Human Immunology 78 (2017) 113–119

Contents lists available at ScienceDirect

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

Review

Suppression of T cells by myeloid-derived suppressor cells in cancer

Jieying Chen [a], Yingnan Ye [a], Pengpeng Liu [b], Wenwen Yu [a], Feng Wei [a], Hui Li [a], Jinpu Yu [a,b,*]

[a] Department of Immunology, National Clinical Research Center of Cancer, Tianjin Key Laboratory of Cancer Immunology and Biotherapy, Tianjin Medical University Cancer Institute and Hospital, Tianjin 300060, China
[b] Cancer Molecular Diagnostic Core, National Clinical Research Center of Cancer, Tianjin Key Laboratory of Cancer Prevention and Therapy, Tianjin Medical University Cancer Institute and Hospital, Tianjin 300060, China

ARTICLE INFO

Article history:
Received 30 January 2016
Revised 2 December 2016
Accepted 5 December 2016
Available online 7 December 2016

Keywords:
Myeloid-derived suppressor cell
Immune suppression
T cell
Targeted therapy
Cancer

ABSTRACT

Myeloid-derived suppressor cells (MDSCs) are a population of immature myeloid cells defined by their immunosuppression. Elevated levels of certain soluble cytokines in tumor microenvironment, such as IL-6 and IL-10, contribute to the recruitment and accumulation of tumor-associated MDSCs. In turn, MDSCs secret IL-6 and IL-10 and form a positive self-feedback to promote self-expansion. MDSCs also release other soluble cytokines such as TGF-β and chemokines to exert their suppressive function by induction of regulatory T cells. Exhaustion of some amino acids by MDSCs with many secretory enzymes or membrane transporters as well as their metabolites leads to blockage of T cells development. The interaction of membrane molecules on MDSCs and T cells leads inactivation and apoptosis of T cells. There may be one or some dominant mechanism(s) by which MDSCs impair the immune system in different tumor microenvironment. Thus, it is important to identify the subpopulations of MDSCs and clarify the dominant mechanism(s) through which MDSCs inhibit antitumor immunity in order to establish a more individual immunotherapy by eliminating MDSCs-mediated suppression. Currently studies concentrated on therapeutic strategies targeting MDSCs have obtained promising results. However, more studies are needed to demonstrate their clinical safety and efficacy.

Contents

* Corresponding author at: Cancer Molecular Diagnostic Core, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Immunology and Biotherapy, Key Laboratory of Cancer Prevention and Therapy, Tianjin 300060, China.
E-mail address: yu_jinpu@sina.com (J. Yu).

http://dx.doi.org/10.1016/j.humimm.2016.12.001
0198-8859/

0. Introduction

Myeloid-derived suppressor cells (MDSCs) were first detected in mouse models bearing human tumors [1] before they were identified in patients with head and neck squamous cancer several years later [2]. Actually, MDSCs are a heterogeneous population of immature myeloid cells including granulocytes, macrophages and dendritic cells [3,4], which display potent inhibitory effect on immunity and result in immune evasion. Commonly, murine MDSCs are characterized by the expression of Gr-1 and CD11b and represent approximately 2–4% of all nucleated splenocytes, but can increase up to 50% in tumor bearing mice [5,6]. The equivalent MDSCs in humans are usually positive for both CD11b and CD33 or express the CD33 but lack the expression of the major histocompatibility complex (MHC) class II molecule HLA-DR. They account for less than 0.5% of peripheral blood mononuclear cells in healthy individuals, but can increase more than 10 folds in circulation of cancer patients [7–10]. There are two main MDSC subtypes both in mice and humans, polymorphonuclear MDSC (PMN-MDSC) and monocytic MDSC (M-MDSC), in which PMN -MDSCs represent the major subset of circulating MDSC [11]. However, the specific markers for MDSC subsets, especially in humans, are vague until now and MDSCs are primarily identified by their suppressive function.

Nowadays, it has been demonstrated that MDSCs are associated with poor prognosis in cancer patients [12], promote tumor angiogenesis [13], and inhibit both innate and adaptive immunity against tumors [14]. Depletion of MDSCs was reported to enhance the antigen presenting cell activity and increase the frequency and activity of the NK and T cell effectors in murine models of lung cancer [15]. Many studies have focused on the cancer-associated immune-suppression mechanisms mediated by MDSCs [16,17], in which inactivation of T cells is underscored. T cells represent a key effector arm of the immune system that is required for cancer control. Dysfunction of T cells fails to response to transformed cells, thus tumor-surveillance is impaired. Therefore, this review aims to introduce the underlying molecular mechanisms of MDSCs recruitment and their suppression on T cells, as well as current therapeutic strategies targeting MDSCs.

1. Soluble cytokines rich in tumor microenvironment recruit MDSCs and contribute to their suppressive function (Fig. 1)

1.1. IL-6

IL-6 is a multifunctional cytokine which plays an important role in the regulation of the immune system. Although IL-6 was first considered as a potent pro-inflammatory cytokine, numerous studies have suggested that IL-6 plays a pivotal role in the pathological processes of numerous human cancers [18]. Increased levels of inflammatory cytokines including IL-6 have been reported in patients with various type of tumors [19], and an elevated level of IL-6 fostering progressive expansion of tumor cells [20] has been associated with poor clinical outcome [21–24]. Recently, more and more studies have demonstrated positive relationship between increased proportion of MDSCs and higher level of IL-6 in cancers [25,24,12]. By studying patients with gastrointestinal malignancies, Mundy-Bosse BL, et al. [24] reported that plasma IL-6 level was correlated with $CD33^{+}HLA\text{-}DR^{-}CD15^{+}$ MDSCs subsets, and the percentage of certain MDSC subsets ($CD15^{+}$ and $CD15^{-}$) were inversely correlated with IFN-α-induced STAT1 phosphorylation in $CD4^{+}$ T cells. However, in Tsukamoto H's study [25], they revealed that IL-6 derived from tumor-bearing mice recruited MDSC enabled MDSC attenuation of Th1 development but not suppression of primary T-cell activation. Effector $CD4^{+}$ T cells sensitized by MDSC-derived IL-6 are defective in eliminating tumors because of their decreased ability to produce IFN-γ and their dampened helper activity for cognate tumor-specific $CD8^{+}$ T cells. A recent study [12] has reported that circulating $CD11b^{+}CD14^{+}HLA\text{-}DR^{-}$ cells were significantly increased and associated with serum IL-6 levels in esophageal squamous cell carcinoma patients, and IL-6 induced human functional MDSC in vitro displayed increased reactive oxygen species (ROS), arginase-1 (ARG-1) and p-STAT3, which are important to inhibit T cell effector function [26,27]. These results indicate that increased IL-6 in tumor microenvironment facilitates the recruitment and suppressive function formation of tumor-associated MDSC.

1.2. IL-10

It was reported that increased MDSC level was correlated with higher level of circulating IL-10 in patients with anaplastic thyroid cancer [28]. In 2011, Hart KM et al. [29] have reported that CD11b+ myeloid cells were the predominant producers of IL-10 in the ascites of ovarian tumor-bearing mice, and in turn IL-10 signaling

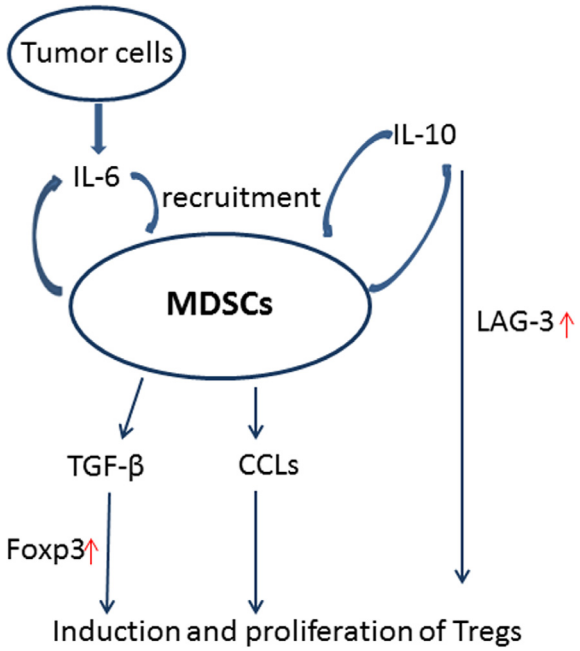

Fig. 1. Soluble cytokines rich in tumor microenvironment recruit MDSCs and contribute to their suppressive function. Elevated levels of IL-6 and IL-10 in tumor microenvironment contribute to the recruitment and accumulation of tumor-associated MDSCs. In turn, MDSCs secret IL-6 and IL-10 and form a positive self-feedback to promote self-expansion. MDSCs also release TGF-β and chemokines (CCLs) to exert their suppressive function by induction of regulatory T cells (Tregs).