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MDSCs in pregnancy: Critical players for a balanced immune system at the feto-maternal interface

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ABSTRACT

Myeloid-derived suppressor cells (MDSCs) have emerged as a new immune regulator at the feto-maternal interface. Although the phenotypes and functions of these cells were primarily studied in pathological conditions such as cancers and infections, new evidence has underscored their beneficial roles in homeostasis and physiological circumstances such as normal pregnancy. In this regard, studies have shown an increased number of MDSCs, particularly granulocytic MDSCs, at the feto-maternal interface. These cells participate in maintaining immunological tolerance between mother and semi-allograft fetus through various mechanisms. They further seem to play critical roles in placentation and fetus growth process. The absence or dysregulation of MDSCs during pregnancy have been reported in several pregnancy complications. These cells are also abundant in the cord blood of neonates so as to balance the immune responses and prevent aggressive inflammatory responses. The current review summarizes and organizes detailed data on MDSCs and their roles during pregnancy.

1. Introduction

Pregnancy is a physiological situation in which the mother's immune system peacefully tolerates semi-allograft fetal tissues. Several immune mechanisms at the feto-maternal interface cooperate to protect the fetus from rejection [1]. During different phases of pregnancy, dynamic changes happen in the frequency and functions of immune cells in the uterus. In a normal pregnancy, a dynamic cross-talk between trophoblasts and decidual immune cells is required to provide a proper milieu for a successful implantation of the embryo as well as the development of the fetus. Most critical immune cells within decidual tissue include uterine natural killer (uNK) cells, different T cell subsets, dendritic cells (DCs), macrophages, innate lymphoid cells (ILCs), and myeloid-derived suppressor cells (MDSCs). Within uterus, immune cells modulate immune responses in favor of an anti-inflammatory condition to sustain a successful pregnancy [1–4]. Moreover, humoral factors such as sex hormones and cytokines secreted by a number of immune and non-immune cells play essential roles in the immune tolerance and maintenance of pregnancy [5].

All the above-mentioned facts emphasize the importance of immune system during pregnancy, and show that a successful feto-maternal immune tolerance is more complicated than a fetus merely protected by physical barriers [6,7]. A deeper understanding of the immunological processes of immune-tolerance in fetal and maternal tissues and the changes in immune cells proportions during normal pregnancy can help better fathom the pathophysiology of pregnancy-related complications

Abbreviations: uNK, Uterine natural killer; DCs, Dendritic cells; ILCs, Innate lymphoid cells; MDSCs, Myeloid derived suppressor cells; TGF-β, Transforming growth factor beta; GM-CSF, Granulocyte/macrophage colony-stimulating factor; PGE2, Prostaglandin E2; M-CSF, Macrophage colony-stimulating factor; COX-2, Cyclooxygenase-2; VEGF, Vascular endothelial growth factor; JAK-STAT, Janus kinases Signal Transducer and Activator of Transcription proteins; C/EBP-β, Enhancer binding protein beta; IRF8, Interferon regulatory factor 8; HIF-1α, Hypoxia inducing factor-1 α; TLRs, Toll-like receptors; NFκB, Nuclear factor κB; PMN-MDSCs, Polymorphonuclear; MDSCs M-MDSCs, Monocytic MDSCs; Arg1, Arginase1; IDO, Indoleamine 2,3-dioxygenase; NO, Nitric oxide; ROS, Reactive oxygen species; PNT, Peroxynitrites; PD-L1, Programmed death-ligand 1; Gal9, Galectin-9; TAM, Tumor associated macrophages MMP, Matrix metalloproteinase; iNOS, Nitric oxide synthases; SLE, Systemic lupus erythematous; RA, Rheumatoid arthritis; iDCs, Immature dendritic cells; ILT-4, Immunoglobulin-like transcript-4; FOXP3, Forkhead box P3; E2, Estradiol; P4, Progesterone; PE, Pre-eclampsia; IVF, In vitro fertilization; NBI, Nosocomial bacterial infections; NEC, Necrotizing enterocolitis

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such as preterm labor, preeclampsia and infertility, and build a foundation for new strategies to improve perinatal outcomes [1,2,8].

The term "myeloid-derived suppressor cells" was first defined in 2007 and primarily used to describe a broad population of immature immunosuppressive cells with a myeloid origin [9]. Recently, a great amount of effort has been made to clarify the phenotypes, biology and pathological roles of MDSCs. These cells are considered as common suppressors of immune responses in various pathological conditions such as inflammation, cancer, trauma, transplantation and autoimmune diseases [9–14]. Recently, several original studies have attempted to find out the functions and applications of MDSCs at the feto-maternal interface [15–18]. Given the immunosuppressive properties of MDSCs in different immunological situations, it is expected that such cells play a role in the maintenance of human pregnancy. The aim of the present review is to provide brief information on MDSCs, their origin, phenotypes and functions, and to discuss, in detail, their probable roles at the feto-maternal interface and in pregnancy-related complications. In the end, a summary of recent findings is further provided on the frequency and function of MDSCs in fetuses and newborns.

2. Origin, differentiation and activation of MDSCs

Immunosuppressive properties of myeloid-derived population were first published in 1987 by Young and coworkers [19]. They described a proportion of bone-marrow derived cells in a lung cancer model with the ability to inhibit T cell proliferation [19]. Later investigations showed that MDSCs are a heterogeneous population of immature granulocytes and monocytes precursors [20]. Based on key properties such as origin, phenotype and functions, MDSCs are now characterized by their myeloid origin, immature state, and ability to suppress T cell response [14].

In vitro or *in vivo* generation of active MDSCs requires two main conditions; the first one is the high rate of myelopoiesis in bone marrow. In this first step, myeloid cells are preserved in their immature state by inhibiting their differentiation into mature myeloid cells. Several factors such as transforming growth factor beta (TGF-β), IL-1, IL-6, IL-10, IL-12, IL-13, granulocyte/macrophage colony-stimulating factor (GM-CSF), prostaglandin E2 (PGE2), macrophage colony-stimulating factor (M-CSF), cyclooxygenase-2 (COX2) and vascular endothelial growth factor (VEGF) are essential for such a condition [21–24]. The foregoing factors mainly use JAK/STAT signaling pathway and the signal transducer and activator of transcription 3 (STAT3) to promote myelopoiesis and preserve myeloid cells in an immature status, resulting in MDSCs expansion. Although STAT3 seems to be the most critical transcription factor, recent findings have introduced STAT5, C/EBP-β, IRF8 and NOTCH as other players in MDSCs expansion process [24,25]. The second condition, essential to activate MDSCs, is a proper microenvironment provided by factors such as interferon-γ (IFN-γ), TGF-β, IL-1β, IL-4, IL-6, IL-10, IL-13, TNF-α, COX-2, hypoxia inducing factor-1 α (HIF-1α) and ligands of pattern recognition receptors such as Toll-like receptors (TLRs) ligands. These factors transduce signals through STAT6, STAT1, and nuclear factor-κB (NF-κB) in order to activate MDSCs [14,26,27].

3. MDSCs phenotypes

In mice, two major markers, namely Gr-1 and CD11b, have been used to define MDSCs. These markers are applicable to identify the general population of MDSCs. However, due to the presence of different subpopulations such as polymorphonuclear MDSCs (PMN-MDSCs) (CD11b+ Ly6G+ $Ly6C^{lo}$), monocytic MDSCs (M-MDSCs) (CD11b+ Ly6G- $Ly6C^{hi}$) and other subgroups, these markers seem to be insufficient to categorize all MDSCs [20,28]. The same subpopulations of MDSCs have been identified in human peripheral blood defined by CD11b+ CD14- CD15+ or CD11b+ CD14- CD66b+ as PMN-MDSCs, and CD11b+ CD14+ $HLA\text{-}DR^{lo}$ CD15- as M-MDSCs. Since a small proportion of CD15+ cells do not express CD11b in humans, CD33 is used instead of CD11b as the myeloid marker. Human M-MDSCs could also be categorized as CD33+ cells, while PMN-MDSCs are $CD33^{dim}$ [29,30]. Although MDSCs are still identified based on the phenotypic markers, a recent review has suggested an algorithm model based on both surface and functional properties for the recognition of MDSCs. In fact, Bronte and coworkers have proposed that if these cells are not able to show noticeable immunosuppressive functions, even in the presence of MDSCs phenotypical markers, they must be considered as DCs, macrophages or neutrophils [31].

4. General immune-suppressive functions of MDSCs

Both PMN-MDSCs and M-MDSCs are able to suppress immune responses by various mechanisms. Some of the suppressive mediators secreted by MDSCs can be used to discriminate MDSCs from mature monocytes and neutrophils. The most major factors employed by MDSCs to inhibit immune responses are arginase1 (Arg1), indoleamine 2,3-dioxygenase (IDO), nitric oxide (NO), reactive oxygen species (ROS), and prostaglandin E2 (PGE2). IDO and Arg1 create a starving milieu through the depletion of essential amino acids such as arginine and tryptophan. Lack of essential nutrients leads to T cells suppression or even depletion [32–34]. The interaction between ROS and NO subsequent products promotes peroxynitrites (PNT) production. In the next step, PNT causes nitration of CD8 T cells receptors, a process disturbing TCR-MHC interaction and inducing T cells unresponsiveness even in the presence of cognate antigens, [14]. Another immune suppressive mechanism attributed to MDSCs is the induction of regulatory T cells (Tregs) via different pathways such as cell-cell contact or secretion of TGF-β [35,36]. Moreover, the up-regulation of immune checkpoints inhibitory molecules including PD-L1 and Gal9 has been introduced as other suppressive functions of MDSCs [37–39].

5. MDSCs in cancer

As mentioned before, MDSCs were primarily observed and defined in cancer investigations, and most studies on MDSCs have been conducted in this area [27,40]. In brief, cancer cells produce a host of factors involved in the myelopoiesis, recruitment and activation of MDSCs. Cancer cells produce several factors such as VEGF, GM-CSF, IL-1β, IL-6, HIF-1α, TGF-β and, COX2 to induce a higher rate of myelopoiesis in the bone marrow. Cancer cells are also able to recruit MDSCs to the tumor site by secreting appropriate chemokines including CCL2, CCL3, CCL4, CCL5, CXCL1 and CXCL8. Subsequently, cancer cells activate MDSCs by producing TNF-α, IL-10, IL-1β, IL-6, IFN-γ, COX2 and HIF-1α. In this cross-talk, activated MDSCs suppress the infiltrated immune cells including DCs, NK cells and T cells via the above-mentioned immunosuppressive mechanisms. They further promote the proliferation and differentiation of Tregs and tumor-associated macrophages (TAM), both of which deflect effective anti-tumor responses and act in favor of tumor progression [27,41]. Beyond their immunosuppressive functions, MDSCs also contribute to tumor proliferation and metastasis through different mechanisms. Soluble factors secreted by MDSCs such as MMPs, VEGF, TGF-β and other angiogenic factors can trigger tumor neovascularization, invasion, proliferation and metastasis [27,42,43].

6. MDSCs in other immunological diseases

Although most efforts to find out the properties and functions of MDSCs have been focused on cancer studies, their roles in other different pathological conditions including infection, autoimmunity and obesity have also been investigated. In the case of infectious diseases, several *in vitro* and *in vivo* studies have indicated MDSCs induction and modulation in the presence of both Gram-positive and Gram-negative bacteria [44]. In this line, it is well documented that in preclinical

models of *Staphylococcus aureus* infection, there is an increase in the number of functional M-MDSCs and PMN-MDSCs with the ability to suppress T cell response. Indeed, the higher frequency of MDSCs is reported to be correlated with the aggravation of infection [45,46]. Moreover, it has been shown that *Mycobacterium tuberculosis* infection can increase expansion and immunosuppression ability of PMN-MDSCs and M-MDSCs in mice [47]. A high frequency of MDSCs also has been reported in individuals affected by sepsis. A positive correlation between the frequency of MDSCs and poor prognosis indicates the pathological roles of MDSCs in sepsis [48]. On the other hand, some evidence attributes the protective roles to MDSCs in bacterial infections. Epidemiologically, the abundance of MDSCs has been shown to be associated with good prognosis and protection against *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* infections [49]. In addition to bacteria, human pathogenic fungi are also capable of inducing the accumulation of MDSCs. In a rat model of *Pneumocystis pneumonia* infection, it was suggested that MDSCs participate in severe conditions by up-regulating Arg1 and iNOS [50]. Also, in HIV and HCV infections, M-MDSCs populations are more abundant, inhibiting specific T cell responses through several mechanisms such as Arg1 up-regulation and PD-L1 expression [51–53].

As discussed, the roles of MDSCs in cancer and infection are mostly in favor of the disease, and deleterious for patients due to the major immunosuppressive nature of these cells; in autoimmune diseases, however, the scenario seems to be more controversial and complex. For instance, it has been reported that PMN-MDSCs and M-MDSCs increase in patients with systemic lupus erythematous (SLE); these increments have a positive correlation with the frequency of Th17 cells and the poor prognosis of the disease [54].

It is further posited that the depletion of MDSCs in the early phases of Rheumatoid arthritis (RA) results in better prognosis by reducing Th17 cells differentiation [54,55]. On the other hand, several reports have documented the protective roles of MDSCs in autoimmune disorders. In a mouse model of RA, MDSCs isolated from synovial fluid were shown to inhibit T cell functions and ameliorate RA symptoms. Also, the frequency of MDSCs has been reported to be negatively associated with the frequency of T cells in synovia of RA patients [56,57]. Moreover, the protective roles of MDSCs have been mentioned in immune-related colitis [58]. These controversial and opposite results may be rooted in the nature of different autoimmune disorders and the difference in the frequency and subtypes of MDSCs presented in the target tissues of the diseases.

In obesity, a condition with continuous chronic micro-inflammation, it has been shown that tissue-infiltrating MDSCs play protective roles and are crucial for controlling obesity-associated inflammation and maintenance of insulin sensitivity. In addition to suppressing T cells (especially CD8+ T cells), MDSCs are able to deviate the polarization of macrophages in favor of M2 phenotype, mostly by producing IL-10 [59]. However, the expansion of MDSCs in obesity seems to act as a double-edged sword as there is evidence corroborating the idea that the frequency of MDSCs in obese individuals is positively correlated with the incidence of cancer [60].

7. MDSCs in pregnancy

From an immunological point of view, pregnancy is a paradox in which a balance between inflammatory and anti-inflammatory responses is required for a successful pregnancy without pernicious complications. Such balance is dynamically adjusted during different phases of pregnancy to support normal implantation, proper gestation and successful delivery. In the first trimester, particularly during the first days, a controlled inflammatory response is required for perfect implantation and placentation. With the passage of time, and mainly in the second trimester, regulatory responses start to be the major immunological events, and later in the third trimester and the last days of pregnancy, inflammatory responses play a dominant role to support delivery [61]. Accordingly, establishing a sustainable maternal-fetal tolerance, particularly during the second trimester, is essential for a successful pregnancy. Different effector cells of the immune system, such as uterus natural killer cells (uNK), immature dendritic cells (iDCs), macrophages, Tregs and Th2 cells play an important role in the induction of tolerance [1,3,62].

There has been a recent increase in the number of studies investigating the roles of MDSCs in pregnancy. It seems that MDSCs participate in pregnancy as important immunosuppressive cells. Increased frequency of MDSCs in all stages of pregnancy has been shown in several studies in both human and mouse models of pregnancy [63,64]. Early investigations in humans have indicated that the frequency of PMN-MDSCs rises in the peripheral blood of healthy pregnant women during all phases of gestation compared to non-pregnant individuals. The remarkable point is that the frequency of M-MDSCs seems to remain unchanged in the peripheral blood of pregnant women [63]. However, one study evidenced that the number of M-MDSCs positively correlates with the serum levels of estrogen and progesterone during pregnancy. They further showed that the administration of 17b-oestradiol up-regulates STAT3, and promotes the expansion and even the inhibitory effects of MDSCs through this signaling pathway. These results demonstrate the importance of 17b-oestradiol-induced STAT3 signaling as a crucial pathway for the activation of MDSCs during human gestation [17]. In line with the foregoing studies, significant expansions of PMN-MDSCs have been shown in several immune organs and decidual tissues of pregnant mice. Increased frequency and suppressive functions of PMN-MDSCs are thought to be facilitated mostly through progesterone and STAT3 signaling. Evidence shows that the activation of progesterone receptor leads to higher expression of STAT3 protein in MDSCs, resulting in the expansion of MDSCs during pregnancy [16]. Beside hormones, there are other factors contributing to the increment of MDSCs. HLA-G, a molecule expressed and secreted by several cells in the feto-maternal interface, is also a critical player in the accumulation of MDSCs in the decidua. Soluble HLA-G binds to its cognate receptor called immunoglobulin-like transcript-4 (ILT-4) and consequently induces the expansion and differentiation of MDSCs from PBMCs via STAT3 signaling, similar to the mentioned hormones [65,66]. Hypoxia and HIF-1α expression are other effective factors in the induction and accumulation of MDSCs at the feto-maternal interface. A recent study showed that the defects in HIF-1α reduce the number of MDSCs. They also documented that HIF-1α deficient MDSCs show impaired immunosuppressive functions and are more prone to apoptosis [67]. To understand the potential importance of MDSCs in pregnancy, it is to be noted that MDSCs are the second most frequent immune cells following uNK cells in mouse decidua tissue, particularly in the second trimester. As discussed above, most of these MDSCs in the decidua seem to be PMN-MDSCs [68]. Trophoblast cells are also effective players in the expansion of MDSCs. An *in vitro* study documented the ability of trophoblast cells to induce MDSCs. It is shown that a trophoblast cell line (HTR8/SVneo) triggers the differentiation of peripheral CD141 myelomonocytic cells into a subpopulation of MDSCs with CD141+, HLA-DR2^{low} phenotype and a high expression of IDO1, ARG-1, and COX2. Interestingly these myelomonocytic cells express a higher level of STAT3 after co-culturing with trophoblast cells, which indicates the potential mechanisms by which trophoblast cells induce MDSCs expansion [69]. Although more investigations are required to understand and identify the main mechanisms and chemoattractants involved in MDSCs recruitment to decidua tissue, one study introduced a major subpopulation of PMN-MDSCs in decidua with a high expression of surface CXCR2. These cells are recruited to the feto-maternal interface as its cognate chemokine, CXCL1, is continuously secreted by decidual cells [70]. The exact location of MDSCs in decidua and feto-maternal interface requires more illustration, but one study suggested that these cells are mainly distributed in the intervillous space of placenta [71]. Altogether, these findings 1) indicate the frequent presence of MDSCs, particularly PMN-

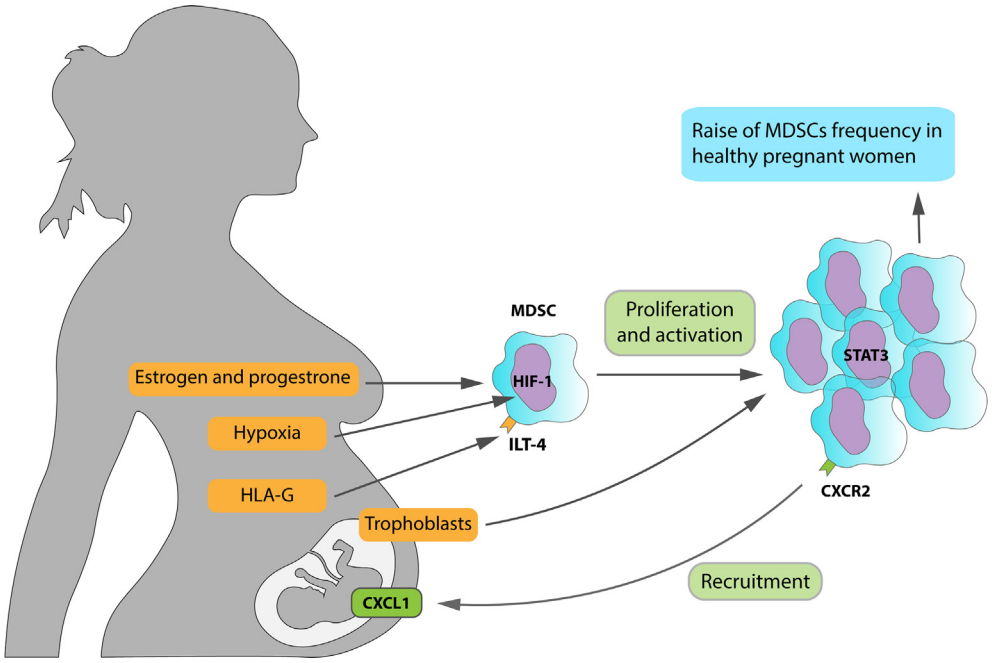

Fig. 1. MDSCs expansion during pregnancy. Several factors cause the expansion and activation of MDSCs in a normal pregnancy. The increase in estrogen and progesterone during pregnancy expands and activates MDSCs through STAT3 signaling pathway. Secretory HLA-G triggers STAT3 signaling pathway and MDSCs proliferation and differentiation through binding to its cognate receptor (ILT-4) on MDSCs. Hypoxia results in the expansion and accumulation of MDSCs by the induction of HIF-1 transcription factor. Trophoblasts induce and trigger the expansion of STAT-3 signaling in MDSCs. Activated MDSCs express CXCR2 on their surface and migrate to the feto-maternal interface where their cognate chemokine CXCL1 is abundant.

MDSCs, at the feto-maternal interface and even in peripheral blood during pregnancy, and 2) introduce STAT-3 and CXCR2 as main factors contributing to the differentiation and accumulation of MDSCs at the feto-maternal interface. General evidence of MDSCs expansion during pregnancy is summarized and illustrated in Fig. 1.

In addition to the investigations on the frequency and induction of MDSCs in pregnant human and mouse models, a great amount of effort has been made to elucidate their roles and potential immunosuppressive effects during pregnancy. In humans, one of the first studies on MDSCs at the feto-maternal interface introduced decidual CD33+ HLA-DR- and CD33+ HLA-DR+ or - cells with the ability to produce high levels of Arg1, iNOS and IDO, and typical anti-inflammatory cytokines such as IL-10 and TGF-β. Both subtypes inhibit T cell proliferation, hence functionally characterized as MDSCs [72]. In accordance with the mentioned study, others have reported isolated PMN-MDSCs as the major MDSCs subpopulation in the peripheral blood of pregnant women, producing immunosuppressive enzymes such as Arg1 and iNOS, and suppressing the proliferation of T cells mostly through ROS. Interestingly, in the peripheral blood of women, the number of these cells decreases quickly following parturition [63]. The potential functions of MDSCs during pregnancy have been confirmed by the depletion of MDSCs in a mouse model. In the absence of MDSCs, DCs and T cells show a higher proliferation capacity. Moreover, in MDSCs-depleted mice, uNK cells and macrophages show defects in supporting successful pregnancy. These data indicate the critical roles played by MDSCs in maternal tolerance not only by suppressing DCs and T cells proliferation but also through supporting uNK cells and resting macrophages [68]. Mechanisms other than the production of enzymes or ROS are also attributed to the immunosuppressive roles of pregnancy-associated MDSCs. For instance, one study proposed that MDSCs not only suppress T cells via ROS production, but they are also able to reduce T cell response in a cell-cell contact manner, the exact mechanism of which needs further explanation [16]. As predicted, the potential role of MDSCs to preserve general immunosuppressive conditions during pregnancy can be played through the induction of Tregs. It is well documented that pregnancy-associated MDSCs induce Foxp3 positive Tregs by producing TGF-β and via TGF-β/β-catenin signaling pathway. The increase in Tregs may also result in the higher frequency of MDSCs in a positive feedback loop manner [73]. MDSCs are further capable of inducing a shift towards the anti-inflammatory subtypes of Th2 cells via cell-cell interaction [71]. Moreover, MDSCs support feto-maternal tolerance, another interesting behavior, through reducing the expression of L-selectin on naïve T cells which inhibit their trafficking towards lymph nodes; however, the exact molecular mechanism of this effect is yet to be fully clarified [15]. There may be other mechanisms which MDSCs apply during pregnancy to support gestation, and extensive work is required to fully fathom all aspects of their function in pregnancy. For instance, it has been reported that MDSCs support angiogenesis in cancerous milieu. Angiogenic effects of MDSCs are also highly important in placentation since the process of placentation deeply depends on angiogenesis and is somehow similar to the invasion process of tumors [74]. Furthermore, in certain conditions, MDSCs show higher expressions of inhibitory immune checkpoints which is another potential mechanism to support tolerance towards the fetus given the frequent presence of MDSCs at the feto-maternal interface [40,75]. The functions and roles of MDSCs during pregnancy are summarized in Fig. 2.

8. MDSCs in pregnancy-related complications

As reviewed and discussed above, MDSCs play inevitable roles during pregnancy and consequently, their absence or dysregulation may lead to complications. In this regard, certain studies have investigated the frequency of MDSCs in women with pregnancy-related complications or in mice models of such disorders. Reduced frequency of MDSCs within both peripheral blood and decidua of patients with miscarriage has been reported. Interestingly, these cells are not only reduced but also seem to be impaired in functions due to their reduced ability to inhibit T cell responses in the patients [64]. A reduction in PMN-MDSCs, but not M-MDSCs, has also been reported in spontaneous abortion disorder [73]. A recent study showed that in women with early miscarriage, reduced levels of estradiol (E2) and progesterone (P4) hormones result in reduced MDSCs, thereby altering Th1/Th2 balance in favor of Th1 cells [76]. In pre-eclampsia (PE), an inflammatory pregnancy-related complication, induction of PMN-MDSCs but not M-MDSCs, seems to be inhibited. Furthermore, the serum level of Arg-1, an important effector molecule for PMN-MDSCs, is significantly lower in PE patients compared to healthy pregnant women [77]. Even in infertile couples, the frequency of MDSCs is an important factor in predicting the treatment outcomes. For example, the chances of a

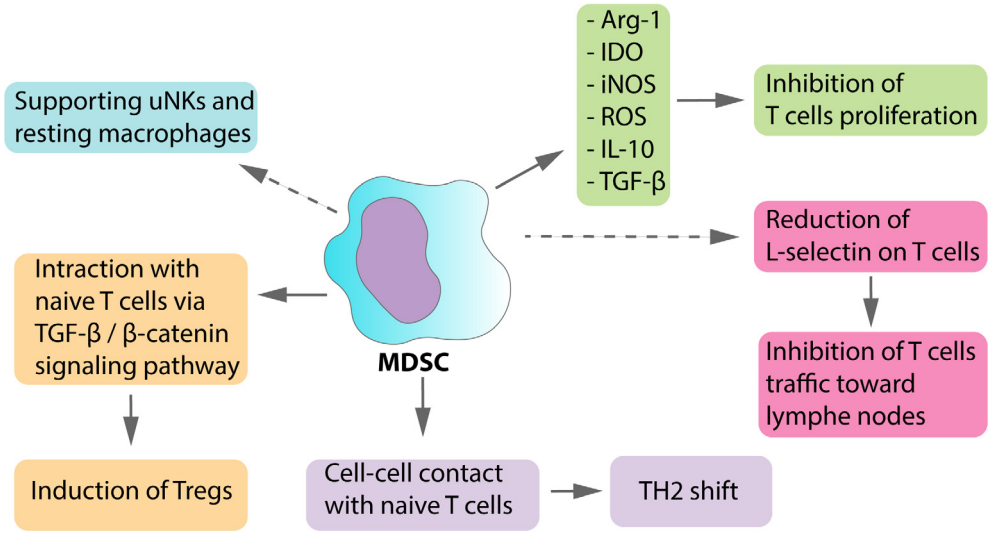

Fig. 2. Roles of MDSCs in feto-maternal tolerance. Active MDSCs produce several factors including Arg-1, IDO, iNOS, ROS, IL-10, and TGF-β, all contributing to T cells inhibition. MDSCs decrease L-selectin expression on T cell via an unexplained mechanism and consequently reduce T cell trafficking. The crosstalk between MDSCs and T cells leads to the induction of Tregs through TGF-β/β-catenin signaling pathway. The interaction between MDSCs and T cells leads to a shift towards Th2 phenotypes in these cells. MDSCs can further preserve feto-maternal tolerance by supporting immune-related cells and resting macrophages, the exact mechanisms of which requires further investigation.

successful pregnancy in women who undergo IVF are significantly greater in cases with a higher number of MDSCs in their peripheral blood [78]. The absence of MDSCs and the effects of this shortage have been further studied in the mouse models of pregnancy complications. In CBA/J × DBA/2 mouse model, a confirmed model for immune-related pregnancy loss, it has been well shown that the frequency of PMN-MDSCs at the feto-maternal interface is significantly reduced, and transferring isolated normal MDSCs to these mice increases the chances of successful pregnancy outcomes. Consistent with these findings, it is also evidenced that the depletion of MDSCs by antibody (anti-GR1) in normal mouse results in miscarriage and/or even infertility [15,16,73]. Recent findings have indicated that the depletion of MDSCs increases the cytotoxic properties of decidual NK cells, while an important feature of a normal pregnancy is the high frequency of non-cytotoxic and low number of cytotoxic NK cells at the feto-maternal interface [18]. Although no therapeutic approaches using MDSCs have been adopted in human pregnancy, these cells are interesting choices for further human studies considering preclinical data. On the other hand, researchers are to be cautious with these cells as they may act as a double-edged sword in certain conditions. For instance, one study documented that in contrast to the increased number of MDSCs during pregnancy, they may severely affect pregnant cases involved with cancer. The effects of pregnancy-induced MDSCs on the metastasis of breast cancer were shown in a mouse model. It seems that the MDSCs accumulated in pregnant mice inhibit NK cells activity and promote the metastasis of tumor in the pregnant mice [79]. A recent study proposed that the high estrogen level during the pregnancy of cases affected by ovarian and breast cancer may accelerate cancer progression through inducing MDSCs [80].

9. MDSCs in fetuses and neonates

During the neonatal period, the immune system should undergo dramatic changes to adapt to postnatal circumstances. The immunosuppressive state needs to transform into a balanced condition in order to provide active protection against bacterial, viral and fungal pathogens. However, inflammatory responses should also be controlled in parallel to avoid immune-related damages, a transitional process [81] during this transitional process, regulatory immune mechanisms play central roles in immune responses. Generally, the cytokine profile of Th2 cells is the major player of immune system behavior in this period. Reduced and controlled CD8+ T cell responses, accumulation of Treg cells and the immaturity of dendritic cells are other features of neonates immune system [82–87]. In addition to the mentioned mechanisms, there are other cells supporting the regulatory responses in newborns. MDSCs, as previously discussed, are strong immunosuppressive cells whose presence in the umbilical cord blood or even the peripheral blood of neonates accounts for the immune suppression in fetuses and neonates. In this review, mention was made of certain studies in this regard, and the evidence regarding MDSCs in fetuses and neonates was further summarized. Further shown was the higher frequency of MDSCs in umbilical cord blood of neonates rather than peripheral blood of adults or even children. Functionally, umbilical cord blood PMN-MDSCs are able to inhibit T cell expansion and reduce the cytokine production of Th1 and Th17 cells. These MDSCs are further capable of suppressing cytotoxic NK cell through a cell-cell contact manner [88]. In accordance with the mentioned document, another study revealed that although MDSCs are very rare in healthy adults, they are highly prevalent in neonates. Interestingly, the number of these cells decreases dramatically during the first months of life. A majority of these MDSCs are PMN-MDSCs, able to inhibit T cell proliferation by cell-cell interaction [89]. As previously noted, Th2 based immune responses are dominant in neonates. In this regards, the role of MDSCs in generation of Th2 phenotype has been studied. It seems that the higher frequency of MDSCs is one of the main reasons for bias towards Th2 responses in neonates. Umbilical cord blood derived MDSCs show great potential for suppressing Th1 responses and inducing Th2 and Treg cells. MDSCs mediate Th2 induction through cell-cell contact, Arg-I and ROS. Treg cell induction by these MDSCs is mediated via iNOS and its products [90]. However, whether the expansion of MDSCs in neonates is completely beneficial or may cause susceptibility to infections is yet to be fully understood. An interesting study reported a higher number of MDSCs in the umbilical cord and peripheral blood of preterm infants. In these infants, MDSCs seem to be kept elevated until 28 days after birth. Authors consider MDSCs as the potential cause for the higher risk of infection in preterm rather than term neonates [91]. On the other hand, it is also suggested that MDSCs in neonates play important roles in the regulation of immune system upon encountering infectious agents and protecting the neonate from an uncontrolled inflammatory response [92]. In another study, the transcriptome of pregnancy-induced MDSCs was compared to tumor-induced MDSCs, and results showed that in both conditions, transcriptomes were very similar. Interestingly, however, pregnancy-induced MDSCs produce a significantly higher amount of antimicrobial agents and may harbor a potential for anti-microbial effects in newborns [93]. Only one study investigated MDSCs in breast milk, where active PMN-MDSCs were significantly higher in both peripheral blood and breast milk of breastfeeding mothers, and were able to suppress T cell activities. They proposed that such proportion of MDSCs in breast milk is able to protect neonates from nosocomial bacterial infections and necrotizing

enterocolitis [94].

10. Concluding remarks

Although pathological MDSCs were the first introduced MDSCs, it seems that now we should consider these cells in their specific contexts in order to understand their nature and roles in the physiological processes of the body. These roles absolutely depend on the conditions they are presented in. An excellent example to show the beneficial and physiological roles of MDSCs is pregnancy. As discussed above, MDSCs increase not only at the feto-maternal interface but also in the peripheral blood or other immune system organs of pregnant women. In the context of pregnancy, MDSCs are critical to the maintenance of tolerance. In general, MDSCs deviate the immune response towards a general Th2 and anti-inflammatory response. They also are able to induce Treg cells at the feto-maternal interface along with suppressing the immune response in a direct manner by producing factors such as IDO, Arg-1, ROS and NO. Other potential mechanisms of MDSCs such as expression of immune checkpoints should be investigated in future studies. In addition to immunosuppressive properties, MDSCs may also participate in placentation and fetus growth as they produce TGF-β and angiogenic factors. The beneficial effects of MDSCs continue even after birth to preserve neonates from extreme inflammatory responses. On the other hand, the increase in MDSCs during pregnancy may be hazardous in those involved with cancer. All these observations indicate that the behavior of MDSCs is to be assessed in an exact context.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cellimm.2019.103990.

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