Journal of Reproductive Immunology 113 (2016) 35–41

Contents lists available at ScienceDirect

Journal of Reproductive Immunology

journal homepage: www.elsevier.com/locate/jreprimm

Review article

New insights into myeloid-derived suppressor cells and their roles in feto-maternal immune cross-talk

Ai-Min Zhao[a,b,*,1], Hai-Jing Xu[a,1], Xiao-Min Kang[a,1], Ai-Min Zhao[a,b], Li-Ming Lu[c,**]

[a] Department of Obstetrics and Gynecology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, PR China
[b] Shanghai Key Laboratory of Gynecologic Oncology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, PR China
[c] Shanghai Institute of Immunology, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, PR China

ARTICLE INFO

Article history:
Received 19 August 2015
Received in revised form 23 October 2015
Accepted 4 November 2015

Keywords:
Myeloid-derived suppressor cells
Immunosuppression
Pregnancy
Feto-maternal cross-talk

ABSTRACT

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous group of myeloid cells that suppress both innate and adaptive immune responses through multiple mechanisms. In recent years, much of our knowledge of the function of MDSCs has come from cancer studies. However, a few recent advances have begun to characterize MDSCs in feto-maternal immune cross-talk. The microenvironment at the fetal-maternal interface is a complex milieu of trophoblasts and maternally-derived cells, which are biased to tolerogenic and Th2-type responses. Current data reveal that MDSCs accumulate at the fetal-maternal interface in healthy pregnancies. Yet, little is known about how MDSCs develop and why the response of MDSCs is heavily granulocytic. In this review, we discuss recent findings on the molecular mechanisms that regulate the expansion and function of MDSCs, in addition to various roles of MDSCs implicated in the modulation of feto-maternal immune cross-talk. Understanding the roles of MDSCs in inducing maternal-fetal tolerance, which is compromised in patients suffering from pregnancy complications, including preeclampsia, intrauterine growth restriction, spontaneous abortion, and preterm birth, we thus propose that the immunomodulatory activity of MDSCs should be carefully considered for the therapeutic approaches targeting pregnancy complications.

1. Introduction

During pregnancy, the maternal immune system needs to provide a special immune milieu at the fetal-maternal interface for tolerating the expression of paternal antigens by the semi-allogeneic fetus without immune rejection and loss of the host defense against a diverse array of possible pathogens, which has been deemed an immunological paradox (Bogovic Crncic et al., 2005; Staff et al., 2014; Lash and Ernerudh, 2015). Dysfunction in the interactions of the invading trophoblasts and maternally-derived cells or dysregulation of maternal-fetal immune tolerance can lead to pregnancy loss or severe complications, such as miscarriage, preeclampsia, preterm delivery, fetal growth restriction and so on (Abrahams and Mor, 2005; Abrahams et al., 2005; Kwak-Kim et al., 2009; Gonzalez et al., 2013; Saito and Nakashima, 2014). It is generally believed that the hormonal and Th1/Th2 cytokine balance plays an important role in the tolerance and maintenance of pregnancy, which sparked a wealth of research in the area of reproductive immunology and led to the recognition that the successful establishment of maternal-fetal immune tolerance is more complicated than the initial concept implied (Arck and Hecher, 2013; Bonney and Brown, 2014).

Over the past few decades, MDSCs have been recognized to be novel key regulatory cells in the context of cancer, inflammation, traumas, transplantation or autoimmune diseases since their first description in patients with cancer (Buessow et al., 1984; Nakamura et al., 2013; Arocena et al., 2014; Beury et al., 2014; Dai et al., 2014; Drujont et al., 2014). Numerous excellent reviews of MDSCs in other fields have been published given their immune suppressive function (Gabrilovich and Nagaraj, 2009; Talmadge and Gabrilovich, 2013; Condamine et al., 2015; Heim et al., 2015).

Recent studies have begun to identify an important role for MDSCs in successful implantation and pregnancy. In this review, we

* Corresponding author at: Department of Obstetrics and Gynecology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, OR Shanghai Key laboratory of Gynecologic Oncology, 1630 Dongfang Road, Shanghai 200127, PR China. Fax: +86 021 6838 3375.
** Corresponding author at: Shanghai Institute of Immunology, Shanghai Jiao Tong University School of Medicine, 280 South Chongqing Road, Shanghai 200025, PR China. Fax: +86 021 63846590.
E-mail addresses: zamzkh0526@126.com (A.-M. Zhao), lulunew2003@163.com (L.-M. Lu).
[1] These first authors contributed equally to this review.

http://dx.doi.org/10.1016/j.jri.2015.11.001
0165-0378/

briefly discuss the main features of MDSCs, followed by outlining advances in their contribution to feto-maternal immune cross-talk. We also propose a model whereby an increased frequency of MDSCs promotes the establishment of feto-maternal tolerance during gestation. New insights into feto-maternal immune cross-talk will facilitate a better understanding of the pathogenesis of pregnancy complications and offer the prospect of novel effective interventions

2. Key features of MDSCs

2.1. Origin and differentiation

First reported in a lung cancer model in 1987, MDSCs were identified as bone marrow-derived cells that inhibited T cell proliferation. They are a heterogeneous cell population consisting of immature granulocytes, macrophages, and dendritic cells, namely monocytes and granulocytic precursors, which are also the intermediates of the normal myeloid development and differentiation stages characterized by their myeloid origin, immature state, and potent T cell-suppressive function.

In healthy individuals, immature myeloid cells (IMCs) generated in bone marrow quickly differentiate into mature granulocytes, macrophages or dendritic cells (DCs) in vitro or in vivo (Gabrilovich and Nagaraj, 2009). In pathological conditions such as cancer, infectious diseases, trauma, bone marrow transplantation or some autoimmune disorders, a partial block in the differentiation of IMCs into mature myeloid cells can result in expansion of the IMC population.

2.2. Phenotypes

In mice, these myeloid cells are commonly defined by the co-expression of the surface markers CD11b and Gr-1 (Ly6G/Ly6C) and have been divided into two subsets: $CD11b^+LY6G^+LY6C^{low}$ (granulocyte, G-MDSCs) and $CD11b^+LY6G^-LY6C^{high}$ (monocyte, M-MDSCs) (Arocena et al., 2014). Unlike mice, human MDSCs do not express Gr-1 antigen. And in general, discerning MDSCs in humans is difficult because of the lack of specific markers, and the heterogeneity of MDSCs complicates their characterization. Human MDSCs are mainly defined as $CD33^+CD11b^+HLA\text{-}DR^{low/-}$ cells, but lack the expression of markers of mature myeloid and lymphoid cells. More recently, two human MDSCs have been reported: $CD14^-CD15^+CD66b^+$ (granulocyte, G-MDSCs) and $CD14^{\pm}CD15^{low/-}$ (monocyte, M-MDSCs) (Serafini 2013; Condamine et al., 2015).

2.3. Mechanisms of expansion and activation

Although it is evident that MDSCs may serve as potential therapeutic targets to promote anti-tumor immune responses or to inhibit inflammatory responses (Ray et al., 2013) such as autoimmune disease or during transplant rejection, further characterization is necessary with regard to molecular markers and pathways to determine how functional MDSCs develop and accumulate (Hegde et al., 2013).

Under normal conditions, mouse MDSCs are usually maintained at relatively low numbers in the bone marrow (20–30% of overall myeloid cells), peripheral blood (2–4%), spleen (2–4%), and lymph nodes (<1% = (Ilkovitch and Lopez, 2009)). In contrast to healthy individuals, in whom <1% of peripheral blood mononuclear cells (PBMC) are MDSCs (Gabrilovich and Nagaraj, 2009), up to a tenfold increase in MDSC numbers was reported in the blood of patients with different types of cancers (Mirza et al., 2006; Diaz-Montero et al., 2009). Furthermore, MDSC numbers increase in elderly mice and humans, in whom immunosenescence may be involved (Enioutina et al., 2011; Verschoor et al., 2013).

The population of MDSCs is primarily influenced by two types of factors. The first one includes those (Table 1) that are produced mainly by tumor cells and promote the expansion of MDSCs through the stimulation of myelopoiesis and inhibiting of the differentiation of mature myeloid cells, including prostaglandins, cyclooxygenase-2 (COX2), granulocyte/macrophage colony-stimulating factor (GM-CSF), macrophage colony-stimulating factor (M-CSF), vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF-β), IL-1β, IL-6, IL-10, IL-12, IL-13, and others (Bunt et al., 2007; Gabitass et al., 2011; Obermajer et al., 2011). Signal transducer and activator of transcription 3 (Stat3), a major signaling molecule of the JAK/STAT pathway, promotes expansion of MDSCs by regulating B-cell lymphoma XL (Bcl-xL), c-myc, cyclin D1, S100A8, S100A9, and survivin (Cheng et al., 2008). The second group of

Table 1
Factors implicated in the expansion of myeloid-derived suppressor cells (MDSCs) in pathological conditions.

Factor	Subtype	Phenotype	Type of disease	Species	Reference
GM-CSF	MDSCs unclassified	$CD34^+$	Head and neck cancer	Human	Pak et al. (1995)
	M-MDSCs	$CD11b^+CD14^+CD33^+$	Allo-HSCT	Human	Lv et al. (2015)
	MDSCs unclassified	$Lin^{-/Lo}$ HLA $DR^-CD33^+CD11b^+$	Solid tumor	Human	Diaz-Montero et al. (2009)
M-CSF	M-MDSCs	$CD14^+CD64^+CD1a^-CD86^-$ $CD80^-HLA\text{-}DR^{low}$	Renal cell carcinoma	Human	Menetrier-Caux et al. (1998)
TGF-β	MDSCs unclassified	$CD11b^+Gr1^+$	Melanoma	Mouse	Li et al. (2014)
VEGF	MDSCs unclassified	$CD11b^+$ $CD33^+$	Digestive system cancer	Human	Nakamura et al. (2013)
	MDSCs unclassified	$Gr\text{-}1^+Mac\text{-}1^+$	Mammary carcinoma	Mouse	Melani et al. (2003)
SCF	MDSCs unclassified	$Gr\text{-}1^+CD115^+$	Metastatic colon cancer	Mouse	Pan et al. (2008)
TNF-α	M-MDSCs/G-MDSCs	$CD11b^+Ly6G^+Ly6C^{low}$/ $CD11b^+Ly6G^-$ $Ly6C^{hi}$	Chronic inflammation	Mouse	Sade-Feldman et al. (2013)
PGE2	M-MDSCs	$CD11b^+CD14^+CD33^+CD34^+$	Ovarian cancer	Human	Obermajer et al. (2011)
	MDSCs unclassified	$CD11b^+Gr1^+$	Mammary carcinoma	Mouse	Sinha et al. (2007)
COX2	M-MDSCs	$CD11b^+CD14^+CD33^+CD34^+$	Ovarian cancer	Human	Obermajer et al. (2011)
IL-1β	MDSCs unclassified	$CD11b^+Gr1^+$	Mammary carcinoma	Mouse	Bunt et al. (2006)
IL-2	G-MDSCs	$CD11b^+$ $CD15^+$ $CD66b^+$	Renal cell carcinoma	Human	Rodriguez et al. (2009)
IL-6	M-MDSCs	$CD14^+CD64^+CD1a^-CD86^-$ $CD80^-HLA\text{-}DR^{low}$	Renal cell carcinoma	Human	Menetrier-Caux et al. (1998)
	MDSCs unclassified	$CD11b^+$ $Gr1^+$	Mammary carcinoma	Mouse	Bunt et al. (2007)
	MDSCs unclassified	$CD11^+Gr1^+$	Acute infection	Mouse	Arocena et al. (2014)
IL-8	M-MDSCs	$CD11b^+CD33^+CD14^+HLA\text{-}DR^{low}$	Melanoma	Human	Rudolph et al. (2014)
IL-12	G-MDSCs	$Ly6G^{high}Ly6C^+$	Prosthetic joint infections	Mouse	Heim et al. (2015)

Abbreviations: Allo-HSCT: haplo-identical allogeneic hematopoietic stem cell transplantation; SCF: stem-cell factor.