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REVIEW

Decidual Macrophages and Their Roles at the Maternal-Fetal Interface

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The semi-allogeneic fetus, whose genome consists of maternally and paternally inherited alleles, must coexist with an active maternal immune system during its 9 months *in utero*. Macrophages are the second most abundant immune cell at the maternal-fetal interface, although populations and functions for these populations remain ill defined. We have previously reported two distinct subsets of $CD14^{+}$ decidual macrophages found to be present in first trimester decidual tissue, 20 percent $CD11c^{HI}$ and 68 percent $CD11c^{LO}$. Interestingly, $CD11c^{HI}$ decidual macrophages express genes associated with lipid metabolism, inflammation, and antigen presentation function and specifically upregulate CD1 molecules. Conversely, $CD11c^{LO}$ decidual macrophages express genes associated with extracellular matrix formation, muscle regulation, and tissue growth. The large abundance of $CD11c^{HI}$ decidual macrophages and their ability to process antigens more efficiently than $CD11c^{LO}$ macrophages suggests that $CD11c^{HI}$ macrophages may be important antigen processing and presenting cells at the maternal-fetal interface, while $CD11c^{LO}$ macrophages may perform necessary homeostatic functions during placental construction. Thus, macrophage heterogeneity may be an important and necessary division of labor that leads to both an induction of maternal immune cell tolerance to fetal antigens as well as basic homeostatic functions in human pregnancy.

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†Abbreviations: APC, antigen presenting cell; CD, cluster of differentiation; DC, dendritic cell; dMϕ, decidual macrophage; dNK, decidual natural killer cell; EVT, extravillous trophoblast; FACS, fluorescence-activated cell sorting; HLA, human leukocyte antigen; IFN-γ, interferon gamma; Ig, immunoglobulin; IL, interleukin; ITAM, immunoreceptor tyrosine-based activating motif; ITIM, immunoreceptor tyrosine-based inhibitory motif, KIR, killer Ig-like receptor; LPS, Lipopolysaccharides; MHC, major histocompatability complex; MR, mannose receptor; PE, phycoerythrin; SA, scavenger receptor; TCR, T cell receptor; TLR, toll like receptor.

Keywords: pregnancy, reproduction, macrophages, antigen presenting cells, NK cells, lipids

INTRODUCTION

Viviparity, or live birth, has evolved independently in several species. Eutheria, from the Greek for "well developed beast," are a clade of viviparous mammals in which the fetus is nourished during gestation by a placenta [1]. The placenta consists of two basic elements: an inner vascular network and an outer epithelium [2]. The outer epithelium, comprised of trophoblast cells, provides the main structural and functional components of the placenta and allows for oxygen and nutrient exchange between mother and child. The inner vasculature and stroma are derived from embryonic mesoderm.

Placentation begins when fetal-derived trophoblast cells from the recently implanted blastocyst invade the uterine lining. Simultaneously, cells of the endometrium also begin to prepare for this invasion, in a process known as decidualization [3]. The mammalian chorioallantoic placenta is essential for the growth and development of the fetus and distinguishes Eutherian mammals from other organisms. There are three main types of Eutherian placentation: epitheliochorial, endotheliochorial, and hemochorial [4]. These distinctions are made based upon contact between trophoblast cells and the uterine lining. In epitheliochorial placentation, trophoblast cells can reach and sometimes fuse with the surface epithelium of the uterus, while in endotheliochorial placentation, trophoblasts can reach the maternal blood vessels [5]. Humans undergo hemochorial placentation, wherein fetal membranes are in direct contact with maternal tissue and blood (Figure 1). This intimate contact between the fetal-placental unit and mother was established in the last common crown group of Eutheria and gives credence that a successful pregnancy requires appropriate allorecognition and tolerance at the maternal-fetal interface [6].

THE HUMAN MATERNAL-FETAL INTERFACE

The maternal-fetal interface is a dynamic site that encompasses multiple cellular interactions in an environment rich in cytokines and hormones [7]. During the first trimester (weeks 1-12 post-fertilization), interstitial and endovascular infiltration of trophoblast cells elicit both the recruitment of maternal immune cells and the production of pro-inflammatory cytokines [8]. It is commonly thought that immune responses by the mother help to protect from trophoblast over-invasion while allowing for the acceptance of the semi-allogeneic fetal-placental unit.

Immunohistochemical staining against the leukocyte common antigen CD45 has shown that 40 percent of cells in the decidua during the first trimester are leukocytes [8]. An estimated 50 to 60 percent of decidual leukocytes are $CD56^{bright}CD3^{-}$ NK cells [9]. The remaining leukocytic infiltrate is comprised of roughly 10 percent T cells, 1 to 2 percent dendritic cells (DCs†), and 20 to 25 percent Mϕs [10]. The decidual macrophage (dMϕ) compartment consists of at least two distinct subsets based upon differential expression of the complement receptor CD11c and are now termed $CD11c^{HI}$ and $CD11c^{LO}$ [11]. Decidual leukocytes at the maternal-fetal interface play important roles in both allorecognition of fetal antigens and in the development of the fetal-placental unit.

IMMUNOBIOLOGY OF REPRODUCTIVE FAILURE IN HUMANS

Statistically, human pregnancy is remarkably inefficient. It has been estimated that approximately 50 to 60 percent of all human concepti die prior to birth [12]. The majority of these deaths occur before implantation; however, between 15 and 20 percent of otherwise successful embryo implants will result in an early spontaneous abortion [13,14]. Although pregnancy loss has been attributed to vague complications such as genetic, endocrinological, and anatomical abnormalities, the majority of miscarriages remain unexplained.

Haemolytic disease of the newborn was the first recognized immunological complication of human pregnancy [15]. This disease develops because the mother is

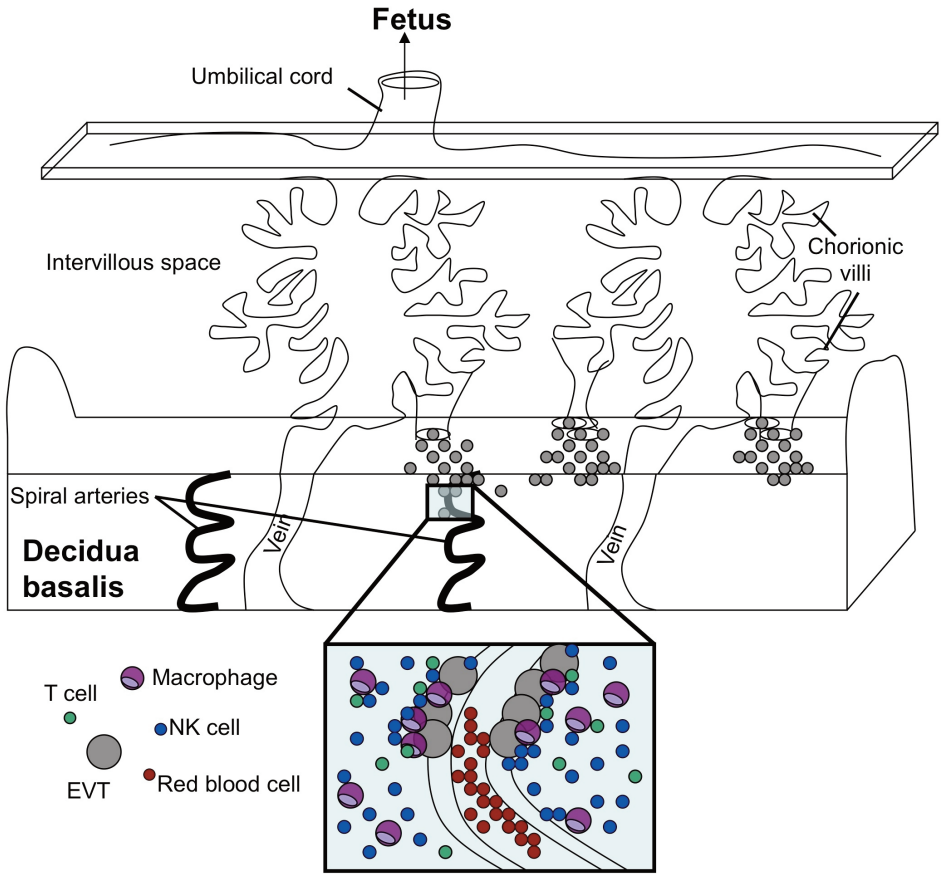

Figure 1. The Human Maternal-Fetal Interface. A block section of the chorioallantoic human placenta shows chorionic villous trees in direct contact with the decidua basalis and the maternal blood supply in order to provide oxygen and nutrients to the growing fetus. The insert shows HLA-G$^+$ extravillious trophoblast cells invading the endothelium and unwinding the maternal spiral artery, allowing for maternal blood to enter the intervillous spaces. At this site, fetal trophoblast cells come into direct contact with maternal immune cells such as dMφs, NK cells, and T cells.

immunized by antigens on fetal erythrocytes from an earlier pregnancy. This leads to antibody-mediated haemolysis of the fetus in a subsequent pregnancy. These antigens are termed "Rhesus factor" (Rh) because early studies utilized red blood cells from Rhesus macaques [16]. These data contributed to Sir Peter Medawar's development of the concept of maternal tolerance to the fetus, and he proposed three potential explanations regarding why the maternal immune system does not reject the fetus: physical separation of mother and fetus, antigenic immaturity of fetal tissues, and immunological inertness of the mother [17,18]. However, none of these three proposed concepts account for maternal tolerance to fetal antigens.

There are now several well-characterized immunological factors known to aid in fetal tolerance, including complement inhibitory receptors [19,20], absence of major MHC expression, expression of non-polymorphic non-classical presenting molecules [21], and cytokine balance. Although the fetal-placental unit is often equated to a vascularized allograft, classical allogeneic rejection of invading fetal cells is avoided because of the absence of MHC class II. However, there are several disorders, including tubal pregnancy, placenta accreta, and preeclampsia, that occur in part due to immune misregulation [5].

Preeclampsia occurs in as many as 10 percent of all human pregnancies [22] and is

the primary pathogenesis of inadequate invasion of extra-villous trophoblasts (EVT) and insufficient remodeling of the maternal-spiral arteries [23-25]. This ultimately leads to a lack of maternal blood flow into the intervillous space and manifests in the mother as proteinuria, edema, and hypertension. Although other factors have been shown to contribute to preeclampsia, it is generally thought of as an immunological manifestation of the misregulation of trophoblast invasion by maternal leukocytes [26]. Further evidence of immunological involvement in preeclampsia has been shown in cases where a primipara who had preeclampsia has a reduced risk with a change in partner [27]. In addition, in the case of oocyte donation in which the fetus is entirely non-self, the risk of preeclampsia is elevated to 30 percent [28].

Mϕs have been shown to play important roles in pregnancy maladies, including preeclampsia. In normal human pregnancies, dMϕs are located in the surrounding stroma and near the spiral arteries; however, in preeclamptic pregnancies, the dMϕs are mostly located within and around the spiral arteries and appear to physically inhibit trophoblast remodeling [29,30]. Moreover, it has been reported through ex vivo studies that dMϕs can limit EVT invasion of spiral arteries through apoptosis mediated secretion of TNF-α [30,31]. In summary, Mϕs at the human maternal-fetal interface play important roles during normal placental development, and the misregulation of these cells can result in pregnancy complications.

MACROPHAGE HETEROGENEITY

Peripheral blood monocytes give rise to Mϕs, tissue resident phagocytic cells whose phenotype is specific to the tissue type. These are involved in tissue homeostasis via apoptotic cell clearance and the production of important cytokines, chemokines, and growth factors [32]. They are foremost prodigious phagocytic cells that clear more than two $2X10^{11}$ erythrocytes per day, recycling iron as a necessary homeostatic process [33]. Moreover, Mϕs are the dedicated janitors of the body, clearing cellular debris from effete cells during tissue remodeling processes without eliciting an immune response. Phagocytosis of cellular components, along with varying environmental cues, may lead to Mϕ plasticity [34]. Such plasticity generates different types of Mϕs possessing distinct phenotypes and functions.

Emulating the Th1/Th2 nomenclature, polarized Mϕs have been broadly categorized as either pro-inflammatory (M1) or anti-inflammatory (M2) [35]. It is well established that classically activated M1 Mϕs are potent inducers of IL-1, TNF-α, and IL-12 following stimulation by a microbial antigen or pro-inflammatory cytokines [34]. Originally described as Mϕs activated by IL-4, alternatively activated Mϕs or M2 Mϕs have been described as anti-inflammatory mediators [36,37]. Polarization of the M2 phenotype can be induced not only with IL-4, but also with immune complexes, IL-10, glucocorticoid, or secosteroid hormones [38]. The M1/M2 paradigm has been comprehensively studied by transcriptional approaches, which defined skewed gene expression based on the stimulus used to generate each type of macrophage [34,39]. Recently, the M1/M2 paradigm has come under scrutiny, as tissue resident Mϕs are neither M1 nor M2 [11,40]. Thus, since Mϕs are uniquely plastic cells, it has been proposed to define Mϕs based on functions that are involved in maintaining homeostasis, such as host defense, wound healing, and immune regulation [33].

Interestingly, Mϕ plasticity plays important roles not only in homeostasis and infection but also in cancer. As early as the late 1970s, it was found that tumor growth was promoted by tumor-associated macrophages (TAMs), a predominant leukocyte population present in tumors with poor prognosis for therapeutic outcome [41-43]. TAMs are different from Gr1+ myeloid-derived suppressor cells (MDSCs) in mice, which are a heterogeneous population of cells of the myeloid lineage also associated with cancer [44]. However, because their defining marker, Gr1, is only found in mice and has no homologue in humans, the precise characterization

Table 1. Macrophage Populations.

Macrophage type	Characteristics and Hallmarks	Function	Humans/Mice	Reference
M1 Mϕ	TLR2/4, CD16/32/64, CD80/86, TNF-α, IL-1, IL-6, CCL2	Microbicidal activity, clearance of pathogen, pro-inflammatory	Humans	[34,38]
M2 Mϕ	SRA/B, MR, CD163, CD23, IL-10, CXCR1, CXCR2, CCL22/24/17	Anti-inflammatory, immune regulators, tissue repair	Humans	[35-38]
TR- Host defense	Induced by T_H1 or NK cell production of IFN-γ or other TLR-stimulated APC TNF-α production	Classical activation, microbicidal activity	Humans/Mice	[33]
TR- Wound healing	Induced by T_H2 or granulocyte production of IL-4	Wound healing	Humans/Mice	[33]
TR- Immune regulation	Induced by T_{REG} IL-10 production or IC, prostaglandins, GPCR ligands, glucocorticoids, apoptotic cells	Anti- inflammatory activity	Humans/Mice	[33]
Tumor associated macrophage (TAM)	Found in cancers, produce angiogenic and lymphoangiogenic factors including VEGF production	Neoplastic assisted growth development	Humans/Mice	[43,45,47]
Myeloid Derived Suppressor Cell (MDSC)	A heterogeneous population of myeloid lineage cells, CD11b+Gr1+ or CD11b+CD14-CD33+, potent suppressors of T cells	Accumulate in lymphoid organs and in tumors in pathological conditions, notably cancer	Mice/Humans (to some degree)	[44]
$CD11c^{HI}$ dMϕ	$CD206^{low}$, $CD209^{low}$, lipid metabolism, inflammatory markers, antigen presentation function, mobile	Antigen presentation and immune regulation	Humans	[11]
$CD11c^{LO}$ dMϕ	$CD206^{hi}$, $CD209^{hi}$, extracellular communication, large phagolysosomes	Clearance of cellular debris and effete cells during tissue remodeling processes	Humans	[11]

and role of MDSCs in human infections and cancer remains ill defined. TAMs, however, have been found to aggregate in the hypoxic regions of tumors, thereby promoting hypoxia-driven programs including angiogenesis, TNF-α and TGF-β production, and CXCL8 secretion [45]. Other chemokines including CXCL1 and related molecules and CCL2 have been associated with TAM accumulation [42]. Although TAMs have been most closely associated to the M2 phenotype, they are known drivers of chronic inflammatory processes that promote epithelial hyperproliferation, tissue remodeling, and angiogenesis. Ultimately, this is followed by dysplasia and invasive carcinoma [46]. Moreover, their production of TNF-α and IL-1β strongly indicates their regulation of cellular metastasis [47].

TAMs, as well as Mϕs in general, also have been shown to have a role in the connection between sex steroids and inflammation in the promotion of cancer [48]. One study focused on gender disparities in hepatocellular carcinoma, a cancer to which males are more susceptible [49]. This study found that liver Mϕs in males produce higher levels of IL-6 during carcinoma development following induction via the hepatitis virus. Furthermore, carcinoma development was inhibited in males that were IL-6 deficient. Interestingly, females produce higher levels of estrogen steroid hormones, which were found to inhibit IL-6 production in liver Mϕs and thereby protect them from the development of cancer. This study emphasizes the link between sex-steroids, inflammation, and Mϕ regulation in the development of some cancers.

Hormones in tissue play important roles in the development of tissue-resident Mϕs. For example, glucocorticoids, which are released by adrenal cells in response to stress, have been shown to inhibit Mϕ-mediated host defenses via the production of pro-inflammatory cytokines, leading to increased susceptibility to pathogen infections [50]. However, other Mϕ functions, such as phagocytosis, are not impaired in the presence of glucocorticoids [51], suggesting that glucocorticoids can directly impact tissue-resident Mϕ immune regulation. Progesterone, an important hormone during the menstrual cycle and pregnancy, has been shown to inhibit Mϕ production of TNF-α in a pre-transcriptional manner [52] as well as IL-12 induced nitric oxide (NO) production in response to TLR4-mediated agonists [53]. Thus, it is conceivable that pregnancy-specific hormones may directly contribute to the rise and frequency of dMϕ populations and their responses to fetal-derived or pathogen-derived antigens.

Environmental cues can lead to Mϕ plasticity and give rise to different populations of Mϕs that occur at various frequencies. Mϕs at the maternal-fetal interface experience a shift in hormonal production both locally and systemically, encounter potential pathogens, clear effete cells, and notably interface and respond to non-self invading trophoblast cells [54]. The variety of environmental cues during placental development can lead to uniquely diverse, in both phenotype and function, dMϕ populations in order to maximize different necessary processes (Table 1). In fact, we have now described two distinct dMϕ populations at the maternal-fetal interface [11].

DECIDUAL MACROPHAGES AS ANTIGEN PRESENTING CELLS

The large abundance of Mϕs and near absence of DCs [55] suggests that dMϕs may be the most important antigen processing and presenting cells at the maternal-fetal interface. dMϕs, as a professional APC, may be important in regulating both adaptive T cell responses as well as innate NK cell responses at the maternal-fetal interface during early human pregnancy.

Mϕs are equipped with a recognition system for a host of different pathogen-associated molecular patterns (PAMPs) and are specialized in the initial capture and processing of these potential antigens. They are also important in the development of an adaptive immune response [56]. Although Mϕs are known for their powerful phagocytic and endocytotic capacities, antigen presentation, by default, is left to the DC.

This may be in part because their high levels of lysosomal proteases completely degrade engulfed antigens, a property not shared with their DC counterparts [57-59]. It has now been shown, however, that through Mϕ activation, early phagosomes actually have limited proteolysis and can effectively generate epitopes and present antigens, while late phagolysosomes maintain highly degradative capacity [60].

Tissue-resident APCs must be simultaneously capable of initiating a T cell response to invading pathogens while avoiding the risk of prematurely priming T cells to seemingly innocuous events such as apoptosis and cellular turnover. During pregnancy, where the fetus is only partially derived from its mother, this delicate balance is necessary for fetal survival. It is known that the maternal adaptive immune system can recognize paternal antigens, including anecdotal evidence from women who had multiple miscarriages but upon a switch in partner they were successfully able to carry a child to term [61]. In addition, mixed lymphocyte reactions have shown that there is maternal immune cell suppression of fetal or paternal antigens during pregnancy [62]. Another study also demonstrated that female mice can accept an allogeneic tumor of paternal origin during the course of their pregnancy, but will reject the same tumor if pregnant with a "third-party" father [63].

Although most studies emphasize the role of suppression or regulation of T cell responses, very few have focused on the role of the APC. An elegant study done in mice demonstrated that DCs lose their ability to migrate to draining lymph nodes following decidualization and are consequently retained within the uterus [64]. Both mouse and human endometrium are largely lacking in lymphatic vessels; however, during human decidualization, there is heightened lymphangiogenesis that is not seen in mice [65]. This suggests that, in humans, if APCs are capable of migrating to draining lymph nodes, they could be equipped with potent signals to alert effector T cells, emphasizing the importance of a non-migratory APC, such as the Mϕ at the maternal-fetal interface.

We have now demonstrated that there are two distinct subsets of dMϕs found in the early human placenta that can be separated based upon CD11c expression and are termed $CD11c^{HI}$ and $CD11c^{LO}$ [11]. Interestingly, $CD11c^{HI}$ dMϕs were more efficient at protein antigen processing and express genes consistent with APC function, including elevated levels of lipid-antigen presenting molecules such as CD1a, CD1c, and CD1d compared to $CD11c^{LO}$ dMϕs.

Although CD11c, a complement receptor, is often exploited as a single marker to track murine DCs, all human monocytes express CD11c and may retain protein expression following tissue extravasation. Furthermore, expression is maintained during DC or Mϕ differentiation processes [66] and therefore cannot be utilized in the same way to differentiate between human DCs and Mϕs [67]. The similarities between murine $CD11c^{+}$ decidual DCs and human $CD11c^{HI}$ dMϕs are apparent based upon antigen processing and presentation capacity ([11] and LG, BLH, JLS manuscript in preparation). However, murine $CD11c^{+}$ decidual DCs are capable of migrating into the draining lymphnodes during pregnancy and are phenotypically distinct from $F4/80^{+}$ Mϕs within the murine decidua tissue [68]. Moreover, both $CD11c^{HI}$ and $CD11c^{LO}$ dMϕs are phenotypically and functionally macrophages and are equivalently capable of phagocytosis [11]. $CD11c^{HI}$ dMϕs are found in abundance compared to $CD14^{-}$ $HLA\text{-}DR^{+}$ DCs [69], which comprise less than 1 percent of the immune cell compartment at the maternal-fetal interface [55]. These differences in abundance suggest that although there may be overlapping functions, they are likely to be performing specialized and distinct functions. However, due to the low numbers of human decidual DCs, experimentation, and therefore a greater understanding of their function, is extremely difficult.

LIPID ANTIGEN PRESENTATION

Lipids are important for normal homeostasis, including wound healing, growth

and hormone production. Blood lipid concentrations are elevated during pregnancy, presumably for necessary fat storage and fetal supply of fatty acids [70]. They are also important for the development of a variety of hormones, which play integral roles during pregnancy. It is therefore important that phagocytic immune cells of the placenta are capable of recognizing lipids derived from cellular debris of effete decidual and trophoblast cells versus lipids derived from bacterial pathogens that threaten the health of the mother and fetus.

Lipids are not water soluble and are therefore always associated with membranes or lipid-binding proteins, thus making the immunogenicity of lipids different from that of peptides. Lipids are transported throughout the body in complex with apolipoproteins, internalized via the LDL receptor, and delivered to the endocytic compartment, where the lipid-protein complex is dismantled and distributed according to cellular need [71]. Other receptors, such as scavenger receptor A (SR-A), lectin-type oxidized LDL receptor 1 (LOX1 or OLR1), CD36, and other C-type lectins, can also bind modified forms of LDL, including that expressed by apoptotic cells [72]. This suggests several potential routes of entry for a range of environmental lipid antigens.

Several lipid antigens that have been characterized are either of bacterial or somatic origin. Generally lipid antigens are found as either glycolipids or lipo-peptides and are differentially distributed among endocytic compartments [72]. Because different types of lipids are sorted into different endocytic compartments, it has been proposed that CD1 trafficking evolved to sample the most appropriate lipid-containing compartment [73]. CD1 molecules are genetically non-polymorphic cell-surface glycoproteins that present glycolipids and lipo-peptides [73]. CD1 genes have a similar intron/exon structure to MHC class I genes and encode integral membrane proteins consisting of three α helices and an associated β-2 microglobulin domain [74,75]. The α3 domain is the most similar between all of the CD1 molecules, but is not completely homologous, to the MHC class I α3 domain [76]. Loaded CD1 molecules that reach the surface will be capable of presenting to T or invariant TCR NK (iNKT) cells. TCRs recognizing group I CD1 loaded with microbial antigens have highly diverse TCR α and β chains, with a level of heterogeneity similar to that of peptide-recognizing TCRs [77].

Based upon protein sequence, CD1 isoforms can be classified into three groups: group 1, which is comprised of CD1a, CD1b, and CD1c; group 2, which is comprised of CD1d; and group 3, which is comprised of CD1e [72]. Humans express all CD1 isoforms, but these are generally restricted to DCs and other professional APCs. It has been shown that CD1a, expressed by Langerhans cells, is able to efficiently present antigens to CD1a-restricted T cells [78]. Dermal DCs and interdigitating DCs in lymph nodes express CD1b [79,80]. CD1c is largely expressed on B cell subsets, including lymph node mantle zones and germinal centers, in marginal zone B cells of spleen and on a subpopulation of B cells in adult and fetal peripheral blood [81-83].

Moreover, human CD1a, CD1b, CD1c, and CD1d are all expressed by DCs, but appear at different stages of the monocyte-DC differentiation process [84]. Different expression patterns of CD1 on the cell surface, early and late endosomal compartments, lead to different rates of internalization into endosomes [85], suggesting that each CD1 isoform may have a distinct role in the immune response [73,86]. The different patterns of CD1 expression are not completely understood. *In vitr*o studies using monocyte-derived DCs have demonstrated that differing amounts of IgG in tissues can direct CD1 expression profiles, an effect shown to be mediated by FcγRIIa on myeloid cells [87]. Also, Leslie and colleagues demonstrated that lysophosphatidic acid and cardiolipin, lipids in normal human serum, are modulators of CD1 expression via peroxisome proliferator-activated receptor (PPAR) nuclear hormone receptors [88].

Placental lipids remain ill defined, and their potential role in dMϕ expression of

CD1 has yet to be characterized. However, CD1 expression and lipid trafficking may play currently unknown roles at the human maternal-fetal interface. Recent observations from our lab found that CD1a and CD1c molecules on the surface of $CD11c^{HI}$ dMϕs are functionally capable of presentation to clonal T cell lines (LG, BLH, and JLS manuscript in preparation). These data, along with the observation that there are CD1 autoreactive decidual T cell clones, lends further credence to the possibility that placental lipids and CD1 presentation may contribute to maternal-fetal immunotolerance. These observations may help to better understand lipids in pregnancy and in other inflammatory processes.

DECIDUAL MACROPHAGES AND NK CELL CROSS TALK

NK cells were originally characterized based on their innate cytolytic capacities, which, unlike cytotoxic T cells, can directly induce death of tumor cells or virus infected cells [89]. NK cells are also integral cytokine producers in both physiological and pathological conditions. Although NK cell cytotoxic responses directly impact infected cells, it is now thought that NK cell cytolytic and cytokine responses can also regulate antigen specific adaptive immunity via APC priming and cross presentation [90].

NK cell function is based upon fine-tuning of cell surface receptors that activate or inhibit their responses [91]. These receptors signal through corresponding secondary molecules that express immunoreceptor tyrosine activation motifs (ITAMs) or immunoreceptor tyrosine inhibitory motifs (ITIMs). Each NK cell has a particular repertoire of inhibitory and activating receptors on their surface [92]. NK cell activation can be induced by overexpression of activating ligands on cellular surfaces in the absence/reduced expression of inhibitory ligands. For example, NKG2D interacts with several ligands that can be upregulated in response to cellular duress, including DNA damage responses, and induces NK cell activation [93]. Alternatively, NK cells can respond to the absence of MHC class I surface expression ("missing self") [94]. MHC class I can be down-regulated by virus infection or cellular transformation. NK cells can become activated because inhibitory ligands such as CD94/NKG2A that would normally recognize HLA-E or a variety of killer Ig-like receptors (KIRs) that recognize HLA-A, B, and C on the cell surface are missing, thereby tipping the balance between inhibitory and activating receptors, leading to NK cell activation [89,95]. These results suggest that NK cells in steady-state conditions with more inhibitory receptors are poised for recognition of missing self and therefore rapid clearance of MHC class I deficient cells, whereas NK cells with lower levels of inhibitory receptors are poised for mobilization in response to pathogen infections [89].

NK cells are the most abundant immune cell type at the maternal-fetal interface [9]. Decidual NK cells are all $CD56^{bright}$ $CD16^{-}$ and contain cytotoxic granules [96] but are unique compared to $CD56^{bright}$ peripheral NK cells [9]. In an autologous setting, healthy cells are spared from cytolysis due to a high expression of self-MHC [97]. However, at the maternal-fetal interface, trophoblast cells lack HLA-A and -B antigens, yet there is no NK cell cytolysis. This may be in part due to the fact that trophoblast cells express the minimally polymorphic HLA-C and other non-classical HLA molecules including HLA-E, -F, and -G [25] that are recognized by dNK cells. Although it is possible to envision that dNK cells contact trophoblast cells with an inhibitory synapse as opposed to an activating synapse, it has now been shown that dNK cells do in fact form an activating synapse with MHC I null cells but are unable to coordinate their microtubule organizing center (MTOC) with perforin-containing cytotoxic granules, thereby disabling them from killing their target [98]. Combined recognition of non-classical HLA molecules along with the inability to polarize granules may spare fetal trophoblast cells from dNK cell-mediated destruction.

The relatively large abundance of dNK cells may be a potent source of cytokines and

growth factors that are necessary for placental development. dNK cells are important regulators of trophoblast invasion during maternal vasculature reconstruction [99]. However, the induction of dNK cell activation as well as regulation of NK cell responses has yet to be characterized. One possible source of dNK cell regulations is the dMϕ population. dNK cells are in close proximity to $CD14^+$ dMϕs or DC-$SIGN^+$ dMϕs [100], implicating dMϕs as potential mediators.

Alternatively, it was found that in mice with MHC class I-negative tumors that $CD11c^+$ DCs adoptively transferred promoted NK cell-dependent anti-tumor effects and that these effects were contact dependent [101]. These results suggest that APCs can regulate NK cell function *in vivo*. Furthermore, it has been shown that constant cross-talk between NK cells and immature DCs leads to DC maturation as well as an initial priming event in NK cells. This suggests that continuous conversations between innate immune cells can lead to enhanced innate and adaptive immune responses [102]. Interestingly, CD1 molecules presented on NK cell target lines that are HLA class I deficient are capable of inhibiting NK cell cytolytic responses [103,104]. Moreover, in the same system, it was demonstrated specifically that targets expressing CD1b pulsed with a known bacterial lipid antigen for CD1b, enhanced NK cell inhibitory effects.

These results together suggest that dMϕs, or a specific population of dMϕs that are functionally close to DCs, might regulate the large abundance of dNK cells at the maternal-fetal interface. Moreover, this particular interaction may occur by non-traditional receptor-ligand interactions such as CD1 molecules. Thus, we propose that the innate plasticity of Mϕs may allow for environmental signals to give rise to distinct dMϕ populations that play specific roles in regulating both innate and adaptive immune responses at the human maternal-fetal interface.

CONCLUSIONS

Human pregnancy and hemochorial placentation challenges the conventional view of the regulation of immune recognition of foreign antigens. The understanding of how Mϕs, or populations of Mϕs, participate in the maintenance of fetal-placental tolerance could lead to a better understanding of how the innate immune system regulates both itself and the adaptive immune system in order to induce tolerance to what are non-self but non-pathogenic antigens. By characterizing these findings, it is possible that the mechanisms discovered could be exploited for the development of therapeutics and/or therapeutic strategies to alleviate human autoimmune and alloimmune disease/complications.

Macrophage heterogeneity plays important roles in the induction and cessation of inflammatory events, including those necessary at the human maternal-fetal interface. We propose that two distinct dMϕ populations, $CD11c^{HI}$ and $CD11c^{LO}$, allow for integral processes to be done in concert by specialized macrophage populations. Specifically, $CD11c^{HI}$ dMϕs are likely to be important for the processing and presentation of lipid antigen to decidual T cells through specific CD1 molecules (Figure 2). This is consistent with a mechanism by which $CD11c^{HI}$ dMϕs are capable of separating pathogenic and non-pathogenic lipids in order to amount to an appropriate immune response at the maternal-fetal interface without interfering with ongoing tolerogenic mechanisms to fetal antigens. It would be interesting to identify the lipid components found at the human maternal-fetal interface and their ability to dictate CD1 expression on dMϕ cell surface. Furthermore, the lipids may vary in their ability to be loaded into different CD1 molecules and their level of antigenicity. Moreover, irrespective of lipid processing and presentation, CD1 expression by $CD11c^{HI}$ dMϕs may be important in regulating dNK cell cytokine responses and cellular expansion.This does not discount the fact that dNK cells, as well as other cells, and $CD11c^{LO}$ dMϕs may also interact in alternative ways to regulate or respond to dNK cells. However, $CD11c^{LO}$ dMϕs may have more phagocyte-specific function, which is important for organogenesis and placental construction.

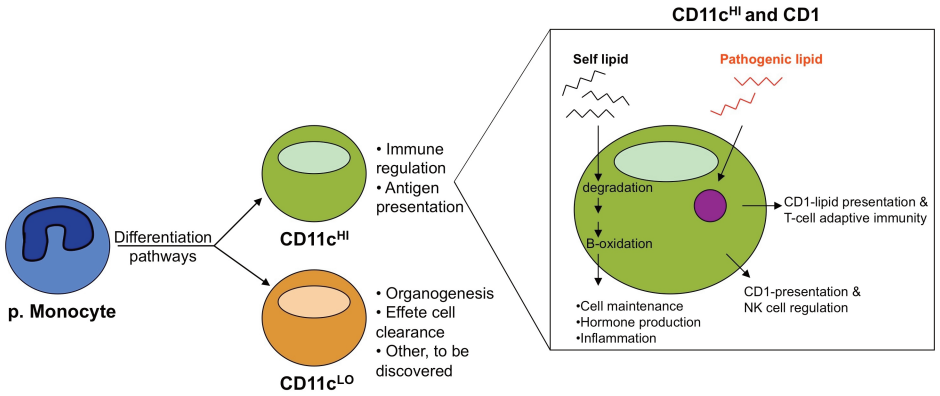

Figure 2. Proposed schematic of CD11c^{HI} and CD11c^{LO} dMϕ heterogeneity. Based on gene expression data, CD11c^{LO} cells appear to be important in organogenesis, phagocytic processes. CD11c^{HI} dMϕs, however, express genes that implicate them as pro-inflammatory, immune regulators, and antigen presenting cells. Further protein and functional data demonstrate that these cells are important in lipid presentation via CD1 molecules. We hypothesize that CD11c^{HI} dMϕs CD1 presentation may be pivotal in the recognition of placental vs. pathogenic lipids. This could enable the amounting of an appropriate adaptive immune response to pathogenic antigens while maintaining tolerance to fetal antigens. Moreover, CD1 molecules, independent of lipid presentation, may be important in regulating NK cell responses in a similar manner to MHC class I molecules at the human maternal-fetal interface.

There are many aspects to understanding how human dMϕ populations confer tolerance to fetal antigens. However, the key may be in immune cell interaction and regulation with a particular emphasis on placental lipid diversity (or specificity) and CD1 molecules. The distinct decidual macrophage populations that we described [11] may help to better understand how macrophage heterogenity in pregnancy, and in other tissues, plays specific roles. Furthermore, the fact that only one population of dMϕs express CD1 molecules may indicate important antigen presentation function and lipid composition at the maternal-fetal interface, an area that remains to be extensively explored.

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