Pharmacological Research 230 (2026) 108274

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Adenosine receptors in blood cells: Biomarkers and beyond

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ARTICLE INFO

Keywords:
Adenosine receptors
Blood
Tissues
Biomarkers
Pharmacological targets

ABSTRACT

The identification of reliable, non-invasive biomarkers that reflect molecular alterations in deep and inaccessible tissues remains a major challenge in translational medicine. In this context, peripheral blood cells have emerged as valuable surrogates of tissue-level pathophysiology. Among molecular systems expressed in circulating cells, adenosine receptors (ARs) represent particularly attractive candidates due to their central role in regulating inflammation, immune responses, vascular function, and tissue homeostasis. This review focuses on the expression and functional modulation of AR subtypes in peripheral blood mononuclear cells and platelets, highlighting their potential as translational biomarkers across a wide spectrum of human diseases. Accumulating evidence demonstrates that disease-associated alterations of A_{2A} and A_3 ARs in circulating cells frequently mirror receptor remodeling occurring in the brain, cardiovascular system, inflamed tissues, and tumors. In neurodegenerative and cardiovascular disorders, peripheral A_{2A}AR dysregulation reflects central or myocardial changes and correlates with disease severity and progression. In contrast, the A_3AR shows a remarkable and consistent parallel overexpression in both pathological tissues and circulating immune cells in cancer and chronic inflammatory diseases, supporting its value as a circulating biomarker of systemic pathologies. Beyond their diagnostic and prognostic relevance, ARs also represent actionable pharmacological targets, bridging biomarker discovery with therapeutic intervention. Collectively, this evidence positions peripheral ARs profiling as a potential tool for non-invasive disease monitoring and for guiding personalized translational pharmacology strategies.

1. Introduction

The challenge of early and accurate diagnosis, alongside effective monitoring, in complex systemic and neurodegenerative pathologies, particularly those affecting deeply inaccessible tissues like the Central Nervous System (CNS) or coronary vasculature, underscores the urgent need for non-invasive molecular tools that reflect pathological processes, thereby establishing the crucial importance of peripheral biomarkers in translational medicine [1,2].

Decades of research have firmly established the principle that molecular components expressed on circulating immune and blood cells can act as a mirror of systemic pathological states, reflecting alterations found in central target organs, a concept originally underpinned by observations of changes in β-adrenoceptors on lymphocytes paralleling those in the failing heart [3–5]. Among these peripheral indicators, the purinergic system, regulated by adenosine, an ubiquitous nucleoside essential for ATP structure and functioning as a critical extracellular autacoid, especially in states of stress, hypoxia, and inflammation, is particularly prominent, with its effects mediated by four G protein-coupled receptor (GPCR) subtypes named A_1, A_{2A}, A_{2B} and A_3. This family of receptors is widely distributed across the body, modulating key physiological functions such as neuroprotection, cardiovascular tone, immune responses, and inflammation [6–8].

Among the four-adenosine receptor (ARs) subtypes, A_{2A} and A_3 have emerged as central regulators across multiple pathological conditions, including neurodegeneration, cardiovascular diseases, cancer, and chronic inflammation. The A_{2A}AR has garnered particular attention for its translational relevance owing to its robust expression in nervous, cardiovascular, and immune cells [9]. This widespread localization has led to the recognition of peripheral blood cells, such as lymphocytes, neutrophils, monocytes, and platelets, as accessible substrates for investigating receptor-related pathophysiological mechanisms [10]. In neurodegenerative and cardiovascular diseases, alterations in A_{2A}AR expression and function in circulating cells have been shown to mirror changes occurring in affected tissues, supporting its development as a non-invasive biomarker in these settings. In oncology, A_{2A}ARs are

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https://doi.org/10.1016/j.phrs.2026.108274
Received 10 April 2026; Received in revised form 28 May 2026; Accepted 29 May 2026
Available online 30 May 2026
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consistently overexpressed within the tumor microenvironment, where they play a pivotal role in adenosine-mediated immunosuppression by inhibiting T- and NK-cell effector functions [11]. However, direct evidence demonstrating parallel modulation of A_{2A}ARs in tumor tissues and peripheral blood mononuclear cells (PBMC) is still lacking, limiting their current validation as peripheral biomarkers in cancer.

In contrast, the A_3AR is increasingly recognized for its preferential and systemic overexpression in solid tumors and chronic inflammatory conditions, with concordant upregulation detected both in diseased tissues and in circulating immune cells [12,13]. Elevated A_3AR levels have been reported in tumor-infiltrating immune cells [14], in colorectal and breast cancer [15,16], mesothelioma [17], and in PBMCs from patients with autoimmune disorders [18] supporting a tissue–blood parallelism that distinguishes A_3AR from other AR subtypes.

This differential pattern reflects a disease-context–dependent distinction between A_{2A} and A_3 ARs. While several reviews have addressed the pharmacology of ARs, here, we primarily focus on blood-cell-based AR profiling as a bridge between molecular pathophysiology and clinical application. In addition, therapeutic perspectives are outlined, highlighting how receptor modulation may complement their biomarker role and open future avenues for translational intervention. Therefore, by focusing on the robust correlation between peripheral AR expression/functionality and the molecular status of deep-seated tissues, we will articulate how peripheral ARs serve as a powerful translational bridge, facilitating non-invasive diagnostics and guiding optimized, personalized therapeutic strategies in highly complex human diseases where traditional monitoring remains challenging. Although ARs have long been considered attractive pharmacological targets, and despite decades of intense research and promising preclinical data, their clinical translation has been relatively modest.

Importantly, the agents that have reached clinical use, most notably the selective A_{2A} antagonist istradefylline for Parkinson's Disease (PD) and the A_{2A} agonist regadenoson for myocardial perfusion imaging, have provided crucial proof of concept for the safety, feasibility, and therapeutic relevance of targeting this receptor family [19–21]. At the same time, the continued clinical development of compounds such as A_3AR agonists, including namodenoson (CF−102, known generically as Cl-IB-MECA) and piclidenoson (CF−101, known generically as IB-MECA), underscores the growing therapeutic potential of adenosinergic modulation in inflammatory and oncological settings [22–27]. Moreover, recent advances in AR structural biology have elucidated the molecular principles governing receptor activation, ligand selectivity, and subtype specificity, thereby informing increasingly sophisticated drug-design strategies [8,28,29]. In this context, the emerging ability to monitor ARs expression and function in PBMC offers a complementary precision-medicine framework that leverages recent structural advances and patient-specific receptor profiling to enable more accurate stratification, dynamic monitoring of receptor remodeling, and the development of tailored adenosinergic therapies.

2. ARs in peripheral blood

2.1. Biology of A_1, A_{2A}, A_{2B}, A_3 ARs

Adenosine is a ubiquitous nucleoside derived primarily from ATP hydrolysis, acting as an extracellular autacoid and regulatory molecule. Under physiological conditions, its concentration remains in the nanomolar range, but it rises significantly in response to metabolic stress, inflammation, tissue injury and cancer. Due to its ability to adjust energy metabolism and tissue perfusion during metabolic stress, such as hypoxia or anoxia is often referred to as a "retaliatory metabolite" [30]. Its biological effects are mediated through four GPCR subtypes, A_1, A_{2A}, A_{2B}, and A_3, collectively known as P1 purinergic receptors. These receptors differ in their affinity for adenosine, G protein coupling, and downstream signaling pathways.

The A_1AR, which displays high affinity (100 nM), couples to G_i and G_o proteins to inhibit adenylyl cyclase (AC) and modulate ion channels [8]. It promotes the activation of pertussis toxin and ATP-sensitive potassium channels and suppresses P, Q and N type calcium channels, thereby contributing to neuroprotection by limiting calcium influx and reducing glutamate release. It is predominantly expressed in the CNS e.g. cortex, hippocampus, cerebellum, spinal cord, brainstem and peripherally in the heart, kidneys, liver, vasculature and immune cells [6,31]. Although the A_1AR is highly expressed in the CNS and is well known for its neuroprotective functions, it is not discussed further because our review specifically focuses on studies that have investigated parallel modulation of adenosine receptors in peripheral blood cells and in the corresponding affected tissues. To date, such parallel PBMC-tissue analyses are not to our knowledge available for A1AR in neurodegenerative or other disorders.

The A_{2A}AR, characterized by high binding affinity (310 nM), couples to G_s proteins in peripheral tissues and Golf proteins in the striatum, stimulating AC and activating protein kinase A (PKA), leading to cyclic AMP (cAMP) response element–binding protein (CREB) phosphorylation [8]. In addition emerging evidence suggests that under specific pathological or structural conditions the receptor may also engage Go, expanding its signaling repertoire [32]. Its long intracellular C-terminal tail of over 80 residues contains regulatory sites for phosphorylation and palmitoylation, influencing receptor desensitization and internalization. A_{2A}AR is highly expressed in the striatum, olfactory tubercle, and immune cells such as leukocytes and platelets, mediating anti-inflammatory, anti-aggregatory, and vasodilatory effects.

The A_{2B}AR, characterized by low affinity (15,000 nM), is activated under pathophysiological conditions such as hypoxia and inflammation [8]. It couples to both G_s and G_q proteins, stimulating AC and phospholipase C (PLC), respectively, thereby increasing cAMP and intracellular Ca^{2+}. Recently, A_{2B}AR has also been shown to couple to Gi proteins, enabling it to activate distinct downstream signaling pathways in different cell types through multiple G-protein partners [33,34]. A_{2B}AR is expressed in the intestine, bladder, lungs, immune cells and vasculature, where it is upregulated during cellular stress and contributes to hypoxia adaptation [35].

Finally, the A_3AR, with high affinity (290 nM), couples to G_i/G_o and G_q proteins, inhibiting AC and activating PLC [8]. This dual signaling is implicated in cell proliferation and apoptosis, particularly in tumor cells. A_3AR is expressed at low levels in most tissues, including the heart, lungs, liver, and immune cells such as eosinophils, neutrophils, monocytes, macrophages, and is emerging as a therapeutic target in autoimmune diseases and cancer due to its role in allergic responses and inflammation [36–38].

All ARs also activate mitogen-activated protein kinase (MAPK) pathways, including extracellular signal–regulated kinase (ERK1/2), p38, and c-Jun N-terminal kinase (JNK), contributing to diverse cellular responses such as proliferation, differentiation, apoptosis, and inflammation, depending on the receptor subtype and cellular context [8,39,40]. An overview of receptor distribution, primary function and the determinants that enhance or reduce ARs activation is provided in Table 1.

3. Disease-associated modulation of ARs in PBMCs and platelets

Accumulating studies demonstrate that AR expression in PBMCs and platelets parallels the receptor changes taking place in inaccessible pathological sites, such as the brain, heart, inflamed joint and cancer, thereby providing a peripheral window into tissue-level disease mechanisms. The following sections examine this translational link, emphasizing the diagnostic and prognostic relevance of AR alterations in various pathological contexts (Fig. 1).

3.1. CNS diseases

The idea that systemic alterations may reflect parallel changes in the

Table 1
Biology of adenosine receptors.

Adenosine receptor (AR)	Main source	Primary function	Activators	Inhibitors
A_1AR	CNS, heart, kidney, liver, vasculature, immune cells	Neuroprotective	Increased extracellular adenosine (hypoxia, inflammation, ischemia, ATP breakdown)	Caffeine, low adenosine availability
A_{2A}AR	Striatum, immune cells, platelets, vasculature	Anti-inflammatory, vasodilatory	Hypoxia, inflammation, high extracellular adenosine	Caffeine, recovery from inflammation
A_{2B}AR	Intestine, lung, vasculature, bladder, immune cells	Hypoxia adaptation, cellular stress	Severe hypoxia, tissue injury, chronic inflammation	Reduced hypoxia and tissue damage
A_3AR	Heart, lungs, liver, immune cells	Cell proliferation, apoptosis, immune modulation	Inflammation, tissue stress, hypoxia	Reduced inflammatory signals

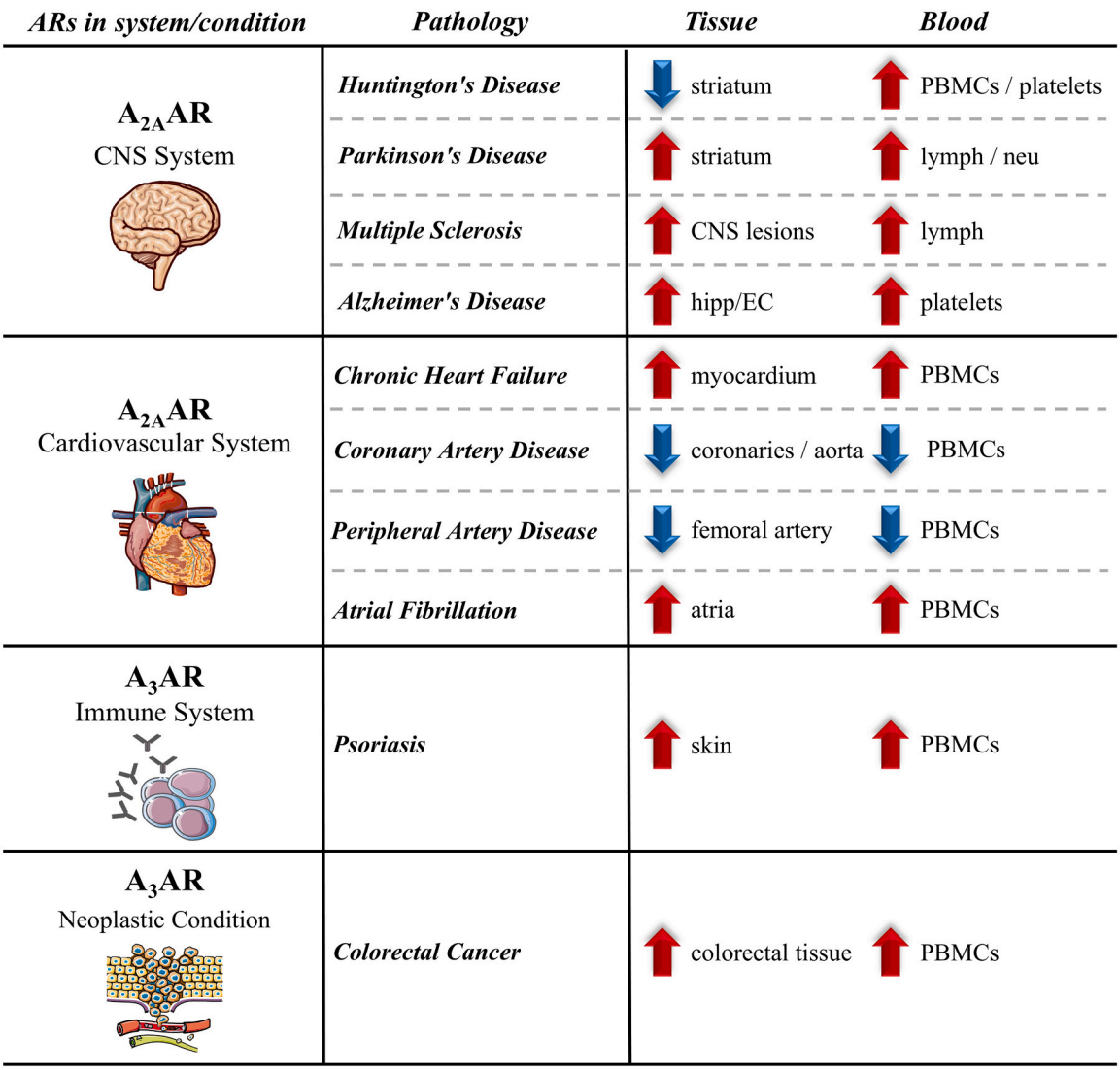


Fig. 1. Peripheral blood adenosine receptors mirror disease-specific tissue remodeling. Detailed overview of disease-specific modulation of A_{2A}AR and A_3AR adenosine receptors (ARs) in peripheral blood cells reflecting receptor changes occurring in deep tissues across neurological, cardiovascular, inflammatory, and oncological diseases. A_{2A}AR displays disease-dependent regulation, with either concordant or divergent patterns between tissue and blood compartments, whereas A_3AR shows a consistent parallel upregulation in both tissues and circulating immune cells in cancer and chronic inflammatory diseases. These findings support peripheral AR profiling as a non-invasive surrogate of tissue receptor status with diagnostic, prognostic, and therapeutic relevance.

CNS has become a key focus in research on neurodegenerative and other neurological diseases (Table 2).

3.1.1. *Huntington's disease (HD)*

HD is a fatal, inherited neurodegenerative disorder associated with progressive breakdown of cerebral neurons. Typically manifests in midlife (ages 35-50), causing severe physical, cognitive, and psychiatric decline over 10-25 years. There is currently no cure, but treatments help manage symptoms [41].

In HD, A_{2A}ARs display a complex regulatory pattern that appears paradoxical. Centrally, multiple studies, including postmortem analyses and transgenic models, report a downregulation of A_{2A}AR expression in the striatum, even in premanifest stages, suggesting an early transcriptional deficit. Mechanistically, mutant huntingtin interferes with CREB

Table 2
Molecular mechanisms underlying the regulation of adenosine receptors (ARs) in human diseases.

PATHOLOGY	ARs MODULATION	MECHANISM OF REGULATION
Huntington's Disease	↓ A_{2A}ARs in striatum	Transcriptional dysregulation: mutant huntingtin reduces CREB binding, decreasing $ADORA_{2A}$ expression [42]. Epigenetic repression: increased 5-methylcytosine and reduced 5-hydroxymethylcytosine within the 5′UTR region suppress $ADORA_{2A}$ transcription [44].
	↑ A_{2A}ARs in PBMCs/platelets	Membrane remodeling: increased membrane fluidity and polarity reorganize lipid microdomains, enhancing A_{2A}AR surface exposure [48].
Parkinson's Disease	↑ A_{2A}ARs in striatum	Histone modifications: reduced H3 methylation and increased H3 acetylation at the $ADORA_{2A}$ promoter enhance transcription [56].
Chronic Heart Failure	↑ A_{2A}ARs in PBMCs	Inflammatory signaling: elevated TNFα levels induce A_{2A}AR upregulation [66].
Coronary Artery Disease	↓ A_{2A}ARs in PBMCs	Homocysteine (HCy)-dependent downregulation: increased HCy reduces A_{2A}AR expression and function [105].
Rheumatoid Arthritis	↑ A_3ARs in PBMCs	Inflammatory signaling: IL−2 and TNFα increase NF-κB that enhances A_3AR expression [18].
	↑ A_{2A}ARs in lymphocytes	Therapeutic modulation: methotrexate, anti-TNFα agents and rituximab reduce A_{2A}AR expression [119].
Solid Tumors	↑ A_{2A}ARs / ↑ A_{2B}ARs tumor tissues	Hypoxia-driven transcription: HIF-1α stabilization increases $ADORA_{2A}$ and $ADORA_{2B}$ expression, contributing to an immuno-suppressive tumor microenvironment [124].

binding at the A_{2A}AR promoter, suppressing transcription and reducing receptor expression [42,43]. Epigenetic modifications, such as increased 5-methylcytosine and decreased 5-hydroxymethylcytosine in the 5′ untranslated region region of A_{2A} gene, further contribute to this reduction, in line with broader epigenetic dysregulation described in HD that affects neuronal identity and synaptic genes [44,45]. These molecular changes occur within a wider disruption of adenosinergic signaling, which functionally interacts with glutamatergic and dopaminergic pathways, thereby modulating excitotoxicity and neuroinflammatory processes that drive HD progression [44].

Conversely, an opposite trend, with increased A_{2A}AR density and amplified receptor-mediated cAMP signaling in PBMCs and platelets from HD patients, both in symptomatic patients and in pre-symptomatic mutation carriers, was observed. The increased receptor density and enhanced cAMP response to agonists in peripheral cells support the hypothesis that A_{2A}AR alterations may emerge early in the disease course and serve as accessible biomarkers of neurodegeneration [46]. These peripheral changes in platelets correlate with CAG repeat length and age at onset, but only in patients whose clinical picture is dominated by chorea over other motor symptoms [47]. Together, these studies show that peripheral A_{2A}AR alterations in HD are consistent, early, and mutation-driven. In addition, in a large multicentric study on HD and other polyglutamine (poliQ) disorders, peripheral lymphocytes from HD patients and pre-symptomatic carriers consistently exhibited elevated A_{2A}AR density, independent of clinical stage or CAG repeat length. This alteration was also observed in spinocerebellar ataxias (SCA1 and SCA2), but not in Friedreich's ataxia or other non-polyQ conditions, suggesting a polyQ-specific cellular effect. In HD, the marked increase in peripheral A_{2A}AR binding does not arise from enhanced receptor synthesis but it reflects changes in membrane properties as lymphocytes from HD patients display significantly greater fluidity and polarity, a biophysical shift that facilitates receptor rearrangement and surface exposure. Such modifications account for the apparent rise in A_{2A}AR density and suggest that peripheral receptor abnormalities mirror systemic lipid alterations driven by mutant huntingtin [48]. In the R6/2 mouse model of HD a transient early increase in striatal A_{2A}AR density and A_{2A}-dependent cAMP production is followed by a marked reduction of A_{2A}AR mRNA at symptomatic stages. This biphasic pattern indicates that, while central A_{2A}AR expression progressively declines during disease progression in mice, peripheral compartments in humans display the opposite trend. Such divergence likely reflects compensatory or disease-specific mechanisms, reinforcing the idea that peripheral A_{2A}AR may act as accessible indicators of underlying central dysfunction [49]. In this context, the intense and ongoing search for reliable biomarkers in HD further underscores the relevance of the A_{2A}AR, whose measurable alterations in peripheral blood cells mirror central pathogenic processes, positioning it as a particularly attractive candidate within current blood-based biomarker discovery efforts [50,51].

3.1.2. Parkinson's disease (PD)

PD is a progressive movement disorder due to loss of dopamine producing neurons in the substantia nigra characterized by tremor, rigidity and bradykinesia. Onset is mostly over the age of 60 [52]. In this context, the hypothesis that PBMCs may reflect CNS alterations in neurodegenerative diseases has gained increasing support over the past two decades, particularly in the context of A_{2A}AR dysregulation in PD. The earliest evidence came from *post-mortem* brain analyses revealing increased A_{2A}AR mRNA expression and receptor binding in the putamen and external globus pallidus of dyskinetic PD patients [53]. Importantly, the upregulation was specific to patients who had developed motor complications following chronic levodopa therapy, suggesting a pathophysiological link between striatopallidal A_{2A}AR overexpression and dyskinesia susceptibility. The absence of significant changes in the caudate nucleus and internal globus pallidus underscores the regional specificity of A_{2A}AR alterations. Subsequent studies extended this observation to peripheral compartments, showing that A_{2A}AR mRNA and protein levels are similarly overexpressed and functionally altered in lymphocytes and neutrophils of PD patients paralleling upregulation observed in the putamen. These peripheral changes were found to correlate strongly with motor symptom severity, as assessed by Unified Parkinson's Disease Rating Scale (UPDRS) scores, and appeared to be independent of age, disease duration, or medication dosage and are associated with elevated plasma levels of tumor necrosis factor-α (TNF-α) and adenosine. These findings suggest that peripheral A_{2A}AR not only reflects disease progression but may also contribute to dopaminergic dysfunction through enhanced receptor activity and cytokine-driven upregulation [54]. Taken together, these peripheral alterations highlight the systemic relevance of A_{2A}AR. This systemic dysregulation may also manifest at the autonomic level, as orthostatic hypotension, one of the most frequent autonomic complications of PD, may partly reflect peripheral A_{2A}AR overexpression, a mechanism previously described in neurally mediated syncope, where increased A_{2A}AR activity contributes to vasodilation and hypotensive susceptibility [55–57]. Moreover, the well-established antagonistic interaction between A_{2A}AR and D2 receptors within basal ganglia circuits implies that changes in A_{2A}AR expression or function may directly influence D2 receptor signaling, as previously discussed [58].

Further studies in lymphocytes of PD patients confirmed that both receptor density and affinity alterations correlated robustly with clinical severity, particularly motor impairment as assessed by UPDRS scores. Patients exhibiting higher A_{2A}AR density and lower affinity were more likely to present with levodopa-induced motor complications such as dyskinesias and fluctuations, independent of age, disease duration, or medication dosage [59]. These findings reinforce the idea of peripheral A_{2A}AR profiling as a non-invasive biomarker for disease progression and treatment response in PD.

In addition, recent evidence underscores the potential of peripheral A_{2A}AR as biomarkers in PD demonstrating a significant upregulation of

A_{2A}AR mRNA and protein levels in the striatum of a PD mouse model as well as in PBMCs from PD patients compared to healthy controls [56]. Notably, this increase inversely correlated with clinical parameters such as age, disease duration, UPDRS scores, and levodopa equivalent daily dose, suggesting that peripheral A_{2A}AR expression might have a potential role as biomarker for PD especially at the initial stages of disease course. The upregulation of A_{2A}AR observed both centrally and peripherally may be driven by systemic inflammatory and oxidative stress signals that converge on epigenetic regulators of gene transcription. Although no significant changes in DNA methylation were detected in PBMCs, evidence from 6-hydroxydopamine (6-OHDA)-lesioned mice highlights that epigenetic mechanisms, particularly a reduction in DNA methylation and increase in histone H3 acetylation at the A_{2A}AR promoter, play a crucial role in driving receptor upregulation in the striatum, reinforcing the translational relevance of peripheral A_{2A}AR alterations as systemic reflections of central pathology [56]. These findings support the use of blood-based A_{2A}AR profiling not only as a diagnostic tool but also as a window into central pathophysiological mechanisms, bridging peripheral biomarkers with therapeutic targets.

The involvement of adenosinergic signaling in PD has been further highlighted emphasizing the role of A_{2A}AR in modulating neuroinflammatory and neurodegenerative processes and supporting their continued investigation as therapeutic targets and potential biomarkers within both central and peripheral compartments [60,61].

3.1.3. Multiple sclerosis (MS)

MS is a chronic autoimmune disease affecting the myelin sheath of neurons in the brain and spinal cord, characterized by loss of vision, sensation and motor power and coordination. Onset is mostly between the age of 20–40 years [62]. Notably, peripheral A_{2A}AR upregulation has also been reported in MS, suggesting that this mechanism extends beyond PD and HD and may represent a broader feature of neuroinflammatory processes across CNS disorders [63]. In vivo imaging studies, through positron emission tomography analysis, revealed increased A_{2A}AR expression in the brains of patients with secondary progressive MS, which correlated with disability scores [64].

In a separate study conducted on a distinct MS cohort, peripheral T lymphocytes of MS patients exhibited a marked increase in A_{2A}AR expression, which correlated with a potent anti-inflammatory response upon receptor stimulation, including reduced cytokine release, inhibition of nuclear factor-κB (NF-κB) activation, and downregulation of very late antigen−4-mediated transmigration [65]. Although these two investigations were not performed on the same patients, the convergence of central and peripheral findings supports the notion that A_{2A}AR regulation reflects the underlying inflammatory milieu characteristic of MS. These findings mirror observations in PD, where peripheral A_{2A}AR density correlates with motor symptom severity and inflammatory markers [54]. Based on the well-known antiinflammatory effects of A_{2A}AR, it is possible to speculate that the receptor upregulation is a compensatory mechanism aimed to counteract the elevated inflammation typical of MS pathogenesis. In this regard, it has been well reported that A_{2A}AR are upregulated in vitro following the treatment of different cell types with proinflammatory stimuli [66,67]. One mechanism proposed to underlie this upregulation involves NF-κB, a transcription factor activated by inflammatory cues and regarded as a key regulator of A_{2A}AR gene expression [68]. By dampening NF-κB activity and reducing the release of pro-inflammatory cytokines, A_{2A}AR signaling appears to function as a feedback mechanism that restrains excessive immune activation. Taken together, the upregulation of A_{2A}ARs observed in CNS lesions and in peripheral immune cells, albeit documented in separate patient cohorts, can be interpreted as complementary manifestations of the same inflammatory drive. This dual pattern highlights A_{2A}ARs not only as local modulators within damaged white matter regions but also as potential systemic biomarkers of immune activation. In this perspective, peripheral lymphocytes, which exhibit enhanced A_{2A} gene and protein levels, may offer an accessible “window” into CNS pathology, reinforcing the relevance of A_{2A}ARs as both therapeutic targets and peripheral indicators of neuroinflammatory processes [66,67,69]. Despite this apparent concordance between peripheral and central findings, evidence from MS and its experimental model, experimental autoimmune encephalomyelitis, indicates that A_{2A}AR signaling does not exert a uniformly protective role. On the contrary, its impact appears to be strongly stage-dependent. In the early phases of disease, A_{2A}AR activation helps restrain peripheral immune cell infiltration and contributes to maintaining blood–brain barrier integrity, in line with the compensatory interpretation suggested by peripheral upregulation. As the disease progresses, however, sustained activation of glial A_{2A}ARs within the CNS shifts this balance, promoting nitric oxide synthase induction and amplifying cytokine production, ultimately exacerbating demyelination and neuroinflammation. This biphasic behavior underscores the complexity of A_{2A}AR-mediated regulation in chronic neuroinflammatory disorders and highlights the need to interpret peripheral–central correlations in light of disease stage [70].

3.1.4. Alzheimer’s disease (AD)

AD is a progressive neurodegenerative disorder characterized by intracellular accumulation of amyloid plaque and neurofibrillary tangles, brain cell shrinkage and death. It is the most common cause of dementia in the elderly [71]. In line with observations in other CNS disorders, peripheral A_{2A}AR upregulation has also been reported in AD, supporting the concept that AR dysregulation in circulating cells may reflect central pathological changes. Accordingly, A_{2A}ARs have emerged as promising biomarkers in AD, not only for their role in central neurodegeneration but also for their peripheral expression profile. A_{2A}AR overexpression in AD has been documented in neurons and astrocytes, where it disrupts synaptic plasticity and promotes neuroinflammation. Mechanistic studies reveal that A_{2A}AR forms functional complexes with N-methyl-D-aspartate receptors, and antagonists such as istradefylline may counteract these effects, offering neuroprotection [72–79]. In addition to selective pharmacological antagonists, naturally occurring non-selective A_{2A}AR antagonists such as caffeine have also been associated with beneficial effects in AD, supported by both epidemiological and experimental evidence [80,81]. In a study involving 26 AD patients with mild to moderate *dementia* and matched controls, A_{2A}AR density was measured in platelets. The results showed a significant upregulation of A_{2A}AR in AD platelets compared to controls, confirming the reliability of this peripheral marker [82]. Parallel analyses were conducted on autoptic brain tissues from 10 donors (6 AD cases with very severe dementia and 4 controls), focusing on frontal white matter, frontal gray matter, and hippocampus/entorhinal cortex (H/EC). A_{2A}AR density was significantly higher in all three regions in AD brains, with the highest levels observed in the H/EC, consistent with the known progression of AD pathology. The concordance between central and peripheral receptor expression strongly supports the hypothesis that platelets can serve as a mirror of neuronal alterations [82]. Taken together, these findings provide robust evidence that A_{2A}AR in platelets reflect central pathological changes in AD, positioning them as both a diagnostic tool and a potential therapeutic target. Accordingly, previous studies focusing exclusively on brain tissue found an altered expression and redistribution of ARs, particularly A_1 and A_{2A}, in AD. Specifically, immunohistochemical analyses of postmortem brain tissues revealed that A_1AR are markedly upregulated in degenerating neurons with neurofibrillary tangles and in dystrophic neurites within senile plaques, showing strong colocalization with both tau and Aβ deposits. While A_1AR mRNA levels remained unchanged, protein levels were slightly elevated in AD hippocampus, suggesting post-transcriptional regulation or impaired receptor degradation. In contrast, A_{2A}ARs, typically confined to striatal neurons in healthy brains, were found to be ectopically expressed in microglial cells in the hippocampus and cortex of AD patients [83]. An increased density of A_1 and A_{2A}ARs has also been reported in the frontal cortex of AD patients, accompanied by enhanced receptor-mediated modulation of adenylyl cyclase activity. Notably, these changes

occurred without corresponding alterations in mRNA levels, suggesting a post-transcriptional regulatory mechanism [84]. These findings suggest a pathological redistribution of ARs, potentially contributing to disease progression. Furthermore, in PBMCs, differential expression of A_{2A}ARs has been observed across dementia subtypes. Notably, lower A_{2A}AR mRNA levels were found in patients with vascular dementia compared to those with AD, suggesting a potential role for A_{2A}AR in distinguishing between these conditions. These findings reinforce the relevance of ARs in both central and peripheral aspects of AD and support their candidacy as biomarkers and therapeutic targets [85,86].

While peripheral A_{2A}AR upregulation in PBMCs of MS and other neurodegenerative conditions is often interpreted as a compensatory anti-inflammatory mechanism, central overexpression of A_{2A}ARs, particularly in neurons, astrocytes, and microglia, appears to exacerbate excitotoxicity and synaptic dysfunction, as shown in AD models. This duality underscores the complexity of A_{2A}AR signaling as its effects depend on cellular context and disease stage, suggesting that therapeutic strategies must consider selective targeting to preserve beneficial peripheral immunomodulation while limiting detrimental CNS overactivation [72,77,87].

3.2. Cardiovascular diseases

ARs are key modulators of cardiovascular physiology, involved in regulating vascular tone, myocardial contractility, and immune responses [88,89]. Among them, the A_{2A}AR is the most extensively investigated in cardiovascular pathophysiology, particularly in peripheral blood cells. Its distinctive distribution makes A_{2A}AR a central player in modulating immune responses and vascular tone, and accumulating evidence shows that A_{2A}AR expression in circulating cells mirrors pathological changes occurring in cardiovascular tissues (Table 2).

3.2.1. Chronic heart failure (CHF)

Chronic heart failure represents a heterogeneous clinical condition encompassing distinct pathophysiological entities, such as heart failure with reduced or preserved ejection fraction [90]. Within this spectrum, the role of ARs may vary depending on the underlying disease mechanisms, and their assessment in peripheral blood cells may be particularly relevant for early disease characterization. Notably, most available evidence derives from patients with advanced heart failure, predominantly with reduced ejection fraction, which may influence the observed patterns of A_{2A}AR modulation and limit their generalizability to earlier stages. In this setting, A_{2A}ARs are markedly upregulated in PBMCs at both gene and protein level, paralleling similar changes in myocardial tissue with increased receptor density, reduced ligand affinity, and enhanced coupling to AC, resulting in amplified cAMP production. Notably, A_{2A}AR expression and function progressively normalize following heart transplantation, in parallel with improvements in hemodynamic parameters and reductions in inflammatory cytokines, such as TNF-α and interleukin−6 (IL−6) [91]. TNF-α itself appears to drive this upregulation as PBMCs from CHF patients exhibit enhanced A_{2A}AR expression and signaling, leading to stronger inhibition of TNF-α release, suggesting a compensatory adenosinergic mechanism aimed at counteracting excessive inflammation [66]. This parallelism between circulating cells and myocardial tissue underscores the systemic nature of adenosinergic dysregulation in CHF [66].

3.2.2. Coronary artery disease (CAD)

CAD encompasses a continuum of ischemic conditions, from subclinical atherosclerosis to overt myocardial ischemia and infarction [92]. In clinically significant ischemia-producing CAD, a tight parallelism between PBMC and tissue has been documented, with A_{2A}ARs consistently downregulated in PBMCs, coronary arteries, and aorta in patients undergoing coronary artery bypass surgery, showing an opposite regulatory direction compared with heart failure [93]. This reduction correlates with impaired receptor function, as shown by diminished basal and agonist-stimulated cAMP production across all compartments. Altogether, these findings support the use of PBMC A_{2A}AR expression as a convenient peripheral indicator for coronary receptor status, allowing indirect assessment of adenosinergic remodeling in CAD. Another clinical observation supporting the diagnostic relevance of peripheral A_{2A}AR profiling in CAD comes from exercise testing. PBMC of patients with a positive treadmill test exhibit significantly lower A_{2A}AR expression and a marked rise in plasma adenosine at peak exercise compared with those with a negative test. This purinergic profile likely reflects an inadequate compensatory vasodilatory response to ischemic stress and may therefore improve the diagnostic accuracy and predictive reliability of treadmill testing [94]. Recent findings further reinforce the diagnostic potential of peripheral A_{2A}AR profiling in CAD. In a pilot study, patients with functionally significant coronary stenosis (fractional flow reserve, FFR < 0.8; an index obtained during coronary angiography that quantifies the hemodynamic impact of a stenosis by measuring the ratio between distal and aortic pressure during maximal hyperemia) exhibited markedly lower A_{2A}AR plasma concentrations compared to those with non-obstructive coronary anatomy, suggesting that evaluation of soluble A_{2A}AR in the plasma may be helpful for screening patients suspected of having CAD [95]. A mechanistic contribution to this downregulation comes from homocysteine metabolism as plasma homocysteine (Hcy) levels inversely correlate with A_{2A}AR expression in plasma of CAD patients presenting an angiographic stenosis $\geq 50\%$. HCy is a sulfur-containing amino acid intermediate whose metabolism is closely interconnected with that of methionine, uric acid, and adenosine. Elevated homocysteine levels, known as hyperhomocysteinemia, are linked to cardiovascular disease and are independently associated with CAD and mortality following myocardial infarction. A_{2A}AR expression by PBMCs was markedly reduced in CAD patients compared to healthy controls and negatively correlated with circulating HCy concentrations [96]. Notably, A_{2A}AR expression declined sharply when HCy exceeded 25 μM, suggesting a threshold effect with potential clinical implications. Complementary in vitro experiments using human lymphoblastoid T cells confirmed that HCy directly suppresses A_{2A}AR expression and impairs receptor-mediated cAMP signaling, both under basal conditions and following agonist stimulation. These findings indicate that elevated HCy may contribute to CAD pathogenesis by attenuating adenosine-mediated vasodilation and immunomodulation, thereby promoting vascular inflammation and atherothrombosis. Importantly, all available human studies have been conducted in patients with functionally significant, ischemia-producing CAD, such as those undergoing coronary artery bypass, individuals with positive exercise tests, or patients with FFR-defined hemodynamically relevant stenoses. Therefore, current evidence indicates that A_{2A}AR dysregulation emerges in the context of myocardial ischemia rather than with mild, non-ischemic CAD. Whether A_{2A}AR alterations occur early enough to detect CAD before clinical symptoms remains an open question that requires dedicated longitudinal studies.

3.2.3. Peripheral arterial disease (PAD)

PAD, which shares a common atherosclerotic pathogenesis with CAD, represents a relevant clinical setting in which AR modulation can be investigated. In patients with lower extremity (LE)-PAD, a condition frequently associated with CAD, A_{2A}AR expression on PBMCs was significantly decreased compared with healthy controls and closely correlated with receptor expression in femoral artery tissue [97]. Functional analyses further showed reduced basal and agonist-stimulated cAMP production, indicating impaired A_{2A}AR signaling. Notably, a high K_D/EC_{50} ratio, consistent with the presence of spare receptors, was identified in patients with concomitant CAD and inducible myocardial ischemia. This finding is particularly relevant for risk stratification, as it suggests a receptor profile associated with heightened susceptibility to myocardial ischemia and therefore useful to identify patients at increased perioperative cardiovascular risk before vascular surgery. Collectively, these results support the use of a simple

blood-based assessment of A_{2A}AR not only as a potential screening tool for LE-PAD, but also as a clinically informative approach for cardiovascular risk stratification in patients with coexisting peripheral and coronary artery disease [97]. Accordingly, in a cohort of 127 patients with suspected CAD, including those with LE-PAD, both the expression levels of A_{2A}ARs and their functionality in terms of cAMP production were significantly lower in patients with positive FFR, indicating obstructive coronary lesions, compared with those with negative FFR. This finding confirm that quantitative and functional profiling of A_{2A}ARs in PBMCs can discriminate patients with myocardial ischemia due to CAD, offering a potential non-invasive biomarker for identifying obstructive CAD in high-risk populations [98]. Overall, available data indicate that AR dysregulation in PAD mirrors that observed in clinically significant CAD and is linked to established, ischemia-producing atherosclerotic disease. Whether similar alterations occur in earlier cardiometabolic conditions, such as obesity, diabetes, hypertension, or metabolic syndrome, remains largely unexplored and warrants further investigation. However peripheral A_{2A}AR expression in PBMCs is altered in hypercholesterolemia, where A_{2A}AR expression in PBMCs is significantly reduced and negatively correlated with low-density lipoprotein cholesterol (LDL-C) levels, likely due to disruption of lipid rafts which are essential for receptor localization and function. This suggests that A_{2A}AR may serve as a sensitive biomarker of cardiovascular risk and inflammatory status [99]. In line with these observations, an ongoing clinical trial is currently investigating whether elevated LDL-C levels modulate A_{2A}AR expression and function in PBMCs and whether these alterations are associated with systemic inflammatory profiles and increased cardiovascular risk in hypercholesterolemic patients [100].

3.2.4. Atrial fibrillation (AF)

AF is a clinically heterogeneous arrhythmia with diverse underlying mechanisms and presentations. It is commonly classified based on its temporal pattern (paroxysmal, persistent, or long-standing persistent) and underlying etiology, including structural heart disease, secondary forms related to conditions such as ischemic heart disease or sleep apnea, lone (idiopathic), and perioperative (POAF) [101].

These findings are consistent with more recent studies showing that adenosine and A_{2A}AR are upregulated in PBMCs of patients with AF, and that their expression correlates with receptor levels in right atrial tissue [102,103]. The peripheral-central correlation was corroborated by elevated plasma adenosine levels and reduced adenosine deaminase activity, indicating a systemic dysregulation of the adenosinergic axis; in patients, this imbalance is associated with abnormal calcium handling in cardiomyocytes, a dysfunction driven by A_{2A}AR gene and protein overexpression that ultimately contributes to cardiac impairment [104,105]. In addition, it has been reported a left-to-right atrial gradient in A_{2A} and A_{2B} ARs expression, with significantly higher receptor levels in the left (LA) compared to the right atrium (RA) [106]. Consistent with these findings, POAF has been associated with a marked upregulation of A_{2A} and A_{2B} ARs across both circulating immune cells and atrial tissue. Patients with underlying structural heart disease undergoing cardiac surgery displayed higher A_{2A} and A_{2B} AR expression in PBMCs compared with healthy controls, and this increase was even more pronounced in those who developed POAF. A similar pattern was observed in atrial samples, where POAF patients exhibited significantly elevated A_{2A} and A_{2B} AR levels in both the LA and RA. Notably, a left-to-right atrial gradient was present, with A_{2A}AR being more abundant in the LA than in the RA. This anatomical asymmetry, combined with the parallel upregulation observed in PBMCs, reinforces the concept of a systemic adenosinergic activation and highlights the potential value of peripheral A_{2A}/A_{2B} AR profiling as a surrogate marker of atrial receptor status and AF susceptibility.

The concept that peripheral receptor profiling can mirror cardiac receptor status is supported not only for A_{2A}AR in heart failure, CAD, LE-PAD, atrial fibrillation and hypercholesterolemia but also historically for β_2-adrenoceptors, where lymphocyte receptor density strongly correlated with atrial β_2-adrenoceptor density and functional responsiveness in patients undergoing coronary artery bypass [3], reinforcing the translational value of PBMC-based biomarker strategies. This concordance confirms that peripheral cells faithfully mirror local pathological changes, reinforcing the systemic nature of adenosinergic remodeling. Collectively, these data support the utility of peripheral A_{2A}AR profiling as a non-invasive tool for monitoring cardiovascular disease progression, therapeutic response, and systemic inflammation. The receptor's dual role in vasodilation and immunomodulation makes it a promising target for future pharmacological interventions.

3.3. Autoimmune diseases

Autoimmune inflammatory diseases are clinically grouped into seropositive for rheumatoid factor, such as rheumatoid arthritis, and a large group of heterogeneous seronegative diseases frequently involving the skin, joints, and gastrointestinal tract, including psoriasis, psoriatic arthritis, ankylosing spondylitis, and Crohn's disease. Within this spectrum, ARs show disease-specific patterns of modulation in both affected tissues and PBMCs (Table 2).

3.3.1. Psoriasis

Psoriasis is a chronic immune-mediated inflammatory disease characterized by dysregulated activation of keratinocytes and immune cells, with a prominent involvement of Th17-driven pathways. In this context, compelling evidence supports a systemic upregulation of the A_3AR. In a pivotal study, increased A_3AR expression was demonstrated both in psoriatic skin biopsies and in PBMCs from patients with moderate-to-severe psoriasis [107,108]. Notably, A_3AR overexpression was observed in lesional keratinocytes as well as in circulating immune cells, reinforcing the concept that A_3AR dysregulation extends beyond the affected tissue and reflects a systemic inflammatory state. Functionally, activation of A_3AR by the selective agonist piclidenoson significantly inhibited the production of IL−17 and IL−23 in human keratinocytes, key cytokines driving psoriasis pathogenesis. This effect was associated with downregulation of NF-κB signaling, highlighting a mechanistic link between A_3AR activation and suppression of pro-inflammatory pathways central to disease progression. Importantly, the concomitant overexpression of A_3AR in both skin tissue and PBMCs supports the use of peripheral A_3AR levels as a non-invasive biomarker of disease activity and therapeutic responsiveness in psoriasis. Clinical development of A_3AR agonists has progressed accordingly with CF101 being currently under evaluation in phase 3 clinical trials for psoriasis and dry eye syndrome [109,110]. In addition to pharmacological approaches, innovative strategies targeting A_3AR are emerging. Notably, a photoswitchable A_3AR agonist enabling optical control of this Gi-coupled receptor through non-invasive topical skin irradiation has been developed in an animal model of psoriasis [111].

Previous studies reported that A_3AR is upregulated in the PBMCs of patients with autoimmune inflammatory conditions like Crohn's disease, rheumatoid arthritis (RA), and psoriasis, compared to healthy subjects [18,112] and this molecular signature aligns with the ongoing phase 3 clinical evaluation of CF101 in psoriasis [113,114].

3.3.2. Rheumatoid arthritis (RA)

The A_{2A}AR and A_3AR have also been extensively investigated in autoimmune and inflammatory joint diseases, particularly RA [115–117].

In particular, A_{2A}ARs are up-regulated in peripheral lymphocytes, where their activation suppresses pro-inflammatory cytokine release and attenuates NF-κB signalling [118]. Furthermore, pharmacological treatment with methotrexate, anti-TNFα agents, or rituximab reduced receptor expression, while receptor stimulation enhanced IL−10 secretion by pathological T cells and elevated serum IL−10 levels in arthritic rats [119]. The A_{2A}AR agonist CGS 21680 was highly effective, as suggested by the marked reduction of clinical signs, in rat adjuvant-induced

arthritis and associated pain. Accordingly, it was later found that A_{2A} and A_3 ARs were upregulated in lymphocytes of patients affected by RA, ankylosing spondylitis and psoriatic arthritis, where receptor activation was responsible for a reduction of inflammatory cytokines release, as well as of metalloproteinases (MMP)−1 and MMP−3 [120]. Additionally, experimental evidence in synoviocyte models indicated that A_{2A}AR activation exerted anti-inflammatory effects [121]. Overall, current evidence indicates that A_{2A}ARs play a relevant immunomodulatory role in inflammatory joint diseases, with most data demonstrating their upregulation and functional activity in PBMC. A_{2A}AR activation in PBMCs consistently suppresses pro-inflammatory cytokine release and inflammatory signaling pathways, supporting their contribution to immune regulation in rheumatoid and related arthritides. However, unlike A_3ARs, parallel evidence directly linking A_{2A}AR modulation in PBMCs to corresponding changes in affected joint tissues remains limited, highlighting the need for further studies addressing tissue-level expression and signaling to fully establish their translational relevance. Concerning A_3AR, its modulation has been extensively studied in arthritis models where treatment with the A_3AR agonist CF502 downregulated A_3AR expression in arthritic paw tissue and PBMCs from adjuvant-induced arthritis animals, accompanied by reduced PKB/Akt and NF-κB activation and decreased TNF-α levels [122]. These findings supported the clinical development of A_3AR agonists, including CF101, which demonstrated clinical improvement in phase 2 trials in RA [123].

3.4. Cancer

3.4.1. Tumor markers

The A_3AR has emerged as a compelling biomarker in oncology, with consistent evidence of its overexpression in solid tumors and peripheral blood cells [124]. A_3AR density was found to be significantly elevated in colorectal adenocarcinoma tissue compared to both adjacent and remote normal mucosa from the same patient [15]. Notably, A_3AR overexpression does not coincide with alterations in mRNA, implying that control is exerted after transcription. The increase in A_3AR protein extended beyond the tumor microenvironment, as peripheral blood lymphocytes and neutrophils from colorectal cancer patients showed a threefold elevation in receptor density compared to healthy controls. This peripheral upregulation normalized following surgical tumor resection, indicating a dynamic and reversible relationship between tumor burden and systemic A_3AR expression. These findings provided the first evidence that A_3AR expression in circulating immune cells could serve as a noninvasive biomarker for colorectal cancer, reflecting tumor-associated molecular alterations and potentially offering a tool for disease monitoring. These data were further confirmed with high A_3AR mRNA and protein levels in colon, breast, and metastatic tissues, with minimal expression in adjacent normal samples. A_3AR overexpression correlated with elevated cyclin D1 and NF-κB, reinforcing its role in tumor proliferation and inflammation [16]. Human clinical studies further demonstrate that the A_3AR is selectively overexpressed in pathological cells and PBMC, providing the biological rationale for A_3AR-targeted therapies and supporting its dual role as a therapeutic target and circulating biomarker [12]. Despite growing evidence supporting peripheral A_3AR expression as a reflection of tumor biology, this concept remains largely unexplored. Additional studies are warranted to confirm and expand these observations across different cancer types and patient populations. Such investigations could help validate A_3AR expression in circulating immune cells as a reliable, noninvasive biomarker and clarify the mechanisms underlying its systemic regulation.

3.4.2. Tumor biology

While the A_3AR remains the most extensively validated AR biomarker in cancer with parallel tissue and peripheral blood evidence, increasing attention has been directed toward the role of A_{2A} and A_{2B} ARs in tumor biology. Both receptors are consistently overexpressed in a wide range of solid tumors, including melanoma, lung, breast, colorectal, renal, hepatocellular and esophageal carcinoma, where they contribute to tumor progression by promoting immune evasion, angiogenesis, and resistance to antitumor immunity [125–127]. In tumor tissues, A_{2A} and A_{2B} AR upregulation is tightly linked to hypoxic conditions and hypoxia-inducible-factor (HIF)−1α activation, leading to enhanced adenosine signaling within the tumor microenvironment (Table 2). In addition, A_{2A} and A_{2B} ARs play key immunomodulatory roles on multiple immune effector populations including T lymphocytes, NK cells, and myeloid cells, where they contribute to suppression of cytotoxic functions, promotion of regulatory phenotypes, and expansion of immunosuppressive myeloid subsets within the tumor microenvironment [124]. Although direct studies simultaneously assessing A_{2A} and A_{2B} AR expression in tumor tissues and PBMC are currently lacking, strong indirect evidence supports the plausibility of a systemic adenosinergic remodeling in cancer patients. Elevated extracellular adenosine levels, increased expression of CD39/CD73, and widespread immune suppression have been documented at the systemic level, suggesting that circulating immune cells are chronically exposed to adenosine-rich conditions.

In this context, A_{2A} and A_{2B} ARs in peripheral immune cells may represent emerging yet unvalidated, peripheral biomarkers of tumor-associated immunosuppression, analogous to the established A_3AR paradigm. Future studies directly correlating receptor expression and function in tumor tissues and PBMCs will be essential to define their biomarker value and to support their integration into non-invasive diagnostic or monitoring strategies [11].

4. Therapeutic targeting of ARs: pharmacological agents and translational status

ARs have long been considered attractive therapeutic targets, but only a limited number of ligands have reached clinical application. Below, we summarize the key pharmacological agents acting on A2A and A3ARs, focusing on their mechanism of action, safety profile, and current translational status. While istradefylline and regadenoson are approved drugs, piclidenoson and namodenoson remain in advanced clinical development and illustrate the growing interest in A_3AR-targeted therapies (Table 3).

4.1. A_{2A}AR–targeting agents

4.1.1. Istradefylline

Istradefylline is a highly selective A_{2A}AR antagonist developed to modulate striatopallidal neurotransmission in PD.

Preclinical laboratory studies demonstrated nanomolar affinity for A_{2A}AR with minimal activity at other AR subtypes, confirming its pharmacological specificity. Blocking A_{2A}AR alters the functional balance at the A_{2A}AR-D2 receptor complex, diminishing A_{2A}AR -mediated inhibition and thereby permitting a more robust activation of D2-dependent dopaminergic signaling [128]. In animal models of PD, including 6-OHDA-lesioned rodents and MPTP-treated primates, istradefylline consistently improved motor deficits, potentiated the antiparkinsonian effects of L-DOPA, and reduced “off”-like behaviors without exacerbating dyskinesia, thereby supporting its translational potential.

Human studies confirmed these preclinical observations. Phase I trials established good oral bioavailability, linear pharmacokinetics, and a favorable safety profile. Multiple phase II and III randomized trials in PD patients with motor fluctuations demonstrated that adjunctive istradefylline significantly reduces daily “off” time and improves motor performance. The most frequent adverse events such as dyskinesia, hallucinations, insomnia and nausea, are consistent with enhanced dopaminergic tone but are generally mild to moderate in severity. Long-term extension studies further supported sustained efficacy and tolerability [129–132]. Based on this integrated body of laboratory,

Table 3
Pharmacological agents targeting A_{2A} and A_3 ARs: mechanism, safety and translational status.

Drug	Receptor Target	Mechanism of Action	Development Stage	Safety Profile
Istradefylline (KW-6002)	A_{2A}AR antagonist	↑Dopaminergic signaling; ↓"off" time	Approved for Parkinson's disease (Japan 2013; USA 2019)	Dyskinesia, hallucinations, insomnia, nausea; generally well tolerated
Regadenoson	A_{2A}AR agonist	Selective, short-acting coronary vasodilator; rapid ↑ cAMP	Approved for myocardial perfusion imaging	Dyspnea, flushing, chest discomfort; rare AV block or seizures
Piclidenoson (CF101 / IB-MECA)	A_3AR agonist	Anti-inflammatory and immunomodulatory effects via NF-κB, PI3K/AKT, Wnt pathways	Phase II/III for rheumatoid arthritis and psoriasis	Very favorable safety profile; no dose-limiting toxicities
Namodenoson (CF102 / Cl-IB-MECA)	A_3AR agonist	Pro-apoptotic and anti-fibrotic effects; modulates NF-κB, PI3K/AKT, Wnt	Phase II/III for hepatocellular carcinoma and non-alcoholic steatohepatitis	Very favorable safety profile; no dose-limiting toxicities

animal and clinical evidence, istradefylline became the first A_{2A}AR antagonist approved for PD, receiving regulatory authorization in Japan (2013) and the United States (2019) [133]. Its clinical success provides proof-of-concept for therapeutic A_{2A}AR antagonism and validates adenosinergic modulation as a viable strategy in movement disorders.

4.1.2. Regadenoson

Regadenoson is a selective A_{2A}AR agonist developed as a pharmacologic stress agent for myocardial perfusion imaging. *In vitro* studies demonstrated affinity for A_{2A}AR with markedly lower activity at A_1AR, A_{2B}AR and A_3AR subtypes, a profile that minimizes undesirable chronotropic and dromotropic effects associated with less selective adenosine analogues. Laboratory assays confirmed rapid receptor activation and transient cAMP elevation, consistent with the short-acting vasodilatory response required for diagnostic use. Preclinical animal studies in rodents showed that regadenoson induces potent, dose-dependent coronary vasodilation with minimal systemic hemodynamic impact [134]. Human studies further validated these findings. Early clinical studies in humans demonstrated rapid onset and short duration of coronary vasodilation compatible with single-bolus administration while formal pharmacokinetic and pharmacodynamic characterization was provided by a subsequent population pharmacokinetics and pharmacodynamic analysis [135,136]. Phase II and III clinical trials established that regadenoson is non-inferior to adenosine for detecting reversible myocardial ischemia, while offering improved tolerability and simplified administration [137,138]. The most common adverse events such as dyspnea, flushing, chest discomfort and headache, were generally transient and self-limiting. Rare cases of atrioventricular block have been reported, but overall safety remains favorable [139]. These data led to regulatory approval in the United States and other countries, making regadenoson the first selective A_{2A}AR agonist used clinically and providing robust proof-of-concept for targeted adenosinergic modulation in cardiovascular diagnostics [19,139].

4.2. A_3AR agonists in clinical development: piclidenoson and namodenoson

Piclidenoson and namodenoson are highly selective A_3AR agonists developed for chronic inflammatory and oncological indications. Both compounds exhibit nanomolar affinity for A_3AR with negligible activity at other AR subtypes, ensuring a high degree of pharmacological specificity [12]. Laboratory studies have shown that A_3AR activation modulates key intracellular pathways, including PI3K/AKT, NF-κB and Wnt, resulting in anti-inflammatory, immunomodulatory and pro-apoptotic effects that are preferentially expressed in cells and tissues with A_3AR overexpression, such as tumor cells and chronically inflamed immune cells [16,112,140,141].

Preclinical animal studies support these mechanistic findings. Piclidenoson demonstrated efficacy in models of RA, colitis and psoriasis, reducing inflammatory cell infiltration and tissue damage [142,143]. Namodenoson showed antitumor activity in hepatocellular carcinoma (HCC) models and exerted anti-fibrotic and anti-steatotic effects in models of chronic liver disease [144]. Both agents displayed excellent safety profiles in toxicology studies, with no significant cardiovascular, hepatic or neurological toxicity at therapeutic doses [12].

Clinical development has further confirmed their favorable tolerability. Piclidenoson has completed phase II/III trials in RA and psoriasis, showing biological activity consistent with A_3AR engagement and clinical improvement in subsets of patients with high baseline A_3AR expression [114,123]. Namodenoson is in phase II/III development for HCC and non-alcoholic steatohepatitis (NASH) [145]. In HCC, signals of efficacy have been observed particularly in patients with Child–Pugh B7 cirrhosis, while in NASH, improvements in liver enzymes, inflammatory markers and metabolic parameters have been reported. Across studies, Namodenoson has shown an excellent safety profile, with no dose-limiting toxicities and good tolerability even in patients with advanced liver disease [144].

Although neither compound has yet achieved regulatory approval, the convergence of laboratory, animal and human evidence supports the therapeutic potential of selective A_3AR activation in inflammatory and oncological diseases and justifies ongoing late-stage clinical evaluation.

5. Conclusions and perspectives

Peripheral ARs have emerged as informative molecular indicators capable of reflecting disease-related alterations occurring in deep and inaccessible tissues. Across neurological, cardiovascular, oncological, and immune-mediated diseases, alterations in A_{2A} and A_3AR expression and function in circulating immune cells consistently mirror, although with disease-specific nuances, the molecular remodeling occurring in deep and otherwise inaccessible tissues. Taken together, current evidence suggests that peripheral ARs profiling may offer more than a descriptive biomarker readout, providing a biologically grounded window into disease mechanisms that could, in the future, support clinical decision-making. The reproducible concordance between peripheral and tissue-level A_3AR upregulation in cancer and chronic inflammation, together with the robust peripheral reflection of A_{2A}AR dysregulation in neurodegeneration and cardiovascular disease, underscores the potential of ARs to serve as early diagnostic indicators, prognostic tools, and dynamic monitors of therapeutic response.

Looking ahead, several avenues hold particular promise. First, large, multicenter longitudinal studies are essential to validate AR-based signatures across disease stages, therapeutic contexts, and diverse patient populations. Second, integrating ARs profiling with additional purinergic biomarkers such as CD39/CD73 activity, adenosine and ATP levels, or P2 receptor expression, alongside inflammatory, metabolic, and omics-derived markers may enhance diagnostic accuracy and predictive power. Third, the convergence of ARs biology with therapeutic innovation invites the development of next-generation modulators, including biased agonists, allosteric regulators, and combination strategies targeting CD39/CD73 or immune checkpoints. Finally, applying machine-learning approaches and computational pharmacology to large ARs datasets may help identify patterns of receptor remodeling and support more personalized therapeutic strategies. In this evolving

landscape, peripheral ARs stand out as versatile tools at the interface of diagnosis and therapy. From a pharmacological perspective, ARs offer dual utility as biomarkers and therapeutic targets. The selective A_{2A}AR antagonist istradefylline and the A_{2A}AR agonist regadenoson illustrate the clinical feasibility of targeting this axis, while A_3AR agonists such as piclidenoson and namodenoson highlight their promise in psoriasis/RA and oncology, respectively. However, the redundancy and compensatory nature of purinergic signaling require multi-target strategies, combining receptor modulators with inhibitors of ectoenzymes and immune checkpoints to overcome resistance mechanisms. Advances in drug delivery systems capable of crossing biological barriers and achieving tissue selectivity will further enhance therapeutic impact. Altogether, these findings position peripheral ARs as a link between disease-related molecular mechanisms and their potential clinical translation, supporting the future development of blood-based approaches for personalized pharmacology.

CRediT authorship contribution statement

Stefania Gessi: Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. **Pier Andrea Borea:** Supervision, Conceptualization. **Katia Varani:** Writing – review & editing. **Stefania Merighi:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization.

Ethics approval

Not applicable.

Funding

This work was supported by the Ministry of University and Research (MUR) under the National Recovery and Resilience Plan (NRRP), Project PE00000006 "MNESYS – A multiscale integrated approach to the study of the nervous system in health and disease" (CUP H93C22000660006; DN 1553, 11 October 2022).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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Data availability

No data was used for the research described in the article.

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