Reproductive BioMedicine Online (2013) 27, 506–514

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SYMPOSIUM: IMPLANTATION
REVIEW

Uterine plasticity and reproductive fitness

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Professor Jan Brosens graduated from the Catholic University Leuven, Belgium in 1990 and pursued postgraduate training in obstetrics and gynaecology in the UK. He became a member of the Royal College of Obstetricians and Gynaecologists in 1995 and a Fellow of the College in 2008. He obtained a PhD from the University of London in 1999, working on the mechanisms underpinning decidualization. He was awarded a Wellcome Trust Clinical Scientist Fellowship in 1998. He joined Imperial College London, first as Chair of Reproductive Sciences (2004) and then Chair of Reproductive Medicine (2008). In May 2011, he was appointed as Chair of Obstetrics and Gynaecology and leader of the newly established Division of Reproductive Health at the University of Warwick.

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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KEYWORDS: chromosomal instability, decidualization, endometrium, implantation, miscarriage, stem cell

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 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,

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http://dx.doi.org/10.1016/j.rbmo.2013.06.012

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, in press, this issue). 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 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

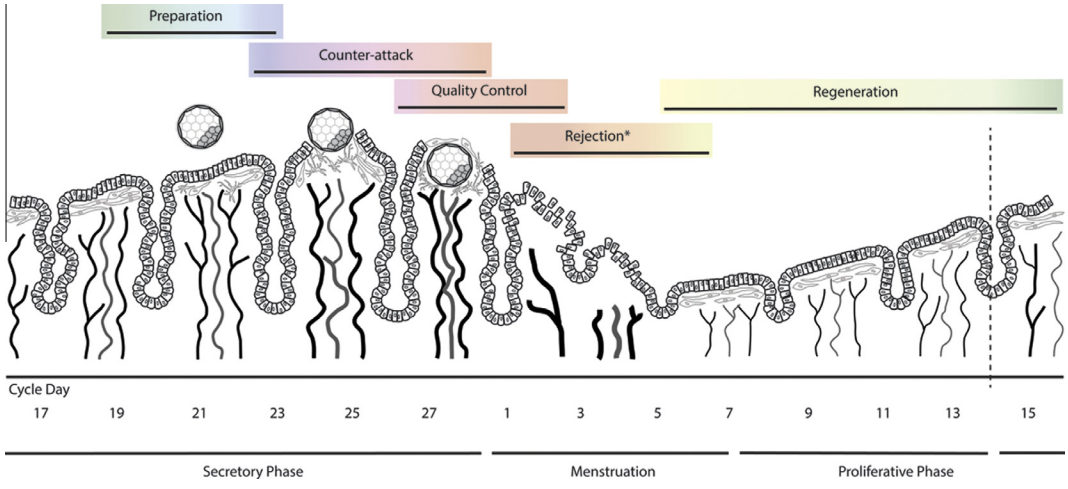

Figure 1 With each cycle, the human endometrium decidualizes spontaneously in preparation for implantation, resulting in the secretory, pro-inflammatory environment characteristic of receptivity. In the presence of an embryo, the decidualizing stromal cells acquire a motile phenotype upon breaching of 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.

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