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Review article

Maternal monocytes in pregnancy and preeclampsia in humans and in rats

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ABSTRACT

Monocytes are short-lived cells, arising from the bone marrow and maturing in the circulation. They play an important role in immune responses and are thought to be important for healthy pregnancy. In humans, 3 subpopulations of monocytes have been identified: classical, intermediate and non-classical monocytes. These subpopulations have different functions and phenotypical characteristics. Healthy pregnancy is characterized by a pro-inflammatory condition, with increased numbers of monocytes and monocyte activation as well as with increased numbers of intermediate monocytes and decreased numbers of classical monocytes. This may suggest monocyte maturation. Preeclampsia is an important pregnancy complication characterized by hypertension and proteinuria developing in the second half of pregnancy. The pathophysiology of preeclampsia is associated with further activation of the inflammatory response, further activation of monocytes and further monocyte maturation. In the present review we focus on the role of monocyte activation and maturation in healthy and preeclamptic pregnancy.

1. Introduction

Pregnancy poses a unique immunological challenge to the mother. Semi-allogeneic placental tissue is in direct contact with circulating and uterine maternal immune cells. Therefore adaptations in the immune response are seen locally in the uterus and decidua, but also peripherally in the maternal blood (Veenstra Van Nieuwenhoven et al., 2003b). It has been suggested that the adaptations of the peripheral immune response are due to the circulation of maternal blood through the placenta and the secretion of placental factors into the maternal circulation (Sacks et al., 1999; Mellembakken et al., 2002). Adaptations in the maternal peripheral immune response are observed in the specific immune response, such as a decreased Th1/Th2 ratio in T cells (Wegmann et al., 1993; Saito et al., 1999; Veenstra Van Nieuwenhoven et al., 2002), increased numbers of regulatory T cells during the first and second trimester of pregnancy (Saito et al., 2010; Ernerudh et al., 2011) and an increased Treg/Th17 ratio (Figueiredo and Schumacher, 2016). Changes are also observed in NK cells (Veenstra Van Nieuwenhoven et al., 2002; Borzychowski et al., 2005). Not only cells of the adaptive immune response, but also cells of the innate immune system, monocytes and granulocytes, are affected by pregnancy. They show an activated phenotype (Sacks et al., 1998).

Preeclampsia is a major complication of the second half of pregnancy. It is characterized by hypertension and proteinuria (Duley, 2009; Steegers et al., 2010). The most severe form of preeclampsia, early onset preeclampsia, is thought to arise from poor placentation (Redman and Sargent, 2009). This results in the production of pro-inflammatory factors by the diseased placenta into the maternal circulation (Hung et al., 2004; Levine et al., 2004; Germain et al., 2007; Spaans et al., 2014a). Such factors may further activate the already activated monocytes in pregnancy and together with activation of other inflammatory cells, such as granulocytes and endothelial cells, finally induce the full blown syndrome of preeclampsia (Redman and Sargent, 2009).

The present review will focus on peripheral monocytes in pregnancy and preeclampsia. Changes in circulating monocytes will be discussed as well as the role these cells may play in the physiology of normal pregnancy and the pathophysiology of preeclampsia. Animal models will be discussed since they are important in understanding the role of monocytes pregnancy and preeclampsia.

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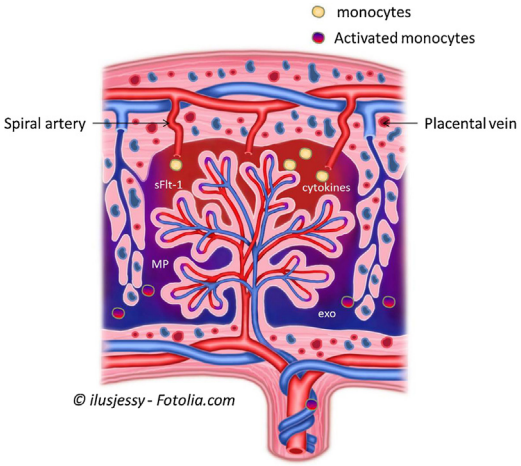

Fig. 1. Monocytes in the utero-placental circulation.
Monocytes get into the intervillous space via the spiral arteries. In the intervillous space they can come into direct contact with the fetal syncytiotrophoblast. The syncytiotrophoblast also produces various factors into the intervillous space (and thus into the maternal circulation), such as syncytiotrophoblast microparticles (MP) or exosomes (exo), cytokines, antiangiogenic factors (such as sFlt-1). Such factors may also activate monocytes in the intervillous space. Activated monocytes leave the intervillous space via the placental veins to get into the maternal circulation.
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1.1. Utero-placental circulation

The placenta is important in maternal-fetal exchange of nutrients and gases. In a human placenta, which is hemochorial, this is enabled by fetal villi bathing in maternal blood in the intervillous space (Boyd JD, 2013). The placenta develops after invasion of fetal trophoblast into the endometrium and the spiral arteries in the endometrium starting 5–6 days after fertilization (Sadler, 2004). Although, the development of the villous structure and the intervillous space starts early in pregnancy, the connection of the intervillous space with the spiral arteries does only develop after 9 weeks of pregnancy (Jauniaux et al., 2000). From that time onward, maternal blood is in close contact with the fetal villi. This enables easy exchange of gases and nutrients between mother and fetus, but also poses a challenge to the mother, since maternal immune cells circulating through the placenta in the intervillous space are in direct contact with fetal semi-allogeneic trophoblast cells. This contact of maternal immune cells with the fetal trophoblast may influence the maternal immune cells. Not only direct contact between fetal trophoblast and maternal immune cells may influence the maternal immune cells, it has also been suggested that the trophoblast secretes many factors into the maternal circulation that also may also affect the maternal immune cells. Such factors may be cytokines (Sacks et al., 2001), fetal DNA (Bianchi et al., 1996) and syncytiotrophoblast microvesicles (Redman et al., 2012) (see Fig. 1).

1.2. Monocytes

Monocytes are short-lived circulating cells, which arise from myelo-monocytic precursors in the bone marrow. They comprise about 5–10% of the circulating blood leukocytes and migrate into the tissue to become macrophages and dendritic cells (Gordon and Taylor, 2005). They have various functions, such as phagocytosis, antigen presentation and cytokine production (Gordon and Taylor, 2005). Monocytes in the peripheral circulation have a heterogeneous morphology, since they can vary in size, show different degrees of granularity and may have different nuclear morphology (Gordon and Taylor, 2005). In humans, monocytes can be identified by expression of the extracellular marker CD14, which is expressed by all monocytes (Gordon and Taylor, 2005).

1.2.1. Monocyte subsets

In humans, three monocyte subsets exist, which can be distinguished based on their expression of CD14 and CD16 (FcγR-III). The main subset, the classical monocytes, representing 90–95% of the monocytes, is a subset, which expresses high levels of CD14, while lacking CD16 expression. Non-classical monocytes are the second subset, which is characterized by low expression of CD14 with high expression of CD16. A third, intermediate subset of monocytes (high CD14 expression and high CD16 expression) has also been defined (Ziegler-Heitbrock et al., 2010). It is thought that classical monocytes arise from the bone marrow and mature in the circulation via intermediate monocytes into non-classical monocytes (Sunderkötter et al., 2004; Ziegler-Heitbrock et al., 2010). The monocyte subsets differ in many aspects (Gordon and Taylor, 2005; Ziegler-Heitbrock et al., 2010). Classical monocytes are able to generate reactive oxygen species (ROS) and produce cytokines after stimulation with Toll-like receptor agonists. They are strong phagocytes. Non-classical monocytes do not generate ROS, but are more efficient producers of pro-inflammatory cytokines after TLR stimulation, while they are weaker phagocytes (Gordon and Taylor, 2005). The non-classical monocytes have a longer half-life and infiltrate into resting and inflamed tissue (Gordon and Taylor, 2005). They are thought to patrol and survey the endothelium and rapidly invade the tissue and initiate the inflammatory response (Auffray et al., 2007; Ziegler-Heitbrock et al., 2010). The function of intermediate monocytes is less clear and in general they have an intermediate function between classical and non-classical monocytes (Wong et al., 2011). Based on their high gene and protein expression of MHC II (Wong et al., 2011; Groen et al., 2015), they may have an important role in antigen presentation and T cell activation. Intermediate monocytes have been shown to be increased in various inflammatory diseases (Rogacev et al., 2012; Ziegler-Heitbrock, 2015; Wong et al., 2012), suggesting that they play a pathophysiological role in these diseases.

2. Maternal monocytes in pregnancy

Changes in the innate immune response are apparent during pregnancy. Most obvious are the increased numbers of circulating monocytes and granulocytes (Siegel and Gleicher, 1981; Kuhnert et al., 1998; Veenstra Van Nieuwenhoven et al., 2003a). However, not only are numbers of monocytes increased during pregnancy, also the monocytes are activated and show functional changes. Phenotypical activation of monocytes during pregnancy has been shown by increased expression of the activation markers CD11b, CD14 and CD64 on monocytes from pregnant women as compared with monocytes from non-pregnant women (Sacks et al., 1998; Naccasha et al., 2001; Luppi et al., 2002a,b). Functional changes in monocytes from pregnant women have been demonstrated by increased production of oxygen free radicals (Sacks et al., 1998) and decreased phagocytosis in pregnancy (Lampe et al., 2015). Also changes in cytokine production have been observed (Veenstra Van Nieuwenhoven et al., 2003a; Faas et al., 2014a). Cytokine production can be studied in unstimulated and stimulated monocytes. Unstimulated monocyte cytokine production represents the in vivo cytokine production, while stimulated monocyte cytokine production represents the ability of monocytes to respond to stimuli in vivo. For unstimulated monocytes, results have been inconsistent, since increased (Luppi et al., 2002a), decreased (Faas et al., 2014a) or unchanged (Veenstra Van Nieuwenhoven et al., 2003a;

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