Purinergic signaling in the modulation of redox biology

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ABSTRACT

Purinergic signaling is a cell communication pathway mediated by extracellular nucleotides and nucleosides. Tri- and diphosphonucleotides are released in physiological and pathological circumstances activating purinergic type 2 receptors (P2 receptors): P2X ion channels and P2Y G protein-coupled receptors. The activation of these receptors triggers the production of reactive oxygen and nitrogen species and alters antioxidant defenses, modulating the redox biology of cells. The activation of P2 receptors is controlled by ecto-enzymes named ectonucleotidases, E-NTPDase1/CD39 and ecto-5'-nucleotidase/CD73 being the most relevant. The first enzyme hydrolyzes adenosine triphosphate (ATP) and adenosine diphosphate (ADP) into adenosine monophosphate (AMP), and the second catalyzes the hydrolysis of AMP to adenosine. The activity of these enzymes is diminished by oxidative stress. Adenosine actives P1 G-coupled receptors that, in general, promote the maintenance of redox hemostasis by decreasing reactive oxygen species (ROS) production and increase antioxidant enzymes. Intracellular purine metabolism can also contribute to ROS generation via xanthine oxidase activity, which converts hypoxanthine into xanthine, and finally, uric acid. In this review, we describe the mechanisms of redox biology modulated by purinergic signaling and how this signaling may be affected by disturbances in the redox homeostasis of cells.

1. Introduction

Purinergic signaling is an evolutionarily conserved cell communication pathway triggered by an increase of extracellular nucleotides surrounding cells, including adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP), uridine triphosphate (UTP), uridine diphosphate (UDP), and the nucleoside adenosine (ADO). This signaling is involved in neurotransmission and other physiological processes; however, nucleotides can also act as alarmins or danger-associated molecular patterns in stress circumstances [1,2].

ATP was first described as a signaling transmitter in the non-adrenergic inhibitory innervation stimuli by Geoffrey Burnstock, considered the father of purinergic signaling [3,4]. Currently, it is well established that nucleotides and the nucleoside adenosine act as ligands of transmembrane purinergic receptors divided into two main families: P1 and P2 receptors. The P1 receptor family is composed of four G-coupled receptor subtypes (A_1, A_{2A}, A_{2B}, and A_3). In turn, P2 receptors are segregated into two subgroups: P2Y, which are metabotropic, and P2X, which are ionotropic proteins. The following physiological agonists activate P2 receptors: P2X and $P2Y_{11}$–ATP; $P2Y_{2,4}$–ATP and –UTP; $P2Y_1$ $P2Y_{12}$, and $P2Y_{13}$–ADP; $P2Y_6$–UDP; and $P2Y_{14}$–UDP–glucose [5–8]. These receptor activities are coordinated by ecto-enzymes known as ectonucleotidases, which metabolize their ligands through hydrolysis. The most prominent ones are E-NTPDase1/CD39, which hydrolyzes ATP and ADP into AMP, and ecto-5'-nucleotidase/CD73, which catalyzes AMP's hydrolysis to ADO, representing the final step of nucleotides degradation into nucleosides [9–11].

Purinergic receptors are expressed among various cell types and species [12–14]. They are critical for short-and long-term signaling, including neuromodulation processes, secretion, cell proliferation, differentiation, ossification, development, and regenerative episodes [15,16]. Purinoceptors encompass significant physiological specific phenomena in a variety of tissues and organs, including vasodilation and vasoconstriction, the release of hormones (e.g., insulin, glucagon, and others), bronchodilation, regulation of acid secretion in the gastrointestinal tract, control of reproductive systems, and other physiological

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functions [17].

Purinergic signaling has also been described in many pathological scenarios, including neurological, inflammatory, and infectious diseases [8,13,18,19]. In these situations of homeostatic disturbance, extracellular nucleotides can trigger the production and release of reactive oxygen species (ROS) and reactive nitrogen species (RNS). In addition, purinergic signaling can affect the activity of antioxidant enzymes promoting changes in the redox biology of cells [1,20,21]. In the present review, we aim to describe the mechanisms of redox biology modulated by purinergic signaling and the modulation of this signaling by disturbances in the redox biology of cells, primarily in neurological, inflammatory, and infectious diseases.

2. Free radical generation and antioxidant defenses

A radical is any molecule that contains one or more unpaired electrons generated from specific elements. In biological systems, oxygen and nitrogen are the most critical elements that generate radicals [22]; they are products of several metabolic pathways, including aerobic metabolism. Some perform essential functions, exerting physiological roles in cellular signaling, immunological responses, and other processes. However, radicals may also exist in free form as highly unstable molecules with unpaired electrons that interact with tissue components, causing oxidation and potentially damage DNA, proteins, and lipids [22, 23].

Three of the most common and biologically important ROS are superoxide anions (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH•). Regarding RNS, the best known are NO, nitrosonium cation (NO^+), nitroxyl anion (NO^-), and peroxynitrite ($ONOO^-$) [24].

The superoxide anion ($O_2^{•-}$) is formed by the univalent reduction of molecular oxygen in a reaction mediated by NADPH oxidases and xanthine oxidase or nonenzymatically through redox-reactive compounds from the mitochondrial electron transport chain [25]. H_2O_2 is not a free radical but an ROS, whose cytotoxicity is likely due to the secondary production of singlet oxygen or hydroxyl radical (·OH) in redox reactions between transition-metal ions dismutations, the so-called Haber-Weiss reaction [26]. Therefore, H_2O_2 can be converted into a hydroxyl radical that is highly reactive and toxic to cells [27].

NO is a highly reactive, labile free radical that is short-lived. It has a vital role in the normal functioning of cells, mediating biological functions such as regulation of cardiac contractility and vasodilation [28, 29]. Nitric oxide synthases (NOS) are isoforms responsible for NO synthesis by converting the amino acid L-arginine to L-citrulline. The NOS family contains three isoforms, neuronal NOS, endothelial NOS (eNOS), and the inducible form, iNOS. All NOS isoforms are similar concerning NO and other biological molecules such as L-citrulline [30].

Superoxide anion, H_2O_2, and NO can be dangerous when acting together and alone or with other molecules. In this context, the superoxide anion may react with NO to form peroxynitrite. H_2O_2 can be converted into hydroxyl radical (·OH) in the presence of reduced transition metals because it is highly reactive and toxic to the cell. H_2O_2 can also react with carbon dioxide, leading to the formation of the carbonate radical, which is a potent oxidant [27].

Reactive oxidants regulate physiological and pathophysiological conditions from prokaryotes to humans. ROS and RNS are constantly produced from internal metabolism and external exposure [31–33]. They act as critical signaling molecules to regulate cell division and programmed cell death [33]. However, uncontrolled production of oxidants results in oxidative stress that impairs cellular functions; this process contributes to the development of several diseases [22,34–36].

Oxidative stress can be characterized as ROS production exceeding the capacity of cellular antioxidant defenses to remove these toxic species, generating an imbalance between oxidizing and antioxidant agents [22,37,38]. Therefore, oxidation-reduction reactions (redox) in living cells are utilized to maintain homeostasis and are collectively referred to as redox signaling or redox control [39]. Redox homeostasis is maintained by redox signaling, which induces protective responses against oxidative stress.

The antioxidant enzyme system and the low-molecular-weight antioxidants have two protective mechanisms in cell scavenging ROS and maintaining redox homeostasis [22]. The low-molecular-weight antioxidants include glutathione, uric acid, ascorbic acid, alpha-tocopherol, and melatonin, which mediate neutralizing activities by causing transition metals' chelation preventing lipid peroxidation and others [40, 41]. Ascorbic acid and alpha-tocopherol act in concert, with ascorbate being necessary to regenerate reduced alpha-tocopherol that provokes a reduction in lipid peroxidation. The peroxidation of lipids has deleterious consequences, disrupting the integrity of cell membranes through the oxidation of polyunsaturated fatty acids. This process may be initiated by highly reactive species such as hydroxyl and peroxyl radicals [42,43]. Thiol compounds such as thioredoxin can detoxify H_2O_2; however, they require conversion back to the reduced form by thioredoxin reductase [44]. This thioredoxin system, including thioredoxin reductase and NADPH, is a significant disulfide reductase system. It is a crucial antioxidant against oxidative stress mediated by its disulfide reductase activity, regulating protein dithiol/disulfide balance [45].

The enzymatic antioxidant defense system includes superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) [46]. There are three metal-containing isoforms of SOD found in various cellular compartments [47,48]: SOD1 (copper-zinc SOD) is in the cytoplasm, nucleus, and plasma membrane; SOD2 (manganese SOD) is mainly in mitochondria [48,49]; and SOD3 (copper-zinc SOD) is unique in scavenging superoxide in the extracellular compartment, dismutating superoxides generated during the inflammatory cascade [48,50]. All isoforms of SOD catalyze the dismutation of superoxide radicals to generate H_2O_2, which is not a free radical and is less reactive than superoxide. However, it is called ROS because it is closely related to the generation and detoxification of free radicals. It can diffuse through cell and organelle membranes, where it acts as a second messenger in signal transduction pathways. H_2O_2 is in turn detoxified to water by CAT and GPx. Animal catalases are heme-containing enzymes that convert H_2O_2 to water and O_2. They are localized mainly in subcellular organelles such as peroxisomes.

In contrast, GPx, a tetrameric selenoprotein, removes H_2O_2 by coupling its reduction with glutathione oxidation. GPx is present in the mitochondrial and cytoplasmic fractions [41,51,52]. GPx also reduces peroxides such as fatty acid hydroperoxides. Most animal tissues contain both CAT and GPx activity [47].

The antioxidant enzymes must act in concert since an imbalance in superoxide and H_2O_2 can result in the much more dangerous hydroxyl radical formation, as described previously. During the action of GPx in the detoxification of H_2O_2, glutathione (the primary cellular thiol redox buffer in cells, synthesized in the cytosol from L-glutamate, L-cysteine, and glycine) is oxidized (the glutathione disulfide form). It is an essential non-enzymatic endogenous antioxidant that can be regenerated by glutathione reductase and is responsible for the regeneration of reduced glutathione (glutathione form) with the consumption of NADPH. The latter is generated through the pentose phosphate pathway, of which glucose-6-phosphate dehydrogenase is the first enzyme [53–55]. In this manner, optimum levels of reduced glutathione are maintained [22]. The endogenous ratio of glutathione to glutathione disulfide indicates redox homeostasis within a cell. Higher glutathione levels also serve as a cofactor for other enzymes, including glyoxalase and peroxidase [56]. It has been suggested that the presence of GPx in the vicinity of folded catalase helps it remain functionally active [57].

The increase in antioxidant capacity removes excessive oxidants and prevents further severe oxidative injury. Therefore, the response of antioxidants to oxidative stress evolved as a critical defense mechanism to combat harmful effects of intrinsic and extrinsic oxidative insults and is preserved in all organisms [58]. Furthermore, *in vivo* studies in mammals suggest that organs and tissues contain distinct antioxidant systems that may form the basis for differential susceptibility to oxidative stress.

Many advances have been made to understand the several antioxidant systems and their regulatory pathways [47].

3. Purine metabolism and redox biology

Nucleotides and nucleosides composing purinergic signaling can influence cell metabolism and fate. Thus, purines are involved with metabolic reprogramming and energy-dependent processes, in addition to composing genetic material and cofactors [59,60]. The availability of purines to bind purinergic receptors and nucleotidases is determined by purine metabolism, notoriously moderated by the purinosome, which is a purinergic metabolon. This temporary multimeric enzymatic complex efficiently binds to promote the physical proximity of the six enzymes involved in de novo purine pathway biosynthesis [61]. This dynamic association contains auxiliary proteins as well. It reverberates the concentration of purine molecules, as its shortage requests the de novo pathway upregulation, starting with the phosphoribosyl pyrophosphate (PRPP) as a substrate, originated from glycolysis and pentose phosphate pathway, and producing inosine 5'-monophosphate (IMP) to then increase nutrient demand with high energy consumption [62].

The purinosome colocalizes with mitochondria; this is a functional colocalization driven by microtubules that provides rapid substrates for this organelle to meet the high cellular demand for purines. This spatial interaction depends on mitochondria mTOR-related regular activity [63, 64]. Notably, the activation of the P2X7 receptor downregulates the PI3K/AKT/mTOR pathway in tumor cell lines, impairing cell growth and, thus, cancer progression [65]. Various kinases may be involved in purinosome regulation, including the PI3/AKT cascade (directly related to mTOR) by managing PRPP availability and many more associated with G-protein-coupled receptors mitogenic signaling [66].

In addition to the de novo pathway, purine levels are controlled by the salvage pathway dependent on PRPP [67]. When purines are at homeostatic concentrations, most of the convertible purine pool (AMP, IMP, xanthosine monophosphate (XMP), and guanosine monophosphate [GMP]) is acquired by the salvage pathway through recycling of degraded nucleoside bases from precursor macromolecules, which requires less energy than the de novo pathway (Fig. 1) [59,66,68].

Purine metabolism is essential considering its association with diseases such as gout, an endocrine condition that occurs due to hyperuricemia, which increases blood urate (the final product of the salvage and de novo pathways). Accumulation and crystallization of urate in joints of patients are due to lack of uricase (urate oxidase), the enzyme that catalyzes the degradation of uric acid into allantoin [69]. Furthermore, monosodium urate crystals (MSU) can induce NLRP3 inflammasome active multimerization through potassium efflux [70]. This feature strongly correlates to P2X7 receptor activation, as the relationship between MSU and this purinergic receptor has already been described in regards to IL-1β and HMGB1 release [71].

The relationship between oxidative stress and neurodegenerative diseases has been widely described over the years, with increasing evidence of the complications being caused and worsened by oxygen-derived free radicals and nonradicals molecules, as well as flaws in the robust antioxidant defense [72]. Despite a strong link, antioxidant therapies have failed to prevent the advance of these pathological conditions. Urate has been described as an endogenous potent non-enzymatic antioxidant molecule. This compound is abundant in the
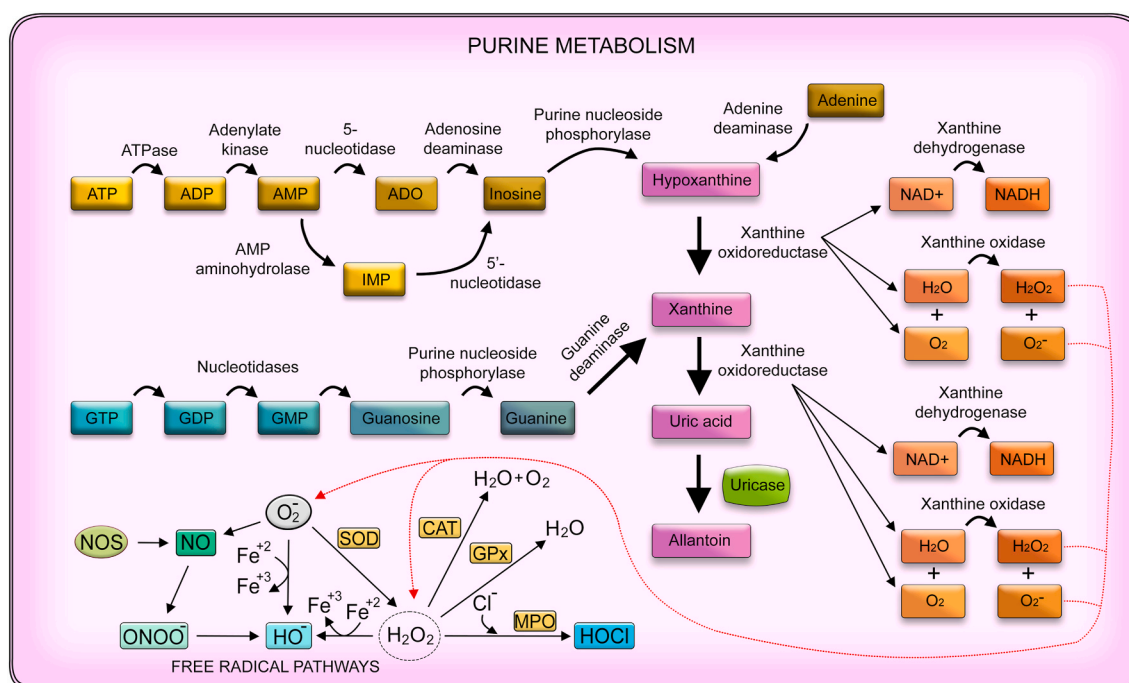

Fig. 1. Purine metabolism and oxidative stress. Purine metabolism involves the hydrolysis of phosphate molecules such as ATP and GTP into nucleosides such as adenine, inosine, and guanine. Briefly, ATP is conversed into ADP by ATPase, then into ADP by adenylate kinase. Next, AMP can be transformed into ADO or IMP by 5'-nucleotidase and AMP aminohydrolase, respectively. Both can be converted into inosine by adenosine deaminase or 5'-nucleotidase as well. Finally, inosine can be metabolized into hypoxanthine, a purine derivative that compounds the salvage pathway that controls purine metabolism. Adenine can be converted into hypoxanthine as well by the action of the adenine deaminase enzyme. Hypoxanthine can be transformed into xanthine by xanthine oxidoreductase. Finally, GTP can be converted into GDP, GMP, and guanosine by different nucleotidases. Then, guanosine can be metabolized by purine nucleoside phosphorylase, generating guanine directly converted into xanthine by guanine deaminase. The purine-based xanthine, by the action of the xanthine oxidoreductase, can be altered to uric acid, representing the final stage of this enzymatic conversions in humans, as they lack the uricase enzyme that converts uric acid in allantoin, present in animals such as mice and rats. Thus, uric acid can accumulate and crystalize in the joints of humans and causes various conditions such as gout due to hyperuricemia. It is noteworthy that xanthine oxidoreductase possesses enzymatic forms, xanthine oxidase, and xanthine dehydrogenase, that in addition to altering purine metabolites, act in redox biology, as the former may produce reactive oxygen species such as superoxide and hydrogen peroxide as by-products and the latter may present NADH oxidase properties and thus, reduces NAD^+ into NADH, contributing to the pro-oxidant system as well.

cerebrospinal fluid and has presented a promising neuroprotective role for treating Parkinson's disease as it reduces dopamine oxidation rate, currently in a phase 3 clinical trial [73].

The antioxidant role of uric acid in oxidative stress is extensive *per se* or by synergy with other antioxidant systems, such as the interaction with the enzyme SOD as a mechanism to inhibit the conversion of superoxide anion to peroxynitrite after reacting with nitric oxide (NO) [74]. Urate is likewise a potent metallic antioxidant. It promotes stable chelation of ferric and ferrous ions, exerting its oxidative ability over ascorbate by forming urate-ion complexes without oxidizing itself and preventing liposomal lipid peroxidation by joining phospholipids within liposomal membranes [75,76].

The enzyme responsible for converting hypoxanthine into xanthine and then into uric acid is xanthine oxidoreductase (XOR), which takes two forms: xanthine dehydrogenase and xanthine oxidase (XO). The reversible interchange between these two forms occurs in numerous physiological and pathological situations, and it relies on an intermediary with both activities dependent on the C-terminal peptide [77]. Beyond urate production, xanthine oxidoreductase in a hypoxia context may also assist the antioxidant system via its nitrite reductase activity, generating NO, along with the withdrawal of electrons to reduce O_2 at the FAD cavity within this enzyme [78].

In addition to antioxidant activity, xanthine oxidoreductase may produce ROS such as superoxide and hydrogen peroxide as subproducts of their oxygen via its XO and NADH oxidase proprieties enzymatic necessity, thereby significantly contributing to the pro-oxidant system (Fig. 1) [79,80]. Ives et al. found that ATP stimulation induces an increase in XO activity via PI3K–AKT signaling pathway forming uric acid and mitochondrial ROS, triggering NLRP3 inflammasome activation and IL-1β secretion [81]. These mechanisms can contribute to inflammation and disease. One of the pathological events that stimulate XO activity is contamination with the influenza virus, increasing free radicals synthesis correlated with the progression of the infection [82]. Hence, inhibition of XOR that attempts to decrease ROS assembly could substantially improve diseases such as hyperuricemia [83].

4. Mechanisms of ATP release

Adenosine triphosphate (ATP) is one of the most evolutionarily conserved nucleotides that acts as a signaling molecule under physiological or pathological contexts as a danger signaling molecule or alarmin [84]. This purine compound presents various features that classify it as an excellent alarmin: First, it can be quickly transported through exocytosis or pore channels; second, the substantial difference between its intra- and extracellular concentrations speeds transport and increases the signal-to-noise ratio nearly without background noise; and third, ATP is soluble in water, which facilitates its diffusion in the extracellular milieu that is predominantly aqueous [85–88]. The receptors that recognize extracellular ATP, mainly P2 receptors, are expressed in almost every cell type, enabling this efficient danger signaling [87].

Hypoxia-mediated damage may induce cells to undergo necrotic death. ATP can be released into the extracellular environment due to cell membrane disruption, activating P2 receptors and NLRP3 inflammasome, creating a pro-inflammatory scenario [89]. Activation of pattern recognition receptors (PRRs) (i.e., Toll-like receptors—TLRs) also induces ATP secretion [90]. P2X7 receptor activation induces massive ATP release via its intrinsic ability to form a membrane pore or leading to secondary activation of pore-forming proteins [18]. Therefore, in addition to passive ATP release by cell rupture, this nucleotide can reach the extracellular medium mostly by active mechanisms such as vesicular exocytosis [91] or pore-forming channels [92]. Vesicular exocytosis is mediated by the vesicular nucleotide transporter VNUT, which controls ATP vesicular storage and consequently exocytosis [91,93]. The mechanism of pore-forming channels is composed of pannexin channels (e.g., pannexin-1), connexin hemichannels (connexin-43), and gasdermin pores [84,92], in addition to volume-regulated anion channels, calcium

homeostasis modulator 1, and maxi-anion channels [94]. ATP non-lytic delivery may also occur utilizing transport vesicles or lysosomes [95].

Although they share some similarities, pannexin-dependent ATP release prevails under physiological conditions, while the role of connexin hemichannels in this context is not well defined [96]. Presumably, the action of connexins is more prominent during pathological circumstances, as their expression is closely associated with TLR activation and the ERK/AP1 signaling pathway [97]. Furthermore, pannexins cannot be classified as hemichannels. Their action does not rely on forming gap junctions between hemichannels from different cell membranes, connecting their cytoplasm directly, but instead on individual membrane channels of cells [98].

The phosphorylation of various connexin hemichannels residues induces conformational and functional changes during its life cycle, controlling its activity from synthesis until degradation, including its activation, permeability, and the open/close state [99,100]. Indeed, the phosphorylation of the serine residue Ser-368 reduces connexin-43 permeability [101]. Similarly, cell stress induced by metabolic inhibition in astrocytes increased the presence of connexin-43 (Cx43) in their membrane, accompanied by dephosphorylation and *S*-nitrosylation (a regular post-translational modification of proteins that usually occurs under oxidative stress). These alterations increase the permeability of the hemichannels, most likely because of inducing the open channel state [102,103]. During enteric neuroinflammation, glial cells stimulate enteric neurons death by producing NO, which in turn activates Cx43, corroborating its opening character, potentializing ATP release, and hence maintaining inflammation [104].

Hypoxic conditions in endothelial cells may reduce ATP release by reducing connexin-43 hemichannels expression concomitantly with an increase in Cx43 phosphorylation [105]. Moreover, the redox signaling could affect other properties within connexin hemichannels, including the oligomerization of the six connexin protein subunits to form the hemichannels and their electrical properties, cytoplasmatic transportation, and permeability [106].

Likewise, the phosphorylation of serine residue Ser-206 in pannexin channels can be modulated by NO in the cell lineage HEK-293 cells, reducing the pore-forming channel activity probably as a defensive mechanism to prevent uncontrolled cell death [107]. The post-translational changes on cysteine residues previously mentioned as *S*-nitrosylation take place in pannexins as well; however, unlike connexins, this modification prompts channel closing [108].

5. P2 receptors signaling in redox biology

In 1989, Kuroki and Minamaki published a seminal article showing that extracellular ATP could modulate redox biology. They found that human neutrophils stimulated by ATP in the presence of cytochalasin B could generate superoxide (O_2^-) [109]. Subsequent studies identified how ATP can induce the generation of free radicals. Nakanishi and colleagues found that peritoneal macrophages from guinea pigs did not require a priming stimulus as human neutrophils to generate O_2^- in response to ATP treatment [110]. ATP and UTP were implicated in O_2^- generation via NADPH oxidase activation [111]. Furthermore, lipopolysaccharide (LPS)-primed macrophages stimulated by extracellular ATP showed an increase in iNOS (nitric oxide synthase) mRNA levels [112,113]. Thus, purinergic signaling began to gain prominence as a signaling pathway capable of interfering with redox biology.

The first evidence linking purinergic receptors and redox signaling came from Shen and colleagues. The authors sought to understand the mechanism by which H_2O_2 was able to trigger contraction in the rat aorta. They found that this effect was mediated by activating ATP receptors [114]. Following this idea, they demonstrated for the first time the possible involvement of P2 receptors in rat aorta contraction activated by H_2O_2 using two non-selective P2 antagonists (suramin and RB-2) that completely abolished aorta contraction [115].

A close relation was established between changes in cytosolic $[Ca^{+2}]$

and ROS generation through the activation of signaling pathways composed by calcium-dependent proteins – isoforms of protein kinase C (PKC), MAP kinase members, and phospholipase A2 [116,117]. These mechanisms promoted the NADPH oxidase activation, the main enzyme involved in O_2^- generation [117]. Motivated by these reports about the relation of intracellular signaling pathways involved in ROS generation and also by the ability of extracellular ATP in triggering these pathways, Cruz and colleagues stimulated primary alveolar macrophages with ATP and other extracellular nucleotides (i.e., ADP, UTP, and UDP) and they measured increased ROS levels [118]. Despite a transient response, high ROS levels activated the phosphatidylinositol-3 kinase (PI3K) pathway, leading to AKT and ERK1/2 phosphorylation contributing to caspase-1 activation and IL-1β and IL-18 secretion (Fig. 2) [119]. Following the elucidative processes behind ATP-induced ROS generation, several reports found that P2 agonists or antagonists modulated ROS production [117].

5.1. P2X receptors

P2X receptors have been implicated in the modulation of redox biology. The P2X7 receptor is the most relevant in this context [13,18, 120]. In the early 2000s, P2X7 receptor activation was described as an inductor of H_2O_2 production in primary rat microglia through a mechanism dependent on Ca^{+2} release from intracellular stores. These results were confirmed by using PPDAS and oxidized-ATP (P2X7 inhibitors) to block H_2O_2 production or BzATP (P2X7 agonist) to stimulate ROS release via activation of NADPH oxidase [121]. Pfeiffer and colleagues reported the same effect in RAW 264.7 murine macrophages. These effects were potentiated in LPS-primed cells, whereas P2X7 absence reduced the cell capacity to produce ROS. The P2X7 agonist BzATP also stimulated MAP kinase phosphorylation [122]. In the same line of evidence, ATP-P2X7 receptor signaling promoted ROS generation via NOX2 in murine macrophages [123,124]. The P2X7 receptor-induced ROS production leads to caspase-3 activation through the ASK1-p38 MAPK pathway resulting in apoptosis [123]. In addition to the relevance of the ATP-P2X7 axis for the MAPK pathway, NADPH oxidase activation and peroxynitrite generation are also crucial for IL-1β processing and release by endotoxin primed-human monocytes (Fig. 2) [125]. Recently, Zhang et al. described that P2X7 receptor activation induces GSH efflux, promoting an accumulation of intracellular ROS and subsequent NLRP3 inflammasome activation in the J774.1 murine macrophage cell line [126]. They also found that GSH and GSSG treatment inhibited NLRP3 inflammasome assembly and IL-1β secretion.

ROS generation via P2X7 receptor activation is not only related to immune cells. Mouse and rat submandibular glands produced ROS via P2X7 receptor activation; however, this occurred by different mechanisms. Rat submandibular glands produced ROS via NADPH oxidase in a calcium-dependent manner after treatment with P2X7 receptor agonists, whereas mice submandibular glands demonstrated a calcium-independent mechanism [127,128]. Primary gingival epithelial cells
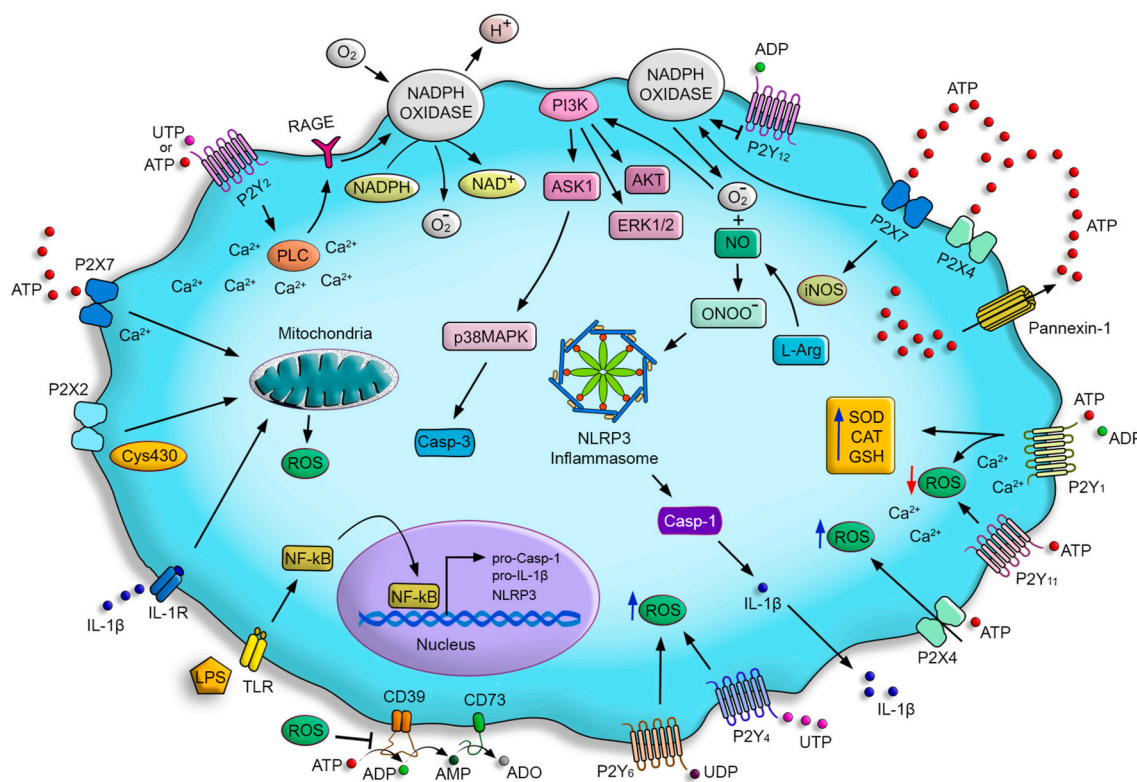

Fig. 2. P2 receptors signaling pathways in the modulation of redox status. Pathogens can release pathogen-associated molecular patterns), such as lipopolysaccharides (LPS), which can activate pattern recognition receptors (PRRs) (i.g, TLRs). This activation leads to the transcription of genes involved in NLRP3 inflammasome activation (NLRP3, pro-casp 1, and pro-IL1β) and ATP release. ATP in high concentrations activates the P2X7 receptor inducing ROS production via NADPH oxidase activation and peroxynitrite. ROS is responsible for activating the phosphatidylinositol-3 kinase (PI3K) pathway, ASK1, AKT, ERK1/2, and p38 MAPK. These mechanisms can induce apoptosis via caspase-3 activation and NLRP3 inflammasome assembly, leading to caspase-1 activation and pro-IL-1β processing. Low concentrations of ATP or UTP can activate the P2Y2 receptor inducing PLC activation and Ca^{+2} mobilization; these components activate NADPH oxidase, responsible for producing ROS in a mechanism dependent on RAGE expression. The ATP also activates the P2X4 receptor that promotes ROS production and potentiates the activity of the P2X7 receptor for activating NADPH oxidase. The P2X7 also induces GSH release, increasing intracellular ROS. P2Y1 receptor increases the expression of antioxidant genes and activity of SOD, CAT, and GSH via intracellular Ca^{+2} signals. The P2Y1 receptor also induces the phosphorylation of endothelial nitric oxide synthase (eNOS). The sensor Cys430 allows the P2X2 receptor to sense the cell redox state in front of ROS production. P2Y4 and P2Y6 receptors promote ROS production, while the activation of the P2Y11 and P2Y12 receptor activation can inhibit ROS generation. ROS inhibits CD39 and CD73 activities.

showed ROS production in response to eATP-P2X7 receptor signaling and NADPH oxidase activation [129]. P2X7 receptor can induce the production of reactive species through NADPH oxidase by increasing the expression of the p47phox subunit that binds to membrane subunit gp91phox producing reactive species [130].

Murine erythroleukemia cells (an erythroid cell line) also produced ROS following P2X7 receptor activation [131]. However, cortical neurons stimulated by P2X7 agonists presented mitochondrial dysfunction and cell death [132]. ATP treatment leads to mitochondrial toxicity and oxidative stress in HEK–hP2X7 cells culminating in apoptosis [133], suggesting some cell types are more susceptible to ATP-induced free radical production.

Interestingly, the P2X7 receptor is not the only P2X receptor that triggers the generation of free radicals. P2X4 receptor also mediates ROS production and autophagy in macrophages, and the mechanism appears to depend on both P2X4 and P2X7 receptors [134]. Regarding other P2X receptors, one that is also involved in the redox processes is the P2X2 receptor, which demonstrated increased activity in front of mitochondrial stress inducers, mercury, and H_2O_2. It is mediated by an intracellular redox sensor Cys430 that allows this receptor to sense the cell redox state [135].

Rat synoviocytes with collagen-induced arthritis presented predominant expression of P2X4 and $P2Y_2$ receptors. When treated with ATP or BzATP, these cells produced ROS. However, treatment with BBG or rhein (a natural bioactive anthraquinone) suppressed ATP/BzATP-induced ROS production, which has been suggested to be controlled by P2X4-mediated extracellular Ca^{+2} entry [136]. In addition, breast cell cancer treated with ivermectin demonstrated a regulated ROS generation mechanism. The authors suggested that ivermectin induces P2X4/P2X7-dependent activation and then ATP release via pannexin-1. This mechanism potentiated P2X7 receptor signaling to activate NADPH oxidase and ROS generation, leading to cancer cell death [137].

Alterations in redox biology triggered by P2X receptors are pivotal to host defense against pathogens [1,138]. *Toxoplasma gondii*-infected macrophages control the parasite load via P2X7 receptor-induced ROS production [139]. P2X7 receptor induces ROS production via NADPH oxidase, while the NLRP3 inflammasome activation and IL-1β secretion induce mitochondrial ROS production via IL-1R activation [140]. Interestingly, in cerebral toxoplasmosis, the P2X7 receptor appears to be relevant for ROS production as its absence resulted in a reduced ROS production and increased number of cysts in the brain [141]. In bacterial sepsis, P2X7 and P2X4-mediated ROS production may be necessary to pathogen control in phagocytes [142]. However, excessive ROS and NO production in sepsis result in oxidative stress, tissue damage, organ dysfunction, and poor outcomes [8,143,144]. In this context, P2X7 receptor deletion attenuated ROS and RNS production in the mice liver and brain, promoting increased SOD and catalase (CAT) activity, which diminishes oxidative stress and protection from organ injury [143,144].

5.2. P2Y receptors

P2Y are G-coupled receptors also identified as modulators of cell redox status. The Gq/11-coupled $P2Y_1$ receptor activated by ADP protected astrocytes from H_2O_2-induced cell death, upregulating the expression of oxidoreductase genes. This effect was observed by treating cells with $P2Y_1$ agonist 2-methylthio-adenosine-5'-diphosphate (2MeSADP). The mechanism was dependent on phospholipase C activation and Ca^{+2} release. When cells were treated with $P2Y_1$ antagonist MRS2179, the protective effect in astrocytes was abolished [145]. Likewise, 2MeSADP treatment reduced ROS generation, while UDP ($P2Y_6$ agonist) increased ROS production in hippocampal astrocyte cultures (Fig. 2) [146].

Rat hippocampal cultures treated with eATP showed neuroprotective effects against oxidative stress and cell death in a mechanism dependent on the $P2Y_1$ receptor. The suppression of the $P2Y_1$ receptor by selective siRNAs inhibited the protection against cell death. A critical molecule

involved in this process is the cytokine IL-6 because 2MeSADP treatment of astrocytes cultures showed increased IL-6 levels, and the neuroprotection was suppressed in the presence of anti-IL-6 antibody [147]. Protective effects of $P2Y_1$ receptor activation also involve intracellular Ca^{+2} release and subsequent expression of antioxidant genes such as CAT, SOD2, SOD3, and genes involved in glutathione (GSH) metabolism (Fig. 2) [148].

Other cell types express $P2Y_1$ receptors, such as cultured endothelial cells. ADP promoted the phosphorylation of endothelial signaling proteins in these cell cultures, such as eNOS. However, this phosphorylation was not observed when these cultures were preincubated with PEG-catalase, which degrades H_2O_2. In this way, endogenous H_2O_2 mediates ADP signaling responses in vascular walls [149]. Skeletal muscle cells with electrical stimulation produce ROS in a mechanism dependent on ATP release and $P2Y_1$ receptor activation. This response is possibly mediated by NOX2 and PKC signaling [150].

Human endothelial cells treated with oxidized-LDL and ATP/UTP showed increased ROS production, NADPH oxidase activation and induced the receptor for advanced glycation end-products (RAGE) expression. This effect was inhibited by the $P2Y_2$ receptor and RAGE siRNA-transfected endothelial cells (ECs), demonstrating that ROS production depended on this receptor and RAGE expression [151]. Similarly, osteoblast-like cells express only the $P2Y_2$ receptor, and in the presence of H_2O_2, these cells release ATP and modify Ca^{+2} metabolism, possibly via $P2Y_2$ [152]. *Leishmania amazonensis*-infected macrophages treated with UTP produced ROS, which might be attributed to $P2Y_2$ and $P2Y_4$ receptors upregulation. The same effect has been demonstrated *in vivo*, once UTP treatment promoted ROS production and phagocytic cells recruitment, limiting parasite replication [153,154].

The $P2Y_{11}$ receptor stimulation attenuated ROS production in aortas isolated from LPS-treated rats [155]. The ATP also exerts an inhibitory action in frog neuromuscular junction, and the P2Y12 receptor-mediated this effect. This was demonstrated using the $P2Y_{12}$ receptor-specific antagonist 2-methylthioadenosine-5'-monophosphate (2-MeSAMP), which did not reduce end-plate currents [156,157]. ATP induces H_2O_2 increases with lipid peroxidation [156]; the authors found that NADPH oxidases (NOX) are probably the primary source of ROS responsible for the inhibitory action of ATP.

Interestingly, a nucleoside 5'-thiophosphate analog, the 2-SMe-ADP (α-S), showed antioxidant/neuroprotective activities in pC12 cells stimulated with $FeSO_4$. This compound acted via $P2Y_1$ and $P2Y_{12}$ receptor activation, inhibiting ROS production [158]. The $P2Y_{12}$ receptor is also involved in diabetic wounding once the ADP can reduce ROS production, mitigating the inflammatory response. Meanwhile, a specific $P2Y_{12}$ antagonist, clopidogrel, restored ROS production [159].

6. Ectonucleotidase functionality and oxidative stress

Ectonucleotidases are nucleotide-metabolizing enzymes critical for the sophisticated regulation of purinergic receptors ligands availability. The ecto-nucleoside triphosphate diphosphohydrolases (E-NTPDases), ecto-nucleotide pyrophosphatase/phosphodiesterases (E-NPPs), and ecto-5'-nucleotidase are the leading ectonucleotidases families. E-NTPDases hydrolyze extracellular tri- and diphosphonucleosides to monophosphonucleosides, while E-NPPs hydrolyze pyrophosphate and phosphodiester bonds in a wide range of substrates, including tri- and diphosphonucleosides [11,160]. Among the ectonucleotidases, E-NTPDase1/CD39 and ecto-5'-nucleotidase/CD73 are the most relevant enzymes [11].

In the 1990s, a seminal paper characterized the biochemical activity of vascular CD39. The authors found that CD39 enzymatic activity and immunocontent were significantly decreased by oxidative stress [161]. Further studies found that saturated fatty acids and antioxidants can restore CD39 activity by reducing lipid peroxidation [161,162]. CD73 activity is also inhibited by oxidative stress, and antioxidants reversed this inhibition (Fig. 2) [163].

CD39 and CD73 are critical enzymes of the immunoregulatory machinery of regulatory T cells (Treg) by scavenging ATP generating adenosine [164,165]. Recently, Gerner et al., 2020 found that the TGF-β-mediated CD39 upregulation in Tregs is impaired by ROS [166]. Furthermore, interferon gamma-producing CD8$^+$ T cells generate ROS, which increases CD39 expression as a regulatory mechanism via JNK and NFκB signaling [167]. The increase of CD39 expression favors adenosine generation and A$_{2A}$ activation with immunoregulatory effects [167].

Although the activity of these enzymes is affected by free radicals, the overexpression of human CD39 and CD73 protects EC against H$_2$O$_2$-induced oxidative stress and damage [168]. Intracellular pathogens have shown the ability to manipulate the host cell, upregulating CD73 expression for decreasing ROS generation [169]. *P. gingivalis*, a gram-negative oral bacterium, significantly boosts CD73 activity and expression in host cells to overcome the microbicidal effects of ROS [169]. CD73 expression in the mouse brain also promotes parasite spreading in a model of cerebral toxoplasmosis [170].

7. P1 receptors signaling in redox biology

As has been extensively discussed elsewhere, adenosine is a powerful vasoactive nucleotide derivative component in hearts submitted with hypoxic stress [171]. Hypoxia may occur because of obstruction or insufficient blood frow, namely ischemia; in these circumstances, adenosine concentration increases substantially and may act through A$_1$ and A$_3$ receptors to promote myocardial ischemic preconditioning, a preventive mechanism after ischemic lesions [172] that aids cytoprotection by a variety of responses, such as inhibited production of ROS by activated neutrophils [173,174].

Adenosine has a close relationship with hypoxia-inducible factor-1 (HIF-1), enhancing its expression in human melanoma cells at the translation level in a hypoxic framework mediated through p44/42 MAP and p38 MAP kinases pathways stimulated by A$_3$ receptor activation [175]. However, HIF-1 might play dual roles in ischemia-induced by hypoxia, being protective or toxic depending on several inducible factors of this illness, as well as the cell type [176]. In this context, agonism of A$_1$ and A$_3$ receptors, together with LPS incitement, suppresses HIF-1 expression and aggregation in astrocytes by inhibiting phosphorylation of MAP kinases such as p44 and p38 MAPK, hence preventing inflammation and aggressive hypoxic injury, for example, by reducing iNOS inflammatory influence in these cells [177]. In high-altitude hypoxia, resolution can be achieved by augmenting CD73 activity, which in turn expands adenosine plasma concentration, instigating A$_{2B}$ receptors in erythrocytes and promoting AMPK-mediated 2,3-bisphosphoglycerate production, a molecule generated in glycolysis that increases these cell's ability to deliver O$_2$ from hemoglobin into urgent sites [178].

The brain tumor glioblastoma possesses a cellular subpopulation of stem-like cells responsible for its high invasiveness capacity stimulated by the hypoxic extracellular adenosine boost conducted by heightening CD73 activity [179]. Still, concerning cerebral ischemia, the upregulation of the A$_1$ receptor diminishes neuronal damage, protecting the brain against the disturbance, unlike the damaging effects produced by the A$_{2A}$ receptor [180,181]. The eventual damage caused after restoring average blood flux following cardiac ischemia is known as ischemia-reperfusion injury. This involves various pathological conditions that oxygen radicals can worsen. Thus, it can be partly attenuated at a long-term period by antioxidants components [182,183].

Activation of the A$_3$ receptor increased the activity of numerous antioxidant enzymes that maintain the cellular redox homeostasis by decreasing ROS concentration, such as SOD, catalase, and glutathione peroxidase [184]. In addition, the use of adenosine analog in mobilizing A$_{2A}$ and A$_{2B}$ receptors after ischemia-reperfusion injury showed the cardioprotective impact of mitochondria *in vivo* and *in vitro* when dampening mitochondrial superoxide generation per electron transport chain [185]. Furthermore, oxygen-derived radicals such as H$_2$O$_2$ elicit a negative feedback loop in cytotoxicity by increasing the expression of cytoprotective A$_1$ receptors at smooth muscle cells in an NF-kB-dependent manner [186]. Once again, the outcome is reversed in A$_{2A}$ receptors, as ROS reduced their NF-kB-dependent expression [187].

P1 receptors can be liable for a variety of other diseases. ROS was accountable for apoptosis in T$_{reg}$ cells in human and mouse tumor cases, a type of programmed cell death that enables these immune structures to create an immunosuppressive microenvironment via active A$_{2A}$ receptors [188]. The A$_{2A}$ receptors are also related to increased intraocular pressure by upregulating inflammatory markers, such as ROS that elicit the release of NO, IL-1β, and TNF, heightening oxidative stress present in other pathological circumstances [189]. The main effects of adenosine receptors on redox biology are summarized in Table 1.

8. Conclusion

Purinergic signaling and purine metabolism are modulators of redox biology in certain circumstances. The final product of purine metabolism in humans, uric acid, has antioxidant effects *per se* or synergy with antioxidant systems such as the interaction with the enzyme SOD as a mechanism to inhibit the conversion of superoxide anion to peroxynitrite. In addition, the enzyme responsible for the conversion of hypoxanthine into xanthine and then into uric acid in humans XO produces ROS such as superoxide and hydrogen peroxide as subproducts of their oxygen enzymatic necessity, thereby contributing to ROS-mediated NLRP3 inflammasome activation and IL-1β secretion.

P2 signaling activated by tri -and diphosphonucleotides can modulate the redox status of cells. In general, P2X receptors, mainly P2X7 and P2X4, have a prominent role in mediating ROS production during inflammation and infection. P2Y receptors can also induce ROS and NO production. However, P2Y$_1$ and P2Y$_{11}$ can exert antioxidant effects, causing protection against oxidative stress due to inflammation or cell damage.

CD39/CD73 axis functionality is impaired during oxidative stress aggravating pathological conditions of inflammation, infection, and tissue injury. By contrast, the upregulation of these enzymes can decrease ATP-induced oxidative stress and minimizes ROS-induced cell damage but favors adenosine generation and pathogen survival during infection. Finally, in general, adenosine receptors have been shown to activate the mechanisms for maintaining redox homeostasis in pathological situations.

Table 1
Modulation of redox status by adenosine receptors.

Adenosine receptor	G-coupled protein	Cell type	Effect redox status of cell
A$_{2A}$	Gs → ↑Adenylate cyclase	Microglial cells	↑ROS, NO, IL-1β, TNF [175]
		Cardiac myoblast cells	↓ROS [171]
A$_{2B}$	Gs → ↑Adenylate cyclase Gq → ↑ PLCγ	Erythrocytes	↑2,3-BPG, ↑O$_2$ [164]
A$_1$	Gi → Ø Adenylate cyclase Go → ↑PLCβ	Neutrophils	↓ROS [159,160]
		Astrocytes	↓HIF-1, iNOS [163]
		Smooth muscle cells	↓ROS, ↑NF-kB [172]
A$_3$	Gi → Ø Adenylate cyclase Gq → ↑PLCγ	Neutrophils	↓ROS [159,160]
		Melanoma cells	↑HIF-1 [161]
		Astrocytes	↓HIF-1, iNOS [163]
		Basophilic leukemia cell	↑SOD, CAT, GPx [170]

PLC: Phospholipase C; ROS: Reactive oxygen species, NO: Nitrogen oxide, IL-1β: Interleukin 1 beta, TNF: Tumor necrosis factor, 2,3-BPG: 2,3-Bisphosphoglyceric acid, HIF-1: Hypoxia inducible factor-1α, iNOS: inducible nitrogen oxide synthase, SOD: superoxide dismutase, CAT: catalase, GPx: glutathione peroxidase.

Therefore, elucidating mechanisms and signaling pathways by which purinergic signaling and purine metabolism can affect the redox biology of the cell may suggest new therapeutic approaches for pathologies caused by oxidative stress, such as P2 receptor antagonists or soluble apyrases for nucleotide degradation. In addition, in infectious diseases where P2 receptor activation contributes to reactive species production and pathogen elimination, the administration of agonists and ectonucleotidase neutralizing antibodies are feasible strategies.

Declaration of competing interest

The authors declare no competing or financial interests.

Acknowledgments

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