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A Role for Placental Mast Cells in Normal and Complicated Pregnancy

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Abstract

Mast cells are often categorized as the main actors of allergy disorders, however their involvement in innate and adaptive immunity is being increasingly recognized. According to their location, mast cells exhibit tissue-specific phenotypes and functions. Uterine mast cells are well-documented as key regulators of implantation, placentation and fetal growth throughout pregnancy, but the role of placental mast cells remains obscure. The present review provides an overview of current knowledge of placental mast cells in terms of location physiology and functions in normal and complicated pregnancy.

Keywords: Placental mast cells; Pregnancy; Placenta; Preeclampsia; Gestational diabetes mellitus; Infection

Introduction

The placenta is a chimeric, highly complex organ consisting of maternal and fetal structures, essential for the course of pregnancy. The placenta ensures adequate nutrition, respiration and protection of the fetus from aggressions. A wide variety of cells are involved in these different placenta functions but also orchestrate the regulation of placenta immune responses to maintain feto-maternal tolerance [1]. They include trophoblast cells and immune cells such as natural killer cells, macrophages, lymphocytes, dendritic cells and Mast Cells (MCs). Their impairment contributes to pregnancy complications [2].

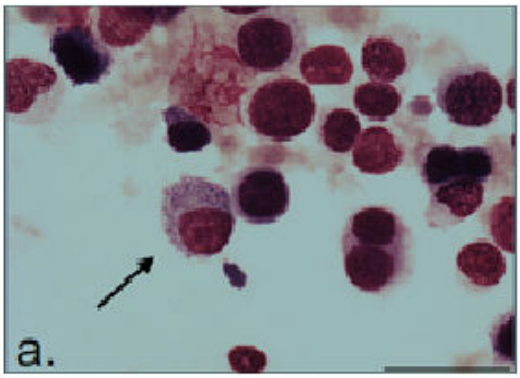
MCs are innate immune cells that express specific markers including CD117 (c-kit) and IgE (FcεR). Their cytosol contains large secretory granules filled with an array of mediators including histamine, several cytokines and proteases such as tryptase, chymase [3]. Since the first description of MCs by Paul Ehrlich in the 19th century [4], their multiple functions are constantly reappraised [5,6]. Their role in allergic reactions is well-documented but MCs are also sentinels of innate immunity and regulator of adaptative responses [7]. In addition, their phenotypic and functional plasticity rely on their tissular location [3]. It has been reported that placental MCs play several roles in pregnancy such as regulation of tissue remodeling, angiogenesis, trophoblast invasion and spiral artery adjustment [8]. Initially described as cells exhibiting characteristic metachromasia, MCs from placenta were identified by Selye in 1965 [9]. Almost thirty years later, Purcell and Hanhoe identified these cells as MCs by means of toluidine blue, alcian blue and chloro-acetate-esterase staining, presence of dense granules using electron microscopy and presence of cell-bound-IgE [10].

We and others contributed to the development of methods to isolate placental cells [11,12] including placental MCs which may open new horizons in MC research [13,14]. The study of isolated placenta MCs with high throughput methods will enable to identify their role in normal and pathological pregnancies. In this review we realized an overview of the functions of placental MCS in normal and complicated pregnancies.

Characterization and Functions of Placental Mast Cells

The placenta is a highly specialized organ with both maternal and fetal segments whose functions are essential for the growth and development of the fetus. It provides oxygen and nutriments to the fetus and facilitates the elimination of carbon dioxide and other waste products. Placental immune cells are located in the different compartments of the placenta and contribute to its functions throughout pregnancy including the immune tolerance, the release of hormones, the maternal/fetal circulation or the protection against pathogens. Among placental immune cells, MCs are present in human and mouse decidual tissue [15]. MCs were present in the decidua of murine normal pregnancies since day 10 of gestation [8]. Using May-Grünwald-Giemsa and Toluidine blue staining we identified the placental MCs population (**Figure 1A**). We established a procedure for specific isolation of MCs from placenta using IgE and CD117 positive selection [14]. We observed by electron microscopy cellular characteristics of placental MCs: ovoid nucleus and presence of dense granules in the cytosol (**Figure 1B**). The use of a high throughput approach of microarrays enabled to us to identify reproduction-related transcriptomic

pathways in placenta including Wnt pathway and genes involved in hormonal responses [16]. We reported modulated genes involved in estrogen and progesterone responses. One of the best means for assessing the role of placental MCs relies on MC deficient mice bearing defective c-Kit signaling [17]. C57BL/6J-Kit$^{W\text{-}sh/W\text{-}sh}$ mice exhibit mutations in the *white spotting* (W) locus (i.e. c-kit) and are devoid of MCs: they exhibit failure for implantation, placentation and alteration of spiral artery remodeling that could be rescued by the transfer of wild-type MCs [8]. However, these studies did not discriminate the role of placental MC from that of uterine MCs [18].



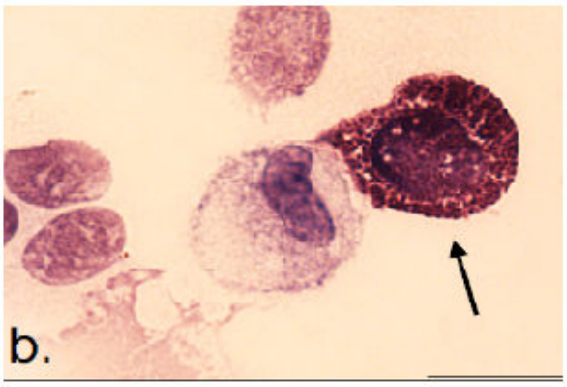


Figure 1A: Placental MCs population.

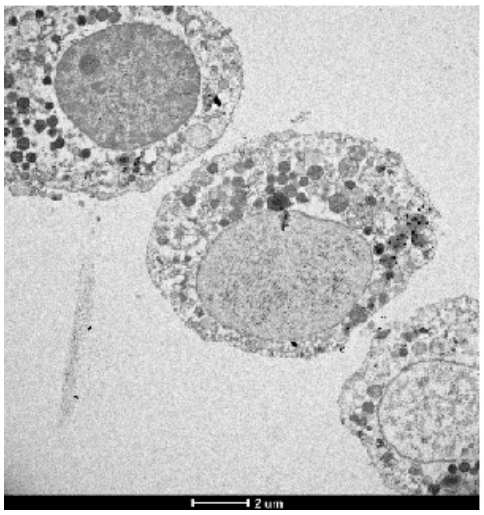


Figure 1B: Presence of dense granules in the cytosol.

The discovery of placental MCs was initiated by the detection of tissue histamine [19,20]. Histamine is synthetized by a progesterone-regulated enzyme, the pyridoxal phosphate containing L-histidine decarboxylase whose expression is 1000 times higher in placenta than in other organs [21]. One single placental MC produces approximately 1 pg of histamine stored in intracellular granules and a human placental tissue contains 7.6 × 105 MCs/g of wet weight [10]. Histamine is released following stimulation of placental MCs with anti-IgE antibodies, calcium ionophore A23187 or the polybasic secretagogue compound 48/80. There is evidence for the involvement of placental MC-derived histamine in different steps of placenta development. Histamine receptors including H1R et H2R are found in decidua, amnion and chorion. Histamine receptors are expressed by placental cells such as cytotrophoblast and syncytiotrophoblast. H1R, but not H2R receptor, is expressed in syncytiotrophoblasts of placental villi. Histamine promotes human cytotrophoblast invasiveness through specific activation of H1R. Histamine increases αvβ3 integrin expression by trophoblast. The binding of histamine to H1R receptor initiates cell renewal of apoptotic trophoblastic cells [22-27]. However, all these results must be analyzed with caution because histamine may also originate from decidual cells distinct of MCs [28].

The use of perfused isolated placentas revealed the effects of other MC mediators. Leukotrienes B4, C4 and D4, thromboxane A2 and prostaglandin PGF2-α are involved in vasoconstriction in the placenta tissue while prostacyclin leads to vasodilation [29-32]. Altogether, these data suggest a key role for placental MC mediators in placenta vasculature, but direct experimental evidence is still lacking. In particular, the individual and combined effects of each MC mediator in placenta homeostasis need to be assessed.

The interaction with microorganisms and their products is another critical role of placental cells. On the other hand, a wide array of recent studies highlighted MCs as master effectors and regulators of the host's responses to microorganisms, since MCs are strategically located in tissues at the host-environment interface [33]. They are able to recognize invading pathogens using Toll-like receptors as microbial sensors, are equipped with microbicidal tools (phagocytosis of microorganisms, release of inflammatory cytokines, anti-microbial agents or extracellular traps) and shape downstream innate and adaptive immune responses [5,6,33-35]. Although direct experimental evidence is lacking, knowledge on placental and MCs responses to microorganisms suggest that placental MCs might be sentinel cells of anti-infectious immunity.

Placental Mast Cell Functions in Pathological Pregnancies

An excessive release of MC mediators is associated with pregnancy complications and pre-term delivery [18]. A relationship between placental MC number and mediators has been reported in preeclampsia, gestational diabetes, intrauterine growth restriction, spontaneous pre-term birth and placental infections such as chorioamniotis. Preeclampsia, a pregnancy-specific disorder, represents one of the major causes of maternal morbidity and mortality with a worldwide prevalence of 5%-8% [36]. Placenta abnormalities such as poor perfusion principally due to shallow spiral artery invasion have been reported in preeclampsia [37]. Because of its vasoconstrictor effect, histamine may play a central role in placental vasculature [38]. Several reports have shown that placental MCs number and histamine concentrations are affected in preeclampsia [10,22,39]. Some studies reported increased number of placental MCs [22] whereas others observed that their number are decreased in the villous part of the placenta. These findings are associated with a low vascularization of placenta in preeclampsia suggesting deficiency in placental MC function. The increase in histamine in preeclampsia is due to placental and not uterine MCs. In severe preeclampsia, placental MCs that are positive for chymase are increased [39-41].

Gestational diabetes mellitus is an endocrine complication of pregnancy [42]. The pathology is a source of complications for the mother but also the developing fetus; this is related to severe placenta damage [43]. Indeed, clinical and immunohistochemistry investigations reported inflammatory lesions and development of villous microvessels in placenta. The concentration of histamine in placenta is higher in diabetic pregnant women than in normal placenta. The increase of histamine concentration is associated with higher number of MCs (with an abnormal MC-tryptase/MC-tryptase-chymase ratio) and vessels networks in the villous part of the placenta [31]. Additionally, the expression of H1 and H4 receptors is increased in diabetic placenta compared to normal pregnancy. Overview of these data provide evidence on a role for placental MCs and histamine in gestational diabete mellitus, but molecular and cellular mechanisms have to be explored.

Sundstrom et al. showed a key role for progenitors and placental MCs in HIV infection [44]. Indeed, they showed that progenitors and placental MCs from HIV-infected women harbored inducible virus and acted as reservoirs for HIV infection. We studied Q fever, a zoonosis due to Coxiella burnetii, an intracellular microorganism [45]. The microorganism has a strong tropism for placenta tissue. We found that circulating MC progenitors decreased in Q fever patients [46-48]. On another hand, we described a previously unknown anti-bacterial mechanism of MCs in *C.burnetii infection*. The interaction of *C. burnetii* with MCs induced the formation of extracellular actin firrrrlaments, named cytonemes (**Figure 1C**) that mediate capture and destruction of entrapped bacteria through the expression of cathelicidin and neutrophil elastase. In contrast, incubation of MCs with *C. burnetii* did not support bacterial uptake or extracellular trap formation, i.e. the usual way of myeloid cells to combat microbes. Instead, MCs produced cytonemes and their associated microbicidal activity depended on the cooperation of the scavenger receptor CD36 and Toll-like receptor-4 (**Figure 2**). Although the role of MCs is now admitted in response to infection, the function of MCs from placenta is poorly investigated.

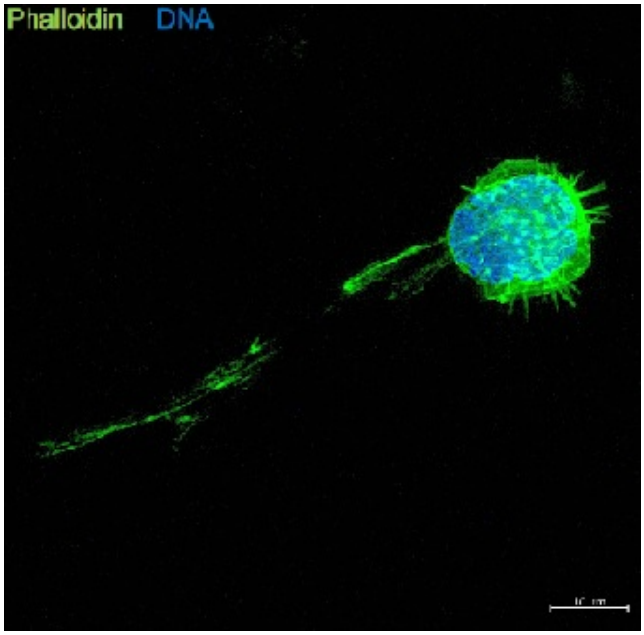


Figure 1C: Cytonemes that mediate capture and destruction of entrapped bacteria.

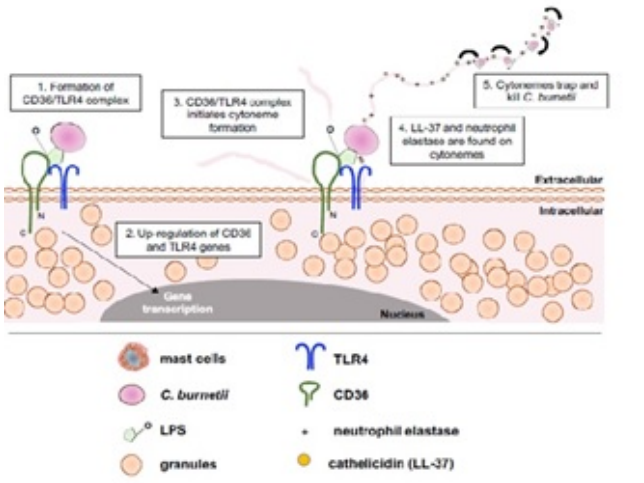


Figure 2: Scavenger receptor CD36 and Toll-like receptor-4.

Conclusion

MCs are an original population of tissue-resident innate immune cells involved in tissue homeostasis, inflammation, and immune responses. The understanding of placental MC role in pregnancy is emerging. Their recent isolation now offers the opportunity for mechanistic studies. The specificity of the response to intracellular bacteria with cytoneme formation will contribute to expand the knowledge of MCs physiology and their pathological dysfunctions.

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Author Contribution

S.M., J.V. and J.L.M. wrote the paper.

Conflict of Interest

The authors declare no competing interests.

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