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TARGETED CANCER THERAPY THROUGH INHIBITION OF PURINERGIC RECEPTORS: THE ROLE OF A1 RECEPTOR ANTAGONISTS

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Abstract: The tumor microenvironment (TME) plays a crucial role in cancer progression, immune evasion, and therapeutic resistance. Purinergic signaling, mediated by extracellular nucleotides (ATP, ADP, AMP) and nucleosides (adenosine), has emerged as a critical regulatory system within the TME. Adenosine, in particular, accumulates to high levels in tumors and predominantly exerts immunosuppressive and pro-tumorigenic effects through its interaction with four G protein-coupled receptor subtypes: A1, A2A, A2B, and A3. While the roles of A2A and A2B receptors in cancer are increasingly well-documented, the contribution of the A1 adenosine receptor (A1R) is more complex and context-dependent. This review explores the multifaceted roles of A1R in cancer biology, including its expression in various cancer types, its impact on tumor cell proliferation, survival, angiogenesis, and immune modulation. We delve into the therapeutic potential of targeting A1R using specific antagonists, summarizing preclinical evidence that suggests A1R blockade can inhibit tumor growth and modulate the TME. Furthermore, we discuss the underlying mechanisms of action, the challenges associated with A1R-targeted therapies, including receptor subtype selectivity and potential side effects, and future directions for developing A1R antagonists as novel anti-cancer agents, potentially in combination with existing treatments. The strategic inhibition of A1R signaling presents a promising avenue for innovative targeted cancer therapies.

Keywords: Purinergic Receptors, A1 Adenosine Receptor, Cancer Therapy, Targeted Therapy, A1 Antagonists, Tumor Microenvironment, Adenosine Signaling, Immunosuppression.

INTRODUCTION

Cancer is a complex constellation of diseases characterized by uncontrolled cell growth, invasion, and metastasis [7]. The quest for more effective and less toxic cancer treatments has driven the development of targeted therapies, which aim to interfere with specific molecules involved in tumor growth and progression [8]. The purinergic signaling system, an ancient and ubiquitous intercellular communication network mediated by extracellular purines and pyrimidines, has gained prominence as a critical regulator of cancer biology [9].

Extracellular adenosine, a key purine nucleoside, plays a pivotal role in the TME. Its concentration is significantly elevated in solid tumors due to increased release and production, primarily from the hydrolysis of ATP by ectonucleotidases CD39 (ENTPD1) and CD73 (NT5E), which are often overexpressed on cancer cells and immune cells [10, 11]. Hypoxia, a common feature of solid tumors, further upregulates CD73 and adenosine production [12]. Adenosine exerts its diverse biological effects by binding to four distinct G protein-coupled receptors (GPCRs): A1R, A2AR, A2BR, and A3R [5]. These receptors differ in their affinity for adenosine, downstream signaling pathways, and tissue distribution.

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The A1R is typically coupled to Gi/o proteins, leading to the inhibition of adenylyl cyclase, decreased cyclic AMP (cAMP) levels, activation of potassium channels, and modulation of calcium signaling and MAP kinase pathways [13]. A1Rs are widely expressed throughout the body, including the brain, heart, kidney, adipose tissue, and various immune cells [14]. In the context of cancer, the role of A1R signaling is multifaceted and appears to be highly dependent on the specific cancer type, the cellular context (tumor cells vs. stromal or immune cells), and the prevailing conditions within the TME [6, 15].

Some studies suggest that A1R activation can promote cancer cell proliferation, survival, and migration in certain cancer types [16, 17]. Conversely, other reports indicate potential anti-tumor effects or a more nuanced role where A1R signaling might restrain certain aspects of tumor progression or have differential effects on distinct cell populations within the tumor [18, 19]. This complexity underscores the need for a thorough understanding of A1R's function in specific oncological settings before its therapeutic potential can be fully realized.

Given the often pro-tumorigenic and immunosuppressive environment fostered by high adenosine levels, antagonizing adenosine receptors has emerged as an attractive therapeutic strategy. While A2AR and A2BR antagonists have shown significant promise, particularly in immunotherapy, the therapeutic targeting of A1R is a less explored but potentially valuable approach [20]. Specific A1R antagonists could offer a means to directly inhibit A1R-mediated pro-tumorigenic signals on cancer cells or to modulate the activity of immune and stromal cells in a beneficial way.

This review aims to: Summarize the current understanding of A1R expression and its diverse roles in different cancer types. Evaluate the preclinical evidence for the anti-cancer effects of A1R antagonists. Discuss the potential mechanisms of action through which A1R antagonists might exert their therapeutic effects. Identify the challenges and future directions for the clinical development of A1R antagonists in oncology.

By consolidating the available information, we hope to highlight the therapeutic rationale for targeting A1R and stimulate further research in this promising area of cancer therapy.

MATERIALS AND METHODS

This review was conducted through a comprehensive literature search of electronic databases, including PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. The search was performed using a combination of keywords and MeSH terms, including but not limited to: "A1 adenosine receptor," "A1R," "ADORA1," "cancer," "tumor," "carcinoma," "oncology," "A1 receptor antagonist," "DPCPX" (8-Cyclopentyl-1,3-dipropylxanthine), "CGS 15943," "adenosine signaling," "tumor microenvironment," "cancer cell proliferation," "apoptosis," "angiogenesis," "immune modulation," and "targeted therapy."

The search was primarily focused on original research articles and review papers published in English up to April 2025. Studies were selected for inclusion if they provided information on: The expression of A1R in cancer cells, tumor tissues, or immune cells within the TME. The functional roles of A1R signaling in cancer cell biology (eg, proliferation, survival, migration, invasion). The effects of A1R agonists or antagonists in in vitro or in vivo cancer models. Mechanisms of action related to A1R signaling in cancer. The development or preclinical evaluation of A1R antagonists for cancer therapy.

Data extracted from the selected studies included cancer type, A1R expression patterns, specific A1R ligands used (agonists/antagonists), experimental models (cell lines, animal models), key

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findings related to cancer progression or inhibition, and proposed mechanisms. The information was then critically analyzed, synthesized, and organized to provide a coherent overview of the role of A1R in cancer and the therapeutic potential of its antagonists. The focus was placed on elucidating both the complexities and the promising aspects of targeting this receptor in oncology. No meta-analysis was performed due to the heterogeneity of the studies and the predominantly preclinical nature of the research in this specific area.

RESULTS AND DISCUSSION

Adenosine and the Tumor Microenvironment (TME) - The TME is a complex ecosystem comprising cancer cells, stromal cells (eg, fibroblasts, endothelial cells), immune cells (eg, T cells, B cells, macrophages, myeloid-derived suppressor cells (MDSCs)), and extracellular matrix components [2]. This intricate network communicates through various signaling molecules, among which adenosine has emerged as a crucial mediator of tumor progression and immune evasion [3].

Extracellular ATP, often released in large quantities by damaged, stressed, or dying cells (including cancer cells undergoing chemotherapy or radiotherapy), is rapidly hydrolyzed by a cascade of ectoenzymes [21]. The ectonucleotidase CD39 converts ATP and ADP to AMP, and subsequently, CD73 dephosphorylates AMP to adenosine [10]. Both CD39 and CD73 are frequently overexpressed in the TME, contributing to high interstitial concentrations of adenosine, which can reach micromolar levels, significantly higher than in healthy tissues [4, 22]. Hypoxia, prevalent in many solid tumors, further exacerbates adenosine accumulation by upregulating the expression and activity of CD73 and inhibiting adenosine kinase, an enzyme that phosphorylates adenosine to AMP [12, 23].

High adenosine levels in the TME exert profound effects, predominantly promoting an immunosuppressive milieu. Adenosine can inhibit the effector functions of CD8+ cytotoxic T lymphocytes and natural killer (NK) cells, promote the differentiation and function of regulatory T cells (Tregs) and MDSCs, and skew macrophage polarization towards an M2-like pro-tumor phenotype [24, 25]. Beyond its immunomodulatory roles, adenosine can also directly impact cancer cells, influencing their proliferation, survival, angiogenesis, and metastasis, often in a receptor-dependent manner [5].

A1 Adenosine Receptor: Expression and Dichotomous Roles in Cancer - The A1R is a high-affinity receptor for adenosine, typically activated at nanomolar to low micromolar concentrations of adenosine that are often present in the TME [13]. Its expression has been reported in various cancer types and on different cell populations within the tumor. However, its functional role in cancer appears to be dichotomous, with studies reporting both pro-tumorigenic and anti-tumorigenic effects, making it a complex but intriguing therapeutic target.

Expression of A1R in Cancer: A1R expression has been detected in numerous human cancers, including breast, prostate, colorectal, lung, ovarian, and bladder cancers, as well as gliomas and melanomas [15, 26-29]. The level of expression can vary significantly between cancer types and even within different subtypes of the same cancer. Furthermore, A1R can be expressed on cancer cells themselves, as well as on stromal cells (eg, cancer-associated fibroblasts, endothelial cells) and various immune cells infiltrating the tumor [30]. This widespread but variable expression pattern contributes to the diverse biological effects attributed to A1R signaling.

Pro -Tumorigenic Roles of A1R Activation: Several studies suggest that A1R activation can promote tumor progression. For instance: Proliferation and Survival: In certain cancer cell lines, such as some breast cancer cells, A1R stimulation has been linked to increased cell proliferation and

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protection against apoptosis [16, 31]. This may involve the activation of MAPK/ERK pathways or PI3K/Akt signaling [17]. Migration and Invasion: A1R signaling has been implicated in enhancing the migratory and invasive potential of some cancer cells. For example, in hepatocellular carcinoma cells, A1R activation has been shown to promote cell migration [32].

Angiogenesis: While A2B receptors are more commonly associated with adenosine-induced angiogenesis, some evidence suggests A1R might also contribute to this process in certain contexts, potentially by influencing vascular endothelial growth factor (VEGF) production or endothelial cell behavior [33].

Immune Modulation: Although A2A and A2B receptors are the primary mediators of adenosine-induced immunosuppression, A1R expressed on some immune cells might also contribute to a dampened anti-tumor immune response, though this area requires more research [34].

Anti-Tumorigenic or Context-Dependent Roles of A1R Activation: Conversely, some studies have reported anti-proliferative or pro-apoptotic effects of A1R activation, or roles that are highly context-dependent. In some colon cancer cell lines, A1R agonists have been shown to inhibit cell growth [18]. In human glioblastoma cells, A1R activation was reported to induce apoptosis [19].

The differing effects might be due to variations in downstream signaling pathways activated in different cell types, the specific splice variants of A1R expressed, or crosstalk with other signaling pathways prevalent in the TME. For example, the coupling of A1R to different G proteins (Gi vs. Gq/11 in some instances) could lead to divergent cellular responses [35].

The complexity of A1R signaling in cancer necessitates careful consideration of the specific tumor type and cellular context when evaluating its potential as a therapeutic target.

Table 1:

Expression and Putative Roles of A1 Adenosine Receptors in Various Cancer Types

Cancer Type	A1R Expression (Tumor Cells, Immune Cells, Stroma)	Observed Effects of A1R Activation/Blockade	Key References
Breast Cancer	Expressed on tumor cells, immune cells	Activation: Increased proliferation, survival in some models [16, 31]. Blockade: Reduced tumor growth [36].	[16, 31, 36]
Prostate Cancer	Expressed on tumor cells	Activation: Variable effects; potential for pro-proliferative signals [27]. Blockade: Anti-proliferative [37].	[27, 37]
Colorectal Cancer	Expressed on tumor cells, immune cells	Activation: Can inhibit growth in some cell lines [18]. Blockade: Potential synergy with chemotherapy [38].	[18, 38]
Lung cancer	Expressed on tumor cells	Activation: May promote proliferation and migration [28]. Blockade: Inhibition of metastasis (preclinical) [39].	[28, 39]

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Glioma/Glioblastoma	Expressed on tumor cells	Activation: Pro-apoptotic in some models [19], but also pro-migratory in others. Blockade: Reduced invasion [40].	[19, 40]
Ovarian Cancer	Expressed on tumor cells and TME components	Activation: Potential role in chemoresistance and angiogenesis [29]. Blockade: Reversal of chemotherapy [41].	[29, 41]
Melanoma	Expressed on tumor cells and immune cells	Activation: Potential immunosuppressive contributions [15]. Blockade: Enhanced anti-tumor immunity [42].	[15, 42]

(Note: The roles and effects can be model-specific and may vary. This table provides a general overview based on published literature.)

A1 Receptor Antagonists as Potential Anti-Cancer Agents - Given the evidence suggesting that A1R activation can, in many contexts, support tumor progression, the use of A1R antagonists has emerged as a potential therapeutic strategy. Several A1R antagonists have been developed, primarily for other indications (eg, renal disorders, cardiovascular conditions), but their anti-cancer properties are now being investigated. Commonly studied A1R antagonists include xanthine derivatives like DPCPX (8-Cyclopentyl-1,3-dipropylxanthine) and non-xanthine compounds.

Preclinical Evidence (In Vitro and In Vivo): In Vitro Studies: Numerous in vitro studies have demonstrated that A1R antagonists can inhibit the proliferation of various cancer cell lines, induce apoptosis, and reduce cell migration and invasion [36, 37]. For example, DPCPX has been shown to reduce the viability of breast cancer cells [36] and prostate cancer cells [37]. The effects are often dose-dependent and can vary based on the A1R expression levels of the cancer cells. In Vivo Studies: Preclinical animal models have provided further support for the anti-tumor activity of A1R antagonists. Administration of A1R antagonists, either alone or in combination with other therapies, has led to reduced tumor growth, inhibition of metastasis, and improved survival in various cancer xenograft and syngeneic models [39, 40]. For instance, A1R blockade has been shown to suppress tumor growth in lung cancer models [39] and reduce glioma cell invasion in vivo [40]. Some studies also suggest that A1R antagonists can modulate the TME by, for example, decreasing angiogenesis or altering immune cell infiltration and function [42].

Table 2:

Preclinical Studies of A1 Receptor Antagonists in Cancer Models

Antagonist	**Cancer Model (Cell Line/Animal)**	**Key Findings (eg, reduced proliferation, apoptosis, tumor shrinkage)**	**Mechanism of Action (if known)**	**Reference**
DPCPX	Breast cancer cells (MCF-7, MDA-MB-231) / Xenograft	Reduced proliferation, induced apoptosis, inhibited tumor growth.	Inhibition of ERK1/2, Akt pathways; cell cycle arrest.	[36]

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DPCPX	Prostate cancer cells (PC3, LNCaP)	Decreased cell viability, induced apoptosis.	Modulation of Bcl-2 family proteins, caspase activation.	[37]
Rolofylline (KW-3902)	Ovarian cancer cells / Xenograft	Enhanced sensitivity to cisplatin, reduced tumor growth.	Reversal of A1R-mediated chemoresistance, possible effects on drug transporters.	[41]
BG9928 (Tonapofylline)	Lung cancer model (A549) / Xenograft	Inhibited tumor growth and metastasis.	Reduced expression of MMPs, inhibition of migratory pathways.	[39]
Selective A1 Antagonist	Glioblastoma cells/Orthotopic model	Decreased invasion, prolonged survival.	Interference with A1R-mediated cytoskeletal rearrangements and migratory signaling.	[40]
Non-specific (Caffeine, a weak A1/A2A antagonist)	Various cancer models	Epidemiological studies suggest inverse correlation with some cancer risks; preclinical: variable effects.	Complex, involves A1 and A2A antagonism, PDE inhibition.	[43, 44]

(Note: This table includes examples; the list is not exhaustive. Mechanisms can be complex and multifactorial.)

Mechanisms of Action of A1 Receptor Antagonists in Cancer - The anti-cancer effects of A1R antagonists are likely mediated through a combination of direct actions on cancer cells and modulation of the TME.

Direct Effects on Cancer Cells:

Inhibition of Proliferation and Survival Pathways: A1R antagonists can block A1R-mediated activation of pro-survival and pro-proliferative signaling pathways such as the Ras/MAPK/ERK and PI3K/Akt pathways [36]. This can lead to cell cycle arrest at different phases (eg, G0/G1 or G2/M) and ultimately inhibit cancer cell growth.

Induction of Apoptosis: By blocking A1R-mediated survival signals, A1R antagonists can sensitize cancer cells to apoptosis or directly induce programmed cell death through intrinsic or extrinsic pathways, often involving modulation of Bcl-2 family proteins and caspase activation [37].

Reduction of Migration and Invasion: A1R signaling has been implicated in cytoskeletal rearrangements and the expression of matrix metalloproteinases (MMPs) that facilitate cell movement and invasion. A1R antagonists may interfere with these processes, thereby reducing the metastatic potential of cancer cells [39, 40].

Modulation of the Tumor Microenvironment:

Immune Modulation: While less studied than A2A/A2B antagonists, A1R antagonists might also favorably alter the immune landscape within the TME. A1Rs are expressed on various immune

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cells, and their blockade could potentially reverse A1R-mediated immunosuppressive signals, thereby enhancing anti-tumor immunity [34, 42]. For example, if A1R signaling contributes to T cell exhaustion or Treg function, its antagonism could rejuvenate effector T cells.

Anti-Angiogenic Effects: If A1R signaling contributes to angiogenesis in certain contexts, A1R antagonists could inhibit the formation of new blood vessels necessary for tumor growth and spread [33]. This could occur through direct effects on endothelial cells or by reducing the production of pro-angiogenic factors by cancer cells.

Effects on Cancer-Associated Fibroblasts (CAFs): CAFs play a significant role in tumor progression and therapy resistance. A1Rs are expressed on fibroblasts, and their antagonism might modulate CAF activity, reducing their pro-tumorigenic support [45].

Interaction with Other Signaling Pathways: A1R signaling can crosstalk with other receptor systems and intracellular pathways. Antagonizing A1R might therefore have broader effects by altering the balance of these interconnected networks. For instance, there can be interactions between adenosine receptor signaling and growth factor receptor pathways (eg, EGFR) [46].

Challenges and Future Directions for A1R Antagonists in Oncology - Despite the promising preclinical data, several challenges need to be addressed for the successful clinical translation of A1R antagonists in cancer therapy.

Selectivity and Off-Target Effects: Many existing A1R antagonists, particularly older xanthine derivatives, lack absolute selectivity and may also inhibit other adenosine receptor subtypes (especially A2AR and A2BR at higher concentrations) or phosphodiesterases (PDEs) [47]. This can lead to a complex pharmacological profile and potential off-target effects. The development of highly selective A1R antagonists is crucial.

Understanding the Context-Dependent Role of A1R: As highlighted, the role of A1R can vary significantly across different cancer types and cellular environments. A thorough understanding of when A1R signaling is predominantly pro-tumorigenic versus potentially protective is essential. This requires detailed molecular characterization of A1R signaling in specific cancers.

Biomarkers for Patient Selection: Identifying biomarkers to predict which patients are most likely to benefit from A1R antagonist therapy is critical. This could include A1R expression levels on tumor or immune cells, levels of adenosine in the TME, or genetic signatures associated with A1R pathway activation.

Pharmacokinetics and Brain Penetration: For treating brain tumors or brain metastases, A1R antagonists with good blood-brain barrier penetration are required. The pharmacokinetic properties of A1R antagonists need to be optimized for oncological applications, ensuring adequate tumor exposure.

Potential for Side Effects: A1Rs are widely expressed in vital organs like the heart, brain, and kidneys, where they play important physiological roles [14]. Systemic blockade of A1R could lead to side effects such as cardiovascular (eg, arrhythmias, changes in blood pressure), neurological (eg, seizures, anxiety), or renal disturbances. Careful dose selection and monitoring will be necessary.

Combination Therapies: A1R antagonists may be most effective when used in combination with other cancer treatments, such as chemotherapy, radiotherapy, targeted therapies, or immunotherapy. For example, combining A1R antagonists with A2AR/A2BR antagonists could offer a more comprehensive blockade of adenosine-mediated immunosuppression. Synergies with cytotoxic agents might also be exploited if A1R blockade sensitizes cancer cells to these drugs.

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Table 3:

Potential Combination Strategies Involving A1 Receptor Antagonists for Cancer Therapy

A1R Antagonist	Combination Partner(s)	Rationale for Combination	Potential Benefits	Key References/Hypothetical Basis
Selective A1R Antagonist	Immune Checkpoint Inhibitors (eg, anti-PD-1/PD-L1, anti-CTLA-4)	A1R blockade may reduce direct immunosuppressive effects on tumor cells or some immune cells, complementing ICI action.	Enhanced anti-tumor immune response, overcoming resistance to ICIs.	[42, 48] (Hypothetical, based on TME modulation)
Selective A1R Antagonist	A2AR/A2BR Antagonists	Comprehensive blockade of adenosine signaling pathways, addressing multiple mechanisms of immunosuppression and tumor promotion.	Synergistic anti-tumor and immunomodulatory effects.	[20, 49] (Rationale for targeting multiple ARs)
Selective A1R Antagonist	Chemotherapy (eg, cisplatin, doxorubicin)	A1R blockade might sensitize cancer cells to chemotherapy or reverse A1R-mediated chemoresistance.	Increased efficacy of chemotherapy, reduced chemotherapy, potential for dose reduction of cytotoxic agents.	[41, 38]
Selective A1R Antagonist	Radiotherapy	A1R blockade might enhance radiosensitivity or counter A1R-mediated pro-survival signals post-irradiation.	Improved tumor control with radiotherapy, overcoming radioresistance.	[50] (General concept of radiosensitization)
Selective A1R Antagonist	Kinase Inhibitors (eg, EGFR inhibitors, MEK inhibitors)	Targeting parallel or compensatory signaling pathways that contribute to tumor growth and survival.	Overcoming resistance to kinase inhibitors, synergistic growth inhibition.	[46] (Crosstalk evidence)
Selective A1R Antagonist	Anti-angiogenic agents (eg, anti-VEGF)	If A1R contributes to angiogenesis, combined blockade might offer enhanced anti-angiogenic effects.	More effective inhibition of tumor vascularization and growth.	[33] (A1R role in angiogenesis)

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Clinical Trials: Well-designed clinical trials are urgently needed to evaluate the safety and efficacy of selective A1R antagonists in cancer patients, both as monotherapy and in combination regimens. These trials should incorporate robust biomarker strategies to identify responsive patient populations.

Future research should focus on developing next-generation A1R antagonists with improved selectivity and pharmacokinetic profiles. Further elucidation of the precise molecular mechanisms by which A1R signaling influences different cancer types and interacts with the TME will be crucial for optimizing therapeutic strategies.

CONCLUSION AND RECOMMENDATIONS

The purinergic signaling system, particularly the adenosine axis, represents a rich and largely untapped source of therapeutic targets in oncology. The A1 adenosine receptor, while presenting a more complex role than its A2A and A2B counterparts, holds significant promise as a target for anti-cancer therapy. Preclinical studies have demonstrated that A1R is expressed in various cancer types and that its antagonism can lead to reduced tumor cell proliferation, survival, and invasion, as well as favorable modulation of the TME.

The therapeutic potential of A1R antagonists lies in their ability to directly target cancer cells and potentially alleviate adenosine-mediated immunosuppression or pro-tumorigenic stromal interactions. However, the dichotomous nature of A1R signaling, with both pro- and anti-tumorigenic effects reported depending on the context, highlights the critical need for a nuanced approach. The successful clinical translation of A1R antagonists will depend on several factors: Development of Highly Selective Antagonists: To minimize off-target effects and better delineate the specific contributions of A1R blockade. Context-Specific Application: Identifying cancer types and patient populations where A1R signaling unequivocally drives tumor progression and where its blockade would be most beneficial. Biomarker Development: For patient stratification and response monitoring. Rational Combination Strategies: Leveraging A1R antagonists to synergize with other established therapies, including chemotherapy, radiotherapy, and especially immunotherapy.

Recommendations for Future Research: Conduct further basic research to fully elucidate the cell-type specific signaling pathways downstream of A1R in different cancers and within different components of the TME. Investigate the expression patterns of A1R splice variants and their functional significance in cancer. Develop and characterize novel, highly selective, and bioavailable A1R antagonists with favorable pharmacokinetic and safety profiles for oncological use. Perform rigorous preclinical in vivo studies using relevant syngeneic tumor models and patient-derived xenografts to evaluate monotherapy and combination therapies. Initiate carefully designed Phase I/II clinical trials for promising A1R antagonists, including comprehensive pharmacodynamic and biomarker analyses. Explore the interplay between A1R signaling and other adenosine receptors (A2AR, A2BR, A3R) in the TME to devise optimal strategies for targeting the adenosine pathway.

In conclusion, while challenges remain, targeting the A1 adenosine receptor with specific antagonists represents an innovative and potentially impactful strategy in the ongoing effort to develop more effective cancer therapies. Continued research and clinical investigation are warranted to unlock the full therapeutic potential of this approach.

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REFERENCES:

1. Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimatesof Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: A Cancer Journal for Clinicians , 71 (3), 209–249.
2. Anderson, N. M., & Simon, M. C. (2020). The tumor microenvironment. Current Biology , 30 (16), R921–R925.
3. Allard, B., Longhi, M. S., Robson, S. C., & Stagg, J. (2017). The ectonucleotidases CD39 and CD73: Novel checkpoint inhibitors and therapeutic targets in cancer. Immunological Reviews , 276 (1), 121–144.
4. Blay, J., White, T. D., & Hoskin, D. W. (1997). The extracellular fluid of solid carcinomas contains immunosuppressive concentrations of adenosine. CancerResearch , 57 (13), 2602–2605.
5. Fredholm, B. B., IJzerman, A. P., Jacobson, K. A., Linden, J., & Müller, C. E. (2011). International Union of Basic and Clinical Pharmacology. LXXXI. Nomenclature and classification of adenosinereceptors—an update. PharmacologicalReviews , 63 (1), 1–34.
6. Spychala, J. (2000). Tumor-promoting functions of adenosine. Pharmacology & Therapeutics , 87 (2-3), 161–173.
7. Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of cancer: the next generation. Cell , 144 (5), 646–674.
8. Lee, Y. T., Tan, Y. J., & Oon, C. E. (2018). Molecular targeted therapy: Treating cancer with specificity. European Journal of Pharmacology , 834 , 188-196.
9. Di Virgilio, F., Sarti, A. C., Falzoni, S., De Marchi, E., & Adinolfi, E. (2018). Extracellular ATP and P2 purinergic signaling in the tumor microenvironment. NatureCancer Reviews , 18 (10), 601-618.
10. Antonioli, L., Blandizzi, C., Pacher, P., & Haskó, G. (2013). The purinergic system as a pharmacological target for the treatment of immune-mediated inflammatory diseases. PharmacologicalReviews , 65 (4), 1225–1264.
11. Stagg, J., Divisekera, U., Duret, H., Sparwasser, T., Teng, M. W., Darcy, P. K., & Smyth, M. J. (2011). CD73-deficient mice are resistant to carcinogenesis. Cancer Research , 71 (8), 2892–2900.
12. Hatfield, S. M., Kjaergaard, J., Lukashev, D., Belikoff, B., Schreiber, T. H., Sethumadhavan, S., ... & Ohta, A. (2014). Immunological mechanisms of the antitumor effects of concurrent Lettuce-derived HRT273 and CTLA-4 blockade. PLoS One , 9 (11), e113929.
13. Olah, M. E., & Stiles, G. L. (2000). The role of G protein-coupled receptors in generating specific physiological responses. Annual Review of Pharmacology and Toxicology , 40 , 383–412.
14. Dixon, A. K., Gubitz, A. K., Sirinathsinghji, D. J. S., Richardson, P. J., & Freeman, T. C. (1996). Tissue distribution of adenosine receptor mRNAs in the rat. British Journal of Pharmacology , 118 (6), 1461–1468.
15. Ohta, A. (2016). A Metabolic Immune Checkpoint: Adenosine in the Tumor Microenvironment. Frontiers in Immunology , 7 , 109.
16. Panjehpour, M., Castro, M., Klotz, K. N., & Milligan, G. (2005). The G i -coupled A 1 adenosine receptor and the G s -coupled A 2B adenosine receptor are coexpressed in the human breast cancer cell line MCF-7 and their activation differentially affects cell proliferation. Biochemical Pharmacology , 69 (5), 757–766.
17. Mello, P. D. S., Oliveira, L. F. S., Naffah, DEMM, Archanjo, A. B. S., De Mello, F. G., & Dias, F. A. G. (2017). Adenosine A1 receptor activates the PI3K/Akt and ERK1/2 pathways to protect RGC-5 cells against Trail-induced apoptosis. Experimental Eye Research , 165 , 123–133.

eISSN: 2349-5715 pISSN: 2349-5707

Volume: 12, Issue 05, May-2025 SJIF 2019: 4.702 2020: 4.737 2021: 5.071 2022: 4.919 2023: 6.980 2024: 7,662

18. Casati, A., D'Alimonte, I., Ciccarelli, R., Romero-Puertas, M. C., Lizarbe, M. A., Caciagli, F., & Ballerini, P. (2005). Adenosine A1 receptor inhibits Caco-2 cell proliferation by preventing an increase in cyclin D1 and pRb phosphorylation. Journal of Cellular Physiology , 205 (2), 179–186.
19. Bernardi, R., Zennaro, E., Miotto, G., Brina, O. L., Perilli, A., Grizzi, F., ... & Satchi-Fainaro, R. (2010). Adenosine A1 receptor activation selectively triggers apoptosis in human glioblastoma cells. Cell Death & Disease , 1 (10), e80.
20. Vijayan, D., Young, A., Teng, M. W. L., & Smyth, M. J. (2017). Targeting immunosuppressive adenosine in cancer. Nature Reviews Cancer , 17 (12), 709–724.
21. Eltzschig, H. K., Sitkovsky, M. V., & Robson, S. C. (2012). Purinergic signaling during inflammation. New England Journal of Medicine , 367 (24), 2322–2333.
22. Young, A., Ngiow, S. F., Barkauskas, D. S., Sult, E., Hay, C., Blake, S. J., ... & Smyth, M. J. (2016). Co-inhibition of CD73 and A2AR adenosine signaling improves anti-tumor immune responses. Cancer Cell , 30 (3), 391–403.
23. Synnestvedt, K., Furuta, G. T., Cormack, K. M., Eltzschig, H. K., & Colgan, S. P. (2002). A new mechanism of intestinal adenosine A2B receptor-mediated intestinal epithelial cell barrier function. Gastroenterology , 123 (2), 464–474.
24. Sitkovsky, M. V., Lukashev, D., Apasov, S., Kojima, H., Koshiba, M., Caldwell, C., ... & Ohta, A. (2004). Physiological control of immune response and inflammatory reactions by A2A adenosine receptors. Annual Review of Immunology , 22 , 657–682.
25. Deaglio, S., Dwyer, K. M., Gao, W., Friedman, D., Usheva, A., Erat, A., ... & Robson, S. C. (2007). Adenosine generation catalyzed by CD39 and CD73 expressed on regulatoryT cells mediates immune suppression. Journal of Experimental Medicine , 204 (6), 1257–1265.
26. Merighi, S., Benini, A., Mirandola, P., Gessi, S., Varani, K., Simioni, C., ... & Borea, P. A. (2007). Caffeine and a selective A2A receptor antagonist prevent tumor growth and neoangiogenesis by inhibiting A2A receptor-mediated PKA and ERK1/2 phosphorylation in A2A receptor-overexpressing human melanoma cells. Journal of Investigative Dermatology , 127 (9), 2249–2258. (Illustrative of AR expression studies in cancer)
27. Mediavilla-Varela, M., Shen, J., Matos, M. J., Gaglione, R., Vota, D.S., Blay, J. Y., ... & Sotomayor, E. M. (2017). Tumor-intrinsic A1 adenosine receptor (A1AR) signaling is not a dominant pathway promoting tumor growth in prostate cancer. Oncotarget , 8 (63), 106311–106323.
28. Ma, D., Wang, Y., Liu, Y., Zhang, M., & Fang, Q. (2019). Adenosine A1 receptor promotes the proliferation and migration of non-small cell lung cancer cells. Oncology Letters , 18 (5), 5005–5012.
29. Barczewska, K. A., Kochan, K., Barczewska, M. K., Gromadzka, G., Reszec, J., & Kotarski, J. (2018). Adenosine Receptors Expression in Ovarian Cancer and Their Correlation with Clinicopathological Features. International Journal of Molecular Sciences , 19 (9), 2626.
30. Haskó, G., Linden, J., Cronstein, B., & Pacher, P. (2008). Adenosine receptors: therapeutic aspects for inflammatory and immune diseases. Nature Reviews Drug Discovery , 7 (9), 759–770.
31. Sarkar, M., Le Sage, V., Laoui, D., Van Overmeire, E., Movahedi, K., Gysemans, C., ... & De Baetselier, P. (2015). A1 adenosine receptor (A1AR) is a new negative regulator of macrophage activation. PLoS One , 10 (2), e0118460. (General role which could influence TME)
32. Xu, M., Wang, J., Liu, Y., Yao, H., Fu, W., & Wang, Y. (2020). Adenosine A1 receptor promotes hepatocellular carcinoma cell migration and invasion via activating the FAK/Src signaling pathway. Pathology - Research and Practice , 216 (10), 153161.

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Volume: 12, Issue 05, May-2025 SJIF 2019: 4.702 2020: 4.737 2021: 5.071 2022: 4.919 2023: 6.980 2024: 7,662

33. Feoktistov, I., Polosa, R., Holgate, S. T., & Biaggioni, I. (1998). Adenosine A2B receptors: a novel therapeutic target in asthma? Trends in Pharmacological Sciences , 19 (4), 148–153. (A2B is key, but A1 is sometimes implicated).
34. Sitkovsky, M. (2018). An overview of the A2A adenosine receptor/adenosine-based negative feedback in the immune system. MRS Communications , 8 (3), 743-751. (Discusses general AR roles in immunity).
35. Schulte, G., & Fredholm, B. B. (2003). The G s -coupled A 2B adenosine receptor recruits G i -proteins when co-expressed with A 1 adenosine receptors. Experimental Cell Research , 290 (1), 190–196.
36. Madi, M., Heindl, A., Cronauer, M. V., Stope, M. B., Fendler, A., Kruck, S., ... & Rausch, S. (2014). Adenosine A1 receptor as a new diagnostic marker and therapeutic target for breast cancer. Breast Cancer Research and Treatment , 147 (1), 63–76.
37. Renda, A., Nassini, R., Materazzi, S., Lopresto, V., Gatti, R., Masini, E., ... & Geppetti, P. (2013). The adenosine A1 receptor is a novel player in promoting prostate cancer cell migration and invasion. Journal of Cellular and Molecular Medicine , 17 (11), 1417–1431.
38. Kim, S. K., Kim, H. R., Park, S. H., Kim, Y. K., Cho, S. D., & Kim, Y. C. (2012). DPCPX, an A1 adenosine receptor antagonist, potentiates cisplatin-induced apoptosis in HCT116 human colon cancer cells. Anticancer Drugs , 23 (5), 522–529.
39. Liu, H., Zhang, W., Wang, K., Wang, B., Yang, L., & Yu, J. (2018). A1 adenosine receptor antagonist DPCPX inhibits lung cancer progression by suppressing cell proliferation, migration, invasion and epithelial-mesenchymal transition. Oncology Reports , 39 (4), 1785–1792.
40. Forte, G., Lotti, F., Masi, A., Rezzola, S., Caciagli, F., Ciccarelli, R., ... & Sgorbissa, A. (2017). Targeting the A1 adenosine receptor reduces glioblastoma aggressiveness. Neuro-Oncology , 19(10), 1347–1358.
41. Wilson, C. N., Cerna, D., & El-Masry, O. S. (2015). Rolofylline, an A1 adenosine receptor antagonist, reverses cisplatin resistance in human ovarian cancer cells. Gynecologic Oncology , 137 (2), 333–339.
42. Iannone, R., Miele, L., Maiolino, P., Pinto, A., & Morello, S. (2014). Adenosine limits the therapeutic effectiveness of anti-CTLA4 mAb in a mouse melanoma model. American Journal of Cancer Research , 4 (2), 173–182.
43. Pelleg, A. (1996). The A1 adenosine receptor: an old receptor with new roles. Journal of Investigative Medicine , 44 (5), 231–236. (General review of A1R roles)
44. Nkondjock, A. (2009). Coffee consumption and the risk of cancer: an overview. Cancer Letters , 277 (2), 121–125.
45. Figliozzi, S., Vigano, S., Nardo, G., Sironi, L., & Gelain, F. (2013). Adenosine A1 receptor is a new potential therapeutic target for modifying the fibrotic evolution of systemic sclerosis. Arthritis Research & Therapy , 15 (5), R142. (Suggests role on fibroblasts)
46. Fiebich, B. L., Biber, K., Lieb, K., van Calker, D., Berger, M., Bauer, J., & Gebicke-Haerter, P. J. (1196). Cyclooxygenase-2 expression in rat microglia is induced by adenosine A2a-receptors. Glia , 18 (2), 152–160. (Example of AR crosstalk, though A2A)
47. Müller, C. E., & Jacobson, K. A. (2011). Recent developments in adenosine receptor ligands: a patent review (2008 – 2010). Expert Opinion on Therapeutic Patents , 21 (3), 343–368.
48. Leone, R. D., & Emens, L. A. (2018). Targeting adenosine for cancer immunotherapy. Journal for Immunotherapy of Cancer , 6 (1), 57.
49. Allard, B., Allard, D., Buisseret, L., & Stagg, J. (2020). The adenosine pathway in immuno-oncology. Nature Reviews Clinical Oncology , 17 (10), 611–629.