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Adenosine Receptor Signaling in Diseases with Focus on Cancer

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Abstract

Various investigation has shown the magnitude role of adenosine receptors in cancer development. The A1, A2A, A2B, and A3 G-protein-coupled cell surface Adenosine Receptors (ARs) are found to be upregulated in many types of cancers. The adenosine receptor function has been affected by specific ligands such as agonists and/or antagonists regulated cancer (Neoplasms) cells proliferation via signaling pathways. Adenosine not only is an important intermediate metabolite but also acts as the essential ligand of adenosine receptors in physiological and pathological conditions. Furthermore, many studies have shown that adenosine receptors expression has increased in many types of cancer. In this review, we first describe adenosine's role in physiological condition and in cancer development. We further, discuss the type of adenosine receptors, distribution, expression, and their roles in cancer.

Keywords: Adenosine [MeSH], Receptors Purinergic P1 [MeSH], Neoplasms [MeSH]

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Highlights

- The A1, A2A, A2B, and A3 G-protein-coupled cell surface are four Adenosine Receptors subtypes.
- Adenosine receptors have a critical role in diseases pathogenesis such as cancers (neoplasm) development.
- The function of ARs affected by natural and synthetic ligands such as agonists and antagonist.

Adenosine

Adenosine is one of the regulators of tissue function, particularly in energy deficiency, due to the capability to maintain energy intake and metabolism (1-4). The adenosine is present in all type of cells and physiological fluids. The adenosine production is an energy-dependent phenomenon in intra/extra cellular pathways (5-8). The four transmembrane adenosine receptors A1, A2, A2B, and A3, conducted the intracellular signaling of adenosine (9). Under the physiological conditions, adenosine is released from all of cell types and its extracellular production is related to Ectonucleoside Triphosphate Diphosphohydrolase 1 (ENTPD1), also known as CD39, and 5'-Nucleotidase Ecto (NT5E), also known as CD73, enzymatic function (Fig. 1) (10-11). The committed step for adenosine production is AMP dephosphorylation and increasing adenosine concentration. Therefore, adenosine concentration is kept constant by reabsorption mechanisms through distinct transporters. (Fig. 2) (12-13). Subsequently, intracellular adenosine is phosphorylated into the AMP through the adenosine kinase or changed to inosine via Adenosine Deaminase (ADA) (14). Afterward, adenosine was transported by Ectonucleoside Nucleoside Transporter 1 (ENT1) and other transporters (15). ATP was released through quite a lot of processes. Entirely, several processes were participated in releasing the ATP (16). Also, ATP was converted to adenosine by ENTPD1 and NT5E (17-18). Besides, Adenosine was metabolized into the inosine, AMP, or S-adenosylhomocysteine (8-19-20).

Adenosine, as the internal nucleoside, has the physiological role with wide extensive effects such as inhibition of platelet aggregation, neurotransmitter release, renal vasoconstriction, cerebrovascular dilatation, decreased heart rate, and atrial and ventricular contractile depression (1-21-26).

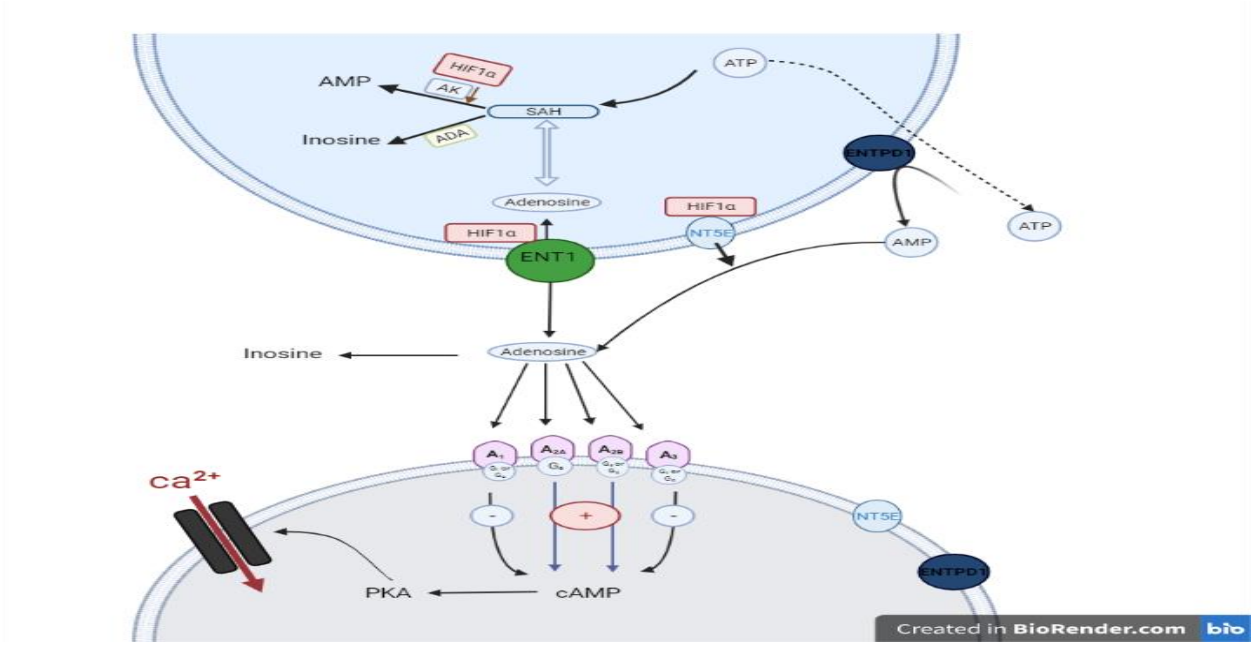

Figure 1. The extracellular and intracellular adenosine signaling pathways and adenosine receptors under physiological conditions.

Under pathological conditions, the adenosine signaling was obviously amplified in response to the hypoxia by the extracellular adenosine concentration flow, leading to increasing the adenosine concentration from the baseline (20–300nM) up to 30µM in ischemic or hypoxic tissues (27-33). Additionally, under pathological conditions the adenosine signaling pathway was controlled by the following factors: increased extracellular adenosine levels by ATP release (34), stimulation of ENTPD1 expression as a result of the transcription factor SP1 and of NT5E expression via hypoxia-inducible factor-1α (HIF1α) (35), stimulation of A2A receptor expression by means of HIF2α and of A2B receptor expression by HIF1α (4, 36-39); suppression of AKT by HIF1α (37, 40, 41) and suppression of ENT1 or ENT2 activity by HIF1α (Fig. 2) (42-44).

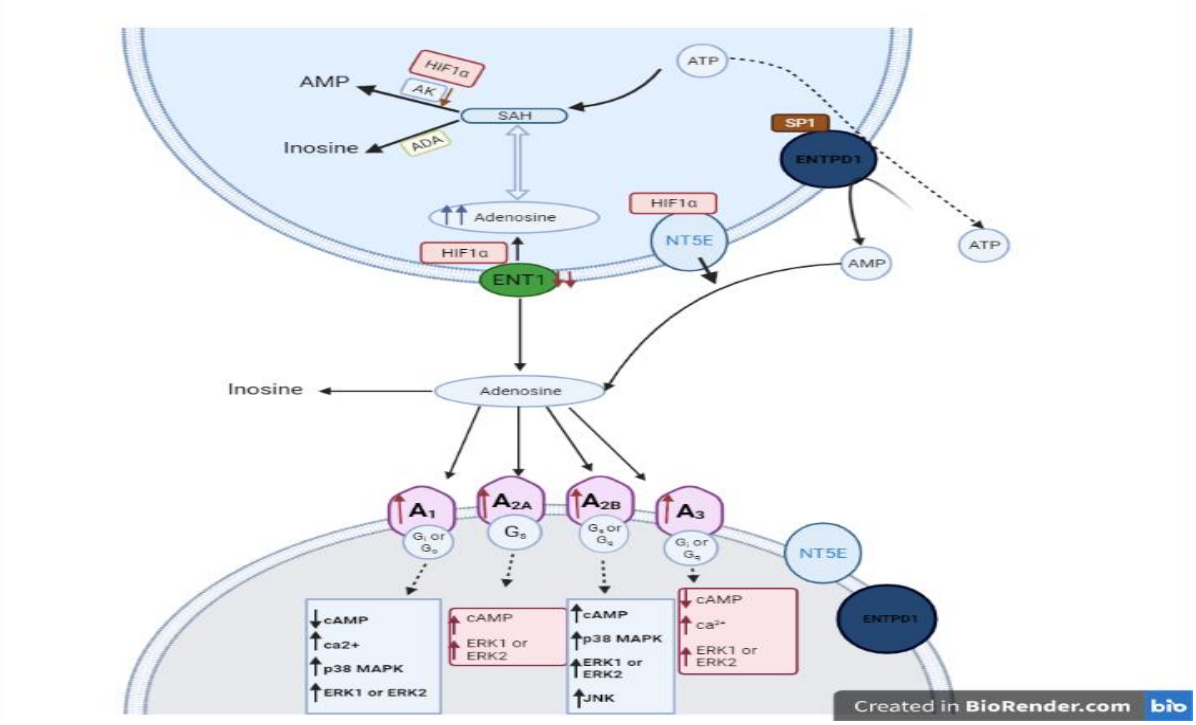

Figure2. Overview of the adenosine signaling pathway and adenosine receptors in pathological conditions

Nomenclature and Types of Adenosine Receptors

Extracellular purines (adenosine, ATP and ADP) and pyrimidines are necessary signaling molecules that exert a multitude of biological effects via cell surface receptors known as purine and pyrimidine receptors (45-47). The two main family of purine receptor is the P1 purinergic receptor and P2 purinergic receptor which adenosine is the endogenous ligand for these receptors (48-54).

Types of Adenosine Receptors

- ***Adenosine A1 Receptor***

The A1 adenosine receptor gene has been localized on chromosome 1q32.1. Generally, A1A adenosine receptor gene is expressed in the upper cortex of the brain, cerebellum, testes, and kidney. Moreover, the A1AR protein contains 326 amino acids (55). Stimulation of A1A receptors in the central nervous system reduces the neurotransmitters release, motor activity, and hypnotic and anti-anxiety effects (56). In addition, the A1 receptors activation in the cardiovascular system led to reduction of the muscle contraction, heart rate, and intensity of nervous message (57).

- ***A2A Adenosine Receptor***

The A2A adenosine receptor gene has been localized on chromosome 22q11.23. Generally, A2AAR protein contains 328 amino acids in humans (55). The A2A receptor inhibits platelet aggregation, reduces the inflammatory response

by inhibiting the secretion of proinflammatory cytokines such as interleukins 6, 8, 12, and TNF. Further, A2AAR led to increased anti-inflammatory cytokines increases secretion of anti-inflammatory cytokines such as interleukin 10 in monocytes and macrophages (58). Additionally, the other roles of A2AAR includes prevention of ROS (Reactive Oxygen Species) release from neutrophils, blockage neutrophils attachment and infiltration to endothelial cells, smooth muscle expansion, blood pressure reduction, and vasodilation (59). Furthermore, The A2A adenosine receptor was involved in inhibition of the interferon-gamma (INF-γ) release from natural killer T cells, immune response regulation through anti-tumor T cells suppression, tumor cells protection against ischemia, and improving hypoxic and metastatic cells (60). Moreover, the adenosine and A2A adenosine receptor inhibited the nuclear factor-kappa B (NF-κB) signaling pathway in inflammation condition. Also eventually, Tian et al. revealed the miR-16 over-expression in human Ulcerative Colitis (UC) could control the activation of the NF-κB signaling pathway through suppressing A2A adenosine receptor (61).

- ***Adenosine A2B Receptor***

The A2BAR gene was found on chromosome 17p11.2. Mainly, the A2BAR protein contains 328 amino acids in humans (55). The A2B adenosine receptor effects in physiological condition includes vascular and intestinal smooth muscle expansion, fibroblasts collagen synthesis inhibition, monocyte and macrophage activity inhibition, and mast cell granules release stimulation (62). Then, in pathological condition the A2B adenosine receptors have an inhibitory effect on TNFα production from monocytes. Moreover, A2BA receptor is involved in asthma induction through broncho-constriction in response to mediators released from mast cells. Also, the release of interleukin 6 (IL-6) and interleukin 8 (IL-8) were activated by A2B adenosine receptor. According to the reports the A2B adenosine receptor has a essential role in increasing the chloride ions secretion into the intestinal epithelial cells and hepatic glucose production (60). Noticeably A2BA adenosine receptor is activated in high physiological concentrations of adenosine and has the lowest affinity to adenosine. As well, the A2BAR plays a dual role in stimulating the growth of arterial endothelial cells and inhibiting the growth of fibroblasts and aortic smooth muscle cells. In-addition the A2BAR has the significant role in cancer development such as human melanoma tumor cells growth stimulation (62). On the other hand, various studies have shown the A2B adenosine receptor was associated with micro-RNA alternation in different diseases, including cancer. Zhang et al. demonstrated the A2BAAR as a direct target of miR-27b which contributes in renal diseases pathogenesis. The miR-27b over-expression caused decrease transcript and protein expression level of A2BAR which induces the podocytes apoptosis (63).

- ***Adenosine A3 Receptor***

The A3 adenosine receptor gene was localized on chromosome 1p13.2 and, its protein contains 318 amino acids in humans (55). In physiological conditions, the A3 agonist has inhibited TNFα production (64). In addition, the A3AR has an essential role in the conductance of the chloride ions to the epithelial cell in the eyes (65-67). Furthermore, different A3AR gene expression has been observed in the embryos. The A3 adenosine receptor contributes to the fetus's development, and its expression pattern varies in several tissues (68). Moreover, the activation of A3 adenosine receptor in the lungs increased inflammation and asthma, that was a dual effect (69). On the other hand, A3 adenosine receptor activation caused the anti-inflammatory effects by inhibiting the eosinophils, neutrophils, monocytes, and macrophage's function. Subsequently, it enhanced the inflammatory effects through basophils and mast cells (70-71). Besides, the A3 adenosine receptor over expression has been reported different type of cancer cells. Mainly, The A3 adenosine receptor has an anti-cancer and anti-metastatic role. The importance of adenosine receptors in different cancers such as breast, the colon has been reported. As well, the A3 receptor was involved in cytotoxicity and apoptosis

through affected the receptor-dependent intracellular signaling pathways (72). The basal level of cAMP-regulated by the A3 adenosine receptor contributed to altering the cellular gene expression, and it was associated with apoptosis and tumor growth inhibition (73). On the other hand, several studies have illustrated the A3 adenosine receptor was associated with micro-RNA alteration in various diseases, including cancer. The sundha et al study illustrated the treatment of HL60 cells by IB-MECA as an A3 receptor agonist reduced the miRNA profile expression (miR-1, miR-27a, miR-133a and miR-133b) were involved in the myocardial injury caused by Sunitinib (74). The adenosine receptors sub-type, G-protein-coupled receptors, and gene location are available in table 1.

Table 1. Adenosine receptors sub-type, G-protein-coupled receptors, and gene location.

Adenosine receptor subtype	Abbreviation	G-protein	Gene location
A1	ADORA1	Gi	1q32.1
A2A	ADORA2A	Gs	22q11.23
A2B	ADORA2B	Gs	17p11.2
A3	ADORA3	Gi	1p13.2

Signaling Pathway of Adenosine Receptors

Generally, the binding of adenosine ligand to each of the adenosine receptor subtypes causes coupled the ARs to the GPCRs protein. It has been activated downstream signaling pathways by altering the intracellular cAMP concentration. Mainly, adenosine receptor subtypes were activated when bound to the adenosine or other agonist ligands (75).

The Role of Adenosine in Cancer

Adenosine has an important role in cancer development such as angiogenesis, immune system anti-cancer activity, tumor cells viability enhancement, and cell proliferation (76-81). In the angiogenesis process, adenosine has an important role in endothelial cells migration via regulating the angiogenic factors release including venous endothelial growth factor (VEGF) and their endothelial proliferation (82-84). Specifically, adenosine DNA synthesis in Human Umbilical Vein Endothelial Cells (HUVEC) as well as stimulates Retinal Microvascular Capillary Endothelial cells (RMEC) Specifically, adenosine stimuli the DNA synthesis in Human Umbilical Vein Endothelial Cells (HUVEC) and Retinal Microvascular Capillary Endothelial Cells (RMEC) (60, 85-88). Additionally, adenosine was involved in the various cells necrosis, including human leukemia cancer cells (HL60), human melanoma A375, and astrocytoma, in which case intracellular adenosine is responsible for cell death (89). Increased extracellular adenosine leads to its rapid absorption by cells and activates caspase generated within the AMP cell. In expanded extracellular adenosine condition, it was rapidly absorbed into the cells, and consequently, AMP accumulation activates the caspase within the cell (90). Hence, adenosine accumulation affects target cells via adenosine receptors (91, 92).

Tissue Distribution of Adenosine Receptors

Adenosine A1 and A3 receptors genes express in all body tissues. The adenosine A2B receptor gene is expressed in the lungs, heart, blood vessels, and immune cells but has lower expression in macrophages, smooth muscle cells, and endothelial cells (71). The expression and role of adenosine receptors in different cancers are shown in Table 2.

Table2. Expression and role of adenosine receptors in different cancers

Researchers	Year	Type Of cancer	Conclusion	reference
khoo et al	1996	colorectal cancer	- Creased expression of a1 receptor gene in tumor tissue relative to tumor margins	(1)
Madi et al	2004	Colon and breast cancer	- Increased a3 receptor expression in tumor tissue relative to tumor margins	(2)
Gessi et al	2004	Colon cancer	- Increased expression of a3 receptor gene in tumor tissue relative to tumor margin	(3)
Xiang et al	2006	liver cancer	- Increased a2b receptor expression compared to tumor margins	(4)
Morello et al	2007	Thyroid cancer	- Increased a3 receptor expression in tumor tissue compared to normal tissue	(5)
Ma et al	2010	Colon cancer	- No difference in A2a receptor expression in tumor tissue compared to tumor peripheral tissue Increased adenosine A2B receptor expression in tumor tissue compared to tumor margins	(6)
Tajadini et al	2014	Breast Cancer	- Increased expression of A1 and A3 receptors in tumor tissue relative to tumor margins	(7)
Mousavi et al	2015	Prostate Cancer	- Increased expression of all 4 receptors in the tumor tissue relative to the tumor margin - Adenosine A2B receptor expression is higher in tumor tissue than other receptors	(8)
Hajiahmadi et al	2015	ovarian cancer	- Increased expression of A3 and A2B receptors compared to other receptors (OVCAR-3, Caov-4 and SKOV-3)	(9)
Zhou et al	2017	kidney cancer	- Increased adenosine A1 receptor expression in tumor tissue compared to tumor margins - Adenosine A1 receptor expression in renal cancer cell lines is higher than other adenosine receptors	(10)
Zhaoiying et al	2019	Colorectal cancer	- Increased expression of A2B receptor in tumor tissue relative to tumor margins	(11)
Yutong Sui et al	2021	Lung adenocarcinoma	- Increased adenosine A2B receptor expression in tumor tissue relative to tumor margins	(12)

The role of ARs receptors in cell proliferation in various cancers is different depending on types of cancer. These different effects are illustrated in several of the studies (Table 3).

The results of studies revealed the expression patterns and role of adenosine receptors are different in various cancers. undoubtedly, the reason for the research controversy was due to differences in cell type, tissue, and adenosine receptors subtypes.

Adenosine receptors potential for pharmacological purposes Adenosine Receptor Pharmacology

Adenosine receptors are the novel target for pharmacologic research in treatment the various type of cancers. The foremost study on adenosine receptors was pharmacological research that focused on the utilization of agonists and antagonists (110). Numerous studies have been performed to identify suitable agonist and antagonist ligands to achieve this goal. Moreover, many in-silico studies have been conducted to determine the binding sites of chemical agents to the primary amino acids of adenosine receptors (111). The A1AR ligands include R-PIA (Ribose 5-phosphate Isomerase A) and DPCPX (8-Cyclopentyl-1,3-dipropylxanthine), selective and specific agonists and antagonists, respectively (58, 112-114). Further, the CGS 21680 is the selective agonist and the xanthine derivatives and nitrogenous poly heterocyclic compounds as A2A adenosine receptor antagonists (115). In Addition, the NECA (5'-N-ethyl carboxamido adenosine) and MRS-1754 is potent agonist and antagonist of A2BAR, respectively (116, 117). The A3 receptor

was recently identified since it was not sensitive to xanthine and its derivatives. The selective A3 adenosine receptor agonist includes CI-IB-MECA and IB-MECA, which have the lipophilic group in the 6-ring amine group (118, 119). All the ligand studies in this review are summarized in Table 4.

Table3. The role of adenosine receptors in a variety of cancer cell lines

Researchers	Year	Cell line studied	Conclusion	Reference
Hajiahmadi et al	2015	Ovarian cancer cell line (OVCAR-3, Caov-4 and SKOV-3)	Activation of the adenosine A2B receptor inhibits the growth and induces apoptosis of ovarian cancer cells.	(9)
Kasama et al	2015	Prostate cancer cell line	Activation of the adenosine A2B receptor induces the growth of prostate cancer cells	(13)
Yasuda et al	2009	Colon cancer cells	Activation of the adenosine A2A receptor inhibits growth and induces apoptosis of colon cancer cells	(14)
Etique et al	2009	breast cancer cells	Activation of the adenosine A2A receptor in cell growth Induces breast cancer cells	(15)
Joshaghani et al	2017	Ovarian cancer cell	Activation of the adenosine A3 receptor inhibits growth.	(16)
Jafari et al	2017	breast cancer stem cells	Activation of the A3 receptor induces cell death and growth arrest by reducing ERK and GLI-1 by hedghog pathway.	(17)
Panjehpour et al	2018	breast cancer cell line	Activation of the A2B receptor induces apoptosis and stops the cell cycle by reducing ERK.	(18)

Table 4. The adenosine receptors ligands, and its roles.

Receptor	Ligand	Role
A1 adenosine receptor	R-PIA	Agonist
A1 adenosine receptor	DPCPX	Antagonist
A2A adenosine receptor	CGS 21680	Agonist
A2A adenosine receptor	Xanthine derivatives	Antagonist
A2A adenosine receptor	Nitrogenous polyheterocyclic compounds	Antagonist
A2B adenosine receptor	NECA	Agonist
A2B adenosine receptor	MRS-1754	Antagonist
A3 adenosine receptor	CI-IB-MECA	Agonist
A3 adenosine receptor	IB-MECA	Agonist

Conclusions

The research illustrated that extracellular adenosine was an essential modulator in physiological and pathological processes. Moreover, studies revealed that adenosine receptors are a safe target in the treatment of various diseases such as cancer. Adenosine receptors play a crucial role in tumorigenesis through angiogenesis and suppression of the immune response. It is noteworthy that the adenosine receptor is involved in the fate of cancer cells. In addition, various studies have shown that the final cell response to death or proliferation signals may depend on essential factors such as cell and tissue types, the presence of different adenosine receptor subtypes on the cell surface, and the adenosine receptors agonist and antagonist concentration. Collectively, adenosine receptors are involved in various stages of the proliferation and differentiation of living organisms.

Further, the ARs have a specific and diverse expression in different physiological and pathophysiological conditions. This study extensively explained the role of ARs ligands in

maintaining anticancer effects through each receptor. Based on the studies conducted in this study, it appears that all AR subtypes are potential targets for the development of new approaches to cancer treatment.

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