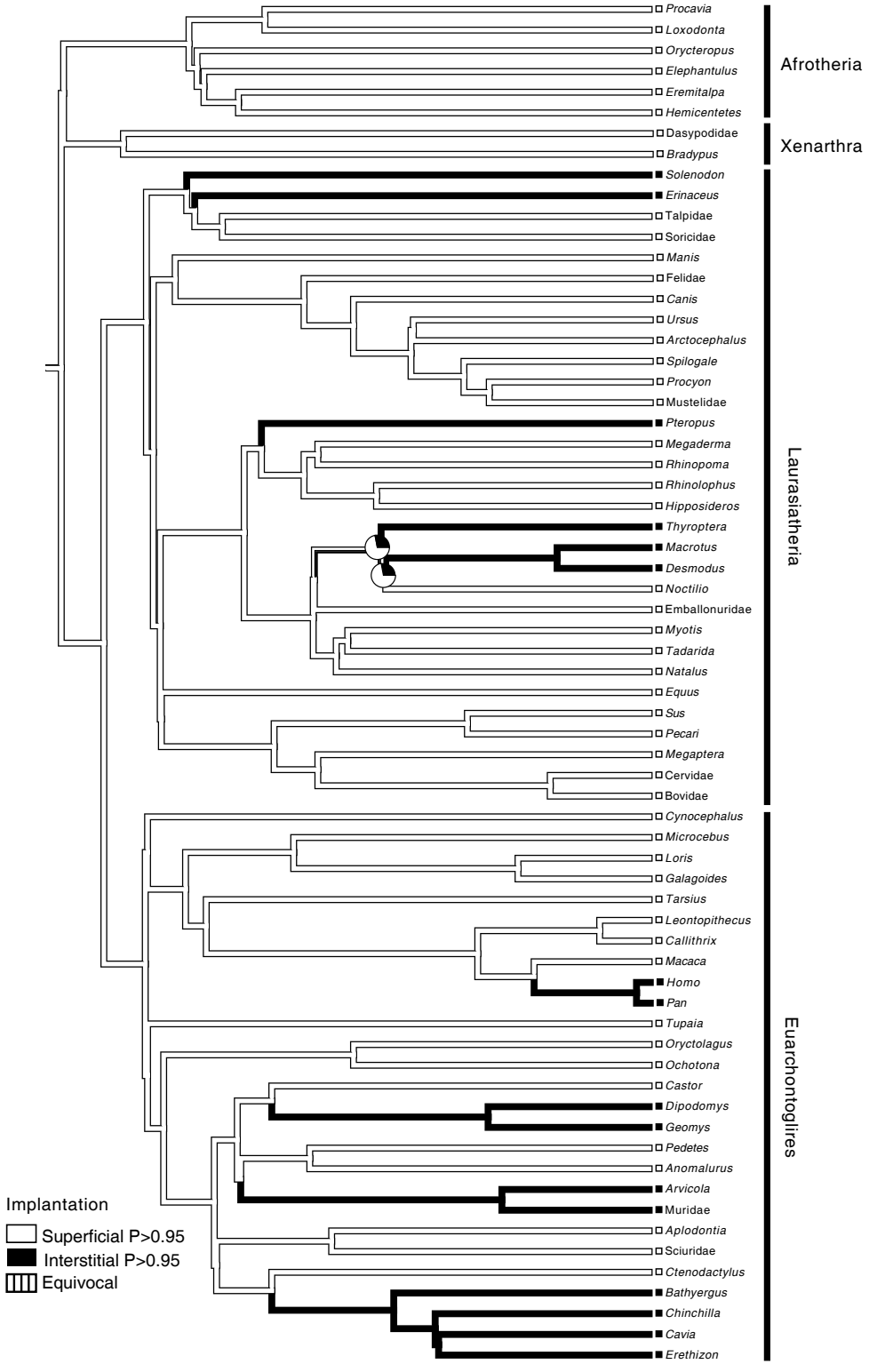

Fig. 1. Maximum likelihood reconstruction (using the Mk1 model) of implantation type in placental mammals with available evidence. *Phylogenetic relationships are form Meredith* et al., *(2011). The colors of each branch signify the presence of superficial (white) or interstitial (black) implantation with probability P>0.95. The two nodes that are represented by pie charts depict lineages without limited confidence for either superficial or interstitial implantation and display the probability of each character state at each node.*

not identified in mouse receptivity (Altmae *et al*., 2012, Wang and Dey, 2006). Very little is known about the expression of these genes during implantation across placental mammal diversity. Therefore, it is currently not known whether the pattern of gene expression seen in humans represents the ancestral or derived state among placental mammals. Regardless, it is likely that these genes could be involved in some of the differences between mouse and human implantation.

During implantation there are different ways in which trophectoderm cells penetrate the uterine epithelium. For example, the trophectoderm of humans and other primates move between uterine cells, while in the mouse, apoptosis of the epithelial cells facilitates penetration of trophectoderm into the endometrium (Carson *et al*., 2000). One important distinction of anthropoid primates compared to other species is the expression of chorionic gonadotropin (CG), a hormone produced by the developing embryo before implantation, and is involved in maintenance of the corpus luteum. The beta peptide of human (and that of other anthropoid primates) chorionic gonadotropin is a derived gene duplicate member of the beta lutenizing hormone family (Nagirnaja *et al.,* 2010). In addition, CG is also involved in cross-talk between the embryo and the endometrium, and is one of the key signals to initiate decidualization of uterine epithelium (Banerjee and Fazleabas, 2010). CG was found to initiate the expression of *LIF*, *SOD2*, *PAEP*, and *MMP7* in baboons (Banerjee and Fazleabas, 2010). *LIF* has been shown to be involved in trophoblast invasion in humans (Tapia *et al*., 2008) and is expressed in the endometrium of other primates and humans (Yue *et al*., 2000; Licht *et al*., 2000). Primates; however, show varying degrees of penetration into the uterine epithelium, with only *Pan* (chimpanzees) and *Homo* of primates yet investigated wholly penetrating below the basal membrane upon implantation. However, there is evidence of penetration in places in the New World monkey *Callithrix* (Enders and Lopata, 1999), and penetration of uterine vessels by the trophectoderm in the macaque and baboon, (Enders, 1995; Enders *et al*., 1996, 1997). This may allow for a more rapid access to maternal blood flow in the face of mostly superficial implantation

TABLE 1

MAJOR CANDIDATE GENES INVOLVED IN THE EVOLUTION OF IMPLANTATION

Gene Symbol	Gene Name	Function in uterus and/or blastocyst
Uterine receptivity and attachment		
MUC1	mucin 1	Prevention of adhesion in prereceptive phase of endometrium
ESR1	estrogen receptor alpha	Detection of estrogen for uterine receptivity
PGR	progesterone receptor	Detection of progesterone for uterine receptivity
LIF	leukemia inhibitory factor	Uterine receptivity and attachment
IL11	interleukin 11	Involved in decidiualization
PTGS2	prostaglandin synthase 2	Production of prostaglandins for increased vascular permeability at blastocyst attachment site
BMP2	bone morphogenetic protein 2	Production of prostaglandins for increased vascular permeability at blastocyst attachment site
CB1	cannabinoid receptor 1	Modulation of implantation window in blastocyst
CB2	cannabinoid receptor 2	Modulation of implantation window in blastocyst
HBEGF	heparin-binding EGF-like growth factor	Induction of attachment, promotion of growth in embryo via receptors
EGFR	epidermal growth factor receptor	receptor for HBEGF in blastocyst
ERBB2	v-erb-b2 erythroblastic leukemia viral oncogene homolog 2	receptor for HBEGF in blastocyst
ERBB4	v-erb-b2 erythroblastic leukemia viral oncogene homolog 4	receptor for HBEGF in blastocyst
HAND2	heart and neural crest derivatives expressed 2	Transcription factor crucial for implantation
IHH	Indian hedgehog	Uterine receptivity
FKBP4 (FKBP52)	FK506 binding protein 4, 59kDa	Optimizes progesterone receptor activity
MSX1	msh homeobox 1	Modulation of implantation window in uterus
MSX2	msh homeobox 2	Modulation of implantation window in uterus
KLF5	Kruppel-like factor 5 (intestinal)	Cell proliferation near blastocyst site
HOXA10	homeobox A10	Uterine receptivity and decidualization
HOXA11	homeobox A11	Uterine receptivity and decidualization
PPARD	peroxisome proliferator-activated receptor delta	Uterine receptivity and decidualization
PPARG	peroxisome proliferator-activated receptor gamma	Uterine receptivity and decidualization
PLA2G4A	phospholipase A2, group IVA (cytosolic, calcium-dependent)	Modulation of implantation window in uterus
LPAR3	lysophosphatidic acid receptor 3	Modulation of implantation window in uterus
Uterine receptivity and attachment (detected in human only)		
APOD	apolipoprotein D	
CLDN4	claudin 4	
C1R	complement component 1R	
CYP2C9	cytochrome P450, family 2, subfamily C, polypeptide 9	
DKK1	dickkopf 1	
DPP4	dipeptidyl-peptidase 4	
EDNRB	endothelin receptor type B	
GADD45A	growth arrest and DNA-damage-inducible, alpha	
GPX3	glutathione peroxidase 3 (plasma)	
HABP2	hyaluronan binding protein 2	
ID4	inhibitor of DNA binding 4, dominant negative helix-loop-helix protein	
IL15	interleukin 15	
LMOD1	leiomodin 1	
MAOA	monoamine oxidase A	
MAP3K5	mitogen-activated protein kinase kinase kinase 5	
MTNR1A	melatonin receptor 1A	
PAEP	progestagen-associated endometrial protein	
SERPING1	serpin peptidase inhibitor, clade G (C1 inhibitor), member 1	
SPP1	secreted phosphoprotein 1	
CCNB1	cyclin B1	
OLFM1	olfactomedin 1	
TGFB1	transforming growth factor, beta 1	
Penetration		
MMP2	matrix metallopeptidase 2	Breakdown of type IV collagen in endometrium
MMP9	matrix metallopeptidase 9	Breakdown of type IV collagen in endometrium

Altmae *et al.*, 2012; Cha *et al.*, 2012; Curry and Osteen, 2003; Dey *et al.*, 2004, Paria *et al.*, 2002; Song *et al.*, 2002; Wang and Dey, 2006; Ye *et al.*, 2005.

(Enders *et al.*, 1997).

The penetration phase of implantation involves a different set of genes with the role of remodeling endometrial tissue. Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases which break down numerous extracellular matrix (ECM) proteins and are involved in multiple aspects of tissue remodeling (Martel-Pelletier *et al.*, 2001). At least some MMPs play a major role in implantation and the remodeling of endometrial tissue (Curry and Osteen, 2003). Evidence of MMP expression during the penetration phase of implantation has been reported from numerous mammalian lineages, including both interstitial and superficial implanting species (Bai *et al.*, 2005, Bischof and Campana, 2000, Bischof *et al.*,

1998, Blankenship and Enders, 1997, Carson *et al.*, 2000, Chou *et al.*, 2003, Gao *et al.*, 2001, Hardy and Spanos, 2002, Herrler *et al.*, 2003, Li *et al.*, 2002, Li *et al.*, 2003, Norwitz *et al.*, 2001) and rodents (Alexander *et al.*, 1996, Canete-Soler *et al.*, 1995, Dai *et al.*, 2003, Feng *et al.*, 1998, Hardy and Spanos, 2002, Hurst and Palmay, 1999, Zhao *et al.*, 2002). MMPs are also expressed in superficially implanting species such as felids (Walter and Schonkypl, 2006) and bovids (Menino *et al.*, 1997, Uekita *et al.*, 2001). Due to their involvement in both superficial and interstitial implanting species, MMPs are likely important in trophoblast invasion in general. Perhaps the most important MMPs to be identified in endometrial penetration are the gelatinases coded by the genes *MMP2* and *MMP9*. Both *MMP2* and *MMP9* play an important role in the establishment of pregnancy (Curry and Osteen, 2003). Indeed *MMP9* is involved in successful cytotrophoblast invasion and specifically dissolves collagen type IV, a major component of the endometrial basal membrane (Librach *et al.*, 1991). Further evidence for the important role of *MMP2* and *MMP9* in successful implantation has been found in the clinic (Yoshii *et al.,* 2013). That study examined the role of these genes in recurrent implantation failure (RIF). Three hundred and sixty patients underwent MMP measurements, and those patients that had high MMP2 and MMP9 levels (as measured by gelatin enzyme zymography) were subsequently treated with antibiotics and steroids. This treatment reduced the MMP levels in the vast majority of patients, and the patients who underwent such treatment had significantly better pregnancy rate as well as a significantly lower miscarriage rate than was observed in control patients (Yoshii *et al.,* 2013). The molecular evolution of *MMP2* and *MMP9* has not been investigated, but we would expect that adaptive evolutionary changes could be associated with the emergence and increased depth of implantation in specific species.

Differences between implantation types may involve direct change in amino acid sequence of the protein, which can be investigated using analyses to detect natural selection (Yang, 2007). Alternatively, these changes may be the result of changes in expression level via *cis*-regulatory mutations, with *MMP2* and *MMP9* having greater expression levels at early phases in development in species with interstitial implantation. Indeed, it has been shown that the normally non-translated 3' region of the *LHB* gene is translated in some cases as the *CGB* gene in equuids and bovids; however the bovid version lacks proper O-glycans; thus, preventing CG activity in artiodactyls (Gabay *et al.,* 2013). This mechanism of peptide generation differs from the gene duplication model seen in anthropoid primatess. Comparative transcriptomics of multiple species has the potential to reveal differences in expression that may have been the result of natural selection (Brawand *et al.*, 2011). However, the scarcity of primate (an other mammal) tissue at various stages of embryonic and placental development may be a critical limiting factor.

Summary and conclusion

We have demonstrated that deep interstitial implantation has originated at least eight times within eutherian mammals. The genetic and epigenetic variation that accounts for this difference among mammalian species is not clear. Mice, rats, and humans share the interstitial type of implantation, thus murids are, for this feature, an appropriate natural model for human embryo implantation. Additionally, multiple genes have been identified interacting at the attachment and penetration phases of implantation. Analysis of the evolution of these genes may reveal the underlying mutations that have led to interstitial implantation and provide clues for treatment of implantation defects in humans.

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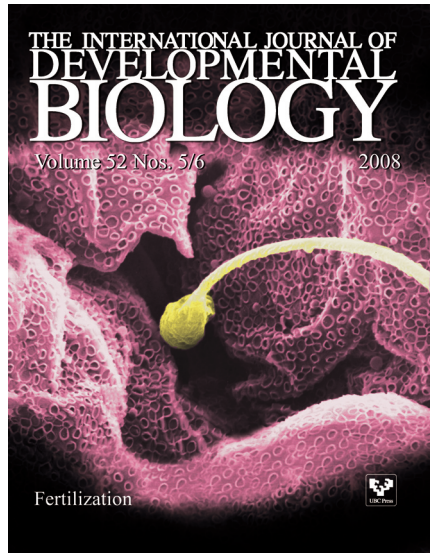

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