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Myeloid derived suppressor cells in human diseases

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Abstract

Myeloid derived suppressor cells (MDSC) have been described as a heterogeneous cell population with potent immune suppressor function in mice. Limited data are available on MDSC in human diseases. Interpretation of these data is complicated by the fact that different markers have been used to analyze human MDSC subtypes in various clinical settings. Human MDSC are $CD11b^+$, $CD33^+$, HLA-$DR^{neg/low}$ and can be divided into granulocytic $CD14^-$ and monocytic $CD14^+$ subtypes. Interleukin 4Rα, VEGFR, CD15 and CD66b have been suggested to be more specific markers for human MDSC, however these markers can only be found on some MDSC subsets. Until today the best marker for human MDSC remains their suppressor function, which can be either direct or indirect through the induction of regulatory T cells. Immune suppressor activity has been associated with high arginase 1 and iNOS activity as well as ROS production by MDSC. Not only in murine models, but even more importantly in patients with cancer, different drugs have been shown to either reverse the immune suppressor function of MDSC or directly target these cells. Systemic treatment with all-trans-retinoic acid has been shown to mature human MDSC and reverse their immune suppressor function. Alternatively, MDSC can be targeted by treatment with the multi-targeted receptor tyrosine kinase inhibitor sunitinib. In this review will provide a comprehensive summary of the recent literature on human MDSC.

Myeloid derived suppressor cells (MDSC) represent a heterogenous population of cells that consists of myeloid progenitor cells and immature myeloid cells (IMCs). Natural suppressor cells (the initial name for MDSC) were already described more than 25 years ago in patients with cancer [1] but in 1998 the interest in these cells was revived based on murine studies by Bronte and colleagues [2]. Murine MDSC are characterized by the expression of Gr-1 and CD11b. $CD11b^+Gr\text{-}1^+$ cells represent approximately 2 to 4 % of all nucleated splenocytes, but can increase up to 50% in tumor bearing mice [3, 4]. These cells are a mixture of immature myeloid cells, immature granulocytes, mononcytes-macrophages, dendritic cells and myeloid progenitor cells. Recently murine MDSC were further subdivided into two major groups: $CD11b^+Gr\text{-}1^{high}$ granulocytic MDSC (which can also be identified as $CD11b^+Ly\text{-}6G^+Ly6C^{low}$ MDSC) and $CD11b^+Gr\text{-}1^{low}$ monocytic MDSC (which can also be identified as $CD11b^+Ly\text{-}6G^-Ly6C^{high}$ MDSC) [5]. We have previously identified CD49d as a marker to distinguish these two cell populations from each other and have shown that monocytic $CD11b^+CD49d^+$ MDSC were more potent suppressors of antigen-specific T cells *in vitro* than $CD11b^+CD49d^-$ granulocytic MDSC and suppressed T cell responses through an NO mediated mechanism [6]. Recently, murine MDSC have been further subdivided into 5 different classes dependent on the relative expression of CD11b and Gr-1 [7] and it is very likely that more subtypes and markers will be identified and described in the near future.

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The heterogeneity of MDSC - which explains the lack of specific markers for these cells–is, along with their multiple suppressor function, [8] a hallmark of MDSC. Murine MDSC have been shown to suppress T cell responses by multiple mechanisms, which have recently been discussed in a comprehensive review [9]. L-arginine represents one important molecule central to the immune suppressive function by MDSC. L-arginine serves as a substrate for both iNOS and Arginase-1, which are both highly expressed in MDSC derived from tumor bearing mice. While utilizing L-arginine, iNOS generates nitric oxide (NO) and can suppress T cell function through different mechanisms. At the same time Arginase-1 depletes from T cells the essential amino acid L-arginine, which in turn leads to CD3 ζ-chain downregulation and cell cylce arrest through upregulation of cyclin D3 and cdk4 [10]. Reactive oxygen species (ROS) represent another suppressor mechanism and recently peroxynitrite has emerged as a crucial mediator of suppression of T cell function by MDSC, and which can lead, among other mechanisms, to nitration of the T-cell receptor and CD8 molecules [11].

Human MDSC subtypes

In humans CD34$^+$ MDSC were reported for the first time in patients with head and neck cancer in 1995 [12]. In contrast to murine MDSC, which are defined by the expression of Gr-1 and CD11b, the corresponding cells in human are inadequately characterized because of the lack of uniform markers. An increased frequency of lin$^-$CD33$^+$CD34$^+$CD15$^+$ immature myeloid cells with immune suppressor function in peripheral blood from patients with head and neck cancer was reported [13] while others reported the suppressor function of CD15$^+$ granulocytes [14]. In further studies human arginase-1 expressing MDSC were defined as CD11b$^+$CD14$^+$CD15$^+$HLA-DR$^-$cells, which were found in the peripheral blood of patients with renal cancer [15]. Similarly, an increase in the frequency of lin$^-$HLA-DR$^-$CD33$^+$ cells was observed in renal cancer patients [16]. Based on our observations of an impaired function of CD1c$^+$, CD19$^-$, CD14$^-$ myeloid dendritic cells in peripheral blood of patients with hepatocellular carcinoma (HCC)[17], we decided to also analyze the function of *in vitro*-generated dendritic cells from patients with HCC, which are usually derived from CD14$^+$ monocytes. Here we observed that the function of dendritic cells was impaired in contrast to *in vitro*-generated dendritic cells from healthy controls. Further analysis demonstrated that a subtype of CD14$^+$ monocytes, CD14$^+$HLA-DR$^{low/neg}$ cells, did not mature into functional dendritic cells and failed to induce an allo-response. Moreover, there was an increase in the frequency of this cell type in peripheral blood and tumor-infiltrating lymphocytes from HCC patients in comparison with healthy controls and control patients with other non-malignant liver diseases [18]. Further studies demonstrated that CD14$^+$HLA-DR$^{low/neg}$ cells suppressed proliferation and cytokine secretion of CD8$^+$ T cells in an L- arginine-dependent manner and depletion of these cells *in vitro* unmasked antigen-specific T cell responses. Based on these findings CD14$^+$HLA-DR$^{low/neg}$ cells are MDSC. A similar cell type had previously been described in the context of melanoma patients vaccinated with an autologous tumor-derived heat shock protein peptide complex gp96 and low-dose GM-CSF [19] and was also found in melanoma patients without specific treatment [20]. Based on these initial studies MDSC were analyzed in a number of different other tumor settings and their phenotype was further characterized (Table 1).

Phenotypical analysis of human MDSC

While murine MDSC subtypes can be divided into a more granulocytic and a monocytic cell type, attempts have been made to also divide human MDSC into a more granulocytic and a monocytic cell type. Both MDSC subtypes express the common myeloid markers CD11b and CD33 but lack expression of markers of mature myeloid cells such as CD40, CD80, CD83 and HLA-DR. It has been suggested that monocytic MDSC are CD14$^+$ and

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granulocytic MDSC express CD15, while both groups of MDSC are HLA-DR$^{low/neg}$ and CD33^{+}. However, more data is needed to corroborate this hypothesis on human MDSC. Similar to murine studies [4], IL-4Ra has been suggested as a specific marker for tumor derived MDSC with suppressor function [21], however this marker has not been evaluated extensively. VEGF-R is another marker, which has recently been described to be expressed on MDSC, which could also explain the effect of certain targeted therapies on MDSC [21, 22] (see below). Future studies will aim at the identification of better markers to distinguish CD14^{+}HLA-DR^{+} moncytes from CD14^{+}HLA-DR$^{low/neg}$ MDSC.

In vitro generated MDSC

Recently a number of protocols have been described to generate MDSC from mice bone marrow [23, 24]. Mouse bone marrow-derived IL4Rα^{+} MDSC which consist of a mixture of immature cells have been shown to posess immune suppressor activity, and can be derived with GM-CSF+G-CSF or GM-CSF+IL-6 or IL-13 [23, 25]. Two different approaches were taken to mimic the situation in a cancer patient in order to induce MDSC. In one setting, CD14^{+} monocytes isolated from healthy donors were differentiated with IL4 and GM-CSF in the presence of tumor-derived microvesicles. This led to the induction of CD14+HLA-DR$^{neg/low}$ MDSC with suppressor activity [26]. In a different setting, PBMC from healthy donors were incubated in the presence of factors known to be implicated in the generation and activation of MDSC. In this study it was shown that human MDSC can be induced after incubation of PBMC with GM-CSF+IL-6 or GM-CSF + IL-1β, PGE2, TNF-α and VEGF [27]. *In vitro*-generated MDSC were potent suppressors of T cell responses and were CD33^{+}, HLA-DR^{low}, CD11b^{+} and CD66b^{+}. Future studies are needed to further investigate the possibility of using these cells for adoptive therapy in different autoimmune settings such as graft versus host disease [25].

MDSC in non-tumor settings

Human MDSC have been described in patients with different tumors (Table 1). However, in murine settings MDSC have been described also in a number of different non-malignant settings such as during bacterial [9], viral [28] and parasitic infections [29], traumatic stress [30] sepsis [31], acute inflammation [7], tolerance [32], graft versus host disease [25] and different autoimmune diseases such as diabetes [33], encephalomyelitis [34] and colitis [6]. Until today, only limited data is available on human MDSC in non-tumor settings. We have described an increase in the frequency of CD14^{+}HLA-DR$^{low/neg}$ MDSC in patients with inflammatory bowel diseases [6] and are currently in the process of analyzing MDSC in this disease in more detail.

Suppressive Mechanisms of human MDSC

Multiple mechanisms have been suggested to be implicated in suppressor activity of murine MDSC and are discussed in recent reviews [9, 35]. In contrast, only limited information is available on how human MDSC exert their suppressor function. One of the first mechanisms for MDSC-mediated T cell suppression in mice has been associated with the metabolism of L-arginine, which serves as a substrate for two enzymes: arginase 1 and iNOS. Both enzymes have been shown to be highly expressed in murine MDSC and to inhibit T cell function. Therefore both ways were also investigated in human MDSC and indeed, were shown to be involved in suppression of T cell responses *in vitro* by human MDSC. MDSC were shown to have elevated arginase activity, which was associated with a decreased CD3ζ chain expression on T cells [14, 15]. NOHA, an arginase inhibitor, and L-NMMA, a potent arginase and NOS2 inhibitor respectively, were able to block MLR suppressor activity of MDSC [36]. Addition of exogenous L-arginine was able to restore IFN-γ release by T cells when co-cultured with CD14^{+}HLA-DR$^{low/neg}$ MDSC [18]. To delineate the suppressive

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mechanisms used by CD14$^+$HLA-DR$^{low/neg}$ MDSC from melanoma patients, quantitative PCR analysis for candidate suppressive molecules (arginase-1, COX-2, IDO, IL-10, i-NOS and TGF-b) was performed. Arg1 was expressed at significantly higher levels in patient-derived CD14$^+$HLA-DR$^{low/neg}$ MDSC, whereas levels of COX 2 and iNOS transcription were significantly lower. No difference in indoleamine 2,3-dioxygenase, IL-10, and TGF-α expression was observed. Inhibition of arginase also improved T-cell proliferation indicating the dominance of this pathway for MDSC mediated inhibition of T cells [37]. However, ROS-mediated suppression of T cell responses has also been shown to be active in CD14$^+$HLA-DR$^{low/neg}$ MDSC in this study. Similarly, CD11b$^+$CD14$^-$CD33$^+$ MDSC have been shown to mediate immune suppression by ROS production [38, 39]. Finally, while TGF-β release by CD14$^+$HLA-DR$^{low/neg}$ cells could be demonstrated when MDSC from melanoma patients were analyzed [19], we could only detect membrane bound TGF-β on MDSC (unpublished data).

Multiple different biological mechanisms have been suggested how murine MDSC suppress immune responses and promote tumor development [8]. These mechanisms include direct inhibition of T cells as discussed above but also indirect immune inhibitory effects. Recently Gabrilovich's group could demonstrate that MDSC from peripheral blood suppress T cells in an antigen specific manner whereas MDSC from the tumor site suppress T cells in a non-specific manner [40]. Our laboratory has shown one indirect method of how MDSC exert their suppressor function. We have examined the effect of in CD14$^+$HLA-DR$^{low/neg}$ MDSC on naïve CD4$^+$ T cells *in vitro*. In contrast to CD14$^+$HLA-DR$^+$ monocytes CD14$^+$HLA-DR$^{low/neg}$, MDSC triggered release of IL-10 by CD4$^+$ T cells and induced the induction of regulatory T cells [18]. Currently we are examining what factors are essential for the induction of regulatory T cells by MDSC and if these markers can be used to distinguish CD14$^+$HLA-DR$^{low/neg}$ MDSC from CD14$^+$HLA-DR$^+$ monocytes.

MDSC NK interaction

NK cells and NKT cells play important roles in innate immune responses. NK cells have shown to be involved in the first defense and regulation of adaptive immune system through the action on APCs. Therefore it is important to understand NK-MDSC interactions. It has been suggested that murine NKT cells facilitate the conversion of immunosuppressive MDSC into immunogenic APCs [41]. Conflicting results have been described on the effect of MDSC on NK cell function in murine tumor models. Different studies demonstrated an inhibition of NK cell function [42, 43]. In one study this inhibition was mediated via membrane-bound TGF-b1 [43], while others report an unexpected activating role of MDSC on NK cells [44], possibly regulated through STAT-1 [45]. In a different study the absence of invariant NKT (iNKT) cells in mice during influenza A virus infection resulted in the expansion of MDSC leading to high IAV titer and increased mortality [36]. Only one study has examined NK-MDSC crosstalk in humans. We have been able to show that NK cell function was impaired in patients with HCC. In *in vitro* studies we showed that MDSC impaired NK cell function, and the depletion of MDSC from PBMC led to an improvement in NK cell lysis, suggesting that the observed increase of MDSC in patients with HCC might be one possible reason for impaired NK cell function. Interestingly, suppression of NK cells was not arginase-1-, iNOS- or ROS mediated, but rather, blockade of NKp30 could partially reverse the inhibitory function of human MDSC on NK cells *in vitro* [46].

Targeting MDSC in patients with cancer

Since MDSC are still a very poorly defined cell population it will be difficult to specifically target these cells in cancer patients with the aim of engaging tumor-specific immune responses. Nevertheless, a number of different approaches have already been evaluated with

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the aim of boosting immune responses by targeting MDSC. In one of the first studies reported, 18 patients with metastatic renal cell carcinoma were treated with all-trans-retinoic acid (ATRA) followed by s.c. interleukin 2 (IL-2) based on *in vitro* studies, which suggested that ATRA matures MDSC [39, 47]. A reduction in the number of Lin^{-} $HLA\text{-}DR^{-}$ $CD33^{+}$ cells accompanied by an improvement of tetanus-toxoid-specific T-cell response was observed [16]. Sunitinib, which is currently being used for the treatment of renal cancer also demonstrated effects on human MDSC. Both circulating $CD33^{+}HLA\text{-}DR^{-}$ and $CD15^{+}$CD14- MDSC declined in response to treatment with sunitinib. In parallel an increase in IFN-g production upon CD3 stimulation by T cells was observed [48]. In contrast, treatment of RCC patients with the anti-VEGF antibody bevacizumab, did not reduce the accumulation of MDSC in peripheral blood [22], despite preclinical data suggesting that VEGF can induce MDSC. Finally, Vitamin D3 has been shown to reduce the number of immune suppressive $CD34^{+}$ cells and to increase HLA-DR expression on PBMC in HNSCC patients.

Outlook

MDSC have gained a lot of attention in recent years mainly in the tumor immunology community. However, based on the results from murine studies in non-tumor settings, human MDSC will need to be analyzed in more detail in non-cancer patients as well. One major hurdle remains the heterogeneity of the cells. The only possibility of overcoming this problem will be through a thorough phenotypical and functional analysis of all potential MDSC subsets in different clinical settings. Identification of better markers will facilitate these studies. More in-depth analysis of the interaction of MDSC with other cell types will help understand the biological function and, finally, the specific targeting of human MDSC and their subtypes will help the effect of immune-based therapies in cancer.

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Table 1

MDSC subtypes in human disease

Subset	Disease type	Reference
$Lin^{-}HLA\text{-}DR^{-}$	HNSCC, lung, breast (N=93)	[13]
Lin^{-} $HLA\text{-}DR^{-}$ $CD33^{+}$	Renal (N=18)	[16]
$Lin^{-}HLA\text{-}DR^{-}CD33^{+}$	Melanoma (N=39)	[49]
$Lin^{-}HLA\text{-}DR^{-}CD33^{+}$	Renal (N=9)	[39]
$Lin^{-/low}HLA\text{-}DR^{-}CD33^{+}CD11b^{+}$	Breast (N=17)	[50]
$CD11b^{+}CD14^{-}CD33^{+}$	HNSCC (N=14) and (N=5)	[38, 40]
$CD33^{+}HLA\text{-}DR^{-}$	Renal (N=23)	[48]
$CD11b^{+}CD14^{-}CD15^{+}$	Renal (N=123)	[15]
$CD11b^{+}CD14^{-}CD15^{+}$	Renal (N=27)	[22]
$CD11b^{+}CD14^{-}CD15^{+}CD33^{+}$	NSCLC (N=87)	[51]
$CD11b^{+}CD33^{+}$	Lung (N=10)	[52]
$CD11b^{+}$	Influenza A virus infection	[36]
$CD15^{+}CD14^{-}$	Renal (N=23)	[48]
$CD15^{+}$ $IL4R\alpha^{+}$	Melanoma (N=14) Colon (N=15)	[21]
$CD14^{+}HLA\text{-}DR^{low/neg}$	Multiple Myeloma (N=76)	[53]
$CD14^{+}HLA\text{-}DR^{low/neg}$	Melanom (N=16)	[19]
$CD14^{+}HLA\text{-}DR^{low/neg}$	Inflammatory Bowel disease (Ulcerative colitis: N=18; Crohn's disease: N=21)	[6]
$CD14^{+}HLA\text{-}DR^{low/neg}$	HCC (N=111)	[18]
$CD14^{+}HLA\text{-}DR^{low/neg}$	Melanoma (N=34)	[37]
$CD14^{+}HLA\text{-}DR^{low/neg}$	Prostate (N=40)	[54]
$CD14^{+}HLA\text{-}DR^{low/neg}$	Renal (N=26)	[55]
$CD14^{+}$	HNSCC (N=7) Multiple Myeloma (N=7)	[56]
$CD14^{+}$ $IL4R\alpha^{+}$	Melanoma (N=14) Colon (N=15)	[21]
$CD15^{+}$ granulocytes	Pancreas (N=19) Colon (N=15) Breast (N=1)	[14]
$SSC^{high}CD66b^{+}$	HNSCC, lung, bladder and ureter (N=113)	[57]

Table 2

Phenotypical analysis of human MDSC (p/n: two populations: positive and/or negative; int: intermediate; l/n: low or negative; hi: high).

SSC	CD3	CD11a	CD11b	CD13	CD14	CD15	CD16	CD19	CD33	CD34	CD40	CD56	CD66b	CD80	CD83	CD86	HLA-DR	VEGFR	IL4Rα	CD125	Disease type	Reference
					neg			neg			neg						neg			neg	HNSCC, lung, breast	[13]
hi			pos				p/n						pos							neg	HNSCC, lung, bladder, ureter	[57]
			pos		pos	neg			pos	neg			neg	neg	neg	int	l/n				HCC	[18]
		neg	pos		neg	pos							neg	neg	neg	neg	neg				RCC	[15]
			pos			p/n			pos												NSCLC	[52]
					neg	pos			pos								neg				RCC	[48]
						neg			pos								neg				RCC	[48]
	neg		pos		neg			neg	pos								neg				RCC	[39]
					pos									pos	pos		neg				Melanoma	[37]
	neg		pos			pos		neg	pos												Lung	[52]
					p/n	p/n													pos		Melanoma Colon	[21]
			pos		neg	pos	pos		pos				pos					pos			RCC	[22]
			pos															pos				[58]

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Table 3

Medical targeting of MDSC#

	Drug	Mechanism	Effect on MDSC	Reference
FDA approved drugs*	Bevacizumab		***no effect*** *in vivo* on human MDSC	[22]
	ATRA	differentiation of MDSC via neutralization of ROS	*in vivo* on human MDSC	[16, 59].
	Sunitinib	STAT3 and c-kit mediated	*in vivo* on human MDSC	[48, 60]
	5-FU	Selective killing of MDSC	*in vivo* on murine MDSC	[61]
	Gemcitabine	apoptosis of MDSC	*in vivo* on murine MDSC	[42]
	PDE5 inhibitors	downregulates IL4Ra and impairs MDSC function	*in vivo* on murine MDSC	[62]
	COX2 inhibitors	blocks arginase 1 induction	*in vivo* on murine MDSC	[63, 64]
	Amino- Bisphosphonate	inhibiting MMP-9 expression	*in vivo* on murine MDSC	[65]
	Vitamin D3	increases HLA-DR and reduces CD34+ cells	*in vivo* on murine and human MDSC	[66, 67]
Compounds in clinical development	VEGF-trap		***no effect*** *on* human MDSC	[68]
	synthetic triterpenoids	ROS blockade	*in vivo* on murine MDSC	[69]
	NO-releasing aspirin	Inhibits ARG1 and NOS2	*in vivo* on murine MDSC	[70]

*FDA approval for different indication than MDSC targeting