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REVIEW

Phenotypic and functional dissection of myeloid-derived suppressor cells

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Abstract Myeloid-derived suppressor cells (MDSCs) are originated and differentiated population from common hematopoietic progenitor cells. Generally, in the late stage of inflammation, MDSCs differentiation and expansion are promoted to suppress the over-activated immune system so that the immune system can maintain the homeostasis. Recently, it has been revealed that MDSCs accumulate in cancer patients and tumor-bearing experimental animals, and these tumor-derived MDSCs suppress anti-tumor immunity by secreting immunosuppressive cytokines including reactive oxygen species and inducible nitric oxide synthase. This fact prompts scientists to shed light on MDSCs as significant targets for anti-cancer immunotherapy. However, due to morphological, phenotypic, and functional heterogeneities of MDSCs, it is not easy to develop therapeutic strategies targeting MDSCs. In this review, we will summarize recent progress on defined subsets of MDSCs and their strategies to suppress T cell-mediated anti-tumor immunity.

Keywords Anti-tumor immunotherapy · Arginase · Inducible nitric oxide synthase · Myeloid-derived suppressor cell · Reactive oxygen species · T cell

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The discovery of MDSCs

MDSCs appeared to the scientific field in the late 1970s (Strober 1984; Holda et al. 1985; Ribechini et al. 2010). At that time, this was just a formerly unknown immune cell population which possesses immunosuppressive features, but it was enough to attract scientists. Firstly, MDSCs were isolated from bone marrow and spleens from tumor-challenged mice, and it was revealed that those isolated cells were able to suppress T cell responses both in vivo and in vitro against tumor cells (Roder et al. 1978; Subiza et al. 1989). Because of its immunosuppressive functions and immature status, MDSCs were also called as natural suppressor cells, immature myeloid cells, and myeloid suppressor cells. Finally, the naming issue has been fixed by Gabrilovich and his colleagues in 2007 as they suggest the unification of the name: "MDSC" which is reflecting both origin of those cells and the function after 37 years of its discovery (Gabrilovich et al. 2007). From that point, MDSCs are uprising as a novel immune cell population that regulates innate and adaptive immunity by inactivating T cells. Studies for MDSCs have been accelerated since 2000, but many things about MDSCs are behind the veil and waiting for being elucidated.

The subsets of MDSCs

Under the united name of MDSC, many subsets of MDSCs have been defined, and these various subsets reflect the heterogeneity and complexity of MDSCs. At first, MDSCs were defined as cells which express Gr-1^{+}CD11b^{+} as cell surface molecules but not express the typical expression marker of mature macrophages and dendritic cells (DC) in mice (Bronte et al. 1998). With specific antibodies that

recognize the surface molecules of MDSCs (Talmadge and Gabrilovich 2013), mouse MDSCs are classified as two major subsets of MDSCs: granulocytic MDSCs (G-MDSCs) have similar morphologies with granulocytes and monocytic MDSCs (M-MDSCs) have similar morphologies with monocytes (Sica and Bronte 2007; Movahedi et al. 2008). Generally, G-MDSCs are distinguished as they express $CD11b^{+}Ly6G^{+}Ly6C^{low}$, while M-MDSCs express $CD11b^{+}Ly6G^{low/-}Ly6C^{high}$ on their surfaces (Movahedi et al. 2008; Youn et al. 2008). Unlike mice, human MDSCs do not express Gr-1. Instead, human MDSCs are characterized as $CD11b^{+}CD33^{+}HLA\text{-}DR^{-}$. Furthermore, $CD15^{+}CD11b^{+}CD33^{+}HLA\text{-}DR^{-}$ population corresponds to G-MDSCs, and $CD14^{+}CD11b^{+}CD33^{+}HLA\text{-}DR^{-}$ population corresponds to M-MDSCs (Nagaraj and Gabrilovich 2010; Greten et al. 2011; Dumitru et al. 2012; Filipazzi et al. 2012; Poschke and Kiessling 2012; Meirow et al. 2015). Until now, there are many subsets that are not clarified because of their ambiguous expression levels of surface molecules like Ly6G and Ly6C. Thus, it is not easy to exactly classify them into G-MDSCs or M-MDSCs. Many of these intermediate subsets of MDSCs are still discovering.

Recently, fibrocytic MDSCs (F-MDSCs) are characterized as a novel MDSC subset in human (Abrams and Waight 2012; Zhang et al. 2013; Mazza et al. 2014; Zoso et al. 2014; Gunaydin et al. 2015). F-MDSCs show tumor-associated circulating fibrocyte phenotypes and have T cell-mediated immunosuppressive functions. F-MDSCs seem to express $CD11b^{low}CD11c^{low}CD33^{+}IL\text{-}4R\alpha^{+}$ on their surfaces (Mazza et al. 2014; Gunaydin et al. 2015). According to Zhang et al. (2013), F-MDSCs might express HLA-DR unlike other human MDSCs. Although it is clear that F-MDSCs with fibrocytic phenotypes show immunosuppressive functions, little is known how F-MDSCs differentiate from common HSCs and suppress T cells.

On the other hand, it is still unclear what factors drive MDSC differentiation into two or more different subsets from same precursor cells. It was revealed that tumor-induced granulocyte colony-stimulating factor (G-CSF) is one of those factors (Waight et al. 2011; Abrams and Waight 2012; Luyckx et al. 2012; Kawano et al. 2015). Our recent study also showed that the serum G-CSF level is associated with the inhibition of expansion and differentiation of G-MDSCs in tumor-bearing adiponectin knockout mice (Han et al. 2013). Nonetheless, the mechanism and crucial factors that drive the differentiation from common progenitor cells into various types of MDSC subsets should be further elucidated and identified.

The immunosuppressive functions of G-MDSCs

MDSCs produce immunosuppressive factors such as reactive oxygen species (ROS), inducible nitric oxide synthase (iNOS), arginase 1, and IL-10 to suppress the proliferation or activities of anti-cancer T cells or macrophages (Fig. 1). Basically, arginase produces urea and ornithine from arginine, which leads to depletion of arginine. In turn, MDSCs suppress the proliferation of T cells effectively, because arginine is a key nutritional substrate for T cell proliferation (Ochoa et al. 2007; Munder 2009; Rodriguez et al. 2009). MDSCs also secret immunosuppressive cytokine IL-10, which leads to immunosuppressive regulatory T cells (Treg) activation as well as the induction of the anti-inflammatory M2 macrophage differentiation, and the expansion of MDSC population by tumor growth contribute to immune escape of tumor cells through these suppressive effects of IL-10 (Sinha et al. 2007; Heim et al. 2015). Besides of these common suppressive mechanism including arginase expression and IL-10 secretion, G-MDSCs tend to primarily use ROS as the mechanism for

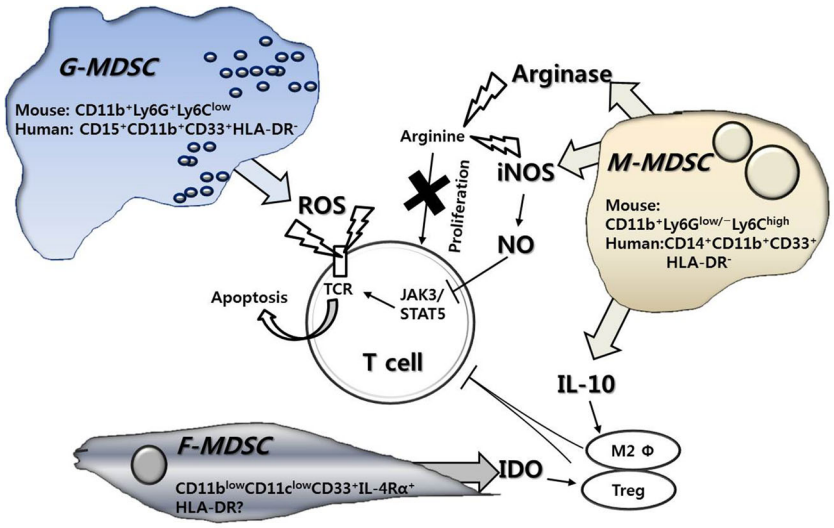

Fig. 1 Strategies of G-, M-, and F-MDSCs for T cell suppression. *MDSC* myeloid-derived suppressor cell, *G-MDSC* granulocytic MDSC, *M-MDSC* monocytic MDSC, *F-MDSC* fibrocytic MDSC, *ROS* reactive oxygen species, *iNOS* inducivle nitric oxide synthase, *NO* nitric oxide, *IL-10* interleukin 10, *IDO* indoleamine oxidase, *TCR* T cell receptor, *Treg* regulatory T cell, *M2 φ* M2 macrophage

immune suppression (Kusmartsev et al. 2004; Sinha et al. 2005; Nagaraj et al. 2007; Nefedova et al. 2007; Ando et al. 2008; Markiewski et al. 2008; Youn et al. 2008; Corzo et al. 2009). G-MDSCs-produced ROS inhibits the antigen-specific T cell responses by disrupting the physical interaction between T cell receptors (TCRs) on T cells and peptide/major histocompatibility complexes (MHCs) on antigen presenting cells (Kusmartsev et al. 2004; Nagaraj et al. 2007; Meirow et al. 2015). Moreover, G-MDSCs-produced ROS reacts with NO, which leads to the production of peroxynitrite. Then, the resulted peroxynitrite strongly induces the nitration of TCRs followed by the apoptosis of T cells (Nagaraj et al. 2007; Corzo et al. 2009; Raber et al. 2014). This finding suggests that G-MDSCs contribute to develop tumor-specific T cell tolerance.

The immunosuppressive functions of M-MDSCs

While G-MDSCs use ROS as the effector of immune suppression, M-MDSCs primarily utilize iNOS, arginase, and IL-10 (Bronte and Zanovello 2005). Similar to arginase which depletes arginine as T cell nutrient, iNOS produces NO and citrulline from arginine, and eventually T cell proliferation is inhibited by arginine depletion. Besides of arginine depletion, iNOS-induced NO also downregulates JAK3/STAT5 signaling which is crucial molecular signaling for T cell survival by reducing the phosphorylation, leading to the apoptosis of T cells (Rodriguez and Ochoa 2008; Dilek et al. 2012). In addition to iNOS and arginase, IL-10 produced from M-MDSCs also contributes to the interruption of T cell activation by inducing Foxp3^{+}Treg (Huang et al. 2006; Serafini et al. 2008). Given that M-MDSCs can effectively suppress T cells by humoral action with their immunosuppressive cytokines, physical interaction between M-MDSCs and T cells may be less required than G-MDSCs.

The immunosuppressive functions of F-MDSCs

Zhang et al. reported that hematopoietic stem cells (HSC)-derived fibrocytes suppress T cell proliferation through indoleamine oxidase (IDO) production, and that those immunosuppressive fibrocytes are suggested as a novel MDSC subset (Zhang et al. 2013). In 2014, Zoso et al. named this population as F-MDSCs and showed that the physical interaction between F-MDSCs and T cells induces the production of IDO in F-MDSCs and that F-MDSCs-produced IDO promotes the expansion of immunosuppressive Foxp3 + Treg cells (Zoso et al. 2014). Previous study showed that tryptophan is an essential amino acid for T cell proliferation and activation, and that IDO depletes

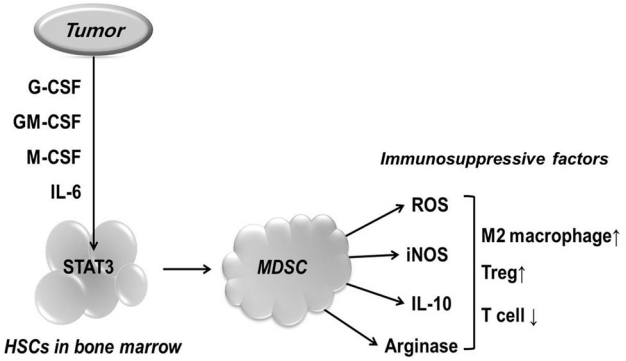

Fig. 2 Tumor-mediated MDSC formation. *G-CSF* granulocyte colony-stimulating factor, *GM-CSF* granulocyte macrophage colony-stimulating factor, *M-CSF* macrophage colony-stimulating factor, *IL-6* interleukin 6, *HSC* hematopoietic stem cell, *MDSC* myeloid-derived suppressor cell, *ROS* reactive oxygen species, *iNOS* inducible nitric oxide synthase, *IL-10* interleukin 10, *Treg* regulatory T cell

tryptophan by degrading it to formylkynurenine, which leads to the inhibition of T cell proliferation during antigen-specific T cell activation in turn (Lee et al. 2002, Zhang et al. 2013). Besides of this previously known tryptophan depletion mechanism, Zoso et al. also showed that 3-hydroxyanthranilic acid, a downstream metabolite for IDO-mediated tryptophan degradation, promotes Treg differentiation by inducing the secretion of immunosuppressive transforming growth factor-β from DCs. (Baban et al. 2009, Yan et al. 2010, Zoso et al. 2014). Therefore, it is conceivable that F-MDSCs-produced IDO is a major immunosuppressive molecule to suppress T cells.

Expansion and activation of MDSCs

Mature lymphocytes are originated from the differentiation of HSCs (Fig. 2) (Sica and Bronte 2007). Under infection or tumor-bearing condition, the HSC differentiation into mature immune cells is unfinished and remained as less differentiated cells, MDSCs (Bronte et al. 2000). This special condition prepares the expansion and accumulation of MDSCs. Then the issue is rising up: do tumors regulate the expansion and accumulation of MDSCs? The answer is yes. MDSCs are expanded and activated by tumor-driven cytokines including stem cell factor (SCF), G-CSF, macrophage colony-stimulating factor (M-CSF), granulocyte–macrophage colony-stimulating factor (GM-SCF), and vascular endothelial growth factor, IL-4, and IL-6. Those cytokines activate signal transducer and activator of transcription 3 (STAT3) which is the key molecule of the expansion and activation of MDSCs (Condamine and Gabrilovich 2011). Cytokine-activated STAT3 upregulates the transcription of gene set related to the expansion and immunosuppressive activity of MDSCs. STAT3 activation upregulates the transcriptions of calcium-binding pro-

inflammatory proteins S100A8 and S100A9 (Foell et al. 2007) in HSCs. In turn, the increase in S100A8 and S100A9 inhibits dendritic cell differentiation and promotes the MDSC expansion, accumulation, and the recruitment the MDSCs to the tumor site (Cheng et al. 2008). CCAAT-enhancer-binding protein β which is reported as a crucial factor for the MDSC expansion is also upregulated by STAT3 (Marigo et al. 2010). In addition, STAT3 increases the transcription of $p47^{phox}$ which is a component of nicotinamide adenine dinucleotide phosphate oxidase (NOX2). Concerning that NOX2 directly increases ROS, it is certain that STAT3 positively regulates the immunosuppressive activities of MDSCs as well as expansion of MDSCs (Corzo et al. 2009).

Conclusion

The nature of MDSCs is to terminate or suppress excessively activated immune system so that the immune systems can be back to the peaceful state after inflammation reaction. This homeostatic immune regulation device contributes to protect our body from autoimmunity. However, due to their immune suppressive roles, tumors easily pervert MDSCs to build up the tumor-friendly environment through the inhibition of T cells and the activation of M2 macrophages and Treg cells. Recently, it has been revealed that MDSCs would suppress the homing of tumor antigen-specific T cells to tumor site by reducing the expression of L-selectin on the surfaces of T cells (Hanson et al. 2009). The novel mechanism that MDSCs prepare tumor-favor environment is unveiling. These accumulating reports support the fact that reducing numbers and interfering functions of MDSCs would be good strategies for the development of anti-cancer therapy in the near future. Therefore, to put this forward, elucidating and understanding of full story of MDSCs is required to use these 'double-edged swords' in a smart way.

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