

Dendritic Cells and the Establishment of Fetomaternal Tolerance for Successful Human Pregnancy

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Abstract

Pregnancy is a remarkable event where the semi-allogeneic fetus develops in the mother's uterus, despite genetic and immunological differences. The antigen handling and processing at the maternal–fetal interface during pregnancy appear to be crucial for the adaptation of the maternal immune system and for tolerance to the developing fetus and placenta. Maternal antigen-presenting cells (APCs), such as macrophages (Mφs) and dendritic cells (DCs), are present at the maternal–fetal interface throughout pregnancy and are believed to play a crucial role in this process. Despite numerous studies focusing on the significance of Mφs, there is limited knowledge regarding the contribution of DCs in fetomaternal tolerance during pregnancy, making it a relatively new and growing field of research. This review focuses on how the behavior of DCs at the maternal–fetal interface adapts to pregnancy's unique demands. Moreover, it discusses how DCs interact with other cells in the decidual leukocyte network to regulate uterine and placental homeostasis and the local maternal immune responses to the fetus. The review particularly examines the different cell lineages of DCs with specific surface markers, which have not been critically reviewed in previous publications. Additionally, it emphasizes the impact that even minor disruptions in DC functions can have on pregnancy-related complications and proposes further research into the potential therapeutic benefits of targeting DCs to manage these complications.

Keywords

Dendritic cells · Pregnancy · Endometrium · Hematopoietic stem cells · Placenta

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Abbreviations

BATF3, Basic leucine zipper ATF-like transcription factor 3; BCL11A, B-cell lymphoma/leukemia 11A; BDCA1*, Blood dendritic cell antigens 1*; CBFB, Core binding factor subunit beta; CD11chi, CD11chi monocyte-derived macrophages; cDC1, Conventional Type 1 Dendritic Cells; CD45RA, Long isoform of CD45 molecule; CEBPA, CCAAT/enhancer-binding protein alpha; DNCR-1, Dendritic cell Natural killer Group Receptor-1; DROSHA, Ribonuclease III double-stranded (ds) RNA-specific endoribonuclease; ER, Endoplasmic Reticulum; FCER1, The high-affinity IgE receptor, also known as FcεRI, or Fc epsilon RI; HLA-DR, Human Leukocyte Antigen – DR isotype; HLA-DRhi, Human Leukocyte Antigen – DR high; HLA-E, Human Leukocyte Antigen E; HO, Heme Oxygenase; ID-2, Inhibitor of DNA Binding 2; IL3R, Interleukin 3 receptor; IRF4, Interferon regulatory factor 4; IRF4hi, Interferon regulatory factor 4 high; IRF8, Interferon regulatory factor 8; JAG1, Jagged canonical Notch ligand 1; KLF4, Kruppel-like

factor 4; KPC1, Kip1 ubiquitination-promoting complex 1; LIF, Leukemia inhibitory factor; Ly6C, Lymphocyte antigen 6 complex, locus C; MAFB, MAF BZIP Transcription Factor B; MAPK, Mitogen-activated protein kinase; MERTK, Myeloid-epithelial-reproductive tyrosine kinase; MHCII, Major Histocompatibility Complex class II; NCOR2, Nuclear receptor Co-Repressor 2; NF-κB, Nuclear factor kappa B; NFIL-3, Nuclear Factor Interleukin 3; NOTCH2, Neurogenic locus notch homolog protein 2; NR4A3, Nuclear receptor subfamily 4, group A, member 3; PDCA-1, Plasmacytoid Dendritic cell antigen-1; pDCs, Plasmacytoid dendritic cells; PLAC8, Placenta associated 8; pre-cDCs, Precursors conventional DCs; pre-pDCs, Precursors plasmacytoid DCs; PU. 1/PU-1, PU. 1 or PU-1 is a tissue-specific transcription factor; RBPJ, Recombination Signal Binding Protein for Immunoglobulin Kappa J Region; RELB, Nuclear factor kappa B subunit RelB; RNA, Ribonucleic acid; RUNX1, Runt-related transcription factor 1; RUNX3, Runt-related transcription factor 3; SIGLECH, Sialic-acid-binding immunoglobulin-like lectin H; SPIB, Spi-B transcription factor; TCF3, - Transcription factor 3; TCF4, Transcription factor 4; TNF-γ, Tumour Necrosis Factor γ; WNT1, Wnt Family Member 1; XCR1, X-C motif chemokine receptor 1; ZBTB46, Zinc Finger and BTB Domain Containing 46; ZEB2, Zinc finger E-box-binding homeobox 2.

1. Introduction

Human pregnancy is a complex physiological event, accommodating the semi-allogenic fetus in the uterus of the mother

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that involves the delicate balance of the immune system. The maternal immune system is presented to fetal/placental allo-antigens at two connecting points (in the uterus by means of apposition of maternal leukocytes with invading trophoblasts, and in the secondary lymphoid organs, i.e., the spleen and lymph nodes [LNs]) via placental material shedding into maternal blood and its circulation all through the body (Laskarin et al. 2011; Tagliani et al. 2011; Tagliani and Erlebacher, 2011). Antigen-presenting cells (APCs) at the maternal–fetal interface are important participants in the induction of immunological responses among the various immune competent cells, including macrophages (Mφs) (Hunt and Robertson 1996), vaginal and uterine epithelial cells (Wira et al. 2002), and dendritic cells (DCs) (Kämmerer et al. 2000). DCs perform an important immunomodulatory role during pregnancy for the acceptance of the fetus by the mother's immune system while maintaining enough defense against infections. In the 1970s, Steinman and Cohn (1973; 1974) and Steinman et al. (1974) discovered DCs in the peripheral lymphoid organs of mice, and deciphered their immunological role. These cells act as a teeterboard between the immune response and tolerance, as well as a link between innate and adaptive immunity. Pathogens can be processed by DCs before they are presented to naive T cells, resulting in an adaptive immunological response (Liu 2001). Additionally, DCs play a role in tolerance induction by producing T cells with regulatory features (Treg cells), which limit the proliferation of effector T cells (Jonuleit et al. 2000; Mahnke et al. 2003) or eliminate antigen-specific T cells (Hawiger et al. 2001; Bonifaz et al. 2002). These cells can promote both central and peripheral tolerance by extending immune homeostasis maintenance and inhibiting autoimmune reactions (Moser 2003). The transcription factor (TF) Foxp3 promotes the differentiation of Treg cells. The Foxp3⁺ Tregs are immunosuppressive and prevent autoimmune reactions. Besides, they have other functions such as promoting tissue repair, stimulating hair follicles, and regulating body metabolism (Feuerer et al. 2009; Burzyn et al. 2013; Arpaia et al. 2015; Ali et al. 2017). It is observed that the Tregs associated with many human and murine tumors restrict the antitumor immunity (Savage et al. 2013). The regulatory activity of the Treg cells is attributed to the CD4⁺ – T cells expressing the interleukin (IL)-2 receptor alpha-chains (CD25) (Sakaguchi et al. 1995; Savage et al. 2020).

Various studies have revealed that the role of DCs is altered in the uterus (especially in the human decidua) and in the peripheral blood (PB) throughout the pregnancy, which suggests that they may play a role in various events of pregnancy such as decidualization and angiogenesis (Laškarin et al. 2007; Barrientos et al. 2009; Collins et al. 2009; Blois et al. 2011; Huang et al. 2016). The DCs are found to play a crucial role in maintaining a balance between immunity (to protect the uterus from infections) and tolerance (to accommodate

the semi-allogenic fetus), although their number is less in the endometrium as compared to other immune cells like natural killer (NK) cells and macrophages (Bachy et al. 2008). The DCs interact with NK cells and promote their homing and maturation in the uterus. The interplay of DCs and NK cells regulates the decidualization of endometrial stromal cells and vascular modifications for successful implantation and pregnancy (Blois et al. 2011). Moreover, the aberrant differentiation and functioning of DCs is also associated with recurrent spontaneous abortion (RSA), preterm birth (PTB), preeclampsia (PE), and infectious pregnancy issues (Ellis et al. 2005; Le Gars et al. 2016; Negishi et al. 2017; Liu et al. 2018; Lu and Hu 2019).

The present review provides in-depth information on the role of DCs in the establishment of fetomaternal tolerance to accommodate the semi-allogenic fetus in the uterus of the mother for successful pregnancy. Moreover, the review discusses the unique surface markers of cell lineages derived from DCs, and more emphasis is given to the link between DCs and other cellular networks (T cells, NK cells, and Mφs) and molecular networks (cytokines and hormones) involved in pregnancy biology. In addition, the review also discusses about the pregnancy complications arising due to the disruption of DC functions and DCs as potential therapeutic targets to manage the complications.

2. Development of DCs

DCs have a short life span and must be replenished on a regular basis by bone marrow (BM) progenitors derived from hematopoietic stem cells (HSCs) (Geissmann et al. 2010). In the common DC development concept, CD34⁺ HSCs in the BM undergo maturation into CD34⁺ CD123⁺ CD45RA⁺ common myeloid progenitors (CMPs), which in turn develop into monocyte and dendritic cell progenitors (MDPs) (Figure 1) (Fogg et al. 2006). MDPs further differentiate into (common monocyte progenitors [cMoPs] that are CD135⁺ Ly6C⁺) and common DC progenitors (cDPs), which express CD135⁺, CD115⁺, and DNGR-1⁺ surface markers. From CDPs, two types of DC progenitors arise, i.e., conventional DCs and plasmacytoid DCs (pDCs), which are also known as Pre-cDCs and Pre-pDCs, respectively (Figure 1) (Naik et al. 2007; Onai et al. 2007). The conventional DCs (cDCs, also called as classical DCs) are the major DC subset that correspond to the cells originally discovered by Steinman and Cohn (1973) in the 1970s and CD24, XCR1, CD172, and CD103 are the unique surface markers used to identify them (Naik et al. 2007). These cells differentiate in the lymphoid and nonlymphoid tissues and are further classified as cDC1 and cDC2 subpopulations. The cDC1 cells are involved in cross presentation and prime the CD8⁺ T cells against the extracellular antigens like bacteria and viruses. The cDC2 cells are found in blood, lymphoid, and nonlymphoid tissues and

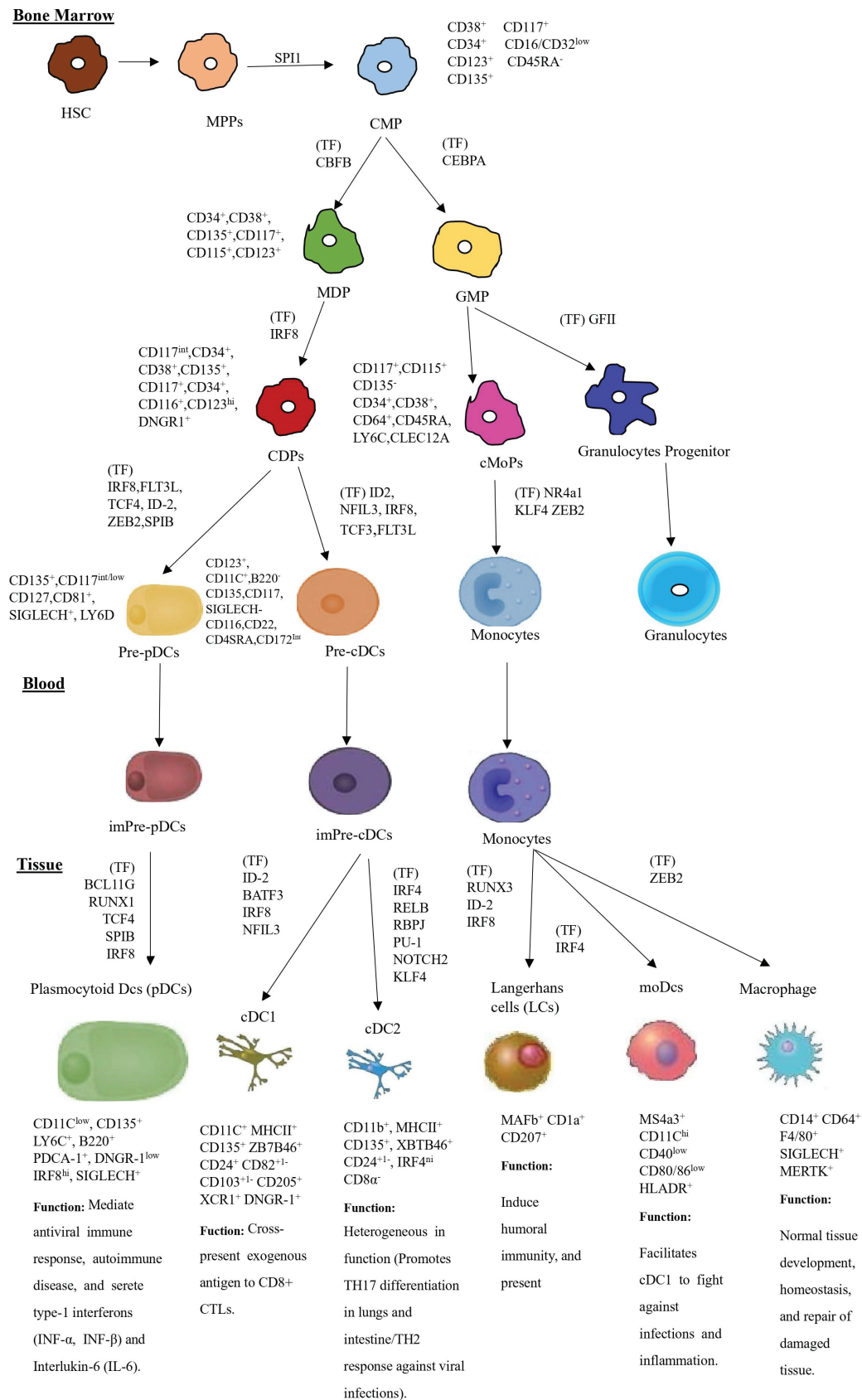


Fig 1. Continued

Fig 1. Development of DCs as an independent cell lineage showing transcriptional regulation, expression of prominent surface markers, and their functional characteristics. The illustration shows how common progenitors give rise to distinct fractions of DCs, monocytes, and macrophages. MPPs, which are produced from HSCs, go through stages of differentiation to create lineage-restricted progenitors of lymphocytes and myeloid cells, called CMPs. The CMPs are separated into two subsets such as MDPs and GMPs on the basis of *Cbfb* and *Cebpa* expression. Based on *GFI1* expression, GMPs are divided into two subsets such as cMoPs and granulocyte progenitors. The cMoPs further give rise to LCs, MoDCs, and macrophages, potentially based on the expression of *RUNX3*, *ID-2*, *IRF8* and *IRF4* and *ZEB2* expression, respectively. The specification of cDC1s and pDCs is correlated with a high level of *IRF8* expression from MDPs. On the other hand, cDC2s are correlated with a high level of *IRF4* expression. cDC1s, type 1 conventional DCs; cDC2s, type 2 conventional DCs; cDCs, conventional DC; cDPs, common dendritic cell progenitors; cMoPs, common monocyte progenitor; CMPs, common myeloid progenitors; DCs, dendritic cells; FLT3L, FAM-like tyrosine kinase 3 ligand; GMP, granulocyte-macrophage progenitor; HSCs, hematopoietic stem cells; IFN- α , interferon- α ; IFN- β , interferon- β ; IL-6, interleukin-6; LCs, Langerhans cells; MDPs, monocyte and dendritic cell progenitors; MoDCs, monocyte derived dendritic cells; MPPs, multipotent progenitors; pDCs, plasmacytoid DCs; TF, transcription factor.

primarily express the Toll-like receptors (TLRs), which promote innate immune response. The cDC2 cells also induce Th1, Th17 cell responses along with induction of the CD4⁺ T cell response (Cabeza-Cabrerizo et al. 2021; Yin et al. 2021). When exposed to pathogens, cDCs fully differentiate into two subtypes, CD11b⁻ and CD11b⁺, in the lymphoid tissues after migrating into the blood and nonlymphoid tissue in their juvenile stage (Figure 1) (Naik et al. 2006; Liu et al. 2009). In addition to this, a murine study, using methods such as fate mapping models, single-cell RNA sequencing, and adoptive transfer, has identified a specific lineage of DCs known as CD16/32⁺CD172a⁺ cDC3 cells. Importantly, they have found that cDC3 cells are distinct from cDC2 cells in terms of their development; they originate from Ly6C⁺ monocyte-derived DC progenitors and go through a developmental process involving Lyz2⁺Ly6C⁺CD11c⁻ pro-cDC3 cells. They also observed analogous DC subsets, developmental stages, and lineages in humans, which indicate that these findings have relevance beyond murine models (Liu et al. 2023). On the other hand, pDCs complete their development in the BM and travel through the blood to the lymphoid tissues (Reizis 2010; Shortman et al. 2013). Monocytes fully differentiate in the BM, just like pDCs, but when they enter lymphoid and non-lymphoid tissues and are guided by environmental signals, they can develop the features of DCs or M ϕ s (Shortman and Naik 2007; Mildner et al. 2013b; Poltorak and Schraml 2015). Figure 1 represents thoroughly the cell surface markers that distinguish the different DC cell subtypes derived through the developmental process, which have not been critically discussed earlier. Supplementary Tables 1 and 2 include the human DC phenotypes and mouse DC phenotypes, respectively, during pregnancy.

2.1. Cytokines influencing DCs development

Many cytokines are involved in the development of DCs from the progenitor cells. FAM-like tyrosine kinase 3 ligand (FLT3L) is a hematopoietic cytokine and a key regulator of these developmental processes, which are also regulated by several TFs (Poltorak and Schraml 2015). FLT3L activates hematopoietic progenitors to increase the number of

immune cells. It works by binding and activating the FAM-like tyrosine kinase 3 (FLT3) receptors, found on multipotent progenitor (MPP) and common lymphoid progenitor cells, as observed in mice (Shortman and Naik 2007). In fact, steady-state DC subsets were profoundly absent in mice lacking the *Flt3L* (McKenna et al. 2000) or *Flt3* gene (Waskow et al. 2008), but FLT3L exogenous supply increased both their diversity and number in mice (Ding et al. 2014) and humans (Anandasabapathy et al. 2015; Bhardwaj et al. 2016). Administration of FLT3L in humanized mice (mice reconstituted with human HSCs) showed an enhanced number of human CD141⁺ DC, CD1c⁺ DC, and to some extent pDC in the blood, spleen, and BM of humanized mice (Ding et al. 2014). In contrast to this, a study with Flt-3 ligand knockout mice showed the development of DCs independent of the endogenous Flt-3 ligand, and they exhibited the same phenotype as that of the steady-state spleen DCs (Fancke et al. 2008; O’Keeffe et al. 2010). FLT3L is essential for cDC1 and cDC2 subset development in both humans and mice (Merad et al. 2013). The TFs IRF8, Batf3, ID2, and Nfil3 are involved in the cDC1 development (Anderson et al. 2018), whereas IRF4 is a crucial TF for the development of the cDC2 subtype (Bajana et al. 2016). The monocyte-derived dendritic cells (MoDCs) are derived from monocyte precursors and the macrophage-colony stimulating factor (M-CSF) induce their development (Greter et al. 2012). The important regulators of MoDCs development (from monocytes) are PU.1, IRF4, aryl hydrocarbon receptor, NR4A3, and NCOR2 proteins; and the C-C motif chemokine receptor 2 (CCR2) protein is essential for the migration of monocytes from BM to the inflamed tissue regions and to the LNs (Yin et al. 2021). The TF TCF4 is essential for the development of pDCs, and other TFs such as IRF8, Bcl11a, Zeb2, and SpiB are also involved in the pDCs development (Reizis 2019). The development of Langerhans cells (LCs) is promoted by IL-34, M-CSF, and transforming growth factor (TGF)- β proteins, and FLT3L has no role in their development. The important regulators of LCs development are RUNX3, PU.1, and ID2 proteins (Kashem et al. 2017).

Granulocyte-macrophage colony-stimulating factor (GM-CSF) also plays a crucial role in supporting the survival

of DCs. Overexpression of GM-CSF in the spleen, thymus, and LNs enhanced the frequency of DCs, which highlights the role of GM-CSF in DCs proliferation (Vremec et al. 1997; Balan et al. 2019). In addition to this, interferon (IFN)- γ and tumor necrosis factor (TNF)- α are the other proinflammatory cytokines that can promote DC maturation by inducing the upregulation of major histocompatibility complex class II (MHC-II) and co-stimulatory molecules on DCs, which in turn enhances their ability to present antigens to T cells (Banchereau et al. 2000; Schroder et al. 2004).

2.2. MicroRNAs (miRNAs) influencing the DC development

MiRNAs play a crucial role in the regulation of DC development (Table 1). Differential miRNA expression has been observed throughout the murine DC developmental process, starting from HSC to matured DC (mDC) formation. Georgantas et al. identified the human HSC miRNA expression profile to better comprehend their function in hematopoiesis and DCs development. In CD34⁺ HSCs, they discovered 33 miRNAs that regulated several mRNAs involved in hematopoietic differentiation (Georgantas et al. 2007). Another study revealed that miR-155 expression is upregulated in human monocyte-derived DCs upon activation, which in turn targets and downregulates the expression of the suppressor of cytokine signaling (SOCS)-1, a negative regulator of the IL-1 signaling pathway. This regulation has direct implications for the immune response as it leads to the increased production of proinflammatory cytokines and the ability of DCs to communicate with other immune cells, suggesting intricate regulatory mechanisms involving miRNAs in DCs and their impact on immune function (Ceppi et al. 2009). Lu et al. (2011) have reported the increased expression of miR-221 and miR-155 in human DCs, suggesting their role in the regulation of different physiological functions of DCs. In addition, miR-221 is found to target and downregulate the expression of p27kip1 (a protein that inhibits cell cycle progression), which in turn promotes DC development and maturation. On the other hand, miR-155 targets and downregulates KPC1 (a protein

associated with apoptosis regulation) and inhibits apoptosis, promotes survival, and potentially enhances the function of DCs. A study has also revealed that miR-155 downregulates SOCS-1 and leads to increased IL-12 (an important cytokine involved in immune responses) production (Lu et al. 2011). The miR-155 also inhibits the pathogen-binding ability of DC-specific intracellular adhesion molecule-3 grabbing non-integrin during maturation (Martinez-Nunez et al. 2009). In another human study, it showed that a slight increase in miR-34a and miR-21 has been observed during the differentiation of monocytes into mature DCs, which in turn leads to the differentiation of DCs by targeting JAG1 and WNT1 (Hashimi et al. 2009). A differential miRNA expression study was performed in CD34⁺ CD38⁻ HSCs, where miR-520h and miR-129 revealed varying degrees of enhanced and decreased expression, respectively (Liao et al. 2008). The miR-520h was found to inhibit the expression of the gene for ATP-binding cassette subfamily G member 2 (ABCG2), which controls the differentiation of HSCs. On the other hand, genes encoding eukaryotic translation initiation factor 2C3 (EIF2C3, a crucial component of miRNA biogenesis) and calmodulin-binding transcription activator 1 (CAMTA1) (a TF involved in cell development) were found to be regulated by the miR-129 (Liao et al. 2008). Furthermore, a study showed differential expression of 391 miRNAs through Illumina sequencing during different stages of DC development (Su et al. 2013). This study identified substantial expression of miR-132 and miR-147 in immature and mDC, but not in HSCs (Su et al. 2013). In another study, miR-125b was found to be downregulated in committed progenitors despite being abundantly expressed in healthy HSCs. miR-125b can encourage HSC survival and growth because of its anti-apoptotic action. Bcl2 modifying factor (BMF) and Krueppel-like factor 13 (KLF13) are two pro-apoptotic targets whose mRNA expression levels are decreased, which causes this antiapoptotic action (Ooi et al. 2010).

CD4⁺ DC formation and maintenance have been linked to miR-142 expression (Mildner et al. 2013a). It is observed that miR-142 is strongly expressed in CD4⁺ DCs that are FLT3 dependent, but not in CD8a⁺ or CD4⁻ CD8a⁻ DCs. It is

Table 1. miRNA influencing DCs development

miRNA	Target	Role	References
miRNA-520h	ABCG2	HSCs differentiation	Liao et al. (2008)
miRNA-129	CAMTA1, EIF2C3	HSCs differentiation	Liao et al. (2008)
miRNA-125b	BMF and KLF13	HSCs survival and growth	Ooi et al. (2010)
miRNA-142	FLT3	Differentiation, development, maintenance of CD4 ⁺ DCs	Mildner et al. (2013a)
miRNA-146a	IRAK1, NFKB	pDCs survival	Karrich et al. (2013)

ABCG2, ATP-binding cassette subfamily G member 2; BMF, Bcl2 modifying factor; CAMTA1, Calmodulin-binding transcription activator 1; DCs, dendritic cells; EIF2C3, Eukaryotic translation initiation factor 2C, 3; FLT3, FAM-like tyrosine kinase 3; HSCs, Hematopoietic stem cells; IRAK1, IL-1 receptor-associated kinase 1; KLF13, Krueppel-like factor 13; miRNA, microRNA; NFKB, TLR-induced nuclear factor-kB; pDCs, plasmacytoid DCs.

also observed that a higher rate of CD4⁺ DC death caused a 60% decrease in Class II CD11c^{hi} DC in mice lacking miR-142. Moreover, in the presence of FLT3L, miR-142-deficient BM cells failed to differentiate into CD4⁺ DCs *in vitro*; however, there was no suppression of CD8a⁺ DC formation, which indicates that miR-142 plays an important role in DCs development and maintenance (Mildner et al. 2013a). The overexpression of miR-146a, another miRNA that has been demonstrated to alter pDC survival, led to apoptosis in a pDC cell line. This may be due to the fact that miR-146a down-regulates anti-apoptotic genes by targeting the IL-1 receptor-associated kinase 1 (IRAK1), which suppresses TLR-induced nuclear factor- κ B activity (Karrich et al. 2013).

A study in murine models has revealed that DC development from the HSC is promoted by the double-stranded RNA-specific endoribonuclease (DROSHA)-dependent cleavage of two mRNAs such as *Myf9* and *Todr1* mRNAs (Johanson et al. 2015). In this study, it was shown that the overexpression of *Myf9* and *Todr1* blocked the DC development, and their knockdown restored the DC development. Consistent with murine HSCs, DROSHA knockdown also hampered the differentiation of human HSCs, which proved that DROSHA plays a significant role in DC development, besides their involvement in miRNA biogenesis function (Gu et al. 2022). miRNAs have been identified in human hematopoietic lineage cells and thus their importance in DC development.

3. Subsets of DCs in Pregnancy

Generally, there are two types of DCs: migratory and resident. Both types can be found in both lymphoid and non-lymphoid tissues. The key distinction lies in their migratory ability, which is unique to migratory DCs. Unique TLRs, which are the pattern-recognition receptors, present in both classes allow them to detect the presence of pathogens and tissue injury. Recently, research has identified DCs with different phenotypes, morphologies, and functions. Lineage position, development status, tissue distribution, immunological function, or surface molecule expression could all be used to classify DC subgroups (Merad et al. 2013; Mildner and Jung 2014).

3.1. cDCs, pDCs, monocyte-derived DCs, and LCs

According to their lineage position, conventional DCs (cDCs, also known as myeloid DCs), pDCs (also known as lymphoid DCs), MoDCs, and LCs are the four subsets of DCs (Wei et al. 2021) (Table 2). Steinman and Cohn (1973) found the cDCs to constitute the vast majority of DCs. They are primarily responsible for capturing, processing, and delivering antigens to T cells, inducing immunological reactions against invasive infections, or enforcing self-tolerance (Pakalniškytė and Schraml 2017). The cDCs are classified into 2 classes,

i.e., cDC1 (effective in presenting antigens to CD8⁺ cytotoxic T lymphocytes [CTLs]) and cDC2 (with diverse functions like activation of naive CD4⁺ T cells and their polarization to Th2, Th17, Treg, and T follicular helper cells depending on the inflammatory state) (Tian et al. 2017; Anderson et al. 2021). The classification of cDCs into cDC1 and cDC2 is based on unique TFs responsible for their development. Both cDC1 and cDC2 encompass migratory and resident subsets; in other words, there are migratory cDC1 and cDC2, as well as resident cDC1 and cDC2. The distinction in their antigen-processing capabilities is instead rooted in the intrinsic differences between cDC1 and cDC2 rather than solely based on their migratory or resident subsets (Collin and Bigley 2018; Eisenbarth 2019; Ferris et al. 2020; Liu et al. 2022; Heger et al. 2023). In mice, cDC1s are typically identified by their characteristics, including being Lin[−]MHC-II⁺CD11c⁺CD8⁺ (referred to as resident cDC1s) or expressing CD103 (referred to as migratory cDC1s), while in humans, they are recognized as Lin[−]CD64[−]HLA-DR⁺CD141⁺ cells. Additionally, both human and mouse cDC1s commonly express XCR1, Clec9A, and CADM1 but in terms of their development, cDC1s rely on specific TFs, namely IRF8, Batf3, ID2, and Nfil3 (Yin et al. 2021). On the other hand, murine type 2 conventional DCs (cDC2s) are characterized as Lin[−]MHC-II⁺CD11c⁺CD11b⁺SIRPα⁺, while in humans, they are identified as Lin[−]HLA-DR⁺CD1c⁺SIRPα⁺ DCs (Yin et al. 2021). In addition to this, cDC2s show the heterogeneous expression of TFs. For example, fetal and adult gut cDC2 showed little to no expression of CD2 and FcR1 markers, while lung cDC2 from both the fetal and adult stages had increased levels of these two markers (McGovern et al. 2017). In response to viral infections, a small subset of DCs exhibit modest levels of MHC-II and costimulatory molecule expression, while secreting large amounts of IFN- α , and are known as pDCs (Swiecki and Colonna 2015; Bird 2017). Human pDCs are HLA-DR⁺CD11cCD4⁺BDCA2⁺BDCA4⁺CD123⁺ cells, while murine pDCs are MHC-II^{int}CD11c^{int}B220⁺Ly6C⁺BST2⁺Siglech⁺ cells (Yin et al. 2021). The MoDCs are extremely rare in homeostasis and are produced from blood monocytes under some inflammatory conditions like autoinflammatory diseases or infection-induced inflammation due to bacterial and viral infections (León et al. 2007; Domínguez and Ardaín 2010; Tang-Huau and Segura 2019; Marzaioli et al. 2020). As compared to the other three categories, LCs have a distinct embryonic genesis. They can come from either yolk sac macrophages or fetal liver monocytes. The LCs continue to serve as resident sentinels in the mucosa and epidermis, where they can gather antigen, travel to LNs, and mature into powerful immune-stimulatory cells (Kaplan 2010; Collin and Milne 2016).

The cDCs and pDCs that were discovered in the PB and decidua have received the most attention in studies on immunological changes during pregnancy (Darmochwal-Kolarz et

Table 2. DC subsets and their surface markers, and TFs regulating their differentiation and function

Subsets	Surface markers	TF regulating differentiation	Function	References
pDCs	CD11c ^{low} , SIGLECH ⁺ , CD135 ⁺ , CD4 ^{hi} , MHC-II ^{low} , LY6C ⁺ , B220 ⁺ , PDCA-1 ⁺ , DNGR-1 ^{low} , IRF8 ^{hi} , and IL3R ^{hi}	TCF4, BCL11a, RUNX1, SPIB, and IRF-8	Mediate antiviral immune response, autoimmune disease, and secrete type-1 interferons (IFN- α , IFN- β) and IL-6	Shortman et al. (2013), Poltorak and Schraml (2015), Tian et al. (2017), and Anderson et al. (2021)
cDC1	CD11c ⁺ , MHC-II ⁺ , CD135 ⁺ , CD24 ⁺ , ZBTB46 ⁺ , CD8 α ⁺ , CD205 ⁺ , XCR1 ⁺ , and DNGR-1 ⁺	ID-2, BATF3, IRF8, and NFIL3	Cross-present exogenous antigen to CD8 ⁺ CTLs	Shortman and Naik (2007), Poltorak and Schraml (2015), Pakalniškytė and Schraml (2017), Tian et al. (2017), and Anderson et al. (2021)
cDC2	CD11b ⁺ , MHC-II ⁺ , CD135 ⁺ , ZBTB46 ⁺ , CD24 ⁺ , IRF4 ^{hi} , and CD8 α	IRF4, RELB, RBPT, PU.1, NOTCH2, and KLF4	Heterogeneous in function (promotes Th17 differentiation in lungs and intestine/Th2 response against viral infections).	Shortman and Naik (2007), Poltorak and Schraml (2015), Pakalniškytė and Schraml (2017), Tian et al. (2017), Anderson et al. (2021), and Wei et al. (2021)
MoDCs	MS4a3 ⁺ , CD11c ^{hi} , CD40 ^{low} , CD80/86 ^{low} , and HLA-DR ⁺	IRF4	Facilitates cDC1 to fight against infections and inflammation	Domínguez and Ardavin (2010), Poltorak and Schraml (2015), Tian et al. (2017), Tang-Huau and Segura (2019), and Anderson et al. (2021)
LCs	MAFB ⁺ , CD1a ⁺ , and CD207 ⁺	RUNX3, ID2, and IRF8	Induce humoral immunity and present antigens to T cells	Kaplan (2010), Poltorak and Schraml (2015), Collin and Milne (2016), Tian et al. (2017), and Anderson et al. (2021)
mDCs	CD83 ⁺ , CD80 ^{hi} , CD40 ^{hi} , and MHC-II ⁺	ND	Produce IFN- γ , TNF- γ , and IL-15. Promote low NK cell proliferation	Peters et al. (1993), Lutz and Schuler (2002), Jeras et al. (2005), Bachy et al. (2008), and Hopkins and Connolly (2012)
imDCs	CD83 ⁻ , SIGN ⁺ , CD209 ⁺	ND	Promote angiogenesis and tolerogenic environment in decidua	Gardner and Moffett (2003), Kämmerer et al. (2003), and Kwan et al. (2014)
Circulatory DCs	ND	ND	Present antigens to T cells and induce humoral response	Merad et al. (2013) and Boltjes and Van Wijk (2014)
Migratory DCs	ND	ND	Present antigens to T cells	Broggi et al. (2013)
Resident DCs	ND	ND	Promote negative selection of T cells and present antigens to CD4 ⁺ T cells	Taglauer et al. (2010) and Zhou and Wu (2017)
Tolerogenic DCs	CD80 ⁺ , and CD86 ⁺	ND	Induce tolerance, Treg differentiation, and reduce T cell proliferation	Smits et al. (2005) and Hubo et al. (2013), Domogalla et al. (2017), and Takenaka and Quintana (2017)
Inflammatory DCs	HLA-DR ^{hi} , CD11c ^{hi} , BDCA1 ⁺ , CD1a ⁺ , CD14 ⁺ , CD172a ⁺ , MHC-II ^{hi} , LY6C, FCER1, CD64 ⁺ , CD107b, CD115, F4/80 ⁺	CCR2, and GM-CSF	Secrete IL-12, -23, -1a, and -1b, which in turn induce Th1 and Th2 response; play critical role in microbial infections	Butts et al. (2007), Poltorak and Schraml (2015), and Balan et al. (2019)

CCR2, C–C motif chemokine receptor 2; cDC, conventional DC; CTLs, cytotoxic T lymphocytes; DCs, dendritic cells; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN- α , interferons- α ; IFN- β , interferons- β ; IFN- γ , interferons- γ ; IL-15, interleukin-15; imDCs, immature DCs; LCs, Langerhans cells; mDCs, matured DCs; MHC-II, major histocompatibility complex class II; moDCs, Monocyte-derived DCs; ND, not defined; NK, natural killer, pDCs, plasmacytoid DCs; TFs, transcription factors, TNF- γ , tumor necrosis factor- γ .

al. 2003). It was observed that greater number of cDCs exist in the decidua of the pregnant women, as compared to that of pDCs (Miyazaki et al. 2003). Researchers have varied conclusions for cDCs and pDCs changes as they have chosen different stages of pregnancy and different surface markers (like MHC class II, CD11c, CD80, CD86 and programmed death-ligand 1 (PD-L1) for cDCs and CD123, CD303, CD304, TLR7 and TLR9 for pDCs). Most of the studies have concluded that there is a higher cDC/pDC ratio during pregnancy because of the increase in cDCs number, either with decrease in or stable number of the pDCs (Darmochwal-Kolarz et al. 2003; Gardner and Moffett 2003; Shin et al. 2009; Ehrentraut et al. 2019). The balance of cDC and pDC number is maintained by the increased secretion of human

chorionic gonadotropin (hCG) hormone during pregnancy (Sauss et al. 2018). In contrast to this, mouse studies have reported decrease in the cDC/pDC ratio throughout pregnancy (Zarnani et al. 2007; Li et al. 2018). Additionally, during pregnancy, there are differences in the surface molecule expression on cDCs and pDCs. There is decreased MHC-II expression to induce immune tolerance, as it can dampen T cell activation and upregulation of tolerogenic markers such as PD-L1 and indoleamine 2,3-dioxygenase (IDO) that in turn inhibit T cell responses and promote immune tolerance. There is reduction of IFN- α production and altered TLR expression in pDCs, suggesting that DC activities are modified in response to their tissue microenvironment (Saito et al. 2010; Svensson-Arvelund et al. 2017). As the pregnancy

progressed, Darmochwal-Kolarz et al. (2012, 2013) found that the expression of CD200, CD200R, B7-H1, and B7-H4 on both the cDCs and pDCs was higher in the first trimester than in the luteal phase of the ovarian cycle, peaked in the second trimester, and then decreased in the third trimester. These changes in the cDCs lead to the reduction in T cell specific antigen response along with increase in the number of CD4⁺CD25^{high}Foxp3⁺ Treg cells (Shah et al. 2017; Ehrentraut et al. 2019). However, the mechanism underlying these modulations needs further study.

Only a few studies have been done on MoDCs and LCs as compared to cDCs and pDCs during pregnancy. A preliminary analysis during the first trimester of pregnancy has shown that there is accumulation of MoDCs in the decidua but that a very less number is found in the blood (Ivanova et al. 2005). Monocytes from pregnant women differentiated into DCs that were less phenotypically developed and had lower levels of the molecules CD80, CD86, and HLA-DR than those from nonpregnant women. Additionally, when exposed to inflammatory stimuli, pregnant women's monocyte-derived DCs responded by upregulating CD86 more than CD80 and secreting more IL-10 rather than IL-12p70 compared to nonpregnant controls (Bachy et al. 2008). Human decidual stromal cells, which are present in the uterine lining during early pregnancy, were found to have a significant impact on the function of monocyte-derived DCs. Shao et al. (2020) have reported that the interaction between decidual stromal cells and DCs leads to functional re-programming of the DCs, resulting in altered DC behavior and function. It is suggested that the crosstalk between GM-CSF and IL-1 β is critical in mediating the functional changes observed in DCs, which in turn induces immune responses that are conducive to maternal-fetal tolerance and crucial for a successful pregnancy (Shao et al. 2020). On the other hand, the role of LCs during pregnancy has been ignored although they are present in the decidua because of their defensive function against the pathogens, which induce the immune responses rather than the immune tolerance (Puts et al. 1986; Morelli et al. 1992; de Jong and Geijtenbeek 2010).

3.2. Immature and mDCs

DCs are classified as immature DCs (imDCs) or mDCs depending on their maturity (Table 2). These two groupings were initially recognized as populations at two unique maturational stages in the context of cDCs (O'doherty et al. 1994). In the BM, HSCs produce imDCs, from where they migrate to the lymphoid organs through the blood and get matured (mDCs) when encounter the antigens. The mDCs show higher expression of CD80, CD86, and CD40 (key costimulatory molecules for T cells) along with the MHC-II, and can be distinguished from monocytes and imDCs by differential marker expression patterns (Peters et al. 1993; Lutz

and Schuler 2002; Jeras et al. 2005; Hopkins and Connolly 2012).

During pregnancy, both types of DCs are present in the decidua along with DC-SIGN⁺CD209⁺DCs, which show similar features of imDCs (Gardner and Moffett 2003; Kämmerer et al. 2003). It is observed that a huge number of imDCs are present in pregnant women decidua than the mDCs in comparison to the nonpregnant women (Aldebert et al. 2007; Bartmann et al. 2014). Similar observations were obtained in pregnant mice (Blois et al. 2004). Although imDCs in the uterus of mice fluctuated upward, downward, upward, mDCs fluctuated downward, upward, and downward during the 1st, 2nd, and 3rd trimesters of pregnancy (Blois et al. 2004; Gu et al. 2019). Human decidual DCs are more specifically divided into three classes by Kwan et al. (2014): imDCs, mDCs, and intermediate DCs, and they also observed that the number of intermediate DCs decreased in the second trimester as compared to the first trimester of pregnancy. The increased level of imDCs during pregnancy could be due to the halt in the developmental process of imDCs to mDCs (Kwan et al. 2014). The imDCs in the decidua have been found to promote an angiogenic and tolerogenic microenvironment. The mDCs in the decidua produce fewer cytokines including IFN- γ , TNF- α , and IL-15 and have a lower proliferative effect on NK cells than the imDCs (Bachy et al. 2008). In contrast to PB mDCs, decidual mDCs have a lower ability to generate IL-12 and elicit a Th2 response (type 2 immune responses secrete cytokines such as IL-4, IL-5, IL-10, and IL-13 to activate and maintain humoral or antibody-mediated immune responses against extracellular parasites, bacteria, allergens, and toxins) (Miyazaki et al. 2003). All these findings suggest that DCs' immune-stimulating activities are diminished in the decidua, which helps to maintain the fetomaternal tolerance.

3.3. Circulatory, migratory, and resident DCs

DCs are divided into three types based on their distribution: circulatory DCs in peripheral circulation/blood, migratory DCs in nonlymphoid tissues, and resident DCs, which live their entire lives in the lymphoid tissues (Table 2) (Merad et al. 2013; Boltjes and Van Wijk 2014; Wei et al. 2021). Circulatory DCs, including mDCs and pDCs, are typically characterized by surface markers such as CD11c, CD11b, CD33, CD1c for mDCs, and CD303 (BDCA-2) and CD304 (BDCA-4) for pDCs. They express higher levels of MHC class II molecules (which are essential for antigen presentation to T cells) and co-stimulatory molecules like CD40, CD80, CD86, and CD83. In addition, they often express chemokine receptor CCR7, which in turn enables their migration to LNs (Banchereau and Steinman 1998). In contrast to circulatory DCs, migratory DCs express tissue-specific markers depending on their location, such as langerin (CD207) or CD103 for DCs in the skin and gut, respectively. They also

express CCR7 to facilitate migration to LNs and MHC class II and co-stimulatory molecules for antigen presentation (Merad and Manz 2009; Ginhoux and Jung 2014). However, resident DCs within tissues express tissue-specific markers such as LCs in the skin expressing langerin (CD207), and intestinal DCs may express CD103. They are specialized for maintaining tolerance and may promote regulatory T cell responses. Expression of pattern recognition receptors (PRRs), like TLRs to detect local pathogens, has also been observed (Coombes and Powrie 2008; Reizis et al. 2011). It is found that the migratory DCs come in contact with the antigen, get activated, and travel to the LNs, where they present the antigens to the T cells (Broggi et al. 2013). While resident DCs in the secondary lymphoid organs carry out the antigen presentation function to CD4⁺ T cells, resident DCs in the central lymphoid organ carry out the negative selection of T cells that kills T cells with T cell receptors (TCRs), which in turn bind very strongly to MHC complexes and are likely to be self-reactive (Allenspach et al. 2008; Zhou and Wu 2017). Also, in contrast to circulating DCs and migrating DCs, variations in resident DCs throughout pregnancy have received less attention, despite the lymphoid organs being a key “hidden” maternal–fetal interface, and detailed study is required in this area (Taglauer et al. 2010).

3.4. Tolerogenic and inflammatory DCs

Based on how they function, DCs can be classified as tolerogenic (also known as regulatory) or inflammatory DCs (Table 2). Since they limit a particular immune response, tolerogenic DCs, which are found in tissues, promote tolerance (Steinman et al. 2003; Smits et al. 2005; Hubo et al. 2013; Domogalla et al. 2017; Takenaka and Quintana 2017). On the other hand, inflammatory DCs show their activity at the time of inflammation and enhance the immunity, by secreting various inflammatory cytokines, which help in clearing pathogens and tumor cells (Shortman and Naik 2007; Segura and Amigorena 2013).

It is hypothesized that during pregnancy, a huge number of tolerogenic DCs are present in the decidua, which help to maintain tolerance at the maternal–fetal interface. Various evidences are found in this favor including the fact that progesterone treatment in a dose-dependent way inhibits DCs' ability to release the pro-inflammatory cytokines TNF- α and IL-1 β . IL-10, a cytokine that suppresses an inflammatory response, however, was unaffected. In addition to this, progesterone treatment reduced the expression of the co-stimulatory molecule CD80 as well as the MHC class II molecule RT1B, and stopped proliferation of T cells, in response to DC stimulation (Butts et al. 2007). Some fetal components also promote tolerogenic DC functions by the inhibition of TNF- α , C-X-C Motif Chemokine Ligand (CXCL) 10, CXCL9, and C-C Motif Chemokine Ligand 5 (CCL5) (inflammatory

cytokines) secretion by the amniotic mesenchymal tissue cells (Magatti et al. 2009; Abomaray et al. 2015). On the contrary, studies also indicate the presence of inflammatory DCs in the decidua during normal pregnancy, and they play a vital role in the implantation of the embryo (Krey et al. 2008; Plaks et al. 2008). Hence, pregnancy is a dynamic event with delicate regulation of both tolerogenic and inflammatory DCs for successful pregnancy (Segeer et al. 2012).

4. Interaction of DCs with Other Immune Cells During Pregnancy

DCs present antigen to T cells and play an important role in immune response activation, polarization, and control (Kwiatek et al. 2015). Besides the role of DCs as APCs, they are also engaged in the interactions with other immune cells at the maternal–fetal interface, including NK cells, T cells, and M ϕ s to induce immune modulatory activities (Laškarin et al. 2007; Tagliani et al. 2011).

4.1. DCs and NK cells interaction

Normal human decidua has abundant CD45⁺ immunocompetent leukocyte subpopulations in the first trimester of pregnancy, which include primarily CD3⁺ CD16⁺ CD56^{bright++} NK cells, T cells, and APCs, allowing for appropriate cellular interactions (Rukavina et al. 1995; Juretic et al. 2004). Throughout pregnancy, there is continual reciprocal crosstalk between DCs and NK cells in the decidua, either directly through cell-to-cell contact or indirectly through cytokine production. In a study, the majority (about 60%) of decidual imDCs have been found to be in intimate interaction with uterine NK cells at the maternal–fetal interface during pregnancy, which suggests the pregnancy-specific interactions of imDCs with NK cells (Kämmerer et al. 2003; Tirado-González et al. 2012). A delicate balance is maintained between the activating and inhibitory signals by the DC–NK cell interaction, to achieve a tolerogenic environment for the semi-allogenic fetus and maintaining the immune-activation state required for protection against pathogens. The mDCs are found to produce the IL-15 cytokine, which recruits the NK cells in decidua and further induce their proliferation and IFN- γ production. Both the IL-15 and IL-15R α (present in the cell surface of imDCs) are involved in NK cell recruitment and proliferation (Ferlazzo et al. 2004). The imDCs induce the release of IFN- γ from decidual NK cells, and these IFN- γ further promote the production of IDO from DCs. The IDO molecules in turn induce the production of Treg cells and thus create a tolerogenic environment (Terness et al. 2007; Vacca et al. 2010). Moreover, the IL-10 produced by decidual natural killer (dNK) cells blocks the maturation of imDCs and thus protects the trophoblast cells from the mDC-driven cytotoxic T-cell responses (Dietl et al. 2006). Besides, dNK cell-produced IL-10 also inhibits

the DC function and induces the Th-2 cytokine production. This physiological state prevents the NK cell-driven cytotoxic effects on trophoblast cells (Leno-Durán et al. 2014). An *in vitro* study has revealed that when CD56⁺ NK cells were co-cultured with imDCs, only one-third of them grew, which suggests that imDCs control the proliferation of NK cells (Juretic et al. 2004; Laškarin et al. 2008). Decidual CD56^{bright} cells had lesser number of NKG2D-activating receptors on their surface after being co-cultured with autologous mDCs, which binds the MICA/B and HLA class I chain-related proteins A and B produced on trophoblast cells (Mincheva-Nilsson et al. 2006). The expression of NKG2A, an inhibitory receptor that is expressed on both T and NK cells and forms a heterodimer with CD94, increased in the decidual CD56^{bright} cell subpopulation under the same conditions. While NKG2C, an activating receptor that CD94 interacts with and forms dimers with, decreased in the CD56^{dim} cell subpopulation, and can bind to HLA-E to cause NK cells to activate (Laškarin et al. 2007). A study has reported that the DC–NK conjugation leads the imDCs to display an apoptotic cell like shape in human decidua, suggesting that NK cells influence the phenotype of DC population (Tirado-González et al. 2012). Karsten et al. (2009) discovered that the implantation sites lacking DCs have lower mRNA and protein levels of IL-15 and IL-12, due to the indirect interaction between DCs and NK cells that is mediated by cytokines, resulting in decreased NK cell frequency, size, and IFN- γ expression. This suggests that DCs in the pregnant uterus serve as a source of IL-15 and IL-12 (Karsten et al. 2009). Altogether, these evidences suggest that DCs play an important role during pregnancy in regulating NK cell function and vice versa, for successful pregnancy.

4.2. DCs and T cells interaction

The immune system's most potent APCs, DCs can cause naive T cells to grow into a variety of subsets, including Th1 (secrete IFN- γ and TNF- α), Th2 (secrete IL-4, IL-5, and IL-13), Th17 (secrete IL-17), and Treg cells (secrete IL-10 and TGF- β) (Zhu and Paul 2008). Saito et al. (2010) revealed that maternal–fetal tolerance is due to a shift from the immunologically active Th1/Th17 predominance to the immune tolerant Th2/Treg predominance, with DCs playing a crucial role in appropriately driving the T cell subpopulation (Saito et al. 2010). It is observed that during pregnancy, DCs promote the T cell polarization toward Tregs and Th2 cells by secreting cytokines like IL-10 and TGF- β , and express co-stimulatory molecules like CD80 and CD86, which, when engaged with TCRs, can guide T cell differentiation. The Th2 response generates an anti-inflammatory microenvironment by promoting the production of cytokines like IL-4, IL-5, and IL-10. This anti-inflammatory environment helps prevent harmful inflammation that could jeopardize the pregnancy (Saito et al. 2010). A study in mouse showed that the Th1/Th2 balance is linked

to the specific type of DC subtypes, i.e., DEC-205⁺ DCs that are responsible for the polarization of Th1 and 33D1⁺ DCs responsible for the induction of Th2 dominance (Negishi et al. 2012). The alteration in DC subtypes indicated that Th1 was diminished throughout pregnancy unless they were required for delivery. On the other hand, it has been observed that in comparison to peripheral cDCs, cDCs in human decidua generated a higher percentage of Th2 cells and secreted less IL-12, suggesting the influence of the microenvironment on cDCs to elicit either a Th1 or a Th2 response (Miyazaki et al. 2003). Decidual CD4⁺CD25⁺ T cells are encouraged to multiply and differentiate into CD4⁺CD25⁺FOXP3⁺ regulatory T cells (Tregs) by thymic stromal lymphopoietin-activated decidual DCs through the action of TGF-1. By secreting cytokines of the Th2 subtype, promoting the invasiveness of trophoblasts and the expression of HLA-G, and reducing the cytotoxicity of CD56^{bright} CD16 NK cells, these newly produced Treg cells demonstrate immunosuppressive features (Du et al. 2014). DCs can upregulate $\alpha\beta$ ⁺ T cells in addition to their impact on CD4⁺ $\alpha\beta$ ⁺ T cells, which have been demonstrated to inhibit the immune response during pregnancy (Szekeres-Bartho et al. 1999; Miranda et al. 2006). In addition, it has been reported that fetal DCs release the enzyme arginase-2, which effectively suppresses the activation and proliferation of T cells by depleting the level of essential amino acid arginine. This immune suppression maintains the tolerogenic environment in the developing fetus (McGovern et al. 2017).

4.3. DCs and macrophages interaction

The DCs and M ϕ s bear several phenotypic characteristics in common; hence, it is difficult to characterize them with distinct phenotypes. DCs and M ϕ s share several morphological and functional traits as well as monocytic origin (Le Gars et al. 2016). The main APCs at the maternal–fetal interface are M ϕ s and DCs, which have complementary immune regulatory functions, due to the lack of B cells in decidua as APCs (Iijima et al. 2008). They are essential for decidualization and implantation as they secrete various cytokines, chemokines, and enzymes, which target the luminal epithelium and play a role in tissue remodeling, angiogenesis, and the development of endometrial receptivity (Jena et al. 2019). The cytokines IL-1 β and TNF- α stimulate the synthesis of chemokines, which recruit M ϕ s and DCs in the first trimester via the NF- κ B and MAPK pathways, resulting in the buildup of DCs and M ϕ s in decidua. The chemokine CCL2 is the major chemoattractant for M ϕ s, whereas CCL5 is the predominant chemoattractant for imDCs (Li et al. 2011). Besides, M-CSF affects M ϕ s and DC-cell migration into decidua in a CCR2-independent way (Tagliani et al. 2011). Intriguingly, decidual M ϕ s were found to differentiate into DC-like cells with immunosuppressive properties in the second trimester of pregnancy, but into DC-like

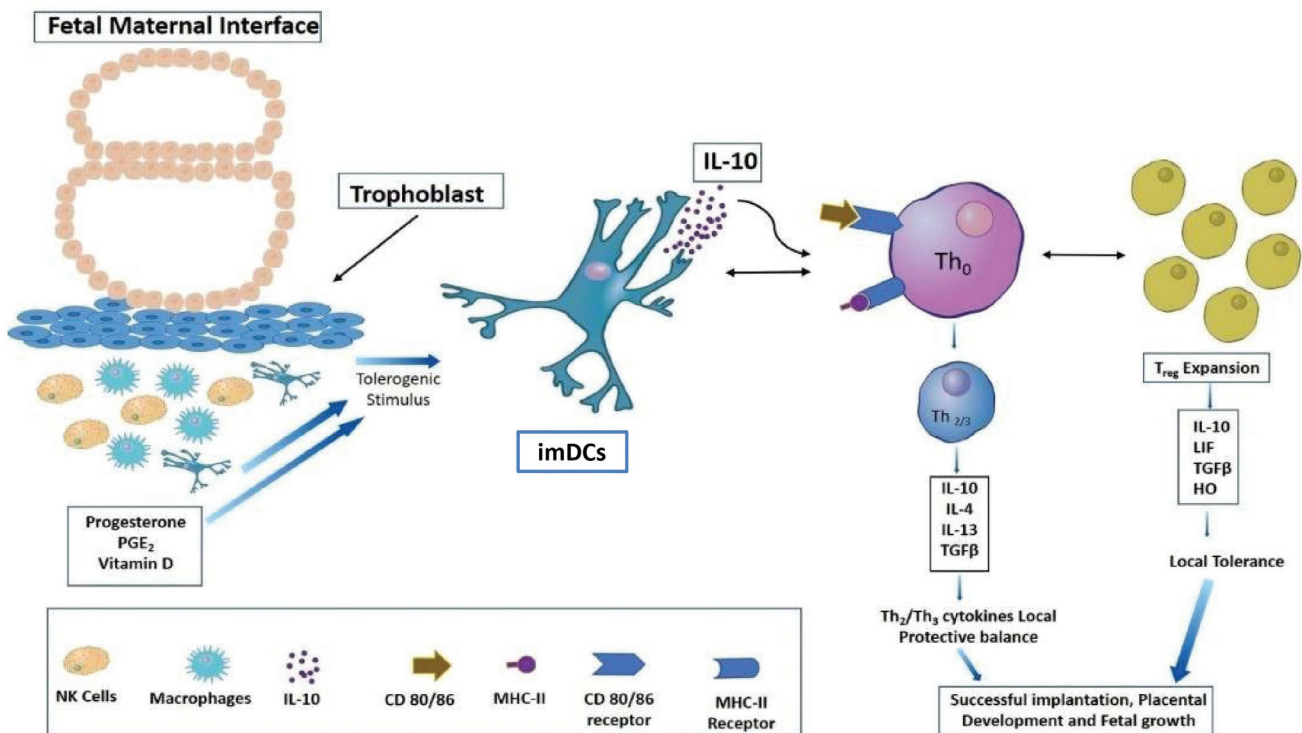


Fig 2. Flowchart illustrating the regulation of immune responses to the conceptus by DCs. During a typical pregnancy, tolerogenic stimuli such as trophoblasts, progesterone, PGE₂, vitamin D, and environmental cells (such as NK cells and Mφs) encourage partial activation of the local DC. As a result, anti-inflammatory cytokines (like IL-10) are produced, which encourages the induction of tolerance at the maternal–fetal interface by activating a number of mechanisms like the production of pregnancy-protective Th₂/Th₃ cytokines and the development of Treg cells, which improve immune system suppression and thereby support fetal tolerance. DC, dendritic cell; imDCs: immature DCs; MHC-II, major histocompatibility complex class II; NK, natural killer; PGE₂, prostaglandin E₂; TGF-β, transforming growth factor-β.

cells with immunostimulatory properties in the third trimester, indicating a switch from maternal–fetal immune tolerance to the maternal–fetal immune rejection state (Wang et al. 2016). The two subsets of Mφs could be immunosuppressive M-2 and immune active M-1, based on their cytokine repertoire and functions (Mills et al. 2000). The M-1 Mφs are proinflammatory in nature, which is triggered by pathogen (lipopolysaccharide [LPS]) exposure and tissue damage caused by IFN and TNF proteins (Martinez et al. 2008; Jena et al. 2019). These Mφs upregulate the level of enzyme-inducible nitric oxide synthase, which subsequently produce the nitric oxide from arginine, besides their role in reactive oxygen species production. In contrast to this, Th₂ cytokines like IL-4 and IL-13, as well as anti-inflammatory IL-10, apoptotic cells, and M-CSF, all induce M-2 Mφs formation, which are anti-inflammatory in nature (Figure 2) (Mantovani et al. 2004). The uterine DCs (uDCs) fine-tune decidual angiogenesis by supplying two key factors, soluble Flt1 (sFlt1) and TGF-β₁, which enhance coordinated blood vessel formation. Regardless of their projected role in immunological tolerance, uDCs appear to regulate tissue remodeling and angiogenesis and promote uterine receptivity (Lee et al. 2011).

4.4. DCs and trophoblast cells interaction

The intricate interplay between DCs and trophoblast cells stands as a critical component of the immune tolerance mechanism that underpins the success of implantation and pregnancy. The interaction of DCs with invading trophoblast cells are multifaceted and dynamic, with the goal of establishing maternal immune tolerance to the semi-allogenic fetal tissues. Key molecules and mechanisms have been elucidated in this context. Salamone et al. (2012) studied the effect of trophoblast cells on the functional profile of DCs and observed that trophoblasts induce a tolerogenic DC population at the maternal–fetal interface. The trophoblasts significantly reduced the production of IL-12p70 and TNF-α, while they enhanced the IL-10 production. The co-culture of DCs and trophoblast cells revealed the suppression of the LPS-stimulated allogenic response. The conditioned DCs enhanced the frequency of CD4⁺ CD25⁺ Foxp3 cells, which further induced enhanced IDO expression in the DCs and thus a tolerogenic environment is created (Salamone et al. 2012). In addition, other studies have further worked on the immune regulatory functions of DCs, emphasizing their

capacity to organize a microenvironment conducive to fetal development and immune homeostasis. These interactions extend beyond mere immune suppression, involving cytokines, antigen presentation, and immunomodulatory molecules (Wei et al. 2021). The crosstalk between DCs and trophoblast cells is a dynamic process, integral to the intricate balancing act that allows the maternal immune system to protect against threats while simultaneously permitting the growth and development of the fetus (Kammerer et al. 2008). A comprehensive understanding of these interactions is pivotal not only for advancing our knowledge of the immunological aspects of pregnancy but also for devising novel therapeutic strategies for complications arising from immune dysregulation during gestation. A study has revealed that a significant number of DCs become trapped within the uterine tissues during pregnancy, particularly in the myometrium (muscular wall of the uterus) and decidua. This entrapment is a unique feature of pregnancy and hinders DCs' ability to effectively patrol and monitor the maternal–fetal interface. As a result, there is a decreased capacity for immune surveillance in this critical area during pregnancy. This altered presence and function of DCs at the maternal–fetal interface influence the activation and regulation of T cell responses, which has implications for maintaining immune tolerance and preventing the rejection of the developing fetus (Collins et al. 2009).

5. Endocrine System Influencing DCs During Pregnancy

Immuno-endocrine crosstalk must be balanced and properly controlled for a healthy pregnancy. Progesterone and estrogen (E2) levels increase 5–10 times during pregnancy, and progesterone levels in the human placenta can be 10–100 times greater than those in serum. For the fetus to be tolerated during pregnancy, progesterone most likely plays a role in the normal lowering of cell-mediated immunity that takes place during pregnancy (Blois et al. 2007). Additionally, it has been observed that at the maternal–fetal interface, progesterone, placenta-secreted estrogen, and chorionic trophoblast-released hCG hormone take part in the differentiation, maturation, and regulation of the function of DCs. When progesterone was added to the culture media for DCs, TNF- α expression was reduced, while the synthesis of Th2-skewing cytokines such as IL-10 was enhanced. This suggests that progesterone keeps DCs in an immature condition for immunological tolerance during pregnancy (Liang et al. 2006; Xu et al. 2011; Pomeroy et al. 2016). E2 also regulates DC development as it was observed that nonsteroidal E2-antagonists prevent human monocyte-derived DCs from differentiating into functional DCs (Komi and Lassila 2000). The DCs were inhibited by the higher level of E2, which led to a decrease in the TNF- α , IL-12,

IFN- γ , and IL1 β secretion at the maternal–fetal interface (Liu et al. 2002). The E2-mediated ER signaling may reduce the number of CMPs, resulting in fewer CMP-derived DCs, and influence immunological activity during pregnancy (Kovats 2012). E2 greatly stimulates the production of IL-10 in both immature and mature DCs at the concentration found in pregnant women's sera (10ng/ml), and progesterone exhibits a similar effect at the same concentration (Huck et al. 2005). Higher concentrations of E2 increased CCL2/MCP-1 synthesis *in vitro*, while progesterone has the reverse effect (Hughes and Clark 2007). It is observed that the pregnancy hormone hCG promotes the production of tolerogenic DCs by inducing IDO (a rate-limiting enzyme for tryptophan breakdown) production in DCs. Since tryptophan is a necessary amino acid for T cell proliferation, IDO-expressing DCs deplete the local tryptophan supply to cause T cells to go into anergy and stop proliferating, which prevents allograft rejection (Schumacher 2017; Schumacher et al. 2017). Besides, Dauven et al. (2016) studied the direct effect of recombinant hCG (rhCG) in murines and concluded that rhCG promotes tolerance to prevent fetal rejection during pregnancy by keeping DCs in an immature state and increasing the Treg cell number (Dauven et al. 2016). It has also been found that in PB DCs, hCG is not a major regulator of cellular changes. But the tolerance maintenance may be aided by the fact that in inflammatory conditions, hCG appears to maintain the delicate balance between pDC and myeloid DC and maintains a tolerogenic myeloid DC profile (Sauss et al. 2018). However, given that hCG affects DC proliferation and the fact that the regulatory immunological mechanisms required for successful reproduction are incredibly complicated, it is obvious that pregnancy loss is caused by a complex failure of immune adaption rather than by a single factor. High amounts of stress may cause this immunological adaption to fail in both mice and humans. Numerous studies have demonstrated that the absolute number and relative proportions of leukocytes in the blood are significantly altered by stress and stress hormones (Dhabhar 2008). There have been reports of stress-related changes in blood leukocyte counts in fish (Pickford et al. 1971), hamsters (Bilbo et al. 2002), mice (Kammerer et al. 2008), rats (Dhabhar et al. 1996; Rinder 1997), and humans (Bosch 2003; Redwine 2004). Studies have also demonstrated that the hormones glucocorticoids (Fauci and Dale 1974, 1975; Dhabhar et al. 1996) and catecholamines (Benschop 1993; Carlson et al. 1997; Mills 2001; Redwine 2003) significantly alter leukocyte distribution and are the primary mediators of the effects of stress.

Intense study is being done on the maturation, migration, and expression of stimulatory and co-stimulatory molecules on DCs in the setting of reproduction because the uDCs may serve as a relay between fetal rejection and tolerance. The endogenous control of DC activity has also been better

understood as a result of stress challenge during early pregnancy in mice. This is because exposure to experimental stressors like sound increased the number of mature APCs. By inhibiting important ligands that mature DCs need in order to trigger T cell activation, mechanisms of fetal tolerance in stress-affected pregnancies are restored (Blois et al. 2005). The adrenal hormone corticosterone (CORT) is produced in higher concentrations during a stress response. CORT, acting through the glucocorticoid receptor, has been found to functionally impede DC maturation, shedding light on the mechanism of stress-associated immunosuppression (Elftman et al. 2007). It is now known that additional stress perception mediators cause a strong inflammatory response, which may therefore result in fetal mortality or poor fetal development. On the contrary, the neuropeptide known as vasoactive intestinal peptide (VIP), which has potent anti-inflammatory properties, is of interest because they decrease in mucosal tissue in response to stress in rats and affect the early stages of DC differentiation and produce immature DCs in response to inflammatory stimuli (Chorny et al. 2006; Shen et al. 2006). VIP plays a crucial role in the control of murine embryonic development, even though it is yet unknown whether stress perception impacts VIP expression and DC phenotype at the maternal–fetal interface (Spong et al. 1999).

6. Association of DCs in Pregnancy Complications

As DCs play an important role during pregnancy to maintain the immune tolerance at the maternal–fetal interface, any abnormality in function of the same may lead to the rejection of the fetus and to various pregnancy complications such as recurrent spontaneous miscarriage, PE, or PTB. This section is focused on how the abnormal function of DCs leads to the pregnancy complications.

6.1. DCs in RSA and implantation failure

“Recurrent spontaneous abortion (RSA) is defined as three or more consecutive pregnancy losses of clinically recognized pregnancies” (El Hachem et al. 2017). Although aberrant chromosomes, endocrinological diseases, and uterine abnormalities were known causes in around half of the instances, the etiology of the other half remains unexplained (Garrido-Gimenez and Alijotas-Reig 2015). In RSA mice, the proportion of cDCs (CD11c⁺B220⁻) was significantly higher, whereas the proportion of pDCs (CD11c⁺B220⁺) and the pDC/cDC ratio were much lower than in the normal pregnant group. Similar findings were observed in humans as well suggesting that the cDCs may play role in RSA, but the mechanism is unknown (Lai et al. 2022). Askelund et al. (2004) were the first to show that mDCs in decidua from women with RSA at 8 weeks’ gestation are higher than in normal controls of

the same gestational age, implying that DCs are implicated in the etiology of RSA (Askelund et al. 2004). In addition, Qian et al. (2015) reported a decrease in imDCs in RSA, as well as an increase in mDCs. These data supported the idea that DC immaturity promotes pregnancy and that DC maturation at an unsuitable time may play a role in RSA pathogenesis (Qian et al. 2015).

Additionally, the uDCs have been linked to a critical developmental function in modulating interactions between the uterus and the embryo during the peri-implantation period (Krey et al. 2008; Plaks et al. 2008). These studies utilized CD11c-DTR transgenic mice, where the CD11c promoter controls the expression of the diphtheria toxin receptor (DTR). This genetic setup makes cells expressing CD11c susceptible to acute removal when exposed to diphtheria toxin (Jung et al. 2002). In the study by Plaks et al. (2008), they conducted a controlled removal of uDCs just before the process of embryo implantation on day 3.5 of embryonic development (E3.5). This removal led to pregnancy failure due to its impact on both the attachment of the embryo to the uterine wall (implantation) and the formation of the decidual tissue (Plaks et al. 2008). The latter effect resulted from impaired growth and transformation of the cells in the uterine lining (endometrial stromal cells). It also involved problems with the development of blood vessels in the uterine tissue, marked by increased permeability of blood vessels and incomplete vessel maturation. These observations were linked to reduced levels of two important factors in the uterus: TGF- β 1, a growth factor, and sFlt1, a protein that acts as a decoy receptor for vascular endothelial growth factor-A (VEGF-A), counteracting the ill-effects of the excess proangiogenic factor VEGF-A. The uDCs themselves contained measurable amounts of sFlt-1, suggesting that these cells might have a role in regulating local concentrations of VEGF-A. Additionally, the authors found that removing DCs after the implantation phase on day 5.5 of murine embryonic development (E5.5) had no impact on the formation of decidual tissue or the survival of the developing embryos. This indicates that uDCs were specifically necessary during the critical period when the embryo attaches to the uterine lining in the implantation process.

Maternal hormones were also sought to identify the processes underlying the DC aberrations in RSA. According to the findings of the studies on spontaneous abortion, progesterone had greater impact on abortion than hCG (Negishi et al. 2012; Ehrentauf et al. 2019). Progesterone inhibited cDCs’ ability to induce NK cell proliferation and secrete IL-15, resulting in human abortion. It was hypothesized that progesterone-shaped DCs cannot efficiently multiply or equip NK cells with the cytotoxic mediators perforin and granulysin during DC/NK cell interaction, which may harm trophoblasts and induce abortion (Laskarin et al. 2018). However, in DBA/2 J-mated CBA/J abortion-prone mice, a substantial

rise in the uterine Treg cell pool was induced by progesterone administration, and the rate of abortion was unaffected. Furthermore, following the application of progesterone, there were no distinct changes in peripheral Treg cell numbers or DC counts. It implied that in this impaired fetal tolerance, progesterone-induced local Treg cell number increase is not adequate to overcome fetal rejection (Schumacher et al. 2017). Hence, progesterone and its influence on DCs might not be enough to account for fetal rejections in RSA. Hence, this aspect needs to be explored further.

6.2. DCs and PE

High blood pressure, proteinuria, and symptoms of damage to organ system (most commonly the liver and kidneys) describe the PE, which is a serious pregnancy complication (Mol et al. 2016). Assessment of the blood vessels in the fetal membranes and the basal plate extravillous trophoblasts (EVTs) (located in the decidua basalis, which is the maternal surface of the placental disc) has unveiled indications that PE may be linked to irregularities in the differentiation, restructuring of blood vessels, and invasion by EVT. These abnormalities appear to be more pronounced in cases of pre-term births and severe forms of pre-eclampsia (Benirschke et al. 2012; Redline et al. 2018). There can be decidual vasculopathy, which is marked by the enlargement and excess growth of the muscular layer in the arterioles of the decidua, as well as the presence of chronic inflammation around these blood vessels, fibrinoid necrosis, and/or the infiltration of foamy macrophages. When decidual vasculopathy is observed alongside the occurrence of multifocal infarctions in the placenta of pregnancies affected by PE or fetal growth restriction (FGR), it strongly indicates a malfunction in the endovascular function of EVTs. This malfunction leads to an insufficient maternal blood supply to the placenta (Redline et al. 2018). Further understanding of the differentiation and performance of EVTs has been gained through placental bed biopsies conducted for research after childbirth. These investigations have indicated that there is restricted alteration of blood vessel structure in both PE and FGR placenta (Farah et al. 2020). More recently, there have been advances in identifying and characterizing specific markers that distinguish between different subtypes of differentiated EVTs in the context of PE. One such example is PLAC8, which has been pinpointed as a marker specific to interstitial EVT. PLAC8 is a protein associated with actin that enhances the migration and invasion abilities of these cells by activating RAC1 and CDC42. Interestingly, in PE placenta, there was an observed increase in the expression of PLAC8 in interstitial EVT. This upregulation is speculated to be a compensatory response to the shallower invasion of these cells in cases of PE (Chang et al. 2018). Another marker is leukocyte-associated immunoglobulin-like receptor 2 (LAIR2), which appears to be specific

to endovascular and vascular plug EVT (Founds et al. 2013). Notably, LAIR2 levels were found to be reduced in chorionic villus samples from placenta associated with the development of PE later in pregnancy (Founds et al. 2009).

Research findings have revealed that PE is a Th1/Th2 immune disorder characterized by a strong Th1 response leading to the inflammatory state, and DCs are considered to play a crucial role in PE by regulating the Th1/Th2 response (Darmochwal-Kolarz 2005). Moreover, it has been observed that after phagocytosis of necrotic and aponecrotic trophoblasts, DCs release type-I cytokines such as TNF- α , IL-12, and IFN- γ , which increase inflammation, leading to apoptosis of extra villous trophoblasts and impaired placentation, as seen in PE (Huppertz et al. 2003; Jena et al. 2019). Some studies have observed the elevated level of DC-recruiting chemokine in the decidua of PE patients, such as GM-CSF, suggesting the accumulation of more DCs in the uterus of PE patients than in controls (Huang et al. 2008, 2010). Also, in PE patients, higher percentage of cDCs, a higher mDC/pDC ratio, and a lower percentage of pDCs have been observed than in normal pregnant individuals (Darmochwal-Kolarz et al. 2003; Wang et al. 2013; Li et al. 2019). These alterations in DC population are linked to a higher number of Th1 cells and a lower number of Th17 cells (Wang et al. 2013). *In vitro* studies confirmed that DCs generated from PE patients' PB mononuclear cells had a greater potential to trigger CD4⁺ T cells to differentiate into Th1/Th17 cells (Wang et al. 2014). Altogether, these findings suggest that altered DCs differentiation and function have a potential role in PE pathogenesis.

6.3. DCs and PTB

PTB is also known as premature birth that occurs before the 37th week of pregnancy and refers to the termination of pregnancy before term (Goldenberg et al. 2008). Infections or physiological factors may be responsible for the inflammation that occurs in PTB (Goldenberg et al. 2008; Cappelletti et al. 2016). In addition to this, genetic predisposition and environmental factors such as stress can influence immune responses during pregnancy. Variations in immune-related gene expression have been associated with increased susceptibility to PTB (Wadhwa et al. 2001). Systemic immune factors, such as maternal infections and inflammation, can impact the risk of PTB. For instance, infections, including urinary tract infections and periodontal disease, have been linked to an increased risk of PTB (Goldenberg et al. 2008). Systemic inflammation, as evidenced by elevated levels of C-reactive protein and other markers, has also been associated with PTB. Research has shown that an imbalance in local immune factors, increased inflammation, and altered immune cell populations can contribute to the onset of PTB (Menon 2016). Aberrant cytokine profiles, including elevated levels of proinflammatory cytokines like IL-1 β and TNF- α ,

have been associated with PTB (Keelan et al. 2003). The lowered expression of the anti-inflammatory cytokine IL-10 (a putative early indicator of preterm delivery) in immature DCs suggests that these cells may play a role in the genesis of premature labor (Ruiz et al. 2012). In addition to this, uDC activation was also observed in the LPS-treated PTB mouse model, a paradigm that mimics infections, suggesting that DCs are implicated in the induction of labor (Bizargity et al. 2009). In TLR4-deficient female mice, longer gestation length was linked to fewer DCs and more Treg cells in the myometrium, leading some to hypothesize that DC activation in infection-related PTB was a downstream effect of TLR4 (Wahid et al. 2015). Another prevalent cause of PTB is acute chorioamnionitis (ACAM), a physiological state of inflammation. A human pregnancy study has revealed that DCs derived from ACAM women selectively promote the growth of the T cell subset invariant natural killer T cells (iNKT) cells (Negishi et al. 2017). Further *in vitro* research showed that decidual iNKT cells co-cultured with LPS-pulsed DCs exhibited considerably decreased extracellular and intracellular IFN- γ production, as well as lower surface expression of CD69 (Li et al. 2015). These results demonstrated that PTB affected the interaction between DCs and NK cells. In addition to this, numerous studies have shown that PTB is associated with heightened inflammatory responses in the maternal–fetal interface. Increased levels of proinflammatory cytokines, such as IL-6 and TNF- α , have been observed in the cervicovaginal fluid and placental tissues of women at risk for PTB, suggesting that PTB is due to a loss of tolerance (including DC) or inability to mount a required immune response (Romero et al. 1994).

7. DCs as a Therapeutic Target in Pregnancy Complications

DCs play an important role in healthy pregnancy, and a little disruption in their differentiation or function leads to the pregnancy-related complications. DCs can be used as a prospective therapeutic target to manage pregnancy disorders. Rapamycin, baicalin, mesenchymal stem cells (MSCs), and heme oxygenase-1 have been found to lower abortion rates in human and mouse models via modifying the DC population (Hackstein et al. 2003; Askelund et al. 2004; Schumacher et al. 2017; Eskandarian and Moazzeni 2019). It has been demonstrated in mice models that baicalin can successfully treat RSA by increasing the amount of pDCs and decreasing the number of cDCs (Darmochwal-Kolarz 2005). Given that PE has an abnormally high ratio of cDC to pDC, it will be critical to determine whether the DC regulators mentioned above can protect PE patients by regulating the cDC and pDC populations. Other than baicalin, treatment with MSCs during the implantation window also showed the potential to reduce abortion rates in mice. The use of MSCs as a

therapeutic agent in the abortion-prone mice increased the number of uDCs to the required level in normal pregnancy. Besides, MSC treatment also decreased the expression of co-stimulatory markers, i.e., CD86, CD40, and MHC-II on uDCs when compared to the control group (Eskandarian and Moazzeni 2019).

The BM-derived DCs can be used to treat RSA. Miranda et al. (2006) discovered that adoptive transfer of BM-derived DC at the maternal–fetal interface reduced abortion in a mouse model by upregulating pregnancy-protective CD8⁺, TCR- $\gamma\delta$ ⁺ T cells, TGF- β 1, and progesterone-induced blocking factor expression. In a mouse model of spontaneous abortion, DCs with a modified Fas ligand (FasL) gene were employed to produce a protective environment. Adoptive transfer of FasL-DCs may develop fetal tolerance by raising FasL expression at the maternal–fetal interface, which causes T cell death in the local decidua but not in the PB (Xiong et al. 2010). However, interventions such as DC transfusion and gene editing have not been applied in the clinic due to a lack of information on the roles, safety, stability, and unique migration paths of DCs *in vivo*.

8. Conclusion

For a pregnancy to be successful, it is essential to understand the immunological conundrum of the mother's tolerance to the fetal allograft, and the decidual leukocyte has received a lot of study in this regard. As previously mentioned, DCs are crucial for both the initiation and control of the immune response in order to preserve homeostasis, maternal–fetal immunotolerance, and defence against harmful microorganisms. DCs are thought to work together to coordinate the spatial and temporal immunological shifts required for implantation and pregnancy progression. Furthermore, decidual DCs interact with a large number of NK cells, T cells, and M ϕ s present in early pregnancy decidua, which is critical for the establishment of the tolerogenic decidual microenvironment that is characteristic of successful mammalian pregnancy. Various pregnancy-related diseases would result from abnormal polarization and dysfunction of DCs. The essential components of DC-based immunotherapy are transplanted DCs that correctly activate immune effector cells at the maternal–fetal interface, cause them to develop an immunotolerance status, and suppress any subsequent inflammatory reactions. The studies mentioned above have made significant progress in our understanding of DC ontogeny, but they have also revealed some unknown facts that need further research.

Author Contributions

Conceptualization: NRN, and MKJ; Writing—original draft preparation: DM and MKJ; Figure making: DM and TK; Writing—review and editing: NRN, SK, PKR, AKS, and BPM.

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Conflicts of Interest

The authors declare no conflict of interest.

References

- Abomaray FM, Al Jumah MA, Kalionis B et al (2015) Human chorionic villous mesenchymal stem cells modify the functions of human dendritic cells, and induce an anti-inflammatory phenotype in CD1+ dendritic cells. *Stem Cell Rev Rep* 11:423–441. <https://doi.org/10.1007/s12015-014-9562-8>
- Aldebert D, Diallo M, Niang M et al (2007) Differences in circulating dendritic cell subtypes in peripheral, placental and cord blood in African pregnant women. *J Reprod Immunol* 73:11–19. <https://doi.org/10.1016/j.jri.2006.05.002>
- Ali N, Zirak B, Rodriguez RS et al (2017) Regulatory T cells in skin facilitate epithelial stem cell differentiation. *Cell* 169:1119–1129. e11. <https://doi.org/10.1016/j.cell.2017.05.002>
- Allenspach EJ, Lemos MP, Porrett PM et al (2008) Migratory and lymphoid-resident dendritic cells cooperate to efficiently prime naive CD4 T cells. *Immunity* 29:795–806. <https://doi.org/10.1016/j.immuni.2008.08.013>
- Anandasabapathy N, Breton G, Hurley A et al (2015) Efficacy and safety of CDX-301, recombinant human Flt3L, at expanding dendritic cells and hematopoietic stem cells in healthy human volunteers. *Bone Marrow Transplant* 50:924–930. <https://doi.org/10.1038/bmt.2015.74>
- Anderson DA 3rd, Murphy KM, Brisen CG (2018) Development, diversity, and function of dendritic cells in mouse and human. *Cold Spring Harb Perspect Biol* 10:a028613. <https://doi.org/10.1101/cshperspect.a028613>
- Anderson DA, Dutertre CA, Ginhoux F et al (2021) Genetic models of human and mouse dendritic cell development and function. *Nat Rev Immunol* 21:101–115. <https://doi.org/10.1038/s41577-020-00413-x>
- Arpaia N, Green JA, Moltedo B et al (2015) A distinct function of regulatory T cells in tissue protection. *Cell* 162:1078–1089. <https://doi.org/10.1016/j.cell.2015.08.021>
- Askelund K, Liddell HS, Zanderigo AM et al (2004) CD83+ dendritic cells in the decidua of women with recurrent miscarriage and normal pregnancy. *Placenta* 25:140–145. [https://doi.org/10.1016/s0143-4004\(03\)00182-6](https://doi.org/10.1016/s0143-4004(03)00182-6)
- Bachy V, Williams DJ, Ibrahim MAA (2008) Altered dendritic cell function in normal pregnancy. *J Reprod Immunol* 78:11–21. <https://doi.org/10.1016/j.jri.2007.09.004>
- Bajana S, Turner S, Paul J et al (2016) IRF4 and IRF8 act in CD11c+ cells to regulate terminal differentiation of lung tissue dendritic cells. *J Immunol* 196:1666–1677. <https://doi.org/10.4049/jimmunol.1501870>
- Balan S, Saxena M, Bhardwaj N (2019) Dendritic cell subsets and locations. *Int Rev Cell Mol Biol* 348:1–68. <https://doi.org/10.1016/bs.ircmb.2019.07.004>
- Banchereau J, Briere F, Caux C et al (2000) Immunobiology of dendritic cells. *Annu Rev Immunol* 18:767–811. <https://doi.org/10.1146/annurev.immunol.18.1.767>
- Banchereau J, Steinman RM (1998) Dendritic cells and the control of immunity. *Nature* 392:245–252. <https://doi.org/10.1038/32588>
- Barrientos G, Tirado-Gonzalez I, Klapp BF et al (2009) The impact of dendritic cells on angiogenic responses at the fetal–maternal interface. *J Reprod Immunol* 83:85–94. <https://doi.org/10.1016/j.jri.2009.07.011>
- Bartmann C, Segerer SE, Rieger L et al (2014) Quantification of the predominant immune cell populations in decidua throughout human pregnancy. *Am J Reprod Immunol* 71:109–119. <https://doi.org/10.1111/aji.12185>
- Benirschke K, Burton GJ, Baergen RN (2012) Pathology of the human placenta. Springer-Verlag, Berlin, Heidelberg.
- Benschop RJ (1993) Beta 2-adrenergic stimulation causes detachment of natural killer cells from cultured endothelium. *Eur J Immunol* 23:3242–3247. <https://doi.org/10.1002/eji.1830231230>
- Bhardwaj N, Pavlick A, Ernst M et al (2016) A Phase II randomized study of CDX-1401, a dendritic cell targeting NY-ESO-1 vaccine, in patients with malignant melanoma pre-treated with recombinant CDX-301, a recombinant human Flt3 ligand. *J Clin Oncol* 34:9589–9589. http://dx.doi.org/10.1200/JCO.2016.34.15_suppl.9589
- Bilbo SD, Dhabhar FS, Viswanathan K (2002) Short day lengths augment stress-induced leukocyte trafficking and stress-induced enhancement of skin immune function. *Proc Natl Acad Sci U S A* 99:4067–4072. <https://doi.org/10.1073/pnas.062001899>
- Bird L (2017) Plasmacytoid dendritic cells: Division of labour. *Nat Rev Immunol* 18:2–3. <https://doi.org/10.1038/nri.2017.153>
- Bizargity P, Del Rio R, Phillippe M et al (2009) Resistance to lipopolysaccharide-induced preterm delivery mediated by regulatory T cell function in mice. *Biol Reprod* 80:874–881. <https://doi.org/10.1095/biolreprod.108.074294>
- Blois S, Tometten M, Kandil J et al (2005) Intercellular adhesion molecule-1/LFA-1 cross talk is a proximate mediator capable of disrupting immune integration and tolerance mechanism at the fetal–maternal interface in murine pregnancies. *J Immunol* 174:1820–1829. <https://doi.org/10.4049/jimmunol.174.4.1820>

- Blois SM, Alba Soto CD, Tometten M et al (2004) Lineage, maturity, and phenotype of uterine murine dendritic cells throughout gestation indicate a protective role in maintaining pregnancy. *Biol Reprod* 70:1018–1023. <https://doi.org/10.1095/biolreprod.103.022640>
- Blois SM, Kammerer U, Soto CA et al (2007) Dendritic cells: Key to fetal tolerance? *Biol Reprod* 77:590–598. <https://doi.org/10.1095/biolreprod.107.060632>
- Blois SM, Klapp BF, Barrientos G (2011) Decidualization and angiogenesis in early pregnancy: Unravelling the functions of DC and NK cells. *J Reprod Immunol* 88:86–92. <https://doi.org/10.1016/j.jri.2010.11.002>
- Boltjes A, Van Wijk F (2014) Human dendritic cell functional specialization in steady-state and inflammation. *Front Immunol* 5:131. <https://doi.org/10.3389/fimmu.2014.00131>
- Bonifaz L, Bonnyay D, Mahnke K et al (2002) Efficient targeting of protein antigen to the dendritic cell receptor DEC-205 in the steady state leads to antigen presentation on major histocompatibility complex class I products and peripheral CD8+ T cell tolerance. *J Exp Med* 196:1627–1638. <https://doi.org/10.1084/jem.20021598>
- Bosch JA (2003) Acute stress evokes selective mobilization of T cells that differ in chemokine receptor expression: A potential pathway linking immunologic reactivity to cardiovascular disease. *Brain Behav Immun* 17:251–259. [https://doi.org/10.1016/s0889-1591\(03\)00054-0](https://doi.org/10.1016/s0889-1591(03)00054-0)
- Broggi A, Zanoni I, Granucci F (2013) Migratory conventional dendritic cells in the induction of peripheral T cell tolerance. *J Leukoc Biol* 94:903–911. <https://doi.org/10.1189/jlb.0413222>
- Burzyn D, Kuswanto W, Kolodin D et al (2013) A special population of regulatory T cells potentiates muscle repair. *Cell* 155:1282–1295. <https://doi.org/10.1016/j.cell.2013.10.054>
- Butts CL, Shukair SA, Duncan KM et al (2007) Progesterone inhibits mature rat dendritic cells in a receptor-mediated fashion. *Int Immunol* 19:287–296. <https://doi.org/10.1093/intimm/dxl145>
- Cabeza-Cabrerizo M, Cardoso A, Minutti CM (2021) Dendritic cells revisited. *Annu Rev Immunol* 39:131–166. <https://doi.org/10.1146/annurev-immunol-061020-053707>
- Cappelletti M, Della Bella S, Ferrazzi E et al (2016) Inflammation and preterm birth. *J Leukoc Biol* 99:67–78. <https://doi.org/10.1189/jlb.3MR0615-272RR>
- Carlson SL, Fox S, Abell KM (1997) Catecholaminemodulation of lymphocyte homing to lymphoid tissues. *Brain Behav Immun* 11:307–320. <https://doi.org/10.1006/brbi.1997.0501>
- Ceppi M, Pereira PM, Dunand-Sauthier I et al (2009) MicroRNA-155 modulates the interleukin-1 signaling pathway in activated human monocyte-derived dendritic cells. *Proc Natl Acad Sci U S A* 106: 2735–2740. <https://doi.org/10.1073/pnas.0811073106>
- Chang WL, Liu YW, Dang YL et al (2018) PLAC8, a new marker for human interstitial extravillous trophoblast cells, promotes their invasion and migration. *Development* 145:dev148932. <https://doi.org/10.1242/dev.148932>
- Chorny A, Gonzalez-Rey E, Delgado M (2006) Regulation of dendritic cell differentiation by vasoactive intestinal peptide: Therapeutic applications on autoimmunity and transplantation. *Ann NY Acad Sci* 1088:187–194. <https://doi.org/10.1196/annals.1366.004>
- Collin M, Bigley V (2018) Human dendritic cell subsets: An update. *Immunology* 154:3–20. <https://doi.org/10.1111/imm.12888>
- Collin M, Milne P (2016) Langerhans cell origin and regulation. *Curr Opin Hematol* 23:28–35. <https://doi.org/10.1097%2FMOH.0000000000000202>
- Collins MK, Tay CS, Erlebacher A (2009) Dendritic cell entrapment within the pregnant uterus inhibits immune surveillance of the maternal/fetal interface in mice. *J Clin Invest* 119:2062–2073. <https://doi.org/10.1172/jci38714>
- Coombes JL, Powrie F (2008) Dendritic cells in intestinal immune regulation. *Nat Rev Immunol* 8:435–446. <https://doi.org/10.1038/nri2335>
- Cordeau M, Herblot S, Charrier E et al (2012) Defects in CD54 and CD86 up-regulation by plasmacytoid dendritic cells during pregnancy. *Immunol Invest* 41:497–506. <https://doi.org/10.3109/08820139.2012.682243>
- Darmochwal-Kolarz D (2005) Pre-eclampsia: Immunological aspects—a role of adhesion molecules, cytokines, dendritic cells, MHC antigens and auto-antibodies. *Curr Womens Health Rev* 1:237–242. <http://dx.doi.org/10.2174/157340405774575204>
- Darmochwal-Kolarz D, Kludka-Sternik M, Kolarz B et al (2013) The expression of B7-H1 and B7-H4 co-stimulatory molecules on myeloid and plasmacytoid dendritic cells in pre-eclampsia and normal pregnancy. *J Reprod Immunol* 99:33–38. <https://doi.org/10.1016/j.jri.2013.04.004>
- Darmochwal-Kolarz D, Rolinski J, Tabarkiewicz J (2003) Myeloid and lymphoid dendritic cells in normal pregnancy and pre-eclampsia. *Clin Exp Immunol* 132:339–344. <https://doi.org/10.1046%2Fj.1365-2249.2003.02136.x>
- Darmochwal-Kolarz DA, Kludka-Sternik M, Chmielewski T et al (2012) The expressions of CD 200 and CD 200 R molecules on myeloid and lymphoid dendritic cells in pre-eclampsia and normal pregnancy. *Am J Reprod Immunol* 67:474–481. <https://doi.org/10.1111/j.1600-0897.2012.01126.x>
- Dauven D, Ehrentauf S, Langwisch S et al (2016) Immune modulatory effects of human chorionic gonadotropin on dendritic cells supporting fetal survival in murine pregnancy. *Front Endocrinol* 7:146. <https://doi.org/10.3389/fendo.2016.00146>
- de Jong MA, Geijtenbeek TB (2010) Langerhans cells in innate defense against pathogens. *Trends Immunol* 31:452–459. <https://doi.org/10.1016/j.it.2010.08.002>
- Della Bella S, Giannelli S, Cozzi V et al (2011) Incomplete activation of peripheral blood dendritic cells during healthy human pregnancy. *Clin Exp Immunol* 164:180–192. <https://doi.org/10.1111/j.1365-2249.2011.04330.x>
- Dhabhar FS (2008) Enhancing versus suppressive effects of stress on immune function: Implications for immunoprotection versus immunopathology. *Allergy Asthma Clin Immunol* 4:2–11. <https://doi.org/10.1186/1710-1492-4-1-2>
- Dhabhar FS, Miller AH, McEwen BS et al (1996) Stress-induced changes in blood leukocyte distribution—role of adrenal steroid

- hormones. *J Immunol* 157:1638–1644. <https://doi.org/10.4049/jimmunol.157.4.1638>
- Dietl J, Hömig A, Kämmerer U et al (2006) Natural killer cells and dendritic cells at the human feto-maternal interface: An effective cooperation? *Placenta* 27:341–347. <https://doi.org/10.1016/j.placenta.2005.05.001>
- Ding Y, Wilkinson A, Idris A et al (2014) FLT3-ligand treatment of humanized mice results in the generation of large numbers of CD141+ and CD1c+ dendritic cells in vivo. *J Immunol* 192:1982–1989. <https://doi.org/10.4049/jimmunol.1302391>
- Domínguez PM, Ardavin C (2010) Differentiation and function of mouse monocyte-derived dendritic cells in steady state and inflammation. *Immunol Rev* 234:90–104. <https://doi.org/10.1111/j.0105-2896.2009.00876.x>
- Domogalla SS, Rostan MP, Raker PV et al (2017) Tolerance through education: How tolerogenic dendritic cells shape immunity. *Front Immunol* 8:1764. <https://doi.org/10.3389/fimmu.2017.01764>
- Du MR, Guo PF, Piao HL et al (2014) Embryonic trophoblasts induce decidual regulatory T cell differentiation and maternal–fetal tolerance through thymic stromal lymphopoietin instructing dendritic cells. *J Immunol* 192:1502–1511. <https://doi.org/10.4049/jimmunol.1203425>
- Ehrentraut S, Sauss K, Neumeister R et al (2019) Human miscarriage is associated with dysregulations in peripheral blood-derived myeloid dendritic cell subsets. *Front Immunol* 10:2440. <https://doi.org/10.3389/fimmu.2019.02440>
- Eisenbarth SC (2019) Dendritic cell subsets in T cell programming: Location dictates function. *Nat Rev Immunol* 19:89–103. <https://doi.org/10.1038/s41577-018-0088-1>
- El Hachem H, Crepau V, May-Panloup P et al (2017) Recurrent pregnancy loss: Current perspectives. *Int J Womens Health* 9:331–345. <http://dx.doi.org/10.2147/IJWH.S100817>
- Elftman MD, Norbury CC, Bonneau RH et al (2007) Corticosterone impairs dendritic cell maturation and function. *Immunology* 122:279–290. <https://doi.org/10.1111/j.1365-2567.2007.02637.x>
- Ellis JE, Ansari AA, Fett JD (2005) Inhibition of progenitor dendritic cell maturation by plasma from patients with peripartum cardiomyopathy: Role in pregnancy-associated heart disease. *Clin Dev Immunol* 12:265–273. <https://doi.org/10.1080/17402520500304352>
- Escribese MM, Rodríguez-García M, Sperling R et al (2011) Alpha-defensins 1–3 release by dendritic cells is reduced by estrogen. *Reprod Biol Endocrinol* 9:118. <https://doi.org/10.1186/1477-7827-9-118>
- Eskandarian M, Moazzeni SM (2019) Uterine dendritic cells modulation by mesenchymal stem cells provides a protective microenvironment at the feto-maternal interface: Improved pregnancy outcome in abortion-prone mice. *Cell J* 21:274–280. <https://doi.org/10.22074/2FCellj.2019.6239>
- Fancke B, Suter M, Hochrein H et al (2008) M-CSF: A novel plasmacytoid and conventional dendritic cell poietin. *Blood* 111:150–159. <https://doi.org/10.1182/blood-2007-05-089292>
- Fang WN, Shi M, Meng CY et al (2016) The balance between conventional DCs and plasmacytoid DCs is pivotal for immunological tolerance during pregnancy in the mouse. *Sci Rep* 6:26984. <https://doi.org/10.1038/srep26984>
- Farah O, Nguyen C, Tekkatte C et al (2020) Trophoblast lineage-specific differentiation and associated alterations in preeclampsia and fetal growth restriction. *Placenta* 102:4–9. <https://doi.org/10.1016/j.placenta.2020.02.007>
- Fauci AS, Dale DC (1974) The effect of in vivo hydrocortisone on subpopulations of human lymphocytes. *J Clin Invest* 53:240–246. <https://doi.org/10.1172/jci107544>
- Fauci AS, Dale DC (1975) The effect of hydrocortisone on the kinetics of normal human lymphocytes. *Blood* 46:235–243. <https://doi.org/10.1182/blood.V46.2.235.235>
- Ferlazzo G, Pack M, Thomas D et al (2004) Distinct roles of IL-12 and IL-15 in human natural killer cell activation by dendritic cells from secondary lymphoid organs. *Proc Natl Acad Sci U S A* 101:16606–16611. <https://doi.org/10.1073/pnas.0407522101>
- Ferris ST, Durai V, Wu R et al (2020) cDC1 prime and are licensed by CD4+ T cells to induce anti-tumour immunity. *Nature* 584:624–629. <https://doi.org/10.1038/s41586-020-2611-3>
- Feuerer M, Herrero L, Cipolletta D et al (2009) Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. *Nat Med* 15:930–939. <https://doi.org/10.1038/nm.2002>
- Fogg DK, Sibon C, Miled C et al (2006) A clonogenic bone marrow progenitor specific for macrophages and dendritic cells. *Science* 311:83–87. <https://doi.org/10.1126/science.1117729>
- Founds SA, Conley YP, Lyons-Weiler JF et al (2009) Altered global gene expression in first trimester placentas of women destined to develop preeclampsia. *Placenta* 30:15–24. <https://doi.org/10.1016/j.placenta.2008.09.015>
- Founds SA, Fallert-Junecko B, Reinhart TA (2013) LAIR2-expressing extravillous trophoblasts associate with maternal spiral arterioles undergoing physiologic conversion. *Placenta* 34:248–255. <https://doi.org/10.1016/j.placenta.2012.09.017>
- Gardner L, Moffett A (2003) Dendritic cells in the human decidua. *Biol Reprod* 69:1438–1446. <https://doi.org/10.1095/biolreprod.103.017574>
- Garrido-Gimenez C, Alijotas-Reig J (2015) Recurrent miscarriage: Causes, evaluation and management. *Postgrad Med J* 91:151–162. <https://doi.org/10.1136/postgradmedj-2014-132672>
- Geissmann F, Manz MG, Jung S et al (2010) Development of monocytes, macrophages, and dendritic cells. *Science* 327:656–661. <https://doi.org/10.1126/science.1178331>
- Georgantas RW, Hildreth R, Morisot S et al (2007) CD34+ hematopoietic stem-progenitor cell microRNA expression and function: A circuit diagram of differentiation control. *Proc Natl Acad Sci U S A* 104:2750–2755. <https://doi.org/10.1073/pnas.0610983104>
- Ginhoux F, Jung S (2014) Monocytes and macrophages: Developmental pathways and tissue homeostasis. *Nat Rev Immunol* 14:392–404. <https://doi.org/10.1038/nri3671>

- Goldenberg RL, Culhane JF, Iams JD et al (2008) Epidemiology and causes of preterm birth. *Lancet* 371:75–84. [https://doi.org/10.1016/s0140-6736\(08\)60074-4](https://doi.org/10.1016/s0140-6736(08)60074-4)
- Greter M, Helft J, Chow A et al (2012) GM-CSF controls nonlymphoid tissue dendritic cell homeostasis but is dispensable for the differentiation of inflammatory dendritic cells. *Immunity* 36:1031–1046. <https://doi.org/10.1016/j.immuni.2012.03.027>
- Gu AQ, Li DD, Wei DP et al (2019) Cytochrome P450 26A1 modulates uterine dendritic cells in mice early pregnancy. *J Cell Mol Med* 23:5403–5414. <https://doi.org/10.1111%2Fjcmm.14423>
- Gu K, Walpole C, Gooneratne S et al (2022) DROSHA but not DICER is required for human haematopoietic stem cell function. *Clin Transl Immunology* 11:e1361. <https://doi.org/10.1002/cti2.1361>
- Hackstein H, Taner T, Zahorchak AF et al (2003) Rapamycin inhibits IL-4-induced dendritic cell maturation in vitro and dendritic cell mobilization and function in vivo. *Blood* 101:4457–4463. <https://doi.org/10.1182/blood-2002-11-3370>
- Hashimi ST, Fulcher JA, Chang MH et al (2009) MicroRNA profiling identifies miR-34a and miR-21 and their target genes JAG1 and WNT1 in the coordinate regulation of dendritic cell differentiation. *Blood* 114:404–414. <https://doi.org/10.1182/blood-2008-09-179150>
- Hawiger D, Inaba K, Dorsett Y et al (2001) Dendritic cells induce peripheral T cell unresponsiveness under steady state conditions in vivo. *J Exp Med* 194:769–780. <https://doi.org/10.1084/jem.194.6.769>
- Heger L, Hatscher L, Liang C et al (2023) XCR1 expression distinguishes human conventional dendritic cell type 1 with full effector functions from their immediate precursors. *Proc Natl Acad Sci U S A* 120:e2300343120. <https://doi.org/10.1073/pnas.2300343120>
- Hopkins RA, Connolly JE (2012) The specialized roles of immature and mature dendritic cells in antigen cross-presentation. *Immunol Res* 53:91–107. <https://doi.org/10.1007/s12026-012-8300-z>
- Huang C, Zhang H, Chen X (2016) Association of peripheral blood dendritic cells with recurrent pregnancy loss: A case-controlled study. *Am J Reprod Immunol* 76:326–332. <https://doi.org/10.1111/aji.12550>
- Huang SJ, Chen CP, Schatz F et al (2008) Pre-eclampsia is associated with dendritic cell recruitment into the uterine decidua. *J Pathol* 214:328–336. <https://doi.org/10.1002/path.2257>
- Huang SJ, Zenclussen AC, Chen CP et al (2010) The implication of aberrant GM-CSF expression in decidual cells in the pathogenesis of preeclampsia. *Am J Pathol* 177:2472–2482. <https://doi.org/10.2353/ajpath.2010.091247>
- Hubo M, Trinschek B, Kryczanowsky F et al (2013) Costimulatory molecules on immunogenic versus tolerogenic human dendritic cells. *Front Immunol* 4:82. <https://doi.org/10.3389/fimmu.2013.00082>
- Huck B, Steck T, Habersack M et al (2005) Pregnancy associated hormones modulate the cytokine production but not the phenotype of PBMC-derived human dendritic cells. *Eur J Obstet Gynecol Reprod Biol* 122:85–94. <https://doi.org/10.1016/j.ejogrb.2005.02.017>
- Hughes GC, Clark EA (2007) Regulation of dendritic cells by female sex steroids: Relevance to immunity and autoimmunity. *Autoimmunity* 40:470–481. <https://doi.org/10.1080/08916930701464764>
- Hunt JS, Robertson SA (1996) Uterine macrophages and environmental programming for pregnancy success. *J Reprod Immunol* 32:1–25. [https://doi.org/10.1016/S0165-0378\(96\)88352-5](https://doi.org/10.1016/S0165-0378(96)88352-5)
- Huppertz B, Kingdom J, Caniggia I et al (2003) Hypoxia favours necrotic versus apoptotic shedding of placental syncytiotrophoblast into the maternal circulation. *Placenta* 24:181–190. <https://doi.org/10.1053/plac.2002.0903>
- Iijima N, Thompson JM, Iwasaki A (2008) Dendritic cells and macrophages in the genitourinary tract. *Mucosal Immunol* 1:451–459. <https://doi.org/10.1038/mi.2008.57>
- Ivanova E, Kyurkchiev D, Altankova I et al (2005) CD83+ monocyte-derived dendritic cells are present in human decidua and progesterone induces their differentiation in vitro. *Am J Reprod Immunol* 53:199–205. <https://doi.org/10.1111/j.1600-0897.2005.00266.x>
- Jena MK, Nayak N, Chen K et al (2019) Role of macrophages in pregnancy and related complications. *Arch Immunol Ther Exp* 67:295–309. <https://doi.org/10.1007%2Fs00005-019-00552-7>
- Jeras M, Bergant M, Repnik U et al (2005) In vitro preparation and functional assessment of human monocyte-derived dendritic cells—potential antigen-specific modulators of in vivo immune responses. *Transplant Immunol* 14:231–244. <https://doi.org/10.1016/j.trim.2005.03.012>
- Johanson TM, Keown AA, Cmero M et al (2015) Droscha controls dendritic cell development by cleaving messenger RNAs encoding inhibitors of myelopoiesis. *Nat Immunol* 16:1134–1141. <https://doi.org/10.1038/ni.3293>
- Jonuleit H, Schmitt E, Schuler G et al (2000) Induction of interleukin 10-producing, nonproliferating CD4+ T cells with regulatory properties by repetitive stimulation with allogeneic immature human dendritic cells. *J Exp Med* 192:1213–1222. <https://doi.org/10.1084/jem.192.9.1213>
- Jung S, Unutmaz D, Wong P et al (2002) In vivo depletion of CD11c+ dendritic cells abrogates priming of CD8+ T cells by exogenous cell-associated antigens. *Immunity* 17:211–220. [https://doi.org/10.1016/s1074-7613\(02\)00365-5](https://doi.org/10.1016/s1074-7613(02)00365-5)
- Juretic K, Strbo N, Crncic TB et al (2004) An insight into the dendritic cells at the maternal–fetal interface. *Am J Reprod Immunol* 52:350–355. <https://doi.org/10.1111/j.1600-0897.2004.00232.x>
- Kämmerer U, Eggert AO, Kapp M et al (2003) Unique appearance of proliferating antigen-presenting cells expressing DC-SIGN (CD209) in the decidua of early human pregnancy. *Am J Pathol* 162:887–896. [https://doi.org/10.1016/s0002-9440\(10\)63884-9](https://doi.org/10.1016/s0002-9440(10)63884-9)
- Kämmerer U, Kruse A, Barrientos G et al (2008) Role of dendritic cells in the regulation of maternal immune responses to the fetus during mammalian gestation. *Immunol Invest* 37:499–533. <https://doi.org/10.1080/08820130802191334>
- Kämmerer U, Schoppet M, McLellan AD et al (2000) Human decidua contains potent immunostimulatory CD83+ dendritic cells. *Am J Pathol* 157:159–169. [https://doi.org/10.1016%2FS0002-9440\(10\)64527-0](https://doi.org/10.1016%2FS0002-9440(10)64527-0)

- Kaplan DH (2010) In vivo function of Langerhans cells and dermal dendritic cells. *Trends Immunol* 31:446–451. <https://doi.org/10.1016%2Fj.it.2010.08.006>
- Karrich JJ, Jachimowski LC, Libouban M et al (2013) MicroRNA-146a regulates survival and maturation of human plasmacytoid dendritic cells. *Blood* 122:3001–3009. <https://doi.org/10.1182/blood-2012-12-475087>
- Karsten CM, Behrends J, Wagner AK et al (2009) DC within the pregnant mouse uterus influence growth and functional properties of uterine NK cells. *Eur J Immunol* 39:2203–2214. <https://doi.org/10.1002/eji.200838844>
- Kashem SW, Haniffa M, Kaplan DH (2017) Antigen-presenting cells in the skin. *Annu Rev Immunol* 35:469–499. <https://doi.org/10.1146/annurev-immunol-051116-052215>
- Keelan JA, Blumenstein M, Helliwell RJ et al (2003) Cytokines, prostaglandins and parturition—a review. *Placenta* 24:S33–S46. <https://doi.org/10.1053/plac.2002.0948>
- Komi J, Lassila O (2000) Nonsteroidal anti-estrogens inhibit the functional differentiation of human monocyte-derived dendritic cells. *Blood* 95:2875–2882. https://doi.org/10.1182/blood.V95.9.2875.009k12_2875_2882
- Kovats S (2012) Estrogen receptors regulate an inflammatory pathway of dendritic cell differentiation: Mechanisms and implications for immunity. *Horm Behav* 62:254–262. <https://doi.org/10.1016%2Fj.yhbeh.2012.04.011>
- Krey G, Frank P, Shaikly V et al (2008) In vivo dendritic cell depletion reduces breeding efficiency, affecting implantation and early placental development in mice. *J Mol Med* 86:999–1011. <https://doi.org/10.1007/s00109-008-0379-2>
- Kwan M, Hazan A, Zhang J et al (2014) Dynamic changes in maternal decidual leukocyte populations from first to second trimester gestation. *Placenta* 35:1027–1034. <https://doi.org/10.1016/j.placenta.2014.09.018>
- Kwiatk M, Gęca T, Krzyżanowski A et al (2015) Peripheral dendritic cells and CD4+CD25+Foxp3+ regulatory T cells in the first trimester of normal pregnancy and in women with recurrent miscarriage. *PLoS One* 10:e0124747. <https://doi.org/10.1371/journal.pone.0124747ssss>
- Lai N, Fu X, Hei G et al (2022) The role of dendritic cell subsets in recurrent spontaneous abortion and the regulatory effect of baicalin on it. *J Immunol Res* 2022:9693064. <https://doi.org/10.1155/2022/9693064>
- Laskarin G, Gulic T, Gacanin LG et al (2018) Assessing whether progesterone-matured dendritic cells are responsible for retention of fertilization products in missed abortion. *Med Hypotheses* 118:169–173. <https://doi.org/10.1016/j.mehy.2018.04.008>
- Laškarin G, Kämmerer U, Rukavina D et al (2007) Antigen-presenting cells and materno-fetal tolerance: An emerging role for dendritic cells. *Am J Reprod Immunol* 58:255–267. <https://doi.org/10.1111/j.1600-0897.2007.00511.x>
- Laškarin G, Redžović A, Rubeša Ž et al (2008) Decidual natural killer cell tuning by autologous dendritic cells. *Am J Reprod Immunol* 59:433–445. <https://doi.org/10.1111/j.1600-0897.2008.00599.x>
- Laskarin G, Redzovic A, Vlastelic I et al (2011) Tumor-associated glycoprotein (TAG-72) is a natural ligand for the C-type lectin-like domain that induces anti-inflammatory orientation of early pregnancy decidual CD1a+ dendritic cells. *J Reprod Immunol* 88:12–23. <https://doi.org/10.1016/j.jri.2010.10.001>
- Le Gars M, Kay AW, Bayless NL (2016) Increased proinflammatory responses of monocytes and plasmacytoid dendritic cells to influenza A virus infection during pregnancy. *J Infect Dis* 214:1666–1671. <https://doi.org/10.1093/infdis/jiw448>
- Lee JY, Lee M, Lee SK (2011) Role of endometrial immune cells in implantation. *Clin Exp Reprod Med* 38:119. <https://doi.org/10.5653%2Fcerm.2011.38.3.119>
- Leno-Durán E, Muñoz-Fernández R, Olivares EG et al (2014) Liaison between natural killer cells and dendritic cells in human gestation. *Cell Mol Immunol* 11:449–455. <https://doi.org/10.1038/cmi.2014.36>
- León B, López-Bravo M, Ardavin C (2007) Monocyte-derived dendritic cells formed at the infection site control the induction of protective T helper 1 responses against Leishmania. *Immunity* 26:519–531. <https://doi.org/10.1016/j.immuni.2007.01.017>
- Li J, Huang L, Wang S et al (2019) The prevalence of regulatory T and dendritic cells is altered in peripheral blood of women with pre-eclampsia. *Pregnancy Hypertens* 17:233–240. <https://doi.org/10.1016/j.preghy.2019.07.003>
- Li L, Yang J, Jiang Y et al (2015) Activation of decidual invariant natural killer T cells promotes lipopolysaccharide-induced preterm birth. *Mol Hum Reprod* 21:369–381. <https://doi.org/10.1093/molehr/gav001>
- Li M, Wu ZM, Yang H et al (2011) NFκB and JNK/MAPK activation mediates the production of major macrophage-or dendritic cell-recruiting chemokine in human first trimester decidual cells in response to proinflammatory stimuli. *J Clin Endocrinol Metab* 96:2502–2511. <https://doi.org/10.1210%2Fjc.2011-0055>
- Li Y, Lopez GE, Vazquez J et al (2018) Decidual-placental immune landscape during syngeneic murine pregnancy. *Front Immunol* 9:2087. <https://doi.org/10.3389%2Ffimmu.2018.02087>
- Liang J, Sun L, Wang Q et al (2006) Progesterone regulates mouse dendritic cells differentiation and maturation. *Int Immunopharmacol* 6:830–838. <https://doi.org/10.1016/j.vetimm.2016.09.007>
- Liao R, Sun J, Zhang L et al (2008) MicroRNAs play a role in the development of human hematopoietic stem cells. *J Cell Biochem* 104:805–817. <https://doi.org/10.1002/jcb.21668>
- Liu HY, Buenafe AC, Matejuk A et al (2002) Estrogen inhibition of EAE involves effects on dendritic cell function. *J Neurosci Res* 70:238–248. <https://doi.org/10.1002/jnr.10409>
- Liu K, Victora GD, Schwickert TA et al (2009) In vivo analysis of dendritic cell development and homeostasis. *Science* 324:392–397. <https://doi.org/10.1126/science.1170540>
- Liu S, Wei H, Li Y et al (2018) Downregulation of ILT 4+ dendritic cells in recurrent miscarriage and recurrent implantation failure. *Am J Reprod Immunol* 80:e12998. <https://doi.org/10.1111/aji.12998>

- Liu TT, Kim S, Desai P et al (2022) Ablation of cDC2 development by triple mutations within the Zeb2 enhancer. *Nature* 607:142–148. <https://doi.org/10.1038/s41586-022-04866-z>
- Liu YJ (2001) Dendritic cell subsets and lineages, and their functions in innate and adaptive immunity. *Cell* 106:259–262. [https://doi.org/10.1016/s0092-8674\(01\)00456-1](https://doi.org/10.1016/s0092-8674(01)00456-1)
- Liu Z, Wang H, Li Z et al (2023) Dendritic cell type 3 arises from Ly6C+ monocyte-dendritic cell progenitors. *Immunity* 56:1761–1777.e6. <https://doi.org/10.1016/j.immuni.2023.07.001>
- Lu C, Huang X, Zhang X et al (2011) miR-221 and miR-155 regulate human dendritic cell development, apoptosis, and IL-12 production through targeting of p27kip1, KPC1, and SOCS-1. *Blood* 117:4293–4303. <https://doi.org/10.1182/blood-2010-12-322503>
- Lu HQ, Hu R (2019) The role of immunity in the pathogenesis and development of pre-eclampsia. *Scan J Immunol* 90:e12756. <https://doi.org/10.1111/sji.12756>
- Lutz MB, Schuler G (2002) Immature, semi-mature and fully mature dendritic cells: Which signals induce tolerance or immunity? *Trends Immunol* 23:445–449. [https://doi.org/10.1016/s1471-4906\(02\)00281-0](https://doi.org/10.1016/s1471-4906(02)00281-0)
- Magatti M, De Munari S, Vertua E et al (2009) Amniotic mesenchymal tissue cells inhibit dendritic cell differentiation of peripheral blood and amnion resident monocytes. *Cell Transplant* 18:899–914. <https://doi.org/10.3727/096368909x471314>
- Mahnke K, Knop J, Enk AH (2003) Induction of tolerogenic DCs: 'you are what you eat'. *Trends Immunol* 24:646–651. <https://doi.org/10.1016/j.it.2003.09.012>
- Mantovani A, Sica A, Sozzani S et al (2004) The chemokine system in diverse forms of macrophage activation and polarization. *Trends Immunol* 25:677–686. <https://doi.org/10.1016/j.it.2004.09.015>
- Martinez FO, Sica A, Mantovani A et al (2008) Macrophage activation and polarization. *Front Biosci* 13:453–461. <https://doi.org/10.2741/2692>
- Martinez-Nunez RT, Louafi F, Friedmann PS et al (2009) MicroRNA-155 modulates the pathogen binding ability of dendritic cells (DCs) by down-regulation of DC-specific intercellular adhesion molecule-3 grabbing non-integrin (DC-SIGN). *J Biol Chem* 284:16334–16342. <https://doi.org/10.1074/jbc.M109.011601>
- Marzaioli V, Canavan M, Floudas A et al (2020) Monocyte-derived dendritic cell differentiation in inflammatory arthritis is regulated by the JAK/STAT axis via NADPH oxidase regulation. *Front Immunol* 11:1406. <https://doi.org/10.3389/fimmu.2020.01406>
- McGovern N, Shin A, Low G et al (2017) Human fetal dendritic cells promote prenatal T-cell immune suppression through arginase-2. *Nature* 546:662–666. <https://doi.org/10.1038/nature22795>
- McKenna HJ, Stocking KL, Miller RE et al (2000) Mice lacking flt3 ligand have deficient hematopoiesis affecting hematopoietic progenitor cells, dendritic cells, and natural killer cells. *Blood* 95:3489–3497. <https://doi.org/10.1182/blood.V95.11.3489>
- Menon R (2016) Spontaneous preterm birth, a clinical dilemma: Etiologic, pathophysiologic and genetic heterogeneities and racial disparity. *Acta Obstet Gynecol Scand* 95:590–605. <https://doi.org/10.1080/00016340802005126>
- Merad M, Manz MG. (2009) Dendritic cell homeostasis. *Blood* 113:3418–3427. <https://doi.org/10.1182/blood-2008-12-180646>
- Merad M, Sathe P, Helft J et al (2013) The dendritic cell lineage: Ontogeny and function of dendritic cells and their subsets in the steady state and the inflamed setting. *Annu Rev Immunol* 31:563–604. <https://doi.org/10.1146/annurev-immunol-020711-074950>
- Mildner A, Chapnik E, Manor O et al (2013a) Mononuclear phagocyte miRNome analysis identifies miR-142 as critical regulator of murine dendritic cell homeostasis. *Blood* 121:1016–1027. <https://doi.org/10.1182/blood-2012-07-445999>
- Mildner A, Jung S (2014) Development and function of dendritic cell subsets. *Immunity* 40:642–656. <https://doi.org/10.1016/j.immuni.2014.04.016>
- Mildner A, Yona S, Jung S (2013b) A close encounter of the third kind: Monocyte-derived cells. *Adv Immunol* 120:69–103. <https://doi.org/10.1016/b978-0-12-417028-5.00003-x>
- Mills CD, Kincaid K, Alt JM et al (2000) M-1/M-2 macrophages and the Th1/Th2 paradigm. *J Immunol* 164:6166–6173. <https://doi.org/10.4049/jimmunol.164.12.6166>
- Mills PJ (2001) Peripheral leukocyte subpopulations and catecholamine levels in astronauts as a function of mission duration. *Psychosom Med* 63:886–90. <https://doi.org/10.1097/00006842-200111000-00006>
- Mincheva-Nilsson L, Nagaeva O, Chen T et al (2006) Placenta-derived soluble MHC class I chain-related molecules down-regulate NKG2D receptor on peripheral blood mononuclear cells during human pregnancy: A possible novel immune escape mechanism for fetal survival. *J Immunol* 176:3585–3592. <https://doi.org/10.4049/jimmunol.176.6.3585>
- Miranda S, Litwin S, Barrientos G et al (2006) Dendritic cells therapy confers a protective microenvironment in murine pregnancy. *Scand J Immunol* 64:493–499. <https://doi.org/10.1111/j.1365-3083.2006.01841.x>
- Miyazaki S, Tsuda H, Sakai M et al (2003) Predominance of Th2-promoting dendritic cells in early human pregnancy decidua. *J Leukoc Biol* 74:514–522. <https://doi.org/10.1189/jlb.1102566>
- Mol BWJ, Roberts CT, Thangaratinam S et al (2016) Pre-eclampsia. *Lancet* 387:999–1011. [https://doi.org/10.1016/S0140-6736\(15\)00070-7](https://doi.org/10.1016/S0140-6736(15)00070-7)
- Morelli AE, Di Paola G, Fainboim L (1992) Density and distribution of Langerhans cells in the human uterine cervix. *Arch Gynecol Obstet* 252:65–71. <https://doi.org/10.1007/bf02389630>
- Moser M (2003) Dendritic cells in immunity and tolerance—do they display opposite functions? *Immunity* 19:5–8. [https://doi.org/10.1016/s1074-7613\(03\)00182-1](https://doi.org/10.1016/s1074-7613(03)00182-1)
- Naik SH, Metcalf D, Van Nieuwenhuijze A et al (2006) Intrasplenic steady-state dendritic cell precursors that are distinct from monocytes. *Nat Immunol* 7:663–671. <https://doi.org/10.1038/ni1340>
- Naik SH, Sathe P, Park HY et al (2007) Development of plasmacytoid and conventional dendritic cell subtypes from single precursor

- cells derived in vitro and in vivo. *Nat Immunol* 8:1217–1226. <https://doi.org/10.1038/ni1522>
- Negishi Y, Shima Y, Takeshita T et al (2017) Distribution of invariant natural killer T cells and dendritic cells in late pre-term birth without acute chorioamnionitis. *Am J Reprod Immunol* 77:e12658. <https://doi.org/10.1111/aji.12658>
- Negishi Y, Wakabayashi A, Shimizu M et al (2012) Disruption of maternal immune balance maintained by innate DC subsets results in spontaneous pregnancy loss in mice. *Immunobiology* 217:951–961. <https://doi.org/10.1016/j.imbio.2012.01.011>
- O'doherty U, Peng M, Gezelter S et al (1994) Human blood contains two subsets of dendritic cells, one immunologically mature and the other immature. *Immunology* 82:487–493
- O'Keeffe M, Fancke B, Hochrein H (2010) The generation of plasmacytoid and conventional dendritic cells with M-CSF. *Methods Mol Biol* 595:187–193. https://doi.org/10.1007/978-1-60761-421-0_12
- Onai N, Obata-Onai A, Schmid MA et al (2007) Identification of clonogenic common Flt3+ M-CSFR+ plasmacytoid and conventional dendritic cell progenitors in mouse bone marrow. *Nat Immunol* 8:1207–1216. <https://doi.org/10.1038/ni1518>
- Ooi AG, Sahoo D, Adorno M et al (2010) MicroRNA-125b expands hematopoietic stem cells and enriches for the lymphoid-balanced and lymphoid-biased subsets. *Proc Natl Acad Sci U S A* 105:21505–21510. <https://doi.org/10.1073/pnas.1016218107>
- Pakalniškytė D, Schraml BU (2017) Tissue-specific diversity and functions of conventional dendritic cells. *Adv Immunol* 134:89–135. <https://doi.org/10.1016/bs.ai.2017.01.003>
- Peters JH, Xu H, Ostermeier D et al (1993) Signals required for differentiating dendritic cells from human monocytes in vitro. *Adv Exp Med Biol* 329:275–280. https://doi.org/10.1007/978-1-4615-2930-9_46
- Pickford GE, Srivastava AK, Slicher AM et al (1971) The stress response in the abundance of circulating leukocytes in the killifish, *Fundulus heteroclitus*. I The cold-shock sequence and the effects of hypophysectomy. *J Exp Zool* 177:89–96. <https://doi.org/10.1002/jez.1401770110>
- Plaks V, Birnberg T, Berkutski T et al (2008) Uterine DCs are crucial for decidua formation during embryo implantation in mice. *J Clin Invest* 118:3954–3965. <https://doi.org/10.1172/JCI36682>
- Poltorak MP, Schraml BU (2015) Fate mapping of dendritic cells. *Front Immunol* 6:199. <https://doi.org/10.3389/fimmu.2015.00199>
- Pomeroy B, Klaessig S, Schukken Y (2016) Impact of in vitro treatments of physiological levels of estradiol and progesterone observed in pregnancy on bovine monocyte-derived dendritic cell differentiation and maturation. *Vet Immunol Immunopathol* 182:37–42. <https://doi.org/10.1016/j.vetimm.2016.09.007>
- Puts JJ, Moesker O, De Waal RM et al (1986) Immunohistochemical identification of Langerhans cells in normal epithelium and in epithelial lesions of the uterine cervix. *Int J Gynecol Pathol* 5:151–162. [https://doi.org/10.1016/0090-8258\(89\)90511-8](https://doi.org/10.1016/0090-8258(89)90511-8)
- Qian ZD, Huang LL, Zhu XM (2015) An immunohistochemical study of CD83 and CD1a-positive dendritic cells in the decidua of women with recurrent spontaneous abortion. *Eur J Med Res* 20:1–7. <http://dx.doi.org/10.1186/s40001-014-0076-2>
- Redline RW, Boyd TK, Roberts DJ (2018) Placental and gestational pathology. Cambridge University Press, Cambridge, UK.
- Redwine L (2003) Acute psychological stress: Effects on chemotaxis and cellular adhesion molecule expression. *Psychosom Med* 65:598–603. <https://doi.org/10.1097/01.psy.0000079377.86193.a8>
- Redwine L (2004) Differential immune cell chemotaxis responses to acute psychological stress in Alzheimer caregivers compared to non-caregiver controls. *Psychosom Med* 66:770–775. <https://doi.org/10.1097/01.psy.0000138118.62018.87>
- Reizis B (2010) Regulation of plasmacytoid dendritic cell development. *Curr Opin Immunol* 22:206–211. <https://doi.org/10.1016/j.coi.2010.01.005>
- Reizis B (2019) Plasmacytoid dendritic cells: Development, regulation, and function. *Immunity* 50:37–50. <https://doi.org/10.1016/j.immuni.2018.12.027>
- Reizis B, Bunin A, Ghosh HS et al (2011) Plasmacytoid dendritic cells: Recent progress and open questions. *Annu Rev Immunol* 29:163–183. <https://doi.org/10.1146/annurev-immunol-031210-101345>
- Rinder CS (1997) Lymphocyte and monocyte subset changes during cardiopulmonary bypass: Effects of aging and gender. *J Lab Clin Med* 129:592–602. [https://doi.org/10.1016/s0022-2143\(97\)90193-1](https://doi.org/10.1016/s0022-2143(97)90193-1)
- Romero R, Mazor M, Munoz H (1994) The preterm labor syndrome. *Ann N Y Acad Sci* 734:414–429. <https://doi.org/10.1111/j.1749-6632.1994.tb21771.x>
- Ruiz RJ, Jallo N, Murphey C et al (2012) Second trimester maternal plasma levels of cytokines IL-1Ra, IL-6 and IL-10 and preterm birth. *J Perinatol* 32:483–490. <https://doi.org/10.1038/jp.2011.193>
- Rukavina D, Rubeša G, Gudelj L et al (1995) Characteristics of perforin expressing lymphocytes within the first trimester decidua of human pregnancy. *Am J Reprod Immunol* 33:394–404. <https://doi.org/10.1111/j.1600-0897.1995.tb00908.x>
- Saito S, Nakashima A, Shima T et al (2010) Th1/Th2/Th17 and regulatory T-cell paradigm in pregnancy. *Am J Reprod Immunol* 63:601–610. <https://doi.org/10.1111/j.1600-0897.2010.00852.x>
- Sakaguchi S, Sakaguchi N, Asano M et al (1995) Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. *J Immunol* 155:1151–1164.
- Salamone G, Fraccaroli L, Gori S et al (2012) Trophoblast cells induce a tolerogenic profile in dendritic cells. *Hum Reprod* 27:2598–2606. <https://doi.org/10.1093/humrep/des208>
- Sauss K, Ehrentraut S, Zenclussen AC et al (2018) The pregnancy hormone human chorionic gonadotropin differentially regulates plasmacytoid and myeloid blood dendritic cell subsets. *Am J Reprod Immunol* 79:e12837. <https://doi.org/10.1111/aji.12837>

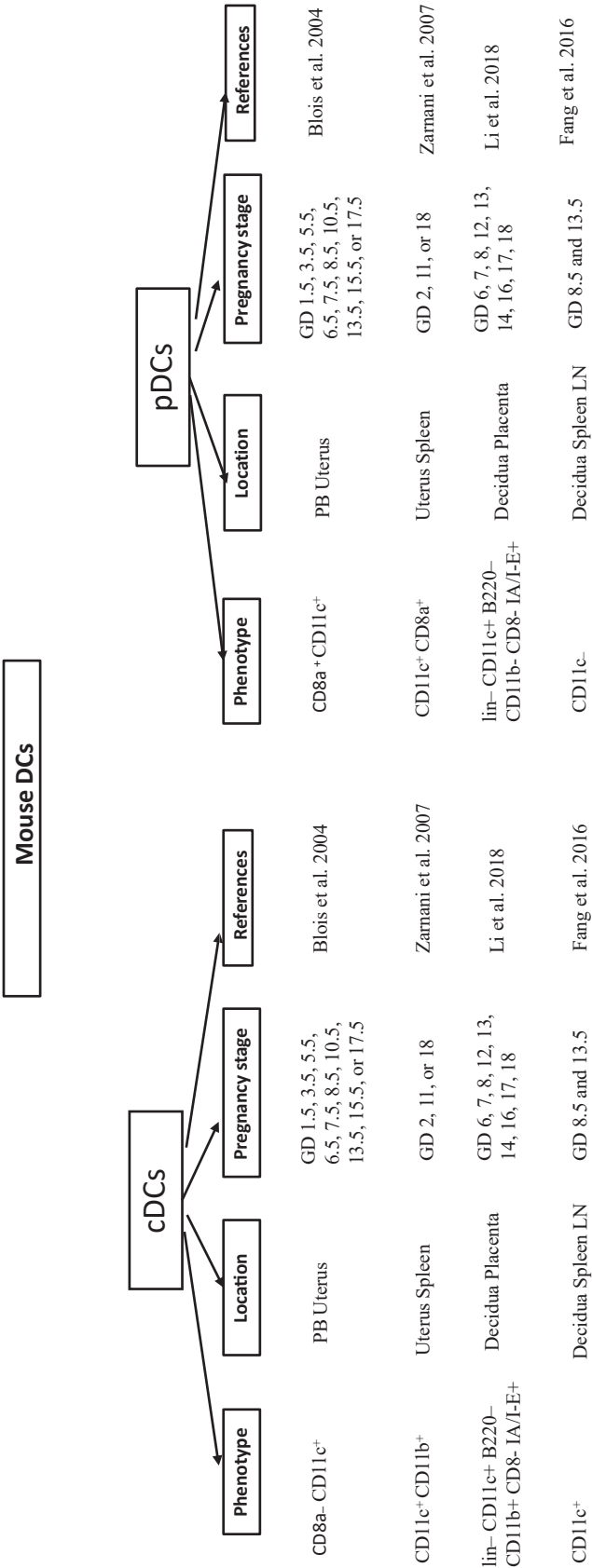
- Savage PA, Klawon DEJ, Miller CH (2020) Regulatory T cell development. *Annu Rev Immunol* 38:421–453. <https://doi.org/10.1146/annurev-immunol-100219-020937>
- Savage PA, Malchow S, Leventhal DS (2013) Basic principles of tumor-associated regulatory T cell biology. *Trends Immunol* 34:33–40. <https://doi.org/10.1016/j.it.2012.08.005>
- Schroder K, Hertzog PJ, Ravasi T et al (2004) Interferon-gamma: An overview of signals, mechanisms and functions. *J Leukoc Biol* 75:163–189. <https://doi.org/10.1189/jlb.0603252>
- Schumacher A (2017) Human chorionic gonadotropin as a pivotal endocrine immune regulator initiating and preserving fetal tolerance. *Int J Mol Sci* 18:2166. <https://doi.org/10.3390/ijms18102166>
- Schumacher A, Dauven D, Zenclussen AC (2017) Progesterone-driven local regulatory T cell induction does not prevent fetal loss in the CBA/J× DBA/2J abortion-prone model. *Am J Reprod Immunol* 77:e12626. <https://doi.org/10.1111/aji.12626>
- Segerer SE, Staib C, Kaemmerer U et al (2012) Dendritic cells: Elegant arbiters in human reproduction. *Curr Pharm Biotechnol* 13:1378–1384. <https://doi.org/10.2174/138920112800784916>
- Segura E, Amigorena S (2013) Inflammatory dendritic cells in mice and humans. *Trends Immunol* 34:440–445. <https://doi.org/10.1016/j.it.2013.06.001>
- Shah NM, Herasimtschuk AA, Boasso A et al (2017) Changes in T cell and dendritic cell phenotype from mid to late pregnancy are indicative of a shift from immune tolerance to immune activation. *Front Immunol* 8:1138. <https://doi.org/10.3389/fimmu.2017.01138>
- Shao Q, Liu X, Huang Y et al (2020) Human decidual stromal cells in early pregnancy induce functional re-programming of monocyte-derived dendritic cells via crosstalk between G-CSF and IL-1 β . *Front Immunol* 11:574270. <https://doi.org/10.3389/fimmu.2020.574270>
- Shen GM, Zhou MQ, Xu GS et al (2006) Role of vasoactive intestinal peptide and nitric oxide in the modulation of electroacupuncture on gastric motility in stressed rats. *World J Gastroenterol* 12: 6156–6160. <https://doi.org/10.3748%2Fwjg.v12.i38.6156>
- Shin S, Jang JY, Roh EY et al (2009) Differences in circulating dendritic cell subtypes in pregnant women, cord blood and healthy adult women. *J Korean Med Sci* 24:853–859. <https://doi.org/10.3346/jkms.2009.24.5.853>
- Shortman K, Naik SH (2007) Steady-state and inflammatory dendritic-cell development. *Nat Rev Immunol* 7:19–30. <https://doi.org/10.1038/nri1996>
- Shortman K, Sathe P, Vremec D et al (2013) Plasmacytoid dendritic cell development. *Adv Immunol* 120:105–126. <https://doi.org/10.1016/B978-0-12-417028-5.00004-1>
- Smits HH, de Jong EC, Wierenga EA (2005) Different faces of regulatory DCs in homeostasis and immunity. *Trends Immunol* 26:123–129. <https://doi.org/10.1016/j.it.2005.01.002>
- Spong CY, Lee SJ, McCune SK et al (1999) Regulation of postimplantation mouse embryonic growth by maternal vasoactive intestinal peptide. *Ann NY Acad Sci* 897:101–108. <https://doi.org/10.1111/j.1749-6632.1999.tb07882.x>
- Steinman RM, Cohn ZA (1973) Identification of a novel cell type in peripheral lymphoid organs of mice: I. Morphology, quantitation, tissue distribution. *J Exp Med* 137:1142–1162. <https://doi.org/10.1084/jem.137.5.1142>
- Steinman RM, Cohn ZA (1974) Identification of a novel cell type in peripheral lymphoid organs of mice: II. Functional properties in vitro. *J Exp Med* 139:380–397. <https://doi.org/10.1084/jem.139.2.380>
- Steinman RM, Hawiger D, Nussenzweig MC (2003) Tolerogenic dendritic cells. *Annu Rev Immunol* 21:685–711. <https://doi.org/10.1146/annurev.immunol.21.120601.141040>
- Steinman RM, Lustig DS, Cohn ZA (1974) Identification of a novel cell type in peripheral lymphoid organs of mice: III. Functional properties in vivo. *J Exp Med* 139:1431–1445. <https://doi.org/10.1084/jem.139.6.1431>
- Su X, Qian C, Zhang Q et al (2013) miRNomes of haematopoietic stem cells and dendritic cells identify miR-30b as a regulator of Notch1. *Nat Commun* 4:2903. <https://doi.org/10.1038/ncomms3903>
- Svensson-Arvelund J, Mehta RB, Lindau R et al (2017) The human fetal placenta promotes tolerance against the semiallogeneic fetus by inducing regulatory T cells and homeostatic M2 macrophages. *J Immunol* 198:3749–3761. <https://doi.org/10.4049/jimmunol.1401536>
- Swiecki M, Colonna M (2015) The multifaceted biology of plasmacytoid dendritic cells. *Nat Rev Immunol* 15:471–485. <https://doi.org/10.1038/nri3865>
- Szekeres-Bartho J, Barakonyi A, Polgar B et al (1999) The role of $\gamma\delta$ T cells in progesterone-mediated immunomodulation during pregnancy: A review. *Am J Reprod Immunol* 42:44–48. <https://doi.org/10.1111/j.1600-0897.1999.tb00464.x>
- Taglauer ES, Waldorf KMA, Petroff MG (2010) The hidden maternal-fetal interface: Events involving the lymphoid organs in maternal-fetal tolerance. *Int J Dev Biol* 54:421. <https://doi.org/10.1387/ijdb.082800et>
- Tagliani E, Erlebacher A (2011) Dendritic cell function at the maternal-fetal interface. *Expert Rev Clin Immunol* 7:593–602. <https://doi.org/10.1586/eci.11.52>
- Tagliani E, Shi C, Nancy P et al (2011) Coordinate regulation of tissue macrophage and dendritic cell population dynamics by CSF-1. *J Exp Med* 208:1901–1916. <https://doi.org/10.1084/jem.20110866>
- Takenaka MC, Quintana FJ (2017) Tolerogenic dendritic cells. *Semin Immunopathol* 39:113–120. <https://doi.org/10.1146/annurev.immunol.21.120601.141040>
- Tang-Huau TL, Segura E (2019) Human in vivo-differentiated monocyte-derived dendritic cells. *Semin Cell Dev Biol* 86:44–49. <https://doi.org/10.1016/j.semcdb.2018.02.018>
- Terness P, Kallikourdis M, Betz AG et al (2007) Tolerance signaling molecules and pregnancy: IDO, galectins, and the renaissance of regulatory T cells. *Am J Reprod Immunol* 58:238–254. <https://doi.org/10.1111/j.1600-0897.2007.00510.x>

- Tian Y, Meng L, Zhang Y (2017) Epigenetic regulation of dendritic cell development and function. *Cancer J* 23:302–307. <https://doi.org/10.1097/PPO.0000000000000280>
- Tirado-González I, Muñoz-Fernández R, Prados A et al (2012) Apoptotic DC-SIGN+ cells in normal human decidua. *Placenta* 33:257–263. <https://doi.org/10.1016/j.placenta.2012.01.003>
- Vacca P, Cantoni C, Vitale M et al (2010) Crosstalk between decidual NK and CD141 myelomonocytic cells results in induction of Tregs and immunosuppression. *Proc Natl Acad Sci U S A* 107:11918–11923. <https://doi.org/10.1073/pnas.1001749107>
- Vremec D, Lieschke GJ, Dunn AR et al (1997) The influence of granulocyte/macrophage colony-stimulating factor on dendritic cell levels in mouse lymphoid organs. *Eur J Immunol* 27:40–44. <https://doi.org/10.1002/eji.1830270107>
- Wadhwa PD, Culhane JF, Rauh V et al (2001) Stress and preterm birth: Neuroendocrine, immune/inflammatory, and vascular mechanisms. *Matern Child Health J* 5:119–125. <https://doi.org/10.1023/a:1011353216619>
- Wahid HH, Dorian CL, Chin PY et al (2015) Toll-like receptor 4 is an essential upstream regulator of on-time parturition and perinatal viability in mice. *Endocrinology* 156:3828–3841. <https://doi.org/10.1210/en.2015-1089>
- Wang H, He M, Hou Y et al (2016) Role of decidual CD14+ macrophages in the homeostasis of maternal–fetal interface and the differentiation capacity of the cells during pregnancy and parturition. *Placenta* 38:76–83. <https://doi.org/10.1016/j.placenta.2015.12.001>
- Wang J, Su L, Zhu T et al (2013) Changes in the subsets of dendritic cells and T cells in peripheral blood of patients with preeclampsia. *Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi* 29:72–75
- Wang J, Tao YM, Cheng XY et al (2014) Dendritic cells derived from preeclampsia patients influence Th1/Th17 cell differentiation in vitro. *Int J Clin Exp Med* 7:5303–5309
- Waskow C, Liu K, Darrasse-Jèze G et al (2008) The receptor tyrosine kinase Flt3 is required for dendritic cell development in peripheral lymphoid tissues. *Nat Immunol* 9:676–683. <https://doi.org/10.1038/ni.1615>
- Wei R, Lai N, Zhao L et al (2021) Dendritic cells in pregnancy and pregnancy-associated diseases. *Biomed Pharmacother* 133:110921. <https://doi.org/10.1016/j.biopha.2020.110921>
- Wira CR, Roche MA, Rossoll RM (2002) Antigen presentation by vaginal cells: Role of TGF β as a mediator of estradiol inhibition of antigen presentation. *Endocrinology* 143:2872–2879. <https://doi.org/10.1210/endo.143.8.8938>
- Xiong M, Lu J, Zhao A et al (2010) Therapy with FasL-gene–modified dendritic cells confers a protective microenvironment in murine pregnancy. *Fertil Steril* 93:2767–2769. <https://doi.org/10.1016/j.fertnstert.2009.11.040>
- Xu Y, He H, Li C et al (2011) Immunosuppressive effect of progesterone on dendritic cells in mice. *J Reprod Immunol* 91:17–23. <https://doi.org/10.1016/j.jri.2011.06.101>
- Yin X, Chen S, Eisenbarth SC (2021) Dendritic cell regulation of T helper cells. *Annu Rev Immunol* 39:759–790. <https://doi.org/10.1146/annurev-immunol-101819-025146>
- Yoshimura T, Inaba M, Sugiura K et al (2003) Analyses of dendritic cell subsets in pregnancy. *Am J Reprod Immunol* 50:137–145. <https://doi.org/10.1034/j.1600-0897.2003.00063.x>
- Zarnani AH, Moazzeni SM, Shokri F et al (2007) Kinetics of murine decidual dendritic cells. *Reproduction* 133:275–283. <https://doi.org/10.1530/rep.1.01232>
- Zhou H, Wu L (2017) The development and function of dendritic cell populations and their regulation by miRNAs. *Protein Cell* 8:501–513. <https://doi.org/10.1007/s13238-017-0398-2>
- Zhu J, Paul WE (2008) CD4 T cells: Fates, functions, and faults. *Blood* 112:1557–1569. <https://doi.org/10.1182/blood-2008-05-078154>

Supplementary Tables

Human DCs							
cDCs				pDCs			
Phenotype	Location	Pregnancy stage	References	Phenotype	Location	Pregnancy stage	References
CD1c ⁺	PB	1 st and 2 nd trim (†)	Ehrentraut et al. 2019	BDCA-1 ⁺ CD123 ⁺	PB	1 st , 2 nd , and 3 rd trim	Darmochwal-Kolarz et al. 2012; Kwiatek et al. 2015
Lin ⁺ HLA-DR ^{high}	PB	2 nd and 3 rd trim (†)	Shah et al. 2017	Lin ⁺ HLA-DR ⁺ D123 ⁺	Decidua	7 th -12 th week of gest	Gardner and Moffett 2003
BDCA-1 ⁺ CD19 ⁻	PB	6 th –13 th week of gestation	Kwiatek et al. 2015	Lin ⁺ HLA-DR ^{high} CD123 ⁺	Both PB & Decidua	6.9 ± 1.3 week of gest	Miyazaki et al. 2003
CD1c ⁺ CD19 ⁻	PB	1 st , 2 nd , and 3 rd trim	Darmochwal-Kolarz et al. 2012	Lin ⁺ CDw123 ⁺ CD11c-HLA-DR ⁺	PB	8-32 week of gest	Yoshimura et al. 2003
Lin ⁺ HLA-DR ⁺ CD1c ⁺	Decidua	7 th -12 th week of gest	Gardner and Moffett 2003	Lin ⁺ HLA-DR ⁺ CD11c ⁻	PB	30 –41 week of gest	Bachy et al. 2008
Lin ⁺ HLA-DR ^{bright} CD11c ⁺	PB and decidua	7 th week of gest	Miyazaki et al. 2003	CD11c ⁻ CD123 ^{bright}	PB	At delivery	Shin et al. 2009
Lin ⁺ CDw123-CD11c ⁺ HLA-DR ⁺	PB	8 th -32 nd week of gest	Yoshimura et al. 2003	HLA-DR ⁺ Lin-CD123 ⁺	PB	1 st , 2 nd , and 3 rd trim	Della Bella et al. 2011
Lin ⁺ HLA-DR ⁺ CD11c ⁺	PB	30 th –41 st week of gest	Bachy et al. 2008	CD303 ⁺	PB	1 st to 20 th week of gest	Escribese et al. 2011; Ehrentraut et al.2019
CD11c ⁺	PB	At delivery	Shin et al. 2009	HLA-DR ⁺ Lin-BDCA4 ⁺	PB	3 rd trim	Cordeau et al. 2012
Lin ⁺ HLA-DR ⁺ CD11c ⁺	PB	All 3 trim.	Della Bella et al. 2011	CD14–CD123 ⁺ , Lin ⁺ HLA-DR ^{high}	PB	2 nd and 3 rd trim (↑)	Shah et al. 2017
CD1c ⁺	PB	1 st –20 th week of gest	Escribese et al. 2011				

Supplementary Table 1. Different human DC phenotypes during pregnancy.



Supplementary Table 2. Different mouse DC phenotypes during pregnancy.