Implications of CD39 in immune-related diseases

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Abstract

Extracellular adenosine triphosphate (eATP) mediates pro-inflammatory responses by recruiting and activating inflammatory cells. eATP is hydrolyzed by CD39 to adenosine monophosphate (AMP), which is converted to the immunosuppressive nucleoside adenosine (ADO) by CD73. CD39 is the rate-limiting enzyme in this cascade and can be viewed as an immunological switch that shifts ATP-driven pro-inflammatory immune cell activity to an anti-inflammatory state mediated by ADO. CD39 is expressed by a broad range of immune cells and can be influenced by genetic and environmental factors. Accumulating evidence suggests that CD39 is involved in several pathophysiological events, such as inflammatory bowel diseases, sepsis, ischemia-reperfusion injury, allergic diseases, systemic lupus erythematosus, diabetes, and cancer. Here, we focus on the current understanding of CD39 in immunity, and presents a comprehensive picture of the multiple roles of CD39 in a variety of disorders.

Keywords: CD39, Inflammation, Cancer

ATP and ADO signaling

Extracellular ATP (eATP) plays an important role in regulating inflammation and immune responses; it is rapidly released through exocytosis during stress, cell injury, and death[1]. The effects of eATP are mediated by P2 cell-surface receptors (P2R), which include trans-cell membrane cationic channels (P2XR) and G-protein coupled receptors (P2YR)[2, 3]. There are 7 P2XR and 8 P2YR, which are expressed in almost all mammalian cells [4]. In addition to its metabolic functions, eATP is an important extracellular signal molecule that triggers and regulates a variety of inflammation-related processes. ATP is involved in the chemotaxis of inflammatory cells [5, 6], production of oxygen free radicals by neutrophils [7] and production of cytokines by inflammatory cells [8]. CD39 is an enzyme that hydrolyzes eATP into adenosine monophosphate (AMP), and AMP is further converted by CD73 into nucleoside adenosine (ADO). Although the production of AMP is thought to be mainly mediated by CD39, AMP is also obtained through the transformation of NAD^+ by CD38 and CD203a [9-12]. The accumulated extracellular ADO performs its regulatory functions by binding to one of four ADO receptors: A_1R, $A_{2A}R$, $A_{2B}R$, and A_3R [13, 14]. All four subtypes are members of the GPCR superfamily, and each subtype has a unique pharmacological profile, tissue distribution, and effector coupling [15]. Upon activation, Gi-coupled A_1R and A_3R inhibit adenylate cyclase and cyclic AMP (cAMP) production [16]while Gs-coupled $A_{2A}R$ and $A_{2B}R$ stimulate cAMP synthesis and its downstream signaling pathways[17, 18]. As a consequence, activation of $A_{2A}R$ and $A_{2B}R$ in immune cells induces strong immunosuppressive effects [19]. Finally, ADO is either removed from the extracellular space by ADO deaminase, which converts it into inosine, or is taken by nucleoside transporters back into the cell and converted back into AMP by ADO kinases[20]. CD39 is the rate-limiting enzyme in the ATP/ADP-ADO pathway. The expression of CD39 is regulated by pro-inflammatory cytokines, such as transforming

growth factor-β (TGF-β), interferons (IFNs), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and prostaglandin E2 [21, 22], and processes, such as oxidative stress production and hypoxia[23, 24].

The functions of CD39 in immune cells

CD39 and T-cells

Within the T-cell population, CD39 is mainly expressed by $CD4^+$ lymphocytes and mainly by regulatory T-cell (Treg) subsets [25]. The expression of CD39 in $CD4^+$ T-cells increases with age and $CD39^+CD4^+$ T-cells were found to be prone to apoptosis and metabolic stress [26]. Both CD39 and CD73 are expressed in Tregs and hydrolyze pericellular ATP into ADO, which contributes to Treg immune suppressive functions[27, 28]. Previous reports indicated that 90% of human $Foxp3^+$Tregs are $CD39^+$[25, 29]. Initial phenotypic and functional analyses demonstrated that $CD4^+CD25^{high}CD39^+CD45RO^+$cells had properties consistent with effector Treg, $CD4^+CD25^{high}CD39^-CD45RO^-$cells were naïve Tregs, and $CD4^+CD25^{high}CD39^-CD45RO^+$cells were predominantly non-Tregs with effector T-cell functions[30]. $CD39^+$Treg cells demonstrated more potent suppressive abilities compared to conventional Treg cells. Tregs induced by $CD39^+$ naive T-cells, $CD39^+$ iTregs, demonstrate enhanced proliferation and suppressive abilities [31]. $CD8^+$iTregs displayed increased CD39 expression in patients with systemic lupus erythematosus (SLE) nephritis, which was shown to play an important role in the suppressive function of human $CD8^+$ iTregs [32]. $CD39^{high}$ Tregs were more stable and functional than $CD39^{low}$ Tregs. Cultured $CD39^{high}$Tregs maintained stable forkhead box protein 3 (Foxp3) expression, whereas $CD39^{low}$ Tregs lost Foxp3 expression and trans-differentiated into Th1 or Th17 cells. Furthermore, human $CD4^+CD39^{high}$ Tregs, but not $CD4^+CD39^{low}$ Tregs, protected against xenograft-versus-host-disease in mice models [33]. Mouse Tregs showed increased CD39 activity only when their T-cell receptor (TCR) was activated, while the CD39 enzyme was found to be ineffective in unstimulated cells [34]. CD39 is also highly expressed in tumor-infiltrating Tregs and participates in Tregs-mediated immunosuppression [35-37]. Some $CD4^+$ T cells do not express FoxP3, but express CD39[25, 38]. These T-cells have a unique phenotype called the memory effect, and they have no immunosuppressive capacities.

CD39 is also expressed in $CD8^+$ cells. It was reported to be highly expressed in a variety of human tumor-infiltrating $CD8^+$ T-cells found in renal cancer, gastric cancer[39], lung cancer, colorectal cancer, breast cancer [40] and head and neck cancer[41]. Tumor-infiltrating $CD39^{high}CD8^+$ T-cells increase with tumor growth and exhibit features of exhaustion[40]. $CD39^+CD8^+$Tc1 cells limit interferon-γ (IFN-γ) production of $CD39^-CD8^+$ T-cells by generating ADO, which acts in a paracrine manner [42].

CD39 is expressed on Th17 cells, and co-expression of CD39 and CD161 by $CD4^+$ T-cells might serve as a biomarker to monitor Th17 responsiveness [43]. The expression of CD39 and CD73 on the surface of Th17 cells is closely regulated by IL-6 and TGF-β, which induce Th17 differentiation [44]. Furthermore, CD39 activity regulates the conversion of Th17 cells into IL-10-producing cells *in vitro* , which is abrogated in the presence of ATP and the CD39-specific inhibitor ARL67156[45]. In a mouse cancer model, Th17 cells produced in the presence of TGF-β were shown to have high expression levels of CD39 and CD73, which inhibit T-cell response and promote tumor growth in an ADO-dependent manner [44]. Moreover, $CD39^+$ Th17 cells in juvenile autoimmune liver disease (AILD) are both quantitatively decreased and qualitatively deficient. Low expression levels of CD39 and A_2AR may contribute to the perpetuation of Th17 cell effector properties and unfettered inflammation in this disease [46].

CD39 is also expressed in other types of T cells. Tissue-resident memory T-cells (Trm) express high levels of PD-1, TIGIT, and CD39 and represent tumor-reactive tumor-infiltrating lymphocytes[47]. CD39 has been reported as a surface marker of mouse regulatory γδT-cells, which have been shown to suppress contact hypersensitivity [48].

CD39 and B cells

The expression of CD39 is ubiquitous in B cells; however, CD73 expression is uncommon. In certain mouse strains, approximately 30–50% of B-1 cells ($B220^+CD23^-$) and IL-10 producing B (B10) cells ($B220^+CD5^+CD1d^{high}$) are $CD73^{high}$, whereas few conventional B-2 cells ($B220^+CD23^+AA4.1^-$) express

CD73. In keeping with expression of both CD73 and CD39, $CD73^+$ B cells produce ADO in the presence of ATP substrate, whereas B-2 cells do not [49]. Figueiro et al. defined $CD39^{high}$ B cells as the major contributor to the regulatory network operated by human B lymphocytes[50]. $CD39^{high}$ B cells co-cultured with autologous effector T cells suppressed T-cell activation/proliferation and increased the secreted levels of IL-6 and IL-10. The proliferation and functions of these $CD39^{high}$ B cells are regulated by A_1R- and $A_{2A}R$-mediated autocrine signaling. Saze et al. found that the production of AMP and ADO by $CD39^+CD73^+$ B cell subsets is related to the control of CD4 and CD8 effector immunity[51]. The absence of CD39 did not change the number of B cells in peripheral blood and spleen. However, $CD39^{-/-}$ mice showed impaired B cell memory response to T-dependent, suggesting that CD39 may contribute to the antibody affinity maturation and the post-germinal centers B cell differentiation[52].

B cells express P2XR and P2YR [53] which allows ATP to regulate B cell activation, adhesion, migration, and IgE secretion [54]. ATP-driven P2X7R activation is crucial for secretion of IgM, indicating that this receptor plays a key role in the humoral response [55]. It can be speculated that CD39 may affect the ATP-mediated B cell regulation.

CD39 and neutrophils

CD39 is widely expressed in neutrophils and plays a key role in regulating neutrophil activity by controlling the extracellular purine energy gradient [56]. In addition, neutrophils express CD73 [57] and all four ADO receptors[58]. Neutrophils directly secrete ADO and inhibit its degradation. Furthermore, they release ATP following activation, which is subsequently hydrolyzed by CD39 and CD73 into ADO[59]. The inadequate activity of the CD39/CD73 axis is related to the amplification and uncontrolled activation of neutrophils [60], enhancement of their chemotactic function [61], and increased neutrophil adhesion to the vascular endothelium [60, 62].

Studies have shown that CD39 plays an important role in regulating neutrophil chemotaxis by facilitating the hydrolysis of eATP. Shah et al. demonstrated that eATP had a regulatory effect on the late stage of neutrophil recruitment [63]. Once neutrophils reach the ATP-rich region, blocking CD39 may promote the stop signal of neutrophil chemotaxis [64]. Chen et al. showed that hydrolysis of ATP by CD39 promoted neutrophil chemotaxis by activating the A3R [5]. Both A3R- and CD39-deficient mice showed impaired recruitment of neutrophils to inflammatory sites [61, 65]. Paradoxically, lipopolysaccharides (LPS)-induced accumulation of neutrophil into the lungs was enhanced in $CD39^{-/-}$ mice, which may be due to the loss of normal endothelial barrier and increased capillary leakage in $CD39^{-/-}$ mice [66].

CD39 and NK cells

It has been reported that the expression of CD39 is very low in resting human NK cells [56]. In murine NK cells, CD39 is the dominant ectonucleotidase and thereby plays a predominant role in the regulation of pericellular nucleotide concentration levels. While murine NK cells do not express CD73 and cannot efficiently generate ADO, they primarily mediate ATP and ADP hydrolysis into AMP[67]. However, the human NK cells were shown to produce ADO via a CD38-mediated pathway [68].

CD39 deficiency and changes in P2 receptor activation abrogate secretion of interferon gamma by NK cells in response to inflammatory mediators, and limiting tissue damage mediated by these innate immune cells during IRI [67]. In addition, CD39 deletion has been shown to have a protective effect in the context of concanavalin A hepatitis induced by NKT cells [69]. Additional protective effects of CD39 deletion have been demonstrated in the context of invariant NKT cell-mediated hyperoxic acute lung injury[70]. After trauma, the subsets of NK cells changed significantly, and the expression of surface CD39 increased in those NK cells. The observed post-injury increase in CD39 expression levels in NK cells provides an explanation for the susceptibility to infection of those patients, and it might represent a potential prognostic marker or drug target [71].

In a tumor setting, the expression of CD39 and the consequential ATP hydrolysis and ADO generation compromise anti-tumor immune responses, including those that may be mediated by NK cells. Zhang et al.

showed that both CD39 and CD73 are up-regulated in lung tumor-infiltrating NK cells [72]. Furthermore, the same study demonstrated that NTPDase inhibitor sodium polyoxotungstate (POM-1) enhanced NK cell-mediated metastatic control and synergized with combined Braf and MEK inhibition, recombinant IL-2, or anti-PD-1 and anti-CTLA-4 checkpoint blockade. Moreover, Yan et al. showed that the anti-metastatic activity of anti-CD39 was NK cell- and IFN-γ-dependent and that the quantity of IFN-γ produced in lung-infiltrating NK cells was enhanced following tumor challenge and anti-CD39 therapy[73].

CD39 and dendritic cells (DCs)

CD39 is expressed in both human and mouse DCs [74, 75]. Mouse bone marrow-derived DCs constitutively express CD39 but do not express CD73; thus, AMP is not converted into ADO[76]. The net effect of CD39 on the regulation of DC function may be determined by a number of factors, including the balance of P2XR and P2YR expression in specific DC populations and the concentration of local eATP, ADP, and certain nucleotides. Mizumoto et al. demonstrated that CD39 expression on dendritic cells is required for the optimal stimulation of hapten-reactive T-cells[75]. CD39 is considered necessary to prevent desensitization of the P2 receptor, which is required for the optimal function of DCs. Langerhans cells are a type of epithelial dendritic cells, which are characterized by high expression levels of CD39 and show a decrease in antigen presentation ability in the absence of CD39[75]. $CD39^{-/-}$ mice have major defects in dendritic cell formation, antigen presentation, and response to semi-antigens [77]. Dwyer et al. proposed that the functional defect of $CD39^{-/-}$ dendritic cells is due to its impaired ability to initiate and maintain cell-cell contact, and that CD39 might be transferred to immune synapses to facilitate cell contact signals during antigen presentation [52]. On the contrary, Yoshida et al. showed that CD39-deficient hepatic dendritic cells exhibit more mature phenotypes, stronger responsiveness to TLR ligands, and stronger pro-inflammatory and immunostimulatory activities [78]. IL-27 can up-regulate CD39 on the surface of DC and then reducing the concentration of ATP and the activation of NLRP3 inflammatory bodies, thus limiting the differentiation of Th1 and Th17 cells and promoting immune tolerance[79]. LPS can down-regulated membrane CD39 expression via endocytosis in bone marrow-derived dendritic cells (BMDCs), which was positively associated with decreased enzymatic activity in ATP metabolism and increased eATP accumulation, leading to the activation of P2X7R, which mediated a pro-inflammatory effect[80].

CD39 and macrophage cells

Anna et al. defined macrophage extracellular purine metabolism as a novel checkpoint in macrophage cell fate decision-making and an attractive target to control pathological macrophages in immune-mediated diseases [81]. The expression of CD39 and CD73 in M2 macrophages was significantly higher than in pro-inflammatory M1 macrophages [82]. By regulating the concentration of purine in the extracellular space, the CD39/CD73 system helps fine-tune the differentiation and activity of macrophages. Moreover, the lack of CD39 can lead to the accumulation of ATP, which stimulates macrophages to release pro-inflammatory cytokines[83, 84]. Depletion of ATP by soluble CD39-like apyrase suppressed macrophage phagocytosis *in vitro*[85]. In the presence of exogenously added ATP, TLR-stimulated macrophages hydrolyze ATP via CD39 to regulate their own activation state, and the loss of CD39 expression blocks the regulatory development of macrophages and leads to fatal inflammatory responses and septic shock in mice [86]. Luiz et al. found that $CD39^{-/-}$ macrophages stimulated with LPS and ATP exhibit increased nuclear factor-kB activation and IL-1β production[87]. In another study, blocking the expression of CD39 on the surface of macrophages enhanced the production of TNF-α and IL-12 significantly but decreased the production of IL-10[87, 88].

ATP-based intercellular communication is mediated by P2X4R and P2X7R, and is a feature of pro-inflammatory macrophages. It was shown that CD39-expressing macrophages played a role in modulating the P2X7R-dependent production of IL-1β [89]. A previous report demonstrated that P2X7R activation triggers the initiation of lipid raft-dependent regulatory pathways that up-regulate CD39 activity. This mechanism could limit macrophage responses in inflammation, hence, restoring homeostasis [90]. A different study showed that cAMP up-regulates the transcription of CD39 in mouse macrophages, which is dependent on protein kinase A (PKA), phosphoinositide 3-kinase (PI3K), and extracellular signal-regulated kinase (ERK) [91].

Tumor associated macrophages (TAMs) are an important component of the tumor microenvironment. In some cancers, TAMs can form up to 50% of tumor tissue and seriously impair anti-tumor immunity[92]. It has been shown that macrophages were reduced in the lungs of tumor-bearing mice treated with anti-CD39[73]. Co-culture of healthy donor monocytes with ovarian cancer cells induced the differentiation of monocytes into anti-inflammatory M2 macrophages expressing high levels of CD73 and CD39. These ADO-producing TAMs were further demonstrated to inhibit $CD4^+$ T-cell activation *in vitro*[92].

CD39 and endothelial cells

Endothelial cells and related vascular smooth muscle cells express CD39, which plays a key role in inflammation and thrombus reduction[93]. CD39 expressed by vascular endothelial cells could limit excessive polymorphonuclear leukocyte infiltration by providing increased ADO concentrations at hypoxic and inflammation sites[60]. The arterial expression and functionality of CD39 is decreased in hypertension. The reduced ectonucleotidase activity of CD39 may enhance pathology-associated vascular damage, increase endothelial permeability and inflammation, and increase the risk of end-organ damage and thrombogenesis [94]. In tumor environment, the expression of CD39 in vascular system, especially endothelial cells, can promote tumor growth by scavenging eATP[95]. The endothelial CD39/CD73 axis regulates hemostasis by transforming the local environment from a prethrombotic state rich in ATP and ADP into an antithrombotic environment rich in ADO[96-98]. CD39 plays the role of an endothelial thromboregulator by demonstrating that CD39-transfected COS cells acquire the ability to inhibit ADP-induced aggregation in platelet-rich plasma [99-101]. Next to inhibition of platelet activation, the local release of CD39 mRNA in atherosclerotic blood vessels supports the integrity of the endothelium and inhibits extracellular nucleotide-induced smooth muscle cell proliferation[102]. Paradoxically, Aho et al. showed that elevated eATP or inhibition of CD39 activity has a protective effect against DNA damage in endothelial cells [103]. However, this effect could not be replicated in cancer cells.

CD39 and platelets

Platelets are known to express both CD39 and CD73 on their surface[104]. CD39 rapidly and preferentially metabolizes ATP and ADP released from activated platelets into AMP, thereby drastically reducing or even abolishing platelet aggregation and recruitment [105]. Unlike P2Y12R inhibitors and GPIIb/IIIa blockers, CD39 does not directly interfere with platelets; instead, it clears ADP around the platelets and maintains platelet functions [106]. A recombinant soluble form of human CD39 strongly inhibits human platelet aggregation induced by agonists [107-109]. Mice over-expressing human CD39 are resistant to arterial thrombosis induced by oxidative damage, which may be due to the decreased activation of platelet fibrinogen receptor αIIb/β3 [110]. CD39-null mice manifest an increase in circulating platelet-leukocyte heteroaggregates, which suggests the presence of heterotypic crosstalk between the coagulation process and inflammatory systems [111]. The expression of CD39 and CD73 increases significantly on the platelet surface upon stimulation with thrombin, which indicates a thrombin-mediated externalization of these ectonucleotidases[112]. Although CD39 has been considered an important inhibitor of platelet activation, Enjyoji et al. reported that CD39 knockout paradoxically leads to disordered hemostasis, and they speculate there is a dual role for adenosine triphosphate diphosphohydrolase in modulating hemostasis and thrombotic reactions.[113].

CD39 and extracellular vesicles (EVs)

Cell membrane-expressed E-NTPDases include CD39 are also found in circulating microparticles in human plasma [114]. Tumor-derived EVs, including exosomes, microvesicles, and apoptotic bodies, have been shown to inhibit anti-tumor T-cells through CD39, CD73, and ADO signaling pathways [115, 116]. Zhang et al. showed that $CD19^+$ EVs from B cells hydrolyzed ATP from chemotherapy-treated tumor cells into ADO via CD39 and CD73 vesicle-incorporated proteins, thus impairing $CD8^+$T-cell responses [117]. In microenvironments containing $CD39^+CD73^+$ exosomes, CD73 is readily available to $CD4^+CD39^+CD73^{neg}$Tregs for the production of immunosuppressive ADO[118]. Increased plasma microparticles (MP) expressing CD39 were observed in patients with liver injury, and plasma CD133 MP levels increased in a CD39-dependent manner during experimental acute liver injury [119]. $CD4^+$T-cell-derived $CD161^+CD39^+$ and $CD39^+CD73^+$

MPs contain pro-inflammatory and anti-inflammatory information, respectively, and could serve as new biomarkers for diseases, such as rheumatoid arthritis[120]. Angioni et al. demonstrated that in response to pro-inflammatory cytokines, bone marrow mesenchymal stromal cells produce EVs that are enriched in TIMP-1,CD39, and CD73, which inhibit angiogenesis by targeting both extracellular matrix remodeling and endothelial cell migration [121]. Furthermore, CD39 expressed in EVs derived from endothelial cells influences thrombus progression [23, 122].

The functions of CD39 in immune-related diseases

CD39 and sepsis

Sepsis is caused by an imbalance in the host immune response to infection, and it can lead to life-threatening organ dysfunction. CD39 attenuates sepsis-associated liver injury by scavenging eATP and ultimately generating ADO. Boosting of CD39 can suppress P2X7R response and trigger adenosinergic signaling to limit systemic inflammation and restore liver homeostasis during the acute phase of sepsis[87]. CD39 enhancement also exhibited an enhancing effect on the ability of renal tubular epithelial cells to resist LPS-induced damage, improve cell viability and apoptosis, and inhibit NLRP3 inflammasome activation [123]. Increase $CD39^+$ Tregs was associated with a poor prognosis for sepsis patients, which suggests that the $CD39^+$ Treg level is a potential biomarker for predicting the outcome of sepsis in patients [124]. CD39 affects the pro-inflammatory response of sepsis mediated by immune cells and endothelial cells. Cohen et al. showed that TLR-stimulated macrophages modulate their activation state by increasing the synthesis and secretion of ATP[86]. Macrophages lacking CD39 are unable to transition to a regulatory state and consequently continue to produce inflammatory cytokines. Furthermore, the macrophage-specific expression of CD39 is critical for preventing lethal hyperinflammatory responses to LPS *in vivo* [86] . Overexpression of CD39 in the endothelium efficiently abrogated the initial phases of ATP secretion in response to LPS endotoxin and markedly inhibited IL-1α release [125]. CD39 expression is up-regulated during sepsis [126, 127]. Bao et al. indicate that ADO, the ADO A_2AR agonist, E2F-1, and CREB are potential factors contributing to the increased expression of CD39 and CD73 on Treg cell surface during sepsis [128]. It was reported miR-155 induces an increased percentage of $CD39^+$ Tregs and thus immunosuppression in sepsis patients [129].

CD39 and inflammatory bowel diseases (IBD)

IBD, including Crohn's disease and ulcerative colitis, is characterized by chronic relapsing intestinal inflammation[130]. The expression of CD39 on endothelial cells or immune cells integrates the dynamic balance of immunity, thereby controlling hemostasis and immunobiological responses, which appear disrupted in IBD [131]. Decreased abundance of CD39-expressing intraepithelial T-cells is common in IBD patients[132]. CD39 expression by Treg was lower in active inflammatory bowel disease and increased significantly after treatment in responders [133]. Single nucleotide polymorphisms (SNPs) adjacent to the CD39 promoter region have been associated with low levels of CD39 mRNA expression which confer susceptibility to Crohn's disease [131]. The number of SupTh17 cells is diminished in Crohn's disease patients; however, they express higher levels of CD39 and effectively generate eAMP and ADO and, hence, can potently suppress effector T-cell responses via $A_{2A}R$ [134]. In the mouse model, changes in ADO production, such as those associated with CD39 or CD73 gene deletions, lead to a more severe course of experimental colitis [131, 135]. Paradoxically, Kunzli et al.[136] found that 2,4,6-trinitrobenzene sulphonic acid colitis was attenuated in CD39-null mice, and impaired adaptive cellular immune reactivity of CD39-null environment appears protective in hapten-mediated Th1-type colitis.

CD39 and ischemia-reperfusion injury (IRI)

In CD39 and CD73 knockout mice, organ damage and inflammation caused by ischemia in the brain [84], heart[137-139], kidney [140, 141], liver [142, 143], intestine[144, 145] and hindlimb[146] were more severe than those in the corresponding wild-type mice. Studies have shown that boosting of CD39 can reduce organ damage caused by IR [147-150]. The protective effect observed in CD39 over-expressing mice on myocardial ischemia has been shown to work through the $A_{2B}R$ dependence mechanism [151]. This protective effect was also observed in pigs over-expressing CD39[152]. A variety of immune cells are involved in the protective effect

of CD39 on IRI. *In vitro* activated Tregs ameliorated IRI through a CD39-dependent mechanism[153]. In addition, deletion of CD39 in NK cells inhibits their activation and protects partial hepatic IRI by diminishing IFN-γ production [67].IRI is inherent in organ transplantation and has an impact on both short-term and long-term outcomes of the transplantation. CD39 expression in mouse liver conventional myeloid DCs (mDCs) limits the pro-inflammatory activity of mDCs and provides protection against the innate immune response against liver transplant IRI [78]. Furthermore, liver grafts from CD39-over-expressing mice have been shown to be protected from IRI due to the reduced numbers of resident $CD4^+$ T-cells [154]. The expression of CD39 can be up-regulated by hypoxia and specificity protein 1 (Sp1)-mediated induction of cardiac CD39 during myocardial ischemia [24].

CD39 and allergic diseases

CD39 expressed in Tregs is involved in a variety of allergic diseases. Tregs can suppress contact hypersensitivity reactions through a CD39, adenosine-dependent mechanism by blocking leukocyte adhesion to endothelium [155]. Tregs remove eATP by CD39 and, therefore, abrogate the shedding of CD62L, leading to defective sensitization in contact hypersensitivity reactions[156]. CD39 mediates the protective role of $CD4^+Foxp3^+$Tregs in allergic airway inflammation by regulating ATP and ADO levels[157]. In allergic asthma, increased Tc2 and Tc17 may be related to insufficient $CD39^+$Tregs[158]. Wang et al. found that the plasticity of Tregs transforming into IL-$17^+Foxp3^+CD4^+$T-cells, the reduced frequency of $CD39^+$ Tregs, and the less effective suppression of IL-17 produced by residual $CD39^+$ Tregs leads to an imbalance of Th17 and Tregs in asthma [159]. CD39 expression was down-regulated in allergic asthma and was positively correlated with serum IL-4, IL-17A, and GATA3 expression and negatively correlated with serum TGF-β and Foxp3 expression [160]. CD39 deficient DCs exhibit limited capacity to induce Th2 immunity in a DC-driven model of allergic airway inflammation *in vivo* [161]. Li et al. demonstrated that a reduction in CD39 expression may be associated with the development of allergic airway inflammation and that apyrase alleviates airway inflammation by decreasing the chemotactic migration of DCs towards eATP [162].

CD39 and SLE

SLE patients exhibit increased levels of ATP which binds to P2XR resulting in activation of the inflammasome and consequent release of cytokines associated with disease pathogenesis[163]. CD39 expression in lymphocytes was increased in SLE patients, suggesting a compensatory mechanism to help control inflammation [164]. However, Loza et al. showed decreased CD39 expression in Tregs from SLE patients, demonstrating a defect restricted to this subset of cells[165].

CD39 and diabetes

Children diagnosed with type 1 diabetes (T1D) show signs of low $CD39^+/CD45RA^+$ Treg cells, which may indicate loss of its suppressive function [166]. Lower expression of CD39 in memory Tregs has been reported as a potential mechanism explaining the defective suppressive function of Tregs in T1D patients [167]. The percentages of $CD39^+$ and $CD39^+CD19^+$ cells were associated with glycated hemoglobin and fasting plasma glucose levels. $CD39^+$ cells might have a balancing regulatory role in the inflammatory process observed in patients with type 2 diabetes (T2D)[168]. The T2D patients with obesity showed significantly lower percentages of $CD39^+$ Treg cells and a negative correlation between $CD39^+$ Treg cells and weight, and body mass index was detected[169]. Mesenchymal stem cells from human gingiva can migrate to the pancreas and local lymph nodes and act through the CD39/CD73 pathway to regulate effector T-cells. Infusion of GMSCs significantly controlled blood glucose levels, delayed diabetes onset, and ameliorated pathology scores in pancreas[170]. CD39 KO mice developed diabetes more rapidly and with higher frequency than WT mice, while CD39 overexpressing mice were protected. Furthermore, adoptive transfer experiments indicated that tissue-restricted overexpression of CD39 conferred robust protection, suggesting that this may be a useful strategy to protect islet grafts from T cell-mediated injury[171].

CD39 and tumor

CD39 is expressed in tumor cells and tumor-infiltrating immune cells and affects tumor development in vari-

ous interrelated ways. CD39 is up-regulated in a variety of human cancers, such as leukemia and head, neck, colorectal, liver, and gastric cancers, and the expression level of CD39 is often related to the stage and severity of a disease[172-178]. CD39 is highly expressed on tumor-infiltrating immune cells, particularly effector T-cells and Tregs. CD39 has been shown to be highly expressed in tumor-infiltrating $CD8^+$ T-cells in a variety of human tumors, including renal cell carcinoma, gastric cancer [39], lung cancer, colorectal cancer, breast cancer [40] and head and neck cancer [41]. Tumor-infiltrating $CD39^{high}CD8^+$ T-cells increase with tumor growth, and exhibit features of exhaustion, including decreased TNF, IL-2, and IFN-γ production as well as increased expression of many inhibitory/checkpoint receptors, such as programmed cell death 1, T cell immunoglobulin and mucin-do-main-containing molecule 3, Lymphocyte-activation gene 3, T cell immunoglobulin and ITIM domain, and 2B4 [40]. Tregs mediate immunosuppression through several mechanisms, including CD39-dependent production of ADO. Transcriptional profiling of Tregs revealed a substantial number of candidate genes with the potential to mediate suppression, including the highly expressed CD39 [36]. CD39 was found expressed in $CD8^+$ Tregs, and CD39 expression correlated with suppression activity mediated by $CD8^+$Tregs [179]. Hu et al. identified a novel $CD39^+$ γδTreg in human colorectal cancer patients[35]. Furthermore, the $CD39^+$γδTregs are the predominant regulatory T-cells observed in colorectal cancer patients, with a more potent immunosuppressive activity than $CD4^+$ or $CD8^+$ Tregs, and acting through the ADO-mediated pathway [35]. Tumor-infiltrating CD39+ Tregs accumulate in colon tumors and exhibit high expression of surface molecules related to immunosuppression, such as inducible co-stimulator, programmed cell death protein ligand 1, and cytotoxic T lymphocyte associated antigen 4. CD39+ Tregs also show potent suppressive capacity on proliferation and IFN-γ secretion by conventional T-cells [37]. In patients with colon cancer, circulating Tregs express high levels of CD39, which contributes to the reduced transendothelial migration of effector T-cells into tumors [180]. Lower baseline levels of circulating Tregs ($CD4^+CD25^{high}CD39^+$) in melanoma patients were associated with better relapse-free survival[181]. There are few studies on the role of CD39 in anti-tumor immunity mediated by NK cells. Zhang et al. found that CD39 was expressed in tumor-infiltrating NK cells. Furthermore, POM-1 suppressed experimental and spontaneous metastases in four tumor models, and its anti-metastatic activity was completely abrogated in NK-cell-depleted mice [72]. The proportion of NK cells significantly decreased, but CD39 was obviously up-regulated in NK cells from cancerous tissues compared to paired peripheral blood in esophageal squamous cell carcinoma patients. Furthermore, tumor-infiltrating $CD39^+$ NK cells exhibited a phenotype of functional impairment and were correlated with poor prognosis [182]. Myeloid-derived suppressor cells (MDSCs) have been recognized as one of major contributors to tumor-induced immunosuppression [183]. MDSCs in peripheral blood and tumor tissues from patients with non-small cell lung cancer were shown to express CD39. Tumor TGF-β stimulated CD39 and CD73 expression in MDSCs, thereby inhibited T cell and NK cell activity, and protected tumor cells from the cytotoxic effect of chemotherapy through ectonucleotidase activity [184]. Compared to other myeloid cells present in the blood of patients with colorectal cancer, gMDSCs that expressed high levels of PD-L1, CD39, and CD73 exerted a robust immunosuppressive activity,[185]. Metformin treatment blocks the suppressive function of MDSCs in patients with ovarian cancer by down-regulating the expression and ectoenzymatic activity of CD39 and CD73 on monocytic and polymononuclear MDSC subsets [186]. In addition, the growth of multiple syngeneic tumors is reduced in global CD39 gene-targeted mice [95, 187, 188]. Similarly, CD39-deficient mice are resistant to the formation of metastasis in models of disseminated disease or spontaneous metastasis[72, 189]. In a dissemination liver metastasis model, MC-26 cell line-derived hepatic metastases grew significantly faster in CD39 over-expressing transgenic mice when compared to those in CD39-deficient mice [190]. Additionally, pharmacological blockade of CD39 activity with an antagonistic antibody or the inhibitor POM-1 was shown to significantly limit tumor growth and improve anti-tumor immunity [187, 189, 191, 192].

Perspectives

CD39 has correlation to various immune cells and plays vital roles in multiple physiological and pathological processes. In particular, CD39 is considered to be a new marker of T-cell exhaustion and an immune checkpoint target for cancer treatment. Targeting of both the A2aR and CD73 has been shown to be efficacious in preclinical cancer models. However, unlike treatment targeting the downstream production or

function of ADO, inhibition of CD39 not only limits the production of ADO, but also prevents the degradation of eATP. So CD39 is uniquely positioned in ATP-adenosine axis. Monoclonal antibodies targeting CD39 have been developed and were demonstrated to significantly reduce tumor growth in preclinical cancer models, including as single agent[64]. Furthermore, targeting CD39 in combination with other anticancer strategies, including immunotherapies, and chemotherapy is another promising combination. It was shown recently that anti-CD39 turns "cold" anti-PD1 resistant tumors "hot" and sensitive [192], so the combination therapy of CD39 and PD-1 is expected. However, not all extracellular ADO was inhibited by anti-CD39, and other adenosine production pathways may also be involved in this process. Actually, AMP can be also obtained through the transformation of NAD^+ by CD38 and CD203a[9-12]. So combination therapy targeting multiple adenosine-generating enzymes may be more effective. Furthermore, CD39 has vast therapeutic potential in a wide variety of disorders. However, considering the extensive physiological effects of eATP and ADO and the opposite effect of CD39 in some diseases, therapy targeting CD39 requires more in-depth research and individualized treatment.

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Competing interests

The authors declare no potential conflicts of interest.

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