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Review

Molecular aspects of implantation failure ☆

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ABSTRACT

Despite expanding global experience with advanced reproductive technologies, the majority of IVF attempts do not result in a successful pregnancy, foremost as a result of implantation failure. The process of embryo implantation, a remarkably dynamic and precisely controlled molecular and cellular event, appears inefficient in humans and is poorly understood. However, insights gained from clinical implantation failure, early pregnancy loss, and emerging techologies that enable molecular interrogation of endometrial–embryo interactions are unravelling this major limiting step in human reproduction. We review current molecular concepts thought to underlie implantation failure, consider the contribution of embryonic and endometrial factors, and discuss the clinical value of putative markers of impaired endometrial receptivity. Finally we highlight the nature of the dialogue between the maternal endometrium and the implanting embryo and discuss the concept of natural embryo selection. This article is part of a Special Issue entitled: Molecular Genetics of Human Reproductive Failure.

1. Introduction

Pregnancy is a unique biological phenomenon. To occur, a competent embryo must attach to a receptive endometrial lining and then invade the underlying decidualizing stroma. Although our knowledge of the molecular mechanisms that govern these early embryo–maternal interactions has increased substantially in recent years, implantation remains the least understood key rate-limiting step in assisted reproductive technology (ART). While normal implantation events in human beings cannot be studied directly, analysis of the factors that contribute to IVF treatment failure do provide insight into the critical steps that determine reproductive success. The aim of this review is to outline our current understanding of embryo implantation failure based on clinical evidence and emerging concepts.

2. Implantation and implantation failure

Implantation is considered to occur when a blastocyst breaches the luminal endometrial epithelium. However, determining precisely when this occurs in the human being is complicated. The only established clinical marker of implantation is human chorionic gonadotrophin (hCG). This glycoprotein hormone, produced by the cytotrophoblast cells of the human blastocyst, is first detectable in urine and blood a few days after implantation and then rises exponentially [1–3]. In ART, implantation is defined as a quantitative rise in hCG level above a threshold level at some point after embryo transfer [4]. The most accurate way to determine the prevalence of implantation events after IVF would be to measure hCG levels in a daily serum sample after embryo transfer. However, this approach is cumbersome and difficult to perform in large numbers of patients. Serial urine sampling offers a less invasive approach and more practical approach to study larger populations [5–7]. It has also been shown to provide data of similar validity as analysis of serum samples [8,9].

The earlier hCG is measured, the more implantation events will be captured, including transient events. Consequently, more cases of early post-implantation pregnancy loss will also be detected [5,6,10]. Thus, the frequency of implantation and implantation failure depends on detection methods and clinical definition.

The clinical definition of 'recurrent' implantation failure (RIF) is equally challenging and arbitrary. The 2005 ESHRE Preimplantation Genetic Diagnosis (PGD) consortium defined the criteria for RIF as the absence of implantation after ≥3 embryo transfers with high-quality embryos or after replacement of a total of 10 or more embryos in multiple transfers, with the exact numbers to be determined by each centre [11].

If RIF is a disorder affecting specific patients, implantation rates should correlate inversely with the number of unsuccessful IVF attempts, reflecting the increasing proportion of true RIF patients. Indeed, studies in oocyte donation programmes show that the pregnancy rate is comparable, approximately 36%, during the first 4 treatment cycles [12]. However, in IVF programmes, pregnancy rates already decline in the

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second cycle and this trend continues in subsequent cycles [13,14]. Therefore, a definition of RIF as three failed IVF cycles is inevitably arbitrary. Further, the definition should include the number of good-quality embryos transferred without achieving a pregnancy. This inclusion criterion is increasingly applied in recent studies [15–18].

To determine the rate of implantation failure in a given patient cohort, it is necessary to first establish the frequency of implantation. This represents the sum of the number of clinical pregnancies and pre-clinical pregnancy losses per embryo transfer [10]. Based on the most recent international datasets from Europe, America and Australia/New Zealand, the clinical pregnancy per transfer is 30–35% [19–21]. This is based on a mean transfer of 2 embryos (range: 1–4). These clinical pregnancy rates are comparable with the 32% reported by Boomsma et al. [10]. In this study, the total implantation rate was 51%, which included a pre-clinical pregnancy loss rate of 19%. Thus, while half of all transferred embryos resulted in a detectable implantation event, half of these were subsequently lost (Fig. 1) [10]. In the absence of consensus criteria, the incidence of RIF is difficult to determine.

In our unit in Utrecht, 10% of patients fail to achieve a clinical pregnancy after 3 IVF/ICSI attempts. Excluding patients over 38 years of age and those with poor ovarian response, the incidence of RIF fell to 4%. If defined by failure to achieve a clinical pregnancy after cumulative transfer of 10 or more good quality embryos, the incidence of RIF would be even lower.

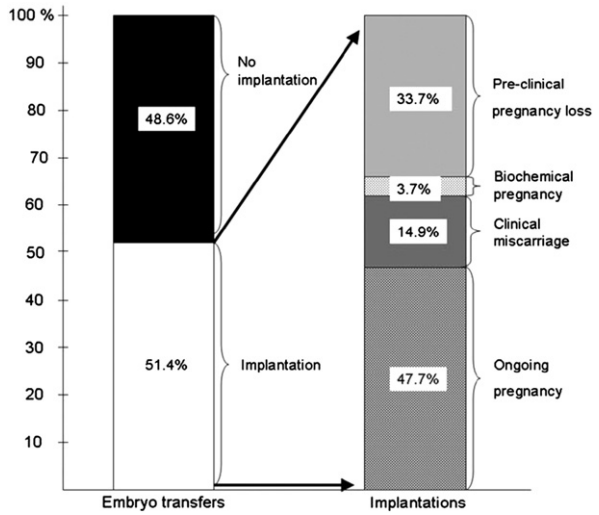

Fig. 1. Treatment outcome after embryo transfer (n = 179) based on hCG measurement in serial daily urine samples collected 9–19 days after oocyte retrieval. Adapted from Boomsma et al. [10], with permission.

3. Mother or embryo?

Whether the primary cause of implantation failure lies with the mother or the embryo is a longstanding and as yet unresolved question. This reflects the difficulties of interrogating the early stages of nidation in humans. Because of this, our understanding of the mechanisms that control early implantation events comes primarily from animal models, particularly from gene deletion studies in mice [22,23]. While these models provide important clues, the degree to which these data can be extrapolated to human implantation events is limited. For instance, endometrial receptivity in the mouse uterus is associated with a decrease in mucin expression [24] whereas the opposite reportedly occurs during the window of implantation in humans [25]. Another case in point is leukaemia inhibitory factor (LIF), which is indispensible for implantation in the mouse [23]. Whether or not this is also true in humans remains controversial [26,27].

In addition to animal models, several in vitro models have been established to study embryo–endometrial interactions [28–30]. These models have yielded some unexpected observations regarding the nature of endometrial–embryonic interactions that seems specific to the human situation. For example, emerging evidence suggests that decidualizing stromal cells are adapted to selectively recognize developmentally impaired human embryos. Furthermore, defects in this process of maternal biosensoring of embryo quality are thought to facilitate implantation of poor quality embryos and compromise the development of normal embryos, thus causing recurrent miscarriages [31,32,17,33].

4. The embryo in implantation failure

Poor embryo quality is considered to be the major cause of implantation failure [34], and by and large reflects the high incidence of chromosomal abnormalities reported for human embryos [35–37]. The frequency of embryonic genetic abnormality increases with age [38,39] but also appears higher among infertile couples than in the general population [35]. These abnormalities may arise from an error during meiosis, resulting in a uniform abnormality present in all cells, or from segregation errors occurring during the first mitotic divisions, resulting in chromosomal mosaicism. Mosaicism has been reported to affect up to 91% of human embryos in the early stages of pre-implantation development [40,41,37]. However, the incidence of mosaicism is significantly lower when the embryo reaches the blastocyst stage [42], which could be explained by the developmental arrest of a significant proportion of mosaic day 4 embryos and/or reduced proliferation or selective apoptosis of aneuploid blastomeres within a mosaic embryo [42]. At the blastocyst stage, a majority of embryos are thought to be uniformly euploid [43].

Studies on couples experiencing RIF show that the proportion of chaotic mosaic embryos may be considerably higher than in unselected IVF patients [41,44]. Theoretically then, pre-implantation genetic screening (PGS) could possibly help to choose the right embryo to transfer and improve outcomes in these patients. However, a randomized controlled trial including 139 RIF patients showed no increase in implantation rate after PGS using FISH technique [15]. Further, studies using the genome-wide array comparative genome hybridization (CGH) screening have reported exceptional high rates of mosaicism in human embryos [37], raising doubts as to whether preimplantation genetic screening (PGS), with either CGH or single nucleotide polymorphism (SNP) arrays, will improve live birth rates. Additional randomised controlled trials (RCTs) are needed before these new technologies can be introduced in clinical management [45].

Metabolic profiling has been employed to determine amino acid turnover in embryo culture medium [46,47]. A low metabolic rate, characteristic of so-called 'silent embryos', is associated with developmental competence, whereas poor quality embryos operate at higher metabolite or nutrient turnover rates ('noisy embryos') [48,49]. Proteomic studies indicated that the embryonic secretome may differ between those that implant and those that fail, although prospective validation studies are as yet lacking [50,51].

In some cases RIF may be linked to an inability of the embryo to hatch out of its zona pellucida [52]. The zona pellucida is a glycoprotein layer, which after fertilization, compresses and shapes the embryo. The zona facilitates the active transport of the embryo trough the Fallopian tubes and protects it from micro-organisms and immune cells [53]. At the blastocyst stage, the embryo needs to break out of the zona to enable invasion of the luminal endometrial epithelium [54]. Failure of this process could be caused by zona hardening arising from IVF culture conditions [55] or cryopreservation [56]. Further, advanced endometrial development caused by ovarian stimulation [57] combined with delayed development of embryos in vitro

[58] could cause a synchronization problem, which requires the embryo to hatch out of the zona prematurely.

Assisted hatching is the artificial rupture of the zona pellucida, which might assist implantation of fresh or cryopreserved IVF embryos [52]. A systematic review of 28 studies showed that assisted hatching significantly increases the clinical pregnancy rate of frozen-thawed embryos in patients with repeated treatment failure. However, assisted hatching also increases multiple pregnancy rates, including monozygotic twinning [59]. A Cochrane review in 2009 showed similar results in the RIF subgroup and concluded that while the clinical pregnancy rate may improve, there is insufficient data on live birth rates and a concerning increase in multiple pregnancies [60].

5. Endometrial factors in implantation failure

The endometrium is a multi-layered, dynamic mucosa that overlays the myometrium of the uterus. It comprises a variety of cells, including luminal and glandular epithelial cells, stromal fibroblasts, and vascular and immune cells. During a menstrual cycle, dramatic changes occur in both the phenotype and abundance of many of these cells, especially in the superficial endometrial layer [61]. Endometrial growth is dependent on oestrogen stimulation whereas the postovulatory rise in progesterone levels triggers a coordinated programme of differentiation, characterized by proliferative arrest and secretory transformation of the epithelial cells, transient oedema, influx of uterine natural cells (uNK), vascular remodelling, and differentiation of stromal fibroblasts into specialized decidual cells [61,62]. A functional consequence of this coordinated remodelling of the endometrium is that it transiently becomes receptive to embryo implantation. This phenomenon is referred to as the 'window of implantation' (WOI) [63]. It starts approximately 6 days after ovulation and thought to last for ~4 days [64]. The end of the implantation window, the refractory phase, coincides with the morphological differentiation of endometrial fibroblasts into secretory, epitheloid decidual cells [65]. The decidual process is indispensable for pregnancy in all species with an invasive placenta, as it establishes maternal immunologic tolerance to foetal antigens, ensures tissue integrity and haemostasis during the process of trophoblast invasion, and, importantly, protects the conceptus from environmental insults [65]. In the vast majority of species, decidualization of the endometrial stromal compartment is triggered by signals from the implanting embryo. However, this is not the case in human beings or Old World Monkeys [66,67]. In these species, decidualization occurs in each cycle and, in the absence of pregnancy, this process is responsible for menstrual shedding of the superficial endometrium [61].

5.1. Morphological markers of endometrial receptivity

A restricted 'window of implantation' is thought to coordinate embryonic and endometrial development, thus minimizing the risk of late implantation of non-viable embryos. However, failure of the endometrium to become receptive is widely thought to be major cause of implantation failure. For over half a century, histological dating was the gold standard to detect defects in the differentiation responses of the endometrium [68,69]. However, this approach is marred by high levels of inter- and intra-observer variation [70], poor inter-cycle association, and tissue fixation artefacts, which all limit the clinical usefulness of histological dating [71].

Electron microscopy allows assessment of endometrial ultrastructures, such as the epithelial cell membrane projections called 'pinopodes', which were considered to play a role in endometrial receptivity [72,73]. However, these enigmatic structures have now been found throughout the entire luteal phase and in early pregnancy [74] and their role remains unclear [75].

5.2. Molecular markers of endometrial receptivity

Several gene- and protein expression profiles of pre-receptive and receptive endometrium in natural [76–83] and ovarian stimulation cycles [84,82,85] have been performed in the last decade. Although all studies have identified numerous biomarkers, overlap in genes between studies is low because of different methods, techniques, patient characteristics and timing [86]. These studies suggest that endometrial receptivity is governed by expression of an evolutionarily conserved network of mediators. Thus far, it has been difficult to associate these factors with reproductive failure in women or to develop them as therapeutic targets. However within studies significant different expression profiles have been identified.

5.2.1. Gene expression

RIF patients show deregulated gene expression during the receptive phase compared to controls [16]. Pathways of cell cycle, Wnt signalling and cellular adhesion, are involved [16]. A recent study comparing implantation failures (IF), recurrent miscarriers (RM) and fertile controls (FC) showed different expression of 2126, 2477 and 2363 genes (IF vs. FC, RM vs. FC, IF vs RM resp.) [17]. Shared deregulated pathways involved DNA transcription and factors in the haematological system. IF showed high-deregulated gene expression in cell mediated immune response and nervous system development, while RM showed abbarent expression in humeral immune response and organ and muscle development [17]. Diaz-Gimeno et al. developed a predictor set of biomarkers for endometrial receptivity which was sensitive and specific for endometrial dating, but had a low specificity for detecting pathological classifications like RIF [83].

Studies focusing on p53 tumour suppressor gene, which regulates cell apoptosis, angiogenesis and is a potential mediator of pregnancy show significantly more homozygous genotypes in RIF patients [87–89].

MSX homeobox gene deletion in mice inhibits blastocyst implantation [90]. Micro-array analysis shows that these genes are down-regulated during the receptive window in humans [77,78,91], similar to what occurs in implantation in mice. These facts, together with failure to initiate implantation in uteri of MSX knock-out animals with a diapause (delayed implantation till favourable conditions are reached), suggest that the MSX genes play a role in the initiation of the window of implantation.

MicroRNA (miRNA) has a function in post-transcriptional regulation of gene expression by targeting mRNAs for degradation and/or translational repression [92,93], and thus have a role in the repression of protein expression. Recent findings suggest a role for miRNA in down regulating the expression of some cell cycle genes in secretory-phase endometrium [94]. In RIF patients 13 miRNAs were differently expressed, the genes involved play a role in Wnt signalling and cell cycle pathways and the formation of adhesion molecules [95].

5.2.2. Prostaglandins (PGs)

PGs are demonstrated to be crucial for successful embryo implantation [96,97]. Cyclooxygenases (COX-1 and COX-2) are the enzymes responsible for the synthesis of a variety of PGs, which are up-regulated by progesterone [98]. In a recent study, patients presenting with RIF expressed reduced levels of cPLA2α and COX-2 compared with controls. In response to this deficiency, sPLA2-IIA was found to be overexpressed [99]. Prostaglandin synthesis therefore appears to be disrupted in patients with repeated IVF failure compared with fertile controls. Reduced levels of COX-2 and several prostaglandins were also detected in patients with unexplained recurrent miscarriage together with a lower level of VEGF [100]. The COX-derived signalling pathway possibly plays an important role in the successful embryo implantation.

5.2.3. Cell adhesion molecules (CAM)

The CAM family is composed of four members: integrins, selectins, cadherins, and immunoglobulins. These surface ligands, usually carbohydrate glycoproteins, mediate cell-to-cell adhesion. Expression of αVβ3 integrin and its ligand osteopontin coincides with the opening of the WOI, was detected by immunohistochemistry on the endometrial luminal epithelial surface and is the first to interact with the trophoblast [101]. Aberrant αVβ3 integrin expression pattern has been associated with unexplained infertility [102–104], and other gynaecological disorders like endometriosis [103] and polycystic ovarian syndrome [105]. Lower integrin mRNA level on day 21 is associated with a 50% lower implantation rate than normal levels [106,107].

Other luminal moieties include oligosaccharide ligands present on the luminal epithelial cells that attach to the embryonal L-selectin [108,109]. It appears that selectins contribute to the early events of embryo–maternal interactions [110]. E-cadherin is the most studied cadherin, with function of cell-to-cell adhesion. It is progesterone depended via calcitonin expression and down-regulation probably plays a role in embryo invasion [110]. To date, the role of selectins or cadherin expression linked to (recurrent) implantation failure is poorly defined.

5.2.4. Mucins

In the endometrium, MUC-1-glycoprotein extends beyond the glycocalyx on the luminal epithelial endometrial layer and acts as a barrier for implantation. Human in vitro implantation models indicate that MUC-1 expression is increased during the receptive window [25] and lost at the site of embryo attachment [111]. Women with recurrent pregnancy loss (RPL) were shown to express reduced endometrial MUC-1, as compared with a normal group of patients [112–114]. MUC-1 is a highly polymorphic gene. An association between the allele size of MUC-1 and implantation failure was shown in 2001 [115]. Patients with implantation failure had significantly shorter extracellular chains that could make embryo apposition to the destined place in the endometrial lining difficult. In contrast, in 2004 a study compared the MUC-1 genotype of 10 fertile and 10 women with implantation failure and proposed that there was no association [116]. Also, in patients with a history of recurrent miscarriage no association was found [117].

5.2.5. Cytokines

Uterine Natural Killer cells (uNK) are the most abundant immune cells present in the endometrium. They secrete various cytokines important for adequate local immune regulation, angiogenesis, placental development, and establishment of pregnancy [33,118].

The autocrine and paracrine effects of the cytokine LIF, such as proliferation, differentiation and cell survival, made researchers investigate its role in implantation. In RIF patients a presumed role of LIF gene mutations has been investigated [119]. LIF secretion by human endometrial cells only weakly increased from the proliferative to secretory phase in patients with RIF and unexplained infertility [120]. However, a first randomized controlled clinical trial performed in 2009, in which recombinant LIF has been administered to patients with at least two failed ART cycles failed to demonstrate higher implantation rates in the intervention group [27].

Relevance of the IL-1 system in the implantation process was established by mouse experiments. Surprisingly, although IL-1 deficient mice were able to reach pregnancy, an intraperitoneal injection of IL-1ra at the appropriate time was enough to prevent blastocyst implantation. This was attributed to the down-regulation of critical integrins at the luminal epithelial surface [121]. Such a phenomenon appears to also occur in human. Indeed, supplementation of IL-1 in the culture media of endometrial epithelial cells (EECs) leads to the increase of integrin β3 expression and thereby to enhanced blastocyst implantation [122].

Expression of IL-15 and IL-18 has been shown to be different in patients with failed implantation after IVF/ICSI compared with fertile controls and both correlate with local uNK recruitment and angiogenesis [18].

IL-6 deficient mice showed reduced implantation sites and reduced fertility. Abnormal expression of IL-6 in late secretory phase was reported in patients with RM [123].

Studies on IL-11 and IL-11rα revealed that expression of these markers were lower in the endometrial biopsies of RM patients compared to fertile controls [124], suggesting a role in endometrial decidualization.

5.2.6. Others

Recent analysis of mid-secretory endometrial samples revealed that increased serum- and glucocorticoid- inducible kinase SGK1, a kinase involved in epithelial ion transport and cell survival, interferes with embryo implantation in endometrial surface epithelium, leading to infertility [125,126]. However, implantation was not impaired in Sgk1-deficient mice, although there was evidence of bleeding and inflammation at the feto-maternal interface in early pregnancy and subsequent foetal demise [126]. Another recent study showed endometrial placental growth factor (PLGF) expression corresponded to the hysteroscopic appearance of the endometrium, and showed a lower expression in patients with implantation failure [127].

6. Clinical challenges

While there has been progress in our knowledge of the aetiologies of implantation failure, a full understanding of in-vivo determinants of human implantation has been hampered by a lack of appropriate models. However, recent developments in diagnostic techniques and molecular tools are now opening the 'black box' of implantation failure. A key step has been the development of less invasive means of assessing of endometrial receptivity. Non-disruptive analysis of the endometrial environment at the moment of embryo replacement can be performed by analysis of endometrial secretions [10]. Endometrial secretion aspiration can be carried out immediately prior to embryo transfer without affecting implantation rates [128]. Proteomic analysis by mass spectrometry showed different protein expression patterns during the prereceptive and receptive phases [129]. A multiplex immunoassay for 17 regulators of implantation showed a cytokine profile conducive to clinical pregnancy [10]. While 2D-DiGE analysis of the human endometrial secretome revealed differences between receptive states in fertile and infertile women [130].

In favour of endometrial biopsy a number of studies showed that endometrial local injury in a cycle prior to IVF/ICSI treatment resulted in increased implantation and pregnancy rates [131–133]. Possible explanation could be induced decidualisation and/or the wound healing effect, accompanied with influx of immune cells, secretion of inflammatory mediators and growth factors, including LIF, IL-11 and HB-EGF [134].

7. Mother and embryo

The technical and ethical obstacles to study human implantation in vivo have necessitated the development of in vitro models to examine embryo–endometrial interactions [30,28,29]. These models can provide a key role in elucidating role of the embryo or the endometrium in initiating or indeed terminating the preimplantation dialogue. Using a human co-culture model, soluble implantation factors where determined in case of developing and arrested embryos by multiplex immunoassay [135]. The model consisted of decidualizing endometrial stromal cells (ESCs) and single hatched blastocysts. Over a 3-day co-culture period, 25% of embryos showed development and the remainder arrested. Surprisingly, the presence of a developing embryo had no significant effect on decidual secretions while an

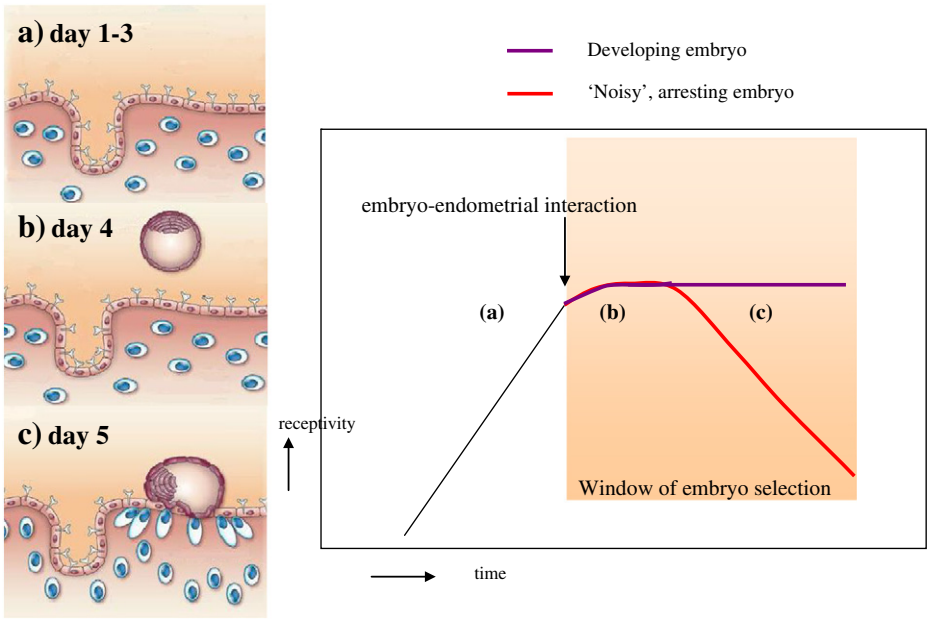

Fig. 2. Mechanisms of embryo selection derived from in vitro models of embryo–endometrial interaction.

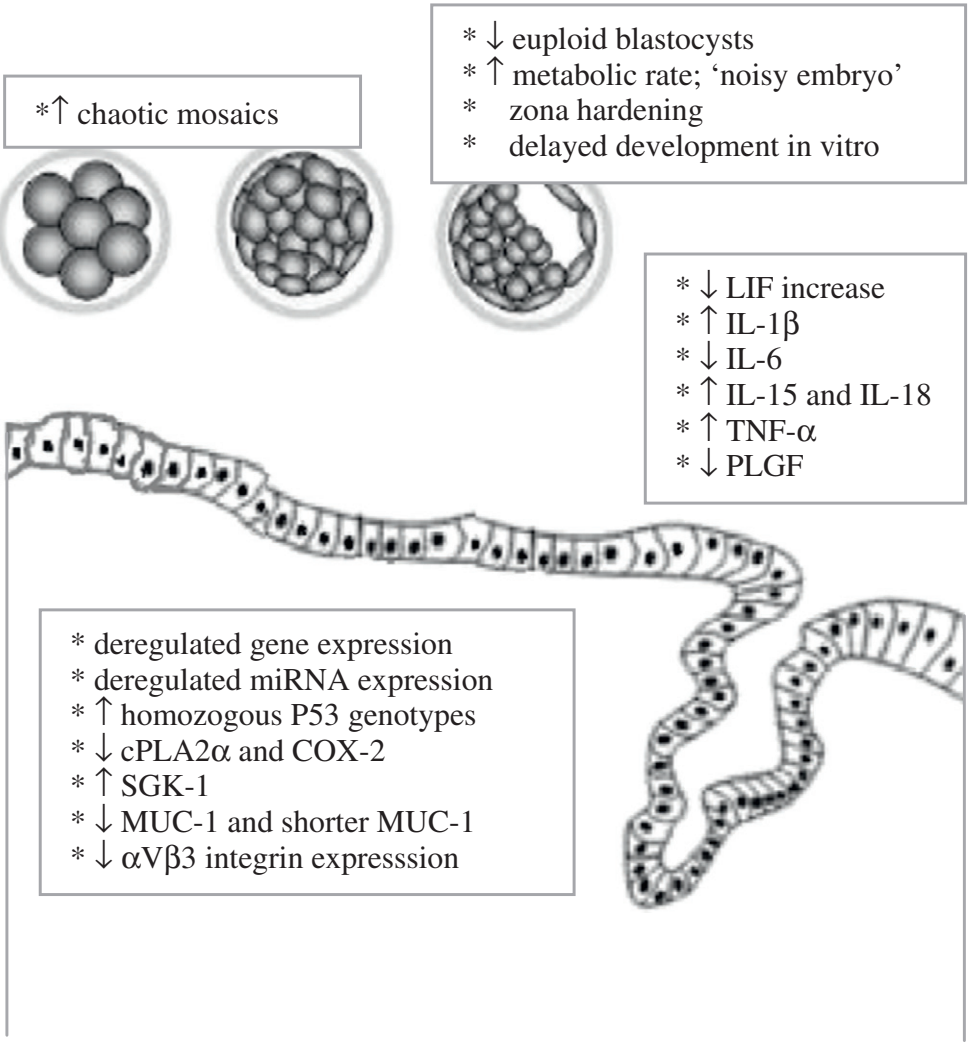

Fig. 3. Embryonal and endometrial factors of human implantation associated with (recurrent) implantation failure.

arresting embryo triggered a strong response (selective inhibition of IL-1b, -6, -10, -17, -18, eotaxin, and HB-EGF secretion). Co-cultures with undifferentiated ESCs showed no effect by the presence of a developing or arresting embryo [135]. These results suggest that the differentiated endometrium can differentiate between good and bad quality embryos and reject the latter; a phenomenon which has been termed natural embryo selection (Fig. 2) [32].

It has been proposed that RPL could be caused by failure of natural embryo quality control [136] whereas RIF patients have a selection mechanism that inappropriately rejects good quality embryos. These mechanisms need further attention in new developed models.

8. Conclusion

Successful implantation of a good quality human embryo in a receptive endometrium requires a remarkable and complex collaboration of factors.

Studies on gene- and protein expression profiles using mRNA micro arrays have led to the identification of numerous putative endometrial biomarkers of both successful and unsuccessful implantations (Fig. 3; factors associated with RIF). With the development of bioinformatics technologies and emerging databases it should become possible to identify genes and proteins that are predictors of endometrial receptivity and pregnancy outcome of clinical value.

Studies using in vitro models suggest that the decidualized endometrium is capable of selecting good quality embryos and, more importantly, reject the incompetent embryos. It has been proposed that this process could be impaired in patients with RPL and RIF.

To conclude future research should focus on integrating data from gene and protein expression studies in endometrial biopsies and secretions to determine markers with clinical significance. Next to this, in vitro models appear a promising mode of interrogating embryo–endometrial interactions to investigate possible interventions designed to reduce RIF and pregnancy failure.

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