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Cytokines, chemokines and growth factors in endometrium related to implantation

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The complexity of the events of embryo implantation and placentation is exemplified by the number and range of cytokines with demonstrated roles in these processes. Disturbance of the normal expression or action of these cytokines results in complete or partial failure of implantation and abnormal placental formation in mice or humans. Of known importance are members of the gp130 family such as interleukin-11 (IL-11) and leukaemia inhibitory factor (LIF), the transforming growth factor β (TGFβ) superfamily including the activins, the colony-stimulating factors (CSF), the IL-1 system and IL-15 system. New data are also emerging for roles for a number of chemokines (chemoattractive cytokines) both in recruiting specific cohorts of leukocytes to implantation sites and in trophoblast differentiation and trafficking. This review focuses on those cytokines and chemokines whose expression pattern in the human endometrium is consistent with a potential role in implantation and placentation and for which some relevant actions are known. It examines what is known of their regulation and action along with alterations in clinically relevant situations.

Key words: chemokines/cytokines/endometrium/implantation/placentation

Introduction

Development of the embryo to the blastocyst stage, its implantation into the uterine endometrium and the formation of a functional placenta are essential steps in the establishment of pregnancy. Each requires interaction between the conceptus (particularly the trophoblast) and one or more of the cell types within the maternal endometrium. The success of implantation ultimately depends on achieving the appropriate extent of trophoblast outgrowth and finely orchestrating its invasion into the endometrium to establish a blood supply for the conceptus. There are marked differences in implantation between species, and these are, in part, related to the differences in the forms of placentation (Wooding and Flint, 1994). Humans are unusual in the aggressiveness of the trophoblast, as evidenced by the occurrence of ectopic pregnancy only in women, and that certain molecular changes in the luminal epithelium occur only directly where embryo contact first occurs, rather than across the entire endometrial surface (Meseguer *et al*., 2001). Furthermore, in humans, initiation of the process of decidualization [differentiation of endometrial stromal fibroblasts and the accompanying influx of uterine-specific natural killer (uNK) cells to form the decidua of pregnancy] occurs spontaneously in the latter part of each menstrual cycle, by comparison with most other species with haemochorial placentation (including rats and mice) in which this process occurs naturally only in the presence of a blastocyst.

Cytokines are small multifunctional glycoprotein mediators whose biological actions are mediated locally by specific receptors and which are linked to most processes in the body, including implantation and immune function. Both pleiotrophy and redundancy exist within the cytokine families, and several different cytokines often exert similar and overlapping functions on certain cells. Their receptors also often display redundancy and utilize different signal transduction pathways (Robertson, 1998). A wide array of cytokines are expressed within the uterus of a range of species. Their cellular source varies and includes somatic cells, particularly endometrial stromal, epithelial or decidual cells and trophoblast cells, but also the subsets of leukocytes (particularly macrophages and uNK cells) that are present at this time, especially in the human. Variation of expression with the menstrual or oestrous cycle suggests regulation at least in part by steroid hormones, although regulation by local factors originating from other cells within the endometrium or by conceptus-derived factors or semen is also apparent.

This review will focus on cytokines thought to be important for the early stages of embryo implantation, with particular focus on the human. Because it is not possible to perform *in vivo* functional studies in women, most of our current knowledge on the functional roles of these mediators at implantation comes from studies of gene manipulation in mice. Perhaps not surprisingly, given the importance of the process of implantation to the continuity of a species and the remarkable flexibility and redundancy of the cytokine network, there is a lack of 'implantation-failure' phenotype in most mice lacking individual cytokines or their receptors (Table I), although inadequacies in placental development are

Table I. Cytokine or cytokine-receptor knockout studies: effects on implantation

Gene	Female reproductive phenotype	Reference
CSF-1	Increased foetal resorption	Pollard *et al*. (1991)
GM-CSF	Implantation rates normal, mean litter sizes small, placental deficiency	Robertson *et al*. (1999)
IL-1Rt1	Implantation normal, minor effect on litter size	Abbondanzo *et al*. (1996)
IL-6	Reduced fertility; viable implantation sites decreased 48%	Robertson *et al*. (2000)
IL-11Rα	Failure of implantation, defective decidualization	Bilinski *et al*. (1998); Robb *et al*. (1998)
gp130[a]	Intrauterine lethality, placental deficiency	Yoshida *et al*. (1996)
LIF	Failure of implantation	Stewart *et al*. (1992)
LIFR[a]	Intrauterine lethality	Ware *et al*. (1995)
SOCS3	Placental defects and embryonic lethality	Roberts *et al*. (2001); Takahashi *et al*. (2003)
BmprIB	Infertile/failure in endometrial gland formation	Yi *et al*. (2001)
TGFβ1[a]	Intrauterine lethality and early postnatal lethality	Schull *et al*. (1992); Kulkarni and Karlsson (1993)

Modified from Salamonsen *et al*. (2000) Cytokines in implantation. Sem Reprod Med 18,299–310. Reprinted with permission.
[a]In each of these mouse strains, the effect of the absence of cytokine signalling could not be assessed because of intrauterine lethality of the null embryos.

often seen. Such placental abnormalities in women can lead to pre-eclampsia, low birthweight babies and long-term health consequences for the infant. In women, analysis of the temporal and cellular expression patterns of the cytokines and their receptors in the endometrium, and application of a limited number of *in vitro* models, have indicated but not proven that cytokines are key regulators of human implantation.

The gp130 cytokines

Some of the redundancy and pleiotrophy between certain cytokines is evidenced at a molecular level by the gp130 cytokines, which share an accessory signal transducing subunit. These cytokines include leukaemia inhibitory factor (LIF), interleukin-6 (IL-6), IL-11, cardiotrophin (CT) 1, ciliary neurotropic factor (CNTF), oncostatin M (OSM) and cardiotropin-like cytokine/cytokine-like factor (CLC–CLF). A number of these (LIF, OSM, CT-1 and CNTF) bind to the LIF receptor α chain, whereas IL-11, IL-6, OSM and CT-1 also have specific low affinity α receptor subunits. Binding of each cytokine to its receptor α triggers dimerization with gp130, forming a high affinity receptor leading to activation of the janus kinase/signal transducer and activator of transcription (JAK/STAT) signal transduction pathway (Heinrich *et al*., 1998). Both membrane bound and soluble forms of the receptor components have been identified, and they may act as inhibitors of cytokine action by competing with cell surface receptors to limit dimerization with gp130 (Heaney and Golde, 1996). Signal transduction from cytokines acting through the JAK/STAT pathway is attenuated via the suppressors of cytokine signalling (SOCS) family of cytoplasmic proteins that complete a negative feedback loop (Alexander, 2002). Of the cytokines that utilize gp130 for signalling, LIF, IL-6 and IL-11 have been implicated in the implantation process.

LIF

LIF was originally identified by its ability to induce the macrophage differentiation of the myeloid leukaemia cell line M1 (Tomida *et al*., 1984; Hilton *et al*., 1988a,b). It has a variety of roles including proliferation, differentiation and cell survival, all functions that are essential for blastocyst development and implantation (Hilton, 1992; Metcalf, 1992). LIF was the first cytokine shown to be critical for implantation in mice (Stewart *et al*., 1992). LIFs pattern of expression in the human endometrium also suggests a role in implantation. In endometrium of women of proven fertility, LIF mRNA is expressed during days 18–28 of the menstrual cycle (Charnock-Jones *et al*., 1994; Kojima *et al*., 1994; Arici *et al*., 1995; Sharkey *et al*., 1995; Vogiagis *et al*., 1996; Dimitriadis *et al*., 2000). Both LIF mRNA and protein are localized in uterine glandular and luminal epithelium (Sharkey *et al*., 1995; Vogiagis *et al*., 1996), whereas immunoreactive LIF has also been observed in stroma (Baird *et al*., 1996; Vogiagis *et al*., 1996; Gemzell-Danielsson and Swahn, 1997; Aghajanova *et al*., 2003). LIF-receptor (LIF-R) mRNA is restricted to luminal and probably also glandular epithelium in the mid-secretory phase (Cullinan *et al*., 1996; Aghajanova *et al*., 2003).

During pregnancy, LIF and LIF-R genes have been detected in the decidua and chorionic villi of first trimester and term placenta in humans (Kojima *et al*., 1994, 1995; Sawai *et al*., 1995a, 1997; Sharkey *et al*., 1999). LIF-R mRNA and immunoreactivity localize in both villous and extravillous trophoblast throughout pregnancy and in endothelial cells of the foetal villi (Sharkey *et al*., 1999). Strong expression of mRNA encoding LIF has also been detected in decidual leukocytes, which are abundant at the implantation site, suggesting that LIF may mediate interactions between maternal decidual leukocytes and invading trophoblast cells (Sharkey *et al*., 1999).

Progesterone is a likely major regulator of LIF expression. Not only does endometrial LIF expression coincide with progesterone domination of the tissue, but treatment of women with the progesterone receptor antagonist, mifepristone (RU486) immediately after ovulation, reduces immunoreactive LIF at the expected time of implantation (Gemzell-Danielsson and Swahn, 1997). However, locally produced factors, including heparin-bound epidermal growth factor (HB-EGF) and transforming growth factor β1 (TGFβ1), have been shown to regulate LIF secretion by cultured endometrial cells (Arici *et al*., 1995; Lessey *et al*., 2002) and may also be relevant *in vivo*.

The biological actions of endometrial LIF are not yet understood although the glandular expression indicates likely secretion into the uterine lumen. LIF protein is maximal in uterine flushings in the mid-late secretory phase of the menstrual cycle at the time of expected implantation in fertile women, suggesting a role in uterine receptivity (Laird *et al*., 1997; Ledee-Bataille *et al*., 2002). Should LIF be released basally from uterine epithelium, paracrine

effects on the underlying stroma and leukocytes would be possible. A recent study in mice suggests an involvement of LIF in the migration of uNK cells in early pregnancy (Schofield and Kimber, 2005), while *in vitro*, a role for LIF in regulating human endometrial stromal cell survival but not decidualization has been demonstrated (Nakajima *et al*., 2003). Furthermore, LIF appears to stimulate the expression of progesterone-regulated genes in the luminal epithelium in mice (Sherwin *et al*., 2004).

LIF may also act on the embryo, as blastocysts produced by *in vitro* fertilization and cultured to the periimplantation stage express LIF-R transcripts (Charnock-Jones *et al*., 1994). A role for LIF in trophoblast cell growth and differentiation has also been shown (Kojima *et al*., 1995; Sawai *et al*., 1995b; Nachtigall *et al*., 1996; Ren *et al*., 1997). Thus in humans, LIF may signal to both embryonic and uterine tissues during implantation.

Evidence suggests that LIF is important for human fertility (Laird *et al*., 1997; Ledee-Bataille *et al*., 2002). LIF is reduced in endometrial flushings from women with unexplained fertility compared with normal fertile women, whereas endometrial explants from infertile women secrete less LIF than those from fertile women (Laird *et al*., 1997; Ledee-Bataille *et al*., 2002). However, the substantial effects of culture on cytokine production from explants were not taken into account in this study. Interestingly, another report revealed that LIF mRNA levels did not differ between fertile and infertile women (Sherwin *et al*., 2002), although lower immunostaining has been demonstrated in endometrium of women who were infertile compared with fertile women (Tsai *et al*., 2000) and in a cohort of women with infertility and endometriosis (Stoikos *et al*., 2003). Furthermore, LIF and LIF-R immunostaining are maximal in both luminal and glandular epithelium between days LH + 6 and LH + 9 coinciding with pinopode formation (Aghajanova *et al*., 2003). A role for LIF in recurrent miscarriage has also been postulated. Decreased production of LIF by decidual T cells from women with unexplained recurrent abortions compared with women with normal gestation may contribute to the development of unexplained recurrent abortions (Piccinni *et al*., 1998). However, in another study examining early abortion, no difference in LIF or LIF-R expression in first-trimester decidua or chorionic villi between women with anembryonic pregnancies and normal pregnancies was found (Chen *et al*., 2004).

IL-11

IL-11 was initially described as a growth factor acting on multiple stages during hematopoiesis, synergizing with other factors (Du and Williams, 1994). More recently, it has been demonstrated to have important anti-inflammatory activities (Sands *et al*., 1999) as well as pleiotropic actions in multiple cell types (Du and Williams, 1994). Mice lacking the receptor for IL-11 have a fertility defect, which, unlike that in the LIF-deficient mice, occurs in the post-implantation response to the implanting blastocyst (Robb *et al*., 1998). A recent study has identified genes regulated by IL-11 in the uterus during pseudopregnancy in mice (White *et al*., 2004).

There is increasing evidence that IL-11 has an important function in implantation in humans. IL-11 is expressed in endometrial glandular and luminal epithelium although there is conflicting data regarding the time of maximal epithelial production, possibly because of differing protocols for immunohistochemistry (Dimitriadis *et al*., 2000; Cork *et al*., 2001; von Rango *et al*., 2004). Importantly, IL-11Rα and gp130 are expressed in both luminal and glandular epithelium (Cullinan *et al*., 1996; Cork *et al*., 2002; von Rango *et al*., 2004). However, it appears that there is no cyclical variation in IL-11Rα expression, and thus the expression pattern of ligand may be critical for IL-11 function in the endometrium. It remains to be evaluated whether epithelial-derived IL-11 is secreted apically into the uterine lumen or basally into the stroma or whether human preimplantation embryos express IL-11 or IL-11Rα.

Several studies have identified both IL-11 and IL-11Rα mRNA and protein in decidual cells from late secretory phase and early pregnant endometrium (Chen *et al*., 2002; Cork *et al*., 2002; Dimitriadis *et al*., 2002, 2003; Karpovich *et al*., 2003). Furthermore, invasive trophoblast cells are a source of IL-11 and IL-11Rα during early pregnancy in primates, suggesting an involvement in placentation (Chen *et al*., 2002; Dimitriadis *et al*., 2003).

IL-11 is involved in decidualization and advances *in vitro* progesterone-induced decidualization of human endometrial stromal cells (Dimitriadis *et al*., 2002). Furthermore, up-regulation of IL-11 mRNA was detected by gene array during progesterone or cAMP-induced *in vitro* decidualization of endometrial stromal cells (Popovici *et al*., 2000; Tierney *et al*., 2003). IL-11 and IL-11Rα immunolocalize to decidualized stromal cells of mid-late secretory phase endometrium in the human, demonstrating a local source for action (Cork *et al*., 2002; Dimitriadis *et al*., 2002). IL-11 secretion and mRNA expression by human endometrial stromal cells are stimulated by locally produced factors, relaxin and prostaglandin estradiol (E_2), acting at least in part via cAMP during human endometrial stromal cell decidualization (Figure 1), although progesterone attenuates IL-11 secretion and mRNA expression (Dimitriadis *et al*., 2005). In agreement, in cultured human endometrial and first-trimester decidua-derived epithelial cells, IL-11 secretion is reduced by co-culture with estrogen and progesterone but stimulated by estrogen alone (von Rango *et al*., 2004). Thus, both local factors and steroid hormones regulate IL-11 mRNA expression and secretion in the human endometrium.

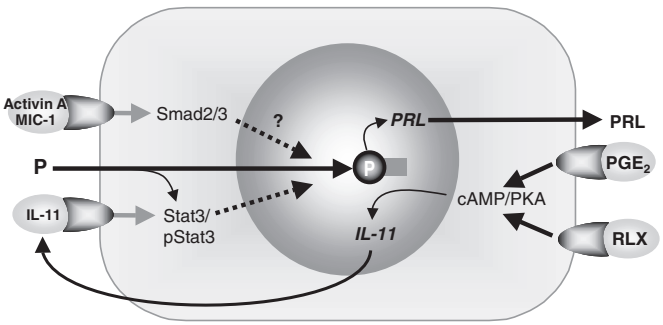

Figure 1. The figure shows as an example, the potential complex interrelationships between progesterone, prostaglandin (PG) estradiol (E_2), relaxin (RLX), interleukin-11 (IL-11), activin A and macrophage inhibitory protein-1 (MIC-1) in stimulating decidualization of human endometrial stromal cells. Prolactin is a marker of decidualization. Progesterone is necessary for decidualization, and its effects can be enhanced *in vitro* by PG E_2 or relaxin, both of which act via cAMP (exogenous cAMP can also drive the process in vitro). Effects of both relaxin and PG E_2 are via stimulation of IL-11 production. Progesterone attenuates IL-11 expression. IL-11 enhances P-induced decidualization via phosphorylation of signal transducer and activator of transcription (STAT3). Both Activin A and MIC-1 also stimulate decidualization via activation of Smads. ● ligand; ◖ receptor.

Interestingly, recent evidence in mice shows that IL-11 signalling is required for decidual-specific maturation of NK cells in mice (Ain *et al*., 2004). As yet, there are no studies examining the role of IL-11 in NK cell function during human implantation.

Emerging evidence indicates that IL-11 is important in the establishment of viable pregnancies. Immunoreactive IL-11 is reduced in the glands in ectopic non-viable tubal pregnancies compared with vital ectopic tubal and normal intrauterine pregnancies, indicating that inadequate IL-11 signalling may result in dysregulation of trophoblast invasion (von Rango *et al*., 2004). Furthermore, in contrast to LIF, IL-11 mRNA expression and immunostaining is reduced in decidua and trophoblast in women with anembryonic pregnancies that result in early abortion, compared with normal pregnancies. IL-11 and IL-11Rα are also reduced in endometrium in cohorts of women with infertility and endometriosis compared with fertile women during the window of implantation (Stoikos *et al*., 2003). Studies are now required to determine the functional significance of these findings.

IL-6

IL-6 is a multifunctional cytokine that regulates various aspects of the immune response, acute phase reaction and hematopoiesis and has some functional redundancy with IL-11 and LIF. IL-6–deficient mice have reduced fertility and a decrease in viable implantation sites (Robertson *et al*., 2000). In humans, IL-6 is weakly expressed during the proliferative phase, but strong immunoreactivity is present during the mid-secretory phase, predominantly in the glandular and luminal epithelial cells (Tabibzadeh *et al*., 1995; Vandermolen and Gu, 1996). Furthermore, IL-6-R is localized in glandular epithelium throughout the menstrual cycle (Tabibzadeh *et al*., 1995). Therefore, a role in the human implantation could also be postulated for this cytokine.

Serum IL-6 has been shown to be augmented in patients with recurrent abortions (Margni and Zenclussen, 2001; Zenclussen *et al*., 2003), although levels in the uterus were not measured. Importantly, when levels of IL-6 secretion were measured from endometrial biopsies isolated from infertile women compared with fertile women between days LH + 6 and LH + 13, no difference was found (Sherwin *et al*., 2002), and it is therefore likely that IL-6 has a redundant role in uterine receptivity. It has also been suggested that IL-6 may contribute to trophoblast growth and placental development in humans (Nishino *et al*., 1990).

Gp130 and gp130 family-soluble receptors

Gp130 deficiency in mice leads to embryonic lethality (Yoshida *et al*., 1996). Both membrane bound and soluble forms of gp130 have been identified, and the latter can act as an inhibitor of cytokine action by competing with membrane-bound receptor for ligand binding (Heaney and Golde, 1996; Heinrich *et al*., 1998). Gp130 mRNA localizes predominantly to glandular and luminal epithelium in human endometrium (Cullinan *et al*., 1996) and has also been demonstrated in human embryos from the three cell to blastocyst stage (Sharkey *et al*., 1995; van Eijk *et al*., 1996).

Naturally occurring soluble receptors for IL-6 and LIF have also been described (Novick *et al*., 1989; Layton *et al*., 1992), and these can bind their respective ligand with a similar low affinity to their transmembrane counterparts in the absence of gp130 (Taga *et al*., 1989; Layton *et al*., 1992; Ward *et al*., 1995). Soluble IL-6R can associate with cell surface gp130 in the presence of IL-6 and transduce a signal (Taga *et al*., 1989). Although the naturally occurring soluble IL-11Rα has not been isolated, recombinant forms can mediate an IL-6 type response in the presence of IL-11 in cells that express gp130 but not the transmembrane IL-11Rα (Baumann *et al*., 1996; Karow *et al*., 1996; Neddermann *et al*., 1996). Therefore, the biological activities of IL-6, LIF and IL-11 are all affected by their soluble receptors.

Immunoreactive gp130 is up-regulated in glandular epithelial cells from fertile women between days LH + 6 and LH + 13 compared with other stages of the menstrual cycle (Sherwin *et al*., 2002). Furthermore, soluble gp130 is secreted from endometrial biopsies obtained from women between days 20 and 26 of the menstrual cycle at a 20-fold higher concentration compared with secretion from proliferative phase tissue (Sherwin *et al*., 2002). Importantly, secretion of soluble gp130 from endometrial biopsies is reduced in infertile women compared with fertile women between days LH + 6 and LH + 13 (Sherwin *et al*., 2002). By contrast, there is no difference in secretion of soluble IL-6-R between the same infertile and fertile women (Sherwin *et al*., 2002).

In first-trimester decidua, gp130 immunostaining is confined to glandular epithelial cells and invading cytotrophoblast cells (Classen-Linke *et al*., 2004). Soluble gp130 is secreted from cultured primary epithelial cells derived from proliferative phase endometrium and first-trimester decidua reaching maximal levels without the addition of hormones. Combined treatment with estrogen and progesterone increased release of soluble gp130 compared to treatment with estrogen alone in these cultures (Classen-Linke *et al*., 2004). Because the presence of such soluble receptors in the endometrium has important implications in cytokine action, it will be important to establish the functional significance of these findings.

STAT

The importance of the JAK/STAT signal-transduction pathway in embryo implantation has been demonstrated by the embryonic lethality of STAT3-deficient mice (Takeda *et al*., 1997). Interestingly, STAT3-deficient embryos implant but die rapidly due to placental defects (Takeda *et al*., 1997), indicating that LIF and IL-11 can utilize alternative signalling pathways during implantation and decidualization. In the mouse uterus, LIF acts primarily through the activation of STAT3 (Cheng *et al*., 2001). Similarly, in human endometrial stromal cells, IL-11 acts via activated STAT3 (Dimitriadis and Salamonsen, 2003; Underhill-Day *et al*., 2003). It remains to be determined when phosphorylated-STAT3 can be detected in human endometrium as this will indicate when the signal-transduction pathway is activated. Interestingly, STAT3 protein production is stimulated by progesterone (Dimitriadis *et al*., 2003) and is activated by IL-11 in human endometrial stromal cells *in vitro* (Dimitriadis *et al*., 2003; Underhill-Day *et al*., 2003). Furthermore, a role for STAT3 activity in trophoblast invasiveness has also been proposed (Corvinus *et al*., 2003).

SOCS

The SOCS protein family consists of eight members: cytokine-inducible Src-homology 2 (SH2) domain-containing protein (CIS) and SOCS1–7 (Hilton, 1999). SOCS proteins are up-regulated in response to cytokine stimulation and inhibit cytokine-induced

signalling pathways. SOCS proteins therefore form part of a classical negative feedback circuit. Deletion of the SOCS3 gene in mice causes embryonic lethality due to placental defects (Roberts *et al*., 2001). Little is known about the expression of SOCS proteins in human endometrium. SOCS1–3 mRNA and protein are expressed in human term placenta and decidua (Blumenstein *et al*., 2002). Furthermore, SOCS2 and 3 mRNA expression in endothelial cells from placental villi is up-regulated in women with umbilical placental vascular disease, indicating that these are major negative regulators in umbilical placental microvessel endothelial cell activation pathways (Wang *et al*., 2003). The expression and role of the SOCS proteins in cycling endometrium and first-trimester decidua and placenta remain to be determined.

The embryonic lethality of SOCS3 deficiency is thought to be a consequence of enhanced LIF activation and excessive trophoblast giant cell differentiation. Inactivation of the LIF receptor rescues SOCS3-deficient mice from embryonic lethality (Takahashi *et al*., 2003), demonstrating that uncontrolled LIF signalling is most likely responsible for this phenotype. However, LIF has not been localized in trophoblast giant cells in mice, and it is possible that other gp130 cytokines known to stimulate SOCS3, such as IL-11 (Auernhammer and Melmed, 1999) that is present in these cells, may contribute to the phenotype (Zourbas *et al*., 2001).

Clinical implications

It is thus clear that members of the gp130 cytokine family are appropriately expressed and positioned to have major roles both in the preparation of the endometrium for implantation and during implantation and placental formation. The clear outcomes of functional studies in mice and the reported disturbances in expression of components of the receptor/ligand complexes and signalling/inhibitory molecules in a range of clinical situations suggest that manipulation of one or more of these components in selected women may offer some assistance towards achieving a pregnancy with a successful outcome.

The TGFβ superfamily

The TGFβ superfamily comprises at least 42 distinct mammalian dimeric proteins that share a similar structure (Kingsley, 1994; Piek *et al*., 1999). These are divided into two subfamilies, the TGFβ/activin/nodal subfamily and the bone morphogenetic protein (BMP)/müllerian inhibiting substance (MIS)/growth and differentiation factor (GDF) subfamily, which are defined by sequence similarity and the specific signalling pathways that they activate. There are also seven type I receptors, five type II receptors and two classes of Smad signal transducers through which the ligands signal (Shi and Massague, 2003). Specificity and diversity can also be determined by ligand traps (such as follistatin) and accessory receptors (such as betaglycan) (Shi and Massague, 2003). Given the level of complexity of this system, it is probably not surprising that disruption of any one member of the family by gene targeting in mice has not resulted in disruption of implantation (Table I). Furthermore, the lack of a uterine-specific promoter which would enable uterine-specific deletions has made it impossible to establish the importance for implantation of certain family members such as the activins which disrupt earlier events in female reproduction or cause lethality prior to reproductive maturity.

The TGFβs

The TGFβs (-1 to -3) are each synthesized as a large precursor molecule from which a propeptide must be cleaved. This occurs before secretion but the propeptide remains attached by a covalent bond. After secretion, most TGFβ is stored bound to extracellular matrix (ECM) components as a complex of TGFβ, propeptide and a peptide called latent TGFβ-binding protein. Release of active TGFβ from the complex is a critical regulatory step (Sinha *et al*., 1998). TGFβs regulate proliferation and differentiation and have profound effects on ECM production and degradative enzymes: therefore they are important mediators of tissue remodelling (Letterio and Roberts, 1997). Given the complexity of the system, understanding of the actions of TGFβs in implantation will require information regarding not only the presence or absence of the ligands and receptors at the trophoblast–endometrial interface, but also knowledge of their state of activation and of the molecules constituting and modulating the TGFβ-signalling cascades.

In the human endometrium, TGFβ-1, -2 and -3 have been localized to both epithelial and stromal cells (Gold *et al*., 1994) with TGFβ-2 being more intense in the stroma and TGFβ-1 and -3 of equal intensity in the two cell types (Godkin and Dore, 1998). Only TGFβ-3 varies across the cycle, being more intense in glandular epithelium during the late secretory phase. Given that the TGFβs are produced and stored as latent factors, it is difficult to predict function at implantation. It may be that they remain in their latent forms until the premenstrual rise in urokinase-type plasminogen activator (PA) stimulates activation (Casslen *et al*., 1998).

Messenger RNA for TGFβ1–3 and their receptors have also been detected at the maternal–foetal interface during the first trimester of pregnancy (Ando *et al*., 1998) with TGFβ protein in syncytiotrophoblast (Vuckovic *et al*., 1992). The detection of TGFβ-binding sites also in a trophoblast cell line (Mitchell *et al*., 1992) suggests that TGFβs may act as autocrine/paracrine factors to regulate placental development and function.

TGFβs may play a role in human implantation via their stimulation of fibronectin or vascular endothelial growth factor production (Feinberg *et al*., 1994; Chung *et al*., 2000) or by promotion of adhesion of trophoblast cells to the ECM (Irving and Lala, 1995). *In vitro*, TGFβ can regulate proteins such as insulin-like growth factor binding protein-1 (IGFBP-1) that are abundantly produced in decidual cells (Mazella *et al*., 2004), whereas trophoblast invasive capacity can be inhibited by treatment with TGFβ1, probably by the inhibition of matrix metalloproteinase-9 (MMP-9) and plasmin (Graham and Lala, 1991; Graham, 1997) and/or by overexpression of endoglin, the TGFβ transmembrane-binding protein (Caniggia *et al*., 1997b). TGFβs are also antiproliferative on first-trimester cytotrophoblast (Morrish *et al*., 1991; Graham *et al*., 1992; Li and Zhuang, 1997; Smith *et al*., 2001) and increase the formation of multinucleated trophoblast cells (Graham *et al*., 1992). In addition, TGFβ inhibits production and/or secretion of human chorionic gonadotrophin, human placental lactogen, progesterone and estradiol (Morrish *et al*., 1991; Song *et al*., 1996; Luo *et al*., 2002) from trophoblast cell lines. How many of these *in vitro* actions are functional *in vivo* where the full repertoire of modulators are present remains to be determined.

Activins

Inhibins and activins are dimeric glycoproteins of the TGFβ superfamily, which share common β subunits and are functional

antagonists. Inhibin is formed by the dimerization of an α with one β subunit, whereas activins A, AB and B arise from dimers of βA and βB subunits. Local actions of activins as paracrine regulators of reproductive function (Mather *et al*., 1992) are now well known. Activin A, in particular, has been attributed with roles in modulating cellular proliferation, differentiation, apoptosis, tissue remodelling and inflammation (Nishihara *et al*., 1993; Robinson and Hennighausen, 1997; Ying *et al*., 1997; Yu and Dolter, 1997; Munz *et al*., 1999). Activins elicit cellular responses through interaction with the serine/threonine kinase receptors (Ethier and Findlay, 2001), activin RI (alk-4) and RII. Ligand binding occurs with a type II receptor, which then recruits and activates a type I receptor leading to signal transduction and promotion of gene expression via selected Smad proteins (Massague and Chen, 2000). Two type II receptors have been identified, ActRIIA and ActRIIB. The local bioactivity of activin is tightly regulated by the co-expression of its binding protein, follistatin, which binds and neutralizes activin with high affinity, by preventing interaction with the type II receptors (Shimonaka *et al*., 1991).

In the human endometrium during the menstrual cycle and early pregnancy, the synthesis of inhibin/activin subunits varies with cycle stage and as the uterus remodels and differentiates to form the decidua (Petraglia *et al*., 1990; Leung *et al*., 1998; Otani *et al*., 1998; Jones *et al*., 2000). In non-pregnant endometrium, inhibin/activinα, βA and βB subunits of mRNA and protein are expressed by glandular and surface epithelium (Leung *et al*., 1998; Jones *et al*., 2000). Furthermore, activin A is present in uterine fluid of cycling women (Petraglia *et al*., 1998). During decidualization, at the end of the menstrual cycle and in early pregnancy, the expression of all subunits is seen in decidualized stroma (Petraglia *et al*., 1990; Jones *et al*., 2000). However, at this time, α subunit is lost from epithelium, whereas βA and βB subunits are maintained in glandular and surface epithelium during early pregnancy. Quantitative mRNA expression studies indicate that expression of all three subunits increases through pregnancy, with maximal expression in third-trimester decidua (Petraglia *et al*., 1990). Further evidence for the up-regulation of inhibin/activin subunit synthesis with decidualization was obtained from studies where the endometrium was extensively decidualized by the intra-uterine delivery of progestin (Jones *et al*., 2000) and in gene array studies examining decidualization-related genes (Kao *et al*., 2002)

The capacity of a particular cell type to produce bioactive inhibin and activin dimers depends on its complement of subunits, and the availability of α subunit is likely to regulate whether inhibins or activins are produced. Thus in non-pregnant endometrial epithelium, there is potentiality to produce both inhibin and activin dimers, whereas in early pregnancy, only activins will be formed. Indeed, both dimeric inhibin and activin are produced from endometrial epithelial cells *in vitro*, although activin A is at a 35-fold higher concentration than inhibin A (Petraglia *et al*., 1998). Stromal cells can produce both inhibins and activins only during and following decidualization. Extremely high concentrations of activin A are secreted by stromal cells following *in vitro* decidualization (Jones *et al*., 2002a), equivalent to levels detectable in maternal serum during the third trimester of pregnancy (Fowler *et al*., 1998). Dimeric activin A has also been detected immunohistochemically in early pregnancy decidua with an antibody specific for the dimeric form (Otani *et al*., 1998).

The activin-binding protein, follistatin, is produced in the endometrium by both glandular epithelium and decidualized stromal cells (Jones *et al*., 2002c), and its expression is significantly elevated in decidual cells in early pregnancy (Otani *et al*., 1998; Jones *et al*., 2000). Co-localization of follistatin with activin subunits and receptors in decidualized stromal cells provides evidence for the tight local regulation of activin action in the periimplantation phase. Secretion of follistatin from epithelial cells might be important for restricting the bioavailability of activin within the uterine lumen. Follistatin might also have activin-independent effects, suggested by the distinct phenotypes observed when the genes encoding follistatin and activin βA subunits are deleted or overexpressed (Matzuk *et al*., 1995; Guo *et al*., 1998). Follistatin can also bind other members of the TGFβ superfamily, including inhibin (Shimonaka *et al*., 1991) and BMPs 2, 4 and 7 (Yamashita *et al*., 1995; Fainsod *et al*., 1997), which are expressed strongly in the decidualized mouse uterus (Ying and Zhao, 2000; Paria *et al*., 2001), but have not yet been reported in the human endometrium.

Inhibin can also regulate activin bioactivity, by competing with activin for binding to ActRII in complex with betaglycan. Betaglycan is synthesized by the human endometrium, in the same cells that express activin receptors and inhibin/activin subunits (Jones *et al*., 2002c). Betaglycan is also up-regulated in the decidua of early pregnancy, correlating to increased synthesis of inhibin α subunit by decidualized stromal cells. This implies that inhibin action is important during early implantation/placentation. Betaglycan might also be important for presenting TGFβs (particularly TGFβ2) to their type II receptor (Lopez-Casillas *et al*., 1991), enhancing TGFβ signalling and action in the endometrium and placenta.

The roles of endometrially derived inhibins and activins are not well known. However, mRNA/protein for all receptor subtypes (ActRIA, IB, IIA and IIB) are present in the endometrium, specifically localized only to stromal cells and vascular endothelium (Jones *et al*., 2002c). Expression is maximal in the early secretory phase and early pregnancy, immediately preceding and during decidualization and implantation. Receptors are also present in isolated endometrial cells in culture (Petraglia *et al*., 1998).

In both the rodent and the human uterus, the expression patterns of activin, follistatin and activin receptors are consistent with a role in decidualization (Gu *et al*., 1995; Jones *et al*., 2000, 2002c). Activin is a potent cytodifferentiation factor (Robinson and Hennighausen, 1997; Ying *et al*., 1997) and additionally plays an active role in repairing and remodelling tissues (Munz *et al*., 1999). Activin A promotes decidualization (Jones *et al*., 2002a; Tierney and Giudice, 2004), an effect that is inhibited by co-treatment with follistatin. Although the downstream targets of activin A in decidual cells have not been explored, in other cell types, activin A stimulates the production of many factors associated with decidualization, such as PGE2, MMP-2 and fibronectin (Petraglia *et al*., 1993; Caniggia *et al*., 1997a).

It is probable that the uterine fluid supporting the preimplantation embryo contains maternally derived activin A, and hence potential actions via activin receptors expressed on the blastocyst could be envisaged (Jones *et al*., 2002b). In many species, activin A is involved in embryogenesis (Smith *et al*., 1990; Thomsen *et al*., 1990) and is expressed dynamically with its receptors and binding proteins during early embryonic development (Kimelman *et al*., 1992; Albano *et al*., 1994). A similar role has not been verified

in humans, although activin subunits and type I and II receptors are expressed by human blastocysts (He *et al*., 1999).

Following the initial implantation events, trophoblast cells invade the maternal decidua and therefore are in intimate cell–cell contact with decidualized stromal cells. Activin A produced by decidualized stromal cells (Jones *et al*., 2002a) might play a further role in augmenting invasion and supporting placental function. Indeed, activin A promotes cytotrophoblast differentiation towards an invasive phenotype and stimulates the production of paracrine agents involved in invasion (Caniggia *et al*., 1997a), along with the placental hormones, hCG, 17β estradiol and progesterone (Petraglia *et al*., 1989; Song *et al*., 1996).

Macrophage inhibitory cytokine 1

Macrophage inhibitory cytokine 1 (MIC-1) is a divergent member of the TGFβ superfamily (Bootcov *et al*., 1997) that is detectable in serum of pregnant women and produced by human placenta where it is localized to syncytiotrophoblast (Moore *et al*., 2000). More recently, roles for MIC-1 have been identified at the maternal–foetal interface during very early pregnancy. It is produced as endometrial cells undergo decidualization *in vitro* and facilitates this differentiation, consistent with roles for a number of TGFβ superfamily members in modulating decidualization. MIC-1 also blocks activation of both MMP-2 and MMP-9 in this model (Marjono *et al*., 2004). This may represent an important mechanism for regulating cytotrophoblast invasion.

IL-1

IL-1 is a pro-inflammatory cytokine with multiple functions in a range of tissues (Bankers-Fulbright *et al*., 1996; Dinarello, 1997). The IL-1 system includes two ligands, IL-1α and IL-1β, the cell-surface receptors, IL-1 receptor type 1 (IL-1R1) and IL-1R2, a non-binding receptor accessory protein (IL1RAcP) and the naturally occurring receptor antagonist (IL-1ra) which competes with IL-1 for receptor binding. IL-1α and IL-1β are encoded by different genes but have identical biological activities. Both IL-1α and IL-1β but not IL-1ra require proteolytic cleavage prior to secretion in their active forms. Soluble forms of IL-1R1 and IL-1R2 are found in serum (Svenson *et al*., 1993; Giri *et al*., 1994). The IL-1R1 is found ubiquitously in low numbers, but the IL-1R2 is primarily on white blood cells. Some novel IL-1 ligands which are little characterized have been described as expressed in the uterus: these include IL-1F5 and IL-1F7, but along with other newly discovered ligands and receptors of this family (Sims *et al*., 2001), their functions are not yet known

IL-1β signalling is mediated by binding to both the IL-1R1 and IL-1RAcP leading to activation of the Mitogen-activated protein kinase (MAPK) and NF-$_K$B pathways and modulation of target gene transcription. Activity of IL-1β is effectively enhanced in the presence of soluble IL-1R1 (Svenson *et al*., 1993; Arend *et al*., 1998) but suppressed in the presence of both cell surface and soluble R2 (Sims *et al*., 1993; Colotta *et al*., 1994). IL-1β is independently regulated at the levels of transcription, translation, activation and secretion (Dinarello, 1997). It is generally found within intracellular vesicles or associated with microtubules in cells. Conversion of the latent to the mature form is by the intracellular protease, IL-1 converting enzyme (ICE; caspase-1), and a combination of mature, latent and pro-piece IL-1 is released by the cell. Extracellular activation of the latent form can result from the non-specific actions of enzymes including elastase, chymase, chymotrypsin and MMP-2, -3 and -9 (Fantuzzi *et al*., 1997; Schonbeck *et al*., 1998), whereas prolonged action of MMP-3 results in the degradation of mature IL-1β. The secreted pro-piece also has biological activity as a chemoattractant for fibroblasts (Higgins *et al*., 1993).

Previous reviews (Robertson *et al*., 1994; Sharkey, 1998; Salamonsen *et al*., 2000; Kelly *et al*., 2001; Fazleabas *et al*., 2004) have emphasized the conflicting nature of functional studies of IL-1 action on reproduction in mice. Ablation of the genes encoding IL-1β, IL-1R1 or caspase-1 did not result in deficient implantation: however in such models, functional compensation by other systems cannot be excluded. In contrast, a strain-specific blockage of implantation resulted from intraperitoneal injection of IL-1ra at the appropriate time (Simon *et al*., 1994b), and this was attributed to down-regulation of critical integrins at the luminal epithelial surface. Evidence for such a mechanism also in humans comes from a study in which the integrin subunit was examined in endometrial epithelial cells in culture and shown to be up-regulated either by co-culture with a human pre-implantation embryo or by the addition of IL-1 to the culture medium (Simon *et al*., 1997a). Furthermore, IL-1β stimulates the secretion of leptin and up-regulation of its receptor Ob-R in endometrial epithelial cells (Gonzalez and Leavis, 2001), and leptin exerts a significantly greater effect on β3 integrin expression than does IL-1 at similar concentrations. Interestingly, components of the IL-1 family (IL-1β, IL-1Ra, IL-1R1) are up-regulated by leptin in both endometrial epithelial and stromal cells in culture (Gonzalez *et al*., 2003). Whether leptin is a major regulator of the IL-1 system in the endometrium *in vivo* remains to be established.

All components of the IL-1 system have been examined in the human endometrium and at the maternal–trophoblast interface during implantation. IL-1β mRNA is maximally expressed in the endometrium during the late secretory phase (Kauma *et al*., 1990) with protein located in endometrial stromal cells, macrophages and endothelial cells (Kauma *et al*., 1990; Simon *et al*., 1993). IL-1R1 is present predominantly in glandular epithelium throughout the cycle (Simon *et al*., 1993) but also in stroma with maximal expression from the mid-late secretory phase (Bigonnesse *et al*., 2001). Immunoreactive IL-1ra has also been detected throughout the menstrual cycle (Tabibzadeh and Sun, 1992) and in decidua during early implantation (Simon *et al*., 1994a). During early pregnancy, IL-1β is present in villous cytotrophoblast, syncytiotrophoblast, decidua and activated macrophages (Simon *et al*., 1994a) at much higher abundance than in non-pregnant endometrium. IL-1R1 is predominant in syncytiotrophoblast and in endometrial glands in early pregnancy, and its mRNA is up-regulated during endometrial stromal cell decidualization *in vitro* (Tierney *et al*., 2003). Furthermore, recent gene array studies have identified IL-1β as one of the genes most up-regulated by IL-11 during decidualization (White *et al*., 2004).

All major components of the IL-1 system, IL-1β, IL-1ra and IL-1R1 have been identified at the protein level in single preimplantation embryos, and in some, but not all cases, IL-1 release into culture medium was also detected (Sheth *et al*., 1991; Zolti *et al*., 1991; Austgulen *et al*., 1995; De los Santos *et al*., 1996; Baranao *et al*., 1997). Importantly, embryo secretion of IL-1β is stimulated by endometrial factors (De los Santos *et al*., 1996; Simon *et al*., 1997b) demonstrating a clear interaction between the maternal

endometrium and embryo prior to implantation. In a study examining single blastomeres, IL-1R1, IL-1β and IL-1ra mRNA were detected in only some of the blastomeres, and the parent preimplantation embryos expressing IL-1ra were more likely to be arrested in early developmental stages (Krussel *et al*., 1998). Further interactions have been demonstrated at slightly later stages in implantation. Treatment of the human first-trimester trophoblast with IL-1 induced HCG secretion (Yagel *et al*., 1989), whereas administration of HCG to IVF patients increased their serum IL-1β levels (Karagouni *et al*., 1998). Some correlations have been demonstrated between IL-1 and success of IVF. Higher levels of IL-1α were detected in follicular fluid in implantation versus non-implantation cycles although a direct causal relationship was not demonstrated (Karagouni *et al*., 1998), whereas high concentrations of IL-1 in IVF culture medium correlates with success of implantation (Sheth *et al*., 1991). *In vitro*, release of IL-1β by cultured cytotrophoblast cells is directly proportional to their invasive capacity (Librach *et al*., 1994), and IL-1β increases the production of MMP-2 and -9 by JEG-3 trophoblast cells (Karmakar and Das, 2002). *In vivo*, it is therefore likely that decidual IL-1β may act in a paracrine manner by binding to IL-1R1 expressed by trophoblasts and regulating MMP-mediated invasion and HCG secretion.

IL-1β consistently acts to inhibit human endometrial stromal cell decidualization *in vitro* (Kariya *et al*., 1991; Vicovac *et al*., 1994; Frank *et al*., 1995), regardless of the stimulus for decidualization (progesterone or cAMP). It is possible that *in vivo*, the high levels of IL-1ra may provide a mechanism for neutralizing these effects during active decidualization although *in vitro*, the ratio of IL-1β to IL-1ra mRNA remains constant (Huang *et al*., 2001). Furthermore, in culture, there is diminished responsiveness to exogenous IL-1β as decidualization proceeds (Yoshino *et al*., 2003).

Other components of decidua may also be influenced by IL-1β. For example, the uNK cells that increase in abundance in the human endometrium during the mid-secretory phase and contribute a major cellular component of the decidua of pregnancy increase their production of granulocyte-macrophage colony-stimulating factor (GM-CSF) in response to IL-1 (Jokhi *et al*., 1994). Furthermore, IL-15, which is produced by decidualizing endometrial stromal cells and which acts to attract uNK cells, is decreased by IL-1β in culture (Okada *et al*., 2004). IL-1β also stimulates the production of endothelin (Lin *et al*., 1998) from cultured endometrial stromal cells, and this may locally regulate vascular tone or cellular proliferation.

Extracellular remodelling is critical to implantation and placentation. IL-1 stimulates production of a number of MMPs and components of the PA/PA-inhibitor cascade from endometrial stromal cells (Singer *et al*., 1999; Salamonsen and Nie, 2002) and also decreases connexin 43 (Semer *et al*., 1991). A proportion of fresh and cultured human decidual cells are phagocytic, and this activity is enhanced in the presence of IL-1 and reduced as decidualization proceeds (Ruiz *et al*., 1997).

Many questions remain regarding the role of the IL-1 system in the human implantation. Current techniques available for analysis of human tissue are limiting. For example, it is not clear whether findings from cell-culture experiments hold *in vivo* where many more paracrine regulators are present; epithelial–stromal interactions are likely to be important. In particular, decidual cells release only low to undetectable levels of mature IL-1 in culture in spite of the presence of substantial mRNA and intracellular protein (Montes *et al*., 1995; Huang *et al*., 2001; White *et al*., unpublished observations). It could be predicted that release of stimuli from surrounding cells, such as uNK cells or macrophages, may be necessary for its release. Techniques which enable careful reconstitution of the *in vivo* situation using the full cohort of human cells of endometrial, leukocyte and trophoblast origin will be required to even partly recapitulate the *in vivo* situation.

IL-15

IL-15 is a 14–15kDa member of the four α-helix bundle cytokine family which includes IL-2. Its effects are mediated by a trimeric membrane receptor comprising the IL-2 receptor β- and α-chains and a specific α-chain. It promotes activation of neutrophils, macrophages and T cells, but importantly, is a core chemokine that controls lymphocyte function and maintenance (Kang and Der, 2004). IL-15 is essential for NK cell development in bone marrow and stimulates the proliferation, cytokine production and cytotoxicity of activated blood NK cells (Burton *et al*., 1994; Carson *et al*., 1994, 1995; Seder *et al*., 1995). NK cells of the $CD5^{bright}$, CD^{16-} phenotype are a major leukocyte population in the mid-late secretory endometrium and first-trimester decidua and themselves are a source of immunoregulatory chemokines including GM-CSF, IL-10, IL-13 and interferon-γ. IL-15 is reported to be essential for type 2 cytokine production by these cells (Cooper *et al*., 2001; Eriksson *et al*., 2004) and also affects their proliferation. Unlike its effects on blood NK cells, it does not transform the uNK cells into potent cytolytic cells (Verma *et al*., 2000). This is critically important for a cell that is present at the maternal–foetal interface where cytolytic activity would destroy trophoblast. It is therefore reasonable to assume that in the human uterus, IL-15 may play a role in promoting uNK cell survival and expansion as has been proposed for mice (Verma *et al*., 2000).

IL-15 mRNA and protein have been demonstrated in non-pregnant human endometrium, decidua and placenta (Kitaya *et al*., 2000; Okada *et al*., 2000b; Verma *et al*., 2000) with the protein being immunolocalized perivascularly in secretory phase stromal cells, in glandular epithelial cells during the proliferative phase (Kitaya *et al*., 2000) and in decidua in the first trimester of pregnancy (Kitaya *et al*., 2000). Macrophages are also an important source of IL-15 in the uterus (Verma *et al*., 2000). Two different mRNA isoforms are present in the endometrium; one representing a secreted protein and another which encodes a cytoplasmic form (Verma *et al*., 2000).

IL-15 mRNA expression and protein secretion increase during *in vitro* decidualization of endometrial stromal cells in culture, although there are some discrepancies in the literature, likely because of the different culture conditions used. It is clear that cells decidualized using either cAMP or progesterone show enhanced IL-15 mRNA expression and protein secretion (Kitaya *et al*., 2000; Okada *et al*., 2000a; Dunn *et al*., 2002) and that this is further enhanced in the presence of interferon-γ although the latter cytokine alone cannot stimulate IL-15 production. The probable source of interferon-γ in the endometrium is the uNK cells (Dunn *et al*., 2002), and thus the likelihood exists of enhancement of IL-15 production from decidualizing cells by adjacent uNK cells. IL-1β appears to play an opposing role as it acts as a negative regulator of IL-15 mRNA and protein during *in vitro* decidualization

(Okada *et al*., 2004) and may act to prevent abnormally high levels of IL-15 in early decidua. Interestingly, in women with unexplained recurrent abortion, there are elevated levels of endometrial IL-15 compared with control endometrium (Chegini *et al*., 2002). This was not however examined in the decidua of early pregnancy or related to the uNK cell number or phenotype in the tissue.

The CSF

CSF-1 is a homodimeric protein that modulates proliferation, differentiation and survival of numerous cell types (Stanley *et al*., 1983). Its receptor, *c-fms*, possesses intrinsic tyrosine kinase activity. Mice devoid of CSF-1 show impaired preimplantation embryo development (Pollard, 1997) and a low rate of mating due to ovulation and libido effects, but when they do mate, about 95% of inseminated females become pregnant and deliver viable litters (Pollard *et al*., 1991). In the human, CSF-1 protein is much higher in the pregnant than the non-pregnant endometrium and is high in the placenta throughout pregnancy (Kauma *et al*., 1991; Daiter *et al*., 1992). Expression of CSF-1 and *c-fms* is apparent in the human first-trimester cytotrophoblast, but the function of the cytokine in placentation is not clear. *In vitro* functional studies are conflicting, with CSF-1 both stimulating and inhibiting proliferation of trophoblast cells (Lewis *et al*., 1996; Hamilton *et al*., 1998) probably reflecting differences in the cell lines used.

GM-CSF has well-defined effects on survival, proliferation and differentiation of myeloid leukocytes and their precursors (Metcalf, 1989). Similar to CSF-1, GM-CSF is synthesized in the human uterus by endometrial luminal and glandular epithelial cells suggesting that it may be secreted into the uterine lumen. Messenger RNA for GM-CSF is maximal in the mid-secretory phase, coinciding with the 'window of implantation' (Zhao and Chegini, 1999). In contrast, GM-CSF receptor mRNA is located primarily in endothelial cells associated with spiral arterioles, stromal cells and inflammatory cells. In the mouse, a surge of GM-CSF is induced following mating by TGFβ in the seminal plasma (in the mouse, seminal plasma is deposited in the uterine lumen), and this is accompanied by a dramatic influx of GM-CSF–responsive leukocytes (Tremellen *et al*., 1998). These leukocytes are likely to play roles in mediating the tissue remodelling required to accommodate pregnancy. In mice rendered null for GM-CSF, implantation rates are normal and viable pups are produced; however, these pups are small and often die late in gestation due to abnormalities in the relative proportions of the different cell types contributing to the placenta (Robertson *et al*., 1999). Interestingly, GM-CSF added to culture medium alleviates the adverse effects of embryo culture on subsequent foetal growth trajectory and placental morphogenesis (Sjoblom *et al*., 2005). It has also been suggested that pregnancy outcome in humans is improved following embryo culture in endometrial culture medium with a GM-CSF content greater than 130 pg/ml prior to transfer (Spandorfer *et al*., 1998).

Chemokines

Chemokines are a large superfamily of structurally and functionally related cytokines with chemotactic activity targeted at specific leukocyte populations. More than 50 chemokines have been identified to date, but there is a large degree of redundancy and overlap of functions (Murphy *et al*., 2000; Bacon *et al*., 2002; Rabin *et al*., 2003). There are four major subfamilies of chemokines, based on the relative positions of their cysteine residues (CC, CXC, C and CX_3C) (Luster, 1998). The original random naming of chemokines has recently been systematized (Thorpe, 2002). Chemokine receptors are G-protein–coupled cell surface receptors which are named depending upon the structure of their ligand (thus, CCR and CXCR). The relatively small number of receptors relative to ligands adds an additional level of redundancy.

Chemokine binding to receptors on specific leukocyte subsets can increase leukocyte adhesion to the endothelium through the up-regulation of adhesion molecules and hence promote extravasation. Chemotaxis then occurs along a concentration gradient of chemokines. Marked morphological changes can be seen within leukocytes following chemokine binding: the cytoskeleton is rearranged, integrin-mediated focal adhesions are formed and the cell binds and detaches from the substrate in a coordinated manner, with extension and retraction of pseudopods responsible for directional migration (Bokoch, 1995; Ward *et al*., 1998).

Chemokines play important roles in both homing of leukocytes to specific regions within a tissue and as potent activators of leukocytes (Papadakis *et al*., 2000; Kunkel and Butcher, 2003). Importantly, the sequential or combinatorial action of multiple chemokines is probably necessary for the recruitment, homing and activation of a single leukocyte subtype (Vaday *et al*., 2001). Chemokines act locally and are rapidly and transiently induced in response to an inflammatory stimulus. However, there is recent evidence for the constitutive expression of certain chemokines that are responsible for immunosurveillance and tissue homeostasis (Zlotnik and Yoshie, 2000; Caux *et al*., 2002; Kunkel and Butcher, 2003). Additional complexity is added by chemokine processing, which further regulates their bioactivity and specificity: such processing is achieved by the actions of MMPs and other proteases (Overall *et al*., 2002; Van den Steen *et al*., 2003a,b; Van Damme *et al*., 2004), many of which are secreted by leukocytes following chemokine stimulation. For example, fractalkine is rapidly cleaved from its transmembrane location by proteolytic enzymes including MMP-9 and released as a soluble chemokine (Bazan *et al*., 1997) which appears to have different chemotactic properties to the bound form and additionally can antagonize monocyte chemotactic protein-1 (MCP-1) action (Vitale *et al*., 2004).

There is a large accumulation of leukocytes in the endometrium in the periimplantation phase of the human menstrual cycle and during early pregnancy (Bulmer *et al*., 1991; King *et al*., 1995; Salamonsen and Woolley, 1999). These are present scattered throughout the stroma, but also seem to be specifically targeted to areas of decidualization. Decidual-/pregnancy-associated leukocytes are predominantly a subpopulation of macrophages and uNK cells (King *et al*., 1995; Ozenci *et al*., 2001). uNK cells begin to infiltrate the endometrium on day LH + 3, specifically accumulate around spiral arterioles and areas of decidualized stroma, and are present in the decidua until the second trimester of pregnancy (Moffett-King, 2002). This highly specialized population of immune cells is a fundamental component of the implantation site, creating an unique immunological environment permissive to, yet regulating, the invasion of foetal cytotrophoblast cells (King *et al*., 2000; Moffett-King *et al*., 2002). Recent evidence from mice lacking NK cells suggests important roles in spiral arteriole remodelling and decidualization (Guimond *et al*., 1998; Greenwood *et al*., 2000; Croy *et al*.,

2003). Macrophages comprise 20% of endometrial leukocytes and are present during periods of endometrial proliferation, differentiation and breakdown. There is a marked accumulation of endometrial macrophages specifically in areas of decidualization and trophoblast invasion. These cells are a source of growth factors, cytokines and proteases, creating local microenvironments permissive to tissue remodelling and have been proposed to participate in foetal–maternal interactions in the implantation site (Hunt *et al*., 2000; Heikkinen *et al*., 2003; Trundley and Moffett, 2004). Therefore, the recruitment and activation of these two distinct groups of leukocyte subpopulations must be tightly and specifically regulated at the time of embryo implantation. This is likely to be achieved by chemokines.

There have been a number of reports describing the expression and regulation of individual chemokines in the endometrium, including IL-8, MCPs-1 and -2, macrophage inhibitory protein (MIP)-1β, eotaxin and regulated on activation and normally T cell expressed and presumably secreted (RANTES; Hornung *et al*., 1997; Jones *et al*., 1997; Akiyama *et al*., 1999; Zhang *et al*., 2000; Hampton *et al*., 2001). More recently, an unbiased gene array approach has provided information on the most abundant chemokines expressed by the endometrium, and interestingly many of those previously studied are not among the nine most abundant (Jones *et al*., 2004). The expression studies were supported by immunolocalization of chemokine protein within the tissue, and the varying cellular localization across the cycle determined. Because chemokines are short lived and very locally acting, identification of cellular location also provides invaluable indicators of function.

Chemokines produced in the decidualizing stromal cells during the mid-late secretory phase of the cycle are likely to be important for recruitment of the NK cells and macrophages that are a component of the decidua. Indeed, most of the chemokines produced by decidualized stromal cells at this time (macrophage-derived chemokine (MDC), MCP-3, fractalkine (FKN), 6Ckine, MIP-1β) are potent NK cell chemoattractants (Jones *et al*., 2004). The precursor uNK cells in blood (CD56+CD16-) bear receptors for and migrate strongly in response to 6Ckine and to a lesser extent MIP-1β and MCP-3 (Taub *et al*., 1995; Polentarutti *et al*., 1997; Robertson *et al*., 2000). During the first trimester of pregnancy, chemokines within the decidua are likely to be important for leukocyte trafficking towards the maternal blood vessels: additional chemokines identified in such cells are granulocyte chemotactic protein (GCP-2), inositol phosphate-10 (IP-10), interferon-inducible T-cell alpha chemoattractant (I-Tac), BRAK, MCP-1 and MIP-1α (Drake *et al*., 2001; Red-Horse *et al*., 2001; Dominguez *et al*., 2003b; Kitaya *et al*., 2003).

Leukocyte recruitment has many features in common with trophoblast invasion and trafficking, and it is therefore likely that chemokines play an important role in implantation. During the apposition phase, the blastocysts must find a location on the endometrial epithelium to implant. In the subsequent invasion phase, the trophoblast must traverse first the epithelial basement membrane and then the decidua to reach the uterine blood vessels. Evidence is now accumulating to support a biologically relevant role for chemokines in these processes (Simon *et al*., 1998; Red-Horse *et al*., 2001; Dominguez *et al*., 2003b; Drake *et al*., 2004; Hannan *et al*., 2004a).

Tables II and III summarize the current published data for chemokine and receptor expression in the preimplantation blastocyst, in the endometrial epithelium in the mid-secretory phase of the cycle

Table II. Chemokines expressed at the embryo–maternal interface during implantation and placentation

Systematic name	Human ligand	Receptor	Ligand localization			
			Blastocyst	Endometrial epithelium mid-secretory	Decidual cells	Invasive cytotrophoblast
CXCL6	GCP-2	CXCR1, CXCR2	Not tested	Not tested	Present	Present
CXCL8	IL-8	CXCR1, CXCR2	Not present	Present/ not present	Not tested	Not tested
CXCL10	IP-10	CXCR3	Not tested	Not tested	Present	Not tested
CXCL11	I-TAC	CXCR3	Not tested	Not tested	Present	Not tested
CXCL12	SDF-1 α/β	CXCR4	Not tested	Not tested	Not tested	Present
CXCL14	BRAK	Unknown	Not tested	Not tested	Present	Not tested
CX3CL1	Fractalkine	CX3CR1	Not tested	Present	Present	Not tested
CCL1	MCP-1	CCR2	Not present	Present	Present	Not tested
CCL3	MIP-1α	CCR1, CCR5	Not tested	Not tested	Present	Present
CCL4	MIP-1β	CCR5	Not tested	Present	Present	Not tested
CCL5	RANTES	CCR1, CCR3, CCR5	Not present	Not tested	Not tested	Not tested
CCL7	MCP-3	CCR1, CCR2, CCR3	Not tested	Present	Present	Not tested
CCL11	Eotaxin	CCR3	Not tested	Present	Present	Not tested
CCL14	HCC-1	CCR1, CCR5	Not tested	Present	Present	Present
CCL16	HCC-4	CCR1, CCR2	Not tested	Present	Present	Not tested
CCL21	6Ckine	CCR7	Not tested	Present	Present	Not tested
CCL22	MDC	CCR4	Not tested	Present	Present	Not tested

IP, inositol phosphate; MCP, monocyte chemotactic protein; RANTES, regulated on activation and normally T cell expressed and presumably secreted. GCP, granulocyte chemotactic protein; I-Tac, interferon-inducible T-cell alphachemoattractant; SDF stroma cell derived factor; MIP, macrophage inhibitory protein; HCC, haemofiltrate CC chemokine; MDC, macrophage derived chemokine.
Data derived from Hampton *et al*. (1999); Jones *et al.* (2000), (2004); Zhang *et al*. (2000); Douglas and Thirkill (2001); Drake *et al.* (2001); Red-Horse *et al*. (2001); Caballero–Campo *et al*. (2002); Dominguez *et al*. (2003b); Kitaya *et al*. (2003); Mulayim *et al*. (2003); Sato *et al*. (2003); Hannan *et al*. (2004a).

Table III. Chemokine receptors at the embryo–maternal interface during implantation and placentation

Receptor	Blastocyst inner cell mass	Trophectoderm	Endometrial epithelium, mid-secretory	Invasive cytotrophoblast	Syncytiotrophoblast
CCR1	Not tested	Not tested	Not tested	Present	Not present
CCR2B	Present	Not tested	Not tested	Not tested	Not tested
CCR3	Not tested	Not tested	Present	Not tested	Not tested
CCR5	Not tested	Present	Present	Present	Not present
CCR8	Not tested	Not tested	Not tested	Not tested	Not present
CXCR1	Not present	Not present	Present	Not tested	Not tested
CXCR2B	Not tested	Not tested	Present	Present	Not tested
CXCR4	Not present	Not present	Present	Not tested	Present
CX3CR1	Not tested	Not tested	Present	Present	Not tested

Data derived from Drake *et al*. (2001); Douglas and Thirkill, (2001); Mulayim *et al*. (2003); Dominguez *et al.* (2003a); Sato *et al*. (2003); Hannan *et al*. (2004a).

and in decidual cells and invasive cytotrophoblast. To date, no chemokines have been identified in preimplantation blastocysts or their culture medium but the receptors CCR2B and CCR5 have been localized in the inner cell mass and trophectoderm, respectively (Dominguez *et al*., 2003a). The uterine epithelium in the mid-secretory phase strongly expresses fractalkine, MIP-1β, MCP-3, eotaxin, HCC-1, HCC-4, 6Ckine and MDC, whereas MCP-3 is weakly expressed (Zhang *et al*., 2000; Hampton *et al*., 2001; Hannan *et al*., 2004a; Jones *et al*., 2004). Chemokine receptors (CXCR1, CXCR4, CCR5 and CCR2B) are also detectable in the human endometrial epithelium during the receptive phase. Thus, it could be predicted that chemokines released into the uterine lumen, or on the surface of the luminal epithelium, play a role in the apposition and adhesion phases of human implantation.

Both chemokines and receptors have been identified on invasive cytotrophoblast during the first trimester of pregnancy, and these include CGP-2, stromal cell-derived factor (SDF)-1 and MIP-1α (Drake *et al*., 2001; Red-Horse *et al*., 2001) and the receptors CCR1 CCR2B, CCR5, CXCR2B and CX3CR1 (Drake *et al*., 2001; Dominguez *et al*., 2003a; Sato *et al*., 2003). Chemokine receptors (CX3CR1, CCR1, 2 and 3) have also been detected on some trophoblast cell lines (Hannan *et al*., 2004b). In addition, in floating and anchoring villi, nearly every chemokine targeted for study was expressed by predominantly two cell types, fibroblasts and macrophages. Cytotrophoblast progenitors in floating villi expressed a broad repertoire of chemokine receptors suggesting that cytotrophoblasts are poised to respond to chemokine signals at the maternal–foetal interface (Drake *et al*., 2004).

From these studies, it is clear that chemokines will be important determinants of successful implantation and placentation by their actions in chemoattracting leukocytes which are critical players at the embryo–maternal interface, by their actions on trophoblast migration and by additional functions such as cell proliferation and modification of adhesion molecule expression. Interestingly, none of the chemokine receptor knockout mice generated thus far have been reported to have reduced fertility (Power, 2003): this may reflect the redundancy in the system, but it may also be that as for a number of other genetically modified mice, small effects on fertility would not be recorded by laboratories for which this is not a major interest.

Conclusions and clinical implications

From the above, it is clear that cytokines are critical contributors to the events of implantation, from their effects on the blastocyst within the uterine lumen, through the phases of initial attraction and attachment to the endometrium, to effects on preparation of the endometrium for pregnancy by formation of the decidua. They also exert effects on the subsequent trafficking of the trophoblast through the prepared endometrium to invade the blood vessels and hence allow provision of nutrients for the developing foetus. These events are summarized in Figure 2.

Although expression of many cytokines (or associated molecules) is disturbed in cohorts of women with disorders associated with establishment and maintenance of pregnancy, it is also evident that there is not a single cytokine whose expression is either increased or decreased in tissue or fluids from all women with a particular disorder. In combination with what is now known of the complexity of the above systems, this suggests that it is unlikely that manipulation of any one cytokine or accessory molecule will provide ‘quick fix’ solutions to clinicians’ requirements. These needs include rapid identification of a receptive endometrium or blastocyst guaranteed to implant, manipulation of the embryo-maternal environment to improve fertility, or provision of fail-safe post-coital contraception.

Taking the need for detection of a receptive endometrium as an example, what is required is the identification of a ‘fingerprint’ for analysis, which includes a number of factors known to alter in the mid-secretory phase, of which some but not necessarily all may be disturbed in an individual with infertility. Cytokine fingerprints could be deduced from the literature, given the wealth of studies on individual cytokines and data from microarray analysis, much of which is summarized here. The deduced fingerprint would then require substantial testing in appropriately selected clinical material. New research should include analyses of clinical material such as endometrium from women with or without infertility, using sensitive proteomic systems. These hold great potential for identifying a clinically useful fingerprint because they can identify proteins in their post-translationally modified and hence biologically relevant forms.

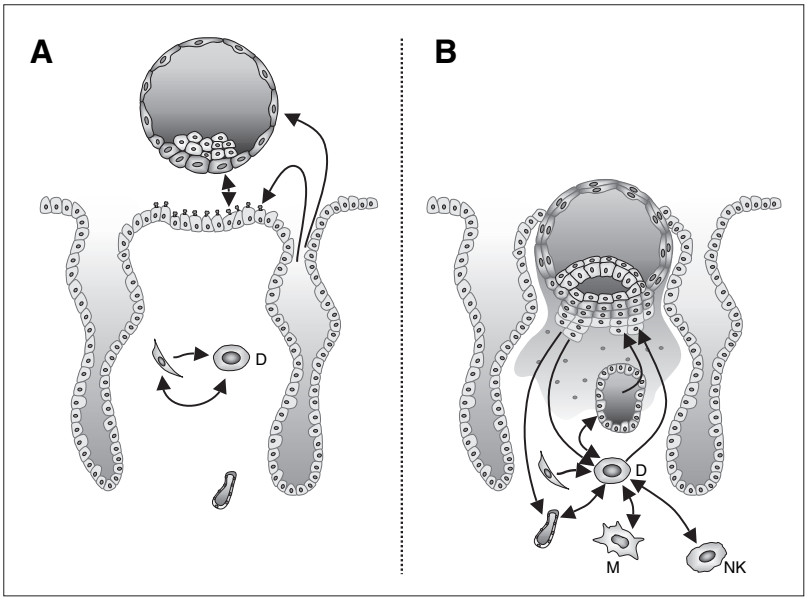

Figure 2. Cross-talk between trophoblast and endometrium, preimplantation (**A**) and immediately post-implantation (**B**) is mediated, in part, by cytokines in the directions shown by the arrows. During the preimplantation phase, cytokines are secreted by uterine glands, by stromal fibroblasts and decidual cells (D) and by trophoblast. These can act separately or in concert on trophoblast, on endometrial epithelium and during decidualization. Once trophoblast invasion is in progress, an array of cytokines produced by glands, decidual cells and leukocytes [predominantly uterine-specific natural killer (uNK) cells and macrophages] are likely to promote cellular differentiation, trafficking of leukocytes and trophoblast and continuing decidualization.

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