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REVIEW ARTICLE

Tumor-resident adenosine-producing mesenchymal stem cells as a potential target for cancer treatment

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Abstract

The development of new therapies based on tumor biology is one of the main topics in cancer treatment. In this regard, investigating the microenvironment and cellular composition of the tumor is of particular interest. Mesenchymal stem cells (MSCs) are a major group of cells in the tumor tissue and play a critical role in tumor growth and development. Investigating the mechanisms by which MSCs influence tumor growth and progression is very useful in establishing new therapeutic approaches. MSCs have some immunological capacities, including anti-inflammatory, immune-regulatory, and immune-suppressive abilities, which help the tumor growth in the inflammatory condition. They can suppress the proliferation and activation of CD4 + T cells and direct them toward the regulatory phenotype through the release of some factors such as indoleamine 2,3-dioxygenase, prostaglandin E2, and HO-1, PD-1 ligands (PD-L1 and PD-L2) and promote tolerance and apoptosis. Besides, these cells are able to produce adenosine. Adenosine has a key role in controlling the immune system by signaling through receptors located on the surface of immune cells. It plays a very essential role in tumor growth and progression. In the present review, we investigate and introduce adenosine-producing mesenchymal stem cells as a potential target for cancer treatment.

Keywords Cancer · Mesenchymal stem cells · Adenosine · CD73

Introduction

The tumor microenvironment contains different types of cells, including the proliferating tumor cells, endothelial cells, immune cells, fibroblasts, and mesenchymal stem cells (MSCs) which have a crucial role in tumor promotion and progression. These cells can be considered as targets in cancer therapy to improve traditional therapies or find new strategies so that treatment resistance could be prevented [1].

Mesenchymal stem cells (MSCs) are a heterogeneous subset of progenitor cells found in different adult tissues such as bone marrow (BM), brain, adipose tissue, lung, heart, umbilical cord, and fetal tissue [2]. MSCs have an adhesion property and fibroblast-like morphology. Also, they show special properties including hematopoiesis support, self-renewal, and capacity to differentiate into several cell lines, including chondrocytes, osteoblasts, adipocytes, dopaminergic neurons, astrocytes, tenocytes, and endothelial cells. MSCs are characterized by the increased expression of CD105, CD73, and CD90, and the decreased expression of CD45, CD34, and CD14 [3].

MSCs function to maintain tissue homeostasis, repair the tissue, and reconstitute the normal condition after receiving a danger signal [2]. During these processes, MSCs exhibit their immunological properties, including anti-inflammatory, immune-regulatory, and immune-suppressive activities [4]. These properties are necessary for the healing and repair process of the wound; however, they promote the tumor growth in the inflammatory condition [5]. MSCs can suppress the proliferation of $CD4^+$ T cells and direct them toward regulatory phenotype through the release of some factors like indoleamine 2,3-dioxygenase (IDO), prostaglandin E2, and HO-1 [6, 7]. Moreover, MSCs have been shown

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to express and secrete PD-1 ligands (PD-L1 and PD-L2), suppress the activation of CD4 T cells, down-regulate interleukin-2 production, and promote tolerance and apoptosis [8].

Adenosine, a potent immune-suppressor produced by tumor cells, can express CD73. It can decrease the function of antitumor T cells by inhibiting a series of T-cell responses, such as the secretion of interleukin-2 (IL-2), interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α), and the up-regulation of CD25 and inducing cytolytic effector molecules (perforin and Fas ligand; and granule exocytosis). In addition, adenosine can suppress natural killer (NK) cell and lymphokine-activated killer (LAK) cell function [9]. It is reasonable to infer that adenosine shows strong immunosuppressive properties and has a high concentration in solid tumors. CD73 and adenosine receptors are overexpressed in various cancers and promote their invasion, migration, and adhesion, and also, they often correlate with poor prognosis in patients [10]. Extracellular adenosine generated by tumor CD73 in vitro and in vivo. Studies on the modulation of adenosine and its activity in various preclinical models of cancer have highlighted the value of this product as a potential target therapy for cancer treatment [11]. The purpose of this review was to investigate and introduce adenosine-producing mesenchymal stem cells as a potential target for cancer treatment.

The role of MSCs in cancer

Biology of MSCs

Recently, it has been established that MSCs play a key role in the initiation, progression, and metastasis of some tumor types [12]. It has been found that MSCs can migrate to the tumor microenvironment and differentiate into cells like tumor-associated MSCs (TA-MSCs) and cancer-associated fibroblasts (CAFs) [13]. Besides, some evidence indicates that TA-MSCs may be able to change naive bone marrow MSCs (BM-MSCs) recruited to the tumor into TA-MSCs via secretion of inflammatory components [14]. Afterward, tumor-associated inflammation and hypoxia activate these cells to produce chemokines of the CC (CC chemokines or β-chemokines, proteins that have two adjacent cysteines (amino acids) near their amino terminus) and CXC (CXC chemokines or α-chemokines are separated by one amino acid, represented in this name with an "*X*") subfamilies that recruit neutrophils, macrophages, monocytes, and myeloid-derived suppressor cells (MDSCs). Furthermore, when TA-MSCs are injected together with tumor cells, they can induce tumor growth in animal models of different cancers such as lymphoma, melanoma, and breast cancer [10]. MSCs communicate with other cells in the tumor medium directly and indirectly. Indirect mechanisms take place via cytokines, chemokines, growth factors, secretion of metabolites, activation of signaling pathways, creation of microvesicles, and production of exosomes. With direct interactions such as Notch signaling, tube formation, and cell fusion, mesenchymal stem cells can alter the function of cancer cells.

MSCs in cancer pathogenesis

Some research groups have reported that cancer-infiltrating MSCs can enhance tumor growth and metastasis and suppress the immune system, which interference with immunologic recognition and elimination of malignant cells [15]. Krueger and colleagues established that endogenous MSCs in prostate cancer diminished T cell proliferation through the cell to cell contact [16]. MSCs derived from gastric cancer (GC–MSCs) exhibited a higher ability for pro-angiogenesis and promoted tumor development by IL-8 secretion [17]. Further, MCSs isolated from HNSCC patients produced large amounts of IL-6, IL-8, and stromal cell-derived factor-1 (SDF1) and contributed to tumor progression [18]. Human MCSs derived from tumor specimens of glioma patients expressed CD105, CD90, and CD73 markers, and a high percentage of these cells correlated with poorer clinical outcomes and predicted the aggressive behavior of tumor [19].

A recent report showed that human BM-MSC-derived exosomes induced cancer cell migration and growth via the activation of the Hedgehog signaling pathway [20]. Moreover, exosomes isolated from MSC-differentiated adipocytes enhanced breast cancer development by the Hippo signaling pathway [21].

One feature of malignant tumors is the epithelial–mesenchymal transition (EMT) that contributes strongly to invasion and metastasis [22]. It has been indicated that tumor-associated MSCs play critical roles in regulating EMT and tumor stem cell-like properties of pancreatic cancer cells via the Notch signaling pathway [23]. Adipose-derived MSCs isolated from ovarian cancer patients and cultured with epithelial ovarian cancer cells differentiated into CAFs via the TGF-β1 signaling pathway and induced invasion and metastasis due to matrix metalloproteinase-2 (MMP2), MMP9 release, and EMT [24].

Mesenchymal stem cells of inflammatory breast cancer tissue promote the differentiation of tumor-infiltrated monocyte into M2 tumor-associated (immune-suppressing) macrophages (TAM). These MSCs produce IL-8/CXCL8 and growth-regulated oncogene (GRO) chemokines that trigger the Janus kinase/signal transducers and activators of transcription 3 (JAK/STAT3) pathway and lead to cancer stem cell (CSC)-like phenotypes and EMT transformation [25].

On the other hand, it is well documented that a group of cancer cells called cancer stem cells (CSCs) with stem cell properties are very aggressive, produce resistance to treatment, and lead to disease relapse; therefore, identifying key signaling events and targeting these can serve as potential strategies for therapeutic intervention [26]. It is assumed that these cells emanate from normal tissue progenitor cells, differentiated somatic cells, or even tumor cells, but the accurate origin of CSCs remains unknown [27]. The MSCs' function in cancer is a double-edged sword. Some studies have reported that MSCs suppressed tumor progression, metastasis, and angiogenesis and induced apoptosis or cell cycle arrest in the G0–G1 phase [28].

In a murine experimental model, the co-culture of glioma cells and MSCs decreased tumor growth and angiogenesis via suppressing the Protein kinase B (Akt) signaling pathway. Another report showed that MSCs reduced the migration and invasion of breast cancer cells by regulating the secretion of metallopeptidase inhibitor 1 (TIMP-1) and TIMP-2. Moreover, these cells were able to significantly decrease the proliferation of chronic myelogenous leukemia through dickkopf-1 (DKK-1) secretion [29]. Human umbilical cord-derived mesenchymal stromal/stem cells (hUC-MSCs) induced apoptosis in human prostatic carcinoma through the activation of c-Jun N-terminal kinase and the inhibition of Akt signaling pathways. Furthermore, these cells induced apoptosis in glioblastoma through the depletion of X-chromosome-linked inhibitor of apoptosis protein (XIAP), which in turn led to the activation of the caspase-9/caspase-3 pathway in the tumor [29].

Targeting MSCs in cancer treatment

It seems that cancer stromal cells including the tumor-infiltrating MSCs could have curative outcomes. The treatment strategy might be to target proteins expressed by stromal cells and signaling interactions [30]. As mentioned above, MSCs generate different cytokine and chemokines in tumor stroma. The blockade of IL-8 produced by GC–MSCs via neutralizing antibody decreased gastric cancer progression [17]. Treatment with AMD3100, an inhibitor of the SDF1 receptor CXCR4, made prostate cells more sensitive to chemotherapy and radiotherapy [7, 8]. In Yin et al.'s study, Resveratrol (3,5,4′-hydroxystilbene, RES), as a cancer preventive drug, inhibited tumor metastasis and EMT by targeting GC–MSCs and Wnt/β-catenin signaling [31]. In the following, we will discuss the CD73 molecule, expressed by MSCs, which has been demonstrated to play a role in tumor invasion.

Adenosine signaling effect in the pathogenesis of cancer

Molecular biology of adenosine

CD73, known as ecto-5′-nucleotidase, is a glycosyl-phosphatidylinositol found in most tissues. CD73 controls a variety of physiologic responses, such as epithelial ion and fluid transport, tissue injury, platelet function, hypoxia, and vascular leak [32].

CD39 cleaves ATP and ADP into AMP, and then, CD73 is essential for the generation of extracellular adenosine from AMP [33]. Adenosine levels increase under some specific conditions such as inflammation, tissue injury, ischemia, or cancer, because of high amounts of ATP release, which protect the tissue from destruction [34]. Adenosine triggers the signaling pathway through four G-protein-coupled receptors (A1R, A2aR, A2bR, and A3R) [35].

Adenosine in tumor environment

Adenosine is given the strong immunosuppressive properties through presumed high levels in solid tumors, and thus it can be concluded that it may constitute an essential part of "the immunologic barrier," leading to a failure of an effective antitumor immune response. CD73 plays a role of a prognostic biomarker for different cancers like breast [36], gastric [37], head and neck [38], ovarian, lung, papillary thyroid, and brain cancer [39]. The overexpression of CD73 in different tumors has been associated with a poor prognosis, tumor outgrowth, metastasis, drug resistance, and a greater ability to repress antitumor immune responses [40].

Tumor medium provides an appropriate condition to increase the adenosine expression. Hypoxia is a specific feature of a broad range of solid tumors, which is associated with the induction of a regulatory network [41]. Low oxygenation in the tumor area induces the hypoxia-inducible factor (HIF), which can stimulate the expression of CD73 in the tumor due to the presence of the HIF response element within the CD73 promoter [42]. HIF-dependent transcription can activate the induction of VEGF that plays a key role in tumor angiogenesis [43]. Additionally, many pro-inflammatory factors support CD73 expression, including TGF-β, IFN-γ, TNF- α, IL-1β, prostaglandin E2, Wnt signaling, and protein kinase-C (PKC) (Fig. 1).

In addition to cancer cells, numerous immune cells, such as B cells (especially on all mature *naive B* cells), T regulatory cells, $CD8^+$ T cells, a small subset of $CD4^+$

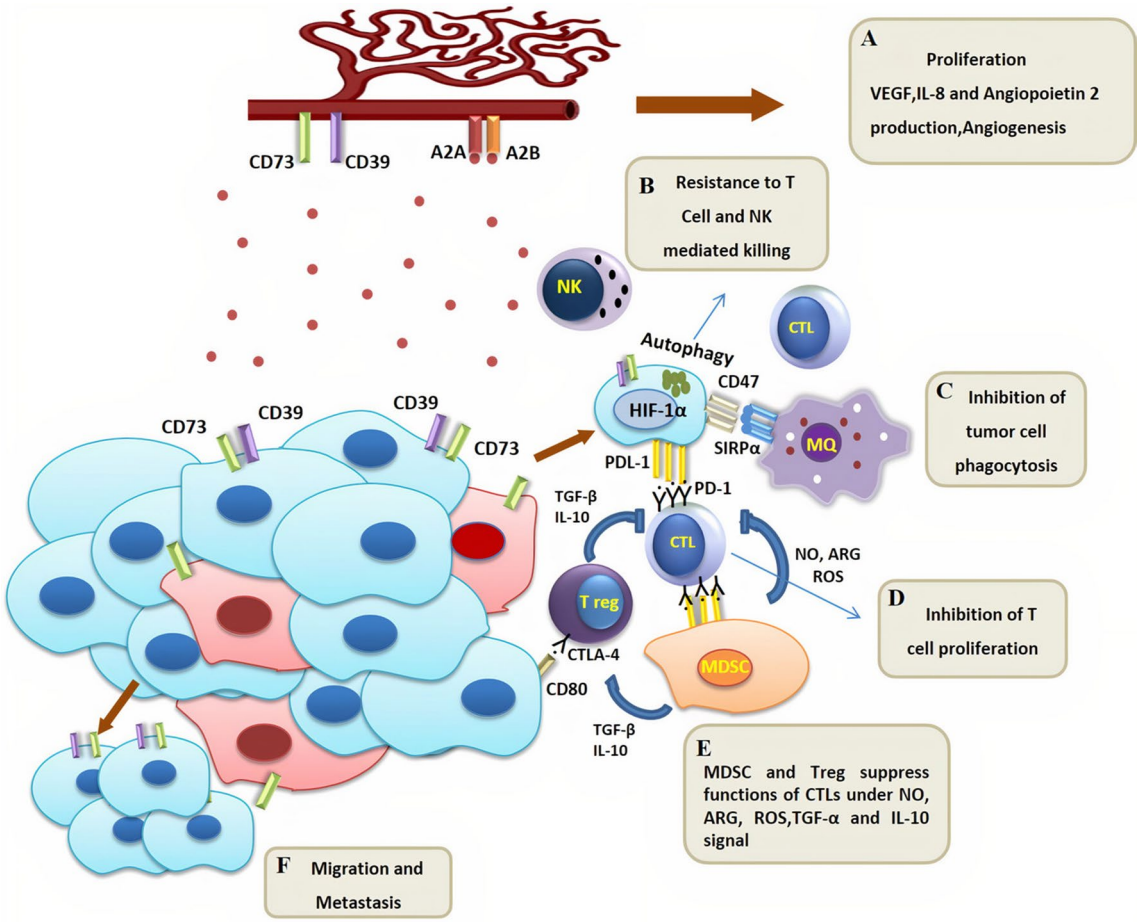

Fig. 1 Features of adenosine-producing MSCs in tumor microenvironments that suppress antitumor immunity. **a** Adenosine stimulates endothelial cell proliferation and enhances VEGF, IL-8, and angiopoietin 2 generation. **b** The activation of autophagy in hypoxic tumor cells causes resistance to cytotoxic T cell and NK-mediated killing. **c** HIF-1α induces the expression of CD47 on the surface of tumor cells. When CD47 binds to SIRPα (present on the surface of macrophages), a strong signal is provided in tumor cells that blocks the phagocytosis property of macrophages. **d** In hypoxia condition, the hypoxia-inducible factor (HIF)-1α in cells up-regulates the expression of programmed death-ligand 1 (PD-L1) and PDL1 in hypoxic tumor cells and MDSCs, respectively. The up-regulation of PD-L1 suppresses T cell proliferation and T cell-mediated lysis. **e** Cytotoxic T lymphocyte (CTLs) is suppressed by TGF-β and IL-10 that regulatory T cells (Tregs) secrete, and arginase (ARG), nitric oxide (NO), and reactive oxygen species (ROS) are secreted by myeloid-derived suppressor cells (MDSCs). **f** Adenosine facilitates EMT process in the tumor that leads to metastasis

T cells, and myeloid-derived suppressor cells (MDSCs) express CD73 molecule [44]. In arthritis patients, CD73 is down-regulated on T cells, and the expression of CD39 is up-regulated. CD39 and CD73 are co-expressed in a subset of Th17 cells with the suppression effect. Th17 cells were present in the lamina propria and decreased gut inflammation in these patients [45]. In mice, peritoneal macrophages, most T cells (Tregs), NK cells, and the B cell compartment (in mature class switched and germinal center B cells) are expressed CD73 [45]. Surely, rarely CD39 and CD73 are co-expressed on human conventional T cells in the periphery, and the expression of CD73 is a scarce event on human Tregs [45].

Tumor cells expressing CD73 would be resistant to apoptosis. It has been reported that CD73-expressing Jurkat leukemic cells are resistant against TNF-α-induced apoptosis. Expression of CD73 was also the cause of resistance to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis in Jurkat leukemia cells. Additionally, the up-regulation of CD73 in breast cancer cells resistant to doxorubicin was demonstrated [46, 47].

There is some evidence showing that adenosine plays a key role in the pathogenesis of head and neck carcinoma (HNC). Advanced pathological grade of HNC is associated with the overexpression of A2AR. The administration of A2AR antagonist (SCH58261) in HNC mouse model was able to suppress tumor growth and increase the antitumor response. Mechanism of the function of A2AR is related to the suppression of immune system by affecting CD8 + T cells in head and neck squamous cell carcinoma

(HNSCC) and inducing the regulatory T cells (Tregs) in the systemic circulation. Adenosine deaminase (ADA, as a cytosolic enzyme) breaks down adenosine to inosine and 2′ deoxyadenosine. ADA levels increased in patients with HNC and decreased in response to conventional therapies such as radiotherapy, chemoradiation, and surgery. As a result, adenosine and ADA involved in the progression of HNC can be applied as both a biomarker for diagnosis and a potential target for HNC therapy [48]. Adenosine regulates apoptosis, becomes toxic in MCF-7 [estrogen receptor positive (ER +)] and MDA-MB 468 [estrogen receptor negative (ER-)] cell lines, and induces apoptosis through mitochondrial/intrinsic pathway [47, 48]. The administration of A3 adenosine receptor agonist [2-chloro-N (6)-(3-iodobenzyl)-5′-N-methylcarbamoyl-4′-thioadenosine (LJ-529)] decreased cell proliferation and cell growth by inducing apoptosis and deregulating the Wnt/β-catenin signaling pathway in ER + and ER- breast cancer cell lines. Also, N-[5-(1-cyclopropyl-2,6-dioxo-3-propyl-2,3,6,7-tetrahydro-1H-purin-8-yl) pyridin-2-yl]-N-ethyl-6-nicotinamide (ATL801), as a selective A2b adenosine receptor antagonist, reduced the growth of breast tumors in mice and decreased the metastasis of breast cancer cells to the lung by up to 85%, and suppressing A2b adenosine receptor inhibited migration, invasiveness, and growth in ER- breast cancer cell lines [48–50]. High levels of ecto-5′-nucleotidase (CD73) in ER-cells may be related to tumor progression by an increased adenosine level. This evidence supports the hypothesis that there is a correlation between the increased expression levels of CD73 and poor prognosis in patients with triple-negative breast cancer. Administration of CD73 antagonist could suppress growth and reduce spontaneous metastasis of breast cancer in mouse models of triple-negative breast cancer. As a result, adenosine affects tumors via different signaling pathways, and the inhibition or enhancement of tumor growth depends upon the activation of different subtypes of adenosine receptors and type of cancer.

Adenosine inhibition and cancer treatment

Stagg and colleagues reported that CD73-deficient mice were resistant to anti-CD73 mAb therapy remarkably inhibited tumor growth and prevented the development of lung metastases. Also, in another study, they reported that the knockdown of CD73 in tumor cells could reduce tumor growth, suppress tumor metastasis, and increase antitumor responses and the efficiency of cancer immunotherapy [32].

Thus, the inhibition of CD73 exerts positive dual effects by extenuating immunosuppression and reducing metastasis [51]. Recent studies showed that the blockage of CD73 by an anti-CD73 monoclonal antibody triggered adaptive antitumor immunity. CD73-siRNA delivery in tumor regions blocked CD73 in breast cancer. As a result, this approach could effectively inhibit CD73 mRNA and protein levels, which were associated with in vivo growth suppression and metastasis prevention [52]. Antibodies that target membrane-associated, soluble forms of CD39 and CD73 induced antitumor immune response through dendritic cells, macrophages, and activated cancer patient's isolated T cells. Some of the clinical trials have investigated adenosine receptor antagonists or anti-CD73 against different solid tumors (Table 1).

Role of MSCs in adenosine production in tumor microenvironment

It is well established that MSCs express four adenosine receptors (A1R, A2AR, A2BR, and A3R), which reflect the autocrine and paracrine role of adenosine in the proliferation, differentiation, and development of MSCs. The A2B receptor is up-regulated in MSCs in the early stages of osteoblastic differentiation; however, in the latter stages of osteoblastic differentiation, A2AR expression is enhanced. Also, MSCs, which differentiate to adipocyte cells, express A1 and A2A receptors [53].

Two simultaneous studies reported that MSCs co-expressed the ecto-enzymes CD73 and CD39 and that they could produce high levels of adenosine. MSCs suppressed the proliferation of activated T lymphocytes through adenosine receptor A2A, and the blocking A2A signaling significantly increased lymphocyte proliferation.

As compared to Treg in the peripheral blood, the expression of CD39 is up-regulated on Treg in the tumor microenvironment [54]. Since MSCs lack functional CD39 on their surface, it is likely that the presence of CD39 + Treg in tumor medium will likely result in the adenosine production [55].

A study by Lee and colleagues investigated the effect of human BMSCs on activated T cells. HMSCs express CD39 and CD73, and when Th17 cells were co-cultured with hMSCs, the expression levels of CD39 on Th17 cells were up-regulated. Moreover, BMSCs effectively inhibited the proliferation of Th17 cells and secretion of both IL-17A and IFN-γ cytokine, and these effects were related to the adenosine generation [9].

Other reports reveal that NK cells express CD39, but the percentage of CD73-expressing NK cells in peripheral blood is very low. Still, the co-culture of NK cells with MSCs led to an increase in the CD73 + NK cells population and adenosine production.

Chen et al. addressed the effect of CD73 pathway in MSCs on an autoimmunity model and revealed that MSCs diminished T cell proliferation through adenosine

Table 1 Clinical trials with adenosine pathway inhibitors

Target	Agent	Company	Cancer	Design overview	Study phase	Launched on	Estimated primary completion date	Code
A2aR	PBF-509	Pablobio (Novartis)	Non-small cell lung cancer	Single agent and in combination PDR001 (anti-PD1)	Phase 1/1b	2015	October 2020	NCT02403193
–	CPI-444	Corvus	Advanced solid malignancies	Single agent and in combination with Atezolizumab	Phase 1/1b	2016	June 2021	NCT02655822
–	AZD4635	AstraZeneca	Advanced solid malignancies	Single agent and in combination with durvalumab (anti-PDL-1)	Phase 1	2016	March 15, 2021	NCT02740985
–	MK-3814	Merck	Advanced solid malignancies	Single agent and in combination with pembrolizumab(anti-PD-1);	Phase 1	2017	February 21, 2018	NCT03099161
–	NIR178	Novartis	Solid tumors and non-Hodgkin lymphoma	In combination with PDR001(anti-PD1 antibody)	Phase 2	2017	December 1, 2021	NCT03549000
A2bR	PBF-1129	Palobiofarma	NSCLC	Single agent	Phase 1	2017	December 31, 2019	NCT03274479
CD73	MEDI9447	Medimmune	Advanced solid malignancies	Single agent and in combination with durvalumab (anti-PDL-1)	Phase 1	2015	June 8, 2022	NCT02503774
-	MEDI9447	Medimmune	Relapsed ovarian cancer	Single agent and in combination with durvalumab (anti-PDL-1), tremelilumab (anti-CTLA4), MEDI 0562 (anti-OX40)	Phase 2	2018	September 30, 2023	NCT03267589
	BMS-986179	Bristol Meyers Squibb	Advanced solid malignancies	Single agent and in combination with nivolumab (anti-PD-1)	Phase 1/2a	2016	September 19, 2022	NCT02754141
–	CPI-006	Corvus	Advanced solid malignancies	Single agent and in combination with CPI-444 (A2Aantagonist), pembrolizumab (anti-PD-1)	Phase 1	2018	December 2023	NCT03454451
–	NZV-930	Novartis	Advanced solid malignancies	Single agent and in combination with spartalizumab (anti-PD-1), NIR178 (A2Aantagonist)	Phase 1	2018	February 14, 2022	NCT03549000
–	TJ004309	TRACON Pharmaceuticals	Solid tumor and metastatic cancer	TJ004309 plus atezolizumab (humanized monoclonal antibody to PD-L1)	Phase 1	2019	September 2021	NCT03835949

production and up-regulated CD73 expression by $CD4^+$ T cells [56].

Kerkela et al. showed that the cooperation of MSCs and other cells, such as activated T cells, is required for adenosine secretion. MSCs and MSC-derived vesicles significantly express CD73 and produce adenosine that inhibits T cell proliferation. A recent study showed that TGF-β1 could promote the generation of extracellular adenosine and the up-regulation of CD73 in human cervical carcinoma, cultured with MSCs [57].

As mentioned, hypoxia increases the production of adenosine due to HIF-dependent activation of CD73 gene expression. It has been demonstrated that chronic hypoxia and HIF-2α activate Wnt and Notch pathways to up-regulate c-Myc expression, which enhances the stemness phenotype in breast cancer stem cells (BCSCs) and induces chemo-resistance [58]. Also, it has recently been found that adenosine receptor 2B (A2BR) is necessary for BCSCs enrichment in response to hypoxia through PKCδ-dependent STAT3 signaling pathway, and the genetic or pharmacological blockage of A2BR reduces the BCSC population in the tumors medium. Pharmacological inhibition of A_3AR decreases cell adhesion, migration, invasion, and the expression of the EMT markers of glioblastoma stem-like cells via HIF-2/PAP-dependent activation of A_3AR under hypoxia [58].

Potential role of MSCs in advanced malignancies

Cancer stem cells (CSCs) as subpopulations of cancer cells with similar characteristics of normal stem or progenitor cells such as self-renewal ability and multi-lineage differentiation drive tumor growth and heterogeneity. So CSCs play a central role in cancer initiation, progression and invasion, therapeutic resistance, and recurrence. Throughout the cancer progression, CSC can be induced from differentiated cancer cells via the adaptation and cross talks with the tumor microenvironment therefore contributes to their heterogeneous phenotypes [59]. So there are different mechanisms involved in CSCs activities. Therefore, in order to deal with and treat advanced cancers, it is necessary to somehow fight these cells or their proliferative mechanisms. Capicua (CIC) is an important developmental transcriptional repressor. (CIC) has emerged as an important rheostat of cell growth regulated by RAS/MAPK signaling. In mammals, it is negatively regulated by MAPK signaling. It showed that CIC could suppress CSC properties in breast cancer cells. Deficiency of CIC enhances CSC self-renewal and multiple CSC subpopulations of breast cancer cells without altering their growth rate or invasiveness through repression of ETV4 and ETV5 expression, consequently promoting self-renewal capability, EpCAM + /CD44 + /CD24low/ − expression, and ALDH activity. CIC deficiency in xenograft models increased CSC frequency and drives tumor initiation through derepression of ETV4. In additon to the experimental data, the CD44high/CD24low CSC-like feature is inversely correlated with CIC levels in breast cancer patients [60]. Complete inactivation of CIC function actively contributes to tumor progression. CIC mutations have subsequently been identified in a variety of cancers such as stomach adenocarcinomas (12.9%), endometrial carcinomas (6.9%), colorectal carcinomas (6.1%), or melanomas (5.2%). Inactivation of CIC has been implicated in metastasis formation. In particular, CIC mutations were associated with advanced-stage lung adenocarcinomas and the inactivation of CIC promoted metastasis in an in vivo orthotropic model of lung cancer [61].

In addition to CIC, p38 mitogen-activated protein kinases (p38 MAPKs), as an important roller in the cellular response to environmental stress, is another important factor that can affect these cells [62]**.** P38 MAPKs are serine/threonine kinases and activated by a wide variety of environmental and cellular stresses or inflammatory cytokines. Tumor-specific microenvironment including inflammatory factors is a key mediator for maintaining the stemness of CSCs through various pathways such as p38 MAPK. Suppression of p38 activity reduced the expression of CSCs markers and sphere formation ability and decreased migratory potential in head and neck squamous cell carcinoma [63].

Accordingly, the expression of both of these factors (CIC and MAPK) is affected by the tumor microenvironment. The tumor microenvironment affects the MAPK signaling pathways and ultimately affects the proliferation, differentiation, and capabilities of CSCs. However, MSCs affecting the tumor microenvironment can play an important role in the development of CSCs through direct or indirect effect on the expression of CIC and MAPK. Several reports showed that MSCs may have a suppressive role in tumor development via p38 MAPK [64]. For example, in leukemic tumor cells, human umbilical cord mesenchymal stem cells inhibited the growth of the tumor via p38 MAPK [65].

Discussion and conclusion

Previous data support the association between adenosine and tumor progression. Different stages of tumor progression, such as initiation, promotion, malignant conversion, invasion, and metastasis, are greatly influenced by adenosine. This nucleotide is produced, in part, by the action of the ectoenzymes CD39 and CD73. Adenosine increases in cancer because of hypoxia and high amounts of ATP release to protect tissue from destruction. Hypoxia stimulates the CD73 expression through hypoxia-inducible factor (HIF). Moreover, pro-inflammatory factors TGF-β, IFNs, TNF, IL-1β, prostaglandin E2, Wnt signaling, and protein kinase C (PKC) support CD73 expression. The CD73 expression on tumor cells induces resistance to apoptosis.

Thus, CD73 is used as a prognostic marker for breast, gastric, head and neck, ovarian, lung, papillary thyroid, and brain cancers, and its overexpression in different tumors has been reported to be associated with a poor prognosis, tumor outgrowth, metastasis, drug resistance, and a greater ability to repress antitumor immune responses.

Interestingly, CD39 and CD73 are expressed on the surface of MSCs. MSCs co-express the ecto-enzymes CD73 and CD39 and can produce high levels of adenosine. Therefore, one of the important sources for adenosine production in tumors is MSCs. Adenosine-producing MSCs have significant immunosuppressive effects through the production of adenosine in the tumor environment and subsequently inhibit tumor cell apoptosis (Fig. 1). Given that the inhibition of CD73 exerts positive dual effects by extenuating immunosuppression and reducing metastasis and that several clinical trials have determined adenosine receptor antagonists or anti-CD73 against different solid tumors, these findings confirm the idea that the adenosine-producing MSCs can be considered as a potential therapeutic target in cancer. It is strongly recommended to implement this approach in experimental studies on different tumors, especially on tumors for which CD73 is used as a prognostic marker.

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Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

Ethical approval This paper is a review article and has not received ethical approval.

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