Immunology of the Fetomaternal Border

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Contents

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2.1 Background

The field of reproductive immunology has been founded in the 1950s by Sir Peter Medawar, who first raised the question of why the allogeneic fetus is not rejected by the maternal immune system (Medawar 1953). Current knowledge of the immunology of reproduction as well as the fetomaternal interface has been summarized in several international publications or special volumes in recent years, which are recommended for more intensive studies of the topic (Svensson-Arvelund et al. 2014; Arck and Hecher 2013; Szekeres-Bartho et al. 2015). The present chapter does not claim to give more than a rough impression of the topic.

2.2 Immunology of the Endometrium

Pregnancy is immunologically prepared even before it begins. The female immune system, especially in the reproductive tract, has to ensure that no immune reaction occurs to the allogeneic sperm and seminal plasma, but that simultaneously protection against germs remains active. The seminal plasma is immunoregulatory active (Filippini et al. 2001), and at the same time, the uterus is an immunologically highly active and complex organ. The endometrium, which renews itself cyclically, must thereby also regularly rebuild its immunological capacities, while permanently ensuring sufficient functional defense. The non-pregnant endometrium contains almost the entire spectrum of immune cells, but with changes adapted to the menstrual cycle (Kammerer et al. 2004).

The number of maternal leukocytes in the uterus increases at the end of the menstrual cycle, especially after the time of possible implantation of the blastocyst. The largest proportion of these cells are uterine natural killer cells (uNK cells), approx. 70% of the immune cells are uNK cells. If implantation takes place, their number further increases. 20–30% of the immune cells are macrophages and about 2% are dendritic cells (Kammerer et al. 2004). Less frequent are T and B cells as well as neutrophilic granulocytes and mast cells. Thus, uNK cells and macrophages form the two largest cell populations of endometrial leukocytes. The functions of the different immune cells are very diverse. uNK cells and macrophages regulate trophoblast cell invasion and are involved in remodeling spiral arteries, while T cells and dendritic cells provide adequate immune tolerance and immune response to uterine infections (Bulmer et al. 2010). Some studies have shown that shifts in the immunological balance in the endometrium, such as those caused by an increase in uterine NK cells, can negatively affect implantation and early placentation (Tuckerman et al. 2010) (Fig. 2.1). The possible effects are currently still controversially discussed (Mor 2008).

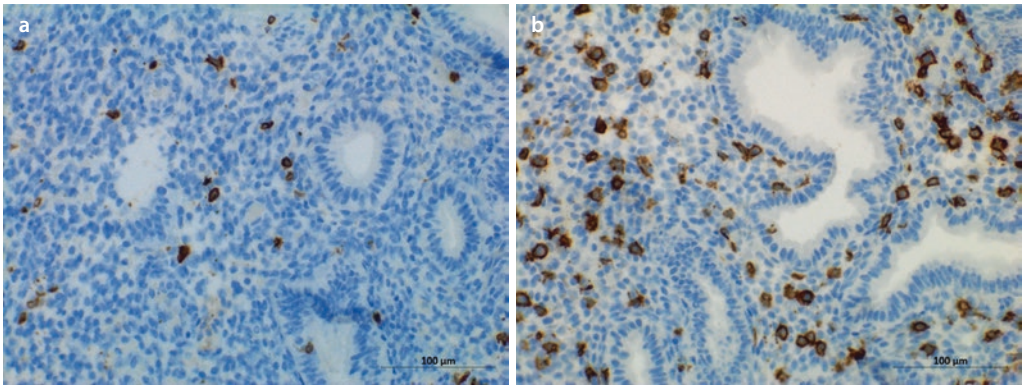

Fig. 2.1 **a**, **b** Uterine killer cells (uNK cells) labelled brown with anti-CD56 in the endometrium of the luteal phase (both on the 21st day of the cycle) (200× magnification). **a** Normal concentration; **b** Increased concentration

2.3 Immunology of Pregnancy

2.3.1 Problems

The immune system plays a special role during pregnancy, because on the one hand it must protect against infections, and on the other hand it must not develop a rejection reaction towards the embryo (Svensson-Arvelund et al. 2014). The embryo or fetus expresses 50% paternal genes that are foreign to the mother, so that a defensive reaction of the maternal immune system would be expected. Thus, it represents an intrauterine allograft that experiences first confrontations with the maternal immune system on its way through the fallopian tube.

During the first trimester, macrophages, dendritic cells and uNK cells accumulate in the decidua around the invading trophoblast cells. The latter release cytokines that interact with the immune cells of the decidua. Through Toll-like receptors, trophoblast cells can recognize bacteria, viruses, and pollutants, which further increase their cytokine secretion (Mor 2008). Thus, successful pregnancy and placental development depend on the function and interaction of trophoblast cells and maternal uterine immune cells (Trundley and Moffett 2004).

This interaction suggests an immune reaction against the fetus (Mor 2008), but it induces tolerance mechanisms, which imply that despite the increase in immune cells, a rejection of the fetus does not occur.

Although pregnancy is defined as an anti-inflammatory state, implantation of the blastocyst into the decidua resembles an inflammatory response with an increase in proinflammatory cytokines (e.g. TNF) and chemokines in the endometrium (Mor 2008; Redman et al. 1999). This may serve to control extensive trophoblast invasion early in pregnancy. The second immunological phase of pregnancy is characterized by rapid fetal growth and an anti-inflammatory state. The initially high concentration of uNK cells decreases, while the concentration of T lymphocytes increases. During the prenatal period, proinflammatory cytokines predominate and are involved in labor development, uterine contraction, delivery, and placental rejection (Mor and Cardenas 2010).

2.3.2 Fetomaternal Interfaces

Two of the obvious tasks of the placenta are to ensure a bidirectional exchange of substances between mother and child, but also to keep the two different individuals and in particular their blood circulations separate from each other. In doing so, two principally different immunologically important interfaces develop: the blood-trophoblast interface and the decidua-trophoblast interface (Fig. 2.2). At the blood-trophoblast interface, maternal blood bathes the syncytiotrophoblast-enveloped placental villi. At this site, most of the mutual exchange of substances takes place. Maternal blood contains high concentrations of humoral and cellular factors of the immune system, which would normally have to recognize the allogeneic villous surface as foreign and attack it, especially since the latter grows to several square meters during pregnancy. Using ex vivo perfusion of human placentas, we were able to show that immune cells are able to penetrate the syncytiotrophoblast barrier from the maternal circulation and migrate into fetal capillaries (Schamberger et al. 2013). The significance of this microchimerism is subject of current research.

The second interface, the one between invading trophoblast cells and decidua proves to be considerably more complicated. Here, fetal extravillous trophoblast cells infiltrate and invade maternal tissues, where the volume concentration of lymphocytes is

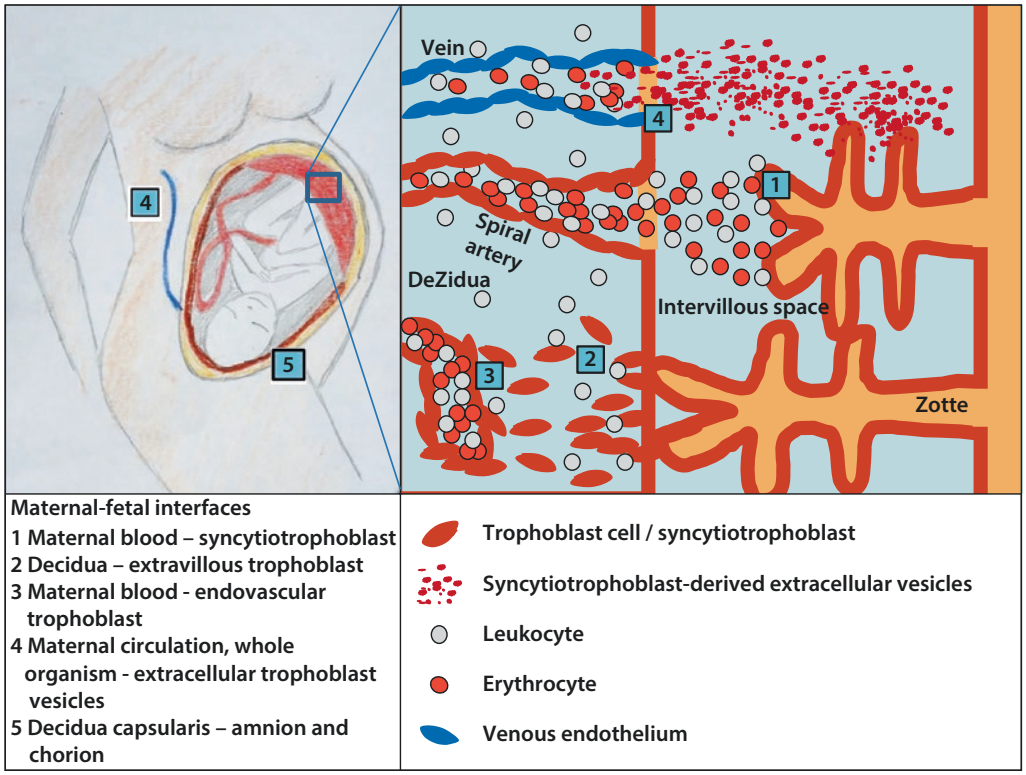

Fig. 2.2 Schematic representation of the five interfaces between mother and fetus at which cells or vesicles of fetal origin come into contact with maternal immune cells or their products

higher than that of blood, but with a different distribution of the various subpopulations: in the first place, uNK cells and cytotoxic $CD8^+$-T lymphocytes appear here, i.e. cells responsible for the elimination of foreign cells (Kammerer et al. 2004). However, the invading trophoblast cells escape or regulate these cytotoxic effects. Apparently, cytokines and growth factors of the activated maternal uNK cells paradoxically serve as stimulators for fetal trophoblast cells to migrate and proliferate (Faas and de Vos 2017). Eventually, trophoblast cells migrate in a purposeful, strand-like manner towards maternal blood vessels in the decidua, pushing between endothelial cells, displacing and replacing them. This process is regulated by immune cells, primarily uNK cells (Smith et al. 2009). The trophoblast cells that have replaced the endothelial cells are in turn in permanent contact with maternal blood, thus forming a third interface. Compared to the contact between blood lymphocytes and trophoblast cells, the contact between tissue-derived defense cells and trophoblast cells is of considerably longer duration, so that the quality of the mutual influence of these cells also differs.

Another interface exists between the fetal chorion and the maternal decidua capsularis, which fuse during pregnancy and press against the opposite decidua parietalis in the cavum uteri to form the fetal membranes. This chorion laeve has distinct immunoregulatory properties (Silini et al. 2017).

A fifth fetomaternal interface is represented by trophoblastic cells or particles in the maternal bloodstream or even in almost the entire body of the mother. Trophoblastic cells were detected in the lungs of deceased preeclamptic patients as early as in the 19th century (Schmorl 1893). Today, extracellular trophoblastic vesicles are in the focus of research on the influence of the placenta on the maternal organism (Foster et al. 2016).

2.3.3 Pregnancy: A Th2 Phenomenon

A crucial component for the non-rejection of the fetus is the immunological balance in the placenta with numerous anti-inflammatory and immunoregulatory factors. This is achieved by suppression of the T helper 1 (Th1) immune response in favor of the Th2 response. Therefore, pregnancy was first described as a Th2 phenomenon in 1993 (Wegmann et al. 1993). Th2 cytokines promote the maintenance of pregnancy, whereas an increase in Th1 cytokines can lead to abortion.

CD4-positive T helper cells can differentiate into Th1 and Th2 cells, which produce various cytokines. Th1 cytokines (tumor necrosis factor [TNF], interferon γ [IFN-γ], interleukins 2, 12, and 18 [IL-2, IL-12, IL-18], and others) activate macrophages and induce an inflammatory response via cellular immune defense. The Th1 immune response is also called cellular response because it leads to activation of NK cells and macrophages with the help of proinflammatory cytokines, such as IL-2, IFNγ, and TNF. Through these processes, intracellular parasites and tumor cells can be eliminated outside pregnancy. Thus, the Th1 response is very important for the defense against numerous infectious diseases. In addition, the pro-inflammatory cellular Th1 response is responsible for transplant rejection reactions and thus potentially dangerous for the allogeneic embryo or fetus. It must therefore be suppressed or regulated to protect the embryo/fetus. Th2 cytokines (IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13) mediate a humoral immune response. The Th2 or humoral immune response stimulates B cells or plasma cells and leads to antibody production. Some Th-2 cytokines have implantation- and invasion-promoting effects on the embryo and trophoblast cells, respectively (Chaouat 2013).

Furthermore, immunosuppressive molecules produced locally by the placenta provide an immunoprotective milieu, including IL-10, prostaglandin E2 (PGE2) and transforming growth factor β (TGFβ). Decidua-derived PGE2 has been shown to block the activation of maternal T cells and NK cells (Moore and Persaud 2007).

2.3.4 Regulatory T Cells

Immune activity in the placenta is controlled by specialized regulatory T lymphocytes (Treg cells). They were already described as suppressor T cells in the 1970s, but were only characterized to a limited extent at that time. They suppress the activation of immune reactions and increase self-tolerance. They can be identified mainly by the expression of CD4, CD25 and Foxp3. Based on their Foxp3 expression, they were first detected in the non-pregnant endometrium in 2005 (Saito et al. 2005). They can be detected to be elevated in maternal blood as early as the early first trimester and accumulate in the decidua (Guerin et al. 2009). In several studies, reduced numbers or dysfunction of Treg cells have been associated with pregnancy complications such as miscarriage and preeclampsia (Steinborn et al. 2012).

2.3.5 γδ-T Cells

γδ-T cells represent a subpopulation of T cells. Although they comprise only a small proportion of the total population (1–10%), they contribute a crucial part to fetal tolerance (Mincheva-Nilsson 2003). The γδ-T lymphocytes have a special activation spectrum and are not limited to the classical human leukocyte antigens (HLA), as is the case with the αβ-T cells. They also recognize the non-classical HLA-G antigens (Barakonyi et al. 2002).

In the proinflammatory early pregnancy phase, (murine) γδ-T cells secrete, among others, TNF and IFN-γ. In the symbiotic later phase, on the other hand, they produce pregnancy-promoting molecules, such as TGF-β, IL-1β, IL-6 and IL-10 (Mincheva-Nilsson 2003). Similar to T helper cells, γδ-T cells also expose CTLA4 on their surface, which inhibits the activity of cytotoxic T cells (Mincheva-Nilsson 2003).

2.3.6 Natural Killer Cells

NK cells are derived from $CD34^+$ hematopoietic progenitor cells and, like B and T cells, belong to the lymphoid cell lineage (Caligiuri 2008). Immunophenotypically, NK cells are characterized by the expression of CD16, the Fcγ receptor III, CD56, an isoform of the neural cell adhesion molecule (NCAM), and by the absence of the T cell marker CD3 (Colucci et al. 2003).

In contrast to B and T cells, NK cells are able to identify certain virus-infected or malignant transformed cells by means of non-antigen-specific receptors and to eliminate them directly, without prior immunization or pre-activation. In addition, they modulate the immune response by secreting various cytokines and chemokines. These capabilities make NK cells a significant component of the nonspecific immune defense, an important mediator between innate and adaptive immune systems (Barakonyi et al. 2002).

Uterine NK Cells

NK cells are detectable in large numbers in the uterus during pregnancy. In the first trimester of pregnancy, about 40% of the decidual stromal cells are leukocytes. With a proportion of up to 70%, the majority of these are $CD56^{bright}$ $CD16^-$-NK cells. Although the number of decidual NK cells decreases in the course of pregnancy, they can still be detected in large numbers in the

decidua in the third trimester of pregnancy (Bulmer et al. 2010).

A striking phenomenon is the localization of decidual NK cells in close proximity to extravillous trophoblast cells and maternal spiral arteries. This position supports the assumption that decidual NK cells are activated by secretion of chemokines such as IL-8, IFN-γ-inducible protein-10 (IP10), or stromal cell-derived factor 1 (SDF-1), regulate the migration of extravillous trophoblast cells, and by releasing angiogenic growth factors such as placental growth factor (PGF) and vascular endothelial growth factor (VEGF), support the remodeling and new formation of maternal blood vessels. In addition, they presumably contribute to the maintenance of immune tolerance to invading extravillous trophoblast cells by inducing regulatory T cells (Vacca et al. 2013).

Although the functions of decidual NK cells as well as the underlying mechanisms have not been conclusively elucidated, their crucial role in pregnancy outcome is undisputed (Jabrane-Ferrat and Siewiera 2014; Seshadri and Sunkara 2014).

The origin of the decidual NK cells is controversially discussed. It is not clear whether they proliferate predominantly in tissue or are continuously recruited from blood. The chemokine receptor CXCR4 is expressed by $CD56^{bright}$ $CD16^{-}$ -NK cells in peripheral blood and binds the chemokine ligand CXCL12, which is detectable on extravillous trophoblast cells. Since extravillous trophoblast cells partially replace the endothelium of the maternal blood vessels in the decidua, they are in direct contact with maternal blood and can attract NK cells contained therein (Tao et al. 2015). Decidua and trophoblast cells produce other chemokines, such as CXCL10, CX3CL1 or CCL3, which elicit a chemotactic response of peripheral NK cells. In vivo, NK cell migration is likely regulated by multiple, sometimes redundant, chemokine signals. Within the decidua, local factors such as IL-11 and IL-15 influence NK cell differentiation and proliferation (Santoni et al. 2008; Carlino et al. 2012).

2.3.7 Uterine $CD14^{+}$ Cells

CD14-positive cells ($CD14^{+}$ cells) include monocytes, macrophages, Langerhans cells, neutrophil granulocytes and B cells. Monocytes arise from pluripotent myeloid stem cells of the bone marrow, which reach various organs and tissues and make up about 5–10% of blood leukocytes. They circulate in the blood for a few days before differentiating into macrophages or dendritic cells (Gordon and Taylor 2005). They can be identified immunohistochemically by their surface proteins CD14 and CD68. CD14 detects bacterial lipopolysaccharides, while CD68 detects lysosomal-associated proteins and is a marker for phagocytotic cells (Bulmer et al. 2010). Macrophages have immunoregulatory properties. They can have immunosuppressive effects and produce Th2 cytokines, e.g. IL-1, IL-6, IL-10, IL-15 and indoleamine-2,3-dioxygenase (IDO) (Heikkinen et al. 2003). They are activated by Th2 cytokines such as IL-4, IL-13 and anti-inflammatory cytokines such as IL-10 and produce prostaglandin E2 (PGE2), which in turn decreases lymphocyte function, lymphocyte proliferation and cytotoxic T cell development in vitro. They are also involved in innate and acquired immunity by presenting antigens via MHC II and releasing proinflammatory Th1 cytokines, such as TNF, IL-1ß and IL-12, and superoxides upon stimulation with bacteria (Singh et al. 2005). Decidual macrophages secrete acid phosphatase, nonspecific esterase, α1-anti protease and

α1-anti chymotrypsin, indicating their phagocytic properties. Accordingly, macrophages can protect against infection, but they are equally important for maintaining tolerance to the fetus (Heikkinen et al. 2003; Mor and Abrahams 2003). Macrophages support spiral artery remodeling via angiogenic factors (Svensson-Arvelund et al. 2014) and promote the invasiveness of extravillous trophoblast cells (Bulmer et al. 2010). They also influence the functions of their neighboring cells, such as trophoblast as well as glandular and vascular cells (Reister et al. 2001).

Following the Th1/Th2 system, macrophages are divided into proinflammatory M1 and immunoregulatory M2 macrophages (Gordon 2003; Gustafsson et al. 2008). M1 macrophages serve to protect against pathogens and induce IL-1, TNF-α and IL-12 release (Martinez et al. 2006). M2 macrophages support immune regulation and are regulated by IL-10 and M-CSF (monocyte colony-stimulating factor) (Svensson et al. 2011). Macrophages can switch between these two phenotypes depending on their environment such as the uterus (McIntire et al. 2008; Porcheray et al. 2005). In normal pregnancy, M2 macrophages are predominantly present in the uterus, while in preeclampsia patients, mostly M1 macrophages are present (Svensson-Arvelund et al. 2014). Trophoblast cells regulate monocyte migration and differentiation into $CD14^+/CD16^+$ macrophages (Aldo et al. 2014). Maternal macrophages are located in the decidua and intervillous space. Fetal macrophages are located in the stroma of the placental villi and are called Hofbauer cells. They show acid phosphatase and nonspecific esterase activity and thus the ability to undergo phagocytosis. They also form a second mobile barrier behind the syncytiotrophoblast layer (Reyes et al. 2017).

2.3.8 Trophoblastic Immunoregulatory Factors

HLA Class Ib

Extravillous trophoblast cells actively contribute to immune regulation through various mechanisms. One of the reasons why they are not eliminated by the maternal immune system is their expression of non-polymorphic MHC class I molecules of the type HLA-G, HLA-E and HLA-F, which are not recognized as foreign by cytotoxic T cells and reduce the cytotoxicity of NK cells (Persson et al. 2017). Binding to HLA-G actively inhibits maternal NK cells or stimulates them to produce anti-inflammatory cytokines. A soluble isotype of HLA-G causes NK cells to be inhibited even without direct contact with trophoblast cells (Poehlmann et al. 2006). Classical MHC class I molecules such as HLA-A or HLA-B are not expressed on trophoblast cells. If HLA-A molecules are transfected into trophoblast cells, their immunogenicity increases (Koc et al. 2003).

Indoleamine 2,3-dioxygenase (IDO)

IDO is an important enzyme for local immunosuppression in the placenta. It is secreted by the syncytiotrophoblast, uterine glands and antigen-presenting cells, among others. There is a concentration gradient between the fetal and maternal side (Blaschitz et al. 2011). Inducer of synthesis is mainly IFN-γ. IDO causes the degradation of tryptophan via a kynurenine cascade to acetoacetate and suppresses T-cell activity due to the resulting tryptophan deficiency, which is of fundamental importance for tolerance to the fetus (Mellor and Munn 2004).

However, immunosuppression is also caused by bioactive tryptophan derivatives. Thus, the deficiency of tryptophan results in both reversibly decreased T-cell prolifera-

tion and reversible inhibition of NK cells by kynurenine (Terness et al. 2007). Furthermore, IDO contributes to the local suppression of the T cell-mediated inflammatory response by inducing the formation of Treg cells (Chen et al. 2008).

2.3.9 Hormones

Numerous immunological regulatory processes are induced and controlled at the transcriptional level by the pregnancy hormones estradiol (E2), estriol (E3), and progesterone (P4), as well as by glucocorticoids (Robinson and Klein 2012).

Various immune cells, including lymphocytes, macrophages and dendritic cells, express progesterone receptors. In addition, P4 also binds to glucocorticoid receptors and thus has an anti-inflammatory effect (Jones et al. 2010). Progesterone induces the synthesis of leukemia inhibitory factor (LIF) and macrophage colony stimulating factor (M-CSF) (Arck et al. 2007) and is thus important for successful implantation and development of the embryo (Szekeres-Bartho et al. 2009).

Progesterone also influences the Th1/Th2 balance by causing the conversion of Th0 cells into Th2 cells, especially at the fetomaternal interface, and by reducing the secretion of Th1 cytokines (Piccinni et al. 2000; Saito 2000; Szekeres-Bartho and Wegmann 1996). Progesterone also leads to an increase in HLA-G production (Arck et al. 2007).

During pregnancy, progesterone receptors on lymphocytes are upregulated. When the hormone binds to the corresponding receptor, the progesterone-induced blocking factor (PIBF) is synthesized (Szekeres-Bartho et al. 2005). Similar to progesterone, it is an efficient inducer of immunosuppression. On the one hand, PIBF causes the shift towards Th2 cytokines (Szekeres-Bartho and Wegmann 1996) and on the other hand it inhibits arachidonic acid synthesis (Szekeres-Bartho et al. 2001). Arachidonic acid is the starting substance for the formation of many inflammatory mediators, such as leukotrienes or the prostaglandin E2.

In addition, PIBF inhibits the degranulation of NK cells and thus their cytotoxic effect on the fetus (Arck et al. 2007). PIBF not only plays an important immunoregulatory role in pregnancy, but is also used by tumors to reduce the immune response (Szekeres-Bartho and Polgar 2010; Ermisch and Markert 2011).

Human Chorionic Gonadotropin (hCG)

Another important immunoregulatory hormone is human chorionic gonadotropin (hCG). It is initially secreted by the blastocyst and later by the syncytiotrophoblast. Important effects of hCG include stimulation of progesterone production in the corpus luteum, activation of regulatory cells, increased angiogenesis through induction of VEGF expression, positive influence on trophoblast differentiation and migration, and increased release of pregnancy-promoting cytokines and growth factors such as M-CSF and LIF (Fournier 2016).

2.3.10 Other Selected Pregnancy-promoting Mechanisms

Fas/Fas Ligand

Fas and its ligand (FasL) are transmembrane proteins that belong to the TNF superfamily. Fas is also known as the "death receptor" and is found on activated lymphocytes, among others. Apoptosis is initiated as soon as a Fas/FasL interaction occurs. If a maternal lymphocyte with Fas binds to the FasL of the syncytiotrophoblast, it can per-

ish via a caspase signal chain by means of apoptosis (Crncic et al. 2005; Aluvihare et al. 2005).

Trophoblast cells co-express Fas and FasL. Therefore, they require a protective mechanism against autocrine-initiated destructive processes. This protective effect is provided by Bcl-2, an anti-apoptotic protein that is expressed by the trophoblast in addition to Fas and FasL (Aluvihare et al. 2005; Uckan et al. 1997).

Th1 cytokines, such as TNF, promote Fas expression in trophoblasts, while Th2 cytokines, such as IL-6 and IL-10, decrease trophoblast expression and sensitivity to Fas-mediated apoptosis (Makrigiannakis et al. 2008).

Galectin-1

Galectin-1 is a glycan-binding protein and also appears to play a significant role in fetal non-rejection. It is secreted mainly in the early gestational period by decidual NK cells, cytotrophoblast cells and the syncytiotrophoblast, among others (Kopcow et al. 2008). It causes a Th2 shift and an increase in progesterone and PIBF synthesis (Makrigiannakis et al. 2008). Galectin-1 also causes apoptosis of activated cytotoxic T cells (Kopcow et al. 2008).

Trophoblastic Extracellular Vesicles

Trophoblastic vesicles of >2 µm diameter were already described as being pinched off as syncytial knots from the syncytiotrophoblast at the end of the 19th century when they were discovered in the lungs of deceased pregnant women (Schmorl 1893). These fetal vesicles thus represent a further boundary or contact surface in the maternal organism.

Microvesicles or ectosomes (diameter: approx. 100–1000 nm), which are released from the apical syncytiotrophoblast membrane, and exosomes (diameter approx. 30–100 nm), which are released from intracellular multivesicular structures, serve to communicate between the fetus or placenta and the maternal organism, including the immune system. The vesicles are composed of proteins, microRNA, RNA and DNA (Chamley et al. 2014). Trophoblastic microvesicles express placental alkaline phosphatase (PLAP), among others, making them easily identifiable and distinguishable from vesicles of other origins (Gohner et al. 2015). In contrast, exosomes carry surface features from the cell interior of their cells of origin.

It has been shown in vitro that factors such as proteins or non-coding RNA produced in trophoblast cells can be transported via extracellular vesicles. When these vesicles are incubated with T lymphocytes, the trophoblast-derived RNA molecules are subsequently detectable in the lymphocytes and can influence the proliferation of target cells and thus the maternal immune system in pregnancy (Delorme-Axford et al. 2013; Ospina-Prieto et al. 2016). The concentration as well as the composition of trophoblastic extracellular vesicles are often altered in pregnancy pathologies. In preeclampsia, their concentration in the blood of pregnant women is significantly increased (VanWijk et al. 2002).

The fact that large amounts of extracellular vesicles enter the maternal circulation from the syncytiotrophoblast is unanimously accepted, but there are controversial results, especially about their composition in different diseases, largely stemming from the technical difficulties of isolation and analysis (Morales-Prieto et al. 2014).

2.4 Summary and Conclusion

In pregnancy, two allogeneic individuals live symbiotically together and their tissues, including the various immune cells, have immediate contact with each other. A num-

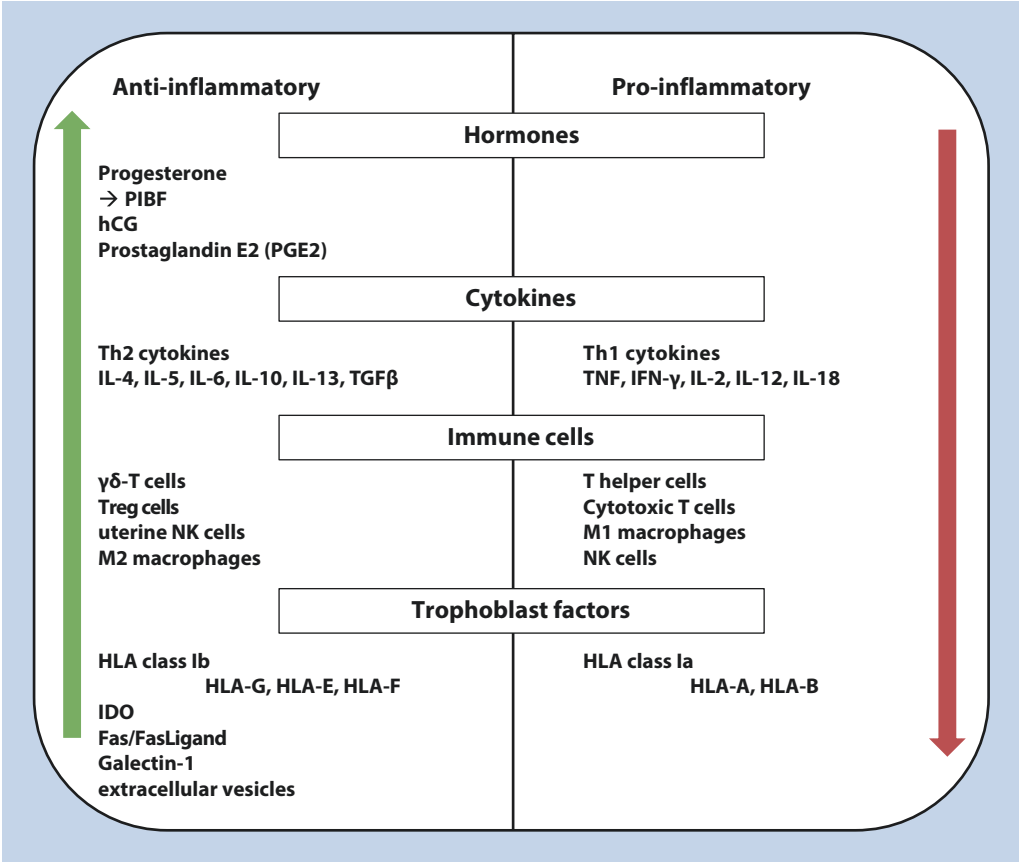

Fig. 2.3 Schematic overview of important immunoregulatory factors at the fetomaternal interface. A relative predominance of anti-inflammatory factors develops. Proinflammatory factors are partly completely absent or significantly reduced

ber of decidual and placental immunoregulatory cells and factors ensure the physiological course of pregnancy. In addition, the placenta releases factors into the maternal circulation that adjust her organism and immune system to pregnancy (Fig. 2.3). It has been widely described that disturbances in the immunological balance can negatively affect fertility and pregnancy and may lead to disorders or disease. Their better understanding will lead to better diagnostic techniques as well as to new therapeutic approaches.

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