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Review Article

Immunosuppression and Metabolic Changes in Tumor Microenvironment induced by Myeloid-derived Suppressor Cells and its Relationship with Cancer Cachexia

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Abstract:

Cancer remain a leading cause of death around the world. Although cancer immunotherapy is widely acknowledged as an important treatment option for cancer, myeloid-derived suppressor cells (MDSCs) have been reported to be a major obstacle to immunotherapy. MDSCs are typically absent or present in very low numbers in healthy individuals; however, they have been reported to markedly increase in pathological conditions including cancer. MDSCs exhibit potent immunosuppressive activity in the tumor microenvironment (TME) through multiple mechanisms, including accumulation of immunosuppressive cells, such as regulatory T cells (Tregs) and tumor associated macrophages (TAMs), as well as the production of reactive oxygen and nitrogen species. Cancer cachexia is characterized by weight loss and hypoalbuminemia, and reported to relate with systemic inflammation that is one of the major inducers of MDSCs. An accumulation of MDSCs is observed in patients with cachexia.

Therapeutic modalities targeting MDSCs are under development, with clinical trials currently in progress. Furthermore, in the field of immune-oncology, novel cancer treatments leveraging advanced technologies to target MDSCs have also been reported.

Key words: immunosuppression ; cancer immunotherapy; myeloid-derived suppressor cells （MDSC）; cancer cachexia; immunosuppressive cells

Introduction

While the survival of cancer patients has been greatly extended in recent years by innovative therapeutic approaches newly introduced to the field, cancers still remain a leading cause of death worldwide [1]. One of the most substantial advances in cancer therapy over the past decades has been the development and success of immune checkpoint inhibitors (ICIs), which can specifically activate immune cells by targeting immune checkpoints, immunosuppressive molecules expressed on immune cells [2].

The process of myelopoiesis involves the differentiation of progenitor cells and myeloid precursors into monocytes, granulocytes, and dendritic cells (DCs) in healthy conditions. Immature myeloid cells (IMC), including myeloid progenitor cells, do not exhibit immunosuppressive activity under normal conditions. However, in chronic inflammatory conditions, such as cancer, chronic infections, and autoimmune diseases, IMC differentiation is suppressed, promoting the accumulation of myeloid-derived suppressor cells (MDSCs), which are pathologically

induced immature myeloid cells [3–6]. MDSCs were firstly discovered in 1970s and finally identified and termed in 2007. MDSCs represent a heterogeneous population of IMC that possess various strong immunosuppressive activities involving multiple immunocompetent cells and are significantly accumulated in patients who did not respond to cancer immunotherapies [7,8]. MDSCs are typically absent or present in very low numbers in healthy individuals, but markedly increase in pathological conditions, such as cancer. In cancer, tumors can secrete soluble factors that promote the expansion of MDSCs; therefore, creating a tumor microenvironment (TME) that favors tumor progression by inhibiting effective local immune control of cancer cells. Thus, MDSCs represent a major obstacle to cancer immunotherapy, and have become a target of interest in cancer treatment. Numerous innovative therapies targeting MDSCs have been explored, and various approaches to inhibit MDSC function are currently being evaluated in clinical trials [9]. In this review, we discuss the origin, functions, and metabolic signature s of MDSCs, and highlight the targeting MDSCs as a promising therapeutic approach to suppress their immunosuppressive functions. Additionally, since MDSCs have been reported to be involved in the development of cancer cachexia, we here discuss the functional relationships between the immunological properties of MDSCs and cancer cachexia.

Origin and phenotypes of MDSCs

Heterogeneous and multipotent myeloid cell populations perform diverse specialized functions that are critical for innate immunity against pathogens, maintenance of homeostasis, and coordination of inflammatory responses [10]. These myeloid cell populations were named MDSCs based on their phenotype and immunosuppressive activities, and are classified into two major subsets: monocytic MDSCs (M-MDSCs) expressing $CD11b^{+}Ly6G^{low}Ly\text{-}6C^{high}$; and granulocytic or polymorphonuclear MDSCs (G-MDSCs, PMN-MDSCs) expressing $CD11b^{+}Ly6G^{+}Ly6C^{low}$ [11,12]. Although both populations of MDSCs exhibit strong immunosuppressive activities, G-MDSCs have been proven to expand significantly during tumor progression in cancer patients, G-MDSC is the primary source of immunosuppression that enables tumor escape and tumor progression. In human studies, MDSCs are typically identified by either the expression of the myeloid marker CD33 and low-or-absent expression of HLA-DR, or the expression of CD11b and low/absence of CD14. Recent studies have introduced additional markers including CD15, CD34, CD45, CD84, and IL-4Rα (CD124), to improve the phenotypic characterization of MDSCs [13,14].

Immunosuppressive mechanisms of MDSC s (Figure 1)

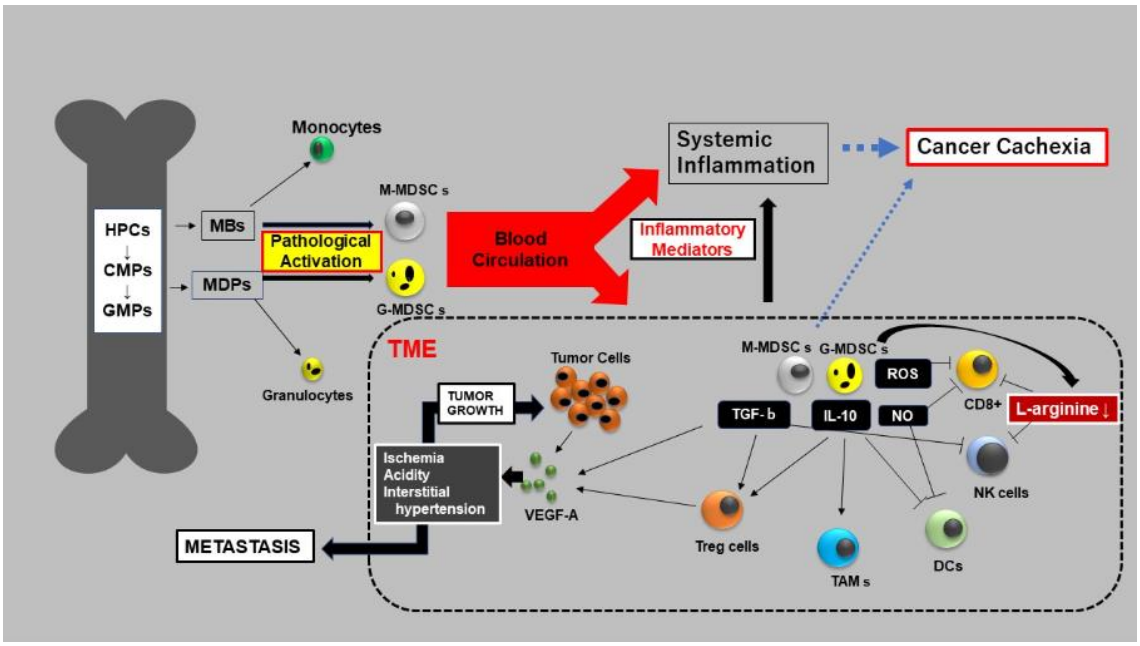

Figure 1: MDSCs and its immunosuppression and metabolic characteristics in TME

By pathological activation such as cancer, chronic infections, and autoimmune diseases, differentiation of myeloid cells is suppressed, promoting the accumulation of MDSCs. MDSCs exert strong immunosuppressive effects in the TME through multiple mechanisms, including the accumulation of immunosuppressive cells, such as regulatory T cells (Tregs) and tumor-associated macrophages (TAM), as well as the production of reactive oxygen and nitrogen species, and depletion of L-arginine [9-12]. TME is characterized by VEGF-A-driven impaired perfusion and increased vascular leakage, leading hypoxia, acidity, and interstitial hypertension, resulting in distant metastasis [34-36,75].

HPCs, hematopoietic progenitor cells; CMPs, common myeloid progenitors; GMP, granulocyte macrophage progenitor; MBs, myeloid-like B cells; MDPs, monocyte-DC progenitor; M-MDSCs, monocytic myeloid-derived suppressor cells; G-MDSCs, granulocytic myeloid-derived suppressor cells; ROS, reactive oxygen species; TGF-b, transforming growth factor-beta; NO, nitric oxides; IL-10, interleukin-10; VEGF-A, vascular endothelial growth factor-A

The immune defense system, composed of cytotoxic T cells, natural killer (NK) cells, DCs, and B cells, is essential for tumor control, however its function is impaired by several immunosuppressive factors, including immunosuppressive cells such as MDSCs. MDSCs exert strong immunosuppressive effects in the TME through multiple mechanisms, including the accumulation of immunosuppressive cells, such as regulatory T cells (Tregs) and tumor-associated macrophages, as well as the production of reactive oxygen and nitrogen species.

Interferon（IFN gamma is necessary for MDSCs-mediated induction of Treg cells, and MDSCs have been shown to induce Treg cells through a mechanism mediated by interleukin (IL)-10 [15]. MDSCs and Tregs have been shown to promote the expression of programmed cell death ligand 1 (PD-L1) to induce T cell anergy through interacting with PD-1 on T cells [16,17]. The induction of Tregs has also been demonstrated through chemokines, such as CCL4 and CCL5, secreted by tumor-infiltrating

MDSCs [18]. MDSCs have also been reported to enhance the immunosuppressive functions of Tregs through the direct interactions of CD80 on MDSCs and cytotoxic T-lymphocyte-associated protein (CTLA)-4 [4]. M-MDSCs have also been shown to produce transforming growth factor (TGF)-beta and IL-10, which contribute to immunosuppression of CD8+ T cells. Additionally, MDSCs induce a shift in macrophages toward an M2-like phenotype with immunosuppressive features [19], leading to reduced IL-12 production by M2-like macrophages and promoting a type 2 shift in $CD4^+$ T cells within the TME.

It is well known that MDSCs produce reactive oxygen species (ROS), which impair the function of tumor-infiltrating lymphocytes. In addition to their direct toxicity of ROS on immune cells to suppress tumor growth, ROS support the expansion of MDSCs. L-arginine, which is critical for the function of the immune system, can be metabolized in MDSCs by four different enzymes: nitric oxide synthases, including NOS1, NOS2, and NOS3; arginases, including Arg-1 and Arg-2; arginine; glycine aminotransferase; and L-arginine decarboxylase [14].

Metabolic characteristics of MDSCs

As mentioned above, MDSCs promote the differentiations of Tregs and M2-like macrophages by producing TGF-beta and IL-10. These soluble inhibitory mediators also downregulate the expression of the activating receptor NK group 2 member D (NHG2D) in NK cells, thereby abrogating their cytotoxicity [20]. Additionally, MDSCs express several ligands for inhibitory receptors on T cells, promote T cell exhaustion through the T cell immunoglobulin and mucin-domain containing-3 (Tim-3)/Galectin-9 pathway, and terminate Th1 immune responses [21,22].

The Warburg effect is the physiological phenomenon of tumor cells that cancer cells predominantly rely on aerobic glycolysis and lactic acid fermentation for energy generation, differing from the typical glucose metabolism in non-cancerous cells [23]. Specifically, in the TME, cancer cells primarily derive their energy from glycolysis, consuming more glucose and producing higher levels of lactate than non-cancerous cells [24]. Immune competent cells choose aerobic glycolysis due to its rapid energy generation. Moreover, M1 macrophages, for instance, primarily rely on glycolysis, with their proinflammatory functions, including phagocytosis and the production of cytokines such as IL-1 beta, tumor necrosis factor (TNF)-alpha, and IL-6, being directly associated with this metabolic pathway. In contrast, M2 macrophages rely more on fatty acid oxidation (FAO) and oxidative phosphorylation (OXPHOS) [25]. MDSCs also use aerobic glycolysis to meet their energy demands and support rapid proliferation, thereby creating an immunosuppressive environment that inhibits anti-tumor activities and promotes tumor growth [26,27]. Cytokines including GM-CSF (granulocyte macrophage-colony stimulating factor), as well as IL-6 produced by tumor cells and macrophages, promote glucose uptake and glycolysis in MDSCs, leading to an increased production of lactate. This end product of pyruvate metabolism during aerobic glycolysis plays the critical role of lactate in suppress tumor surveillance [23]. CD8+T cells primarily utilize aerobic glycolysis, while Tregs rely on OXPHOS, which is an important metabolic pathway for immunosuppression and tumor progression. Moreover, in the TME, CD39 and CD73 on tumor cells metabolize ATP (adenosine triphosphate) to adenosine while indoleamine 2,3-dioxygenase (IDO) converts tryptophan into kynurenine, and the resulting accumulation of adenosine and kynurenine supports Tregs [25]. It is also important to focus on adenosine metabolism since emerging evidence have been reported on adenosinergic signaling in immune system. Hypoxia and TGF-beta represent the key drivers of the adenosinergic pathway. A2B, one of the adenosine receptors, predominantly exert immunosuppressive functions, and control some important effects of MDSCs in TME. The adenosine-generating enzymes and possibly adenosine receptors are expressed on MDSCs and regulated by hypoxia and chronic inflammatory factors. MDSCs, therefore, produce adenosine within TME as an additional mechanisms of immunosuppression in TME [28,29]. MDSCs have been reported to produce pro-angiogenic factors, vascular endothelial growth factor (VEGF)-A in a STAT-3 dependent manner and it was shown that adenosine receptor A2B stimulation enhanced the production of VEGF, and pharmacological blockade of A2B reduced tumor angiogenesis, MDSCs accumulation and growth retardation of tumor. This A2B receptor blockade inhibit MDSCs and may be effective as an anti-VEGF agent [30,31].

To meet the high energy demands required for proliferation and the enhancement of immunosuppressive and tumor-promoting functions, MDSCs undergo metabolic reprogramming in the TME, shifting their main energy source from glycolysis to FAO [14]. It has also been reported that MDSCs rely on FAO as the major metabolic pathway for the production of immunosuppressive cytokines. However, the critical factors underlying the metabolic shift between glycolysis and FAO are not yet well understood [32].

Angiogenesis, hypoxia and, MDSCs

Hypoxia is another important feature that is induced not only by metabolic characteristics but also by other factors such as tumor angiogenesis.

In 2011, Hanahan and Weinberg updated the hallmarks of cancer, adding avoiding immune destruction as a new characteristic [33]. Importantly, they included the inhibition of VEGF as a key strategy to suppress the hallmarks of cancer. Tumor vasculature, typically driven by VEGF-A, is structurally and functionally distinct from that of non-malignant tissue, characterized by impaired perfusion and increased vascular leakage, leading hypoxia and acidity in the TME (34). MDSCs are one of the major sources of VEGF-A as well as tumor cells, Tregs, and M2 macrophages. As a result, oxygen and immune competent cells such as CD8+ cells cannot perfuse in the TME, leading to an increase in interstitial pressure due to fluid leakage. Ultimately, even if these lymphocytes circulate within the blood vessels in the TME, they are unable to migrate out of the vessels [35]. There is also a difference between CD8+T cells and Tregs; CD8+T cells utilize aerobic glycolysis and cannot survive in hypoxic conditions, while Tregs are activated in environments with high levels of adenosine and kynurenine. Due to the high vascular permeability and increased interstitial fluid pressure, tumor cells in the TME can easily enter the systemic circulation, resulting in metastasis to distant organs [36].

Another important molecular mechanism is mediated by the transcription factor hypoxia-inducible factor-1 (HIF-1), which is a heterodimer consisting of HIF-1 alpha and HIF-1 beta. HIF-1 alpha induces the upregulation of Arg-1 and increases nitric oxide synthase in hypoxic conditions, thereby enhancing the ability of MDSCs to suppress T cell functions. HIF-1 alpha has been reported to act as a negative regulator of Tregs differentiation and is essential for their immunosuppressive activity [37].

Cancer cachexia, immunosuppression, and MDSCs (Figure 2)

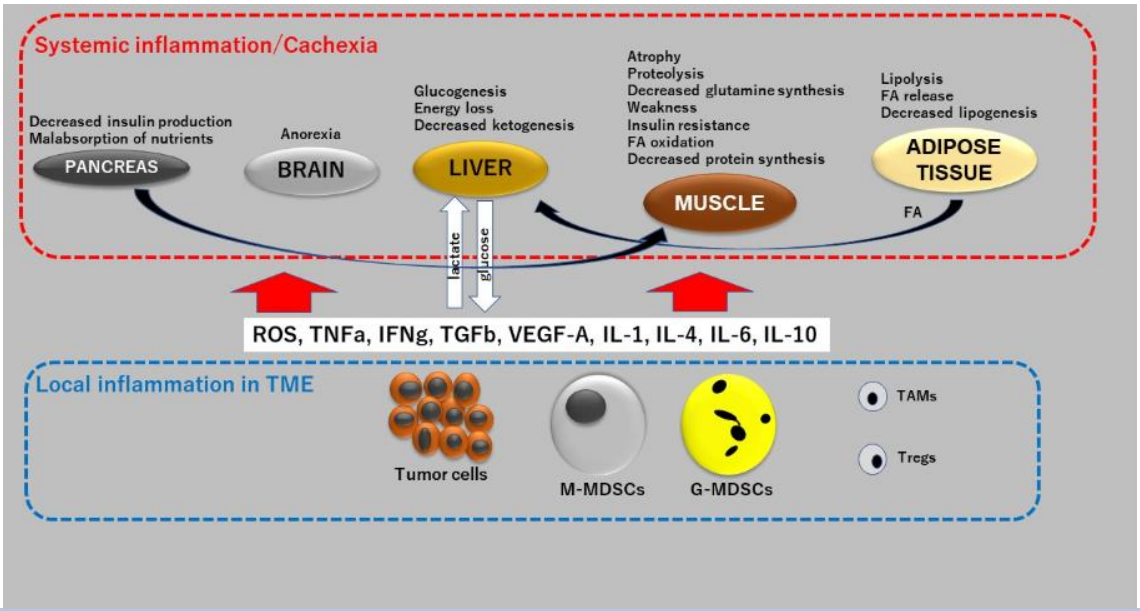

Figure 2: Development of cachexia: Systemic inflammation induced by locally produced inflammatory mediators

MDSCs in cancer patients play an important role in the development of cachexia through the mechanism of inflammatory mediators produced in TME [52-54]. The release of TNF-alpha has been linked directly to muscle wasting. increased levels of IL-1, IL-8 and IL-10 in patients with cancer cachexia result in increased energy expenditure, loss of appetite and muscle atrophy through a mechanism involving multiple organs such as pancreas, brain, liver, muscle and adipose tissue. Insulin plays critical roles of regulating muscle proteolysis and insulin resistance in cancer cachexia, can contribute to muscle wasting [55]. It is also demonstrated that circulating IL-6 reduces dopamine release in the nucleus accumbens, leading lowering motivation and anorexia [59,60].

ROS, reactive oxygen species; TNFa, tumor necrosis factor alpha; IFNg, interferon gamma; TGFb, transforming growth factor beta; VEGF-A, vascular endothelial growth factor-A; IL-1, interleukin-1; IL-4interleukin-4; IL6, interleukin-6; IL-10, interleukin-10; M-MDSCs, monocytic myeloid-derived suppressor cells; G-MDSC, granulocytic myeloid-derived suppressor cells; TAMs, tumor associated macrophages; Tregs, regulatory T cells; FA, fatty acid

Although metabolic features of lipid, glucose, and amino acids have been studied, there have not been reported well on protein metabolism in the biology of MDSCs.

Cachexia is a syndrome that is characterized by weight loss and hypoalbuminemia and cannot be completely recovered by conventional nutritional support. Cancer cachexia specifically arises as a result of cancer [38]. Cancer cachexia is observed in approximately 70% of cancer patients, and accounts for 22% of cancer-related deaths [39]. It is divided into three categories: pre-cachexia, characterized by early clinical and metabolic signs, with < 5% weight loss; cachexia with > 5% weight loss; and refractory cachexia, which is unresponsive to treatments [39]. Additionally, cancer cachexia has been observed as a negative outcome of cancer treatments, resulting in impaired physical function, resistance to cancer chemotherapies, and poor prognosis [40]. The mechanisms underlying cancer cachexia include tumor cell metabolism, psychiatric effects of the patients, as well as physical and mental changes caused by treatments such as radiotherapy, immunotherapy, and chemotherapy. Among these, the role of the host immune response has been extensively studied for many years and is recognized as essential. We previously focused on the immune alterations observed in cachectic patients, and reported that cancer cachexia is characterized by a Th2-dominant state in $CD4^+$ cells, high production of proinflammatory cytokines, and the presence of refractory anti-inflammatory cytokines such as IL-10, as well as refractory immunoregulatory proteins, including soluble receptors for IL-2 and TNF alpha [41-44]. In addition, we measured phytohemagglutinin (PHA)-stimulated lymphocyte proliferation as a measure of cell-mediated immune response, calculating the stimulation index (SI). Our findings revealed that SIs progressively decrease with advancing cancer stages and demonstrate a significant correlation with nutritional parameters. Our previous research also demonstrated that inflammatory indicators, such as neutrophil to lymphocyte ratio (NLR) or C-reactive protein (CRP, clinical indicator of inflammation and IL-6 production), were significantly correlated with nutritional impairments, including decreased serum protein levels, in various cancers [45,46]. Proteins are regulated by the balance between their synthesis and degradation. In cachexia, clinically characterized by hypoproteinemia, metabolic features involving both protein synthesis and degradation have been reported; however, the underlying mechanisms of hypoalbuminemia remain unclear. Moreover, our laboratory has demonstrated that circulating MDSCs (CD11b+, CD14-, CD33+) were increased in patients with various types of cancer, and significant correlations were observed amongst the numbers of MDSCs, systemic inflammation markers, and decreased levels of rapid turnover proteins [47-51]. Among several proinflammatory mediators, we have focused on VEGF-A and IL-17 as inducers of MDSCs [49,51]. Cuenca et al. have reported a novel role of tumor-induced MDSCs in the development of cancer cachexia syndrome [52]. They demonstrated that MDSCs expansion and tumor burden are associated with a decrease in adipose tissue, as well as increases in acute-phase proteins and oxygen consumption, suggesting that MDSCs induces inflammation and play a pivotal role in cancer cachexia (Figure 2). The role of MDSCs-mediated immune system including increased macrophages (TAM) typically shifted to M2, and Tregs, is one of the biggest drivers of cancer cachexia [53]. The release of TNF-alpha has been linked directly to muscle wasting. TNF-a exerts its catabolic function by stimulating the degradation of muscle protein through the activation of E3 ligase pathway [54]. Moreover, increased levels of IL-1, IL-8 and IL-10 in patients with cancer cachexia result in increased energy expenditure, loss of appetite and muscle atrophy through a mechanism involving multiple organs such as pancreas, brain, liver, muscle and adipose tissue [55]. In the mouse model of cancer cachexia, higher loss of adipose tissue and increased consumption of oxygen which is one of the

characteristics of cancer cachexia were significantly demonstrated in the mice with expansion of MDSCs compared to those without it [56]. Insulin produced by pancreas and IGF1 (insulin-like growth factor 1) produced by liver activate a cascade of phosphorylation of key-regulators for muscle metabolism. Insulin plays a critical roles of regulating muscle proteolysis and insulin resistance in cancer cachexia, can contribute to muscle wasting [40,57]. IL-6 has been shown to exacerbate cancer cachexia by promoting the wasting of adipose tissues, activating mechanisms that enhance lipolysis and proteolysis through the JAK/STAT3 pathway [58], resulting in weakness and waste of muscle. It is also demonstrated that circulating IL-6 reduces dopamine release in the nucleus accumbens of the brain, leading lowering motivation and anorexia [59]. Zhang and Bonomi reported that anti-cancer therapies targeting MDSCs may not only be effective against immunosuppression but also against cancer cachexia promoted by MDSCs [60],

The anti-aging gene Sirtuin-1 is a NAD+ sensitive deacetylase and mono-transferases, and SIRT1, a member of the sirtuin family, plays a significant role in regulating the creation of ROS [61]. SIRT1 is reported to be critical to systemic inflammation and can control cancer cachexia, and is also demonstrated to control the production of TNF alpha and TGF beta by MDSCs [62,63], thereby the use of SIRT1 activators may be important as therapeutic modalities for cancer cachexia and MDSCs.

Although the mechanisms that induce cancer cachexia has been widely studied, detailed mechanisms and relationship among inflammatory mediators and organs affected in cancer cachexia are not fully clarified yet.

Therapeutic targeting MDSCs and plasticity of M-MDSC in TME

Multiple trials and approaches to overcome the immunosuppressive actions of MDSCs in cancer have been proposed. Present approaches are divided into 4 categories: 1. Depletion of MDSCs; 2. inhibition of MDSCs immunosuppressive functions; 3. blockade of MDSCs development of recruitment; 4. MDSCs reprogramming or repolarization.

MDSCs are migrated to TME in response to various different growth factors, cytokines and chemokines. The TME is characterized by hypoxia, high concentrations of oxidative factors such as ROS and NO, proinflammatory cytokines, and the metabolic feature of low concentration of glucose and high concentration of lactate. The differentiation and immunosuppressive actions of MDSCs are affected by these conditions [64,65]. Among these factors, hypoxia, especially HIF-1-alpha, which is critical in the induction of M2-type TAMs from monocyte, is important in the TME. Hypoxia also differentiate M-MDSCs to TAMs and provide later events of tumor progression. Colony stimulating factor (CSF)1, CSF2 and VEGF-A produced by tumor are known to be involved in the differentiation of myeloid cells in the TME, and recently, blockade of CSF1/CSFR1 pathway has been demonstrated a significant decrease of the infiltrations of M-MDSCs and TAMs in the TME [66,67]. The CCL2/CCR2 pathway was reported to be necessary in migration of M-MDSCs into TME, and inhibition of CCL2/CCR2 demonstrated significantly decreased infiltration of TAMs and delayed tumor growth [68,69]. Thus, M-MDSC and TAMs showed a closely connected to the differentiation of MDSCs in the TME. M-MDSC represent a potential therapeutic target for cancer therapy, not only because of the ability to control immunosuppression, but also because of high plasticity and differentiation potential [70].

Targeting MDSCs by blocking VEGF-A

Since cancer immunotherapy using ICIs is one of the major treatment modalities for cancer and significant accumulation of MDSCs is often observed in patients with poor responses to such therapies (3,71-73), treatment modalities targeting MDSCs are extremely important in clinical oncology. Hofer et al. described treatment modalities targeting MDSCs, including MDSC depletion, inhibition of MDSC recruitment, blockade of MDSC differentiation into mature immunosuppressive cells, and suppression of MDSC activity. They also summarized related clinical trials. [14]. Li et al. reviewed clinical trials on MDSCs-targeting therapy combined with cancer immunotherapy [13]. VEGF-A possess strong impacts on the induction, activation and proliferation of MDSCs, and there is a close relationship between chronic inflammation underlying MDSCs accumulation and the development of cancer cachexia, as reported in our previous research [36,47,50]. In the present review, we focus particularly on the strategy of blocking VEGF-A signaling in combination with ICI therapies [36,47,50].

There are several characteristics of abnormal vasculature in the TME driven by VEGF-A, inefficient blood supply, increased permeability, dilated and tortuous vessels, decreased pericyte coverage, irregular basement membrane and resultant interstitial hypertension leading tumor expansion and distant metastasis [75]. VEGF-R (receptor)2 is expressed on MDSCs, and VEGF-A secreted by MDSCs induces self-expansion in the TME; thus, targeting the VEGF-A/VEGFR signaling pathway can inhibit the recruitment, accumulation, and proliferation of MDSCs [75].

Currently, clinically available anti-VEGF-A therapies are categorized as follows: 1. neutralizing antibodies to VEGF-A (e.g., bevacizumab), or to VEGF-A receptors (e.g., ramucirumab); 2. tyrosine kinase inhibitors (e.g., sunitinib and sorafenib); and 3. inhibitors of mTOR pathway (e.g., everolimus). Some anti-VEGF-A therapies have been proven to inhibit MDSC accumulation, and bevacizumab-based chemotherapy has been shown in multiple clinical trials to significantly reduce circulating MDSCs and enhance the infiltration of cytotoxic immune cells into the TME [13,76-79]. The increased production of VEGF-A in the patients with cachexia is observed in the clinics and induce massive infiltration and expansion of MDSCs and Tregs. Although it has been reported that blocking VEGF-A induce an immunosupportive condition with normalized vasculature, less MDSCs, and less Treg cells in the TME [72-74], the changes in cachexia have not reported yet.

Conclusions and future directions in MDSCs-targeted therapies

MDSCs are a major obstacle to host immune reaction s in various pathological conditions, including cancer and chronic infection. In chronic infection, therapeutic modalities targeting the metabolism of MDSCs can be beneficial [80], However, compared to cancer, clinical trials in this area remain insufficient. Although MDSCs play a critical role in specific clinical contexts, particularly in autoimmune diseases and pregnancy [4], therapeutic strategies aimed at inducing MDSCs in these patients have not been thoroughly explored or discussed. Additionally, the relationships of MDSCs with cancer cachexia is addressed in this review.

Currently, therapies targeting MDSCs are primarily focused on cancer, and evidence from basic research in this field, as well as clinical benefits of MDSCs-targeting treatments such as anti-VEGF-A therapies including ICIs, has been accumulating [13,14]. As novel anticancer treatment modalities, gene modification of MDSCs by CRISPR (clustered regularly interspaced short palindromic repeats) technology has been demonstrated to eliminate immunosuppressive activities, and CRISPR-loaded nanoparticles may decrease MDSC-derived immunosuppression [81-83]. Although these technologies are currently utilized in basic and translational studies, their future development is expected to expand into clinical applications.

Conclusively, MDSCs possess variety of biological functions leading to immunosuppression, tumor progression and nutritional damages in patients with cancer. Clinical studies of MDSCs-targeting strategies have just started and we hope new therapeutic modalities will arise in the clinic soon.

Authors' contributions

MS, KK, TN and ST were involved in the conceptualization, WS, TI, MT, TY, NI and TM contributed to the literature search, TS, KG and MS wrote the manuscript draft, and KK reviewed and edited.

Conflict of interest

The authors declare that they have no competing interests.

References

1. Bray, Freddie, Laversanne, Mathieu, Sung, Hyuna, et al. (2024) Global cancer statics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA, Cancer J Clin 74: 229-63. doi.org/10.3322/caac.21834
2. Meng, Liangjiao, Wu, Haotian, Wu, Jiaxiang, et al. (2024) Mechanisms of immune checkpoint inhibitors: insights into the regulation of RNAS involved in cancer hallmarks. Cell Death Dis (2024) 15:3; https//doi.org/10.1038/s41419-023-06389-5
3. Talmadge, James E, and Gabrilovich, Dmitry I. (2013) History of myeloid-derived suppressor cells. Nat. Rev Cancer ;13:739-52.https://doi.org/10.1038/nrc3581.
4. Shibata, Masahiko, Nanno, Kotaro, Yoshimori, Daigo, et al. (2022) Myeloid-derived suppressor cells: Cancer, autoimmune diseases, and more. Oncotarget 13:1273-85, doi: 10.18632/oncotarget.28303.
5. Iannou, Marianna, Alissafi, Themis, Lazaridis, Iakovos, et al. (2012) Crutial role of granulocytic myeloid-derived suppressor cells in the regulation of central nervous system autoimmune disease. J Immunol 188: 1136-46. doi: 10.4049/jimmunol.1101816
6. Dorhoi, Anca, and Piessis, Nelita. (2018) Monocytic myeloid-derived suppressor cells in chronic infections. Front Immunol 8: 1895. doi: 10.3389/fimmu.2017.01895
7. Arihara, Fumitaka, Mizukoshi, Eishiro, Kitahara, Masaaki, et al. (2013) Increase in CD4+HLA-DR-/low myeloid-derived suppressor cells in hepatocellular carcinoma patients and its impact on prognosis. Cancer Immuno Immunother 62(8): 1421-1430. Doi:10.1007/s00262-013-1447-8.
8. Huang, Ang, Zhang, Bo, Wang, Bo, et al. (2013) Increased CD4(+)HLA-DR(-/low) myeloid-derived suppressor cells correlate with extrathoracic metastasis and poor response to chemotherapy in non-small cell lung cancer patients. Cancer Immunol Immunother 62(9): 1439-1451. Doi:10.1007/s00262-013-1450-6
9. Hou, Aohan, Hou, Kaiyu, Huang, Qiubo, et al. (2020) Targeting myeloid-derived suppressor cell, a promising strategy to overcome resistance to immune checkpoint inhibitors. Front Immunol 11:783. Doi: 10.3389/fimmu.2020.00783
10. Kawamoto, Hiroshi, and Minato, Nagahiro. (2004) Myeloid cells. Int J Biochem Cell Biol 36: 1374-9.doi.10.1016/j.biocel.2024.01.020
11. Veglia, Filippo, Perego, Michela, and Gabrilovich, Dmitry. (2018) Myeloid-derived suppressor cells coming of age. Nat Immunol 19:108-19, doi:10/1038/s41590-017-0022-x
12. Gabrilovich, Dmitry I, Bronte, Vincenzo, Chen, Shu-Hsia, et al. (2007) The terminology issue for myeloid-derived suppressor cells. Cancer Res. 67:425.doi:10.1158/0008-5472.CAN-06-3037.
13. Li, Kai, Shi, Houhui, Zhang, Benxia, et al. (2021) Myeloid-derived suppressor cells as immunosuppressive regulators and therapeutic targets in cancer. Signal Transduct Target Ther 6: 362 doi:10.1038/s41392-021-00670-9.
14. Hofer, Francesca, Di Sario, Gianna, Misiu, Chiara, et al. (2021) A complex metabolic network confers immunosuppressive functions to myeloid-derived suppressor cells (MDSCs) within the tumor microenvironment. Cells 10, 2700.doi: 10.3390/cells10102700
15. Huang, Bo, Pan, Ping-Ying, Li, Qingsheng, et al. (2006) Gr-1+CD115+immature myeloid suppressor cells mediate the development of tumor-induced T regulatory cells and T cell anergy in tumor bearing host. Cancer Res 66: 1123-31.doi: 10.1158/0008-5472.CAN-05-1299.
16. Antonios, Joseph P, Soto, Horacio, Everson, Richard G, et al. (2017) Immunosuppressive tumor-infiltrating myeloid cells mediate adaptive immune resistance via a PD-1/PD-L1 mechanism in glioblastoma. Neuro Oncol 19: 796-807. doi: 10.1093/neuonc/now287.
17. Fujimura, Taku, Ring, Sabine, Umansky, Viktor, et al. (2012) Regulatory T cells stimulate B7-H1 expression in myeloid-derived suppressor cells in ret melanomas. J Invest Dermatol 132: 1239-46. doi: 10.1038/jid.2011.416.
18. Schlecker, Eva, Stojanovic, Ana, Eisen, Christian, et al. (2012) Tumor-infiltrating monocytic myeloid-derived suppressor cells mediate CCR5-dependent recruitment of regulatory T cells favoring tumor growth. J Immunol 189, 5602-11. doi: 10.4049/jimmunol.1201018.
19. Beury, Daniel W, Parker, Katherine, Parker H, et al. (2014) Cross-talk among myeloid-derived suppressor cells, macrophages, and tumor cells impacts the inflammatory milieu of solid tumors. J Leukoc Biol 96: 1109-18, doi: 10.1189/jlb.3A0414-210R.
20. Groth, Christopher, Hu, Xiaoying, Weber, Rebekka, et al. (2019) Immunosuppression mediated by myeloid-derived suppressor cells (MDSCs) during tumor progression. Br J Cancer 120:16-25. doi.10.1038/s41416-018-0333-1
21. Li, Hequan, Han, Yanmei, Guo, Qiuli, et al. (2009) Cancer-expanded myeloid-derived suppressor cells induce anergy of NK cells through membrane-bound TGF-beta1. J Immunol 182: 240-9. doi: 10.4049/jimmunol.182.1.240.
22. Dardalhon,Valerie, Anderson, Ana C, Karmen, Josef, et al. (2010) Tim-3/Galectin-9 pathway: Regulation of Th1 immunity through promotion of CD11b+Ly-6G+myeloid cells. J Immunol 185: 1383-92. doi: 10.4049/jimmunol.0903275.
23. Warburg, O. (1956) On the origin of cancer cells. Science 123: 309-14. doi: 10.1126/science.123.3191.309.
24. Li, Mengyuan, Yang Yuhan, Xiang Liting, et al. (2023) Metabolism, metabolite, and macrophages in cancer. J Hematol Oncol 16:80. Doi:1011186/s13045-023-01478-6.
25. Shibata, Masahiko, Inukai, Atsushi, Yoshimori, Daigo, et al. (2022) Metabolic impact of immune-suppressor cells in cancer patients. J Surg Res 5: 134-44. Doi: 10.26502/jsr.10020207
26. Hu, Cong, Pang, Bo, Lin, Guangzhu, et al. (2020) Energy metabolism manipulates the fate and function of tumour myeloid-derived suppressor cells. Brit J Cancer 122: 23-29, doi: 10.1036/s41416-019-0644-x
27. Goldmann, Oliver, and Medina, Eva. (2024) Metabolic pathways fueling the suppressive activity of myeloid-derived suppressor cells. Front Immunol, 15:1461455. Doi:10.3389/fimmu.2024.1461455
28. Vijayan, Dipti, Young, Anabella, Teng, Michele WL, Smyth, Mark J. (2017) Targeting immunosuppressive adenosine in cancer. Nat Rev Cancer 17, 709-724. doi.10.1038/nrc.2017.86
29. Vigano, Selena, Alatzoglou, Dmitroios, Irving, Melita, et al. (2019) Targeting adenosine in cancer immunotherapy to enhance T-cell function. Front Immunol 10.doi.10.3389/fimmu.2019.00925
30. Sorrentino, Claudia, Miele, Lucio, Porta, Amalia, Pinto Aldo, Morello, Silvana. (2015) Myeloid-derived suppressor cells contribute to A2Badenosine receptor-induced VEGF production and angiogenesis in a mouse melanoma model. Oncotarget 6.29. doi.org/10.18632/oncotarget.4393
31. Morello, Silvana, Pinto, Aldo, Blandizzi, Corrado, Antonioli, Luca. (2015) Myeloid cells in the tumor microenvironment: Role of adenosine. Oncoimmunol 5 (2016)doi.org/10.1080/2162402X.2015.1108515

32. Hu, Cong, Pang, Bo, Lin, Guangzhu, Zhen, Yu, Yi, Huanta. (2020) Energy metabolism manipulates the fate and function of tumour myeloid-derived suppressor cells. Br J Cancer 122: 23-9, doi: 10.1038/s41416-019-0644-x.
33. Hanahan, Douglas, Weinberg, Robert A. (2011) Hallmarks of cancer: the next generations. Cell 144: 646-674 doi.org.10.3016/j-cell.2011/02.013
34. Tamura, Ryota, Tanaka, Toshihide, Akasaki, Yasuharu, Maruyama, Yuichi, Yoshida, Kazunari, Sasaki, Hikaru. (2019) The role of vascular endothelial growth factor in the hypoxic and immunosuppressive tumor microenvironment: perspectives for therapeutic implications. Med Oncol 2020.37:2. Doi: 10.1007/s12032-019-1329-2
35. Bai, Ruixue, Li, Yunong, Jian, Lingyan, Yang, Yuehui, Zhao, Lin, Wei, Minjie. (2022) The hypoxia-deriven crosstalk between tumor and tumor-associated macrophages: mechanisms and clinical treatment strategies. Mol Cancer 2022,21: 177. Doi: 10.1186/s12943-022-01645-2
36. Shibata, Masahiko, Kono, Koji and Takenoshita, Seiichi. (2022) Inhibiting VEGF in cancer immunotherapy. Clin Immunol Comm 12-6. https: //doi.org /10.1016/j.clicom.2021.12.003
37. Clambey, Eric T, McNamee, Eoin N, Westrich, Joseph A, et al. (2012) Hypoxia-inducible factor-1 alpha dependent induction of FoxP3 Drives regulatory T cell abundance and function during inflammatory hypoxia of the mucosa. Proc Natl Acad Sci USA 109: E2784-2793.doi: 10.1073/pnas.1202366109
38. Watanabe, Hayato, Oshima, Takashi. (2023) The latest treatments for cancer cachexia: an overview. Anticancer Res 43(2): 511-21. doi: 10.21873/anticanres.16188.
39. Fearon, Kenneth, Strasser, Florian, Anker, Stefan D, et al. (2011) Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 12: 489-95. doi: 10.1016/S1470-2045(10)70218-7.
40. Setiawan, Tania, Sari, Ita Novita, Wijaya, Yoseph, Toni, et al. (2023) Cancer cachexia: molecular mechanisms and treatment strategies. J Hematol Oncol 16: 54. doi: 10.1186/s13045-023-01454-0.
41. Shibata, Masahiko, Nezu, Takeshi, Takekawa, Motoo, et al. (1996) Serum levels of interleukin-10 and interleukin-12 in patients with colorectal cancer. Ann N Y Acad Sci 795: 410-2, doi: 10.1111/j.1749-6632.1996.tb52707.x.
42. Shibata, Masahiko, Takekawa, Motoo, and Amano, Sadao. (1998) Increased serum concentrations of circulating soluble tumor necrosis factor receptor 1 in noncachectic and cachectic patients with advanced gastric and colorectal cancer. Surg Today 28: 884-8, doi: 10.1007/s005950050247.
43. Shibata, Masahiko, Nezu, Tskeshi, Kanou, Hisao, et al. (2002) Decreased production of interleukin-12 and type 2 immune responses are marked in cachectic patients with colorectal and gastric cancer. J Clin Gastroenterol 34: 416-420, doi: 10.1097/00004836-200204000-00006.
44. Shibata, Masahiko, Takekawa, Motoo. (1999) Increased serum concentration of circulating soluble receptor for interleukin-2 and its effect as a prognostic indicator in cachectic patients with gastric and colorectal cancer. Oncology 56: 54-8, doi: 10.1159/000011930.
45. Gonda, Kenji, Shibata, Masahiko, Sato, Yu, et al. (2017) Elevated neutrophil to lymphocyte ratio is associated with nutritional impairment, immune suppression, resistance to S-1 plus cisplatin, and poor prognosis in patients with stage IV gastric cancer. Mol Clin Oncol 7: 1073-8, doi: 10.3892/mco.2017.1438.
46. Sato, Yu, Gonda, Kenji, Harada, Maiko, et al. (2017) Increased neutrophil-to-lymphocyte ratio is novel marker for nutrition, inflammation and chemotherapy outcome in patients with locally advanced and metastatic esophageal squamous cell carcinoma. Biomed Rep 7: 79-84, doi: 10.3892/br.2017.924.
47. Nakamura, Izumi, Shibata, Masahiko, Gonda, Kenji, et al. (2013) Serum levels of vascular endothelial growth factor are increased and correlate with immunosuppression involving MDSCs and systemic inflammation in patients with cancer of the digestive system. Oncol Let 5: 1682-6, doi: 10.3892/ol.2013.1231.
48. Ohki, Shinnji, Shibata, Masahiko, Gonda, Kenji, et al. (2012) Circulating myeloid-derived suppressor cells are increased and correlated to immune suppression and hypoalbuminemia in patients with cancer. Oncol Rep 28: 453-8, doi: 10.3892/or.2012.1812.
49. Yazawa, Takashi, Shibata, Masahiko, Gonda, Kenji, et al. (2013) Increased IL-17 production correlates with immunosuppression involving myeloid-derived suppressor cells and nutritional impairment in patients with various gastrointestinal cancers. Mol Clin Oncol 1: 675-9, doi: 10.3892/mco.2013.134.
50. Tachibana, Kazunoshin, Shibata, Masahiko, Gonda, Kenji, et al. (2017) IL-17 and VEGF are increased and correlated to systemic inflammation, immune suppression, and malnutrition in patients with breast cancer. Eur J Inflamm 20: 1-10. doi 10.1177/1721727X17739514
51. Suzuki, Shinichi, Shibata, Masahiko, Gonda, Kenji, et al. (2013) Immunosuppression involving increased myeloid-derived suppressor cell levels, systemic inflammation and hypoalbuminemia are present in patients with anaplastic thyroid cancer. Mol Clin Oncol 1: 959-64, doi.10.3892/mco.2013.170
52. 52. Cuenca, Alex G, Cuenca, Angela L, Winfield, Robert D, et al. (2014) Novel role of tumor-induced myeloid-derived suppressor cells in cancer cachexia. J Immunol 192: 6111-9. doi: 10.4049/jimmunol.1302895
53. VanderVeen, Brandon N, Murphy, E Angela, and Carson, James A. (2020) The impact of immune cells on the skeletal muscle microenvironment during cancer cachexia. Front Physiol 11; 1037. Doi: 10.3389/fphys.2020.0137
54. Kang, Eun A, Park, Jong M, Jin, Wook, Tchahc, Hann, Kwon, Kwang A, Hahn, Ki B. (2022) Amelioration of cancer cachexia with preemptive administration of tumor necrosis factor-alpha blocker. J Clin Biochem Nutr 70(2): 117-128. Doi: 10.3164/jcbn.21-21.
55. Sartori, Roberta, Romanello, Vanina, and Sandri, Marco. (2021) Mechanisms of muscle atrophy and hypertrophy: implications in health and disease. Nat Comm 12:330.doi: 10.1038/s41467-020-20123-1
56. Yan, Dehong, Adeshakin, Adeleye O, Xu, Meichen, et al. (2019) Lipid metabolic pathways confer the immunosuppressive function of myeloid-derived suppressor cells in tumor. Front Immunol 10, 1399. Doi: 10.3389/fimm.2019.01399.
57. Winfield, Robert D, Delano, Matthew J, Pande, Kalyan, Scumpia, Philip O, LaFace, Drake, Moldawer, Lyle. (2008) Myeloid-derived suppressor cells in cancer cachexia syndrome: A new explanation for an old problem. J Parenter Enter Nutr 32:651-655.doi:10.1177/0148607108325075
58. 58. Agca, Samet, and Kir, Serkan. (2024) The role of interleukin-6 family cytokines in cancer cachexia. FEBS J 291(18):4009-4023.doi: 10.1111/febs.17224.
59. 59. Zhu, X Aelita, Starosta, Sarah, Ferrer, Miriam, et al. (2025) A neuroimmune circuit mediates cancer cachexia-associated apathy. Science 11;388(6743): eadm8857.doi: 10.1126/science.adm8857.
60. Zhang, Lingbing, and Bonomi Philip D. (2024) Immune system disorder and cancer-associated cachexia. Cancers 16, 1709.doi.11.3390/cancers16091709

61. Singh, Vivek, and Ubaid, Saba. (2020) Role of silent information regulator 1 (SIRT1) in regulating oxidative stress and inflammation. Inflammation 43, 59: 1589-1598. Doi: 10.1007/s10753-020-01242-9.
62. Dong, Lin, Bi, Yujing, Jia, Anna, et al. (2020) Crucial role of histone deacetylase SIRT1 in myeloid-derived suppressor cell-mediated reprogramming of CD4+ T-cell differentiation. Cell Mol Immunol 17;785-787. Doi: 10.1038/s41423-020-0419-6.
63. Lin, Guangwei, Bi, Yujing, Shen, Bo, et al. (2014) SIRT1 limits the function and fate of myeloid-derived suppressor cells in tumors by orchestrating HIF-1 alpha-dependent glycolysis. Cancer Res 74(3) 727-737.doi: 10.1158/0008-5472.CAN-13-2584
64. Kumar, Vinit, Patel, Sima, Tcyganov, Evgenii, Gabrilovich, Dmitri I. (2016) The nature of myeloid-derived suppressor cells in the tumor microenvironment. Trends Immunol 37: 208-220. doi: 10.1016/j.it.2016.01.004.
65. Gabrilovich, Dmitri I, Ostrand-Rosenberg, Suzanne, Bronte, Vincenzo. (2012) Coordinated regulation od myeloid cells by tumors. Nat Rev Immunol 12: 253-268. Doi: 10.1038 /nri3175.
66. 66. Zhu, Yu, Knolhoff, Brett L, Meyer, Melissa A, et al. (2014) CSF1/CSF1R blockade reprograms tumor-infiltrating macrophages and improves response to T-cell checkpoint immunotherapy in pancreatic cancer models. Cancer Res 74: 5057-5069. doi: 10.1158/0008-5472.CAN-13-3723. Epub 2014 Jul 31.
67. Xu, Jingying, Escamilla, Jemima, Mok, Stephen, et al. (2013) CSF1R signaling blockade stanches tumor-infiltrating myeloid-derived suppressor cells and improves the efficacy of radiotherapy in prostate cancer. Cancer Res 1;73(9):2782-94.doi: 10.1158/0008-5472.CAN-12-3981.
68. Qian, Bing-Zhi, Li, Jiufeng, Zhang, Hui, et al. (2011) CCL2 recruits inflammatory monocytes to facilitate breast-tumour metastasis. Nature 8;475(7355):222-5. doi: 10.1038/nature10138.
69. 69. Hartwig, Torsten, Montinaro, Antonella, von Karstedt, Silvia, et al. (2017) The TRAIL-Induced Cancer Secretome Promotes a Tumor-Supportive Immune Microenvironment via CCR2. Mol Cell16;65(4):730-742.e5.doi: 10.1016/j.molcel.2017.01.021.
70. Tcyganov, Evgenii, Mastio, Jerome, Chen, Eric, Gabrilovich, Dmitry I. (2018) Plasticity of myeloid-derived suppressor cells in cancer. Curr Opin Immunol 2018; 51: 76-82. Doi:10.1016/j.coi.2018.03.009.
Shiravand, Yavar, Khodadadi, Faezeh, Mohammad AK, Seyyed, et al. (2022) Immune checkpoint inhibitors in cancer therapy. Curr Oncol 29: 3044-60, doi: 10.3390/curronco129050247
71. Petrova, Vera, Groth Christopher, Bitch Rebekka, et al. (2023) Immunosuppressive capacity of circulating MDSC predicts response to immune checkpoint inhibitors in melanoma patients. Front Immunol 13:14:1065767. Doi: 10.3389/fimmu.2023.1065767.
72. Gabrilovich, Dmitry I. (2017) Myeloid-derived suppressor cells: Cancer Immunol Res5: 3-8. Doi: 10.1158/2326-6066.CIR-16-0297.
73. Fukumura, Dai, Kloepper, Jonas, Amoozgar, Zohreh, Duda, Dan G, Jain, Rakesh K. (2018) Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges, Nat Rev Clin Oncol 15: 325-40.doi: 10.1038/nrclinonc:2018,29.
74. Geindreau, Mannon, Ghiringhelli, Frances, Bruchard, Melanie (2021) Vascular endothelial growth factor, a key modulator of the anti-tumor immune response. Int J Med Sci 4;22(9): 4871.doi: 10.3390/ijms22094871.
75. Koinis, Filippos, Vetsika, Elen K, Aggouraki, Ddepoina, et al. (2016) Effect of first-line treatment on myeloid-derived suppressor cells' subpopulations in the peripheral blood of patients with non-small cell lung cancer. J Thorac Oncol 11, 1263-72,doi: 10.1016/j.jtho.2016.04.026.
76. Peereboom, David M, Alban, Tyler J, Grabowski, Mathew M, et al. (2019) Metronomic capecitabine as an immune modulator in glioblastoma patients reduces myeloid-derived suppressor cells. JCI insight 4: e130748, doi: 10.1172/jci.insight.130748
77. Limagne, Emeric, Euvrand, Romain, Thibaudin, Marion, et al. (2016) Accumulation of MDSC and Th17 cells in patients with metastatic colorectal cancer predicts the efficacy of FOLFOX-Bevacizumab drug treatment regimen. Cancer Res 76: 5241-52. doi: 10.1158/0008-5472.CAN-15-3164
78. Feng, Po H, Chen, Kuan Y, Huang, Yu C, et al. (2018) Bevacizumab reduces S100A9-positive MDSCs linked to intracranial control in patients with EGFR-mutant lung adenocarcinoma. J Thorac Oncol 13(7):958-67. doi:10.1016/j.jtho.2018.03.032
79. Dietrich, Oliver, Heinz, Alexander, Goldmann, Oliver, et al. (2022) Dysregulated immunometabolism is associated with the generation of myeloid-derived suppressor cells in Staphylocccus aureus chronic infection. J Innate Immun 14: 257-74, doi:10.1159/000519306
80. Knott, Gavin J, and Doudna, Jennifer A. (2018) CRISPR-Cas guides the future of genetic engineering. Science 361: 866-869. doi: 10.1126/science.aat5011
81. Sonda, Nada, Simonato, Francesca, Peranzoni, Elisa, et al. (2013) miR-142-3p prevents macrophage differentiation during cancer-induced myelopoiesis. Immunity 38: 1236-49. doi: 10.1016/j.immuni.2013.06.004
82. Kaczanowska, Sabina, Beury, Daniel W, Gopalan, Vishaka, et al. (2021) Genetically engineered myeloid cells rebalance the core immune suppression program in metastasis. Cell 184: 2033-2052. e21.doi: 10.1016/j.cell.2021.02.048.

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