Shift in Macrophage Polarity and Preeclampsia

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Editorial

Preeclampsia is a serious pregnancy disorder with incidence rates ranging from 3-7% [1] that causes approximately 14% of all pregnancy-related maternal deaths and 15% of premature births worldwide [2]. This condition is characterized by maternal hypertension, glomerular endotheliosis, and proteinuria which usually occur in the last trimester of pregnancy. The complete pathogenesis of preeclampsia is still unclear [3].

Dramatic changes occur in the uterine immune cell population after embryonic implantation and the development of the decidua's. In the first trimester leukocytes account for almost 40% of the total decidual cell population [4]. During early pregnancy natural killer (NK) cells and macrophages become the prominent uterine immune cells [5]. Decidual leukocytes include about 20-30% macrophages, versatile cells with plasticity, that play roles in both innate and adaptive immunity [6]. The ability of macrophages to respond quickly and efficiently to the microenvironment and alter antigen-presentation and cytokine production underpins the rapidity of macrophage-mediated immunomodulation. Macrophages play essential roles in fetal tolerance, trophoblast invasion, and tissue and vascular remodelling [7].

Macrophages are functionally sub-divided into classically activated (M1) and alternatively activated (M2) [8] subtypes based on their cytokine expression patterns. Pathogenic LPS and tissue damage-induced IFN-γ and TNF induce pro-inflammatory M1 macrophages [9] which up-regulate iNOS enzyme expression to produce ROS and NO from arginine leading to microorganism killing. M1 macrophages produce higher level of IL-12, IL-23, and lower level of IL-10 [10]. In contrast M2 macrophages are anti-inflammatory and are induced by apoptotic cells and MCSF as well as Th2 cytokines such as IL-4, IL-13, IL-10. M2 macrophages produce higher level of IL-10 and lower level of IL-12 and IL-23 [11]. They up-regulate arginase enzyme expression leading to ornithine production from arginine and participate in tissue repair and remodelling as well as scavenging of apoptotic cells [12].

The ability of decidual macrophages to acquire an M2 phenotype provides the immune tolerance that the fetus requires for a successful pregnancy [13]. The cellular microenvironment dictates whether macrophages acquire a proinflammatory (M1) or anti-inflammatory (M2) phenotype. To date a limited number of studies have focused on phenotyping decidual macrophage lineages and subsets. Throughout the pregnancy decidual macrophages shift polarity between M1 and M2 phenotypes. The M1 subtype predominates during the peri-implantation period [14] and macrophages transition to a mixed M1/M2 phenotype as trophoblasts invade the endometrial stroma and become established in the endometrial lining. This mixed population pattern persists until the early phase of 2nd trimester [15]. Once the placenta is developed, an M2 phenotype predominates, which prevents fetal rejection throughout the pregnancy [7].

With preeclampsia the decidual macrophage phenotype shifts from an M2 to an M1 phenotype [16]. During a normal pregnancy trophoblasts invade uteroplacental arteries and are largely devoid of macrophages. Whereas in IUGR and preeclampsia apoptotic trophoblasts are found in the vicinity of arterial walls and there is reduced trophoblast invasion of uteroplacental arteries [17]. Increased trophoblast apoptosis may initiate inflammatory events that promote further trophoblast cell death thus preventing normal trophoblast invasion [18]. MI macrophages increase Fas expression and enhance trophoblast sensitivity to Fas-mediated apoptosis [19]. The trophoblast endovascular pathway is affected by macrophage-induced apoptosis resulting in the pregnancy complications associated with preeclampsia with increased expression of TNF-α and IFN-γ and EVT apoptosis [20]. Increased macrophage and dendritic cell numbers are present at the implantation site in preeclampsia [21]. GM-CSF, a potent inducer of macrophage differentiation, may also influence the pathogenesis of preeclampsia as its levels are increased in the preeclamptic decidua due to increased levels of the proinflammatory cytokines TNF-α and IL-1β [21]. Hypoxic conditions, oxidative stress, and inflammation induce necrosis or aponecrosis of trophoblasts [22]. After phagocytosis of necrotic and aponecrotic trophoblasts, macrophages and dendritic cells produce type-I cytokines and aggravate inflammation [22]. This may induce apoptosis of EVTs culminating in the inferior placentation observed in preeclampsia [20].

Macrophages are novel therapeutic targets that can be used to deliver nanoparticles in the treatment of genetic disorders

associated with macrophage dysfunction or persistent infections. Macrophage-delivered nanoparticles can also induce macrophage death, modulate accessory functions of macrophages and be used to diagnose pathologic conditions such as cancer [23]. The M2 pro-inflammatory macrophage phenotype can modulate various anti-cancer therapies. Indeed, macrophages can now be manipulated from an M2 to an M1 phenotype so that they can phagocytose tumour cells [24]. Use of histidine-rich glycoprotein (HRG), which induces down-regulation of macrophage PlGF, promotes blood vessel normalization and increases the delivery and efficacy of chemotherapy in mouse tumour models [25]. Alternatively up-regulation of nuclear factor κB signalling [26] or exposure of M2 macrophages to anti- IL10R antibodies combined with the TLR 9 ligand, CpG, induces haemorrhagic tumour necrosis, activation of DCs and cytotoxic T cells, and tumour clearance [27].

Strategies can be adopted to manipulate macrophage polarity at the maternal-fetal interface favouring the M2 sub-type to subdue pregnancy complications. Some pregnancy complications such as spontaneous abortions and disorders caused due to inadequate spiral artery remodelling are associated with decidual M1/M2 imbalances in the early inflammatory phase of pregnancy when the M1 subtype predominates [28]. Decreased numbers of M2 macrophages are observed in preeclampsia [29] and the number of non-classical monocytes increases which may play a role in inflammation [30]. Polarization of M1 macrophages to an M2 subtype may be a therapeutic target for preeclampsia since the M1 macrophage phenotype predominates in preeclampsia where severe inflammatory conditions prevails at the maternal-fetal interface.

In conclusion, decidual macrophages play significant roles in pregnancy due to their immune suppressive properties and plasticity. They are involved in tissue and vascular remodelling in early pregnancy as well as antigen presentation to T lymphocytes to induce adaptive immunity against microbial attack. They also likely have a significant role in the pathogenesis of preeclampsia and may be involved in other pregnancy disorders such as IUGR and RSA. Novel therapeutics against these pregnancy-related diseases should be identified using system biology approaches to understand how decidual macrophages switch phenotypes and their role in physiological and pathological conditions.

Acknowledgments

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