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Review: Putative roles for the macrophage migratory inhibitory factor at the maternal fetal interface

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ABSTRACT

Complex and dynamic networks of molecules participate in the essential interactions between maternal organism, placenta and fetus in a healthy and successful pregnancy. Macrophage migratory inhibitory factor (MIF) is one of several molecules produced at implantation sites; MIF is mostly expressed by trophoblast cells. This has led to expectations of MIF's relevance as a partner in the maternal/fetal dialog. MIF is known by its biological interactions and functional roles as an activator of innate immunity, regulating subsequent adaptive responses, which include inhibition of migration of mononuclear cells in vitro, antagonism of glucocorticoids, and regulation of expression of Toll-like receptor 4. Beyond roles in the inflammatory response, MIF can interfere with proliferative activities in different cell types, as well as with cell death pathways. This intriguing factor found at the human, porcine, ovine, bovine and rodent maternal–fetal interfaces is present in a time- and spatially-dependent manner, indicating regulatory roles in the process of embryo implantation, placental development, maintenance of pregnancy and birth. Here, we will review MIF participation in placental physiology, including new evidence for a dialog with uterine cells, and a potential role in protection of uterine decidual cells.

1. Introduction

Macrophage migration inhibitory factor (MIF) is a soluble pro-inflammatory cytokine released by activated leukocytes and immune-competent cells. MIF inhibits the macrophage random migration from peritoneal exudates [1,2]. The gene and protein expression of MIF has been reported in different organs and cells, including leukocytes, placenta and uterus [1,3–7]. Its expression can be constitutive or induced, depending on the cell type and, in pregnancy is regulated by proinflammatory factors, glucocorticoids, and hypoxic factors acting on AP-1, CREB, and HIF-1α response elements [1,8–11].

The association of MIF with inflammation and immune defense has been explored after LPS administration to rats, where preformed MIF is rapidly released by different cell types (alveolar macrophages, hepatocytes, Kupffer cells, adrenal cortex fasciculata and glomerulosa zones, T and B cells), but mainly macrophages [12]. Under this condition, MIF may act as an activator of innate immunity, regulating subsequent adaptive immune responses and modulating T and B cell responses [12]. MIF production by macrophages and T-cells leads to autocrine regulation of proinflammatory cytokine production (IL-2, IL-4, IL-5, IL-13, IFN-gamma, etc.) [2].

The biological activities of MIF suggest that it can inhibit mononuclear cell migration in vitro and, antagonize immunosuppressive effects of glucocorticoids by several mechanisms, which include: sustaining ERK1/2MAP kinase activation, inhibition of the glucocorticoid-induced expression of the nuclear factor-κB inhibitor (IκB) and, inhibition of the glucocorticoid induction of MAP kinase phosphatase (MPK1) [10,11]. MIF also can act by regulating the expression of Toll-like receptor 4 (TLR-4) [13] and suppress induced apoptosis that is dependent on p53 [14,15]. These effects are particularly important in triggering inflammatory responses and proliferative activity in different cell types [1]. Cloning of MIF from corticotrophic pituitary cells also suggests a systemic regulatory role in both immune and neuroendocrine systems [16].

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Plasma levels of MIF increase in relation to adrenocorticotrophic hormone after stress or infectious stimuli; whereas ACTH stimulates glucocorticoid production, MIF counter-regulates the immunosuppressive action of glucocorticoids [16].

In macrophages, MIF binds to the surface receptor CD74 (Invariant chain or li) resulting in the initiation of a signaling pathway [17,18] involving phosphorylation of CD44 [P-glycoprotein-1 (Pgp-1), lymphocyte antigen (Ly-24)], which in turn triggers the phosphorylation of ERK1 and ERK2 MAP kinases involved in the expression of cyclin D1 and growth factors [19]. Moreover, since MIF antagonizes the actions of glucocorticoids [10,11], it can abolish the effects of immunosuppressive drugs [20] by activating macrophages and T cells [2], and inhibiting p53 expression, thus acting as an inhibitor of apoptosis in macrophages [14,15].

2. MIF in mammalian reproductive organs and gestation

The role of MIF in reproduction has been studied in different species. In the diffuse folded epitheliochorial placenta of the pig, MIF was mainly expressed by the columnar trophoblast cells and maternal epithelium throughout gestation. There was a dramatic decrease in MIF in the maternal epithelium during late gestation while immunostaining in trophoblast remained relatively high [21]. Spatio-temporal expression of MIF has been also extensively described in the bovine placenta as well as in the pregnant and non-pregnant uterus [22,23]. In the bovine placenta MIF is expressed in uterine glands and endometrial intercaruncular epithelium and in caruncular and trophoblast epithelium of the placentomes during establishment of vascularization, suggesting a regulatory role in the interhemal barrier [22].

In mouse, MIF expression was found in the ovary, particularly in the developing oocytes, in the oviduct and in the uterus [3,4]. More recently, we demonstrated that MIF gene and protein expression increases in murine placenta from gd7.5, with peak levels between gd10.5 and 13.5, an interval that coincides with completion of placental development. This suggests an additional function in maintenance of gestation [5]. The main cell types expressing MIF belong to the trophoblast lineage (trophoblast giant cells and spongiotrophoblast cells), although other components of the maternal–fetal interface contribute to MIF production [5].

MIF expression occurs in human female reproductive organs, throughout the menstrual cycle and across pregnancy [6,7]. MIF mRNA and protein expression is variable throughout the menstrual cycle, which may directly or indirectly affect cell proliferation, angiogenesis and tissue remodeling [24,25].

Events occurring in the early phases of human gestation, including implantation and establishment of the placenta, are characterized by inflammatory-like processes, and roles for pro-inflammatory cytokines including MIF have been emphasized [26]. Arcuri et al. showed that MIF reduces the cytotoxicity of uterine natural killer cells and consequently, contributes to the immune privilege of the maternal–fetal interface in humans [26,27]. Intraperitoneal injection of recombinant MIF to pregnant mice induces endometrial increases in alpha v, beta 3 integrin subunits and in VEGF expression, both markers of uterine receptivity [28]. Accordingly, pregnant MIF-treated mice have higher rates of embryo implantation compared to untreated control mice [28]. In addition, putative roles in the inflammatory events that lead to delivery [29] and in placental responses against local pathogens have been reported [30].

In humans MIF expression is mainly localized to proliferative villous cytotrophoblast and to extravillous cell columns, suggesting regulatory roles in the processes of embryo implantation and maintenance of pregnancy [7,27]. In placental tissues, MIF mRNA and protein levels are higher at the beginning of pregnancy (6–10 weeks of gestation) and decline in the late first trimester (12 weeks of gestation) [29,31,32]. By using chorionic villus explant cultures from first trimester placentas, we showed that MIF protein and mRNA is up-regulated by low oxygen tensions, comparable to those occurring at the first stages of placentation [32]. MIF protein remains present in term placenta in extravillous trophoblast and villi. It is also found in amniotic fluid and in maternal serum during normal pregnancy [29,31]. In addition, we have recently demonstrated that 17β-estradiol, a major steroid hormone in pregnancy, plays a key role in regulating MIF secretion by trophoblast [33].

In human maternal serum MIF concentrations do not change throughout physiological pregnancy but are higher than in non-pregnant females [29,34,35]. Decreased maternal MIF serum levels during early gestation are associated with recurrent miscarriage, while higher levels during early and mid-gestation are linked with subsequent preterm-delivery [34,36,37]. Increased levels of MIF in maternal serum and altered protein expression by different placental compartments have also been reported in pregnancies complicated by preeclampsia, reinforcing the inflammatory nature of this disease and emphasizing the relevance of MIF as a potential therapeutic target [38,39].

3. MIF and placental infections

Parasitic infections are important causes of fetal morbidity and mortality in humans [40]. These infections elicit innate and adaptive immune responses and a plethora of important inflammatory modulators, pivotal for disease progression or remission [40]. MIF is up-regulated in parasitic infections and particularly involved in the control of placental infections such as malaria and toxoplasmosis [30,41]. Previous studies have shown that in humans, mononuclear blood cells inhabiting the intervillous space produce higher amounts of MIF than peripheral blood mononuclear cells. Moreover, when infected with *Plasmodium falciparum*, this placental compartment exhibits an MIF profile still higher than uninfected placentas, suggesting a potential role for MIF in combating placental intracellular parasites [42]. In addition, the trophoblast cell line, BeWo, secretes MIF in response to the adherence of erythrocytes infected with *P. falciparum* but not to other nonspecific stimuli [42]. Experimental evidence also has suggested an important role for MIF in the temporal susceptibility to *Toxoplasma gondii* infection over gestation. First-trimester placental explants incubated with *T. gondii* show significant upregulation of MIF and are less susceptible to *T. gondii* infection, whereas third trimester placental explants lack MIF upregulation after experimental infection and are more susceptible to parasite infection [43,44]. Recent studies using BeWo cells also revealed that these trophoblast-like cells are able to modulate monocyte activity, resulting in the control of *T. gondii* infection. Notwithstanding the growing interest in studies associating MIF and intracellular parasite replication at the maternal–fetal interface, the exact MIF-associated regulatory mechanisms still need clarification.

4. Decidual cells as putative targets for MIF

The biological activity of MIF is predominantly associated with its binding to the receptor/co-receptor complex CD74 and CD44, which can result in activation of different signaling pathways [17,25]. CD44 is part of the CD74-associated receptor complex in so far as its intracytoplasmic domain is required for MIF signal transduction. When only CD74 is expressed at the cellular surface, MIF can bind to the receptor, but activation of specific signaling pathways does not occur [17,18]. Recent studies, however, showed that extracellular MIF can be efficiently endocytosed and translocated into the cytosol, triggering downstream MIF signaling in a