Immune dysfunction induced by myeloid-derived suppressor cells in lymphoma

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Lymphoma cancer cells have strongly orchestrated interactions with immune cells and also other surrounding stromal cells in tumor microenvironment. Myeloid derived suppressor cells (MDSC) is believed to have major role in induction of immune suppressive effects in tumor microenvironment. This heterogeneous population of immature myeloid cells influence on immune cells function by indirectly Treg differentiation and directly oxidative stress induction and nutrient depletion in tumor milieu. Our understanding of the role of MDSCs in tumor microenvironment suggests novel immunotherapeutic approaches and need to be more explored. In this article we briefly discuss the main MDSCs immune dysfunction mechanisms with more focus in lymphoma.

Keywords: Myeloid derived suppressor cells (MDSC); Tumor microenvironment (TME); Lymphoma; Immune evasion

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Introduction

Progress in the field of cancer immunology and the necessity of more investigations in order to discover new targets emphasized the pivotal effects of tumor niches on tumor development and also confirmed that tumor growth is not promoted solely by tumor cells. Recent studies demonstrated the existence of a complex and not well-understood network between tumor and their surrounding cells and soluble mediators; known as tumor microenvironment (TME).

Interaction of tumor and infiltrated immune cells with TME directly and indirectly shapes the next situation in tumor growth. This elaborated crosstalk, that lead to tumor progression, becomes more evident in immunotherapy of solid tumors and hematological malignancies when the strategies by which tumor cells employ for immune evasion make the immunotherapeutic approaches to fail [1].

Major components of immune suppressive TME are believed to be tumor-associated macrophages (TAMs), regulatory T (Treg) cells and Myeloid-derived suppressor cells (MDSCs). These components are found to be mainly responsible for the host T-cell anti-tumor activity impairment against tumor associated antigens and consequently lead to fail the anticancer immunotherapeutic approaches [2].

So far, the majority of studies have been focused on MDSCs’ phenotypical and functional role in cancers and also their value (as a prognostic factor) in different clinical stages, to discover possible therapeutic approaches for elimination.
of their immunosuppressive activity, tumor supportive and improvement of impaired T cell anti-tumor immune responses. We should note that while extensive investigations on MDSCs (as a heterogeneous population of immature myeloid cells) characterization in cancer have been performed, yet multitudinous questions regarding their phenotype and function have remained unanswered.

Successful immunotherapeutic approaches in hematological malignancies (in particular astonishing therapeutic developments on monoclonal antibodies [3]) in the recent years pave the way to dig further into the cancer immunology studies in hematological malignancies and emerging evidences on the tumor supportive role of MDSC in hematological malignancies make it as a potential target for immunotherapy [4]. Consequently, in this abridged review article we aim to briefly discuss immune evasion mechanisms of MDSCs and also summarize their effects in lymphoma, to highlight their promising role in the future clinical settings.

MDSCs Subtypes andSuppressive Mechanisms

Until now two main subsets of MDSCs in mouse bearing tumor have been reported: 1) granulocytic MDSCs, and 2) monocytic MDSCs. Granulocytic (G) MDSCs (or polymorphonuclear-like MDSCs) composed 70–80% of the MDSC population [3], whereas monocytic (M) MDSCs (or mononuclear MDSCs) account for 20–30% of MDSCs [6]. MDSC subsets identification in humans is more intricate than in mouse and multiple populations of MDSCs have been defined in various solid tumors (see Lindau’s et al. Table-1 [2] for a list of MDSCs subsets in human tumors), but generally they are being considered as myeloid cells CD33+/CD11b+/HLA-DR low or negative [7].

The mechanisms that MDSCs use to regulate immune responses in tumor microenvironment often differ from one subtype to another one although they have shown some similar mechanisms to dampen immune responses as well. M-MDSCs generate high amounts of Nitric oxide (NO) and low amounts of Reactive oxygen species (ROS) and consequently mainly suppress T-cell function through NOS-mediated mechanisms [5]. They can act effectively in both antigen dependent and independent manners to suppress T-cell function. In contrast, G-MDSCs have high production of ROS but only small amounts of NO, representing that ROS are the main mediators of their suppressive functions [6]. G-MDSCs suppressive functions are generally dependent to antigen specific interactions with T cells [8]. Although G-MDSCs are the main MDSC population in the peripheral lymphoid organs [6] yet the M-MDSC subset possesses more potent suppressive function [5]. These immunosuppression mechanisms are schematically illustrated in Figure-1 and can be categorized in two classes: indirect immune suppressive function and direct immune suppressive function.

As an example of MDSCs’ indirect immune suppressive functions, they can induce differentiation of immune suppressive Treg cells in a way that MDSCs accompanied by Tumor Associated Macrophages (TAMs) secrete chemokines which contribute to Treg recruitment [9]. MDSCs also promote macrophage differentiation toward an M2 phenotype which has impaired production of functional IL-12 [10]. Decreased functional level of IL-12 can be further worsened by the macrophages in which TAMs stimulate.
further IL-10 secretion by MDSCs, thus this negative loop mediated by both MDSCs and TAMs can disrupt intratumoral balance of IL-10/IL-12 which is important for T lymphocyte Responses [11].

Among direct immune suppressive effects of MDSCs, nutrient depletion and induction of oxidative stress have been studied the most. The suppressive activity of MDSCs is reported to be related to the metabolism of L-arginine in tumor microenvironment. MDSCs deplete arginine resources in local microenvironment by production of arginase, which metabolize L-arginine, and also uptake of excess arginine by the CAT-2B transporter [12] and it has been reported that depletion of this amino acid is associated with T-cell function impairment and proliferation inhibition [13]. A recent study has also concluded that murine MDSCs can suppress T-cell activation by cysteine depletion from the tumor microenvironment [14] since cysteine is an essential amino acid for T-cell differentiation, proliferation and activation.

Another set of direct suppressive mechanisms of MDSCs deal with oxidative stress induction. Nitric Oxide (NO) production via inducible nitric oxide synthase (iNOS) in MDSCs is a powerful oxidative modulator which has been shown to inhibit T-cell activation, proliferation, adhesion, and migration [15, 16]. Hyper-production of ROS by MDSCs has been demonstrated in both mouse tumor models and in human cancer which have been associated with the inhibition of antigen-specific CD8+ T-cell responses in tumor-harboring mice [17]. Also it was reported ROS are able to decrease Bel-2 expression and therefore play a direct role in inducing apoptosis of activated T cells [18]. Peroxynitrite (ONOO−) as a reactive nitrogen-oxide species (RNOS) mainly act on modification of proteins by oxidation or nitration of the amino acids. High levels of peroxynitrite produced by MDSCs allow them to modify tyrosine residues in the TCR and CD8 co-receptor, resulting in conformational changes of the TCR chains and impaired interactions with MHC, thus suppressing antigen-specific, cytotoxic T-cell responses [8].

**MDSCs in Lymphoma**

Despite tremendous amount of work on the role of MDSCs in solid tumors it has been attracted only recently the attention of scientists for further investigations on its role in hematologic malignancies. To study MDSC subpopulations and their functions in lymphoma two subcutaneous lymphoma models have been described: EG7 and EL4 [19]. By investigation on RMA-S lymphoma-bearing mice researchers found both subpopulations of MDSC (i.e. M-MDSC and G-MDSC) can be accumulated in blood, spleen, and tumor tissue [9] but their specific characteristics in human lymphoma patients are not well understood.

In B-cell (Non Hodgkin Lymphoma) NHL, coincubation of peripheral blood mono nuclear cell (PBMC) with monocytes derived from NHL patients have shown less T cell proliferation and in addition, monocyte depletion led to restored T cell proliferation. It has been demonstrated that monocytes derived from NHL patients had defect in phosphorylation of STAT1 and IFNα production upon stimulation. A significant decrease in HLA-DR expression of monocytes from peripheral blood sample of NHL patients was observed in compared to healthy group and it was shown to be correlated with suppression of immune functions and disease progression. Furthermore, increased plasma levels of arginase-1 was observed in NHL patients [4].

The frequency of MDSC have correlation with clinical stage and faster rates of disease progression in NHL [19]. It was also demonstrated that tumor growth were inhibited by depletion of MDSCs in a mouse model of lymphoma [20]. Lin and colleagues [21] identified a CD14+ /HLA-DR low or negative population in the peripheral blood of patients with B-cell NHL. They reported these monocytes induce T cell suppression by using a mechanism involving arginine metabolism in NHL. Therefore they concluded that enhancement frequency of this suppressive subpopulation is associate with overall survival and disease progression. These findings were confirmed by studies in T-cell lymphoma [22], highlighting the role of HLA-DR expression in determining MDSCs in hematologic malignancies.

Moreover, in vitro and in vivo experiments showed Treg proliferation and tumor-induced tolerance in T cells can be reduced by inhibition of MDSC function [23]. In another study which were performed on A20 lymphoma mouse model, MDSCs promoted antigen-specific Tregs activation which is dependent on arginase and is independent of TGF-β [24], and proliferation, that subsequently lead to suppression and anergy of effector T cells [25]. Schlecker et al. demonstrated tumor-resident MDSCs in the RMA-S T cell lymphoma model have increased levels of CCR5 ligands (CCL5, CCL4, and CCL3), which were also correlated with regulatory T cell recruitment [9].

In addition, it was shown that high amount of tumor antigen was up taken by monocytes with MDSC phenotype. It can be interfered that these cells not only induce T cell inactivation but also diminish the amount of antigen that can be presented by other professional APCs [26]. More recently Schouppe et al. demonstrated that the effect of MDSCs in lymphoma can be intricate, since EG7 lymphoma-induced MDSC influence differently CD8 + T cell activation, CD8+ T cell proliferative capability and IL-2 secretion decreased.
and the IFNγ production capacity increased in the presence of MDSC\textsuperscript{[25]}, all demanding further dedicated investigations for the elucidation of underlay MDSCs immune dysfunction mechanisms.

**Conclusions**

Extensive efforts have been made toward the understanding of tumor immunology, cancer microenvironment, and the interactions of tumor with tumor surrounding cells and mediators. Previous studies have been determined that tumor growth does not depend solely on the features of the malignant cells but also their interactions with majority of other cells, that have a central role in tumorigenesis, are crucial players.

MDSCs (as a main immune suppressive player of tumor microenvironment) consist of immature myeloid cells and have a broad diversity of phenotypes. Recently their dominant suppressive effects in lymphoma has attracted scientists’ attentions. The mechanisms by which they can perform their immune suppressive effects in lymphoma are similar to other tumors and can be classified in three main mechanisms: nutrient depletion, oxidative stress and also differentiation of Tregs.

This heterogeneous population of immature myeloid cells are potent target in novel approaches of cancer immunotherapy since they have important role in immune evasion of tumor cells. It is completely reasonable to investigate MDSCs in a network in interaction with other resident or recruited cells in tumor microenvironment. Therefor in vivo experiment on immune suppressive and also tumor supportive effects of MDSCs might be more reliable than in vitro experiments. However for understanding extra molecular details of events in MDSCs and also various fundamental signaling pathways, it would certainly be useful to study MDSCs in vitro.

We also need to screen mediators in tumor microenvironment in lymphoma patients at DNA, RNA and protein level. That would help to find key elements in differentiation and function of these suppressive cells in order to explore new targets for novel immunotherapeutic approaches. In addition, the crosstalk between MDSCs and TAM as another main player in tumor niche required to be explored thoroughly.

Finally, metabolical alterations made by MDSCs in TME significantly influence T cell function as a main antitumor player of immune system and thus further investigation of tumor milieu from a metabolical window could potentially benefit the understanding of MDSCs role in immune suppression.

**Conflict of interests**

The author declares that there is no conflict of interests regarding the publication of this article.

**References**


