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SYMPOSIUM: FUTURES IN REPRODUCTION
REVIEW

Reprint of: Uterine plasticity and reproductive fitness☆

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Abstract Reproduction in humans is unique in two major aspects. First, the incidence of chromosomally abnormal and developmentally compromised human preimplantation embryos is exceptionally high, and second, the uterus decidualizes spontaneously each cycle, a process also responsible for the menstrual shedding of the endometrium in the absence of pregnancy. Emerging evidence suggests that these distinctive reproductive traits are functionally linked. Thus, the decidual process enables the mother to limit investment in compromised pregnancies, while menstruation imposes a need for constant recruitment of mesenchymal stem cells to regenerate and renew the endometrium each cycle. Endometrial stem cells are immune-privileged compared with other types of adult stem cells, suggesting a role for these cells in accommodating deeply invading semi-allogenic fetal trophoblast. Thus, by coupling reproductive competence to a process of constant tissue renewal, decidualization enables the human uterus to adapt to pregnancy failure and a changing ecology.

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Introduction

Being a predominantly monotocous species with deeply invasive embryos that display intrinsic chromosomal instability, reproductive success is far from guaranteed in human beings. Recent studies have highlighted just how abnormal 'normal' human embryos are (Mertzanidou et al., 2013; Vanneste et al., 2009). Mertzanidou and colleagues used

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array comparative genomic hybridization to analyse all the blastomeres of normally developing cleavage-stage embryos that were part of a cohort of embryos that resulted in healthy births. In line with other studies, chromosomal errors were detected in 70% of these top-quality embryos (Mertzanidou et al., 2013). The mitotic error rate in cleavage stage embryos is higher than the meiotic aneuploidy rate. Consequently, the genome of an individual blastomere is not representative of the genome of other cells in the embryo. While these observations explain the unequivocal failure of preimplantation genetic screening to improve the efficacy of IVF treatment to date (Harper and Sengupta, 2012), they also raise important and as-yet unresolved questions regarding the origins and significance of embryonic mosaicism during early stages of development. Time-lapse image analysis suggested that exchange of chromosome-containing fragments between blastomeres may contribute to the generation of human embryonic aneuploidies (Chavez et al., 2012). Whatever the underlying mechanisms, it is clear that human beings generate extraordinarily diverse preimplantation embryos, which are occasionally entirely diploid, mostly mosaic and not uncommonly completely chromosomally chaotic. Culture as part of assisted reproduction treatment may also result in subtle epigenetic changes that compromise the long-term developmental potential of embryos (reviewed in Lucas, 2013; Mann and Denomme, 2013). This situation presents the mother with an important dilemma: how to maximize the likelihood of reproductive success when faced with such an extraordinary prevalence of highly invasive but chromosomally abnormal embryos?

Conflicts between parent and offspring are thought to drive reproductive evolution and innovation (Haig, 1993). Because of these innate differences in evolutionary interests, it has been postulated that the embryonic genome evolves to extract as much as possible from the mother to ensure its own propagation, whereas maternal genes evolve to safeguard success not only of current but also future offspring. This hypothesis predicts that reproductive success depends on a constant homeostatic rebalancing of embryonic and maternal traits. An evolutionary change in one of the parties must be met by adaptation in the other (Chuong et al., 2013; Crespi and Semeniuk, 2004; Emera et al., 2012b). In view of the intrinsic genomic instability that characterizes human preimplantation embryonic development, the maternal–fetal conflict hypothesis predicts that a strategy must have emerged to safeguard the mother against prolonged investment in invasive but developmentally abnormal embryos. It also predicts that the diversity inherent in human embryos must be met by an intrinsic ability to adapt the maternal response to an individual conceptus.

This review describes the specialist functions of the endometrium that enables it to meet the challenges imposed by human embryos. For didactic purposes, we have divided these functions into a five-step programme for reproductive fitness (**Figure 1**).

Step 1: Be prepared

The most salient feature of the human reproductive cycle is 'spontaneous' decidualization, which refers to the fact that the endometrium mounts a pregnancy response in each menstrual cycle (Brosens et al., 2002; Gellersen et al., 2007). Decidualization is defined by the mesenchymal to epithelial transformation of endometrial fibroblasts into secretory decidual cells. In most mammalian species, decidualization is triggered by embryonic signals, but in humans and a handful of other species, it is initiated in response to elevated circulating progesterone concentrations and rising tissue concentrations of cyclic AMP (Brosens et al., 1999; Jones et al., 2006).

The adjective 'spontaneous' is somewhat misleading, as the decidual process in the human endometrium is under tight spatiotemporal control. It is initiated in the mid-luteal

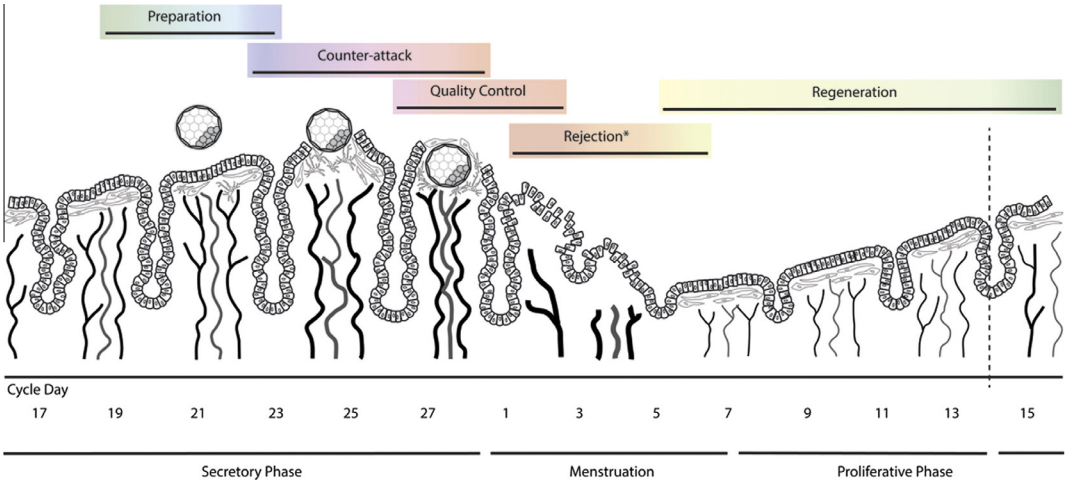


Figure 1 With each cycle, the human endometrium decidualizes spontaneously in preparation for implantation, resulting in the secretory, pro-inflammatory environment characteristic of receptivity. In the presence of an embryo, the decidualizing stromal cells acquire a motile phenotype upon breaching of the luminal epithelium by the embryo and mount a counter-invasive attack to limit the embryonic assault. Encapsulation of the embryo not only lends it protection, but also provides the opportunity for a maternal quality control process to occur. Identification of an unsuitable embryo results in default rejection along with shedding of the superficial endometrial cells in menstruation, as would be the case in non-conception cycles. Regeneration of the endometrium then takes place through recruitment of adult stem cells from their perivascular niche in preparation for the next cycle.

phase of the cycle, beginning in stromal cells surrounding the terminal spiral arteries and underlying the luminal epithelium. During the late secretory phase, the process will encompass the entire superficial endometrial layer. The expression of decidual genes is hardwired through the presence of regulatory transposable elements found only in placental mammals. The insertion of these mobile DNA elements in the genome established new boundaries between inactive and active chromatin in stromal cells and introduced novel *cis*-regulatory elements (enhancer/repressor elements and promoters) that have co-opted the cyclic AMP and progesterone signalling pathways to drive expression of decidua-specific genes (Lynch et al., 2011a,b). A case in point is the hAT-Charlie family DNA transposon MER20, which, upon binding of a composite transcriptional complex consisting of the liganded progesterone receptor and cyclic AMP-dependent transcription factors (e.g. FOXO1, C/EBPβ and HOXA10/11), drives the expression of *PRL* (prolactin) and numerous other decidual genes (Lynch et al., 2011a).

Decidualization bestows a secretory phenotype on endometrial stromal cells. In view of the topography of this differentiation process, decidualizing cells are strategically placed to develop a specialist microenvironment conducive of implantation. This microenvironment will change dynamically as the decidual process unfolds. Initially, the decidual process resembles an acute-phase pro-inflammatory response, characterized by the endogenous production of free radicals by differentiating endometrial stromal cells and the co-ordinated expression of chemokines, interleukins and other inflammatory mediators (Al-Sabbagh et al., 2011; Salker et al., 2012). Amongst the cytokines released are several, including interleukin (IL)-11, IL-33, and IL-15 (Ain et al., 2004; Bourgeois et al., 2009; Manaster et al., 2008) that are involved in recruitment, differentiation and modulation of uterine natural killer cells. At a functional level, this transient pro-inflammatory decidual response seems to be a key regulator of the window of implantation. This notion is based on the observation that only during the pro-inflammatory decidual response does the secretome of human endometrial stromal cells induce the expression of key receptivity genes, as assessed by exposing the lumen of a mouse uterus to the human secretome by flushing it through. This decidual response then enables pregnancy to occur followed the transfer of murine embryos (Salker et al., 2012). Amongst the essential implantation genes that are regulated in the mouse uterus in response to soluble factors from decidualizing human endometrial stromal cells are leukaemia inhibitory factor, bone morphogenetic protein 2, wingless-type MMTV integration site family member 4 and heparin-binding EGF-like growth factor.

By activating feedback pathways, the inflammatory decidual response is self-limiting and followed by a profound anti-inflammatory response in decidualizing cells, characterized by simultaneous down-regulation of numerous chemokines and inflammatory mediators (Salker et al., 2012). Silencing of chemokine expression prevents effector T cells from entering the decidua (Nancy et al., 2012). In concert, continued progesterone signalling will massively up-regulate 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1), an enzyme that converts inert cortisone to active cortisol (Kuroda et al., 2013). Notably, *HSD11B1*, the gene that encodes 11βHSD1, is also under the control of a MER20 promoter element in endometrial cells (Lynch et al., 2011a). Consequently, decidualizing cells establish a cortisol gradient in the endometrium, which probably provides additional protection to the invading allogeneic fetal trophoblast against a maternal immune response (Gilmour et al., 2006). Importantly, human endometrial stromal cells express the full complement of 3-ketosteroid receptor subfamily of nuclear receptors. Besides the progesterone receptor and androgen receptor, this subfamily is made up by the cortisol-responsive glucocorticoid and mineralocorticoid receptors. Upon decidualization, glucocorticoid receptor expression declines whereas mineralocorticoid receptor is reciprocally up-regulated (Kuroda et al., 2013). Small interfering RNA-mediated knockdown experiments demonstrated that activation of this progesterone—11βHSD1—mineralocorticoid receptor axis induces the expression of several key enzymes involved in lipid metabolism and retinoid acid biosynthesis and storage. Thus, local cortisol biosynthesis, induction and activation of mineralocorticoid receptor may be the primary trigger that kickstarts the histiotrophic support essential for embryo development prior to the onset of placental perfusion around 10—11 weeks of gestation (Burton et al., 2011). Further, retinoic acid, the biologically active metabolite of vitamin A, is essential for embryogenesis. However, the supply of retinoic acid must be tightly controlled as both deficiency and excess cause severe fetal malformation (Han et al., 2010; Niederreither and Dolle, 2008; Xia et al., 2010).

Taken together, these observations indicate that 'spontaneous' decidualization ensures that the transient period of endometrial receptivity is coupled to a post-nidation environment that is both supportive and tolerant of the embryonic semi-allograft.

Step 2: Attack is the best form of defence

Implantation is commonly depicted as a step-wise process involving apposition and adhesion of a blastocyst to the endometrium, followed by breaching of the luminal epithelium and then active invasion of embryonic trophectoderm into the uterine stroma (Dey et al., 2004; Fazleabas and Kim, 2003; Genbacev et al., 2003). For obvious reasons, this concept is based on animal models, especially murine studies. Whether or not this model is truly applicable to implantation in humans is anyone's guess. It is not, however, an academic issue as most of the attempts to predict and regulate endometrial receptivity, especially in the context of IVF, are based on this model. The identification of markers for assessing endometrial receptivity is reviewed in Salamonsen et al. (2013). So far, attempts to control uterine receptivity (i.e. switch 'on') have failed, which should raise at least an element of doubt about the accuracy of the implantation paradigm. Further, there are some important differences in the implantation process among species. Reproductive success in mice — unlike primates — is based on quantity, as exemplified by rapid breeding cycles, multiple implantation events and large litter sizes. Mouse embryos are capable of temporarily suspending development while awaiting the right maternal signals for implantation, a process termed embryonic 'diapause' (Lopes et al.,

2004). This maternal signal is a surge in ovarian oestradiol, which triggers synchronized implantation of chromosomally stable mouse embryos (Hamatani et al., 2004). By contrast, human embryos do not normally exhibit diapause, are highly invasive and — as aforementioned — often chromosomally unstable. In view of these characteristics, it seems reasonable to query the fate of the numerous IVF embryos that are transferred each day but which fail to give rise to an ongoing pregnancy. The common answer to this rather metaphysical question seems to be that lack of endometrial receptivity forces embryos to remain free-floating in the uterine lumen until they degenerate and die. Free-floating human embryos have indeed been recovered by uterine flushing in natural cycles from donor women and transferred successfully to recipient infertile patients (Formigli et al., 1990). Further, pioneering work from Croxatto has shown that between 120 and 168 h after the LH surge, transcervical flushing is particularly efficient at retrieving embryos from the uterine cavity (Diaz et al., 1980). While these studies provide insights into the length of the journey of the ovum through the Fallopian tube, they do not prove that failed implantation equates to failure of the embryo to breach the luminal epithelium.

Whether the luminal epithelium is a genuine barrier in the implantation process or not, once breached, decidualizing stromal cells will actively migrate and surround the implanting human embryo (Quenby and Brosens, 2013). The notion that maternal cells drive the tissue remodelling that enables an embryo to embed in the stroma originated from time-lapse imaging studies of human blastocysts placed on a monolayer of decidualizing endometrial stromal cells (Grewal et al., 2008, 2010). Decidualizing cells in the proximity of the blastocyst are highly motile, and, importantly, inhibition of the migratory activity of decidualizing stromal cells suppresses embryo trophoblast invasion into the monolayer. This observation was recapitulated in co-cultures of decidualizing human endometrial stromal cells with mouse blastocysts (Grewal et al., 2010). Gellersen and colleagues (Gellersen et al., 2010, 2013; Schwenke et al., 2013) established an alternative implantation model based on trophoblast spheroids instead of blastocysts. Again, trophoblast expansion was promoted upon decidualization of endometrial stromal cells. The same group also used various migration assays to measure chemotaxis (directed locomotion) as well as chemokinesis (non-directional locomotion) in endometrial stromal cell and trophoblast co-cultures (Gellersen et al., 2013). These studies showed that both decidualizing cells and trophoblast actively signal to enhance each other's migration. Several key implantation factors, including heparin-binding EGF-like growth factor, interleukin-1β (IL-1β) and leukaemia inhibitory factor, were shown to enhance both directional and non-directional motility of decidualizing cells. Trophoblast signals, however, only stimulated directional migration of decidualizing stromal cells, a response attenuated by a blocking antibody against dimeric platelet-derived growth (PDGF) factor A. Interestingly, transcripts encoding PDGF-A are detectable in the human oocyte, 8-cell, morula and blastocyst stages but not in the 4-cell stage (Osterlund et al., 1996). CXCL12 (also known as stromal-derived factor 1α) may be another important factor to stimulate migration of endometrial stromal cells. Trophoblast cell-derived CXCL12 was shown to up-regulate CXCR4 (the receptor for CXCL12) in decidual stromal cells isolated from first-trimester pregnancies, and to promote their invasiveness (Ren et al., 2012).

When placed within the context of an evolutionary tug-of-war between maternal and fetal genomes, the above studies suggest that decidualizing endometrial stromal cells are programmed to mount a counter-invasive response to the invasive nature of human embryos. If so, early implantation events are more akin to host—pathogen interactions, in which the host mounts a robust cellular response, typically characterized by tissue swelling due to cell recruitment and matrix expansion and resulting in encapsulation of the parasite. To avoid collateral damage, the endometrium may arguably need to temporarily suspend its normal anti-infection defences during the window of implantation. Interferon ε was recently identified as a potent antipathogen expressed exclusively in the female reproductive tract, including the luminal and glandular uterine epithelium. Expression of interferon ε decreases dramatically during the implantation window, at least in mice (Fung et al., 2013).

Step 3: Quality control and personalized implantation

Encapsulation by decidual cells may serve to protect the early conceptus from maternal perturbations related to metabolism, stress, infections, oxygen tension or endocrine disruptors. A prominent feature of decidual cells is indeed their ability to resist environmental stressors, including oxidative stress (Kajihara et al., 2006; Leitao et al., 2010, 2011). This extraordinary resistance is based not only on the induction of various free radical scavengers but also on the selective silencing of stress-activated signalling pathways such as JNK and down-stream pro-apoptotic transcription factors (e.g. FOXO3a). Conversely, compelling evidence suggests that encapsulating decidual cells are important to ensure maternal recognition of abnormal embryos. This notion is based on some striking finding reported by Teklenburg and colleagues (Teklenburg et al., 2010b, Weimar et al., 2013). These investigators employed a human co-culture model, consisting of hatched blastocysts cultured on decidualizing endometrial stromal cells, to identify key factors involved in the embryo—maternal cross-talk. The co-culture supernatants were collected after 3 days and subjected to a multiplex immunoassay capable of simultaneously measuring 14 putative implantation cytokines, growth factors and chemokines. Expression levels were then compared with that in decidualizing endometrial stromal cells in the absence of an embryo. The experimental design could be described as rather hopeful: no fewer than 50,000 decidualizing endometrial cells were co-cultured with single embryos. Taking this imbalance into account, it was perhaps not surprising that the presence of a developing human embryo had no measurable effects on the expression of implantation factors by decidualizing cells. However, a marked and selective response was noted when embryos became compromised during the co-culture period. This maternal response was characterized by selective inhibition of IL-1β, -6, -10, -17, -18, chemokine (C-C motif) ligand 11 (also known as eotaxin) and heparin-binding EGF-like growth factor secretion. Repeat co-culture experiments with undifferentiated human endometrial stromal cells yielded no

maternal response irrespective of embryo quality (Teklenburg et al., 2010b). Further, in a follow-up study, the same group reported that migration of decidualizing cells is selectively inhibited in response to soluble signals from low-grade but not high-grade human embryos (Weimar et al., 2012). Taken together, these observations indicate that human endometrial stromal cells become biosensors of embryo quality upon differentiation into decidual cells (Teklenburg et al., 2010a; Telgmann and Gellersen, 1998).

The notion that the endometrium is capable of sensing and adapting its response to individual embryos originated from livestock experiments (Mansouri-Attia et al., 2009). In ruminants, assisted reproduction technology and somatic cell nuclear transfer are associated with developmental abnormalities and postnatal disorders, such as large offspring syndrome (Barnes, 2000). Microarray analyses in the cow have shown that endometrial gene expression will adapt to the developmental origins (e.g. somatic cell nuclear transfer, IVF, artificial insemination) and potential of the embryo (Mansouri-Attia et al., 2009). Thus, endometrial plasticity, here defined as the ability to mount a maternal response tailored to individual embryos, seems to be critical for reproductive success in a wide range of mammals. The inference is that endometrial plasticity must be an evolutionarily enhanced reproductive feature of the human uterus.

Step 4: Default rejection

Menstruation is rarely mentioned in the context of the implantation process, undoubtedly because this extraordinary biological phenomenon is almost absent in non-primate animal models such as mice. Yet an inducible disposal mechanism for unwanted concepti seems a logical requirement if the endometrium engages — as asserted — in embryo recognition and natural selection at implantation. Menstruation, defined as the cyclic bleeding caused by shedding of the superficial endometrium, is confined to those species that exhibit spontaneous decidualization: i.e. higher primates, some bats, and the elephant shrew (Emera et al., 2012b). Notably, pregnancy in all menstruating species is dependent on a deeply invading haemochorial placenta and results in the birth of only one or two well-developed offspring (Martin, 2003). Chromosomal instability is prevalent in rhesus macaque preimplantation embryos (Dupont et al., 2009), although it is not yet known if this reproductive trait extends to all menstruating species. Amongst menstruating primates, the extent of the decidual process and the degree of cyclic bleeding match the progression in the degree of placental invasiveness from tarsiers through New World monkeys, Old World monkeys and apes to a maximum in humans (Martin, 2003; Parham, 2013).

A cardinal feature of the decidual cells is that they are poised to self-destruct in response to defined cues (Brosens and Gellersen, 2006). The principle trigger, at least in the absence of a conceptus, is a fall in circulating progesterone concentrations, which in turn reactivates the expression of inflammatory mediators, triggering apoptosis, influx of immune cells, extracellular matrix breakdown and ultimately menstrual shedding. In pregnancy, human chorionic gonadotrophin (HCG) produced by the invading trophoblast will drive ovarian progesterone production until this function is taken over by the placenta. Notably, HCG also acts directly on decidualizing cells and modulates the activity of several pathways, including the Notch pathway involved in cell-to-cell signalling (Afshar et al., 2012a,b). Further, the transforming growth factor β type II receptor was recently identified as a bona-fide receptor for hyperglycosylated HCG (Berndt et al., 2013). Taken together, one can envisage several pathways that enable decidual cells to induce a menstruation-like response to signals from developmentally compromised human embryos. For example, by shutting down the expression of key implantation factors, decidual cells may induce a microenvironment that, directly or indirectly, interferes with trophoblast HCG production. However, it is also conceivable that signals emanating from developmentally impaired embryos interfere with progesterone receptor activity in decidual cells, thus triggering menstruation-like disposal of the conceptus regardless of the concentration of HCG or circulating progesterone. In fact, there is compelling evidence that 'functional' progesterone withdrawal can trigger decidual collapse even in advanced pregnancy, resulting in preterm labour. Whatever the underlying mechanism, it has been estimated that between 30–60% of all human embryos are disposed of this way before any telltale signs of pregnancy are detected (Macklon et al., 2002).

Step 5: Regenerate and adapt

Most cycles during the reproductive years are non-conception cycles. Consequently, menstruation is viewed as a non-adaptive consequence of uterine evolution, i.e. it is an unfortunate by-product of spontaneous decidualization that serves no purpose other than to reinitiate the endometrial cycle to allow a future pregnancy (Emera et al., 2012a; Finn, 1998). However, it is striking that a number of other reproductive traits have evolved in parallel, all of which promote menstruation over pregnancy. For example, in comparison with many mammals with rapid reproductive turnover, ovulation in humans and other primates occurs spontaneously rather than triggered by mating. Humans also do not exhibit overt oestrous behaviour and 90% of all cycles in the first 2 years after menarche are anovulatory (Brosens et al., 2009). In fact, the first shedding of the endometrium in response to withdrawal of sex steroids happens within the first week after birth, after which the endometrium is quiescent for several years.

Menstruation is akin to an ischaemia-reperfusion tissue injury. A ubiquitous phenomenon in all organs in the body is that a succession of short periods of ischaemia and reperfusion prior to a prolonged and severe ischaemic insult protects against tissue destruction (Jennings et al., 1990; Murry et al., 1990; Otani, 2008). Extrapolating this to the human uterus, it is conceivable that repeated menstrual 'priming' or 'preconditioning' of uterine tissues and its vasculature during non-conception cycles confers protection against the hyper-inflammation associated with deep placentation and parturition. This conjecture fits well with the observation that pre-eclampsia is more prevalent and severe in a first pregnancy and especially so in young women in whom fewer opportunities for pre-protection have occurred (Brosens et al., 2009).

Another — more obvious — consequence of menstruation is that it imposes the need for cyclic renewal of the endometrium. In fact, the regenerative capacity of the endometrium is remarkable and reflects the abundance of adult stem cells (ASC) (Du and Taylor, 2010; Du et al., 2012; Gargett and Ye, 2012; Gargett et al., 2012). These ASC are thought to reside predominantly around the vessels and are recruited to the endometrium in response to hypoxic, proteolytic and inflammatory stimuli associated with cyclic menstruation, miscarriage, trauma or parturition (Du et al., 2012). Endometrial ASC are also immune privileged compared with other types of stem cells, rendering them a promising resource for cell-based therapies. Recently, decidua-derived human ASC have been shown to migrate and invade and inhibit mammary tumour formation in a preclinical rat model of breast cancer (Vegh et al., 2013). Notably, purified mature human endometrial stromal cells also express elevated concentrations of pluripotent factors and are more amenable to induced pluripotent stem cell reprogramming compared with conventional somatic cells (Park et al., 2011). Further, genetic fate mapping in mice strongly indicated that postpartum re-epithelization of the endometrium is effected by transdifferentiation of progenitor cells within the endometrial stromal compartment (Huang et al., 2012; Patterson et al., 2013). Extrapolated to the human uterus, these findings imply that a mesenchymal-to-epithelial transition is a key biological process that underlies the regeneration of the endometrium after menstruation, upon embryo implantation and following pregnancy.

Molecular phenotyping has shown that endometrial stromal cells are most closely related to follicular dendritic cells (FDC) (Munoz-Fernandez et al., 2006, 2012). Like endometrial stromal cells, FDC originate from perivascular adult stem/precursor cells expressing PDGF receptor β and which differentiate in response to inflammatory signals (Krautler et al., 2012). FDC are the stromal constituents of B cell follicles with the remarkable ability to retain complement-fixed antigens on their cell surface for extended periods of time. These antigen complexes are presented to B-cells and drive antibody affinity maturation. Interestingly, decidualizing stromal cells and FDC share several phenotypic markers with ASC (e.g. CD14, CD21 and CD23), which underscore their close kinship. Although B cells are absent from the feto—maternal interface, decidual cells *in vitro* exhibit several specialist functions ascribed to FDC, including inhibiting B lymphocyte apoptosis in co-cultures and secreting C—X—C motif chemokine 13 (Munoz-Fernandez et al., 2012). Further, while decidualizing stromal cells are indispensable for immune tolerance at the feto—maternal interface, FDC are implicated in maintaining peripheral immune tolerance in pregnancy (McCloskey et al., 2011).

Thus, plasticity of the endometrium depends on stromal cells that are akin to ASC and capable of exerting specialist accessory immune functions upon differentiation into decidual cells. This stromal cell population is constantly renewed in the human endometrium. While a precise definition of the cues responsible for recruitment of ASC and their subsequent differentiation into mature stromal cells is as-yet missing, it is likely that they will differ, quantitatively if not qualitatively, following menstruation, miscarriage or parturition. Consequently, reproductive failure may be prevalent but the ability of the human endometrium to adapt is extraordinary. This innate adaptability explains why most women suffering miscarriage, whether sporadic or consecutive losses, will achieve a successful pregnancy without — or even in spite of — medical intervention.

Conclusions and perspective

Based on the prevalence of whole chromosomal aneuploidies and complex imbalances in human preimplantation embryos, pregnancy failure should be the norm in healthy couples, perhaps occasionally punctuated by the birth of a healthy baby. The fact that most couples are reproductively successful attests, at least in part, to the extraordinary plasticity embedded in the human uterus. The primary driver is spontaneous decidualization and cyclic menstruation, which also bestow on the human endometrium several innovative functions, such as the propensity to migrate towards the embryo, to engage in quality control and to promptly reject an unwanted conceptus. Deregulation of these evolutionary innovative functions of the endometrium has been shown to underpin clinical miscarriage (Salker et al., 2010, 2011, 2012; Weimar et al., 2012), the most common complication of pregnancy. It is conceivable that other defects during the peri-implantation period become amplified as pregnancy unfolds, leading to pre-eclampsia, fetal growth restriction or preterm labour (Cha et al., 2012).

A detailed understanding of the human implantation process promises to overhaul reproductive medicine and perhaps antenatal care. However, before this can be achieved some key issues need to be resolved. For example, there is as yet no insight into the nature of the cues that signal embryo quality at implantation or into the molecular pathways responsible for maternal recognition. Several strategies have been proposed, including uNK cell testing (Tang et al., 2013), to identify an endometrial environment that predisposes for reproductive failure. While promising, large randomized prospective trials are needed to assess whether endometrial assessment prior to conception actually improves pregnancy outcome in women at risk of reproductive failure. Finally, a much deeper understanding of the mechanisms responsible for uterine plasticity is required before precision interventions can be developed that ensure reproductive fitness.

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