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Review article

What are the roles of macrophages and monocytes in human pregnancy?

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ABSTRACT

During pregnancy, the maternal immune system is challenged by the semi-allogeneic fetus, which leads to systemic and local immunity. Systemic immunity, including enhanced innate immunity with increased activation of monocytes, is induced by various placental factors. Maternal immune adaptations are most evident at the feto-maternal interface, where macrophages are enriched and communicate with various decidual leukocytes. These cells are not only contributing to the protection of the growing fetus from microorganisms, but also aiding placental development by promoting trophoblast invasion and spiral artery remodeling, and the parturition process. Thus, monocytes and macrophages concurrently play important roles throughout the trimesters. Dysregulation of these cells may thus lead to pregnancy complications, such as pre-eclampsia and preterm labor. In this review, monocytes and macrophage subsets and their roles in normal and pathological pregnancies are reviewed.

1. Introduction

During pregnancy, the maternal immune system is challenged by the semi-allogeneic fetus and maternal immune adaptation occurs systemically and locally.

In the peripheral blood, alteration of the innate immune system is evident by its activation with an increased number of innate immune cells, especially monocytes. From the second trimester onward, these cells display activated phenotypes comparable with those observed in systemic sepsis without clinical manifestation. Given that normal pregnancy, particularly from the second trimester onward to parturition, can be considered a status of controlled inflammation. In contrast, uncontrolled severe inflammatory phenotypes are often associated with obstetrical complications such as pre-eclampsia (PE) and preterm labor (PTL) (Norman et al., 2007; Al-Ofi et al., 2014).

At the feto-maternal interface, from the beginning of normal pregnancy, there is an increase in innate immune cells, such as macrophages and NK cells. These cells appear to play a critical role in trophoblast invasion, vascular remodeling, and placentation (Svensson-Arvelund et al., 2014). Increasing evidence suggests that circulating monocytes specifically infiltrate the decidua at the onset of pregnancy and develop into either macrophages or dendritic cells (Svensson et al., 2011). Therefore, composition of peripheral blood monocytes may affect the development of decidual immune effectors. During normal pregnancy, most of the decidual macrophages (DMs) are characterized by an immunosuppressive phenotype with M2 polarization, supporting the notion that these cells play a major role in feto-maternal immune tolerance (Gustafsson et al., 2008; Svensson et al., 2011). In contrast, in pregnancy complications such as PE, there appears to be an increased number of M1 macrophages, which contributes to poor placental development (Medeiros et al., 2014). Macrophages also represent a major subset of antigen-presenting cells (APCs) in the human decidua, and decidual APCs are involved in the regulation of local immunological homeostasis, which appears to be essential for successful pregnancy (Nagamatsu and Schust, 2010).

Therefore, monocytes and macrophages may concurrently play important roles in pregnancy, and in this review the role of monocytes/macrophages and their subsets in normal and pathological pregnancies is addressed.

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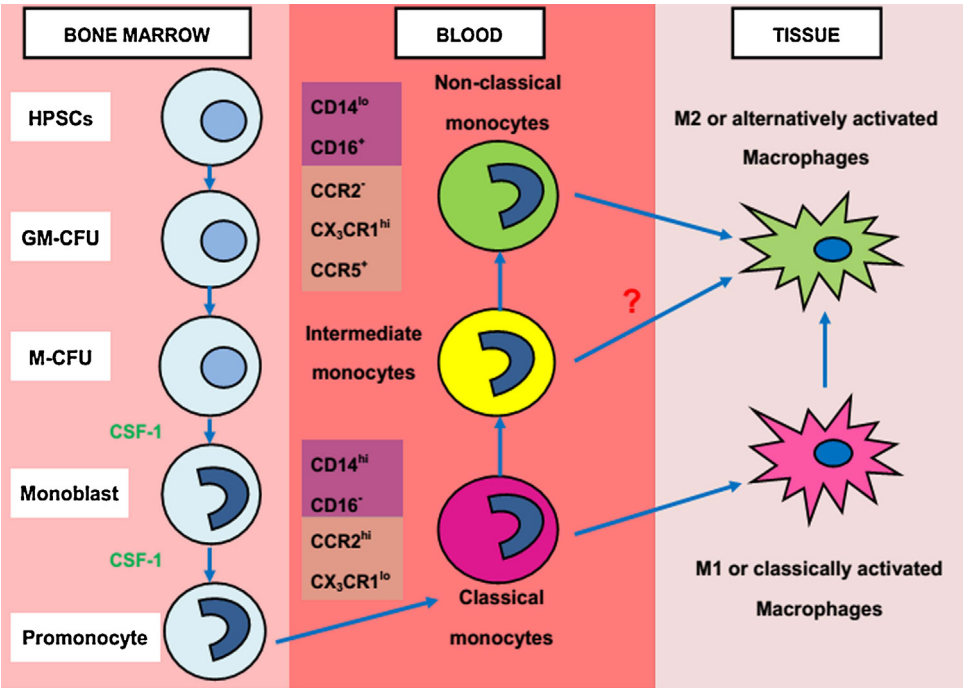

Fig. 1. Origins and differentiation of monocytes and macrophages. Monocytes and macrophages are derived from hematopoietic stem cells (HPSCs) in bone marrow, which differentiate into monocytes and macrophages through multipotent progenitor stages, from granulocyte/macrophage colony-forming units (GM-CFUs) to monocyte colony-forming units (M-CFUs), monoblasts, and promonocytes under the regulation of colony-stimulating factor 1 (CSF-1). Promonocytes are further converted to monocytes in peripheral blood. Based on the expression levels of CD14 and CD16, human monocytes are classified into three subpopulations, namely, classical, intermediate, and nonclassical monocytes. After migration to the tissues, monocytes differentiate into M1 or M2 macrophages. Modified from the figure in Lee et al. (2013).

2. Peripheral blood monocytes, their subsets and function

Monocytes arise from precursors in the bone marrow and these cells have pivotal functions in immune homeostasis, defense against infection, tissue repair, and inflammation (Fig. 1). Recent evidence shows that circulating monocytes are a heterogeneous population (Ziegler-Heitbrock et al., 2010) that can be categorized into three subsets based on the expression levels of the lipopolysaccharide (LPS) receptor, CD14, and the Fcγ-III receptor, CD16: "classical" monocytes ($CD14^{hi}CD16^{neg}$), "intermediate" monocytes ($CD14^{hi}CD16^{pos}$), and "nonclassical" monocytes ($CD14^{dim}CD16^{pos}$) (Ziegler-Heitbrock et al., 2010). The three monocyte subsets represent sequential maturation stages in the differentiation of peripheral monocytes; namely, the classical monocytes originate from the bone marrow and mature into nonclassical monocytes via intermediate monocytes (Ziegler-Heitbrock et al., 2010). Some studies show that the intermediate subset shares greater similarity with the nonclassical than with the classical subset (Wong et al., 2011; Zawada et al., 2011). However, another study indicates a close relationship between the intermediate and classical monocyte subsets (Cros et al., 2010). These findings suggest that there might be a developmental relationship among these subsets (Ziegler-Heitbrock et al., 2010) (Fig. 1); however, conflicting results indicate a need for further characterization.

These three subsets show differences in phenotypes, function, and inflammatory potential (Table 1) (Wong et al., 2012). The classical monocytes (comprising approximately 90% of total monocytes) specialize in phagocytosis, production of reactive oxygen species (ROS), and secretion of inflammatory cytokines in response to the binding of ligands, such as LPS to extracellular Toll-like receptors (TLRs) (Saha and Geissmann, 2011). Compared with classical monocytes, the intermediate monocytes (approximately 5%) display the characteristics of activated cells, such as increased expressions of MHC class II (HLA-DR) antigens and intracytoplasmic TNF-α (Rossol et al., 2012). By contrast, nonclassical monocytes (approximately 5% of monocytes) do not generate ROS and possess weak phagocytic activity, although they secrete high amounts of pro-inflammatory cytokines (TNF-α and IL-1β) after TLR activation by LPS, viruses or nucleic acids (Wong et al., 2011). These cells patrol vascular endothelium and readily remove virally infected or injured cells. Indeed, $CD16^{pos}$ monocytes (intermediate/nonclassical monocytes) are reported to be involved in the pathogenesis of inflammatory diseases (Zimmermann et al., 2010; Wong et al., 2012).

3. Tissue macrophages and their subsets

Circulating monocytes can give rise to tissue macrophages. Generally, tissue macrophages are divided into two subsets: classically activated macrophages, or M1 macrophages, and alternatively activated macrophages, or M2 macrophages (Mantovani et al., 2013). These subsets differ with regard to surface markers, cytokine secretion and effector function (Table 2) (Italiani and Boraschi, 2014). M1 macrophages are involved in inflammatory responses with elevated production of TNF-α and IL-12, whereas M2 macrophages have immunosuppressive properties and participate in biological activities, such as scavenging for apoptotic cells and tissue remodeling (Mantovani et al., 2013). The M1 and M2 macrophage subsets can shift from one to the other phenotype depending on the local tissue microenvironment (Crane et al., 2014). Recent studies have shown that M1 subsets could differentiate into M2 subset and vice versa, under different culture conditions (Italiani et al., 2014) when exposed to IFN-γ or TLR-ligands (Stout et al., 2005; Mylonas et al., 2009). Therefore, these two macrophage subsets represent the extremes of immune polarizations and may switch their phenotypes in response to microenvironmental cues (Italiani and Boraschi, 2014).

Moreover, peripheral blood monocytes are recruited into the tissue by encountering different microenvironmental milieus, such as growth factors, cytokines and microorganism-associated molecu-