The Role of Purinergic Signaling in Heart Transplantation

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Heart transplantation remains the optimal treatment option for patients with end-stage heart disease. Growing evidence demonstrates that purinergic signals mediated by purine nucleotides and nucleosides play vital roles in heart transplantation, especially in the era of ischemia-reperfusion injury (IRI) and allograft rejection. Purinergic signaling consists of extracellular nucleotides and nucleosides, ecto-enzymes, and cell surface receptors; it participates in the regulation of many physiological and pathological processes. During transplantation, excess adenosine triphosphate (ATP) levels are released from damaged cells, and driver detrimental inflammatory responses largely *via* purinergic P2 receptors. Ecto-nucleosidases sequentially dephosphorylate extracellular ATP to ADP, AMP, and finally adenosine. Adenosine exerts a cardioprotective effect by its anti-inflammatory, antiplatelet, and vasodilation properties. This review focused on the role of purinergic signaling in IRI and rejection after heart transplantation, as well as the clinical applications and prospects of purinergic signaling.

Keywords: purinergic signaling, ATP, adenosine, ischemia reperfusion injury, heart transplantation

INTRODUCTION

Heart transplantation is the ideal therapeutic approach for patients with end-stage heart disease (1), with the number of heart transplants performed each year continuing to increase globally throughout the past decade (2). Due to advances in surgical techniques, organ preservation methods, and application of novel immunosuppressants, tremendous progress has been achieved in the field of heart transplantation. The International Society of Heart and Lung Transplantation reported that, currently, more than 6,000 heart transplants are performed worldwide each year (3). Additionally, according to the latest data from 481 adult heart transplant centers and 210 pediatric heart transplant centers around the world, the median survival times of adult and child heart recipients are 12.1 years and 24.5 years, respectively (3–5). However, severe complications, such as rejection, infection, and post-operative malignancy have severely hindered the development of heart transplantation as a treatment option, with an annual mortality rate of approximately 3–4% (6). Furthermore, the heart is more vulnerable to ischemia-reperfusion injury (IRI) than the liver or kidney, which limits clinical preservation time to 4–6 hours, resulting in a critical shortage of donor hearts (7). Therefore, a better understanding of the factors that negatively affect heart transplantation is of utmost importance.

Purinergic signaling is a kind of evolutionarily conserved communication pathway between cells, and participates in the regulation of many physiological and pathological processes (8, 9). It consists

of extracellular nucleotides and nucleosides, ecto-enzymes, and cell surface receptors (10). Recent evidence shows involvement of these nucleotides and cell surface receptors in both IRI and rejection in heart transplantation (11). In addition, studies have indicated that purinergic signaling elements were potential targets for preventing inflammation and rejection. Specifically, adenosine plays a significant role in the diagnosis and treatment of complications following heart transplantation. The strategy of the study was illustrated in **Figure 1**. In this review, we introduced the purinergic signaling molecules, the ecto-nucleotidases, the purinergic receptors and their role in IRI and rejection after heart transplantation. Briefly, adenosine triphosphate (ATP) promotes acute injury and inflammation after heart transplantation, whereas adenosine has anti-inflammatory and protective effects in IRI and donor heart preservation, as well as function on immune cells and promote tolerance after transplantation. Therefore, balancing ATP and adenosine using ATP hydrolysis, modulating purinergic receptors, and increasing adenosine level are promising strategies for reducing posttransplant inflammation, rejection, and graft failure and prolonging the graft survival. This review aimed to present in-depth information on purinergic signaling in heart transplantation.
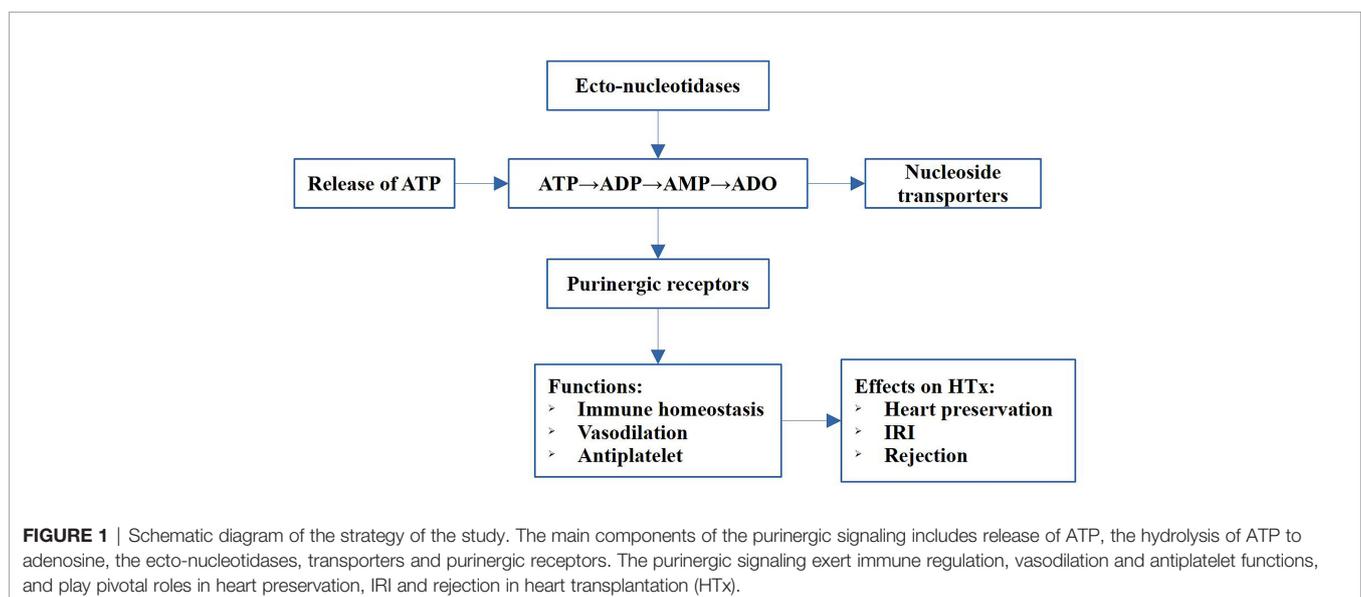
PURINERGIC SIGNALING MOLECULES

Extracellular purinergic signaling molecules, consisting of ATP, adenosine diphosphate (ADP), and adenosine (**Figure 2**), play significant roles in the transplantation process. In this process, ATP is an important priming factor. ATP was first conceived as a neurotransmitter in 1972 (12); it gradually gained further acceptance as different receptor subtypes were discovered (13). Currently, ATP has been shown consistently to be an important extracellular ligand for autocrine signal transduction, cell-to-cell communication, and neurotransmission (10). ATP is released

during cell lysis or by means of specialized ATP release mechanisms involving exocytosis, transporters (such as ATP-binding cassette transporter superfamily) or ATP-permeable channels. Extracellular ATP (eATP) levels are minimal under normal physiological conditions. However, large amounts of ATP and ADP are released when cells or tissues are damaged during IRI or during acute rejection after transplantation. Additionally, inflammation-induced ATP released by endothelial cells and platelets overwhelms ATP metabolism. High levels of ATP are important damage-associated molecular patterns (DAMPs) that promote chemotaxis and excitation of immune cells within hours (14). Ecto-nucleosidases rapidly dephosphorylate eATPs to ADP, adenosine monophosphate (AMP), and finally adenosine (15–17). Adenosine molecules are transported intracellularly or extracellularly, once they are synthesized by nucleoside transporters, including the concentrative nucleoside transporters (CNTs) and the equilibrative nucleoside transporters (ENTs). CNTs comprise three members (CNT1-3) and facilitate adenosine transport against its concentration gradient, both intracellularly and extracellularly (18). ENTs, including ENT1-4, which transport adenosine across the cell membrane, depend on the concentration gradient (19). Adenosine molecules function by cytoprotection and protect cell damage from ischemia and hypoxia. Moreover, adenosine is widely used as antiarrhythmic drugs and an important component of organ preservation solutions for heart transplantation.

ECTO-NUCLEOTIDASES

Ecto-nucleotidases are indispensable key factors in the process of purinergic signal transduction. They regulate the hydrolysis of ATP to ADP, AMP, and adenosine, thereby controlling the balance of ATP and adenosine (**Figure 2**). The primary ecto-nucleotidases involved in regulating the process of ATP hydrolysis to adenosine include the ecto-nucleoside triphosphate diphosphohydrolase

FIGURE 1 | Schematic diagram of the strategy of the study. The main components of the purinergic signaling includes release of ATP, the hydrolysis of ATP to adenosine, the ecto-nucleotidases, transporters and purinergic receptors. The purinergic signaling exert immune regulation, vasodilation and antiplatelet functions, and play pivotal roles in heart preservation, IRI and rejection in heart transplantation (HTx).
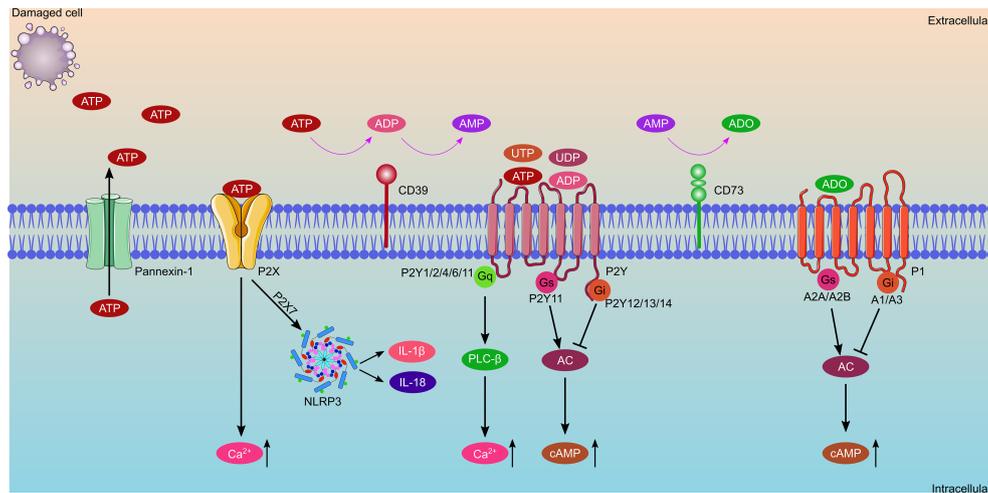
FIGURE 2 | Schematic diagram of purinergic signaling components, which consist of extracellular nucleotides and nucleosides, ecto-enzymes, and cell surface receptors. ATP is released from damaged cells or through the Pannexin-1 channel, and then is rapidly dephosphorylated to ADP and AMP by CD39, with AMP further catalyzed to adenosine by CD73. Purinergic receptors consist of P1 receptors and P2 receptors. P1 receptors bind with adenosine, which consist of A1, A2A, A2B and A3 receptors. A1Rs and A3Rs are coupled with Gi proteins and inhibit adenylate cyclase, whereas A2ARs and A2BRs coupled with Gs proteins and stimulate adenylate cyclase. P2 receptors consist of P2X and P2Y receptors, of which, P2XRs bind with ATP only, while P2YRs can bind with ATP, ADP, UTP, and UDP. Activation of P2XRs increases the concentration of intracellular Ca^{2+}. Activation of P2YRs causes a change in the concentration of intracellular Ca^{2+} or cAMP.

family (E-NTPDases), ecto-5'-nucleotidase (NT5E/CD73), ecto-nucleotide pyrophosphatases (E-NPPases), adenosine deaminase, NAD glycohydrolase, CD38/NADase, alkaline phosphatase (AP), adenylate kinase (AK), and nucleoside diphosphate kinase (10). E-NTPDases are widely distributed in all tissues and contain eight members (E-NTPDase1-8). Four E-NTPDases (1–3, 8) are surface-located; among which, CD39 (NTPDase 1) is the most representative ecto-nucleotidases for ATP hydrolysis. CD39 is primarily expressed on lymphocytes and resting vascular endothelial cells, and its main function is to break down extracellular ATP into ADP and AMP. CD73, mainly expressed on follicular dendritic cells (DCs), T lymphocytes, and B lymphocytes, further catalyzes extracellular AMP into adenosine. Finally, adenosine can be degraded into inosine by adenosine deaminase or transported into the cell by a nucleoside transporter (20–22). Previous studies have revealed that the combination of CD39 and CD73 converts ATP to adenosine much faster than E-NTPDase2/CD73 and E-NTPDase8/CD73. Therefore, the theory of the CD39-adenosinergic axis was proposed (23, 24). In the field of heart transplantation, CD39 and CD73 are vital regulators of eATP and adenosine balance, and the shift in the conversion of ATP to adenosine is important for anti-inflammation, suppression of organ transplantation rejection, and promotion of graft survival (25). Zhong et al. (26) engineered CD39/CD73 bifunctional fusion proteins, which are expected to be a therapeutic agent for scavenging ATP and producing adenosine for anti-inflammatory and immunomodulatory functions. E-NPPs have several substrates, including ATP, ADP, NAD+, and lysophosphatidylcholine (LPC). Currently seven members (NPP1-7) have been identified, among which NPP1 and NPP2 were well investigated. NPP1 is mainly expressed on inflammatory cells, whereas NPP2 is expressed on

inflammatory and tumor cells. The main function of NPP2 is to convert LPC to lysophosphatidic acid (LPA) (27). APs are the only ectoenzymes that can hydrolyze ATP, ADP, and AMP. Currently, four APs have been identified, and they are named according to their tissue distribution characteristics: placental AP (PLAP), germ-cell AP, intestinal AP (IAP), and the tissue-nonspecific form of AP (TNAP). TNAP is mainly involved in bone mineralization, and disturbance of phosphate metabolism in chronic kidney disease (28, 29). In addition, AK is the critical enzyme responsible for cellular adenine nucleotide homeostasis through the catalysis of the reaction $2ADP \leftrightarrow ATP + AMP$. It is also involved in extracellular adenine nucleotide metabolism by minimal ecto-expression or released from cells into the extracellular space (30).

THE PURINERGIC RECEPTORS

Purinergic receptors are distributed widely throughout different organs, such as the brain, kidney, heart, and blood vessels. Part of earlier work examining extracellular purinergic signaling was performed on the cardiac system. Purinergic receptors in the heart are primarily distributed in the myocardium and coronary vascular smooth muscle, as well as cardiac adrenergic and cholinergic nerve terminals (31). ATP binds to purinergic receptors once they are released into the extracellular space. Purinergic receptors currently consist of two main families: adenosine receptors (P1 receptors) and purine nucleotide (ATP and ADP) receptors (P2 receptors) (**Figure 2**) (10). P1 receptors were first characterized and cloned in the early 1990s (32). They are a class of G-protein-coupled receptors, including A1, A2A, A2B, and A3 receptors (33). P2 receptors consist of two subtypes:

the ion-channel receptor P2X and G-protein-coupled receptors P2Y (P2Y1, P2Y2, P2Y4, P2Y6, P2Y11, P2Y12, P2Y13, and P2Y14) (34, 35). Generally, eATP induces an inflammatory response through P2 receptors, such as P2X7 and P2Y2 receptors. Conversely, levels of adenosine rise along with ATP hydrolysis, which exerts anti-inflammatory functions through P1 receptors such as A2A and A2B receptors (36–38).

P1 receptors contain four receptor subtypes that have been named by the order of their discovery as A1, A2A, A2B, and A3 receptors. Among these receptors, A1 and A2A receptors are far more sensitive to adenosine and its agonists than the others, as the former works in the nanomolar range, whereas the latter works in the micromolar range (39). P1 receptors are G-protein-coupled receptors that are composed of two domains—the extracellular domains (N-terminus) that comprise specific glycosylation sites and extracellular loops, and the intracellular domains (C-terminus) with phosphorylation and palmitoylation sites and intracellular loops (33). A1 and A3 receptors are coupled with Gi proteins, and inhibit adenylate cyclase. Conversely, A2A and A2B receptors are coupled with Gs proteins, and stimulate adenylate cyclase (40). Recent studies have demonstrated that A1 receptors are involved in renal fibrosis (41), hepatocyte glucose metabolism (42), cerebral ischemia-reperfusion-induced cognitive impairment (43), and chronic heart failure (44). A2A receptor agonists had a protective effect on IRI in the kidney (45), brain (46), liver (47) and heart (48). Additionally, A2A receptor agonists were used to inhibit COVID-19-induced lung inflammation and thrombogenesis (49). Both A2B and A3 receptors have been reported to have protective effects on IRI (50–52) and show infarct-sparing effects in a myocardial infarction model in mice (53). Additionally, A2B receptors have been identified as biomarkers for lung cancer diagnosis and prognosis (54), whereas A3 receptors have been shown to participate in tumorigenesis and chemotherapy (55, 56).

P2X receptors are ligand-gated receptors and consist of seven subtypes (P2X1–7) (57). Generally, P2X receptors show a lower affinity for ATP than P2Y receptors (36). A higher concentration of ATP is needed to open channels (58). ATP binding with P2X receptors causes Na^+, K^+, and Ca^{2+} cations to flow across the cell membrane, resulting in specialized functions (59). Low levels of P2X1 receptors were detected on cardiac myocytes, with P2X1 receptors mainly expressed on vascular smooth muscle, causing arterial contractions when activated by ATP (60, 61). Additionally, P2X1 receptors are expressed on platelets, mediating shape changes, and resulting in aggregation (62). Furthermore, P2X1 receptors have been reported to regulate IL-22 and are involved in efficient liver regeneration (63). P2X3 and P2X4 receptors are involved in myocardial ischemic injury and neuropathy in type 2 diabetes (64–67). Whereas few studies have examined P2X5 and P2X6 receptors, several studies have explored how P2X7 receptors promote IRI and play an important role in immunity and inflammation (68).

P2Y receptors are metabotropic receptors that can bind with ATP, ADP, uridine triphosphate (UTP), and uridine diphosphate (UDP). Some P2Y receptors (P2Y1, P2Y2, P2Y4, P2Y6, and P2Y11) couple with Gq proteins and activate phospholipase C-β, leading to an increase in intracellular Ca^{2+} level; whereas others (P2Y12, P2Y13, and P2Y14) couple with Gi proteins and inhibit adenylyl cyclase, resulting in a decrease in cAMP level (69). P2Y receptors play a wide range of regulatory roles, such as in tumor progression (70), platelet aggregation and thrombosis (71), immune response (72), obesity and metabolism (73), pain transmission (74), organ fibrosis (75), and IRI (76). P2Y receptors have been shown to be activated by DAMPs, such as ATP and UTP, and recruit surrounding neutrophil granulocytes to mediate the inflammatory response. Conversely, P2Y receptors on phagocytes upregulate and help to clear apoptotic cells (77–79). P2Y receptors are involved in bacterial, viral, and parasitic infections. Although P2Y12 receptors were reported protective in sepsis; however, other studies have indicated that P2Y12 receptors induce lung injury (80–82). Furthermore, P2Y2 receptors have been reported to be cardioprotective, because activation of P2Y2 receptors causes reduced inflammation, which, in turn, reduces infarct size and improves cardiac function (83).

Currently, P2Y receptors that are reportedly involved in myocardial infarction include P2Y1, P2Y4, P2Y6, P2Y11, and P2Y13 receptors (82, 84–88). P2Y receptors have been thoroughly studied in thrombosis, among which, P2Y1 and P2Y12 receptors expressed on platelets can be activated by eATP and ADP, leading to the recruitment of platelets to the thrombus. The P2Y12 receptors are key players in thrombosis, and inhibition of P2Y12 receptors is widely used as a clinical thrombosis prevention strategy, with primary preparations, such as clopidogrel and ticagrelor (89, 90).

EFFECT OF PURINERGIC SIGNALING ON IRI

IRI is an inevitable event that occurs during heart transplantation, leading to delayed graft function, rejection, and decreased graft survival. Donor hearts are particularly more vulnerable to IRI than livers and kidneys, which can only be safely preserved for 4–6 hours using principally static cold storage methods in clinical practice (91). Purinergic signaling plays a vital role in IRI (**Figure 3**). During ischemia, cellular ATP is progressively exhausted and resynthesized *via* aerobic metabolism, which produces a lower level of ATP and rapidly leads to acidosis and necrosis of the myocardium (92). The resultant low level of cellular ATP cannot maintain cellular ion and membrane homeostasis, leading to cell death. During reperfusion, cellular ATP is recovered, accompanied with a reactive oxygen species burst and Ca^{2+} overload, causing cell damage and subsequent release of DAMPs and inflammatory responses. Extracellular ATP is a ubiquitous and an extremely efficient DAMP molecule that promotes inflammation following IRI (93, 94). Extracellular ATP exacerbates detrimental inflammatory responses largely through purinergic P2 receptors on the surface of immune cells (95). P2X7 receptors are mostly involved in inflammatory processes among purinergic
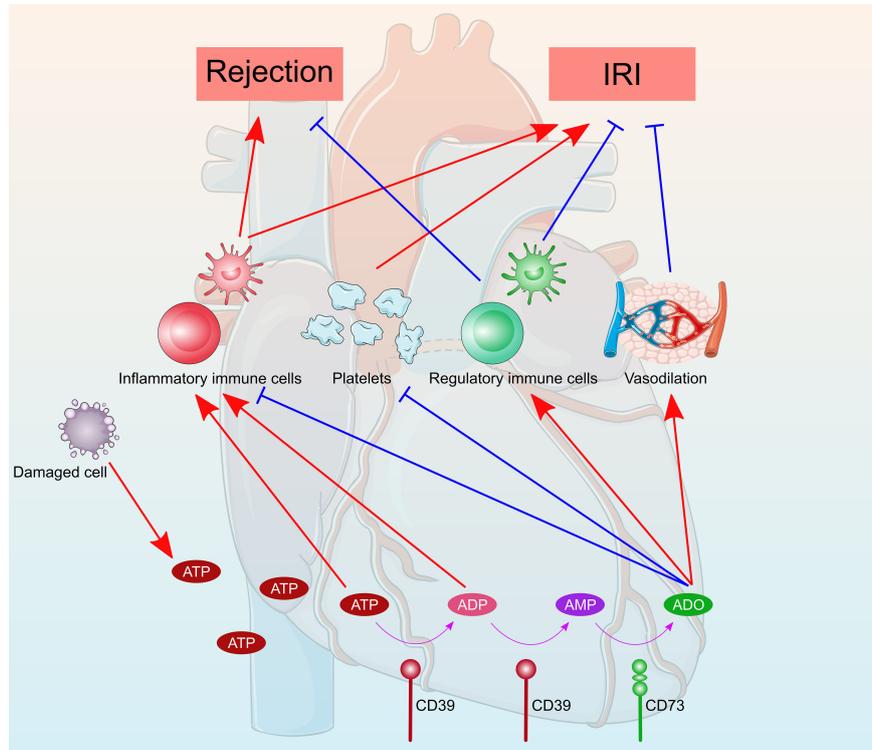
FIGURE 3 | Schematic diagram of the role of purinergic signaling in heart transplantation. ATP were released from damaged cells during the transplantation process. ATP were converted into ADP and AMP by CD39 and then catalyzed to adenosine by CD73. Extracellular ATP and ADP promote inflammatory responses and exacerbate detrimental rejection and cardiac ischemia reperfusion injury. Whereas, adenosine generally has anti-inflammatory and immunosuppressive properties, which protect the heart from rejection and ischemia reperfusion injury. Furthermore, the antiplatelet and vasodilatory effects of adenosine attenuate heart rejection and ischemia reperfusion injury.

P2 receptors, which triggers NLRP3 inflammasome activation and subsequent release of proinflammatory cytokines, such as IL-1β and IL-18 (96). P2X7 receptors mediate the NLRP3 inflammation pathway, promoting myocardial damage and cardiac fibrosis, thus leading to impaired cardiac function (97–100). Whereas ischemia preconditioning or postconditioning by activation of P2X7 receptors has been reported to be protective in cardiac IRI, where the cardioprotective effect was facilitated through the release of sphingosine-I-phosphate and adenosine *via* pannexin-1 and the P2X7 receptor-formed channel (101–103). Contrary to P2X receptors, emerging evidence has revealed a cardioprotective role of P2Y receptors, which has been extensively reviewed elsewhere (76). Notably, P2Y12 receptor antagonists (i.e., antiplatelet agents) have shown promising myocardial protection independent of platelet antiaggregatory effects in cardiac IRI and translated clinical studies (104, 105).

The cardioprotective effect of adenosine has long been recognized, and all four adenosine receptors have been implicated. Adenosine is used as an additive in blood cardioplegia to induce a more rapid polarized cardiac arrest *via* the A1 receptors (106, 107). A polarized membrane potential during initial reperfusion may minimize intracellular Ca^{2+} overload and reduce cardiac IRI. Utilize of adenosine-lidocaine based cardioplegia or preservation solution

showed superior preservatory effect of donation after circulatory death heart grafts in preclinical models (108–110). Additionally, adenosine is known to induce vasodilation by binding to A2A and A2B receptors (111–113). A2A and A2B receptor-induced vasodilation attenuates myocardial ischemia by increasing nutrients/oxygen supply and blood flow (114–116). In addition to vasodilation, A2B receptors contribute to cardioprotection by stabilizing the rhythm protein Per2 in an HIF-dependent manner (114, 117). A1 receptors signaling protects ischemic hearts by limiting oxidant damage; however, the precise mechanism underlying A3 receptors-induced cardioprotection remains to be elucidated (118, 119). The ecto-nucleotidases CD39 and CD73, which convert ATP to adenosine, have been demonstrated to be protective in cardiac IRI (120–124). Furthermore, the antiplatelet effect of CD39 also plays a protective role in cardiac IRI by preventing thrombosis. A single-chain antibody-CD39 fusion protein, targeting activated platelets by specifically binding to activated glycoprotein (GP)IIb/IIIa, holds strong promise for effective protection from cardiac IRI (125). AK are abundant phosphotransferase enzymes that catalyze the interconversion of adenine nucleotides (ATP, ADP, and AMP), and thus regulate the adenine nucleotide homeostasis in different intracellular compartments. AK1 deficiency in the heart exacerbates cardiac

IRI and compromises post-ischemic coronary reflow as a consequence of reduced adenosine (126, 127). Modest elevation of AK1 protects the heart against cardiac IRI by underpinning myocardial adenine nucleotides homeostasis.

EFFECT OF PURINERGIC SIGNALING ON HEART ALLOGRAFT REJECTION

Allograft rejection, the process by which a recipient's immune system recognizes and exerts immune response to the donor heart, is a major concern post-transplantation. Purinergic signaling plays a pivotal role in the alloimmune response (**Figure 3**), which is a complex process that results from the interplay among multiple different cell types, including lymphocytes, monocytes, macrophages, and dendritic cells. Following transplantation, ATP is rapidly released from damaged or stressed cells *via* Panx1 channels, vesicular release, or cell rupture. eATP acts as a "danger signal" to promote proliferation and activation of immune cells by binding to excitatory ATP receptors, including inotropic P2X receptor and metabotropic P2Y receptor subtypes. Several recent studies have recognized that eATP accumulation and subsequent purinergic signaling play significant roles in heart allograft rejection. Upregulation of P2X7 receptors on graft-infiltrating lymphocytes have been observed in cardiac-transplanted humans and mice, and targeting of the P2X7 receptors with periodate-oxidized ATP promoted long-term cardiac transplant survival in murine cardiac transplantation models (128). Blocking P2X7 receptors signaling by oxidized ATP inhibited M2 macrophage infiltration, prevented transplant vasculopathy, and induced long-term heart allograft survival in a murine model of chronic rejection (129). Although eATP was considered to promote immune responses and allograft rejection, the protective effects of ATP receptors on allograft rejection have been reported. Loss-of-function mutation of P2X7 receptors disrupted NLR Family Pyrin Domain Containing 3 (NLRP3)-mediated Th2 programming, leading to excessive Th17 generation and subsequently poor cardiac allograft outcomes (68). Pharmacologic P2Y11 receptors stimulation protected heart allograft from ischemia/reperfusion and rejection injuries, and prolonged cardiac allograft survival (130, 131).

In the extracellular space, ecto-nucleotidase hydrolyzes ATP to ADP, and subsequently to AMP and adenosine. Adenosine binds to G protein–coupled P1 receptors, and generally have anti-inflammatory and immunosuppressive properties. Both CD39 and CD73 have been implicated in modulation of heart allograft rejection. Overexpression of CD39 or administration of soluble CD39 improved cardiac xenograft survival with reduced vascular thrombosis (132–134). In a mouse cardiac transplantation model, CD73 deficiency in either donors or recipients promoted inflammatory cascades, resulting in reduced cardiac allograft survival and vasculopathy development (135). Hu et al. (136) reported that CD73 expression was critical for mesenchymal-like endometrial regenerative cell-mediated cardiac allograft protection.

CLINICAL APPLICATION AND PROSPECTS

Studies on the molecular mechanisms of extracellular nucleoside signals provide several therapeutic targets for human disease. Any participants of purinergic signaling, such as the main purines (ATP, ADP, AMP, and adenosine), key enzymes (CD39 and CD73), and purinergic receptors (four P1 receptors, seven P2X receptors, and eight P2Y receptors) could be potential targets for human disease treatment. One promising strategy is to target the release of ATP during damage. For example, blocking the Panx1 channel can reduce the release of ATP to limit the downstream inflammatory response and activation of immune cells. The Panx1 inhibitor carbenoxolone has been reported to improve islet transplantation outcomes (137), ameliorate acute pain of rats (138), and reduce brain and lung IRI (139, 140). However, studies on carbenoxolone in heart transplantation are currently unavailable. Another well investigated ATP release inhibitor is clodronate, which is reported to improve renal IRI (141) and induce skin allograft tolerance (142). Clodronate has been used for selective macrophage depletion, with results showing that clodronate was protective against heart transplant rejection (143). Another approach is to increase ATP degradation in addition to reducing ATP release. Hence, targeting CD39 and CD73 has a promising future, considering that CD39 and CD73 are two of the most important enzymes for ATP hydrolysis. Targeting CD39 exhibits anti-inflammatory and anti-thrombolytic effects, and treatment with soluble CD39 prolongs the survival of heart transplant by preventing thrombosis (20, 134, 144). Furthermore, the expression of CD73 increases anti-inflammatory cytokine levels, leading to endometrial regenerative cell-induced inhibition of cardiac allograft rejection (136). Moreover, purinergic receptors are potential therapeutic targets. For example, stimulating the P2Y11 receptors in mice has been shown to protect heart transplants from IRI and decrease immune rejection response (131). Targeting P2Y12 receptors is one of the most well-studied strategies for its critical role in antithrombosis. Several P2Y12 receptors antagonists, such as clopidogrel, ticlopidine, prasugrel, ticagrelor, and cangrelor, have been widely used in clinical applications (70, 145, 146).

Another promising strategy is to increase the level of circulating adenosine with exogenous adenosine or to selectively activate adenosine receptors, considering that adenosine plays a significant role in heart transplantation (**Table 1**). First, adenosine is an essential component of the University of Wisconsin solution (UW) and Institut Georges Lopez-1 (IGL-1) preservation solutions. Researchers have reported that the adenosine-containing Histidine-tryptophan-ketoglutarate (HTK) preservation solution has a better protective effect on myocardium than the standard HTK preservation solution, which prevents myocardial cell swelling and necrosis by reducing oxidative and nitrosative stress (147). Pre-treatment with adenosine prolongs donor heart storage and protects heart grafts from IRI (148, 149). Second, adenosine is a common antiarrhythmic drug, and low dose adenosine protects the transplanted heart from post-

TABLE 1 | Clinical trials of purinergic signaling involved in heart transplantation.

ClinicalTrials.gov Identifier	Year	Drug	Conditions	Study Title
NCT02462941	2015	Adenosine	Sinus Bradycardia, Atrioventricular Block	Analysis of Adenosine on Sinus and Atrioventricular Nodal Conduction in the Pediatric Transplanted Heart
NCT03231371	2008	Adenosine	Orthotopic Heart Transplant	Coronary Artery Vasculopathy in Pediatric Heart Transplant Patients
NCT03102125	2019	Regadenoson	Heart Transplant Failure and Rejection	Allograft Dysfunction in Heart Transplant
NCT02597543	2015	Regadenoson	Heart Transplant, Acute Graft Rejection, Chronic Graft Rejection	Stress Cardiac MRI for Evaluation of Nonspecific Allograft Dysfunction
NCT05081115	2021	Adenosine, regadenoson	Coronary Artery Disease, Heart Failure, Hypertrophic Cardiomyopathy	Stress Echo 2030: the Novel ABCDE-(FGLPR) Protocol to Define the Future of Imaging

transplantation arrhythmias (150). Furthermore, a prospective clinical study was conducted to investigate the safety and efficacy of adenosine in supraventricular tachycardia after heart transplantation and the results showed that low doses of adenosine convert supraventricular tachycardia to a sinus rhythm of <140 beats/minute (NCT02462941) (151). Moreover, adenosine has been used in the diagnosis of coronary artery vasculopathy (CAV), a common complication after heart transplantation. Adenosine stress perfusion cardiac magnetic resonance imaging (MRI) is a safe and noninvasive method for the diagnosis of CAV after heart transplantation (152, 153). Adenosine or adenosine receptor agonist was used in several clinical trials as a vasodilator for stress echo in a stress MRI (NCT03231371, NCT03102125, NCT02597543, and NCT05081115). Other drugs targeting adenosine receptors have been investigated. For example, the partial adenosine A1 receptor agonist neladenoson bialanate has been commonly used in chronic heart failure treatment (154, 155). Adenosine A2A receptor agonist CGS21680 reduces the inflammatory response of lung transplantation (156, 157) and liver transplantation (47). It can as well significantly reduce the infarct area of isolated perfused mouse hearts (48).

CONCLUSIONS

In this review, purinergic signaling and its role in IRI and cardiac allograft rejection, as well as clinical applications and prospects were discussed. ATP plays significant roles in inflammation and allograft rejection, whereas adenosine shows anti-inflammatory capabilities and the ability to induce immune tolerance. Balancing ATP and adenosine signaling pathways will be a key factor in regulating immune rejection or immune tolerance, as well as maintaining the long-term survival of heart transplants.

Currently, several therapeutic strategies targeting purinergic signaling, such as reducing ATP release or raising levels of adenosine, are available. However, current knowledge on the role of purinergic signaling receptors in heart transplantation remains insufficient. Further studies are required to investigate the maintenance of ATP and adenosine signaling balance, as well as better short- and long-term survival outcomes in patients who underwent heart transplantation.

AUTHOR CONTRIBUTIONS

YJ and JL wrote the manuscript. HZ revised the manuscript and figures. PZ designed this project. All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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