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Review article

Immune checkpoints represent a promising breakthrough in targeted therapy and prognosis of myelodysplastic syndrome

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ABSTRACT

Myelodysplastic syndrome (MDS) is a hematological malignancy of undetermined etiology, possibly linked to chromosomal structural alterations, genetic mutations, presentation and carcinogenicity of variant antigens on cell surface, and the generation of pro-inflammatory microenvironment in the bone marrow. Current drugs are unable to cure this disease, and therefore, decreasing the survival and proliferation of malignant cells to delay disease progression and extend the survival time of patients becomes the primary approach to management. In recent years, the immune system has received increasing attention for its potential role in the occurrence and development of MDS, leading to the emergence of immunoregulation as a viable treatment option. The current review provides a brief overview of pathogenesis of MDS and current treatment principles. In the meantime, the significance of immune proteins in treatment and prognosis of MDS is also discussed.

1. Introduction

Myelodysplastic syndrome (MDS) is a group of heterogeneous hematological malignancies identified by ineffective hematopoiesis. It is accompanied by varying degrees of myelodysplasia, decrease in hematopoietic cells, and a risk of progression to acute myelogenous leukemia (AML) [1]. By now, the pathogenesis of MDS remains an open issue. Most immune cells and downstream signaling pathways play roles in the pathogenesis and progression of MDS. The dysregulation of the immune system in AML/MDS can either facilitate or hinder the dysregulation at the balance point of malignant cloning via inducing inflammatory responses, altering adaptive immunity, and causing somatic mutation, etc. For instance, the up-regulation of some immune checkpoints helps tumor cells escape from immune surveillance, reduces the count of some immune cells (e.g., ILC1) and increases the number of some malignant cells (e.g., myeloid-derived suppressor cells, MDSC), which then promote the occurrence and development of disease. It has been reported that immune-related treatment is available for treatment of various types of MDS [2]. In this context, it may be feasible to address MDS by targeting immune-related signaling pathways and protein molecules that are involved in the onset of MDS.

Therapeutic regimens, including monoclonal antibody (mAb) therapy, CAR-T cell therapy and adoptive cellular therapy, have become hot topics in immunotherapy for MDS. mAbs for MDS mainly fall into the following three categories: antibody-drug conjugates (ADC), bispecific T cell engagers (BiTEs), and immune checkpoint inhibitors (ICIs). In recent years, the emergence of ICIs has made a significant breakthrough in cancer treatment, and their successful application in various solid tumors has changed the research

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Table 1

Current progress in the development of immunosuppressants corresponding to the small molecules of immune proteins mentioned in this paper. HR-MDS high risk myelodysplastic syndromes, MDS myelodysplastic syndromes, AML acute myeloid leukemia, CLL chronic lymphocytic leukemia, MM multiple myeloma, FDA food and drug administration, PBMC peripheral blood mononuclear cell.

MDS immune checkpoint related drugs								
type	drug	NCT number	experimental site	particular year	subjects	experimental progress	effect	security
Anti-cd47 antibody	magrolimab	NCT03248479	America	2017-9 to 2025	Patients with HR-MDS (including TP53 mutation)/AML	Phase Ib	good	good
Anti-cd47 antibody	magrolimab	NCT04313881	America	2020-9 to 2026	MDS patients	Phase III	/	/
Anti-cd47 antibody	magrolimab	NCT05079230	America	2022-7 to 2025	AML patients	Phase III	/	/
Anti-cd47 antibody	magrolimab	NCT04435691	America	2020-7 to 2024	AML patients	Phase Ib/II	/	/
Anti-cd47 antibody	magrolimab	NCT02678338	America	2016-2 to 2019-2	Patients with relapsed or refractory AML/ MDS	Phase I	good	good
Anti-cd47 antibody	magrolimab	NCT03922477	America	2019-10 to 2020-3	Patients with relapsed or refractory AML	Phase Ib	/	/
Anti-cd47 antibody	CC-90002	NCT02641002	America	2016-3 to 2018-7	Patients with relapsed or refractory AML/ HR-MDS	Phase I	Poor (forced to stop halfway, lack of objectivity)	good
Anti-cd27 agonist antibody	Varlilumab	NCT01460134	America	2011-10 to 2017-10	Patients with B and T cell malignancies and patients with renal cell carcinoma	Phase I	good	good
Anti-cd70 antibody	Vorsetuzumab mafodotin (SGN-75)	NCT01015911	America	2009 to 2012	Patients with relapsed or refractory NHL with CD70 positive, and patients with metastatic renal cell carcinoma	Phase I	good	good
Anti-cd70 antibody	cusatuzumab	NCT03030612	France and Switzerland	2017-1 to 2022	Elderly patients with newly diagnosed AML and HR-MDS	Phase II	good	good
Anti-cd33 antibody	gemtuzumab ozogamicin	NCT04337138	America	2020-4 to 2020-7	AML patients	It has been approved by the FDA for use in AML	good	good
Anti-cd33 antibody	gemtuzumab ozogamicin	NCT00882102	America	2009-4 to 2013-9	AML/HR-MDS patients	Phase II	/	/
CD33/CD3 T cell binding agent	AMV564	NCT03516591	America	2018-6 to 2020-7	LR/HR-MDS patients	Phase I	good	good
CD33/CD3 T cell binding agent	AMV564	NCT03144245	America	2017-3 to 2020-5	Patients with relapsed or refractory AML	Phase I	/	/
CD16xCD33 bispecific killer cell binder	BIKE	/	America	2014	Blasts from patients with MDS	Preclinical in vitro cell experiments	It could enhance NK cell activity in all MDS groups	/
Anti-cd33 antibody	BI 836858	NCT01690624	America	2012-9 to 2018	Patients with relapsed or refractory AML	Phase I	The experiment was terminated prematurely and could not be evaluated	bad
Anti-cd33 antibody	BI 836858	NCT02240706	America	2015-1 to 2019-11	Patients with low-intermediate risk MDS	It has been approved by the FDA for the treatment of MDS	good	good
Anti-cd33 antibody	BI 836858	NCT02632721	America	2016-6 to 2023-1	AML patients	Phase I/II	/	/
CD33 Antibody-conjugate Drug (ADC)	SGN-CD33A	NCT02785900	America	2016-5 to 2017-10	Patients with newly diagnosed AML	Phase III	/	/

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Table 1 (*continued*)

MDS immune checkpoint related drugs								
type	drug	NCT number	experimental site	particular year	subjects	experimental progress	effect	security
CD33 Antibody-conjugate Drug (ADC)	SGN-CD33A	NCT01902329	America	2016-5 to 2017	AML (include M3) patients	Phase III	good	bad
CD33 Antibody-conjugate Drug (ADC)	SGN-CD33A	NCT02706899	America	2016-3 to 2017-11	Patients with intermediate and high-risk MDS	Phase I/II	/	/
CD33 Antibody-conjugate Drug (ADC)	SGN-CD33A	NCT02326584	America	2014-12 to 2018-4	Patients with AML other than M3	Phase I	/	/
Antiepileptic drugs (inhibiting NFE2 activity)	VAL	/	Britain	2021	Blasts from patients with AML	Preclinical in vitro cell experiments	AML cell survival time was shortened	/
Iron chelator (inhibits NFE2 activity)	Deferasirox	NCT01868477	Spain	2013-6 to 2017-4	Patients with low-intermediate risk MDS	Phase II	good	good
Iron chelator (inhibits NFE2 activity)	Deferasirox	NCT01326845	France	2011-3 to 2012-9	Patients with low-intermediate risk MDS	Phase IV	/	/
Anti-cd200 antibody	Fully humanized IgG1 antibody	/	America	2021	Different degrees of PBMC humanized NSG mice	Preclinical animal studies	good	good
Anti-cd200 antibody	Samalizumab	NCT00648739	America	2008-6 to 2010-12	CLL, MM patients	Phase I/II	good	good
Anti-cd200 antibody	Samalizumab	NCT03013998	America	2017-1 to 2023	AML patients	Phase Ib/II	good	good
Anti-cd200 antibody	TTI-CD200	/	Britain	2020	NSG mice injected with AML cells	Preclinical animal studies	good	good
Anti-TIGIT antibody	Tiragolumab	NCT05259319	America	2022 to 2030	Metastatic non-small cell lung cancer, metastatic bladder cancer, metastatic renal cell cancer, metastatic head and neck cancer	Phase I	/	/
Anti-TIGIT antibody	Tiragolumab	NCT04308785	China	2020-3 to 2023	Small cell lung cancer	Phase II	/	/
Anti-TIGIT antibody	Etigilimab	NCT04761198	America, Britain	2021 to 2023	Locally advanced or metastatic solid tumors	Phase Ib/II	/	/
Anti-TIGIT antibody	AB154	NCT03628677	America	2018-3 to 2023	Advanced solid tumors	Phase III	/	/
Anti-CD155 antibody	COM701	NCT04354246	America	2020 to 2024	Advanced solid tumors and multiple myeloma	Phase I	/	/
FLT3 Inhibitors	quizartinib	NCT02984995	Japan	2016-12 to 2018-9	Refractory/relapsed AML	Phase III	/	/
FLT3 Inhibitors	quizartinib	NCT03723681	China	2018-11 to 2022-3	Patients with newly diagnosed AML	Phase I	/	/
FLT3 Inhibitors	gilteritinib	NCT03625505	America	2018-10 to 2021-8	Refractory/relapsed AML	Phase I	/	/
FLT3 Inhibitors	gilteritinib	NCT05024552	America	2021-8 to 2025-8	Relapsed or refractory FLT3-mutated AML	Phase I	/	/
FLT3 Inhibitors	gilteritinib	NCT03730012	America	2019-6 to 2021-6	AML and AML with FLT3 mutation	Phase II	/	/

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Table 1 (*continued*)

MDS immune checkpoint related drugs								
type	drug	NCT number	experimental site	particular year	subjects	experimental progress	effect	security
FLT3 Inhibitors	gilteritinib	NCT04027309	Australia	2019-7 to 2033	Patients with newly diagnosed AML and MDS-EB2 with FLT3 mutations	Phase III, which is currently suspended	good	
Anti-CD276 antibody	Enoblituzumab	NCT02475213	America	2015-6 to 2021	Head and neck squamous cell carcinoma, non-small cell lung cancer, urothelial carcinoma	Phase I	good	good
Anti-CD73 antibody	IPH5301	NCT05143970	America	2021-3 to 2024	Advanced solid tumors	Phase I	/	/
Anti-CTLA-4 antibody	ipilimumab	NCT01757639	America	2012-12 to 2016-12	Relapsed/refractory MDS and AML with MRD	Phase I	/	/
Anti-CTLA-4 antibody	ipilimumab	NCT00039091	America	2003 to 2018	MDS patients in whom hypomethylating agents failed	Phase I	good	good
Anti-CTLA-4 antibody	ipilimumab	NCT03912064	America	2019-4 to 2024	Patients with AML/MDS/MPN/CML/ myelofibrosis	Phase I	/	/
Anti-CTLA-4 antibody	ipilimumab	NCT00060372	America	2003-5 to 2013-3	Recurrent hematologic malignancy after hematopoietic stem cell transplantation	Phase Ib	good	good
VISTA monoclonal antibody	JNJ-61610588	NCT02671955	America	2016-2 to 2017-7	Patients with advanced lung, pancreatic, cervical, colorectal, head and neck cancer	Phase I, which is currently suspended	/	/
VISTA Inhibitors	CA-170	NCT02812875	America	2016-6 to 2020-7	Patients with advanced cancer and lymphoma	Phase I	/	/
VISTA monoclonal antibody	HMBD-002	NCT05082610	America	2022-1 to 2025-1	Patients with advanced solid tumors	Phase I/II	/	/

direction and treatment pattern for hematological malignancies. ICI-targeted therapy for MDS works with multiple pathways, with ICIs specifically targeting tissues with distinct immune functions. Currently, several novel drugs directed towards small-molecule immune targets are undergoing preclinical evaluation. DNA-demethylating drugs remain the mainstay of first-line treatment for AML/MDS at present. Guidelines recommend that patients with relapsed/refractory AML or MDS and not suitable for allogenic transplantation can be included into clinical trials of DNA-demethylating drugs. The combination of DNA-demethylating drugs and small-molecule targeted drugs/immunosuppressive agents is the primary treatment option for MDS in current clinical trials.

This review provides a brief overview of the possible pathogenesis of MDS by describing the potentially involved signaling pathways and immune proteins (Fig. 3 and Fig. 4.). Additionally, the prognosis and progression of MDS are discussed from the aspect of ICIs (Table 1.). The main purpose of the current review is to introduce the protein molecules which have been found in studies on MDS/AML and are capable of predicting disease severity and risk of progression. Furthermore, the prospect of ICIs in treatment for MDS is also described.

ICIs that are already approved for clinical use in MDS treatment include.

2. CD47

2.1. Introduction of CD47 and its mechanism of action

CD47 is a cell surface glycoprotein [3] that can bind various proteins including integrin, thrombospondin-1 and signal regulatory protein α (SIRPα) [4,3]. It is ubiquitously expressed on normal cells and show excessive expression in a large number of tumor cells. Usually, CD47 functions as a receptor that facilitates immune evasion and prevents micropinocytosis, protecting normal cells against injury from the immune system (Fig. 1) [5]. It was first regarded as the regulator of self-renewal of erythrocytes and later found to exhibit wide expression in other cell types with a significant role in different homeostatic systems. It was reported that the down-regulation of CD47 could potentiate the elimination of aging and redundant cells via phagocytosis [6].

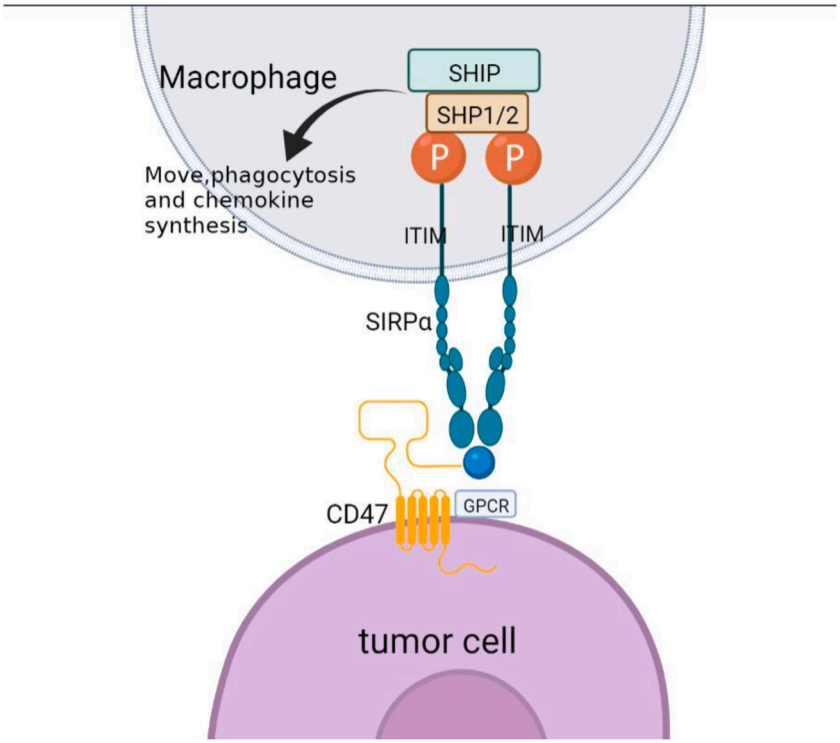

Fig. 1. Schematic diagram of signal transmission of CD47. CD47 is a transmembrane protein containing *N*-terminal extra-cellular lgV-like domains,5 transmembrane domains and a short *C*-terminal cytoplasmic tail. CD47 induces and interacts with SIRPαto tyrosine phosphorylation of ITM motifs in SIRPαcells, resulting in the recruitment of SHP-1 and SHP-2 phosphatases, the polymerization of F-actin and the contraction of myosin. These processes control the movement, phagocytosis and chemokine synthesis of macrophages, as well as the cross antigen presentation and stimulation of the STING (IFN gene stimulator)/GAS (cyclic GMP-AMP synthase)pathway of dendritic cells. Figures were created in BioRender.com.

2.2. Role of CD47 in MDS

A previous study found that leukemic stem cells (LSC) -transplanted mice survived shorter when CD47 was highly expressed [7]. Another study found that low-risk MDS progenitors had increased expression of CRT on their surface but did not express CD47, and they were readily to be phagocytosed by macrophages. To the contrary, high-risk MDS progenitors expressed more CD47 and could evade from being phagocytosed [8]. This is likely due to that CD47 overexpression confers anti-phagocytosis activity on MDS progenitors, which allows them to escape from immune recognition by counteracting the CRT signaling on phagocytic cells. In other words, the CD47 overexpression in MDS progenitors can induce pro-tumor responses and then gradually affect the immune microenvironment in the bone marrow. Collectively, the expression of CD47 may be highly involved in the disease progression and prognosis of MDS.

2.3. Research prospect of CD47

For the past few years, CD47-targeted therapy has become a hot topic in research of MDS treatment, and multiple drugs, either alone or in combination, have advanced to clinical trials. Previous clinical trials combined Magrolimab (anti-CD47 monoclonal antibody) and Azacitidine (hypomethylating agent, HMA) in treatment of patients with myeloid malignancy (including patients with mutations in TP53). They reported that such strategy had a lasting effect with the synergistic activity of the two agents and could be well tolerated by the patients with a safe profile [9,10]. CC-90002 is another anti-CD47 antibody that can inhibit the interaction between CD47 and SIRPα. It was proved that whether CC-90002 was used alone or in combination with other anti-tumor drugs, patients with hematological malignancies still benefited from it and had a high remission rate, whereas the treatment was discontinued due to the presence of anti-drug antibodies [11]. CD47 is a key molecule with activity against phagocytosis, and the combination of anti-CD47 agent and some anti-tumor agents (e.g., AZA and Ruxolitinib) has become a new direction for research of AML and relapsed/refractory HR-MDS.

The immune regulators that are currently under exploration include.

3. CD33

3.1. Introduction of CD33 and its mechanism of action

CD33 is a transmembrane protein, myeloid-specific sialic acid-binding receptor and hematopoietic differentiation antigen. It is excessively expressed in most primitive leukemic cells and undergoes receptor-mediated endocytosis in-vivo [12]. CD33 plays an essential role in the regulation of immune functions. CD33 binding with the ligand can lead to dephosphorylation of cellular proteins and then down-regulate relevant signaling pathways [13]. Additionally, activated CD33 plays an immunosuppressive role by recruiting inhibitory proteins, activating myeloid-derived suppressor cells (MDSC) and inducing the secretion of inhibitory cytokines IL-10 and TGF-β through its ITIM-like domain [14]. Moreover, CD33 is also involved in cell adhesion and apoptosis [15,16].

3.2. Research significance of CD33 for MDS

Chen et al. [12] reported that CD33 was excessively expressed on MDS-MDSC. Upon binding with its ligand, CD33 potentiated the activation, proliferation and inhibitory function of MDSCs, contributing to the progression of inflammation in the marrow microenvironment and then leading to a hematopoietic failure [12]. Other studies found that the expression of CD33 was the highest in AML, followed by MDS [17–19], and its expression was positively associated with the disease risk in MDS patients [18]. Moreover, increasing evidence has suggested that cCD33 level can be used as an independent factor for prognosis of AML and MDS, which provides a novel insight for the clinical treatment of the two diseases.

3.3. Research prospect of CD33

By now, there is only one drug termed BI 836858, an anti-CD33 antibody-drug conjugate (ADC), that has been approved for use in MDS treatment, while Gemtuzumab, Ozogamicin and BI 836858 have been approved to be used in treatment of AML. Other drugs are still in testing stage. For example, the anti-CD33 ADC, SGN-CD33A, showed favorable efficacy in previous clinical trials, whereas the safety was poorly satisfied. Besides, it was abandoned in some related clinical trials in 2016, as its side effect, myelosuppression, led to an increased number of infection-related deaths [20]. The CD33/CD3+ T cell-specific binding agent AMV564 has been potentially used in treatment of myeloid solid tumors and hematological malignancies, and it can advance the activation and proliferation of T cells in MDS patients, enhance IFN-γ activity, and induce cytotoxic T cell activation [14,13,21–23]. MDSCs are important participants in immune evasion and tumor progression, while the bi-specific anti-CD16/CD33 T-cell engaging (BiTE) antibody can further inhibit the immunosuppressive effect of MDSCs and enhance the CD33+- specific function of NK cells [24]. In spite of the different mechanisms of action, the drugs mentioned above eventually show favorable efficacy in treatment of MDS.

4. NFE2

4.1. Introduction of NFE2 and its function

Previous research found that NFE2 transcription factor mainly acted on hematopoietic cells such as erythroid cells, megakaryocytes and mast cells, etc., and NFE2 deficiency would result in severe disruption of platelets. Recent research also revealed its expression in non-hematopoietic structures, such as trophoblast cells and bone tissues [25]. NFE2 acts on megakaryocytes mainly via regulating their maturation and platelet transcription. The deficiency of NFE2 can affect not only hematopoietic function but also the inflammatory system. It has been proven that the NFE2/HO-1 axis plays a major role in inflammatory resistance, as NFE2 induces the expression of HO-1 gene to promote the degradation of heme to anti-inflammatory compounds including carbon monoxide and free iron. In addition, the NFE2/HO-1 axis has been used as a therapeutic target for treatment of inflammation-related diseases [26]. Another significant axis associated with inflammation is the NFE2/ARE axis. Upon activation, NF-κB activation is limited and the pro-inflammatory cytokines (e.g., IL-6, TNF-α, iNOS, IL-1 and COX-2) which are hyper-produced following NF-κB activation is disrupted. Notably, the elevation of HO-1 expression can also suppress the activity of NF-κB [27]. Activated NFE2 can prevent the lipopolysaccharide (LPS) -induced transcriptional up-regulation of pro-inflammatory cytokines, such as IL-6 and IL-1β, and also inhibit the production of downstream IL-17 and other inflammatory factors including TH1 and TH17 [28,29]. A bold guess is made that NFE2 and NF-κB signaling cooperate to control the transcription or activity of downstream target proteins and thereby inhibit inflammatory process (Fig. 2).

4.2. Significance of NFE2 in hematologic diseases

NFE2 exhibits increased expression in a variety of malignancies, such as AML [30], gastric cancer [31], ovarian cancer [32] and gallbladder cancer [27]. In addition, NFE2 is also overexpressed in patients with polycythemia vera (PV) and myeloproliferative neoplasms (MPNs), showing a relationship with the disease severity [33,34]. Other research demonstrated that NFE2 could induce AML chemoresistance via activating the JNK/c-Jun signaling pathway and decreasing the expression of MSH2 in AML cells [30]. A recent study also identified the role of NFE2 in chronic lymphocytic leukemia (CLL) chemoresistance [35]. Lin et al. [36] found that

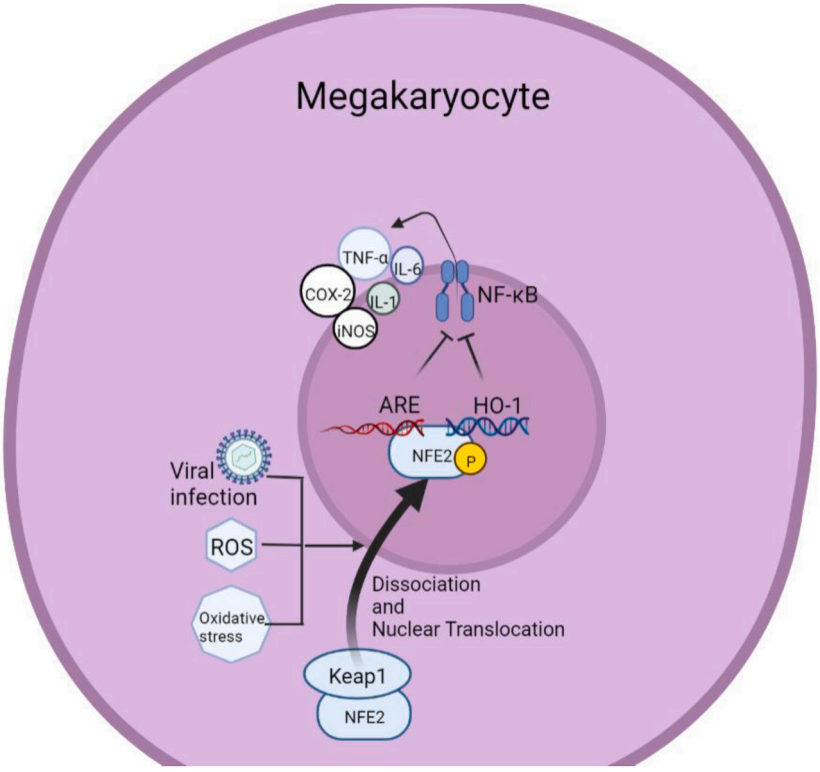

Fig. 2. Schematic diagram of NFE2 functioning. NFE2 induces expression of HO-1 gene to promote the degradation of heme to anti-inflammatory compounds including carbon monoxide and free iron. Upon activation of NFE2/ARE axis, NF-κB activation will be limited and the pro-inflammatory cytokines (e.g., IL-6, TNF-α, iNOS, IL-1 and COX-2) which are hyper-produced following NF-κB activation will be disrupted. Figures were created in BioRender.com.

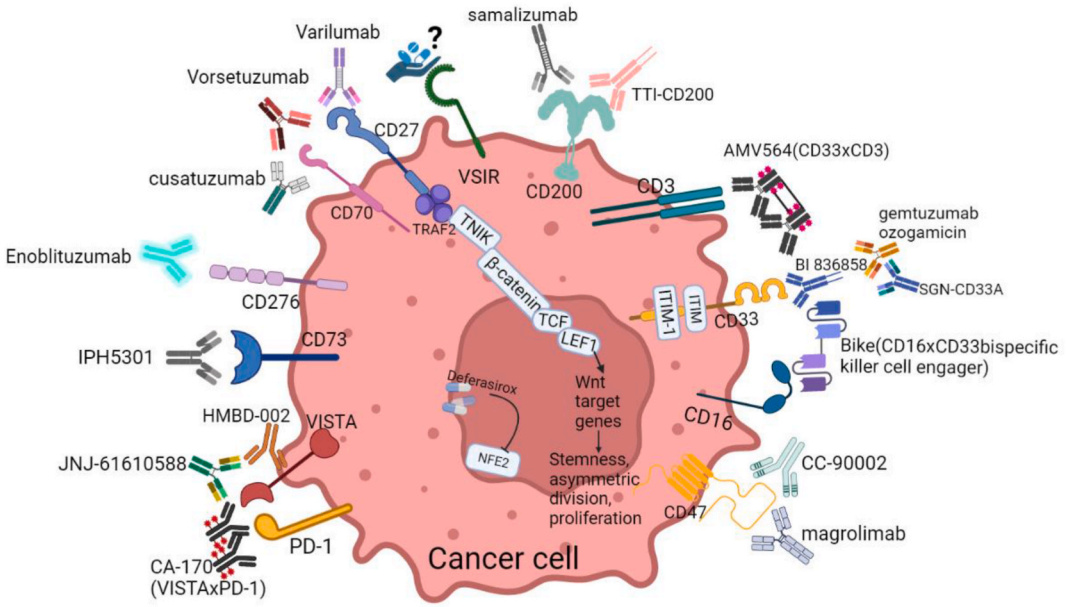

Fig. 3. Small molecules of clinically significant immune proteins expressed in tumor cells and corresponding immunosuppressants developed against these small molecules. Figures were created in BioRender.com.

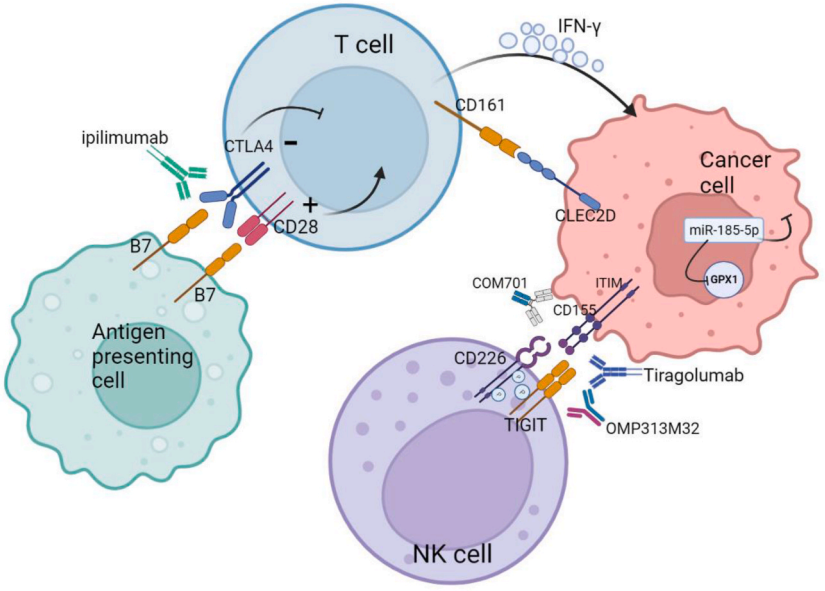

Fig. 4. Small molecules of immune proteins expressed on immune cells and affecting the development and progression of tumors and their immunosuppressants. Figures were created in BioRender.com.

NFE2 was excessively expressed in MDS patients, especially in those at a high risk, and higher levels of NFE2 were prognostic for poorer outcomes in this population. Another study indicated that NFE2 could mediate the Ara-C (cytarabine) resistance in high-risk MDS patients by directly targeting DUSP1, and NFE2 knock-out could lead to re-sensitization [36]. These findings suggest that NFE2 is also the basis of development of drug resistance in MDS cells.

4.3. Research prospect of NFE2

Previous research found that VAL, an inhibitor of NFE2 activity, in combination with low-dose medroxyprogesterone acetate (MPA), could correct the counts of platelet, erythrocyte and neutrophil in AML patients, reduce transfusion dependency and delay or

decrease the conversion from MDS to AML, offering positive implications for the improvement of patients's quality of life and survival [37]. The iron chelator Deferasirox could act as an inhibitor of NFE2 by inducing down-regulation of genes related to the NF-κB signaling pathway. Previous study also reported that Deferasirox could reduce inflammatory responses and increase hematopoiesis in MDS patients [38]. Collectively, agents targeting NFE2 may have effects in the management of inflammatory symptoms, as well as in the prevention and treatment of diseases such as myeloproliferative disease and cancer. However, the role of NFE2 signaling in MDS has not been adequately studied yet.

5. CD200

5.1. Introduction of CD200 and its mechanism of action

CD200 (also known as a single-channel protein), a type 1a transmembrane glycoprotein belonging to the immunoglobulin superfamily, exhibits extensive expression in neurons, endothelial cells, thymocytes, B and T lymphocytes [39]. CD200 receptor has a relatively limited expression range as confined to immune cells only (mainly bone marrow cells, NK cells, B and T lymphocytes) [40]. It remains unclear about the role of CD200 in hematopoiesis, but the immunosuppressive implications instead upon binding with its receptor. For the past few years, growing evidence has supported the role of CD200 in human bone marrow cells as an immune suppressor, except the conventional immunoregulatory role in cases of infection, autoimmune disease (AID) and allergic diseases [41]. CD200 binding with its receptor induces T-lymphocyte in-vitro differentiation to CD4CD25Foxp3 Tregs [42] and suppresses corresponding inflammatory responses in various inflammatory diseases. In the meantime, their interaction can also regulate tumor microenvironment via affecting tumor-related bone marrow cells, thereby playing a key role in tumor-related inflammation and angiogenesis [42,43].

5.2. Significance of CD200 in MDS/AML

CD200 has excessive expression in MM, AML and CLL [42,44–46]. In addition, CD200 also has implications for progression of head and neck carcinoma, renal carcinoma, colon carcinoma and neurodegenerative disease [47,48]. Jenny M Ho et al. [49] found that CD200 exhibited extremely high expression in LSCs of AML patients but were absent in normal hematopoietic stem cells (HSCs) and LSCs. Shelley Herbrich et al. [50] found high levels of CD200 in some diseases with complex karyotype or a tendency of recurrence and reported a significantly decreased survival rate in this population. Another study also demonstrated that high expression levels of CD200 were associated with a poorer outcome, a shorter overall survival time and a higher risk of progression to AML in MDS patients [51]. Moreover, Chen et al. [52] proved that the CD200-positive rate increased with increasing malignancy degree of MDS, i.e., CD200 expression was tightly associated with the subclassification and clinical staging of MDS. The studies above indicate that CD200 may be a marker of primitive leukemic hematopoietic cells and is significantly associated with the malignancy degree and prognosis of MDS/AML.

5.3. Research prospect of CD200

Shelley Herbrich et al. [50] developed a CD200-targeted, fully humanized IgG1 antibody and applied it in humanized peripheral blood mononuclear cell-engrafted NSG mice with various degrees of graft-versus-host disease (GVHD). They found that mice administrated with such antibody improved significantly and eventually were free of leukemia. Currently, multiple CD200-targeted drugs have been developed. For instance, the humanized monoclonal antibody Samalizumab has advanced to phase I clinical trials for CLL and MM, showing good efficacy (partial remission) and tolerance [53]. TTI-CD200 is a fully humanized antibody capable of enhancing autoimmune cell functions and evidently increasing the effects of immune cells on AML cells. Paraskevi Diamanti et al. [54,55] found that NGS mice treated with TTI-CD200 had an increased survival rate. CD200 as an immune suppressor with high expression in hematological malignancies should be highly valued for its potential role as a therapeutic target.

6. CD155

6.1. Introduction of CD155

CD155 (a type I transmembrane glycoprotein of the immunoglobulin superfamily) is one of adhesion molecules that was first discovered as a poliovirus receptor [56]. It is distributed in epithelial and endothelial cells of multiple tissues with low expression levels. In malignant cells, it reversely has excessive expression and participates in cell adhesion, migration and proliferation. In addition, CD155 is also tightly associated with the outcome of some cancers, including breast cancer [57], melanoma [58], glioblastoma [59], and soft tissue sarcoma [60], etc. Recently, CD155 has been proved as an immunomodulatory receptor that can either activate NK cells via interacting with CD226 and CD96 or suppressing their immune activity through acting on TIGIT. Notably, TIGIT is increasingly expressed in NK cells during the process of cancerization [59,61–63].

6.2. Research significance of CD155 in hematological malignancies

Meng et al. [64] reported that the decline in the proportion and function of NK and T cells in MDS patients was associated with the

abnormal expression of TIGIT and CD155. Another study found that NK cells in MDS patients were largely suppressed by MDSCs, which could be reversed by knock-out of TIGIT [65]. The study of Anna Chashchina et al. [66] revealed that CD226 and CD155 cooperated to induce the release of immunoregulatory cytokines (IL-6, IL-8, IL-10 and TNF-α) from AML cells, and that the elevation of CD226 expression in AML cells was prognostic for the prolonged survival in these patients. In all, C155-TIGIT blockade or CD155-CD226 augmentation may be a viable treatment option for MDS/AML.

6.3. Research prospect of CD155

Since CD155 and TIGIT are usually excessively expressed in cancers, blockade of the interaction between CD155 and TIGIT may provide a new insight for anti-tumor treatment. By now, *anti*-TIGIT antibodies are in testing stage for treatment of solid tumors. For example, the *anti*-TIGIT monoclonal antibody OMP-313M32 has advanced to phase I clinical trials as a monotherapy or combination therapy with *anti*-PD-1 antibodies for solid tumors. Tiragolumab, another *anti*-TIGIT monoclonal antibody developed by Genentech/Roche (also known as MTIG7192A or RG6058), is in phase II clinical trial [67]. Although the intervention of CD155-TIGIT blockade has not been applied in treatment of hematological diseases yet, there is still some experience that can be obtained from its successful application in treatment of solid tumors. It was also reported that FLT3 inhibitors (Quizartinib and Gilteritinib) could down-regulate the expression of CD155 in AML cells [68].

7. VSIR

7.1. Introduction of VSIR

VSIR is a type of immunoregulatory receptor that can suppress the effector function of T cells. It was reported that the increase in VSIR in tumor is closely related to tumor immune infiltration, expression of related antigens and canonical immune checkpoints. Additionally, VSIR also exhibits high expression in many tumor cells and hematopoietic tissues, and it contributes to an immunosuppressive tumor microenvironment in some cancers and then results in tumor progression and a lower survival rate [69].

7.2. Clinical significance of VSIR in AML/MDS

VSIR can inhibit T-cell activation, and immunodeficiency represents one of the important mechanisms that leads to AML/MDS. Under this background, the clinical significance of VSIR in AML/MDS has been increasingly studied. The analytical results reveal that VSIR has the highest expression in AML among all cancers, and meanwhile, it is also the protein with the highest expression in AML among all immune checkpoints. Moreover, the increased expression of VSIR was associated with a shorter survival time of AML patients and an increased risk of progression from MDS to AML [70]. In this context, VSIR has the potential to be employed as a target in AML/MDS immunotherapy, and it may play an important role in preventing the progression from proliferating MDS primitive cells to AML.

7.3. Current progress in VSIR

Currently, VSIR has been studied in multiple diseases such as renal carcinoma, AML, MDS, and psoriasis. However, whether VSIR can be applied as an emerging immune target in clinical AML/MDS treatment requires validation with huge number of studies and experimental data.

Small-molecule targets that have the potential to be used in MDS immunotherapy but have not been studied include.

8. CD27/CD70

8.1. Introduction of CD27/CD70 and their mechanism of action

CD27 is a member of the tumor necrosis factor (TNF) receptor superfamily and widely expressed in human lymphocytes [71]. CD70 is the only ligand of CD27 that belongs to the TNF superfamily and only exhibits expression in activated lymphocytes and myeloid cells [72]. $CD27^{-}CD70$ binding is key to the activation of T cells and B cells. Upon binding, CD27 activates the NF-κB signaling pathway via binding TRAF2 and TRAF5, resulting in activation of T, B and natural killer (NK) cells followed by cytokine production and cytotoxic T-cell responses [73,74]. Usually, the $CD27^{-}CD70$ binding is tightly regulated to prevent excessive expression and lymphocyte over-activation. The co-stimulation subsequent to their binding has self-regulation skills. CD70 down-regulates CD27 expression after binding and reverses the signal transduction. In the meantime, CD27 also decreases the level of CD70, and the deficiency of CD27 can further stimulate the high expression of CD70 [75–77]. It is significantly different from our previous conclusion that CD27 and CD70 exhibited high expression in multiple hematological malignancies and solid tumors, such as lymphoma [78], renal cell carcinoma (RCC) [79], nasopharyngeal carcinoma (NPC) [80] and breast cancer [81], and predicted poor prognosis. Thus, we reasoned that $CD27^{-}CD70$ binding may play a role in tumor cell survival and proliferation.

8.2. Role of CD27/CD70 in hematological malignancies

The dysregulation of CD70^{-}CD27 axis is associated with tumor progression and immunosuppression. In hematological malignancies, CD70 and CD27 are co-expressed in tumor cells and interact with each other to increase the number of inhibitory regulatory T cells (Tregs), inducing T cell exhaustion and apoptosis, which potentiates the survival and proliferation of tumor cells [82]. Research found that both CD70 and CD27 were expressed by LSCs in patients with AML, chronic myelogenous leukemia (CML) and non-Hodgkin lymphoma (NHL) subtypes. It was also reported that sCD27 presented a high level in serum samples of AML patients and predicted a poor disease prognosis [71,83,84]. Other studies also noted that the CD27 signal transduction in patients with AML and CML could induce Wnt pathway activation, while impaired Wnt signaling activation could result in proliferation and drug resistance in LSCs [71, 83]. To the contrary, CD27 deficiency could increase the susceptibility to EBV infection and relevant lymphoproliferative disorders (PTLD) [85]. Moreover, expression of CD70 and CD27 could be also observed in the malignant plasma cells of patients with multiple myeloma (MM), and the expression of CD27 would decrease with disease progression [86]. Collectively, we believed that CD27 deficiency may be a high risk factor of EBV infection, PTLD and plasma cell proliferative disorders. An interesting finding reported by Suwen Zhao et al. [87] is that patients suffering from aplastic anemia had increased CD27 but decreased CD70. This result suggests that CD27 may be important for abnormal T-cell activation in aplastic anemia patients, and CD70 may play its role dependent on their pathological environment.

8.3. Clinical prospect of CD27/CD70

Currently, increasing drugs targeting CD27/CD70 have advanced to clinical trials. For example, Varlilumab, the agonist antibody targeting CD27 developed by Celldex Therapeutics for treatment of solid tumors and lymphoid malignancies, is still in testing stage and has shown good efficacy [88]. Experimental study found that Varlilumab and ICIs (Nivolumab or Atezolizumab) could exhibit synergistic effect against the tumor microenvironment in patients with T-cell, B-cell malignancies and renal carcinoma [89]. Antibodies targeting CD70 have shown significance in chemotherapy for tumors, as they can suppress proliferation of tumor cells and decrease chemo-resistance [90,91]. However, such strategy may increase the effect of anti-CD70 antibodies on malignant cells, which prompts us to obtain more experimental data to help formulate more suitable treatment regimens. The CD70^{-}CD27 axis is currently considered as a promising target in immunotherapy for cancers. Nan Guo Ring et al. [82] used anti-CD70 antibody Vorsetuzumab and KWAR23 to treat SRG mice with Burkitt lymphoma and obtained similar outcome with Rituximab treatment. Since most existing clinical trials were performed in lymphomas, the efficacy of antibodies targeting CD70 and CD27 in treatment for MDS remains an open issue, which may be a direction in future research.

9. CD276

9.1. Introduction of CD276 and its function

CD276 is a recently identified immunoregulatory protein belonging to the B7 family, and it has activities against T-cell activation and is involved in cell proliferation, apoptosis, invasion, differentiation, autophagy, epithelial-mesenchymal transition (EMT), and formation of tumor microenvironment [92,93]. Interestingly, CD276 plays a dual role in the immune system. On the one hand, CD276 advances proliferation of CD4^{+} and CD8^{+} T cells and augments cytotoxic T lymphocyte (CTL) activity [94]. On the other hand, CD276 decreases the production of IL-2 and IFN-γ via suppressing a series of signaling pathways (e.g., NF-κB, nuclear factor of activated T cells and activator protein-1, etc.) and concurrently inhibits proliferation of CD4^{+} and CD8^{+} T cells as well as NK cell activity [95–98]. Usually, CD276 is poorly expressed in the majority of normal tissues but increasingly expressed in malignant tumor tissues. Studies also reported that high levels of CD276 are prognostic for poor outcomes of patients with cancers, such as bladder cancer [99], breast cancer [100] and colorectal cancer [101].

9.2. Clinical significance of CD276 in hematologic diseases

Multiple studies revealed that CD276 exhibited significantly increased expression in AML patients and was remarkably associated with poor outcomes [102,103]. Despite that there is no research on the role of CD276 in MDS patients, the current evidence also suggests its potential prognostic significance.

9.3. Current research progress on CD276

Anti-CD276 strategies have advanced to pre-clinical and clinical trials. For instance, the humanized anti-CD276 monoclonal antibody Enoblituzumab (MGA271) can mediate the antibody-dependent cell-mediated cytotoxicity (ADCC) in diverse tumors and has been used in treatment for melanoma, osteosarcoma, Ewing's Sarcoma, renal carcinoma and bladder cancer [104]. Clinical trials concentrating on CD276 activity suppression have been performed in both solid tumors and hematological malignancies. A previous animal experiment assessed the efficacy of CD276-specific chimeric antigen receptor T cells in AML mice and reported CD276 as a promising therapeutic target for treatment of AML with a safety profile [105]. Thus, anti-CD276 mAb is a promising therapeutic target for AML treatment, but further study is warranted to explore its role in MDS progression.

10. CD73

10.1. Introduction of CD73 and its mechanism of action

CD73 is an enzyme that catalyzes AMP to immunosuppressive adenosine. It interacts with CD39 in normal tissues to prevent excessive immune activation. However, it can also help tumor cells achieve self-protection and evade immune cell attacks, conducive to tumor growth, metastasis and formation of tumor microenvironment [106–108]. CD73 exhibits high expression in most solid tumors, such as malignant glioma, melanoma, ovarian cancer, colon carcinoma and hematological malignancies, and it is highly associated with the invasiveness and metastasis of these tumors [109,110].

10.2. Clinical significance of CD73 overexpression in hematological malignancies

CD73 with activities against anti-tumor immunity is excessively expressed by tumor cells. Either in solid tumors or hematological malignancies, CD73 up-regulation usually results in production of extracellular adenosine, which activates adenosine signaling and eventually advances tumor progression [111]. To the contrary, Kong et al. [112] found that increased CD73 expression in $CD8^+$ T cells was prognostic for increased immune responses in and good prognosis of AML, and that $CD73^-$ $CD8^+$ T cells showed progressive depletion. Similarly, a German study reported the same research result [113]. These studies suggest that CD37 may represent a double-edged sword. More experiments are required to validate its immunoregulatory role in hematological diseases, and meanwhile, a good understanding on the specific role of CD73 in various cancers and under different disease statuses is essential for further clinical cancer treatment.

10.3. Research prospect of CD73

A French trial [114] revealed that anti-CD73 monoclonal antibody IPH5301 could increase ATP and induce anti-tumor activity of Oxaliplatin in CD73 knock-out mice. By now, few studies are concentrating on the role of CD73 in hematologic diseases. Nevertheless, all results of the studies above indicate that the combination of CD73-targeted agents and other ICIs has the potential as a promising treatment scheme for hematologic diseases.

11. CD161

11.1. Introduction of CD161 and its mechanism of action

CD161 is a *C*-type lectin receptor (CLR) highly expressed on immune cells such as NK, NKT, $CD8^+$ T and $CD4^+$ T cells, and binding with its ligand LLT1 can inhibit the function of NK cells [115]. RNAseq data revealed that CD161 expression is closely associated with T cell infiltration and expression of related immune checkpoints, immune activation genes, immunosuppressive genes, chemokines and their receptors. CD161, therefore, has the potential to be a tumor marker and may play a role in regulating immune environment by cooperating with other immune checkpoints [116].

11.2. Clinical significance of CD161 in AML

Previous research found that CD161 is a marker of long-lived antigen-specific memory T cells. T cells expressing CD161 can selectively express multidrug resistance membrane transporter (MDR1), conducive to prolonging the survival time of virus-specific memory T cells. Thus, CD161-positive T cells may play a key role in immunotherapy for viral disorders and tumor [117]. It was reported that Valpha24 TC R + CD161+ NKT (Valpha24+ NKT) cells can be activated by α-galactosylceramide and then exhibit anti-tumor effect on multiple tumor cells. The number of Valpha24+ NKT cells decreases significantly in hematopoietic malignancies, such as AML and MDS [118]. In contrast, a recent study of Chevalier MF et al. found that the $CD4^+$ T cells expressing TIGIT and CD161 were associated with AML relapse in patients undergoing haemopoietic stem-cell transplant (HSCT) [119].

11.3. Current progress on CD161

There have been studies that identified expression of inhibitory CD161 receptor on infiltrating T cells in liver cancer and glioma using single-cell sequencing and related experiments [120,121]. Thus, CD161 may provide a deeper insight into the immune evasion mechanisms related to tumor progression and relapse. Relevant studies proved that ILC1 cells help control the growth of AML tumor cells, and human ILC1 cells can eliminate leukemia stem cells (LSCs) by inducing the production of IFN-γ. A recent study found that ILC1 cells expressing CD161 targeted LSCs and affected theprogression of AML [122]. Although no validation has yet been made, this suggests the necessity of a further study on the role of CD161 in hematologic tumors, especially in AML/MDS.

12. GPX1

12.1. Introduction of GPX1 and its mechanism of action

GPX1 is the first reported selenoprotein and antioxidant enzyme. It is widely and abundantly expressed and crucial to maintain organismal homeostasis and cellular physiological functions. Previous research reported that the expression of GPX1 is abnormally elevated in most cancers, such as prostate cancer, lung cancer, bladder cancer, and breast cancer, etc [123].

12.2. Clinical significance of GPX1 in AML

Zhang et al. applied bioinformatics methods to analyze the transcript expression profiles in human AML samples and then performed validation with GEO sample data and basic experiments. They found that GPX1 played a significant role in the phase of immunosuppression in AML, and meanwhile, it had positive associations with the depletion of myeloid-derived suppressor cells (MDSCs), monocytes and T cells and the expression of MDSC markers but negative associations with the levels of $CD4^+$ and $CD8^+$ T cells. Moreover, this study noted that AML patients highly expressing GPX1 had poor outcomes and increased levels of NOTCH, WNT and TLR signal transduction that can promote drug resistance [124]. Recent studies have shown that GPX1 is a downstream target of miR-185–5p, and overexpression of miR-185–5p can suppress the proliferation of AML cells and decrease the expression of GPX1 both in vivo and in vitro, impeding the progression of AML [125]. Thus, the miR-185–5p/GPX1 axis may play a key role in AML treatment.

12.3. Current progress on GPX1

Current studies of GPX1 are still in basic experiments, and no related clinical trials have yet been performed. In spite of the many studies of GPX1 in AML, the role of GPX1 in MDS has not yet been investigated. We believe that GPX1 may be a new target that deserves analysis in MDS treatment.

13. VISTA

13.1. Introduction of VISTA

VISTA is a recognized anti-tumor regulator of immunity, and it is also one of the targets that have been extensively studied in tumor immunotherapy. Additionally, VISTA is an immunoglobulin highly expressed on naive T cells, hematopoietic stem cells (HSCs), myeloid progenitors, MDSCs and APCs [126,127]. Relevant research revealed that VISTA has important clinical implications for hematologic diseases.

13.2. Clinical significance of VISTA in AML

A recent study proved that VISTA is highly expressed in AML and associated with the poor prognosis of AML patients. Zheng et al. found increased expression of VISTA on peripheral MDSCs of AML patients, and that specific VISTA knock-down restored the immune activity of $CD8^+$ T cells suppressed by MDSCs. Moreover, the expression of VISTA on MDSCs was found to be positively associated with the expression of PD-1 on T cells [127]. Another study reported that high expression of VISTA was positively associated with the expression of STAT3 in AML patients, and suppression of STAT3 down-regulated the expression of VISTA and then activated T cell immune activity [128]. In addition, it was also found that Gal-9 was a ligand of VISTA, and interaction between VISTA and Gal-9 facilitated the Gal-9-mediated T-cell apoptosis and then suppressed immunity [129]. These findings indicate that targeting VISTA alone or suppressing both VISTA and PD-1 or STAT3 may play a significant role in the effective control of leukemia. VISTA may serve as a regulator of early immune response to suppress the immune activation in cancer, providing a basis for diagnosing patients at a high risk of recurrence.

13.3. Current progress on VISTA

Zhang et al. developed an effective inhibitor for STAT3, named W1046. W1046 can downregulate the expression of VISTA by inhibiting STAT3 signal transduction, thereby activating T cells and strengthening the function of VISTA-targeting mAb, eventually significantly inhibiting the proliferation and activity of malignant AML hematopoietic cells [130]. JNJ-61610588 is a VISTA-targeted mAb produced by Johnson & Johnson and used for assessing the therapeutic efficacy and safety in patients with advanced solid tumor [131]. Other inhibitors for VISTA include CA-170 and HMBD-002. The former can target both PD-1 and VISTA, while the latter has been proved to be effective in treatment for colorectal cancer, breast cancer and lung cancer. By now, the role of VISTA in AML has been explored in several studies. However, no relevant clinical trials have yet been carried out, and its role in MDS model is still a blank. We hold the view that VISTA is a promising target in MDS immunotherapy.

14. CTLA-4

14.1. Introduction of CTLA-4 and its mechanism of action

CTLA-4 is also known as CD152. It is highly homologous to CD28, and both of them are receptors predominantly distributed on T lymphocytes with reverse mediating effects on T cells. CD28 mediates T-cell co-stimulatory signaling by interacting with CD80 and CD86 receptors, while CTLA-4 inhibits T-cell immune responses via binding the two receptors [132–134]. There are two possible speculations: 1) CTLA-4 competes for common ligands with CD28 and then mediates the endocytosis of CD80 and CD86 [135]; 2) CTLA-4 enhances the function of Treg by inducing their growth, thereby suppressing immune responses [136].

14.2. Clinical significance of CTLA-4 in MDS/AML

Studies demonstrated that proportions of CTLA-4+ $CD3^+$, CTLA-4+ $CD4^+$ and CTLA-4+ $CD8^+$ T cells increased in patients with CLL [137] and AML [138]. Similar changing trend of CTLA-4+ cells could also be obtained in MDS patients. In a study involving 57 MDS patients, the serum level of CTLA-4 was increased and positively associated with the risk stratification in these patients [139].

14.3. Current research progress on CTLA-4

There have been multiple AML-related antigens approved or in the testing stage as potential therapeutic targets, including the *anti*-CTLA-4 antibody Ipilimumab. In a phase I trial that applied Ipilimumab to treat the recurrent hematological malignancies following hematopoietic stem cell transplantation, CTLA-4 expression was suppressed and the risk of recurrence was effectively reduced [140]. Another multi-center phase Ib study showed that Ipilimumab could enhance T-cell activation and immune responses in patients with high-risk MDS, with a safety profile [141]. Collectively, CTLA-4-targeted agents are expected to be applied in clinical treatment for MDS.

15. Summary and future prospect

In conclusion, primary MDS cells alter immune microenvironment under multiple mechanisms. For instance, the up-regulation of some immune checkpoints help malignant hematopoietic cells escape from immunosurveillance, and myeloid malignancies exhibit varying degrees of immune dysregulation at different clinical stages. HMA remains the preferred therapeutic agent for managing high-risk MDS at present, but its efficacy is limited to only less than 20% of patients and the effect is not sustained [142]. Therefore, it is urgent to find alternatives. The latest guideline recommends that patients with relapsed/refractory AML or MDS and not suitable for allogenic transplantation can be included into clinical trials of developing drugs. Similar to some solid tumors, MDS/AML can be well managed by treatment strategies that can enhance the anti-tumor immunity, such as immunosuppression of tumor microenvironment, and therapies targeting relevant vaccines and cytokines. Statistically, approximately 30–40% of MDS cases will progress to AML, which makes early prevention of tumor progression a focus that deserves attention in hematologists.

In future immune-targeted therapy for MDS, how immune regulator proteins and small-molecule targets act during the initiation and progression of MDS should be clarified at first. In addition, the conditions in clinical application of ICIs and the effect of their combinations should be more distinct. Before drug application, large-scale clinical trials are warranted to comprehensively analyze the safety, effectiveness, universal applicability and the optimal timing of the use of ICIs. Moreover, we are encouraged to look for more immune targets and then perform a large number of basic experiments to validate their clinical implications. It is necessary for the development of treatment for AML/MDS. In the context of the current pandemic, whether SARS-CoV has an impact on the efficacy of immunosuppressive drugs also deserves more attention in the future.

Immune phenotypes with clinical significance are tightly associated with the malignancy degree, treatment and prognosis of MDS/AML, and immunosuppressive agents targeting these phenotypes are potentially effective and have received attention in current research. Notably, due to the risk of MDS progression to AML, immune proteins that have implications for AML may also have important clinical significance for MDS, and AML-targeting molecular drugs can be also available for treatment of MDS. As the pathogenesis and clinical features of MDS are increasingly well understood, it is possible to formulate preventive strategies for the healthy people at a high risk of having MDS in the near future.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

No data was used for the research described in the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

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