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Review Article

Myeloid-Derived Suppressor Cells in *Pneumocystis* Pneumonia

Guang-Sheng Lei, Chao-Hung Lee, and Chen Zhang*

Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN 46202

Corresponding author

Chen Zhang, Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, 350 W. 11th ST, Indianapolis, IN 46202, Tel: (317) 491-6211; E-mail: chenzhan@iupui.edu

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Abstract

First described 20 years ago in patients with cancer, myeloid-derived suppressor cells (MDSCs) have not been extensively studied regarding their roles in infectious diseases. Here we summarize the recent findings about MDSCs in *Pneumocystis* pneumonia (PcP), the most common opportunistic infection in immune compromised patients. Previous studies as well as ongoing research focusing on the roles of MDSCs in the pathogenesis of PcP, and the development of novel treatment for PcP targeting MDSCs are reviewed.

Myeloid-Derived Suppressor Cells (MDSCs)

MDSCs are a heterogeneous population of myeloid progenitor cells and immature myeloid cells that have the morphology similar to that of granulocytes or monocytes. In healthy individuals, immature myeloid cells are generated in the bone marrow and quickly differentiate into mature granulocytes, macrophages, or dendritic cells. Immature myeloid cells are generally absent in peripheral lymphoid organs. MDSCs were first described more than 20 years ago in tumor-bearing mice and in patients with cancer as immune suppressor cells that inhibit T-cell proliferation and functions. In mice, MDSCs are characterized by co-expression of the myeloid-cell lineage differentiation antigen Gr-1 and CD11b. In rats, MDSCs are characterized by co-expression of His48 and CD11bc [1]. In humans, MDSCs are most commonly defined as CD14–CD11b+ cells that express the common myeloid marker CD33 but lack the expression of markers of mature myeloid and lymphoid cells, and of the MHC class II molecule HLA-DR. CD33 negative MDSCs have also been described in human peripheral blood [2].

The suppressive activity of MDSCs has been associated with the metabolism of L-arginine, which is a substrate for two enzymes, iNOS and arginase 1. MDSCs express high levels of both arginase 1 and iNOS, and inhibit T-cell function by depleting environmental L-arginine and producing immunosuppressive substances such as Nitric Oxide (NO) and Reactive Oxygen Species (ROS) [3]. Most of current understandings about MDSCs are derived from the studies in cancer-associated conditions, although MDSCs have been shown to accumulate in many other pathological conditions such as traumatic injury and various infections. Relatively few studies have been focused on the roles of MDSCs in infectious diseases.

MDSCs in Pneumocystis pneumonia (PcP)

PcP, the most common opportunistic disease in immune compromised patients such as those with AIDS, is caused by a fungal pathogen *Pneumocystis jirovecii*. *P. carinii* refers to the major form of *Pneumocystis* found in rats. Mouse *Pneumocystis* is called *P. murina*. *Pneumocystis* (Pc) infections usually result in a severe inflammatory damage to the lung. Adjunctive corticosteroid therapy has been shown to alleviate the inflammation and improve the survival of AIDS patients with PcP [4,5]. Alveolar macrophages (AMs) are the major cell type responsible for the clearance of *Pneumocystis* organisms. Our previous studies have shown that AMs are defective in phagocytosis, and that their number is decreased during PcP [6,7]. The mechanism through which Pc infection causes AM defects is unknown, but is associated with down-regulation of phagocytic receptors such as Dectin-1[8].

Recently, our study demonstrates that MDSCs accumulate in large numbers in the lungs of mice and rats with PcP [9]. Accumulation of MDSCs in human lungs during PcP has also been suggested by the presence of a population of CD33-/HLADR-/CD15+ granular cells in bronchoalveolar lavage fluid (BALF) (unpublished data). MDSCs in PcP morphologically resemble granular cells, demonstrate high levels of arginase I and iNOS expressions, and are able to inhibit T-cell proliferation in response to stimulants. MDSCs cause direct injury to the lungs, indicated by increased albumin and LDH levels in BALF caused by adoptive transfer of MDSCs from PcP mice to healthy hosts [9]. MDSCs also play immunosuppressive roles during PcP by suppressing AM phagocytic activities. Co-incubation of MDSCs with normal AMs leads to down-regulation of PU.1 (unpublished data), which is known to cause the down-regulation of phagocytic

receptor Dectin-1 in AMs [8]. Evidences from our ongoing study suggest that MDSCs inhibit PU.1 expression in AMs through the PD-1/PDL-1 signaling (unpublished data).

Given both the direct lung injury and the immunosuppressive roles of MDSCs during PcP, treatment strategies targeting MDSCs have been developed using all-trans retinoic acid (ATRA) alone or in combination with other antimicrobials. ATRA is one form of vitamin A-derived retinoids, which has been shown to stimulate MDSCs to further differentiate to dendritic cells and macrophages [10,11]. Previous studies show that administration of therapeutic concentrations of ATRA can substantially decrease the number of MDSCs in tumor-bearing mice and in patients with cancer, improving their T-cell response to specific antigens [12,13]. Our recent study [14] shows that ATRA alone is able to eliminate MDSCs in the lungs, increase numbers of AMs and control Pc infection. Combination of ATRA with primaquine is as effective as the traditional treatment combination of trimethoprim and sulfamethoxazole (TMP-SMX) in mice and rats with PcP. Currently, TMP-SMX remains the single most effective regimen for treatment of human PcP. Unfortunately, approximately 10% of people in the general population are allergic to sulfa-containing drugs, and about 50% of AIDS patients fail therapy with TMP-SMX. Other alternative regimens are available but not as effective. Once the treatment combination of ATRA and primaquine is proved effective in treating and preventing human PcP, it will make tremendous improvements in the care of immune compromised patients. This novel approach treats PcP by converting immune suppressive cells to immune protective ones so that the hosts became able to effectively defend the infection. It may also serve as a model for development of new therapies for other microbial diseases, such as toxoplasmosis [15], leishmaniasis [16], and candidiasis [17], that also cause MDSC accumulations. The mechanism through which ATRA induces MDSC differentiation needs further investigation.

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