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REVIEW ARTICLE

CD39-adenosinergic axis in renal pathophysiology and therapeutics

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Abstract

Extracellular ATP interacts with purinergic type 2 (P2) receptors and elicits many crucial biological functions. Extracellular ATP is sequentially hydrolyzed to ADP and AMP by the actions of defined nucleotidases, such as CD39, and AMP is converted to adenosine, largely by CD73, an ecto-5′-nucleotidase. Extracellular adenosine interacts with P1 receptors and often opposes the effects of P2 receptor activation. The balance between extracellular ATP and adenosine in the blood and extracellular fluid is regulated chiefly by the activities of CD39 and CD73, which constitute the *CD39-adenosinergic axis.* In recent years, several studies have shown this axis to play critical roles in transport of water/sodium, tubuloglomerular feedback, renin secretion, ischemia reperfusion injury, renal fibrosis, hypertension, diabetic nephropathy, transplantation, inflammation, and macrophage transformation. Important developments include global and targeted gene knockout and/or transgenic mouse models of CD39 or CD73, biological or small molecule inhibitors, and soluble engineered ectonucleotidases to directly impact the CD39-adenosinergic axis. This review presents a comprehensive picture of the multiple roles of CD39-adenosinergic axis in renal physiology, pathophysiology, and therapeutics. Scientific advances and greater understanding of the role of this axis in the kidney, in both health and illness, will direct development of innovative therapies for renal diseases.

Keywords Purinergic signaling · Ectonucleotidases · Extracellular nucleotides · P2 receptors · P1 receptors · Kidney · Transplantation

Prologue Ever since Dr. Geoffrey Burnstock first coined the term in 1970s, the field of "purinergic signaling" has transformed into a distinct and complex system [1–6], registering an exponential growth since early 1990s. Purinergic signaling has implications for virtually in every mammalian system, playing one or more critical roles in physiology and/or pathophysiology thereby offering novel drug targets for the treatment of a variety of diseases [7–13]. The situation is both exciting and complex with respect to the kidney, where purinergic signaling plays a variety of roles in health and disease, many of which offer therapeutic potential. In recent years, excellent reviews have been published on the physiology, pathophysiology, and experimental therapeutics of purinergic signaling in the kidney [14–36]. This review is not intended to update the scope of the purinergic receptors in the kidney, but it specifically focuses on *CD39-adenosinergic axis*, which functions as a dynamic pathway that regulates the availability of ligands for P2 and P1 receptors in the extracellular milieu, and thus has profound implications in renal physiology, pathophysiology, and therapeutics. As the readers will soon realize, at this stage, our knowledge of *CD39-adenosinergic axis* signaling remains rudimentary.

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Organization of CD39-adenosinergic axis Despite its high intracellular concentrations (3–5 mM), adenosine triphosphate (ATP) cannot freely diffuse out of cells due to its negative charge. However, ATP can be released from healthy cells by

regulated exocytosis or through specific transport processes, such as nucleotide transporters (NT) or pannexin (PNX) or connexin (CNX) hemichannels or through multi-drug resistance (MDR) gene products [3, 37, 38]. Intracellular ATP can also be released in an unregulated fashion during hypoxia or following cell death. Extracellular concentrations of ATP even in low micromolar range (5 to 20 μM), which is an order lower than its intracellular concentrations, can elicit a variety of biological functions in mammalian systems by interacting with P2Y or P2X receptor subtypes. P2X receptors (subtypes 1–7) are ATP-gated channels that open up, allowing ions (Na^+, K^+, Ca^{2+}) to either influx or efflux. P2Y receptors (subtypes 1, 2, 4, 6, and 11–14) are G protein-coupled with downstream effector signaling pathways that cause an increase in either intracellular free Ca^{2+} or cyclic adenosine monophosphate (cAMP). Both P2Y and P2X receptor subtypes are widely expressed along the mammalian nephron and collecting duct system [20, 24, 27, 31, 39]. However, as shown in Fig. 1, the released ATP is sequentially hydrolyzed to ADP and AMP by CD39 or NTPDase1 (nucleoside triphosphate diphosphohydrolase-1), which is expressed in vascular and tubular structures of the kidney [40–42]. ATP can also be directly hydrolyzed to AMP by nucleotide pyrophosphatases (NPPs), expressed in the kidney [41]. AMP is converted to adenosine by the action of CD73 (5′-ectonucleotidase), which is also expressed in the kidney. While ATP binds to P2Y and P2X receptors, adenosine is a potent agonist of P1 receptors (subtypes A_1, A_{2A}, A_{2B}, and A_3). Similar to P2Y receptors, P1 receptors are G protein-coupled, with complex downstream signaling pathways. The activation P1 receptor subtypes result in increased or decreased activity of adenylyl cyclase (AC), thus altering cellular cAMP levels. This pathway leading from ATP to the generation of adenosine, known as the CD39-adenosinergic axis (enclosed in the gray box in Fig. 1), is active locally, and it apparently regulates the balance between P2 and P1 receptor activity in cells. In many organs or cells, the activation of P1 receptors opposes the biological effects initiated by the P2 receptors, thus acting as a feedback loop, which is apparently regulated by the activities of CD39 and CD73 [43–47]. While the expression of purinergic receptors and the ectonucleotidases and their functions are documented in many organs, how the expression and activities of the latter are regulated is not understood at this stage. This is a major gap in our knowledge of the operation of CD39-adenosinergic axis. However, the availability of CD39 or CD73 gene knockout mice or mice overexpressing human CD39 (hCD39), and reagents such as potato apyrase, soluble engineered ectonucleotidases, and small molecules that interact with P1 or P2 receptors or CD39 (polyoxymetalates) have enabled us to gain insights into the roles of CD39-adenosinergic axis in renal physiology and pathophysiology. In the following, we will provide an overview of the role of this axis in several pathophysiological conditions that are relevant to the kidney and direct the readers for review articles that provide more details and in-depth presentation.

Extracellular cAMP-adenosine pathway Although the CD39-adenosinergic axis represents the major pathway for the generation of extracellular adenosine, there is evidence that under certain circumstances, extracellular cAMP can also be a source of adenosine, which is referred to as the *extracellular cAMP-adenosine pathway* (shown in the vertical box in Fig. 1). Extracellular cAMP has two sources: the blood and tissues. Unlike ATP, which is unstable in extracellular milieu, cAMP is relatively stable and can be transported to distant organs through the blood circulation, where it can be converted to adenosine. cAMP released from organs such as the liver in the context of high glucagon levels in the blood (e.g., diabetes mellitus, pancreatitis, cirrhosis of liver) can reach the kidney through blood circulation. cAMP can also be released locally within the kidney during heightened receptor-mediated activation of adenylyl cyclase (AC). Intracellular cAMP reaches the extracellular milieu through the same transport system used by ATP and other nucleotides. Extracellular cAMP is converted to AMP by the action of ecto-phosphodiesterase (ePDE) or tissue-nonspecific alkaline phosphatase (ns-AP). The AMP thus formed is converted to adenosine by CD73.

The above two pathways have their specific advantages and disadvantages. Generation of adenosine locally by the activity of the CD39-adenosinergic axis has the advantage of tissue-specific tight local regulation. While the extracellular cAMP-adenosine pathway works more like a hormonal system, but without feedback regulation, the CD39-adenosinergic axis functions as an autocrine/paracrine purinergic signaling with tight feedback regulation [30].

Adenine (P0) receptor In recent years, another purinergic receptor that selectively binds adenine base, but not adenosine (adenine base + sugar), has been reported. Extracellular adenosine is not converted to adenine, but is broken down to inosine by the action of adenosine deaminase. Adenine is generated in the cells during purine salvage pathway, and it can be transported out of the cells by the same nucleotide transporters (Fig. 1). Similar to P2Y and P1 receptors, the adenine receptor (also known as P0 receptor) is G protein-coupled that selectively binds adenine, but not adenosine. Although not the focus of this review, we have localized the adenine (P0) receptor in the rat kidney and showed that adenine is a signaling molecule in the kidney [48, 49]. In this context, it is interesting to note that blood levels of adenine are markedly increased in patients with chronic renal failure, and positively correlate with severity of the disease [50].

CD39-adenosinergic axis in renal physiology

Tubular transport of water and sodium One of the main functions of the kidney is maintenance of water and sodium

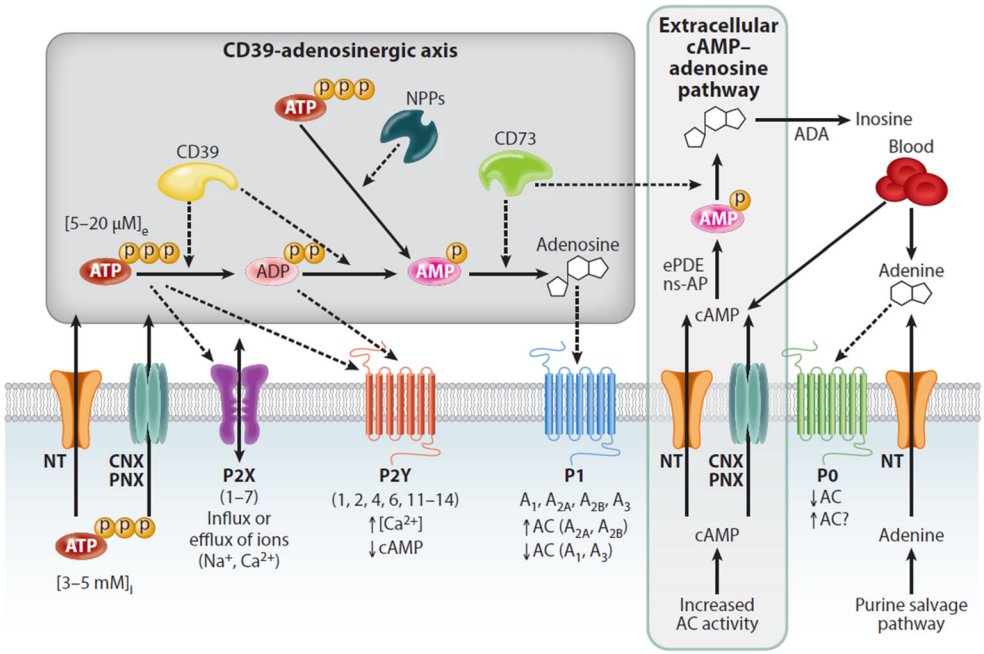

Fig. 1 Schematic representation of the components of the complex purinergic signaling pathways mediated by extracellular nucleotides. The horizontal gray colored box shows the components of CD39-adenosinergic axis. The vertical box encloses the components of extracellular cAMP-adenosine pathway. On the extreme right, the formation of extracellular adenine and its interaction with adenine receptor are shown. NT nucleotide transporter; PNX pannexin; CNX connexin; cAMP cyclic AMP; CD39 nucleoside triphosphate diphosphohydrolase 1 (NTPDase1); NPP nucleotide pyrophosphatase; CD73 5′-ectonucleotidase; AC adenylyl cyclase; ePDE ecto-phosphodiesterase; ns-AP tissue-nonspecific alkaline phosphatases; AdeR adenine receptor; ADA adenosine deaminase. For further details, refer to the text (with permission from Peti-Peterdi et al. [30])

homeostasis of the body by regulating tubular transport. The roles of the neurohypophyseal peptide hormones arginine vasopressin (AVP) or anti-diuretic hormone (ADH) in regulating the water homeostasis, and the mineralocorticoid hormone aldosterone, in regulating sodium homeostasis are well known [51, 52]. In recent years, it has been established that extracellular nucleotides, acting through $P2Y_2$ and $P2Y_{12}$ receptors, also play significant roles in the transport of water and sodium in the kidney, mainly by opposing the actions of one or both hormones on the kidney [13, 16, 18, 20, 21, 23]. We used a transgenic (TG) mouse model globally overexpressing hCD39 including in the kidney, which had elevated tissue and blood levels of adenosine [53] and showed that these mice manifest defective water and sodium handling [42, 54]. Under basal conditions, TG mice exhibited impaired urinary concentrating ability despite normal AVP levels and had impaired AVP release in response to water deprivation. However, TG mice kidneys were responsive to exogenous desmopressin (dDAVP), a selective vasopressin V2 receptor agonist [54]. Thus, ectonucleotidases modulated purinergic signaling impacting urinary concentration. Furthermore, high-salt diet and aldosterone clamping experiments in TG mice conducted by us supported the concept that nucleotides facilitate natriuresis by countering aldosterone effect and also revealed aldosterone-independent down-regulation of major sodium transporters and channel subunits by purinergic signaling [42]. Thus, scavenging of extracellular ATP by overexpression of hCD39 resulted in some unexpected observations.

Tubuloglomerular feedback and renin secretion The renal blood flow (RBF) and glomerular filtration rate (GFR) are maintained independent of renal perfusion pressure (RPP) over a defined range (80–180 mmHg). This autoregulation is possible due to two intrarenal mechanisms, namely the myogenic mechanism and the tubuloglomerular feedback (TGF) [55, 56]. TGF operates by sensing of salt concentration of the distal nephron by the macula densa cells of the juxtaglomerular apparatus (JGA), leading to signal transduction to the afferent arteriole thus regulating the GFR. Both ATP and adenosine have been shown to play mediator roles in TGF (Fig. 2). While ATP is the initial signaling molecule [57, 58], adenosine released from the hydrolysis of ATP appears to be the ultimate signaling molecule for TGF [59, 60]. Accordingly, TGF responses were blunted in mice lacking either adenosine A_1 receptor [61, 62] or 5′-ectonucleotidase/CD73 [63]. However, it appears that synchronous release of renin from macula dense cells is dependent on ATP-mediated propagation of intra- and intercellular Ca^{2+} waves through juxtaglomerular cells [64]. Accordingly, it has been shown that maximum TGF responses were reduced in *Cd39* null

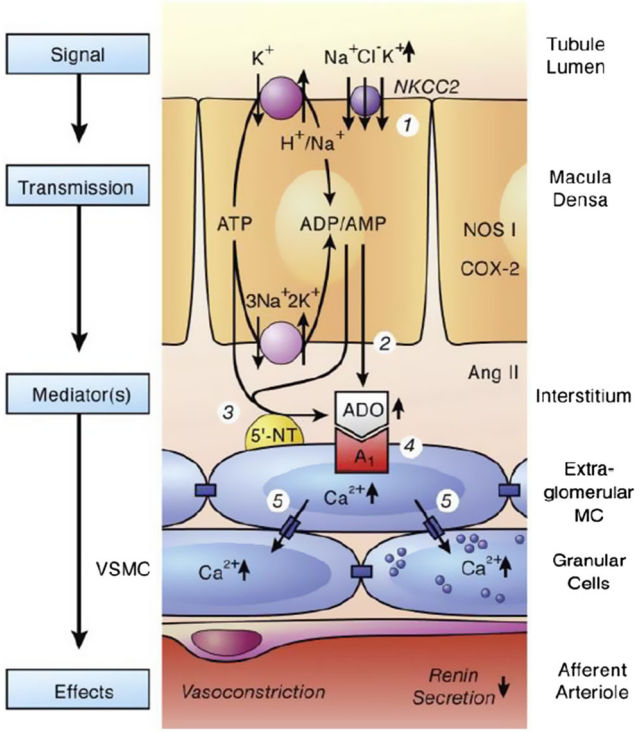

Fig. 2 Suggested role of CD39-adenosinergic axis in the regulation of tubuloglomerular feedback mechanism. Numbers in circles refer to the following sequence of events. *1*, Increase in concentration-dependent uptake of Na^+, K^+, and Cl^- via the bumetanide-sensitive Na^+-K^+-$2Cl^-$ co-transporter (NKCC2); *2* and *3*, transport-dependent, intra- and/or extracellular generation of adenosine (ADO); the extracellular generation involves ecto-5′-nucleotidase (5′-NT); *4*, extracellular ADO activates adenosine A_1 receptors triggering an increase in cytosolic Ca^{2+} in extraglomerular mesangial cells (MC); *5*, the intensive coupling between extraglomerular MC, granular cells containing renin, and smooth muscle cells of the afferent arteriole (VSMC) by gap junctions allows propagation of the increased Ca^{2+} signal resulting in afferent arteriolar vasoconstriction and inhibition of renin release. Factors such as nitric oxide, arachidonic acid breakdown products, or angiotensin (ANG) II modulate the described cascade. NOS 1, neuronal nitric oxide synthase; COX-2, cyclooxygenase-2 (with permission from Vallon et al. [65])

mice, whereas macula densa- and pressure-dependent inhibition of renin secretion remained intact as compared to wild-type mice [66].

CD39-adenosinergic axis in acute kidney injury

Ischemia reperfusion injury Ischemia reperfusion injury (IRI) continues to be the major form of acute kidney injury (AKI) in the hospital setting and is associated with significant morbidity and mortality [67]. IRI occurs when there is interruption of blood flow to the kidneys after which blood flow is re-established. Although essential to prevent ongoing ischemic damage, reperfusion triggers a robust inflammation and oxidative stress response, resulting in organ dysfunction [68]. Although the pathophysiology of IRI is not completely understood [69], several studies have documented the role of CD39-adenosinergic axis in IRI [17, 70–74]. As shown in Fig. 3, during IRI, ATP is released from the inflammatory, apoptotic, or necrotic cells into the extracellular space. In IRI occurring in the kidney, liver, bowel, heart, lung, brain, and islet cells, CD39 is the major generator of adenosine [26], which is an innate anti-inflammatory metabolite and tissue protectant, especially during hypoxic conditions, that serves to limit tissue injury. Hypoxia induces the expression of both *Cd39* and *Cd73*, through hypoxia-inducible specificity protein 1 (Sp1) and hypoxia-inducible factor (HIF), respectively. *Cd39* is also upregulated within the kidney following ischemic preconditioning, which results in higher pericellular adenosine concentration and less renal IRI [70]. Finally, adenosine itself increases the expression of CD73. As shown in Fig. 3, adenosine mediates its anti-inflammatory effects via A_1 receptors on proximal tubular cells (PTC), A_{2A} receptors on T regulatory cells (Treg), and A_{2B} receptor on endothelial cells (EC) and circulating neutrophils. During ischemia, HIF inhibits transcription of equilibrative nucleoside transporter-1 (ENT1) enabling adenosine to remain in the extracellular space (Fig. 3). HIF also increases the expression of A_1 and A_{2B} receptors. Sphingosine kinase-1 (SK1) and sphingosine-1-phosphate receptor ($S1P_1R$) in the PTC augment the adenosine-A_1R interactions. In the Treg, $A_{2A}R$ activation increases the protein expression of programmed death-1 (PD-1), which suppresses innate immune responses (Fig. 3). Consistent with these mechanisms, IRI in *Cd39* null mice in which hydrolysis of ATP is severely diminished [17], or mice treated with POM-1 (polyoxymetalate-1) an inhibitor of *Cd39* [70], is severe.

We have previously shown that transgenic mice overexpressing hCD39 are protected from both warm and cold IRI of the kidneys [71] and IRI of the heart [75]. Furthermore, less severe hepatic injury was observed in donor livers from transgenic mice overexpressing hCD39 transplanted into wild-type recipients after prolonged (18 h) cold storage [76]. Similarly, the administration of apyrase, a soluble form of CD39, which increases tissue levels of adenosine abolished IRI in the kidney [70], heart [77], liver [78, 79], and intestines [80].

In contrast to CD39, the impact of CD73 in renal IRI is variable. Some studies have reported a protective role for CD73 [70, 81], whereas in mild renal IRI, CD73 deficiency or inhibition appears protective [82]. This latter observation may be due to accumulation of AMP, although direct evidence supporting this hypothesis is currently lacking. Interestingly, the volatile anesthetic isoflurane induces CD73 and protects against renal IRI [83].

Adenosine receptors are widely expressed on circulating leukocytes, immune cells, and vascular cells, which all play an important role in IRI. Notably, the A_{2B} receptor has a hypoxia responsive element (hypoxia-inducible factor (HIF)) within the promoter region modifying the expression of the

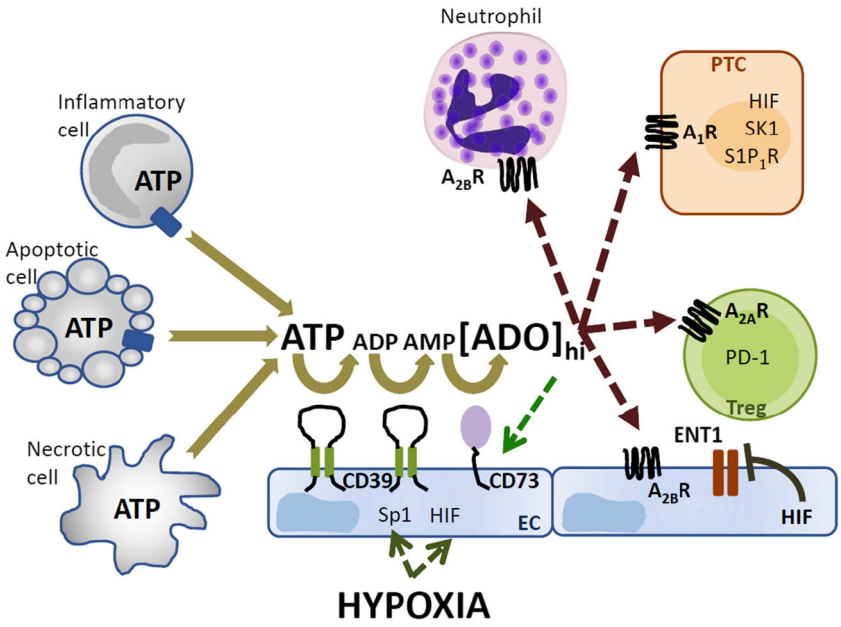

Fig. 3 CD39-adenosinergic axis in the pathophysiology of ischemia-reperfusion injury. ADO adenosine; Sp1 hypoxia-inducible specificity protein 1; HIF hypoxia-inducible factor; PTC proximal tubule cells; Treg T regulatory cells; EC endothelial cells; ENT1 equilibrative nucleoside transporter; SK1 sphingosine kinase-1; $S1P_1R$ sphingosine-1-phosphate receptor; PD-1 programmed-death 1. For further details, refer to the text (modified from Roberts et al. [26] and reproduced with permission)

receptor [84]. Indeed, the A_{2B} receptor is upregulated within the kidney as early as 24 h following IRI [85] and it is the expression on the renovasculature which is essential for mitigating IRI [86].

Role of Treg in AKI vis-à-vis CD39-adenosinergic axis Regulatory T cells (Treg) have an intrinsic reno-protective function. By multiple mechanisms, Tregs suppress inflammation and prevent AKI. Through a series of experiments, Kinsey et al. have shown that depletion of Treg exacerbates renal IRI [87] whereas following ischemic preconditioning, which augments pericellular adenosine concentrations [70, 88], Treg numbers are increased and renal IRI is constrained [89, 90]. The authors went on to show the mechanism underpinning the observed protective effect: adenosine, generated by CD73 on Treg, increased the expression of PD-1 through the A_{2A} receptor, both of which are expressed on Treg [91, 92]. With the advent of Treg therapy to control inflammation, these data may provide a novel therapeutic approach to ameliorate acute kidney injury (AKI) following IRI [93].

Macrophage transformation and inflammation in AKI Macrophages are critical mediators and regulators of inflammation in various pathophysiological conditions, including AKI [94, 95]. Macrophage phenotype also controls long-term AKI outcomes—kidney regeneration versus progression to chronic kidney disease (CKD) characterized by fibrosis (see below) [93, 96]. Recent studies revealed that CD39 and CD73 aid in macrophage transformation. M1 macrophages (classically activated macrophages) develop early after renal injury and propagate inflammation by elaborating pro-inflammatory factors. M2 macrophages (alternatively activated macrophages), which appear later, produce anti-inflammatory factors and support renal repair. As shown in Fig. 4, the CD39-adenosinergic axis influences the balance between the M1 and M2 macrophages and thereby inflammation and repair processes in the kidney following injury [26].

Renal fibrosis Fibrosis is a characteristic feature of all forms of chronic kidney disease, culminating in renal failure [97]. Despite significant advances in deciphering the pathophysiological mechanisms of renal fibrosis, mostly derived from animal models [98], there are very few options to prevent or slow the progression of fibrosis in clinical settings. Fibrosis is preceded by inflammation, and although short-term activation of A_{2A} and A_{2B} adenosine receptors decreases inflammation, chronic exposure to adenosine promotes inflammation and fibrosis through A_{2B} receptor [85, 99, 100]. T cells precede the influx of macrophages and can independently promote renal fibrosis. Signaling through A_{2A} receptors inhibits T cell proliferation (Fig. 5). Accordingly, fibrosis is exacerbated in A_{2A} receptor knockout mice [26, 85, 99, 100]. Conversely, chronic signaling through A_{2B} receptor, predominantly expressed on fibroblasts, promotes renal fibrosis [101]. Furthermore, increased signaling through A_{2B} also appears to play a role in the development of tubulointerstitial fibrosis in angiotensin II-treated mice [102]. Indeed, in kidney biopsies from patients with CKD, elevated levels of CD73 and A_{2B} receptor mRNA expression have been demonstrated as compared to patients without CKD [102]. Intriguingly, impaired ability to generate adenosine in CD73 knockout mice results in renal fibrosis by 6 months of age [103].

Adenosine signaling plays a complex role in the development of renal fibrosis following IRI. A_{2B} adenosine receptor activation offers protection acutely, but may contribute to the progression of fibrosis following an episode of ischemia. The

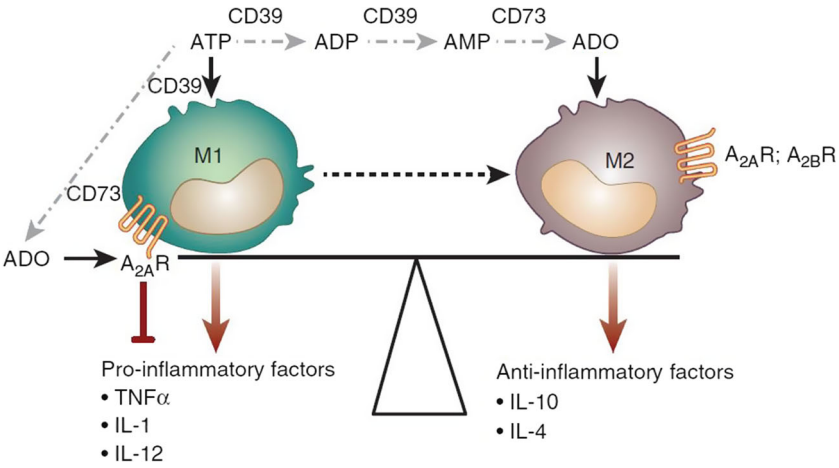

Fig. 4 Role of CD39-adenosinergic axis in macrophage transformation. Adenosine inhibits the expression of pro-inflammatory cytokines by M1 macrophages via A2AR signaling and promotes a shift to the anti-inflammatory M2 phenotype via A2BR signaling. For further details, refer to the text (with permission from Roberts et al. [99])

A_{2B} receptor is upregulated 24 h following renal IRI which persists for 4 weeks following IRI [85, 99]. Intriguingly, whereas the administration of apyrase or the overexpression of hCD39 confers similar acute protection, the effect on chronic IRI is contrasting. Mice treated with a single dose of apyrase do not develop chronic kidney disease and the upregulation of A_{2B} receptor is blunted. In contrast, hCD39-TG mice develop chronic kidney disease following IRI despite acute protection coincident with increased renal adenosine content [100]. Notably, the whole animal overexpression of human CD39 does not attenuate the development of renal fibrosis in unilateral ureteral obstruction (UUO) model [104] presumably an effect of the underpinning mechanism of fibrosis in this model.

CD39-adenosinergic axis in renal transplantation Renal transplantation remains the optimal form of renal replacement therapy for patients with end stage renal disease. Despite exceptional short-term survival, long-term survival is limited by the development of chronic allograft dysfunction which in the kidney manifests with interstitial fibrosis and tubular atrophy [105]. Recently, novel approaches have been proposed to improve allograft outcomes [106]. IRI (see above) is an obligatory insult in transplantation, which may lead to delayed graft function which is a risk for acute rejection and long-term graft loss. Intracellular ATP is released in the donor kidney at the time of harvesting due to ischemia and again at the time of vascular anastomosis following reperfusion. Unique to transplantation is a period of cold ischemia occurring between the time of procurement and engraftment. We have shown the expression of CD39 on endothelial cells, monocytes, dendritic cells, Langerhans cells, NK (natural killer) cells, and natural killer T cells [107]. Organs that overexpress CD39 have improved graft function in both kidney [71] and liver [76] mouse transplant models encompassing extended cold preservation. Moreover, several studies during the past two decades indicated that the activity of CD39 influences severity of inflammation and autoimmune response [108–113].

Treg are essential to transplantation tolerance and their therapeutic efficacy is well documented in animal models.

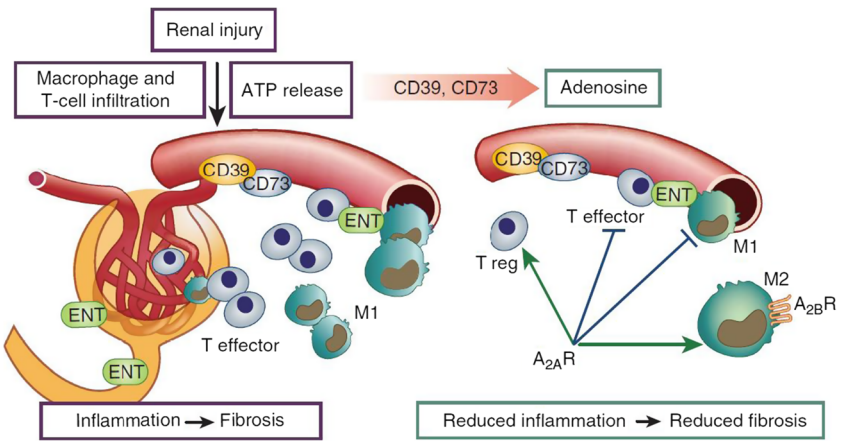

Fig. 5 Adenosine signaling via A_{2A} and A_{2B} receptors reduces inflammation, resulting in reduced fibrosis. Left: renal injury promotes macrophage and T-effector cell infiltration that are associated with increased inflammation and fibrosis. Right: adenosine signaling via A_{2A}R and A_{2B}R reduces infiltration of T-effector and M1 macrophages and promotes generation of Treg and M2 macrophages, which are associated with reduced inflammation and less fibrosis. For further details, refer to the text (with permission from Roberts et al. [99])

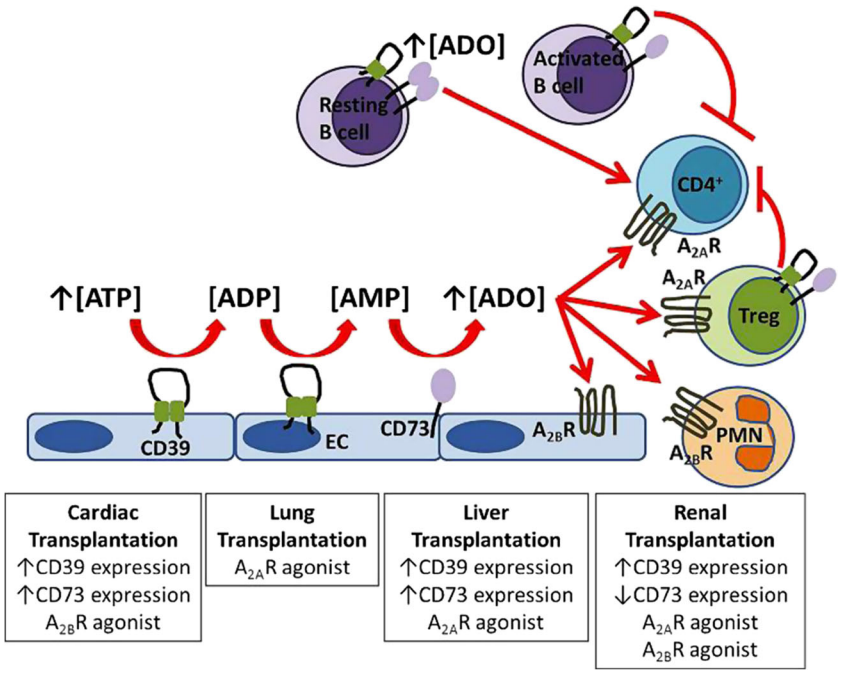

Fig. 6 Protective mechanisms in solid organ transplantation. Extracellular adenosine is generated from the enzymatic hydrolysis of nucleotides by CD39 and CD73 expressed on endothelial cells (EC) and B cells. Adenosine signals via $A_{2A}R$ on circulating cells including regulatory T cells (Treg) and via $A_{2B}R$ expressed both on the vasculature and inflammatory cells. Experimental strategies which improve graft outcome for each solid organ transplant are listed in boxes (with permission from Roberts et al. [125])

CD39 has been identified as a marker of both murine [114, 115] and human Treg [116]. Furthermore, in mice, the generation of adenosine by the concerted actions of CD39 and CD73 is integral to their function and the transfer of Treg from CD39 deficient mice resulted in more rapid rejection of skin grafts [114]. Using the markers of CD4, CD25, and CD39, human Treg can be monitored in patients with end stage renal failure and following renal transplantation with a reduction in Treg number noted during acute transplant rejection [116, 117]. Ex vivo Treg expansion and delivery into renal transplant recipients as a therapy are currently undergoing rigorous study [118]. Figure 6 summarizes our current knowledge about the purinergic protective mechanisms in solid organ transplantation.

CD39-adenosinergic axis in hypertension and diabetic nephropathy Hypertension and diabetic nephropathy continue to be the major causes of chronic kidney disease (CKD), leading to end-stage renal disease (ESRD) that requires maintenance hemodialysis or renal transplantation. The hydrolysis of

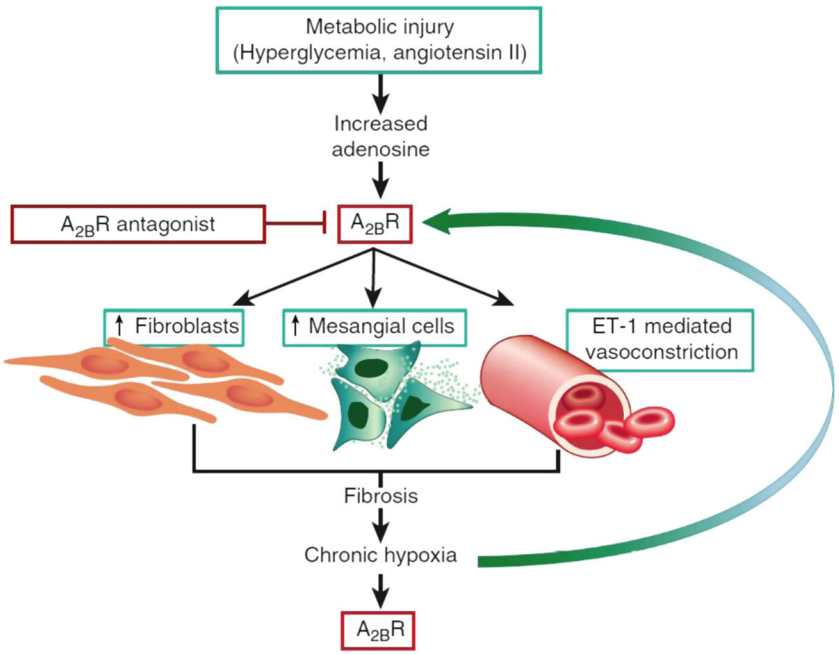

Fig. 7 Experimental models of hypertension and diabetes reveal increased adenosine generation and A_{2B} receptor expression. $A_{2B}R$ activation on fibroblasts and mesangial cells promotes extracellular matrix deposition driving the development of renal fibrosis. Vasoconstriction mediated by endothelin-1 promotes hypoxia which is perpetuated by renal fibrosis. Chronic hypoxia further drives adenosine generation and $A_{2B}R$ activity, creating a vicious cycle of chronic hypoxia and renal fibrosis (with permission from Roberts et al. [99])

adenine nucleotides has been reported to be enhanced in platelets of patients with diabetes and hypertension and was associated with increased expression of CD39. Increasing glucose concentration apparently had a direct effect on ATP hydrolysis [119, 120]. Functional CD39 polymorphism influences the susceptibility to type 2 diabetes mellitus (T2DM) and diabetic nephropathy in African-Americans [121]. Hyperglycemia induced formation of extracellular adenosine in glomeruli and podocytes, apparently due to increased expression of CD73 [122, 123]. Hyperglycemia upregulated expression of HIF-1α [124], which in turn impacted and increased A_{2B} receptor expression in mesangial cells and podocytes [84, 123]. This observation, coupled with increased expression of TGF-β and vascular endothelial growth factor (VEGF) in glomeruli, resulted in the development of glomerulosclerosis. These alterations were reduced by the pharmacological inhibition of A_{2B} receptor (Fig. 7) [99, 125].

Therapeutic implications

The CD39-adenosinergic axis is a potential platform with multiple anchors for the development of novel therapeutic modalities for the treatment or management of renal conditions described above. One potential strategy involves modulation or tilting the axis more toward formation of adenosine relative to the extracellular ATP/ADP concentrations, so that the activity of adenosine or P1 receptors is higher with beneficial effects. This can be achieved by the administration of enzymes that hydrolyze ATP to ADP and AMP, such as soluble engineered ectonucleotidases. Initial studies using a commercially available (APT102) engineered human nucleoside triphosphate diphosphhydrolase-3 (CD39L3) in a canine model of arterial thrombosis were very encouraging [126]. Conversely, various inhibitors of ectonucleotidases patented during the past few years [127], and the availability of therapeutic antibodies that selectively inhibit CD73 [128], widened the scope for modulating the CD39-adenosinergic axis in experimental therapeutics.

The other strategy is to modulate the activity of adenosine or P1 receptor subtypes. In this context, the field of adenosine receptors as drug targets is further advanced with the availability of agonists and/or antagonists for various subtypes [12, 129, 130]. Comparatively, the availability of selective agonists or antagonists of P2 receptors is limited.

Summary points

- The CD39-adenosinergic axis is central to the regulation of purinergic signaling in the kidney
- The regulated generation of adenosine by CD39 and CD73 has major impacts on renal physiology with respect to water/salt excretion, tubuloglomerular feedback/renin secretion with blood pressure control.
- Alterations in the balance of extracellular nucleotides to nucleosides in disease states have major effects on inflammation and impact outcomes of ischemic reperfusion and metabolic stress.
- Differential expression of CD39 and CD73 by the vascular, T regulatory cells, and other immunity cells modulates inflammatory and immune reactions in experimental models of renal inflammation, fibrosis, and transplantation.
- Strategies for developing therapeutic modalities that can treat or manage kidney diseases by modulating the CD39-adenosinergic axis are available, and they need to be tested in animal models of various kidney diseases.

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Compliance with ethical standards

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Simon C. Robson declares that he has no conflict of interest.
Karen M. Dwyer declares that she has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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