Therapies Targeting Myeloid-Derived Suppressor Cells in the Tumor Microenvironment

Introduction

Cancer remained one of the major public health problems that threaten human health. Studying the tumor microenvironment helps improve the understanding of cancer. The tumor microenvironment is the internal environment for tumor cell production and survival, including not only thymus-dependent lymphocytes, burse-dependent lymphocytes, tumor-associated macrophages, myeloid-derived suppressor cells (MDSCs), tumor-associated neutrophils, dendritic cells, and natural killer lymphocytes, but also cytokines, chemokinesand growth factors in the nearby areas[1]. MDSCs are the main immunosuppressive cells that maintain cancer progression which exist in the tumor microenvironment. MDSCs may be used as prognostic markers and potential therapeutic targets in patients with cancer to eliminate immunosuppressive activities and enhance antitumor immune responses.

MDSCs inhibit the antitumor immune response and play an important role in promoting tumor occurrence and development. Therefore, MDSCs in the tumor microenvironment become one of the main targets to improve the efficacy of tumor immunotherapy. Immunotherapy strategies that target MDSCs include the MDSC populations and infiltration depletion, MDSC recruitment and transport inhibition, and anticytokine therapy. These studies may provide new directions for cancer treatment[2].

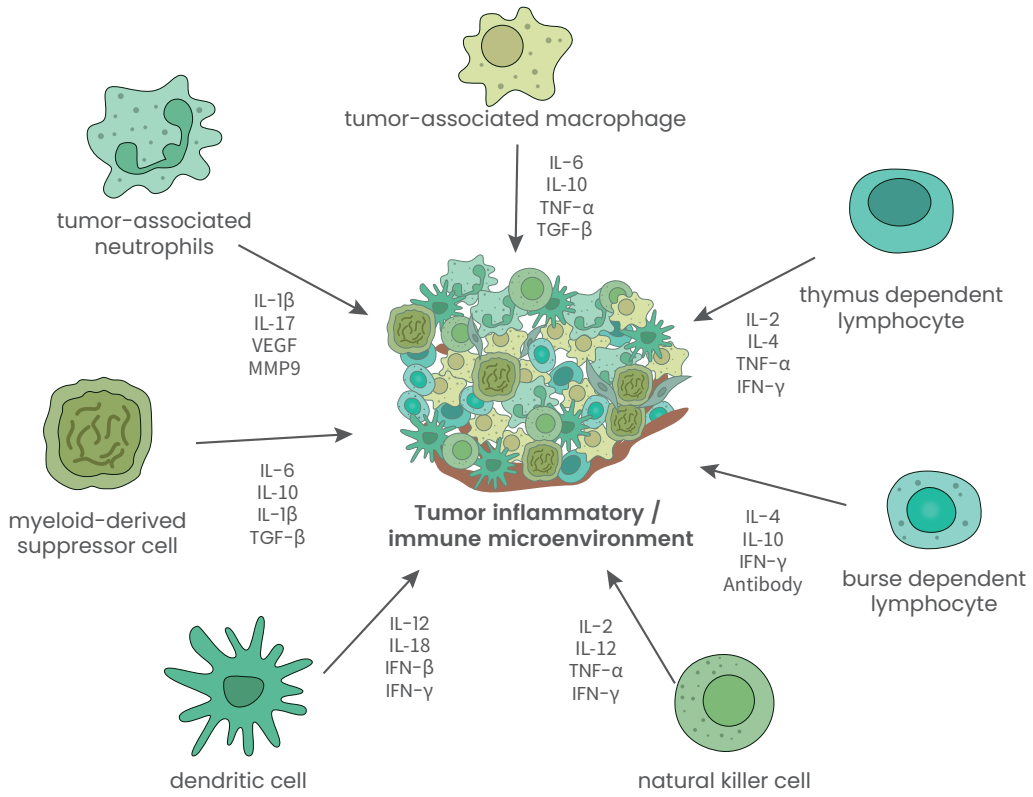

Figure 1. Major immune cells and related cytokines secreted in the tumor microenvironment [1].

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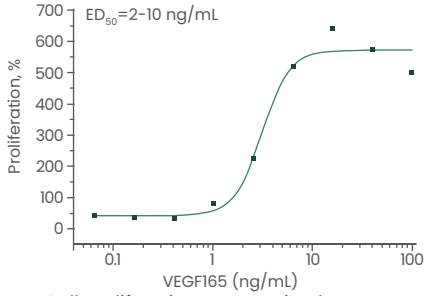
Depletion of MDSC populations and infiltration

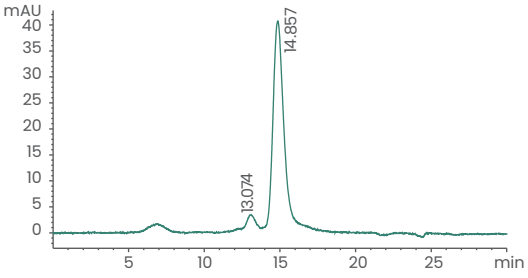
Vascular endothelial growth factor (VEGF) is the key mediator of tumor angiogenesis and the main target of antiangiogenesis therapy for various malignant tumors[3]. VEGF secretion in the tumor microenvironment increases the MDSC infiltration, promotes tumor angiogenesis, accelerates tumor progression, and enhances the immunosuppressive effect[4]. Studies revealed that VEGF-induced MDSCs possess stronger immunosuppressive properties than other MDSCs. The VEGF down-regulation in tumor cells results in decreased MDSC infiltration, and targeting VEGF-induced MDSCs is an effective tumor therapy[5]. Hence, sunitinib and sorafenib, which are anti-VEGF or VEGF receptor (VEGFR) drugs, were successfully used to block the VEGF pathway, which can not only produce antiangiogenic effects but also decrease the MDSC populations in patients with cancer, thereby producing immune support effects. Additionally, chemotherapy treatments, such as 5-fluorouracil (5FU), paclitaxel, cisplatin, and gemcitabine, were found to deplete MDSCs and enhance antitumor immune activity[4].

Therefore, Sino Biological has developed high-activity and high-purity VEGFs and receptor proteins from various species to support this therapy research. A vast majority of these recombinant proteins were expressed in eukaryotic cells, which ensures proper protein modification and higher activity. All proteins are produced at home and available in stock, with customized services. These high-quality reagents have been validated using various methods to provide consistent and reproducible results.

A: Human/Cynomolgus VEGF165 Protein (Cat#: 11066-HANH)

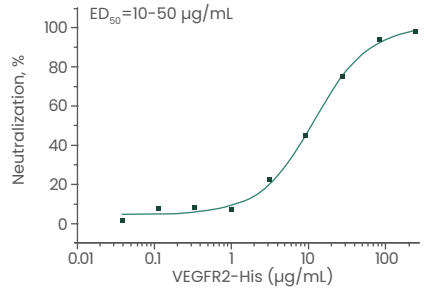


Cell proliferation assay using human umbilical vein endothelial cells (HUVEC)

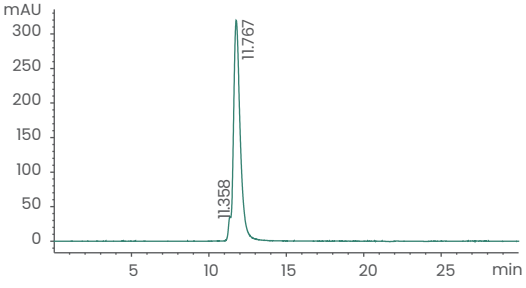


Purity: >90% as determined by SEC-HPLC

B: Human VEGFR2 Protein (Cat#: 10012-H08H)



Inhibit the VEGF-dependent proliferation of human unbilical vein endothelial cell (HUVEC)



Purity: >90% as determined by SEC-HPLC

Figure 2. Examples of high-quality VEGF and VEGFR

Inhibition of MDSC recruitment and transport

A large number of chemokines was found in the tumor microenvironment, which was the key factor to migrate MDSCs to the tumor site. Therefore, targeting chemokines receptors on MDSCs will be an effective cancer therapy strategy. Colony stimulating factor 1 receptor (CSF-1R) is a tyrosine kinase receptor, which can promote the migration of MDSCs to tumor sites, thereby inhibiting antitumor immunity. CSF-1R can not only promote the myeloid cell migration to the tumor sites but also promote the myeloid cell differentiation to MDSCs and tumor-related macrophages after combining with ligand CSF-1. CSF-1/CSF-1R signaling inhibition was found to regulate the number and function of MDSCs in tumors of murine, which can be reprogrammed into an antitumor phenotype. Additionally, CSF-1R inhibitor combined with CTLA-4 blockade therapy induces antitumor T-cell response and tumor regression in many tumor models. Therefore, MDSCs are targeted to regulate the tumor microenvironment, and the CSF-1/CSF-1R signaling blockade is crucial to improve the checkpoint-based immunotherapy response[6].

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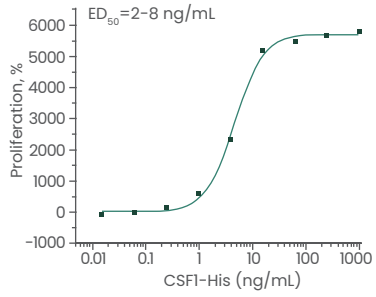
The nuclear factor-κ-gene binding (NF-κB) signaling pathway plays an important role in MDSC expansion during tumor initiation and progression. Amp-activated protein kinase (AMPK) is an important protein kinase that regulates energy metabolism and innate adaptive immunity by targeting major signal pathways. AMPK activation reduces the MDSC expansion and activation by inhibiting multiple signal pathways, such as STATs and NF-κB pathways[2].

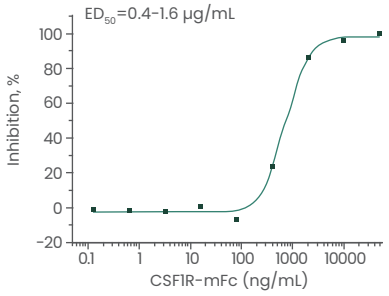
Therefore, Sino Biological has developed high-activity and high-purity CSF ligand and receptor proteins and CTLA-4 proteins from various species to support this therapy research. Additionally, Sino Biological has also developed a series of antibodies with high affinity and sensitivity for CSF growth factor and receptor, which can be used in flow cytometry (FCM), enzyme-linked immunoabsorbent assay (ELISA), and Western blotting (WB). All proteins and antibodies are produced at home and available in stock, with customized services. These high-quality reagents have been validated using various methods to provide consistent and reproducible results.

Human M-CSF/CSF1 Protein (His tag)
(Cat#: 11792-H08H)



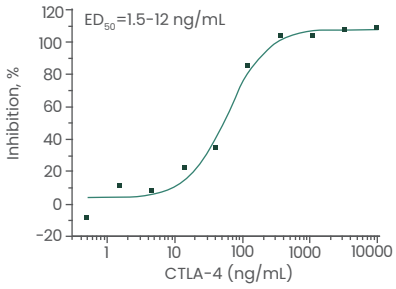
Measuredin a cell proliferation assay using M-NFS-60 mouse myelogenous leukemia lymphoblast cells

Human CSF1R Protein (mFc tag)
(Cat#: 10161-H38H)



Ability to inhibit the human CSF-induced proliferation of M-NFS-60 mouse myelogenous leukemia lymphoblast cells

Human CTLA-4 Protein (His tag)
(Cat#: 11159-H08H)



Immobilized Human CD86 (Cat#: 10699-H02H) can bind Human CTLA-4

Figure 3. Featured products of high-quality CSF1, CSF1R, and CTLA-4

Anticytokine therapy of MDSCs

Cytokines are low molecular proteins that mediate intercellular communication, which regulates cell activity, differentiation, immune cell activation, cell migration, and death[7]. Immunosuppressive cytokines secreted by MDSCs are important factors in the tumor microenvironment to inhibit antitumor immune response and promote tumor progression. The great success of anticytokine therapy in immunology has greatly promoted its wide application in oncology.

IL-1β promotes angiogenesis, tumor invasiveness, and carcinogenesis and affects immune function in various ways, including indirectly affecting immune function by inducing MDSC accumulation in the tumor microenvironment. Anti-IL-1β monoclonal antibodies can reduce PMN–MDSCs in tumors and delay tumor growth[8-9]. Additionally, studies revealed that IL-6 and IL-10 from ascites will lead to large amounts of M-MDSC accumulation in the peripheral blood and patients with ascites of ovarian cancer[10]. IL-6 and IL-8 play an important role in patients with melanoma. IL-6 potentially expands peripheral MDSCs, while IL-8 recruits these highly immunosuppressed cells into the tumor microenvironment[11]. The above results provide a potential novel therapeutic scheme for patients with cancer, which can improve the antitumor efficacy by locally targeting MDSCs.

Therefore, Sino Biological has developed high-activity, high-purity, and low-endotoxin proteins from various species, including IL-1β and IL-6, to support this therapy research. Additionally, Sino Biological has developed a comprehensive panel of antibodies targeting cytokines and receptors, which can be used in ELISA, WB, immunohistochemistry (IHC), and immunoprecipitation (IP). All proteins and antibodies are produced at home and available in stock, with customized services. These high-quality reagents have been validated using various methods to provide consistent and reproducible results.

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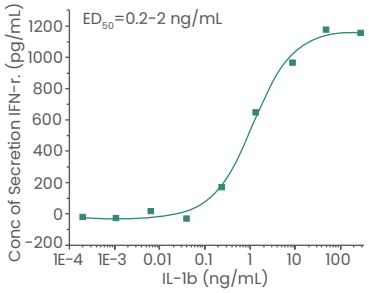
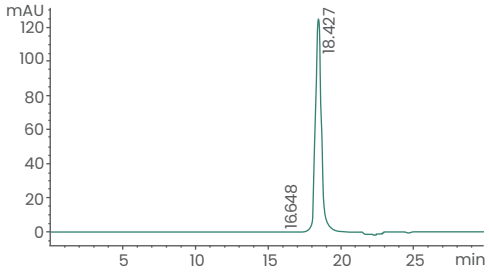
A: Human IL-1β protein and antibody

Human IL-1β Protein (Cat#: 10139-HNAE)

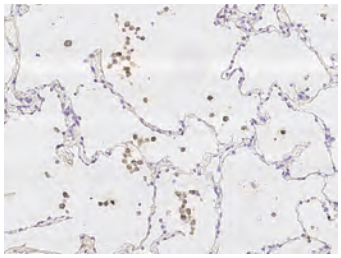


Ability to induce Interferon gammasecretion by humannatural killer lymphoma NK-92 cells



Purity: >95% as determined by SEC-HPLC

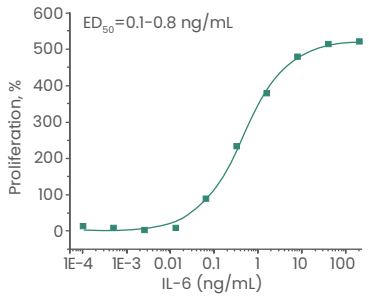
Anti-IL-1β Antibody (Cat#: 10139-MM39)



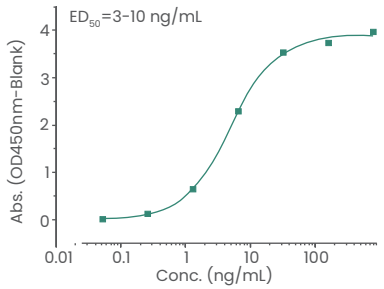
Immunochemical staining of human IL1β in human lung cells

B: Human IL-6 protein and antibody

Human IL-6 Protein (Cat#: 10395-HNAE)

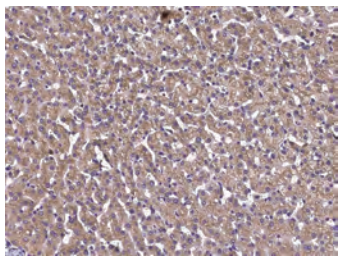


Cell proliferation assay using TF-1 human erythroleukemic cells



Immobilized Human IL-6 (Cat#: 10395-HNAE) can bind human IL-6R hFc (Cat#: 10398-H02H)

Anti-IL-6 Antibody (Cat#: 10395-MM10)



Immunochemical staining of human IL6 in human liver

Figure 4. Examples of high-quality IL-1β and IL-6 protein and antibody

Conclusion

Cancer remained a major disease that threatens human health. This mini-review aimed to provide novel directions for the treatment of patients with cancer from the perspective of targeting MDSCs in the tumor microenvironment. The immunotherapy strategies include depleting the populations and infiltration, inhibiting the recruitment and transport, and anticytokine therapy. These efforts will bring considerable opportunities for existing cancer treatments.

References

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