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REVIEW

Role of Macrophages in Pregnancy and Related Complications

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Abstract

Macrophages (MΦs) are the leukocytes produced from differentiation of monocytes and are located in almost all tissues of human body. They are involved in various processes, such as phagocytosis, innate and adaptive immunity, proinflammatory (M1) and anti-inflammatory (M2) activity, depending on the tissue microenvironment. They play a crucial role in pregnancy, and their dysfunction or alteration of polarity is involved in pregnancy disorders, like preeclampsia, recurrent spontaneous abortion, infertility, intrauterine growth restriction, and preterm labor. About 50–60% of decidual leukocytes are natural killer (NK) cells followed by MΦs (the second largest population). MΦs are actively involved in trophoblast invasion, tissue and vascular remodeling during early pregnancy, besides their role as major antigen-presenting cells in the decidua. These cells have different phenotypes and polarities in different stages of pregnancy. They have also been observed to enhance tumor growth by their anti-inflammatory activity (M2 type) and prevent immunogenic rejection. Targeted alteration of polarity (M1–M2 or vice versa) could be a major focus in the future treatment of pregnancy complications. This review is focused on the role of MΦs in pregnancy, their involvement in pregnancy disorders, and decidual MΦs as possible therapeutic targets for the treatment of pregnancy complications.

Keywords Macrophage · Human pregnancy · Decidualization · Polarity · VEGF · Preeclampsia

Introduction

The trophoblast cells of the implanted blastocyst invade the uterine endometrium of the mother through a process called placentation. The endometrial stromal cells differentiate (decidualization) and establish an environment conducive to trophoblast invasion (Hunt 2006). Three types of placentation exist among mammals—epitheliochorial, endotheliochorial, and hemochorial placentation (Vogel 2005) based on the contact pattern of trophoblast cells and the uterine lining. Hemochorial placentation is seen in human and mice, where the fetal membrane directly contacts with the maternal tissue and blood. This deep placentation signifies appropriate recognition and tolerance to the semiallogeneic fetus for a successful pregnancy, where maternal immune cells play a critical role (Wildman et al. 2006).

The leukocyte population in the uterus undergoes significant changes after implantation and decidual development. The T-cell and B-cell aggregates observed in the cycling uterus disappear, along with intangible eosinophils and mast cells. Natural killer (NK) cells and macrophages (MΦs) dominate during early pregnancy (Hunt et al. 2000). Large number of leukocytes (MΦs, NK cells, T cells, and dendritic cells) infiltrate into the pregnant decidua. Almost 40% of all cells in the decidua in the first trimester are leukocytes (von Rango 2008). An estimated 20–30% of leukocytes are MΦs, playing a role in tolerance to the semiallogeneic fetus, trophoblast invasion, and tissue and vascular remodeling (Mizuno et al. 1994; Lidström et al. 2003; Nagamatsu and Schust 2010a; Renaud and Graham 2008; Li et al. 2019). The factors that attract MΦs to the decidua include chemokines, colony-stimulating factor-1 (CSF-1) and granulocyte

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macrophage-colony-stimulating factor (GM-CSF), which are mostly produced in response to hormonal stimulation (Pollard 1998). The vascular endothelial growth factor receptor-1 (VEGFR-1) plays a pivotal role in recruitment of MΦs and angiogenesis at implantation sites (Douglas et al. 2014). MΦs can be distinguished from other leukocytes by distinct cell surface markers, such as CD14, CD68, and human leukocyte antigen (HLA) like HLA-DR (Heikkinen et al. 2003; Nagamatsu and Schust 2010a). They have plasticity to alter their functions in response to a changing microenvironment in tissues, thus widely involved in physiological functions and diseases (Stout and Suttles 2004). They are classified as classically activated (M1) and alternatively activated (M2) phenotypes based on their function and repertoire of cytokine production (Gordon 2003; Martinez et al. 2008) (Fig. 1). The M1MΦs are proinflammatory in nature and are induced by pathogen (lipopolysaccharide) exposure, and tissue damage through interferon-γ (IFN-γ) and tumor necrosis factor (TNF) proteins (Martinez et al. 2008; Mosser 2003). These MΦs produce reactive oxygen species (ROS) and nitric oxide (NO) from arginine by upregulation of the enzyme inducible NO Synthase (iNOS), to kill pathogens. They also produce higher level of cytokines like IL-12 and IL-23, and lower IL-10 level (Verreck et al. 2004). M2MΦs are induced by Th2 cytokines, such as IL-4, and IL-13, as well as by anti-inflammatory IL-10, apoptotic cells, and macrophage colony-stimulating factor (MCSF, also called CSF-1) (Mantovani et al. 2004; Gough et al. 2001). These MΦs produce higher level of IL-10 and lower level of IL-12 and IL-23 cytokines (Mills et al. 2000). They produce ornithine from arginine by upregulating arginase level and are anti-inflammatory in nature, involved in scavenging the apoptotic cells, tissue repair and remodeling (Xu et al. 2006). MΦs predominately expressing iNOS over arginase are termed M1MΦs and those predominately expressing arginase over iNOS are termed M2MΦs. Studies reveal that decidual MΦs acquire an M2 phenotype, promoting immune tolerance toward the fetus, required for successful pregnancy (Lidström et al. 2003). Recent study (Zhang et al. 2019) has revealed that the programmed cell death-1 (PD-1)/PD-1 ligand-1 (PDL-1) signaling regulates the macrophage differentiation in early pregnancy, promoting the polarization to M2 phenotype which supports the pregnancy. In fact, tissue MΦs acquire different functional phenotypes ranging from proinflammatory (M1) to anti-inflammatory (M2) in response to the environmental milieu. It has been observed that M1MΦs skew to the M2 phenotype when cultured in 1st trimester gravid serum, as revealed by a decrease in procalcitonin (a marker for evaluating bacterial infections) level, indicative of the M2 type (Rami et al. 2014). However, the M1/M2 concept has been reviewed, and it has been found that decidual MΦs do not follow the typical M1/M2 paradigm, and that the M2 phenotype is not always induced by Th2 cytokines. Rather M-CSF and IL-10 are found to be efficient M2MΦ markers' (CD163 and CD206) inducers (Houser et al. 2011; Svensson et al. 2011). Another classification system separates MΦs into classically activated MΦs (CAMs) or type-I MΦs, and alternatively activated MΦs (AAMs) or type-II MΦs (Porcheray et al. 2005). Most of the tumor-associated MΦs (TAMs) are type-II (Tripathi

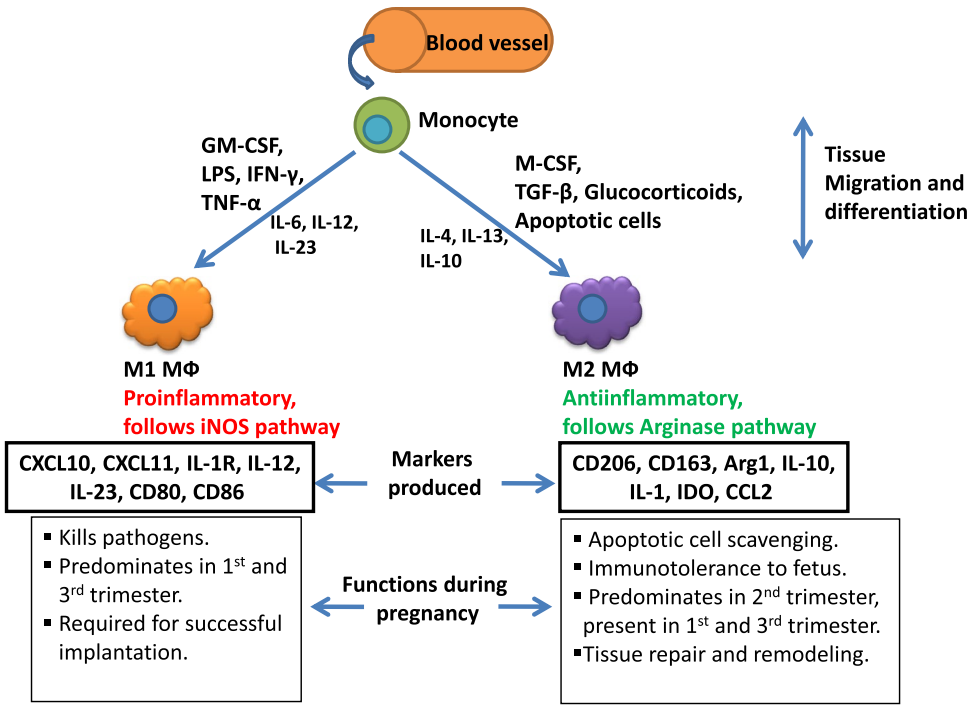

Fig. 1 Macrophage differentiation and polarization in the decidua during pregnancy

et al. 2014). Gene expression analysis of decidual MΦs has revealed an AAM phenotype (Gustafsson et al. 2008). There are few reviews discussing the role of decidual MΦs in different stages of pregnancy (Ning et al. 2016; Svensson-Arvelund and Ernerudh 2015; Zhang et al. 2017). In this review, we have discussed the detailed role of MΦs in pregnancy, their involvement in pregnancy disorders, and the possibility of these cells as therapeutic targets.

Current Paradigms of MΦ Differentiation and Function

Several hypotheses exist pertaining to the origin of endometrial leukocytes (Lee et al. 2015). One hypothesis describes leukocytes coming to endometrium through circulating blood. In this process, the circulating leukocytes extravasated from blood vessels across endothelial cell barriers. Endothelial cells express adhesion molecules which facilitate invasion by binding as ligands to homing receptors of immune cells (Johansson et al. 1999). Another hypothesis describes in situ proliferation of the resident immune cells (van den Heuvel et al. 2005; Kitaya et al. 2007). Yet another hypothesis proposes that hematopoietic precursors are recruited to and differentiate within the endometrium (Keskin et al. 2007; Manaster and Mandelboim 2010). Immune cells recruited from circulation probably undergo tissue-specific differentiation in response to local factors, and conferring characteristics on these cells that deviate from those of the parental cells (Keskin et al. 2007; King 2000).

About 50–60% of decidual leukocytes are NK cells followed by MΦs (Houser 2012; Faas and de Vos 2017). Regulatory molecules such as steroid hormones, growth factors, bioactive peptides, and lipids influence the activities of these multifunctional cells in pregnant uterus and placenta, thus contributing to the complex cellular and molecular interactions required for successful pregnancy. The circulating blood monocytes are influenced by multiple factors to migrate and differentiate into tissue MΦs, which express tissue-specific subpopulation markers (Gordon 2003). Movement of blood monocytes to tissue depends on specific cytokines and chemokines and their receptors. Tissue-specific environmental signals induce specific phenotypic profiles (McIntire et al. 2008). The decidual MΦs of mammals have drawn remarkable attention for their wide variety of functions, such as (a) phagocytosis and tissue remodeling, (b) defense against infections, (c) influence over the function of surrounding cells like invasive cytotrophoblasts, glandular epithelium, and endothelial cells of arteries, (d) antigen presentation, and (e) production of cytokines, such as IL-10 and IL-15, which leads to successful pregnancy (Laskarin et al. 2005; Lidström et al. 2003; Heikkinen et al. 2003; Mor and Abrahams 2003; Reister et al. 2001; Verma et al. 2000). Their recruitment and function are influenced by conditioning factors in the human uterus. The protein IFN-γ, produced by NK cells, activates MΦs in the pregnant uterus of mice and humans, leading to display of HLA class II antigens (Xie et al. 2005). The protein CSF-I (M-CSF) is another crucial factor, contributing to the development of the phenotypic profile of MΦs in the pregnant uterus. This protein is highly expressed by the uterine epithelial cells of pregnant mice and humans (Pollard 1997) Besides, the decidual stromal cells are also important source for M-CSF production.

MΦs in the Female Reproductive Tract

There is a strong impact on fertility and reproductive health from the interaction between immune system and female reproductive system. Physiological events in the female reproductive system, such as ovulation, menstruation, implantation, and onset of labor, are inflammatory processes. MΦs play a crucial role in the initiation and resolution of inflammation, and they are detected in all phases of the menstrual cycle, scattered throughout the endometrium, being more prevalent around the endometrial gland (Yang et al. 2011; Salamonsen and Lathbury 2000). Their population increases in the early secretory phase and continues to increase in the late secretory phase of the menstrual cycle, with the sex hormones (estrogen and progesterone) playing a major role in their distribution in the endometrium (DeLoia et al. 2002; Keenihan and Robertson 2004; Jones et al. 2004). As uterine CD45+ leukocytes do not express estrogen and progesterone receptors, these sex hormones are likely to control uterine leukocytes indirectly. There is a cross-talk between the decidual immune cells, endometrial cells, epithelial cells, and stromal cells, delicately controlled by estrogen and progesterone (Salamonsen and Lathbury 2000). Physiologic levels of estrogen induce MΦ proliferation and function, and estrogen has both positive and negative regulatory effects on the production of the chemokine CCL2, an MΦ chemoattractant (Carruba et al. 2003). Besides CCL2, the level of other MΦ chemoattractants, such as CCL7, CX3CL1, and CCL4, also increases in the perimenstrual period in the endometrium (Keenihan and Robertson 2004; Jones et al. 2004; Wira et al. 2005). Vaginal MΦ number remains constant during the menstrual cycle (Amjadi et al. 2014). MΦs have been observed to modulate ovarian functions, such as follicular atresia and luteolysis (Pate and Landis Keyes 2001; Penny 2000; Duncan 2000). The theca cell layers of the ovary are rich in these cells, where matrix metalloproteinases (MMPs) (secreted by MΦs) get activated during ovulation. Endometrial MΦs have been observed to have an M2-like phenotype ($CD68^{+}CD163^{+}CD206^{+}IL10^{high}$) like those of the decidua; however, they express certain markers differently and secrete

different amounts of pro- and anti-inflammatory cytokines and, hence, belong to different subpopulations (Quillay et al. 2015). Endometrial MΦs express CD163, CD80, CD64, CD16, CD11c, CCR5, CXCR4, and DC-SIGN significantly less strongly than do decidual MΦs. Furthermore, decidual MΦs play a role in the phagocytosis of apoptotic trophoblasts, whereas endometrial MΦs phagocytose endometrial tissue debris (Thiruchelvam et al. 2013).

MΦs in Fertilization, Implantation, and Decidualization

The mid-secretory phase (days 19–23 of the menstrual cycle) is called the 'window of implantation', when the uterus becomes receptive (Gnainsky et al. 2010). There is an increased level of proinflammatory cytokines, such as IL-6, leukemia inhibitory factor (LIF), and TNF-α in the endometrium which characterize early implantation (van Mourik et al. 2009).

MΦs and dendritic cells (DCs) play a crucial role in decidualization and implantation (Lea and Clark 1991; Gardner and Moffett 2003; Plaks et al. 2008; Blois et al. 2004). They are involved in tissue remodeling and angiogenesis through the production of an array of cytokines, chemokines, and enzymes (Abrahams et al. 2004; David Dong et al. 2009). Additionally, these molecules target the luminal epithelium and subsequently contribute to the acquisition of endometrial receptivity. It has been proposed that the increased receptivity of the uterus after biopsy treatment may be mediated by the immune cells recruited by the chemoattractant molecule macrophage inflammatory protein-1β (MIP-1-β, also known as CCL4) (Gnainsky et al. 2010). The regulatory protein osteopontin, which is an adhesive molecule and a biomarker of receptive endometrium, seems to regulate MIP-1-β secretion positively, facilitating the recruitment of MΦs/DCs (Goetzl et al. 1996).

Several regulatory proteins play a vital role in implantation of the embryo. The level of the protein CSF-I (secreted by uterine epithelium) increases at the time of implantation and reaches its peak during placentation (Horcajadas et al. 2007). DCs secrete sFlt-1(Flt-1: Fms-like tyrosine kinase 1; also called VEGFR1) and transforming growth factor-β1 (TGF-β1) which regulate endometrial angiogenesis and blood vessel maturation and are also involved in $T_{regulatory}$ cell (Treg cell) development (Gardner and Moffett 2003). M2 polarization process (induced by glucocorticoids and the Th2 cytokines) enhances innate immunity receptors, such as scavenger receptors and MΦ mannose receptors, part of the M2 phenotype, which supports implantation (Nagamatsu and Schust 2010b; Pollard 2008; Laskarin et al. 2005).

Additionally, the transcription factor PU.1 (Ets–family member) is observed to regulate the development and differentiation of MΦs, B cells, T cells, and NK cells (Lee et al. 2011; Dakic et al. 2005). This transcription factor also modulates the C1q (the first component of classical component activation) gene expression in MΦs and DCs (Iwasaki et al. 2005). The C1q component is significantly involved in fetal tolerance, migration of trophoblasts, and spiral artery remodeling. Thus, PU.1 plays a crucial role in implantation through regulation of C1q expression in decidua (Chen et al. 2011).

Tissue MΦs influence the biochemical events occurring in the endometrial cell lining in early pregnancy to promote uterine receptivity and facilitate embryo attachment and implantation. In this process, LIF (derived from MΦs) regulates the structure of surface glycans in epithelial cells and makes the endometrium receptive (Madhukaran et al. 2015). Cell–cell communication is very crucial for maternal–embryonic recognition, and endometrial MΦs act as determinants of uterine receptivity. It has been observed that the two dendritic cell-associated molecules CD200 and MD-1 have immune regulatory activity toward MΦs, contributing to successful pregnancy. Increased expression of CD200R in MΦs enhances indoleamine 2,3-dioxygenase (IDO) activity, thus contributing to an immune-suppressive environment needed for successful implantation (Nakamura et al. 2012).

Regulation and Function of MΦs at the Maternal–Fetal Interface

MΦs play an important role in the preparation of a receptive endometrium during the window of implantation and subsequently decidualization of the endometrial stroma (Gorczynski et al. 2002).

MΦs in Early Pregnancy

Decidual MΦs play vital roles in apoptosis and cell clearance during pregnancy. The quick and effective removal of apoptotic cells prevents the leakage of self-antigens and inflammation. MΦs have a capacity for alloantigen presentation, immunosuppressive activity and less ability to produce IL-1 than do peripheral monocytes (Mizuno et al. 1994). Their immune-suppressive activity may be due to their high levels of IL-10 and IDO production, along with the production of prostaglandin-E_2 (PGE_2), which blocks the activation of cytotoxic leukocytes (Kats et al. 2005). IDO degrades tryptophan and thereby prevents maternal T cell activation, which requires tryptophan. It has been observed that serum tryptophan levels decrease from the first trimester of human pregnancy (Miwa et al. 2005). IDO expression in MΦs is regulated by $CD4^+$ $CD25^+$ Treg cells, which upregulate their IDO levels through cytotoxic

T-lymphocyte-associated protein 4 (CTLA-4), present on the cell surface (Schrocksnadel et al. 1996) (Fig. 2). The enzyme IDO is also secreted by decidual DCs, extravillous trophoblasts (EVTs), and villous trophoblasts in human (Sedlmayr et al. 2002; Kudo et al. 2004; Honig et al. 2004; Hwu et al. 2000; Munn et al. 2002). Many MΦ-derived proangiogenic factors are involved in vascular remodeling for proper uteroplacental circulation. MΦs and NK cells are enriched in the vicinity of the trophoblast invasion front during early pregnancy (Helige et al. 2014). Both cell types are involved in spiral arteriole remodeling. The vascular remodeling process occurs in distinct trophoblast-independent (early changes) and trophoblast-dependent stages. In the early stage, vascular smooth muscle cells are disrupted and disorganized before the arrival of endovascular trophoblasts. This process is associated with MΦ and NK cell infiltration, secretion of MMP-7 and -9, and apoptosis of smooth muscle cells and endothelial cells (Smith et al. 2009). When EVTs invade the decidua, they come across NK cells and MΦs (NK cells and MΦs are in close proximity) and cross-talk among those cells occur within the uterine wall. It has been found that NK cells have a cytolytic activity toward EVTs, but this activity is prevented by MΦs through a TGF-β1-dependent mechanism (Co et al. 2013). EVTs are unique in their expression of HLA molecules, as they do not have the highly polymorphic (HLA-A and HLA-B) classical class I HLAs, but they express HLA-C and the non-classical (HLA-E, HLA-F, and HLA–G) class-I molecules (King et al. 2000a, b; Shobu et al. 2006). The HLA-G molecule has four membrane-bound (HLA-G1-4) and three soluble isoforms (HLA-G5-7) produced by alternative splicing (Shakhawat et al. 2010). Decidual MΦs express the HLA-G receptors leukocyte Ig-like receptor B1 (LILRB1) (also known as Ig-like transcript-2, ILT2) and LILRB2 (ILT4). Trophoblast-derived HLA molecules HLA-C and HLA-G are observed to regulate MΦ function by making them immune tolerant through interaction with the ILT2 and ILT4 receptors (Petroff et al. 2002). The HLA-G homodimer engagement of ILT2 on MΦs triggers the secretion of IL-6, IL-8, and to a lesser degree TNF-α (Li et al. 2009). In addition, HLA-G5 (soluble form) induces IL-4 secretion, which is important for successful pregnancy, acting to modulate expression of the ILT2 receptor on T_H cells and MΦs (Lombardelli et al. 2013).

Costimulatory molecules play a significant role in immunomodulation by regulating signaling pathways. The B7 family is a major costimulatory ligand group that includes B7.1, B7.2, B7-H1, B7-DC, B7-H2, B7-H3, B7-H4, and B7-H6 (Sayama et al. 2013). MΦs of early pregnancy express the B7-H1 ligand molecule, which is inhibitory in action. Expression of this ligand molecule is not observed in term MΦs and peripheral monocytes of pregnant women. This ligand binds to its receptor programmed death-1 (PD-1), which is highly expressed in T cells, and this interaction suppresses IFN-γ production by activated T cells, thus making them immune suppressive. This inhibitory signaling fine tunes the IFN-γ level and balances the maternal immune response during early human pregnancy (Sayama et al. 2013). There is also downregulation of PI3/Akt pathway signaling leading to inhibition of the T cell activity (Parry et al. 2005). The MΦ-derived cytokine IL-33 is found to be a critical factor for placental growth in early pregnancy, increasing the proliferation of primary trophoblasts, villous cytotrophoblasts, and cell column trophoblasts. IL-33 is a

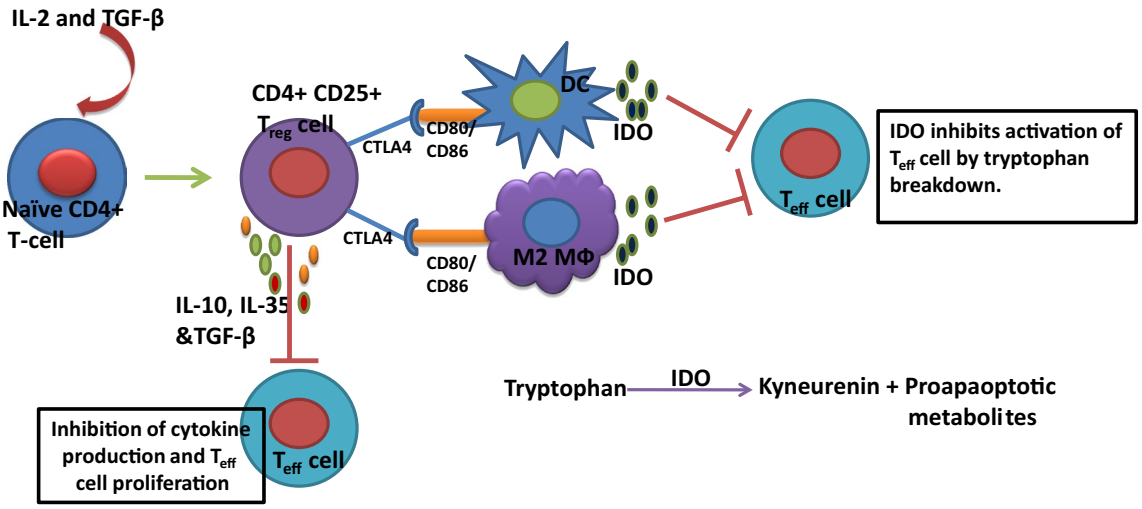

Fig. 2 T_{reg} cells showing immunotolerance through M2 MΦs and dendritic cells (DCs). The naïve T cells are induced by IL-2 and TGF-β in the decidua, forming Treg cells. Treg cells express the surface molecule CTLA4 which interacts with CD80/CD86 of DCs and MΦs, thus inducing those cells for IDO production. IDO inhibits T_{eff} cell proliferation. The cytokines IL-10, IL-35, and TGF-β produced from Treg cells also inhibit T_{eff} cell proliferation. IDO = Indoleamine 2, 3-dioxygenase, T_{reg} = T regulatory, T_{eff} = T effector

member of the IL-1 family, and MΦs seem to maintain its expression until term. IL-33-induced proliferation is mediated by PI3 K/AKT and MAPK/ERK signaling (Fock et al. 2013). It has also been observed that GM-CSF and M-CSF, secreted from induced first trimester decidual cells, promote MΦ activation, and these activated cells induce EVT apoptosis through a caspase 3/7-dependent pathway (Wu et al. 2012).

MΦs in Late Pregnancy

MΦ number decreases at term, becoming the smallest component of decidual leukocytes, whereas CD3+ T lymphocytes are the largest (Williams et al. 2009). However, their number increases by infiltration during term and preterm labor in human and rat decidua, showing evidence of decidual inflammation preceding labor (Hamilton et al. 2012). MΦs accumulated in the lower uterine segment are involved in cervical ripening during late pregnancy. They play prominent roles in intrauterine defense by producing superoxide radicals and TNF-α in response to pathogens, thus protecting the fetus against infections and preventing preterm labor (Singh et al. 2005). There is alteration in the level of maternal immune tolerance toward fetal antigens at the initiation of labor. The subpopulation of $FoxP3^+$ T cells (Treg cells) seems to decrease, whereas the immune-suppressive $B7\text{-}H4^+$ MΦ subpopulation remains unchanged as labor progresses. Besides, IL-10 produced by the decidual MΦs contributes to the immune-suppressive environment (Heikkinen et al. 2003). This phenomenon reflects a balancing act of brief activation of the maternal immune system with an associated mechanism to restrict this action for term delivery (Galazka et al. 2009). Preterm delivery (PTD) and term delivery probably follow a common downstream pathway with increased release of MMP and collagen degradation; however, the source of MMP seems to be MΦs in PTD, and cervical stromal fibroblasts and columnar epithelial cells at term. The trigger mechanism also seems to be different, with progesterone withdrawal triggering MMP release at term and anaphylatoxin C5a as a trigger for MMP release in PTD (Gonzalez et al. 2011).

A multi-domain protein stabilin-1, present in lymphatic and vascular endothelial cells and in type-II MΦs, acts as a scavenging receptor and adhesion molecule. Analysis of its expression on MΦs of term placenta has revealed its presence both in decidual and placental MΦs; these may be involved in regulating leukocyte migration and scavenging during fetal development (Palani et al. 2011). In addition, the systemic hormone relaxin is secreted from the corpus luteum (CL) at low level during pregnancy and high level in late pregnancy and early parturition (Lafayette et al. 2011). This hormone modulates the activity of MΦs by acting on both the glucocorticoid receptor (GR) and relaxin receptor expressed on these cells. The low level of relaxin during pregnancy may be anti-inflammatory, acting through the GR and supporting pregnancy, whereas its high level acts through the relaxin receptor, increasing proinflammatory IL-6 production by MΦs, which contributes to a sterile inflammatory milieu required for initiation of parturition (Horton et al. 2011).

Angiogenic Functions of Decidual MΦs

Angiogenesis (development of blood vessels from preexisting vasculature) plays a crucial role in both normal and pathological conditions, and the VEGFR isoforms VEGFR-1, -2, and -3 play a key role as mediators of angiogenic response (Petrova et al. 1999). Of these isoforms, VEGFR-1 plays an important role in angiogenesis and MΦ recruitment at implantation sites. The role of VEGF (paracrine signal) in making and maintaining blood vessels has been studied comprehensively (Heloterä and Alitalo 2007). Vascular homeostasis is maintained by VEGF produced endogenously by endothelial cells (Lee et al. 2007).

Decidual MΦs act significantly in angiogenesis and spiral artery remodeling during the first and second trimester, establishing maternal blood flow essential for the growth of the fetus. During these processes, there is a remarkable loss of vascular smooth muscle, replacement of endothelial cells by EVTs, and decreased resistance by the spiral arteries to blood flow to the placenta (Burrows et al. 1996). MΦs produce various proangiogenic factors in response to hypoxia and other micro-environmental signals as observed in tumor progression and wound healing (Coffelt et al. 2009). Similar hypoxic conditions also prevail in the decidual endometrium during the first trimester. There is an abundant infiltration of MΦs and NK cells in the initial stage of vascular remodeling and these leukocytes produce MMP-9 and -7, which degrade the ECM and promote endovascular trophoblast invasion. There is impaired vascular development in conditionally ablated $CD11c^+$ DCs during implantation in transgenic mice, demonstrating the importance of MΦs in fine-tuning uteroplacental circulation in human pregnancy (Gardner and Moffett 2003).

The VEGF family members play a crucial role in angiogenesis and vasculature development in pregnancy (Sugino et al. 2002; Zhou et al. 2002). The VEGF protein acts by binding the receptors Flt-1 and kinase insert domain receptor (KDR). Another member of the VEGF family, placental growth factor (PlGF), is produced by the placenta and acts by binding to Flt-1 (Clark et al. 1998). VEGF and Flt-1 expression are increased in MΦs during early pregnancy, regulated by hormones. EVTs also produce VEGF and PlGF abundantly along with the MΦs. PlGF causes activation of monocytes via activation of Flt-1 (Selvaraj et al. 2003). Flt-1

is observed as a functional receptor for VEGF and PlGF in monocytes and endothelial cells, and acts as a mediator of monocyte recruitment (Clauss et al. 1996). Studies in our laboratory have shown that VEGF may play a crucial role in MΦ recruitment and M2 polarization in the human decidua (Wheeler et al. 2017).

Phenotypes of Decidual MΦs

Immature monocytes are released from the bone marrow, recruited to tissues by chemokines after circulating in the blood, and differentiate into MΦs (Imhof and Aurrand-Lions 2004). Few studies have been performed on phenotyping MΦ lineages and subsets. MΦs possess functional plasticity with reversible adaptation to changing environments. The ability of monocytes and tissue MΦs to adapt to variation in their microenvironment challenges the assumption that MΦs display unique specific markers and makes it difficult to categorize them in particular lineages.

MΦ polarization has been observed between M1 and M2 phenotypes throughout pregnancy (Table 1). During the peri-implantation period, the M1 type predominates, after which there is a transition to a mixed population of M1 and M2 types, during which trophoblasts invade the stroma and settle in the endometrial lining (Jaiswal et al. 2012). The mixed population thrives until early in the second trimester (Mor et al. 2011). Subsequently, the pro-M2 phenotype predominates as the placenta is established, and this prevents rejection of the fetus. It is likely that the immune-suppressive environment is maintained throughout pregnancy by the M2 macrophages. These phenotypes dominate in the decidua, and they are responsible for immunotolerance, which is a prerequisite for successful implantation and fetal development. In fact, the polarization of M1 phenotype to M2 phenotype during second trimester and again back to M1 phenotype at delivery is not well defined and needs further study.

$CD14^-/CD68^+$ cells were found to be more abundant in the decidua and $CD14^+/CD68^+$ cells more abundant in the myometrium of preeclampsia and preterm labor cases (Kim et al. 2007). A comparison of the MΦ phenotypes in preterm preeclamptic, preterm control, and term control placentas showed higher expression of CD14 and CD163 in decidua basalis of preterm preeclamptic than that of preterm control cases (Schonkeren et al. 2011). The percentage of cells expressing CD163 (scavenger receptor), CD206 (mannose receptor), CD209 (DC-SIGN), and neuropilin-1 (NRP1) was found to be significantly higher in the $CD14^+$ decidual MΦ population than in $CD14^+$ blood monocytes (Svensson et al. 2011). Comparison of $CD14^+$ MΦs and $CD14^+$ monocytes revealed higher HLA-DR and lower CD86 (costimulatory) expression in MΦs than in monocytes during pregnancy (Heikkinen et al. 2003). Some discrepancies were observed in the 1st trimester MΦ phenotypes, with one study showing dominance of the M2 phenotype and the other study showing two distinct subsets of $CD14^+$ decidual MΦs ($CD11C^{HI}$ and $CD11c^{LO}$) in 1st trimester decidual tissue in humans, not fitting the conventional M1/M2 categorization (Cupurdija et al. 2004; Houser et al. 2011; Houser 2012). A study on MΦs of 1st trimester human deciduas showed that they express markers associated with alternative activation (M2). The markers stabilin-1 (MS-1) and coagulation factor XIIIa were present in the interior of decidual MΦs (Cupurdija et al. 2004). These discrepancies may be attributed to the anatomical plane of the feto-maternal junction analyzed and varying antibodies used for detection (Kim et al. 2007).

Table 1 Different phenotypes of macrophages during pregnancy

MΦ phenotype	Cytokine production	Function	References
M1	IL-12, IL-1β, TNF-α, IL-6, NO, CXCL10, CCR7	Promotes embryo implantation	Wheeler et al. (2017), Zhang et al. (2017)
M2a	Fibronectin, Arginase-1, IL-10, IL-6, CCL-17, CCL-18	Th2 activation, tissue repair	Wheeler et al. (2017), Ning et al. (2016)
M2b	IL-10, IL-1β, $IL\text{-}12^{low}$	Immunoregulatory and Th2 activation	Ning et al. (2016)
M2c	IL-10, TGF-β	Immunotolerance, matrix remodeling and repair	Ning et al. (2016)
M2d	IL-10, VEGF	Proangiogenic	Ning et al. (2016)
$CD14+CD11C^{HI}$	Upregulates CD1, genes associated with lipid metabolism, inflammation, Ag presentation	Antigen processing and presentation	Houser (2012)
$CD14+CD11C^{LO}$	Expresses genes associated with ECM formation, tissue growth, etc.	Homeostatic function during placental growth	Houser (2012)

MΦ Dysfunction in Common Pregnancy-Related Disorders

Infertility

MΦs exhibit wide plasticity and are sensitive to small changes in the microenvironment. Factors like nutritional status, smoking habits, toxins (environmental), inflammatory conditions, and physiological stress impart adverse effects on fertility (Zhang and Mosser 2008; Martinez et al. 2009). Although endometrial MΦ numbers do not correlate with infertility diagnoses, their phenotypes and cytokine secretory profiles have discernible effects (Dechaud et al. 1998; Leung et al. 1998). The colocalization of CD68 and the secreted cytokines IL1A, IL1B, and IL-6 show variation in conjunction with fertility status. Oviductal MΦs are potential mediators of infertility and have been observed to have morphologic characteristics similar to those of peritoneal MΦs (ability to phagocytose normal sperm) and occur in patients with infertility problems. These MΦs might obstruct fertilization by phagocytosis of sperm (Haney et al. 1983).

Recurrent spontaneous abortion (RSA)

The protein cathepsin E is an endolysosomal aspartic proteinase expressed mainly in immune cells and is highly secreted by activated phagocytes (Nishioku et al. 2002). It prevents tumor growth and metastasis by inducing apoptosis, inhibiting angiogenesis, and increasing immune responses (Shin et al. 2007). A study on the role of cathepsin E in early pregnancy in decidual MΦs of patients with recurrent miscarriage (RM) revealed decreased activity of cathepsin E produced by MΦs, which may be responsible for induction of miscarriage (Goto et al. 2014). Studies have also shown the dysregulation of MΦ activation by Treg cells, leading to unexplained RM cases (Wang et al. 2011). Thrombospondin 1 (TSP1) is mainly expressed in blood platelets which exists in tissue fluid in a free state but can bind the surfaces of MΦs. The binding partners of TSP1 are CD36 (scavenger receptor), CD47, and heparin sulphate proteoglycan, which are expressed on MΦs (Bornstein 1995; Yamauchi et al. 2002). TSP1 may play a role in regulating MΦ function through interactions with these binding partners. A study on the effects of TSP1 on decidual MΦs in RSA revealed that its expression was decreased in those cells, along with decreased IL-10 level, as compared to that of normal pregnant women. TSP1 also enhanced IL-10 expression in decidual MΦs in vitro, suggesting its involvement in regulating secretion of IL-10 and induction of immune tolerance at the maternal–fetal interface (Jin et al. 2009).

Preeclampsia and intra-uterine growth restriction (IUGR)

Decidual MΦs induce apoptosis and limit endovascular trophoblast invasion in preeclamptic women. The uteroplacental arteries are invaded by trophoblasts and are largely devoid of MΦs in normal pregnancy, whereas reduced trophoblast invasion of uteroplacental arteries and accumulations of apoptotic trophoblasts in the vicinity of arterial walls are found in IUGR and preeclampsia (Reister et al. 1999). An increase in trophoblast apoptosis may initiate inflammatory events, promoting further death of trophoblast cells and thus preventing normal trophoblast invasion, which may lead to pregnancy disorders, such as preeclampsia and IUGR (Mor and Abrahams 2003). The proinflammatory cytokines secreted by M1MΦs increase Fas expression and enhance trophoblast sensitivity to Fas-mediated apoptosis (Aschkenazi et al. 2002; Neale et al. 2003). Hence, MΦ-induced apoptosis affects the endovascular pathway of trophoblasts in pregnancy complications (Huppertz et al. 2006). Recent study (Li et al. 2019) revealed polarization of proinflammatory M1 subtype to anti-inflammatory M2 subtype through activation of Tim-3/Gal-9 signaling pathway in the preeclamptic rat model. There is a significant increase in MΦ numbers in the decidua of preeclamptic patients (Lockwood et al. 2006). In contrast, Burk et al. (2001) observed reduced numbers of MΦs with a CD14-, HLA-DR-, and mannose receptor-positive phenotype in placentas of preeclamptic women as compared to normal placentas (Burk et al. 2001). Pregnancies complicated by preeclampsia or IUGR showed activated MΦs producing proinflammatory cytokines, such as TNF-α and IFN-γ, and inducing the apoptosis of EVTs (Blois et al. 2004).

Preeclampsia is accompanied by an increased number of both MΦs and DCs at implantation sites, along with enhanced levels of recruiting chemokines, implicating impaired trophoblast invasion. There is an enhanced level of GM-CSF (a potent inducer of macrophage differentiation) in preeclamptic deciduas induced by the proinflammatory cytokines TNF-α and IL-1β, suggesting involvement of GM-CSF in the pathogenesis of preeclampsia (Huang et al. 2010). Hypoxic conditions, oxidative stress, and inflammation induce necrosis or aponecrosis of trophoblasts. MΦs and DCs produce type-I cytokines, such as TNF-α, IL-12, and IFN-γ, after phagocytosis of necrotic and aponecrotic trophoblasts and aggravate the inflammation (Huppertz et al. 2003). This condition probably induces apoptosis of EVTs, culminating in poor placentation, as observed in preeclampsia (Saito and Sakai 2003). The hormone corticotropin-releasing hormone (CRH) plays a vital role in mediating the stress response through the activation of the hypothalamic–pituitary–adrenal axis (Bale and Vale 2004). Evidence suggests a role for CRH in reproductive physiology,

with its abnormal function implicated in the pathogenesis of preeclampsia (Karteris et al. 2005). CRH and its receptors are expressed in the placenta and are involved in regulation of trophoblast invasion, placental vasculature, myometrial contractility, and onset of labor. CRH expression is upregulated in preeclamptic placentas, inducing FasL expression in maternal MΦs. These activated MΦs cause Fas-mediated EVT apoptosis, perturbing placentation (Petsas et al. 2012).

Preterm Labor

It is important to understand the host immune responses against uterine invading microbes in early pregnancy, as there is a correlation persisting between extremely premature births and intrauterine infection. It has been observed that MΦs modulate the decidual immune response against *Listeria monocytogenes* infections in early pregnancy in mice (Qiu et al. 2009). The MΦ migration inhibitory factor (MIF) is a soluble proinflammatory cytokine released by activated leukocytes (Bevilacqua et al. 2014). MIF inhibits random MΦ migration from peritoneal exudates, and its expression is confined to proliferative villous cytotrophoblasts and extravillous cell columns, indicating regulatory roles in the process of embryo implantation and pregnancy maintenance (Bucala 2007; Calandra and Roger 2003; Arcuri et al. 1999, 2007). Decreased maternal MIF serum level is linked with recurrent miscarriage in early gestation, whereas increased levels in early and mid-gestation are associated with subsequent preterm delivery (Yamada et al. 2003; Pearce et al. 2008, 2010). Enhanced maternal serum levels of MIF and altered expression of other proteins in placental compartments is also observed in preeclampsia, implicating MIF as a potential target for therapy (Todros et al. 2005; Cardaropoli et al. 2012).

Decidual Endometrium Mimics The Tumor Environment

Significant similarities exist between the proliferative, migratory, and invasive properties of placental cells and cancer cells, with shared molecular circuits (Ferretti et al. 2007; Genbacev et al. 1997). The penetrative nature of hemochorial placentation mimics the phenomena observed with highly invasive tumors (Strickland and Richards 1992). A study on the tumor suppressor gene maspin revealed that it is differentially regulated in cytotrophoblasts during human placental development, with its downregulation being critical during implantation and early placental development (Dokras et al. 2002). The process of decidualization in the first trimester of pregnancy occurs in physiological hypoxia in the uterine endometrium, thus favoring leukocyte recruitment. A similarly hypoxic environment exists at sites of tumor development, and MΦ recruitment (M2) occurs in tumor tissues in response to cytokine secretion by tumor cells. M2MΦs further help tumor cell growth and angiogenesis by secreting VEGF. There may be increased production of VEGF by MΦs in preeclamptic cases, which leads to vascular dysfunction and severe disease (Fan et al. 2014). Further study is needed to unravel the link between MΦs and VEGF production in normal pregnancy and in pregnancy complications, as well as the involvement of macrophages in the pathogenesis of preeclampsia.

Mouse Models for Studying MΦ Function in Pregnancy

MΦs are involved in various functions depending on their anatomical locations and body physiology. The mechanisms behind their function are of great scientific interest; however, the unavailability of sufficient numbers of primary tissue MΦs with high purity makes the study of this population difficult. Therefore, mouse models play vital roles in the study of MΦ functions. Their functional role in reproduction has been revealed to some extent by studies in the osteopetrotic Csf^{op}/Csf^{op} mouse (having a naturally occurring Csf-null mutation). The CSF-1 (M-CSF) molecule is the major stimulant of MΦ proliferation, differentiation, and recruitment. The Csf^{op}/Csf^{op} mice severely lack MΦs in many tissues, with the ovary and uterus being almost devoid of them (Wiktor-Jedrzejczak et al. 1990). They show extended estrous cycles and lower ovulation rates due to impaired function of the hypothalamic–pituitary–gonadal axis and intra-ovarian defects (Cohen et al. 2002). The CSF-1 null mutants have drawbacks for the study of MΦ functions in the establishment and maintenance of pregnancy because cytokines and chemokines other than M-CSF also play roles in recruiting MΦs to the ovary and uterus and as a decreased proportion of these animals have normal pregnancies. The density of $F4/80^+$ MΦs in these mice is about 53% of the wild type level, and in corpora lutea, 35% of the wild type level on day 1 post-coitum (Pollard et al. 1998; Robertson et al. 1998). The transgenic mouse Cd11b-Dtr provides a reliable approach to the study of MΦ function in pregnancy (Duffield et al. 2005). These mice show severe depletion of $CD11b^+$ MΦs in systemic circulation after administration of diphtheria toxin (DT) at nanogram levels. Care et al. (2013) have reported that acute depletion of $CD11b^+$ MΦs during early pregnancy in these mice results in a complete failure of implantation which is alleviated by administration of DT-resistant, wild type MΦs. MΦs also play a crucial role in regulating CL development during embryo implantation in mice (Care et al. 2013). Fejer et al. (2013) have developed a method yielding self-renewing, nontransformed, GM-CSF/STAT5—dependent MΦs (Max Planck Institute cells) from

the mouse fetal liver, reflecting innate immune status of alveolar MΦs (Fejer et al. 2013).

Therapeutic Targeting of MΦs in Pregnancy-Related Disorders

MΦs are currently getting attention as therapeutic targets. Various nanoparticles have been used to deliver therapeutic agents to MΦs in the body to treat genetic disorders and persistent infections, induce MΦ death, regulate accessory functions of MΦs, and diagnose pathologic conditions, like cancer (Moghimi et al. 2005). Particulate systems, such as liposomes, polymeric micelles, and polymeric micro- and nanoparticles contribute efficiently to the delivery of therapeutic agents to MΦs in different physiological portals of entry (Moghimi et al. 2012). MΦ-derived foam cells have emerged as therapeutic targets in atherosclerosis, and folate receptor-mediated targeting of therapeutic and imaging agents to activated MΦs might play a role in destroying FR (folate receptor)-expressing MΦs in rheumatoid arthritis (Choudhury et al. 2005; Paulos et al. 2004). There is great interest in cancer biology for MΦs to be used as therapeutic targets. The TAMs have been shown to modulate the effects of various anti-cancer therapies and promote tumor growth and angiogenesis. Preclinical studies have shown ways to polarize TAMs from the M2 to the M1 type in tumors so that the macrophages phagocytose tumor cells (De Palma and Lewis 2013). One of these strategies includes the use of histidine-rich glycoprotein (HRG), which induces downregulation of MΦ PlGF, promotes blood vessel normalization, and increases the delivery and efficacy of chemotherapy in tumor models in mice (Rolny et al. 2011). Another strategy involves nuclear factor κB signaling, or exposure of TAMs to anti-IL10R antibodies combined with the TLR-9 ligand CpG (Hagemann et al. 2008; Guiducci et al. 2005). This strategy was shown to induce hemorrhagic tumor necrosis, activate DCs and cytotoxic T cells, and cause tumor remnant clearance. Trabectedin, a recent chemotherapeutic agent, has been observed to deplete monocytes/MΦs in the blood, spleen, and tumors and to reduce angiogenesis in mouse models (Germano et al. 2013).

Some pregnancy complications are linked with M1/M2 imbalances in early inflammatory phase of pregnancy. It seems that the M1 subtype predominates over the M2 subtype in those cases, such as spontaneous abortions and disorders caused by inadequate spiral artery remodeling (Brown et al. 2014). Strategies to manipulate MΦ polarity at the maternal–fetal interface and shift the MΦ balance from M1 to M2 may alleviate pregnancy complications. In preeclampsia, the number of non-classical monocytes increases, which may promote inflammation (Faas et al. 2014). It has been observed that in preeclampsia, there are fewer M2MΦs (Martinez et al. 2009). Instead, M1MΦs predominate in preeclampsia, as severe inflammatory conditions prevail in maternal–fetal interface. The process of M1–M2MΦ type polarization may be the therapeutic target for treatment of preeclampsia.

Conclusions and Future Directions

Decidual MΦs play significant roles in successful pregnancy, with wide plasticity according to the environmental milieu. M1MΦs (proinflammatory) promote embryo implantation in early pregnancy and are actively involved in protection of the fetus from intrauterine infection, cervical ripening, and parturition. M2MΦs provide an immunotolerant environment for the semiallogeneic fetus to be carried in the uterus throughout pregnancy. T_{reg} cells also promote an immune-suppressive environment by suppressing $T_{effector}$ cells through cell–cell interactions with other immune cells, like M2MΦs and DCs. Many pregnancy complications, such as preeclampsia, IUGR, and RSA, have indications of abnormal MΦ responses. Extensive studies have been done to unravel the cell response in different types of cancers and pregnancy complications using mouse models. The switching of MΦ polarity could be a potential therapeutic target to treat pregnancy complications, as is predicted for cancer treatment. These cells have great potential to be targeted and exploited for treatment of pregnancy complications as well as for cancer therapy in the future. The signaling pathways (which induce the polarization) can also be targeted to achieve the required phenotype of MΦ and recovery from the diseased condition. The plasticity property of MΦs could be exploited for the development of therapeutics in pregnancy complications. Future investigations regarding decidual MΦs and their roles in physiological and pathological conditions through system biology approaches will give direction to the development of therapeutics.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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