Send orders for print-reprints and e-prints to reprints@benthamscience.net

Current Pharmaceutical Design, **2019**, *25*, 1-14 1

REVIEW ARTICLE

Adenosine Receptors as Novel Targets for the Treatment of Various Cancers

Bapi Gorain[1], Hira Choudhury[2,*], Gan Sook Yee[3] and Subrat Kumar Bhattamisra[3,**]

[1]*School of Pharmacy, Faculty of Health and Medical Science, Taylor's University, Subang Jaya, Selangor, Malaysia;* [2]*Department of Pharmaceutical Technology, School of Pharmacy, International Medical University, Bukit Jalil 57000, Kuala Lumpur, Malaysia;* [3]*Department of Life Sciences, School of Pharmacy, International Medical University, Bukit Jalil 57000, Kuala Lumpur, Malaysia*

ARTICLE HISTORY

Received: May 30 , 2019
Accepted: July 1, 2019

DOI:
10.2174/1381612825666190716102037

Abstract: Adenosine is a ubiquitous signaling nucleoside molecule, released from different cells within the body to act on vasculature and immunoescape. The physiological action on the proliferation of tumour cell has been reported by the presence of high concentration of adenosine within the tumour microenvironment, which results in the progression of the tumour, even leading to metastases. The activity of adenosine exclusively depends upon the interaction with four subtypes of heterodimeric G-protein-coupled adenosine receptors (AR), A_1, A_{2A}, A_{2B}, and A_3-ARs on the cell surface. Research evidence supports that the activation of those receptors via specific agonist or antagonist can modulate the proliferation of tumour cells. The first category of AR, A_1 is known to play an antitumour activity via tumour-associated microglial cells to prevent the development of glioblastomas. A_{2A}AR are found in melanoma, lung, and breast cancer cells, where tumour proliferation is stimulated due to inhibition of the immune response via inhibition of natural killer cells cytotoxicity, T cell activity, and tumour-specific CD4+/CD8+ activity. Alternatively, A_{2B}AR helps in the development of tumour upon activation via upregulation of angiogenin factor in the microvascular endothelial cells, inhibition of MAPK and ERK 1/2 phosphorylation activity. Lastly, A_3AR is expressed in low levels in normal cells whereas the expression is upregulated in tumour cells, however, agonists to this receptor inhibit tumour proliferation through modulation of Wnt and NF-κB signaling pathways. Several researchers are in search for potential agents to modulate the overexpressed ARs to control cancer. Active components of A_{2A}AR antagonists and A_3AR agonists have already entered in Phase-I clinical research to prove their safety in human. This review focused on novel research targets towards the prevention of cancer progression through stimulation of the overexpressed ARs with the hope to protect lives and advance human health.

Keywords: Adenosine, adenosine receptors, receptor modulators, cancer, signalling pathways.

1. INTRODUCTION

Specific target proteins that are mostly expressed in tumour cells as compared to normal cells have been studied in the last few decades. Among these targets, purine nucleoside adenosine is found at a sufficient concentration in the interstitial fluid of tumour microenvironment that can modulate the tumour growth. These physiological effects of adenosine are determined by the four adenosine receptors (ARs) whose expression is altered in tumour cells as compared to the normal cells. Adenosine is released from almost all cells and is ubiquitously generated by the ATP breakdown by ectoenzymes [1]. Intracellular adenosine formation is dependent on the hydrolysis of AMP or S-adenosylhomocysteine [2]. Metabolically unfavourable conditions increase the availability of adenosine, for example, ATP breakdown in hypoxia leads to the generation of excessive adenosine. Adenosine was identified as the major autacoid that regulates the cellular functions in the absence of energy and meets the cellular energy demand. It can condition the cells to meet the metabolic demand with less/lack of energy, therefore it has earned thename of "retaliatory metabolite" in 1980 [3]. Extracellular adenosine released in these unfavourable conditions restores the cellular function by its cytoprotective mechanism. It protects cells by increasing the oxygen supply, prevents ischaemic damage by cell preconditioning, and promotes anti-inflammatory responses and angiogenesis [4]. All these cellular responses of adenosine are strictly regulated by its receptors. There are four subtypes of the ARs (A_1, A_{2A}, A_{2B} and A_3) are the GPCRs and are expressed transcellularly. The cellular distribution and pharmacological responses of these receptors are different and unique. Out of these four receptors, A_1 and A_3 share 49% of similarity whereas, A_{2A} and A_{2B} share 59% of sequence similarity [5]. The selective modulators of these receptors are widely studied for several pathological conditions such as inflammation, neurodegeneration, ischaemia, cardiovascular disorders and cancer. However, their therapeutic application is still elusive. In this review, the association between the AR subtypes and tumour development are discussed extensively. Furthermore, the possibilities of these receptor subtypes as the novel therapeutic target against cancer are discussed.

2. ADENOSINE RECEPTORS AND SIGNALLING PATHWAYS

ARs are classified under GPCRs and their signalling is associated with the activation/inhibition of adenylyl cyclase. In addition, other pathways of PLC, MAPKs and alteration of intracellular Ca^{2+} concentration are also involved. A_1AR and A_3AR share a similar signal transduction process. Activation of A_1AR and A_3AR receptors inhibit adenylyl cyclase through pertussis toxin-sensitive Gi proteins activation and increased PLC activity via Gq proteins [6]. Inhibition of adenylyl cyclase leads to a decreased cAMP concentration in cells which further modulates the PKA that phosphorylates MAPK and protein kinase B/Akt signalling pathways [7,8]. Induction of signalling cascade with increased intracellular calcium concentration, PLC and PLD activation leads to the cellular proliferation and apoptosis [9]. A_{2A} and A_{2B} receptor activation increases adenylyl cyclase activity through Gs proteins. Gs activation is the

*Address correspondence to this author at the Department of Life Sciences, School of Pharmacy, International Medical University, Bukit Jalil, Kuala Lumpur, Malaysia; Tel: +60327317310; Fax: +60386567229;
E-mail: subratkumar@imu.edu.my; bhattamisra@yahoo.co.in
School of Pharmacy, International Medical University, Bukit Jalil, Kuala Lumpur, Malaysia; Tel: +60327317575; Fax: +60386567229;
E-mail: hirachoudhury02@gmail.com; HiraChoudhury@imu.edu.my

primary mechanism of A_{2A}ARs, whereas, A_{2B} triggers PLC activity through Gq protein. The principal functions of A_{2B}ARs are demonstrated by Gq activation and increase in inositol phosphate formation. The other signal transduction process by A_{2A}ARs activation involves inositol phosphate formation and increased intracellular calcium concentration that further activates protein kinase C via pertussis toxin-insensitive Gα15 and Gα16 proteins [10,11].

3. ADENOSINE RECEPTORS AND THEIR ROLE IN CANCER

3.1. A_1 Adenosine Receptors in Cancer

The A_1ARs are monomeric glycoproteins of approximately 36-kDa [12]. They couple to several effectors such as adenylate cyclase, guanylate cyclase and various ion channels including Ca^{2+}, Cl^- and K^+ channels. Furthermore, they are coupled to guanine nucleotide regulatory proteins or G proteins leading to the activation of G-protein and are involved in the physiological regulation of nucleotide adenosine. Overproduction of adenosine from ATP by both immune and cancerous cells correlates with cancer progression [13]. It acts as an immunosuppressive metabolite and enables tumour cells to overcome anti-tumour immune mechanisms [14]. The dual effects of A_1AR, either anti-inflammatory or pro-inflammatory have been observed [15]. A_1AR induced phagocytic function of neutrophils [16] and the formation of giant cells by monocytes [17]. Conversely, anti-inflammatory activities of A_1AR have been reported in various diseases or tissue injuries [18–21]. In addition, through the binding with agonists, A_1AR causes the inhibition of ADCY which catalyses the production of cAMP from ATP, resulting in reduced levels of cAMP [22]. cAMP produced through ADCY catalysis, subsequently induced CREB phosphorylation through the cAMP/PKA signalling pathway [23]. Several reports have suggested the roles of ADCY, cAMP and CREB in carcinogenesis and tumourigenesis [24–28]. Overexpression of ADCY3 found in human gastric cancer cell lines and tissues promotes cancer progression. Increased levels of cAMP, phosphorylated CREB, MMP2 and MMP9 were also observed in HEK293 cells overexpressing ADCY3 (transfected with pAcGFP-ADCY3) [28]. ADCY3 silencing suppressed tumourigenesis and cell proliferation. Moreover, ADCY2 was reported as a marker for poor prognosis in colorectal cancer [27]. These observations are consistent with the inhibitory effects of A_1AR agonists on the proliferation of Sertoli-like TM4 cells [29] as well as glioblastoma growth in the presence of microglial cells [30]. Furthermore, adenosine was shown to reduce microglial proliferation in the presence of A_1AR agonist while A_1AR deletion resulted in high density of microglia surrounding tumour [30]. However, stimulation of microglial proliferation by adenosine via cooperative interactions between ARs A_1 and A_2, was also reported [31]. In another report, A_1AR antagonist was shown to inhibit adenosine-induced apoptosis while the A_1AR agonist induced cell death in human colonic cancer (CW2) cells suggesting the involvement of A_1AR in the tumour suppressive roles of adenosine [32]. Adenosine was shown to induce apoptosis through a series of caspase activation. Interestingly, A_1AR was reported to exert a protective effect against cisplatin-associated ototoxicity through its anti-apoptotic and anti-inflammatory activities [33].

Overexpression of A_1AR in cancers might result from the increased levels of adenosine within the tumour microenvironment possibly due to hypoxia or oxygen deficiency [14,34,35]. In Jurkat cells or human leukemia cells, A_1AR was simultaneously expressed together with A_{2A}, A_{2B} and A_3 to facilitate the activation of various pathways by the selective adenosine [36]. Up-regulation of A_1AR expression was also recorded in the human colorectal adenocarcinomas and breast tumour tissues when compared to normal tissues [37,38]. The tumourigenic roles of A_1AR were demonstrated the by down-regulation of A_1AR in breast [38] and renal carcinomas [39] via RNA interference and A_1AR antagonist (DPCPX) respectively. In addition to its ability to induce apoptosis in breast cancer cells, A_1AR siRNA inhibited tumour growth and caused cell arrest at G_2/M phase with reduced cell population at the S phase [38]. This incident might be due to the overexpression of p27 protein and downregulation of CDK4 protein. It was observed that A_1AR antagonist (DPCPX) could inhibit cell proliferation and promote cell migration the regulation of MMP expressions in renal cancer cells [39]. Furthermore, DPCPX upregulated the levels of p53 and caspases that led to apoptosis in MCF-7 cells [40]. In other studies, A_1AR demonstrated metastatic role by regulating adenosine-induced motility in the melanoma cells [41] and promoted angiogenesis by inducing the release of VEGF from monocytes [42]. Angiogenesis is critical for tumour progression and VEGF plays an important role as its activator by inducing the formation of blood vessels surrounding tumours as the source of nutrients and oxygen [43].

3.2. A_2 Adenosine Receptors in Cancer

The two genes – $ADORA_{2A}$ and $ADORA_{2B}$ were found encoded in A_2 receptors, to express A_{2A}AR and A_{2B}AR, respectively, where these A_2 receptors are attached to G_s subunit of G_α proteins. It has been reported that the affinity of adenosine towards ARs is as follows: A_1 (100 nM)> A_3AR (290 nm)> A_{2A}AR (310 nM)> A_{2B}AR (Ki=15,000 nM). Activation of these A_2 receptors releases G_s subunit for the dimers ($G_{\beta\gamma}$) in order to activate adenylyl cyclases. Activation of adenylyl cyclase promotes the conversion of cellular ATP to cAMP [44]. Because of increased cAMP level, it activates PKA as depicted in Fig. **1** *via* formation of the consecutive complex between two cAMP molecules and regulatory subunits, which releases active catalytic monomer to phosphorylate other substrates [44,45].

Activated PKA isoform, gets , affixed to the TCR in T-cell. Therefore, phosphorylation of proximal C-terminal Src kinase of the TCR inhibits activation of Fyn and Lck tyrosine kinases, which prevents the signalling pathway of TCR [45]. Thus, at an elevated level of cAMP, it has been established that these regulatory T cells, specialized T cells that suppress the immune response, facilitates the progression of cancer [46]. Evasion into the immune system is also a well-accepted platform for cancer. Therefore, increased level of cAMP caused by the action of adenosine correspondingly dampens the immune system, where the cAMP-PKA signalling phosphorylates nuclear factor of activated T-cells and transcription factor CREB, thereby decreasing the formation of type I cytokines, IFN-γ [45,47].

Alternatively, an increased level of cAMP independently activates guanine exchange factor, which is responsible to control the cellular functions [45,48]. Thus, activation of guanine exchange factor, Epac further acts on small GTP_{ases}, Rap1 and Rap2 and activates them. Activation of Epac regulates several cellular functions, viz. adhesion, differentiation, proliferation and secretion [49]. Additionally, due to Rho members of the Ras superfamily, these Rap1 and Rap2 facilitate MAPK signalling [50]. Furthermore, increased Rap1 activation decreases IL-2 gene transcription, which is a common consequence of T-cell functions following stimulation of TCR [51]. Therefore, increased level of cAMP can act and suppress T-cells in both PKA-dependent and independent manner to promote disease states including cancer.

ARs are identified for their inflammatory responses in various inflammatory diseased conditions *via* modulation of pro-inflammatory activities [52]. It has also been postulated that matured dendritic cells upregulate the expression of A_{2A} and A_{2B}AR, whereas activation of A_{2B}ARs in the absence of toll-like receptors induces chronic inflammation *via* Th17 polarization of CD4+ T-cells and release of the pro-inflammatory cytokine, IL-6 [53]. As discussed earlier, for the low affinity of A_{2B}ARs towards adenosine, activation of A_{2B} ARs requires accumulation of adenosine at the disease site, such as cancer [54]. Further, these dendritic cells and

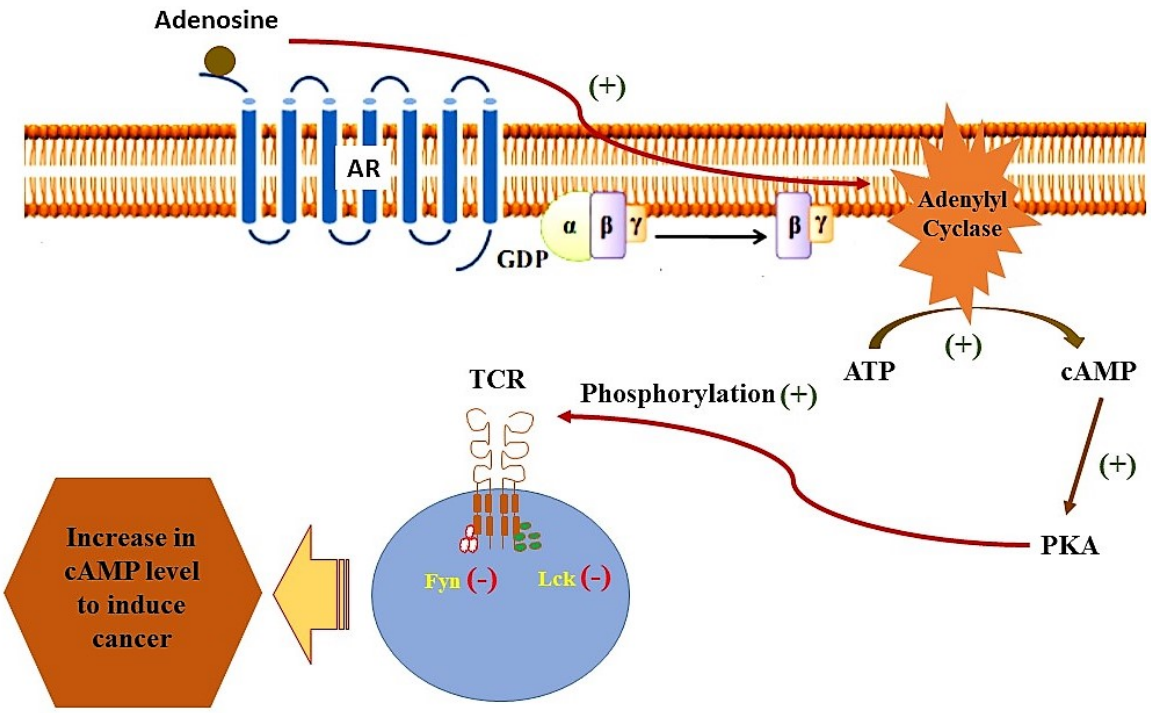

Fig. (1). Activation pathway of adenosine receptor to inhibit the activation of T-cell receptors and induce diseases like cancer.

macrophages are found to be sensitive towards adenosine. Exposure of these cells to adenosine has shown to decrease TNFα and IL-12 secretion, Th1 polarization of naïve CD4+ T-cells, and an increase in anti-inflammatory IL-10 formation [55,56]. Therapeutic consequences of A_{2A} and A_{2B}ARs will be discussed in the connecting sections.

3.2.1. A_{2A} Adenosine Receptors in Cancer

The purine nucleoside, adenosine, shows high specificity towards the A_{2A}AR, which is expressed at different levels in different body tissues. Normally, the existence of A_{2A}AR has been reported in blood platelets, leukocytes, thymus, spleen, and brain at a higher degree, where expression of this receptor in blood vessels, lung and heart is intermediate [57,58]. However, overexpression of A_{2A}ARs has a direct relationship with cancer , as adenosine helps to regulate all cancer developmental phases, angiogenesis, cell proliferation, immunoescaping and metastasis. Therefore, it is presumed that the overexpression of A_{2A}ARs is a common phenomenon in cancer microenvironment for the uncontrolled growth of cells [59,60].

Alternatively, as discussed earlier, the recognition of the cancerous cells by immune cells, such as by the cytosolic T cells, is also affected by the overexpression of A_{2A}ARs [61–63]. Such actions usually result from the depression of the immune cells by the effect of adenosine in A_{2A}ARs, which progress to increase in hypoxic tumour cell survival and immunoescaping. Attention towards overcoming such immunosuppression due to the action of adenosine on A_{2A}ARs resulted in with several research outputs with resolving inflammatory responses, engagement of TCR on CD4+ T-cells inhibiting IFN-γ production, increased propagation of antigen-activated CD4+ and CD8+ T-cells in experimental animal models [54,64,65]. Therefore, decreased expression of A_{2A}ARs in experimental mice with particular genetic deletion of A_{2A}ARs could be reflected by intense cellular immunity–particularly antitumour immunity, and prolonged survival of the animals with the rejection of established immunogenic tumours. Interestingly, it has also been proposed that accumulated cAMP in the regulatory T-cells due to activation of A_{2A}ARs was transferred to the effector T-cells through GAP junctions [54,64,65]. Furthermore, angiogenesis property of the A_{2A}ARs promotes wound healing along with the promotion of breast cancer and melanoma cells proliferation [66–69]. Expression of CD73 is known to cause metastasis of the cancer cells during stimulation of A_{2A}ARs, whereas metastasis can be prevented in A_{2A} genetic deleted mice. Several other studies on the blockade of A_{2A}ARs have revealed inhibition of tumour growth, as well as metastasis [54,70,71]. Thus, it can be concluded that an inhibitor of A_{2A}ARs could attenuate the cancerous condition and can lead to increased survival.

3.2.2. A_{2B} Adenosine Receptors in Cancer

Specificity of adenosine towards the A_{2B}AR is very low, which is also expressed in a variety of body tissues, such as intestine, brain, vasculature, immune-cells (e.g., macrophages, dendritic cells, neutrophils, mast cells and lymphocytes), neurons, astrocytes and endothelial cells [72]. Overexpression of this receptor subtypes is also reflected in various diseases, like acute and chronic lung disease, vascular disorders, renal complications, diabetes including cancer [45,72]. Pro-tumourigenic role of A_{2B}AR has been reflected by decreased TNFα- and chemotherapy-induced cancer cell deaths in A_{2B}AR overexpressed prostate cancer cell [73].

Progression of tumour growth by A_{2B}ARsis caused through various mechanisms. In addition to the general mechanism of cAMP accumulation, stimulation of phospholipase-C-β *via* Gq protein attached to A_{2B}ARs ensues by the activation of the receptor, thereby leading to PKC activation or mobilization of second messenger (calcium) in an IP_3-dependent manner [45]. Thus, the potential to trigger the A_{2B}ARs has two discrete signalling cascades.

Tumour progression mechanisms *via* A_{2B}ARs can be promoted by many ways through the action of adenosine and it has been represented in Fig. **2**. As discussed earlier, the common mechanism for A_{2A} and A_{2B}ARs *via* activation of cAMP-PKA signalling hampers the activation of T-cell by inhibiting TCR proximal kinases (Fyn and Lck). Simultaneously, activation of Epac by the raised cAMP level diminishes MAPK signalling downstream of TCR stimulation,

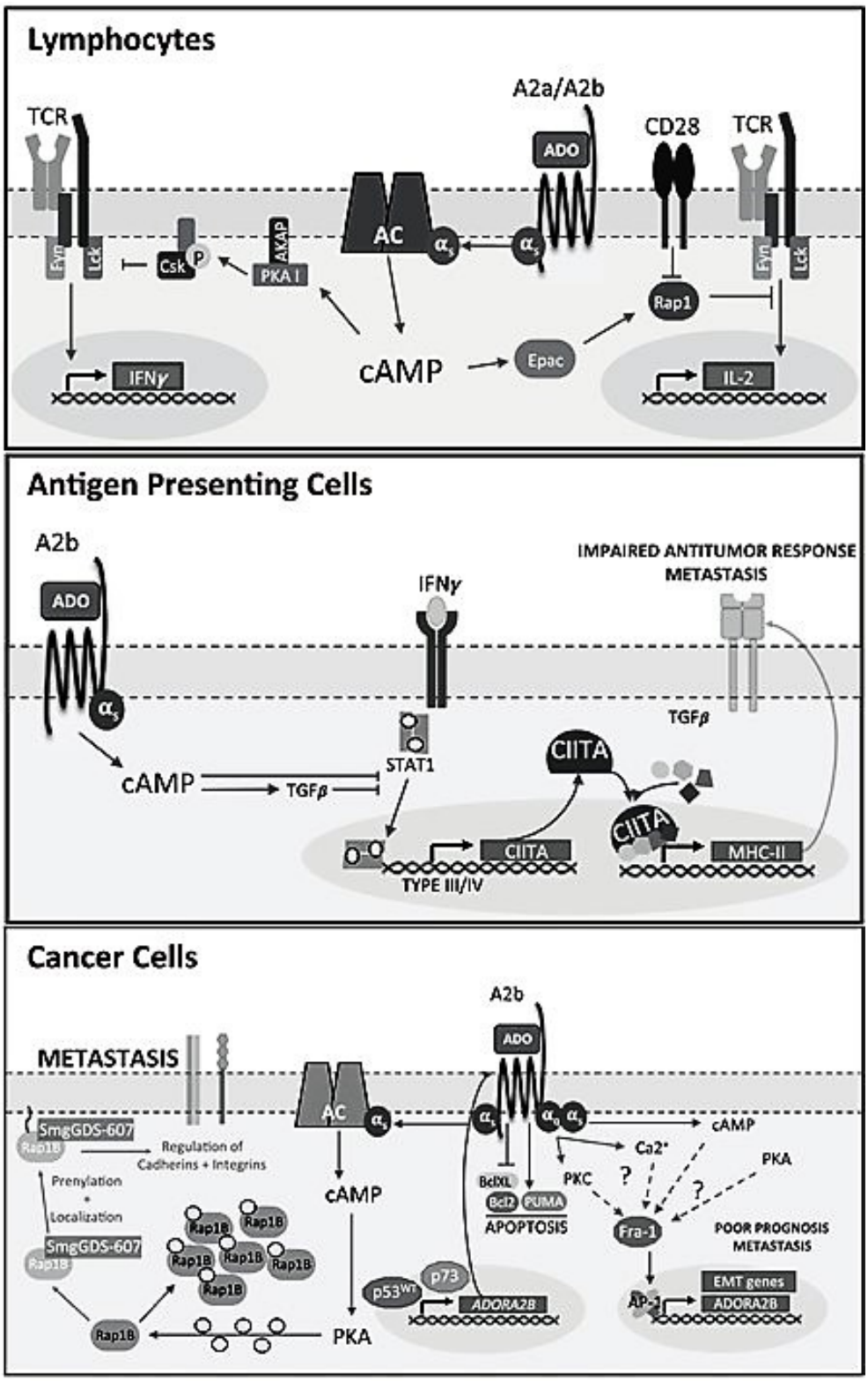

Fig. (2). A_{2B} adenosine receptor is a cancer target [45].

and thus hinders T-cell differentiation and proliferation *via* the small GTPase Rap1. Additionally, diffusion of cAMP from the GAP junction of the regulatory T-cells, and other implications on cancer cell signalling are noticeable.

Early events of metastatic function, i.e., cell motility and migration of cancer cells, are promoted *via* the stimulation of A_{2B}ARs. This receptor is the special AR, which activates MAPK signalling pathways to promote metastasis. Thus, all the three components of MAPK family, the JNK, the stress-activated protein kinases p38, and the ERK 1/2, are coupled to A_{2B}ARs [74]. As depicted in figure2, stress in cell stimulates expression of A_{2B}ARs in a p53-dependent manner. At the same time, A_{2B}ARs potentiates p53-

mediated cell death in normal cells. Lack of such pro-apoptotic response, apoptotic process discontinues in cancer cells. In due course of action, A_{2B}ARs hinders Rap1B localization on the cell surface, thereby leading to initial steps of cancer metastasis because the cells start scattering. Phosphorylation of Rap1B is a consequence of A_{2B}ARs stimulation, which prevents localization at the cell membrane [75]. Therefore, prevention of the phosphorylation process of Rap1B can be targeted to prevent cell scattering during tumour metastasis.

Similarly, expression of A_{2B}ARs on the cancer cell surface is induced by the pro-metastatic Fra-1 transcription factor, where antagonising the overexpressed receptors by selective antagonist resulted in the inhibition of metastasis in Fra-1-expressing cells [76]. Expression of Fra-1 reflected by motility, proliferation, invasiveness and metastasis [77], and inhibition of A_{2B}ARs showed a comparable effect to Fra-1 depletion in terms of metastasis growth, development of filopodia and membrane protrusion [76]. Finally, the presentation of abnormal cells as antigen is impaired by the expression of A_{2B}ARs, which actually interferes with the expression of MHC on the cell surface. Expression of A_{2B}ARs on cancer cell suppresses class-II trans-activator (CIITA), which in turn harms MHC class-II transcription in IFN-γ-stimulated cells [78]. The mechanism behind such action can be explained by the decreased phosphorylation of STAT1 due to A_{2B}ARs induced accumulation of cAMP, because of which binding of phosphorylated-STAT1 to CIITA is impaired. Consecutively, the situation boosts the synthesis of TGF-β which antagonizes MCH II transactivation [78,79]. Thus, as an effect of overexpressed A_{2B}ARs on the cancer cell surface, there is a decreased level of MHC class II and CIITA during metastasis [80]. Thus, blockade of overexpressed A_{2B}ARs can reverse the apoptotic potential and immunity of the cancer cells, therefore growth of the cancer cells can be controlled. There are several reports available in the literature, e.g., agonistic action of BAY 60-6583 on A_{2B}ARs reflected by *in vitro* proliferation and migration of breast cancer cells and production of IL-10 [81,82], whereas selective antagonist to A_{2B}ARs, ATL801, has shown to decrease the *in vivo* proliferation rate of 4T1 breast tumour and MB49 bladder cancer cells [83].

3.3. A_3 Adenosine Receptors in Cancer

The gene coding for A_3AR was located at 1p13.3 on the human chromosome [84]. It is widely expressed in various tissues including brain, heart, lung and liver although with different degrees of expression intensity as well as in various glial and immune cells [85]. A_3AR has promising roles as a cancer marker and therapeutic target as its overexpression was recorded in a wide range of cancer cells and tissues [85,86]. Both positive and negative effects on cell proliferation and apoptosis were observed with A_3AR in cancers possibly due to various factors including agonist concentration, cell type, simultaneous AR interactions and tumour microenvironment [85]. Simultaneous involvement of both ARs, A_{2B} and A_3 in human mast cells, was found to induce angiogenesis [87]. Stimulation of A_3AR was reported to increase the levels of MMP-9 in human glioblastoma cells via the activation of ERK 1/2 and AKT/PKB pathways resulting in enhanced cell invasiveness [88]. In addition, adenosine-induced the expression of VEGF through the upregulation of HIF-1 by A_3AR [89]. An elevated level of HIF-1 is implicated in high cancer mortality rate and its inhibition reduced angiogenesis and tumour progression [90]. Silencing of A_3AR via siRNA approach and the use of A_3AR antagonists reduced chemoresistance to paclitaxel, thus enhancing apoptosis in glioblastoma cells [91].

Conversely, agonist 1-deoxy-1-[6-[[(3-iodophenyl)-methyl] amino]-9*H*-purine-9-yl]-*N*-methyl-β-D-ribofuranuronamide (IB-MECA) activation of G-protein-coupled A_3AR regulated tumour growth suppressive mechanisms in melanoma which involved receptor internalisation, resynthesis and externalization as well as deregulation of Wnt pathways [92]. Like A_1AR, activation of A_3AR negatively regulates ADCY activity resulting in the reduction of cAMP and PKA levels [36]. In the presence of adenosine, high levels of cAMP were observed in the A_3AR knock-out mice [93]. Activated A_3AR inhibited PKA activities and prevented the subsequent phosphorylation or inactivation of GSK-3β. The active GSK-3β induced the phosphorylation or inactivation of β-catenin which resulted in reduced levels of c-Myc and cyclin D1, thus reducing proliferation of melanoma cells (Fig. **3**). In another study, A_3AR activation was reported to inhibit PKA-mediated ERK 1/2 activation and subsequent NADPH oxidase activities in prostate cancer cells, thus resulting in reduced cell proliferation and invasiveness [94]. Alternatively, A_3AR could reduce cell proliferation by down-regulating the Akt/NF-κB signalling pathway [95]. A_3AR agonist (CF102) was found to demonstrate protective effects against liver inflammation by decreasing the serum levels of glutamic oxaloacetic transaminase and glutamic pyruvic transaminase as well as the levels of NF-κB and TNF-α which are possibly due to the reduced levels of phosphorylated GSK-3β [96]. Moreover, CF102 exhibited anti-cancer activities by inducing apoptosis through the up-regulation of pro-apoptotic genes and caspase activation. In addition, induction of apoptosis by A_3AR agonists was demonstrated in malignant mesothelioma [95] and leukaemia cells [97]. The agonist 2-chloro-N^6-(3-iodobenzyl)-adenosine-5′-*N*-methyl-uronamide (Cl-IB-MECA) induced apoptosis and cell cycle arrest at G0/G1, but reduced telomeric signal and suppressed metastasis in melanoma [98]. Adenosine at low concentrations (5-25 μM) prevented the growth of lymphoma cells via A_3AR in the similar cytostatic pathway [99].

4. PERSPECTIVES OF ADENOSINE RECEPTOR MODULATORS TOWARDS ANTICANCER ACTIVITY

Under physiological and pathological conditions, adenosine acts as a modulator for cells and attenuates the stress response in cells [100,101]. Thus therapeutic applications of ARs agonist and antagonists were studied extensively. A number of molecules targeting these receptors were synthesized which are selective agonists or antagonists for these receptors. Therapeutic applications of agonists based on their selectivity towards receptor subtypes are reported to have neuroprotective (A_{2A}) [102], cardioprotective (A_1, A_3 and A_{2B}ARs)[103], renoprotective (A_1)[104], cerebroprotective (A_1 and A_3) [105], anti-inflammatory (A_{2A} and A_3) [100], and a wide range of autoimmune inflammatory conditions (A_3AR) [106–108]. Similarly, some adenosine antagonists have therapeutic potential to treat neurodegenerative diseases [109], although KW6002 (Istradefylline), an A_{2A}AR antagonist was not approved by FDA for the treatment of Parkinson's disease [110]. Selective agonists and antagonists were studied for their anticancer activity by many researchers and significant response against cancer cell lines was reported.

The role of four ARs in the progression of tumour growth and metastasis has been discussed so far. This section of the article will focus on different modulators on the ARs to improve the condition of various cancers. Several researches are ongoing to synthesize potential candidate to modulate the functionalities of ARs [111–116]. A_1AR modulators have shown good potential in fighting cancer growth. For example, Hosseinzadeh and team had reported that the A_1AR agonists have a potential inhibitory effect on cancer cell proliferation. In due course of their experiments, the authors tested CHA or R-PIA, two A_1AR agonists [117], on different *in vitro* cancer cells, where they observed that these A_1AR agonists are responsible for the inhibitory effect on tumour cell proliferation [118]. Interestingly, the action of these A_1AR agonists was too specific to the cancer cells and could not act on normal human cell lines, e.g., fibroblast cells. The authors also presented that such inhibitory effects are diminished by the presence of A_1AR antagonists [118]. In contrast, various researchers have pointed out reverse reports on the role of A_1AR in relation to the pathogenesis of cancer. For ex-

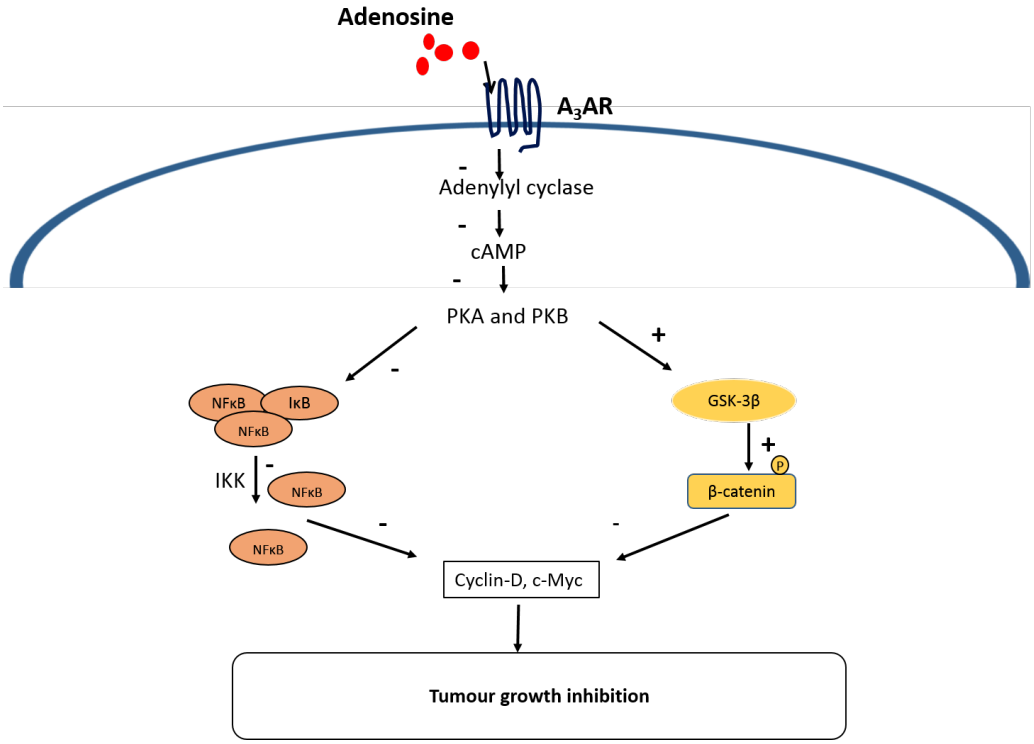

Fig. (3). Tumour growth inhibition by A_3AR activation.
+: stimulation; -: inhibition; PKA: Protein kinase A; PKB: Protein kinase B, GSK-3β: glycogen synthase kinase- 3β; NKκB: Nuclear factor kappa B; IKK : IκB kinase

Table 1. Adenosine receptors and their link to different cancers.

Adenosine Receptors	Cancers
A1ARs	• Increase the cell growth and cell proliferation • Human colorectal adenocarcinomas, Breast tumour, Melanoma, Cervical cancer, Human leukemia, Human melanoma
A_{2A}ARs	• Increase the endothelial cell proliferation, angiogenesis, erythropoietin (EPO) production • Hepatocellular carcinoma, Breast cancer
A_{2B}ARs	• Increase the endothelial cell proliferation, angiogenesis • Colon cancer, Glioblastoma, Melanoma
A_3ARs	• Mediates cell cycle progression and proliferation • Lymphoma, Leukemia, Mesothelioma, Colon cancer, Prostate cancer, Breast cancer, Glioblastoma, Melanoma, small-cell lung carcinoma, pancreatic carcinoma, hepatocellular carcinoma

ample, agonistic action of N6-cyclopentyladenosine (CPA) on A_1AR revealed the downregulation of mRNA expression for caspases 3, 8 and 9 and p53, which ultimately lead to increased viability of breast cancer cells with reduced apoptotic potential [40,119]. Similarly, Lin and co-workers demonstrated the effect of specific A_1AR antagonists, 1,3-dipropyl-8-cyclopentylxanthine (DPCPX), on breast cancer cell growth [120]. The authors revealed the dual role of DPCPX to target estradiol/ERα and to regulate ERα transcriptional activity. They showed that the knockdown of A_1AR by siRNA ablation in ERα-positive breast cancer cells reduced cell proliferation, whereas overexpression of the receptors in ERα-negative cells induced proliferation [120]. Similar research on breast cancer cell line (MCF-7) with DPCPX has recently revealed that the antagonistic action induced the expression of p53 and caspase 3, 8 and 9 in the breast cancer cells, and thus promoted cancer cell apoptosis [40,119]. An extension of research with DPCPX had also reported the inhibition of *in vitro* cancer cell proliferation in A_1AR upregulated renal cell carcinoma cells and decreased *in vivo* growth of the developed tumour. Therefore, the effects of A_1AR on different cancer cells may have multiple effects. The exploration of novel targets with an understanding of the actual A_1AR conformation could help the researchers to fit or accommodate allosteric and orthosteric ligands in order to achieve successive modulatory action [121] towards the improvement of cancer therapy as discussed so far.

The presence of elevated level of extracellular adenosine in the tumour microenvironment plays a potential role in tumour growth, immune-escaping and metastasis. Higher expression of $A_{2A}AR$ had attracted research focus towards the improvement of survival and

quality of life. Competitive antagonism of the A_{2A}AR antagonists requires a higher level of dosage to completely inhibit the target receptors. To develop increased affinity of the compound towards targeted receptor, Houthuys and team developed a novel potent compound that is effective at sub-nanomolar K_i and IC_{50}. This new generation compound, iTeos, was found to reverse cAMP-mediated suppression of T-cell, agonist-induced reduction in the production of TNFα, and improve CD8 T-cell cytotoxicity, offering a potential compound in immune-oncology [122]. Similarly, another highly selective antagonist with high affinity towards A_{2A}AR, 2-(2-furanyl)-N5-(2-methoxybenzyl)[1,3]thiazolo[5,4-d]pyrimidine-5,7-diammine (TP455), was analysed by Gessi and team [63]. This specific antagonist was found to revert the cell proliferative action of A_{2A}AR agonist, CGS21680, in MRMT1, A549, and A375 cancer cells. On evaluation, TP455 counteracted the action of CGS21680 in terms of Akt, ERK 1/2, and JNK in cancer cells [63].

With the same concept, another highly A_{2A}AR specific antagonist PBF-509 was investigated in both *in vitro* and *in vivo* models to evaluate lung metastasis. With satisfactory outcomes of the reported investigations, the authors also revealed increased expression of A_{2A}AR in CD4+ cells in freshly resected tumour-infiltrating lymphocytes, whereas, in CD4+ cells, the expression was variable. Co-treatment of anti-PD-L1 or anti-PD-1 with PBF-509 revealed synergistic inhibition of tumour growth in *ex vivo* experiments [123]. Activation of A_{2A}AR is associated with cell growth in MCF-7 breast, A375 melanoma and A549 lung carcinoma [124]. A_{2A}AR antagonists showed a direct increase in the apoptotic effect in A549 cell line [125]. In a recent study by Gessi et al., A_{2A}AR activation was linked to the modulation of cell proliferation in A375 melanoma, A549 lung and MRMT-1 breast carcinoma. In all the three cancer cell lines, A_{2A}AR are expressed with an order of A375 > A549 > MRMT-1. A selective A_{2A}AR agonist treatment resulted in a significant increase in cell proliferation in MRMT-1 cells which is due to PLC and PKC-d stimulation. The mechanism of cell proliferation through A_{2A}AR was linked to the phosphorylation of ERK 1/2, $JNK_{1/2}$, and AKT that is dependent on PLC and PKC-d stimulation [63]. Further, Gessi et al reported that the tumourigenic effect is activated by A_{2A}AR agonists, whereas the effect is reversed by A_{2A}AR antagonist ZM241385. Another antagonist TP455 is able to block A_{2A}AR induced cancer cell proliferation [63]. Interestingly, this class of compounds is already under clinical phase due to its anti-Parkinson effects and is well-tolerated and safe [126,127].

Being the vital checkpoint of immune responses, increased adenosine level in the tumour microenvironment is due to specialized metabolism of tumour cells, A_{2A}AR inhibitors are proposed for immunotherapy. Another A_{2A}AR antagonist, CPI-444, which was investigated by Leone and team had projected towards improved immunologic responses. The authors mentioned that blockade of the receptor by CPI-444 decreases the expression of lymphocyte-activation gene-3 and check-point inhibitor–PD-1, on both FoxP3+ CD4+ regulatory T-cells and CD8+ effector T-cells in tumour bearing mice. However, the action was not shown in A_{2A}AR knockout model. This concept opens up a new avenue to design novel immunotherapy regimens [128]. In a separate study, CPI-444 was shown to inhibit tumour growth (MC38 cells) in a dose-dependent manner, where co-treatment of anti-PD-L1 revealed synergistic inhibition of tumour growth, even 90% of treated animals were completely treated from cancer [129]. Re-challenging the cured mice with MC38 cells had shown systemic anti-tumour immune memory to stop the tumour growth completely. In addition to this, the authors also reported that the immune-checkpoints were also modulated by treatment with CPI-444, including LAG3, GITR, OX40 on circulating T-cells and tumour infiltrating lymphocytes [129]. Thereforethe previous two reports demonstrated the extensive role for adenosine-mediated immunosuppression *via* A_{2A}AR. Accordingly, experiments on A_{2B}ARs antagonist, CPI-444, crossed the laboratory barriers and reached the bedside of the patients. The affinity of CPI-444 towards A_{2B}ARs showed 50 fold higher selectivity over other ARs, and with a Ki of 3.5 nM [130]. A phase 1/1b multi-centre, open label clinical trial has been registered to evaluate the efficacy of CPI-444 in various solid tumour patients as a single agent and in combination with a PD-L1 inhibitor, atezolizumab [131]. However, the outcome of the study is yet to be published [131].

Consideration of potential side effects caused by the A_{2A}AR antagonist [132] is also an important parameter to be considered when treating cancer because these cancer cells can be accompanied by augmented auto-immunity if the treatment collides with sub-threshold auto-immunity or acute inflammatory condition [133]. So far, there is a scarcity of well-characterized, highly specific A_{2A}AR antagonists, which has attracted the attention of the researchers which could be facilitated by the available molecular structure of the receptor [133]. It can also be inferred that these A_{2A}AR antagonists could provide a potential platform for immunotherapeutic strategies in the treatment of cancer.

A number of reports on A_{2B}ARs antagonists, alone or in combination, for the investigation of therapeutic potential against tumour growth and metastasis are available in the literature. Researchers have shown the expression of a high level of A_{2B}ARs in MBA-MD-231 (estrogen-receptor negative breast cancer cell line) for a suitable human AR model [134]. Recent research had revealed that agonistic stimulation of A_{2B}ARs in MBA-MD-231 breast cancer cells resulted in decreased phosphorylation state of ERK 1/2 [135]. This could be targeted to control the growth in A_{2B}ARs over-expressed cancer cells. In continuation of the previous explanation on agonistic action of BAY 60-6583 on A_{2B}ARs in melanoma had revealed increased growth of melanoma lesion in an experimental murine model [82]. Such action of the agonists was explained by the increased level of IL-10 and monocyte chemoattractant protein 1. at the same time, there was accumulation of cancer-associated CD11b (+ve) Gr1 (+ve) cells, myeloid-derived suppressor cells [82]. The action of BAY 60-6583 was reported to be reversed in melanoma by the application of specific antagonist to the A_{2B}ARs, PSB1115. Further, the authors also reported that the antitumour activity of dacarbazine was enhanced by the co-application of PSB1115 in melanoma. Thus, antagonists of A_{2B}ARs could provide synergistic action if delivered with chemotherapeutic agents in order to control the disease an improved way [82]. With a similar target, the effect of PSB1115 was investigated with immune checkpoint inhibitors, and the authors concluded that the combined effect of the two provides synergistic action towards the reduction of tumour growth and reversal of immune-suppression in myeloid-derived suppressor cells [136].

Antagonistic action of PSB-603 on A_{2B}ARs had shown to alter cellular redox potential without affecting the viability of the cells *via* the promotion of oxidative phosphorylation. The action was further explained by AR-independent activity; however actual mechanistic role needs to be established. Further, PSB-603 enhanced reactive oxygen species within the colorectal cancer cells, where the agent acted synergistically with chemotherapy cocktail, oxaliplatin and 5-fluorouracil to enhance cancer cell death [137].

Another recent research was presented with a novel series of selective and potent dual inhibitors, A_{2A}ARs and A_{2B}ARs [138]. The activities of the compounds depicted a dose-dependent restoration of functional activities of CD4+ and CD8+ human T-lymphocytes, when adenosine impaired the functionality. The compounds also relieved suppressive action of adenosine agonists in NK cells cytotoxicity. The research has been extended to compounds with an improved pharmacological profile that are targeted to the A_{2A}ARs in clinical research [138].

Decades of research has brought to the conclusion that along with A_{2A}AR antagonists, A_3AR agonists are also a promising platform for drug development against cancer. Expression of A_3ARs at

a high level in various cancers, from lymphoma and leukemia to mesothelioma, colon cancer, prostate cancer, breast cancer, glioblastoma and melanoma projected towards research to find a novel therapy [88,89,94,139–143]. Research had revealed the action of pulsed electromagnetic fields, which showed an improved anti-tumour effect against neural cancer and glioblastoma cells *via* A_3AR [144]. The action was achieved by a reduction of cell proliferation and NF-kB transcription factor level. Consequently, activation of A_3AR and application of pulsed electromagnetic field resulted in an increased p53 level with increase in apoptotic death and cytotoxicity of cancer cells [144]. Dual activities of A_3AR agonists in normal and cancerous cells have attracted researchers to explorefurther [145]. However, these A_3AR agonists displayed activation of granulocyte colony-stimulating factor by peripheral blood mononuclear cells to induce immunosuppressive effects in solid tumour cells, because of which proliferation of murine bone marrow cell occurred [143,146]. On evaluation, it had been established that stimulation of NF-kB, PKB/Akt, and PI3K/IKK signalling pathways is the possible consequence of such action [147,148]. In addition to that, activation of A_3AR increases the activity of natural killer cells which simultaneously reduced the tumour cells by damaging them [149,150]. Alternatively, A_3AR agonist in CD8+ lymphocytes in experimental mice model produced anticancer activity through increased production of TNF-α [151].

Experiment on A_3AR agonists (IB-MECA and Cl-IB-MECA) has been extended in various animal models of different cancers, where stable oral administration of the compounds showed good bioavailability [152,153]. Subsequent research outcomes of Cl-IB-MECA had shown blockade of lung metastasis of the melanoma-bearing mice, synergistic research outcomes with cyclophosphamide for the control of tumour with the prevention of myelotoxic effect [139,147]. The role of IB-MECA had also been evaluated for the control of prostate cancer in a xenograft model [139]. The role of IB-MECA (CF101) against expansion of primary colon cancer in syngeneic model showed the prevention of liver metastasis of the colon cancer cells by increasing the activity of NK cells and enhancing the release of IL-12, whereas administration of IB-MECA with 5-fluorouracil in xenograft models showed synergistic anti-cancer activity with the prevention of myelotoxicity of 5-fluorouracil [149,154]. Inhibition of colon cancer growth in mouse models had been ascribed by the involvement of key proteins NF-kB and GSK-3β. The action of Cl-IB-MECA compound was also found to be positive against the hepatocellular tumour, liver inflammation, rat bone-residing breast cancer, and its associated pain [96,141,155]. Positive results in several pre-clinical experiments with Cl-IB-MECA (Namodenoson, CF102) reached the bedside of the patients for advanced hepatocellular carcinoma therapy. The Phase-I/II clinical trial (NCT00790218) reported the compound as safe, efficacious and well tolerated, to increase the survival time of the patients by 7.8 months [156]. The phase II trial of the compound is ongoing to have the data from the patients for improved therapy against cancer [157]. Relative higher expression of A_3AR in tumour cells has been reported as compared to the normal cells, thus ligands targeting A_3AR have potential application in tumour growth [86]. In a transgenic mouse model, overexpression of A_3AR resulted in embryonic lethality [158], which suggests its use in cancer therapy. In both in vitro and in vivo models, A_3AR activation resulted in tumour growth inhibition [98]. A_3AR agonists have the property of induction or inhibition ofapoptosis in human eosinophils and human promyelocytic HL-60 cells based on their concentration [97,159]. C1-IB-MECA induces apoptosis at higher concentration, whereas, IB-MECA inhibits apoptosis in RBL-2H3 cells induced by ultraviolet irradiation [160]. Besides its effect on apoptosis, it downregulates estrogen receptors in human breast cancer cell lines and completely blocks the cell growth [161]. Thio-Cl–IB–MECA, a highly specific A_3AR agonist increased apoptosis via deregulation of the Wnt signaling pathway in lung cancer cells and HL-60 promyelocytic leukemia cells. Further, the levels of phosphorylated forms of GSK-3β, β-catenin and Akt were down-regulated upon treatment with thio-Cl–IB–MECA in a time-dependent manner [97,162]. It is worth mentioning that currently various innovative computer aided drug design strategies are emerging for rational design and discovery of novel molecules targeting adenosine receptors as possible anticancer agents [163-168].

CONCLUSION

In conclusion, adenosine is an endogenous ligand that is released in a stresssed environment and elicits a protective effect on the organ or tissue. This protective effect of adenosine is exerted by its four ARs which are expressed in almost all cell types in the body. Extracellular adenosine concentration is tremendously elevated in tumour microenvironment that provokes the ARs to exert their anticancer activity. The anticancer activity of these four AR subtypes is extensively discussed in this review. Based on the literature related to the AR subtypes, all the receptor subtypes play a pivotal role in cancer which is confirmed in in vitro and in vivo experiments. Thus, all four AR subtypes are considered to be putative targets for the development of novel therapeutic approaches in cancer treatment. In recent decades, many synthetic analogues were developed as selective agonist and antagonist to AR subtypes. Some of these selective agonists have been studied in clinical phases for the treatment of pain, neuropathy, inflammatory conditions, and cancer. Similarly, selective antagonists were studied in clinical trials for the treatment of Parkinson's disease and heart failure. However, the development of a therapeutic molecule for cancer treatment is still elusive. With the advancement in adenosine research, it is expected that agents having less undesirable and more efficacious effects will be developed soon .

LIST OF ABBREVIATIONS

A_1AR	=	A_1 adenosine receptors
$A_{2A}AR$	=	A_{2A} adenosine receptors
$A_{2B}AR$	=	A_{2B} adenosine receptors
A_3AR	=	A_3 adenosine receptors
ADCY	=	Adenylate cyclases
ADCY2	=	Adenylate cyclases 2
ADCY3	=	Adenylate cyclases 3
AMP	=	Adenosine monophosphate
ATP	=	Adenosine triphosphate
cAMP	=	cyclic adenosine-3',5'-monophosphate
CIITA	=	Class-II trans-activator
CREB	=	cAMP response element binding protein
ER- α	=	Estrogen receptor-α
ERK 1/2	=	Extracellular signal-regulated kinases 1/2
GPCRs	=	G-protein coupled receptors
GSK-3β	=	glycogen synthase kinase- 3β
HIF-1	=	Hypoxia-inducible factor-1
IKK	=	IκB kinase
IL-2	=	Interleukin 2
IL-6	=	Interleukin 6
IL-10	=	Interleukin 10
IL-12	=	Interleukin 10
INFγ	=	Interferon γ
IP_3	=	Inositol triphosphate
JNK	=	c-jun N-terminal kinase
MAPK	=	Mitogen-activated protein kinase

MHC	=	Major histocompatibility complex
MMP2	=	Matrix metalloproteinases 2
MMP9	=	Matrix metalloproteinases 9
NADPH	=	Nicotinamide adenine dinucleotide phosphate
NF-κB	=	Nuclear factor κB
NK κB	=	Nuclear factor kappa B
PKA	=	Protein kinase A
PKB/Akt	=	Protein kinase B
PKC	=	Protein kinase C
PLC	=	Phospholipase C
PLD	=	Phospholipase D
STAT1	=	Signal transducer and activator of transcription 1
TCR	=	T-cell receptor
TGF-β	=	Transforming growth factor β
TNFα	=	Tumour necrosis factor α
VEGF	=	Vascular endothelial growth factor

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENT

Dr. Bhattamishra, Dr. Sook Yee and Dr. Choudhury would like to acknowledge School of Pharmacy, International Medical University, Malaysia and Dr. Gorain would like to acknowledge School of Pharmacy, Taylor's University, Selangor, Malaysia for providing resources and support in completing this work.

REFERENCES

[1] Zimmermann H. Extracellular metabolism of ATP and other nucleotides. Naunyn Schmiedebergs Arch Pharmacol 2000; 362(4-5): 299-309. [http://dx.doi.org/10.1007/s002100000309] [PMID: 11111825]

[2] Fredholm BB. Adenosine receptors as drug targets. Exp Cell Res 2010; 316(8): 1284-8. [http://dx.doi.org/10.1016/j.yexcr.2010.02.004] [PMID: 20153317]

[3] Newby AC. Adenosine and the concept of "retaliatory metabolites.". Trends Biochem Sci 1984; 9(2): 42-4. [http://dx.doi.org/10.1016/0968-0004(84)90176-2]

[4] Linden J. Adenosine in tissue protection and tissue regeneration. Mol Pharmacol 2005; 67(5): 1385-7. [http://dx.doi.org/10.1124/mol.105.011783] [PMID: 15703375]

[5] McGaraughty S, Cowart M, Jarvis MF, Berman RF. Anticonvulsant and antinociceptive actions of novel adenosine kinase inhibitors. Curr Top Med Chem 2005; 5(1): 43-58. [http://dx.doi.org/10.2174/1568026053386845] [PMID: 15638777]

[6] van Calker D, Müller M, Hamprecht B. Adenosine regulates via two different types of receptors, the accumulation of cyclic AMP in cultured brain cells. J Neurochem 1979; 33(5): 999-1005. [http://dx.doi.org/10.1111/j.1471-4159.1979.tb05236.x] [PMID: 228008]

[7] Seino S, Shibasaki T. PKA-dependent and PKA-independent pathways for cAMP-regulated exocytosis. Physiol Rev 2005; 85(4): 1303-42. [http://dx.doi.org/10.1152/physrev.00001.2005] [PMID: 16183914]

[8] Poulsen SA, Quinn RJ. Adenosine receptors: new opportunities for future drugs. Bioorg Med Chem 1998; 6(6): 619-41. [http://dx.doi.org/10.1016/S0968-0896(98)00038-8] [PMID: 9681130]

[9] Glukhova A, Thal DM, Nguyen AT, *et al.* Structure of the Adenosine A_1 Receptor Reveals the Basis for Subtype Selectivity. Cell 2017; 168(5): 867-877.e13. [http://dx.doi.org/10.1016/j.cell.2017.01.042] [PMID: 28235198]

[10] Offermanns S, Simon MI. G alpha 15 and G alpha 16 couple a wide variety of receptors to phospholipase C. J Biol Chem 1995; 270(25): 15175-80. [http://dx.doi.org/10.1074/jbc.270.25.15175] [PMID: 7797501]

[11] Fresco P, Diniz C, Gonçalves J. Facilitation of noradrenaline release by activation of adenosine A(2A) receptors triggers both phospholipase C and adenylate cyclase pathways in rat tail artery. Cardiovasc Res 2004; 63(4): 739-46. [http://dx.doi.org/10.1016/j.cardiores.2004.05.015] [PMID: 15306230]

[12] Linden J. Structure and function of A1 adenosine receptors. FASEB J 1991; 5(12): 2668-76. [http://dx.doi.org/10.1096/fasebj.5.12.1916091] [PMID: 1916091]

[13] Kazemi MH, Raoofi Mohseni S, Hojjat-Farsangi M, *et al.* Adenosine and adenosine receptors in the immunopathogenesis and treatment of cancer. J Cell Physiol 2018; 233(3): 2032-57. [http://dx.doi.org/10.1002/jcp.25873] [PMID: 28233320]

[14] Leone RD, Emens LA. Targeting adenosine for cancer immunotherapy. J Immunother Cancer 2018; 6(1): 57. [http://dx.doi.org/10.1186/s40425-018-0360-8] [PMID: 29914571]

[15] Fishman P, Bar-Yehuda S, Synowitz M, Powell JD, Klotz KN, Gessi S, *et al.* Adenosine receptors and cancer.Adenosine Receptors in Health and Disease 2009; 399-441. [http://dx.doi.org/10.1007/978-3-540-89615-9_14]

[16] Salmon JE, Cronstein BN. Fc gamma receptor-mediated functions in neutrophils are modulated by adenosine receptor occupancy. A1 receptors are stimulatory and A2 receptors are inhibitory. J Immunol 1990; 145(7): 2235-40. [PMID: 2168919]

[17] Merrill JT, Shen C, Schreibman D, *et al.* Adenosine A1 receptor promotion of multinucleated giant cell formation by human monocytes: a mechanism for methotrexate-induced nodulosis in rheumatoid arthritis. Arthritis Rheum 1997; 40(7): 1308-15. [PMID: 9214432]

[18] Lee HT, Gallos G, Nasr SH, Emala CW. A1 adenosine receptor activation inhibits inflammation, necrosis, and apoptosis after renal ischemia-reperfusion injury in mice. J Am Soc Nephrol 2004; 15(1): 102-11. [http://dx.doi.org/10.1097/01.ASN.0000102474.68613.AE] [PMID: 14694162]

[19] Tsutsui S, Schnermann J, Noorbakhsh F, *et al.* A1 adenosine receptor upregulation and activation attenuates neuroinflammation and demyelination in a model of multiple sclerosis. J Neurosci 2004; 24(6): 1521-9. [http://dx.doi.org/10.1523/JNEUROSCI.4271-03.2004] [PMID: 14960625]

[20] Liao Y, Takashima S, Asano Y, *et al.* Activation of adenosine A1 receptor attenuates cardiac hypertrophy and prevents heart failure in murine left ventricular pressure-overload model. Circ Res 2003; 93(8): 759-66. [http://dx.doi.org/10.1161/01.RES.0000094744.88220.62] [PMID: 12970111]

[21] Sun C-X, Young HW, Molina JG, Volmer JB, Schnermann J, Blackburn MR. A protective role for the A1 adenosine receptor in adenosine-dependent pulmonary injury. J Clin Invest 2005; 115(1): 35-43. [http://dx.doi.org/10.1172/JCI22656] [PMID: 15630442]

[22] van Galen PJ, Stiles GL, Michaels G, Jacobson KA. Adenosine A1 and A2 receptors: structure--function relationships. Med Res Rev 1992; 12(5): 423-71. [http://dx.doi.org/10.1002/med.2610120502] [PMID: 1513184]

[23] Rosenberg D, Groussin L, Jullian E, Perlemoine K, Bertagna X, Bertherat J. Role of the PKA-regulated transcription factor CREB in development and tumorigenesis of endocrine tissues. Ann N Y Acad Sci 2002; 968: 65-74. [http://dx.doi.org/10.1111/j.1749-6632.2002.tb04327.x] [PMID: 12119268]

[24] Löffler I, Grün M, Böhmer FD, Rubio I. Role of cAMP in the promotion of colorectal cancer cell growth by prostaglandin E2. BMC Cancer 2008; 8: 380. [http://dx.doi.org/10.1186/1471-2407-8-380] [PMID: 19099561]

[25] Sakamoto KM, Frank DA. CREB in the pathophysiology of cancer: implications for targeting transcription factors for cancer therapy. Clin Cancer Res 2009; 15(8): 2583-7. [http://dx.doi.org/10.1158/1078-0432.CCR-08-1137] [PMID: 19351775]

[26] Boettcher M, Lawson A, Ladenburger V, *et al.* High throughput synthetic lethality screen reveals a tumorigenic role of adenylate cyclase in fumarate hydratase-deficient cancer cells. BMC Genomics 2014; 15: 158. [http://dx.doi.org/10.1186/1471-2164-15-158] [PMID: 24568598]

[27] Yu S-J, Yu J-K, Ge W-T, Hu H-G, Yuan Y, Zheng S. SPARCL1, Shp2, MSH2, E-cadherin, p53, ADCY-2 and MAPK are prognosis-related in colorectal cancer. World J Gastroenterol 2011; 17(15): 2028-36. [http://dx.doi.org/10.3748/wjg.v17.i15.2028] [PMID: 21528083]

[28] Hong S-H, Goh S-H, Lee S-J, *et al.* Upregulation of adenylate cyclase 3 (ADCY3) increases the tumorigenic potential of cells by activating the CREB pathway. Oncotarget 2013; 4(10): 1791-803. [http://dx.doi.org/10.18632/oncotarget.1324] [PMID: 24113161]

[29] Shaban M, Smith RA, Stone TW. Purine suppression of proliferation of Sertoli-like TM4 cells in culture. Cell Prolif 1995; 28(12): 673-82. [http://dx.doi.org/10.1111/j.1365-2184.1995.tb00053.x] [PMID: 8634374]

[30] Synowitz M, Glass R, Färber K, *et al.* A1 adenosine receptors in microglia control glioblastoma-host interaction. Cancer Res 2006; 66(17): 8550-7. [http://dx.doi.org/10.1158/0008-5472.CAN-06-0365] [PMID: 16951167]

[31] Gebicke-Haerter PJ, Christoffel F, Timmer J, Northoff H, Berger M, Van Calker D. Both adenosine A1- and A2-receptors are required to stimulate microglial proliferation. Neurochem Int 1996; 29(1): 37-42. [http://dx.doi.org/10.1016/0197-0186(95)00137-9] [PMID: 8808787]

[32] Saito M, Yaguchi T, Yasuda Y, Nakano T, Nishizaki T. Adenosine suppresses CW2 human colonic cancer growth by inducing apoptosis via A(1) adenosine receptors. Cancer Lett 2010; 290(2): 211-5. [http://dx.doi.org/10.1016/j.canlet.2009.09.011] [PMID: 19822392]

[33] Kaur T, Borse V, Sheth S, Sheehan XK, Ghosh S, Tupal S, *et al.* Cellular/Molecular Adenosine A 1 Receptor Protects Against Cisplatin Ototoxicity by Suppressing the NOX3/STAT1 Inflammatory Pathway in the Cochlea 2016; 36(14): 3962-77.

[34] Blay J. Adenosine and Tumor Microenvironment Encyclopedia of Cancer 2011; 49-52.

[35] Ghiringhelli F, Bruchard M, Chalmin F, Rébé C. Production of adenosine by ectonucleotidases: a key factor in tumor immunoescape. J Biomed Biotechnol 2012; 2012473712 [http://dx.doi.org/10.1155/2012/473712] [PMID: 23133312]

[36] Gessi S, Varani K, Merighi S, *et al.* Pharmacological and biochemical characterization of A3 adenosine receptors in Jurkat T cells. Br J Pharmacol 2001; 134(1): 116-26. [http://dx.doi.org/10.1038/sj.bjp.0704254] [PMID: 11522603]

[37] Khoo H-E, Ho C-L, Chhatwal VJS, Chan STF, Ngoi S-S, Moochhala SM. Differential expression of adenosine A1 receptors in colorectal cancer and related mucosa. Cancer Lett 1996; 106(1): 17-21. [http://dx.doi.org/10.1016/0304-3835(96)04289-9] [PMID: 8827042]

[38] Mirza A, Basso A, Black S, *et al.* RNA interference targeting of A1 receptor-overexpressing breast carcinoma cells leads to diminished rates of cell proliferation and induction of apoptosis. Cancer Biol Ther 2005; 4(12): 1355-60. [http://dx.doi.org/10.4161/cbt.4.12.2196] [PMID: 16294023]

[39] Zhou Y, Tong L, Chu X, *et al.* The Adenosine A1 Receptor Antagonist DPCPX Inhibits Tumor Progression via the ERK/JNK Pathway in Renal Cell Carcinoma. Cell Physiol Biochem 2017; 43(2): 733-42. [http://dx.doi.org/10.1159/000481557] [PMID: 28950257]

[40] Dastjerdi MN, Rarani MZ, Valiani A, Mahmoudieh M. The effect of adenosine A1 receptor agonist and antagonist on p53 and caspase 3, 8, and 9 expression and apoptosis rate in MCF-7 breast cancer cell line. Res Pharm Sci 2016; 11(4): 303-10. [http://dx.doi.org/10.4103/1735-5362.189301] [PMID: 27651810]

[41] Woodhouse EC, Amanatullah DF, Schetz JA, Liotta LA, Stracke ML, Clair T. Adenosine receptor mediates motility in human melanoma cells. Biochem Biophys Res Commun 1998; 246(3): 888-94. [http://dx.doi.org/10.1006/bbrc.1998.8714] [PMID: 9618307]

[42] Clark AN, Youkey R, Liu X, *et al.* A1 adenosine receptor activation promotes angiogenesis and release of VEGF from monocytes. Circ Res 2007; 101(11): 1130-8. [http://dx.doi.org/10.1161/CIRCRESAHA.107.150110] [PMID: 17901362]

[43] Carmeliet P. VEGF as a key mediator of angiogenesis in cancer. Oncology 2005; 69(Suppl. 3): 4-10. [http://dx.doi.org/10.1159/000088478] [PMID: 16301830]

[44] Mosenden R, Taskén K. Cyclic AMP-mediated immune regulation--overview of mechanisms of action in T cells. Cell Signal 2011; 23(6): 1009-16. [http://dx.doi.org/10.1016/j.cellsig.2010.11.018] [PMID: 21130867]

[45] Allard D, Turcotte M, Stagg J. Targeting A2 adenosine receptors in cancer. Immunol Cell Biol 2017; 95(4): 333-9. [http://dx.doi.org/10.1038/icb.2017.8] [PMID: 28174424]

[46] Stagg J, Divisekera U, Duret H, *et al.* CD73-deficient mice have increased antitumor immunity and are resistant to experimental metastasis. Cancer Res 2011; 71(8): 2892-900. [http://dx.doi.org/10.1158/0008-5472.CAN-10-4246] [PMID: 21292811]

[47] Jimenez JL, Punzón C, Navarro J, Muñoz-Fernández MA, Fresno M. Phosphodiesterase 4 inhibitors prevent cytokine secretion by T lymphocytes by inhibiting nuclear factor-kappaB and nuclear factor of activated T cells activation. J Pharmacol Exp Ther 2001; 299(2): 753-9. [PMID: 11602691]

[48] Bos JL, Rehmann H, Wittinghofer A. GEFs and GAPs: critical elements in the control of small G proteins. Cell 2007; 129(5): 865-77. [http://dx.doi.org/10.1016/j.cell.2007.05.018] [PMID: 17540168]

[49] Cheng X, Ji Z, Tsalkova T, Mei F. Epac and PKA: a tale of two intracellular cAMP receptors. Acta Biochim Biophys Sin (Shanghai) 2008; 40(7): 651-62. [http://dx.doi.org/10.1111/j.1745-7270.2008.00438.x] [PMID: 18604457]

[50] Chrzanowska-Wodnicka M, Kraus AE, Gale D, White GC II, Vansluys J. Defective angiogenesis, endothelial migration, proliferation, and MAPK signaling in Rap1b-deficient mice. Blood 2008; 111(5): 2647-56. [http://dx.doi.org/10.1182/blood-2007-08-109710] [PMID: 17993608]

[51] Boussiotis VA, Freeman GJ, Berezovskaya A, Barber DL, Nadler LM. Maintenance of human T cell anergy: blocking of IL-2 gene transcription by activated Rap1. Science 1997; 278(5335): 124-8. [http://dx.doi.org/10.1126/science.278.5335.124] [PMID: 9311917]

[52] Blackburn MR, Vance CO, Morschl E, Wilson CN. Adenosine Receptors and Inflammation 2009; 215-69.

[53] Wilson JM, Kurtz CC, Black SG, *et al.* The A2B adenosine receptor promotes Th17 differentiation via stimulation of dendritic cell IL-6. J Immunol 2011; 186(12): 6746-52. [http://dx.doi.org/10.4049/jimmunol.1100117] [PMID: 21593380]

[54] Ohta A, Gorelik E, Prasad SJ, Ronchese F, Lukashev D, Wong MKK, *et al.* A2A adenosine receptor protects tumors from antitumor T cells. Proc Natl Acad Sci U S A 2006; 103: 13132-7. [http://dx.doi.org/10.1073/pnas.0605251103]

[55] Németh ZH, Lutz CS, Csóka B, *et al.* Adenosine augments IL-10 production by macrophages through an A2B receptor-mediated posttranscriptional mechanism. J Immunol 2005; 175(12): 8260-70. [http://dx.doi.org/10.4049/jimmunol.175.12.8260] [PMID: 16339566]

[56] Haskó G, Kuhel DG, Chen J-F, *et al.* Adenosine inhibits IL-12 and TNF-[α] production via adenosine A2a receptor-dependent and independent mechanisms. FASEB J 2000; 14(13): 2065-74. [http://dx.doi.org/10.1096/fj.99-0508com] [PMID: 11023991]

[57] Peterfreund RA, MacCollin M, Gusella J, Fink JS. Characterization and expression of the human A2a adenosine receptor gene. J Neurochem 1996; 66(1): 362-8. [http://dx.doi.org/10.1046/j.1471-4159.1996.66010362.x] [PMID: 8522976]

[58] Wei CJ, Li W, Chen J-F. Normal and abnormal functions of adenosine receptors in the central nervous system revealed by genetic knockout studies. Biochim Biophys Acta 2011; 1808(5): 1358-79. [http://dx.doi.org/10.1016/j.bbamem.2010.12.018] [PMID: 21185258]

[59] Antonioli L, Blandizzi C, Pacher P, Haskó G. Immunity, inflammation and cancer: a leading role for adenosine. Nat Rev Cancer 2013; 13(12): 842-57. [http://dx.doi.org/10.1038/nrc3613] [PMID: 24226193]

[60] Borea PA, Gessi S, Merighi S, Vincenzi F, Varani K. Pathological overproduction: the bad side of adenosine. Br J Pharmacol 2017; 174: 1945-1960. 3. [http://dx.doi.org/10.1111/bph.13763]

[61] Merighi S, Mirandola P, Varani K, *et al.* A glance at adenosine receptors: novel target for antitumor therapy. Pharmacol Ther 2003; 100(1): 31-48. [http://dx.doi.org/10.1016/S0163-7258(03)00084-6] [PMID: 14550503]

[62] Muller-Haegele S, Muller L, Whiteside TL. Immunoregulatory activity of adenosine and its role in human cancer progression. Expert Rev Clin Immunol 2014; 10(7): 897-914. [http://dx.doi.org/10.1586/1744666X.2014.915739] [PMID: 24871693]

[63] Gessi S, Bencivenni S, Battistello E, *et al.* Inhibition of A_{2A} Adenosine Receptor Signaling in Cancer Cells Proliferation by the Novel Antagonist TP455. Front Pharmacol 2017; 8: 888. [http://dx.doi.org/10.3389/fphar.2017.00888] [PMID: 29249971]

[64] Young A, Ngiow SF, Barkauskas DS, *et al.* Co-inhibition of CD73 and A2AR Adenosine Signaling Improves Anti-tumor Immune Responses. Cancer Cell 2016; 30(3): 391-403. [http://dx.doi.org/10.1016/j.ccell.2016.06.025] [PMID: 27622332]

[65] Sitkovsky MV, Kjaergaard J, Lukashev D, Ohta A. Hypoxia-adenosinergic immunosuppression: tumor protection by T regulatory cells and cancerous tissue hypoxia. Clin Cancer Res 2008; 14(19): 5947-52. [http://dx.doi.org/10.1158/1078-0432.CCR-08-0229] [PMID: 18829471]

[66] Merighi S, Mirandola P, Milani D, *et al.* Adenosine receptors as mediators of both cell proliferation and cell death of cultured human melanoma cells. J Invest Dermatol 2002; 119(4): 923-33. [http://dx.doi.org/10.1046/j.1523-1747.2002.00111.x] [PMID: 12406340]

[67] Etique N, Grillier-Vuissoz I, Lecomte J, Flament S. Crosstalk between adenosine receptor (A2A isoform) and ERalpha mediates ethanol action in MCF-7 breast cancer cells. Oncol Rep 2009; 21(4): 977-81. [PMID: 19287996]

[68] Koszałka P, Gołuńska M, Urban A, *et al.* Specific activation of A3, A2A and A1 adenosine receptors in CD73-knockout mice affects B16F10 melanoma growth, neovascularization, angiogenesis and macrophage infiltration. PLoS One 2016; 11(3)e0151420 [http://dx.doi.org/10.1371/journal.pone.0151420] [PMID: 26964090]

[69] Perez-Aso M, Mediero A, Low YC, Levine J, Cronstein BN. Adenosine A2A receptor plays an important role in radiation-induced dermal injury. FASEB J 2016; 30(1): 457-65. [http://dx.doi.org/10.1096/fj.15-280388] [PMID: 26415936]

[70] Beavis PA, Divisekera U, Paget C, *et al.* Blockade of A2A receptors potently suppresses the metastasis of CD73+ tumors. Proc Natl Acad Sci USA 2013; 110(36): 14711-6. [http://dx.doi.org/10.1073/pnas.1308209110] [PMID: 23964122]

[71] Waickman AT, Alme A, Senaldi L, Zarek PE, Horton M, Powell JD. Enhancement of tumor immunotherapy by deletion of the A2A adenosine receptor. Cancer Immunol Immunother 2012; 61(6): 917-26. [http://dx.doi.org/10.1007/s00262-011-1155-7] [PMID: 22116345]

[72] Sun Y, Huang P. Adenosine A2B Receptor: From Cell Biology to Human Diseases. Front Chem 2016; 4: 37. [http://dx.doi.org/10.3389/fchem.2016.00037] [PMID: 27606311]

[73] Wei W, Du C, Lv J, *et al.* Blocking A2B adenosine receptor alleviates pathogenesis of experimental autoimmune encephalomyelitis via inhibition of IL-6 production and Th17 differentiation. J Immunol 2013; 190(1): 138-46. [http://dx.doi.org/10.4049/jimmunol.1103721] [PMID: 23225885]

[74] Schulte G, Fredholm BB. Signalling from adenosine receptors to mitogen-activated protein kinases. Cell Signal 2003; 15(9): 813-27. [http://dx.doi.org/10.1016/S0898-6568(03)00058-5] [PMID: 12834807]

[75] Ntantie E, Gonyo P, Lorimer EL, *et al.* An adenosine-mediated signaling pathway suppresses prenylation of the GTPase Rap1B and promotes cell scattering. Sci Signal 2013; 6(277): ra39-9. [http://dx.doi.org/10.1126/scisignal.2003374] [PMID: 23716716]

[76] Desmet CJ, Gallenne T, Prieur A, *et al.* Identification of a pharmacologically tractable Fra-1/ADORA2B axis promoting breast cancer metastasis. Proc Natl Acad Sci USA 2013; 110(13): 5139-44. [http://dx.doi.org/10.1073/pnas.1222085110] [PMID: 23483055]

[77] Adiseshaiah P, Lindner DJ, Kalvakolanu DV, Reddy SP. FRA-1 proto-oncogene induces lung epithelial cell invasion and anchorage-independent growth in vitro, but is insufficient to promote tumor growth in vivo. Cancer Res 2007; 67(13): 6204-11. [http://dx.doi.org/10.1158/0008-5472.CAN-06-4687] [PMID: 17616677]

[78] Fang M, Xia J, Wu X, *et al.* Adenosine signaling inhibits CIITA-mediated MHC class II transactivation in lung fibroblast cells. Eur J Immunol 2013; 43(8): 2162-73. [http://dx.doi.org/10.1002/eji.201343461] [PMID: 23681904]

[79] Xia J, Fang M, Wu X, *et al.* A2b adenosine signaling represses CIITA transcription via an epigenetic mechanism in vascular smooth muscle cells. Biochim Biophys Acta 2015; 1849(6): 665-76. [http://dx.doi.org/10.1016/j.bbagrm.2015.03.001] [PMID: 25765819]

[80] Shi B, Vinyals A, Alia P, *et al.* Differential expression of MHC class II molecules in highly metastatic breast cancer cells is mediated by the regulation of the CIITA transcription Implication of CIITA in tumor and metastasis development. Int J Biochem Cell Biol 2006; 38(4): 544-62. [http://dx.doi.org/10.1016/j.biocel.2005.07.012] [PMID: 16343978]

[81] Fernandez-Gallardo M, González-Ramírez R, Sandoval A, Felix R, Monjaraz E. Adenosine stimulate proliferation and migration in triple negative breast cancer cells. PLoS One 2016; 11(12)e0167445 [http://dx.doi.org/10.1371/journal.pone.0167445] [PMID: 27911956]

[82] Iannone R, Miele L, Maiolino P, Pinto A, Morello S. Blockade of A2b adenosine receptor reduces tumor growth and immune suppression mediated by myeloid-derived suppressor cells in a mouse model of melanoma. Neoplasia 2013; 15(12): 1400-9. [http://dx.doi.org/10.1593/neo.131748] [PMID: 24403862]

[83] Cekic C, Sag D, Li Y, Theodorescu D, Strieter RM, Linden J. Adenosine A2B receptor blockade slows growth of bladder and breast tumors. J Immunol 2012; 188(1): 198-205. [http://dx.doi.org/10.4049/jimmunol.1101845] [PMID: 22116822]

[84] Atkinson MR, Townsend-Nicholson A, Nicholl JK, Sutherland GR, Schofield PR. Cloning, characterisation and chromosomal assignment of the human adenosine A3 receptor (ADORA3) gene. Neurosci Res 1997; 29(1): 73-9. [http://dx.doi.org/10.1016/S0168-0102(97)00073-4] [PMID: 9293494]

[85] Borea PA, Varani K, Vincenzi F, *et al.* The A3 adenosine receptor: history and perspectives. Pharmacol Rev 2015; 67(1): 74-102. [http://dx.doi.org/10.1124/pr.113.008540] [PMID: 25387804]

[86] Madi L, Ochaion A, Rath-Wolfson L, *et al.* The A3 adenosine receptor is highly expressed in tumor versus normal cells: potential target for tumor growth inhibition. Clin Cancer Res 2004; 10(13): 4472-9. [http://dx.doi.org/10.1158/1078-0432.CCR-03-0651] [PMID: 15240539]

[87] Feoktistov I, Ryzhov S, Goldstein AE, Biaggioni I. Mast cell-mediated stimulation of angiogenesis: cooperative interaction between A2B and A3 adenosine receptors. Circ Res 2003; 92(5): 485-92. [http://dx.doi.org/10.1161/01.RES.0000061572.10929.2D] [PMID: 12600879]

[88] Gessi S, Sacchetto V, Fogli E, *et al.* Modulation of metalloproteinase-9 in U87MG glioblastoma cells by A3 adenosine receptors. Biochem Pharmacol 2010; 79(10): 1483-95. [http://dx.doi.org/10.1016/j.bcp.2010.01.009] [PMID: 20096265]

[89] Merighi S, Benini A, Mirandola P, *et al.* Adenosine modulates vascular endothelial growth factor expression via hypoxia-inducible factor-1 in human glioblastoma cells. Biochem Pharmacol 2006; 72(1): 19-31. [http://dx.doi.org/10.1016/j.bcp.2006.03.020] [PMID: 16682012]

[90] Semenza GL. Targeting HIF-1 for cancer therapy. Nat Rev Cancer 2003; 3(10): 721-32. [http://dx.doi.org/10.1038/nrc1187] [PMID: 13130303]

[91] Merighi S, Benini A, Mirandola P, *et al.* Hypoxia inhibits paclitaxel-induced apoptosis through adenosine-mediated phosphoryla-

tion of bad in glioblastoma cells. Mol Pharmacol 2007; 72(1): 162-72.
[http://dx.doi.org/10.1124/mol.106.031849] [PMID: 17400763]

[92] Madi L, Bar-Yehuda S, Barer F, Ardon E, Ochaion A, Fishman P. A3 adenosine receptor activation in melanoma cells: association between receptor fate and tumor growth inhibition. J Biol Chem 2003; 278(43): 42121-30.
[http://dx.doi.org/10.1074/jbc.M301243200] [PMID: 12865431]

[93] Zhao Z, Makaritsis K, Francis CE, Gavras H, Ravid K. A role for the A3 adenosine receptor in determining tissue levels of cAMP and blood pressure: studies in knock-out mice. Biochim Biophys Acta 2000; 1500(3): 280-90.
[http://dx.doi.org/10.1016/S0925-4439(99)00111-8] [PMID: 10699369]

[94] Jajoo S, Mukherjea D, Watabe K, Ramkumar V. Adenosine A(3) receptor suppresses prostate cancer metastasis by inhibiting NADPH oxidase activity. Neoplasia 2009; 11(11): 1132-45.
[http://dx.doi.org/10.1593/neo.09744] [PMID: 19881949]

[95] Varani K, Maniero S, Vincenzi F, Targa M, Stefanelli A, Maniscalco P, *et al.* 3 receptors are overexpressed in pleura from patients with mesothelioma and reduce cell growth via Akt/Nuclear factor-kB pathway 2011; 183(4): 522-30.

[96] Cohen S, Stemmer SM, Zozulya G, *et al.* CF102 an A3 adenosine receptor agonist mediates anti-tumor and anti-inflammatory effects in the liver. J Cell Physiol 2011; 226(9): 2438-47.
[http://dx.doi.org/10.1002/jcp.22593] [PMID: 21660967]

[97] Lee E-J, Min H-Y, Chung H-J, *et al.* A novel adenosine analog, thio-Cl-IB-MECA, induces G0/G1 cell cycle arrest and apoptosis in human promyelocytic leukemia HL-60 cells. Biochem Pharmacol 2005; 70(6): 918-24.
[http://dx.doi.org/10.1016/j.bcp.2005.06.017] [PMID: 16051194]

[98] Fishman P, Bar-Yehuda S, Barer F, Madi L, Multani AS, Pathak S. The A3 adenosine receptor as a new target for cancer therapy and chemoprotection. Exp Cell Res 2001; 269(2): 230-6.
[http://dx.doi.org/10.1006/excr.2001.5327] [PMID: 11570815]

[99] Fishman P, Bar-Yehuda S, Ohana G, Pathak S, Wasserman L, Barer F, *et al.* Adenosine acts as an inhibitor of lymphoma cell growth: a major role for the A3 adenosine receptor 2000; 36(11): 1452-8.

[100] Haskó G, Linden J, Cronstein B, Pacher P. Adenosine receptors: therapeutic aspects for inflammatory and immune diseases. Nat Rev Drug Discov 2008; 7(9): 759-70.
[http://dx.doi.org/10.1038/nrd2638] [PMID: 18758473]

[101] Jacobson KA, Gao ZG. Adenosine receptors as therapeutic targets. Nat Rev Drug Discov 2006; 5(3): 247-64.
[http://dx.doi.org/10.1038/nrd1983] [PMID: 16518376]

[102] Yu L, Huang Z, Mariani J, Wang Y, Moskowitz M, Chen J-F. Selective inactivation or reconstitution of adenosine A2A receptors in bone marrow cells reveals their significant contribution to the development of ischemic brain injury. Nat Med 2004; 10(10): 1081-7.
[http://dx.doi.org/10.1038/nm1103] [PMID: 15448683]

[103] Cohen MV, Downey JM. Adenosine: trigger and mediator of cardioprotection. Basic Res Cardiol 2008; 103(3): 203-15.
[http://dx.doi.org/10.1007/s00395-007-0687-7] [PMID: 17999026]

[104] Gottlieb SS, Brater DC, Thomas I, *et al.* BG9719 (CVT-124), an A1 adenosine receptor antagonist, protects against the decline in renal function observed with diuretic therapy. Circulation 2002; 105(11): 1348-53.
[http://dx.doi.org/10.1161/hc1102.105264] [PMID: 11901047]

[105] Chen G-J, Harvey BK, Shen H, Chou J, Victor A, Wang Y. Activation of adenosine A3 receptors reduces ischemic brain injury in rodents. J Neurosci Res 2006; 84(8): 1848-55.
[http://dx.doi.org/10.1002/jnr.21071] [PMID: 17016854]

[106] Guzman J, Yu JG, Suntres Z, *et al.* ADOA3R as a therapeutic target in experimental colitis: proof by validated high-density oligonucleotide microarray analysis. Inflamm Bowel Dis 2006; 12(8): 766-89.
[http://dx.doi.org/10.1097/00054725-200608000-00014] [PMID: 16917233]

[107] Kolachala VL, Bajaj R, Chalasani M, Sitaraman SV. Purinergic receptors in gastrointestinal inflammation. Am J Physiol Gastrointest Liver Physiol 2008; 294(2): G401-10.
[http://dx.doi.org/10.1152/ajpgi.00454.2007] [PMID: 18063703]

[108] Madi L, Cohen S, Ochayin A, Bar-Yehuda S, Barer F, Fishman P. Overexpression of A3 adenosine receptor in peripheral blood mononuclear cells in rheumatoid arthritis: involvement of nuclear factor-kappaB in mediating receptor level. J Rheumatol 2007; 34(1): 20-6.
[PMID: 17216675]

[109] Schwarzschild MA, Agnati L, Fuxe K, Chen JF, Morelli M. Targeting adenosine A2A receptors in Parkinson's disease. Trends Neurosci 2006; 29(11): 647-54.
[http://dx.doi.org/10.1016/j.tins.2006.09.004] [PMID: 17030429]

[110] LeWitt PA, Guttman M, Tetrud JW, *et al.* Adenosine A2A receptor antagonist istradefylline (KW-6002) reduces "off" time in Parkinson's disease: a double-blind, randomized, multicenter clinical trial (6002-US-005). Ann Neurol 2008; 63(3): 295-302.
[http://dx.doi.org/10.1002/ana.21315] [PMID: 18306243]

[111] Khasim S, Pran Kishore D, Raghuprasad M, *et al.* 7-Amino-2-aryl/heteroaryl-5-oxo-5,8-dihydro[1,2,4]triazolo[1,5-a]pyridine-6-carbonitriles: Synthesis and Adenosine Receptor Binding Studies. Chem Biol Drug Des 2019.
[http://dx.doi.org/10.1111/cbdd.13528]

[112] Chandrasekaran B, Kishore Deb P, Rao Akkinepalli R. Structure-based Design and Pharmacological Study of Fluorinated Fused Quinazolines as Adenosine A 2B Receptor Antagonists. JSM Chem 2017; 5: 1041.

[113] Balakumar C, Kishore DP, Rao KV, Narayana BL, Rajwinder K, Rajkumar V, *et al.* Design, microwave-assisted synthesis and in silico docking studies of new 4H-pyrimido[2,1-b]benzothiazole-2-arylamino-3-cyano-4-ones as possible adenosine A2B receptor antagonists. Indian J Chem 2012; 51B: 1105-13.

[114] Chandrasekaran B, Deb PK, Kachler S, Akkinepalli RR, Mailavaram R, Klotz K-N. Synthesis and adenosine receptors binding studies of new fluorinated analogues of pyrido[2,3-d]pyrimidines and quinazolines. Med Chem Res 2018; 27: 756-67.
[http://dx.doi.org/10.1007/s00044-017-2099-z]

[115] Pran Kishore D, Balakumar C, Raghuram Rao A, Roy PP, Roy K. QSAR of adenosine receptor antagonists: Exploring physicochemical requirements for binding of pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine derivatives with human adenosine A(3) receptor subtype. Bioorg Med Chem Lett 2011; 21(2): 818-23.
[http://dx.doi.org/10.1016/j.bmcl.2010.11.094] [PMID: 21163647]

[116] Deb PK, Mailavaram R, Chandrasekaran B, *et al.* Synthesis, adenosine receptor binding and molecular modelling studies of novel thieno[2,3-d]pyrimidine derivatives. Chem Biol Drug Des 2018; 91(4): 962-9.
[http://dx.doi.org/10.1111/cbdd.13155] [PMID: 29194979]

[117] Hosseinzadeh H, Stone T. Adenosine in the central nervous system. Med J Islam Repub Iran 1996; 9: 361-8.

[118] Hosseinzadeh H, Jaafari MR, Shamsara J. Selective inhibitory effect of adenosine A1 receptor agonists on the proliferation of human tumor cell lines. Iran Biomed J 2008; 12(4): 203-8.
[PMID: 19079533]

[119] Dastjerdi MN, Valiani A, Mardani M, Ra MZ. Adenosine A1 receptor modifies P53 expression and apoptosis in breast cancer cell line Mcf-7. Bratisl Lek Listy 2016; 117(4): 242-6.
[http://dx.doi.org/10.4149/BLL_2016_046] [PMID: 27075390]

[120] Lin Z, Yin P, Reierstad S, *et al.* Adenosine A1 receptor, a target and regulator of estrogen receptoralpha action, mediates the proliferative effects of estradiol in breast cancer. Oncogene 2010; 29(8): 1114-22.
[http://dx.doi.org/10.1038/onc.2009.409] [PMID: 19935720]

[121] Glukhova A, Thal DM, Nguyen AT, *et al.* Structure of the Adenosine A_1 Receptor Reveals the Basis for Subtype Selectivity. Cell 2017; 168(5): 867-877.e13.
[http://dx.doi.org/10.1016/j.cell.2017.01.042] [PMID: 28235198]

[122] Houthuys E, Brouwer M, Nyawouame F, Pirson R, Marillier R, Deregnaucourt T, *et al.* A novel adenosine A2A receptor antagonist optimized for high potency in adenosine-rich tumor microenvironment boosts antitumor immunity. Cancer Res 2017; 77: 1683-3.

[123] Mediavilla-Varela M, Castro J, Chiappori A, *et al.* A novel antagonist of the immune checkpoint protein adenosine A2a receptor restores tumor-infiltrating lymphocyte activity in the context of the tumor microenvironment. Neoplasia 2017; 19(7): 530-6.
[http://dx.doi.org/10.1016/j.neo.2017.02.004] [PMID: 28582704]

[124] Gessi S, Merighi S, Sacchetto V, Simioni C, Borea PA. Adenosine receptors and cancer. Biochim Biophys Acta 2011; 1808(5): 1400-12. [d].
[http://dx.doi.org/10.1016/j.bbamem.2010.09.020] [PMID: 20888788]

[125] Mediavilla-Varela M, Luddy K, Noyes D, *et al.* Antagonism of adenosine A2A receptor expressed by lung adenocarcinoma tumor cells and cancer associated fibroblasts inhibits their growth. Cancer Biol Ther 2013; 14(9): 860-8. [http://dx.doi.org/10.4161/cbt.25643] [PMID: 23917542]

[126] Preti D, Baraldi PG, Moorman AR, Borea PA, Varani K. History and perspectives of A2A adenosine receptor antagonists as potential therapeutic agents. Med Res Rev 2015; 35(4): 790-848. [http://dx.doi.org/10.1002/med.21344] [PMID: 25821194]

[127] Jazayeri A, Andrews SP, Marshall FH. Structurally enabled discovery of adenosine a2a receptor antagonists. Chem Rev 2017; 117(1): 21-37. [http://dx.doi.org/10.1021/acs.chemrev.6b00119] [PMID: 27333206]

[128] Leone RD, Sun I-M, Oh M-H, *et al.* Inhibition of the adenosine A2a receptor modulates expression of T cell coinhibitory receptors and improves effector function for enhanced checkpoint blockade and ACT in murine cancer models. Cancer Immunol Immunother 2018; 67(8): 1271-84. [http://dx.doi.org/10.1007/s00262-018-2186-0] [PMID: 29923026]

[129] Willingham S, Ho P, Leone R, Choy C, Powell J, McCaffery I, *et al.* Adenosine A2A receptor antagonist, CPI-444, blocks adenosine-mediated T cell suppression and exhibits anti-tumor activity alone and in combination with anti-PD-1 and anti-PD-L1. Ann Oncol 2016; 27. [http://dx.doi.org/10.1093/annonc/mdw378.22]

[130] Patnaik A, Powderly J, Luke J, Miller R, Laport G. Phase 1/1b multicenter trial of the adenosine A2a receptor antagonist (A2aR) CPI-444 as single agent and in combination with atezolizumab (ATZ) in patients(Pts) with advanced cancers. Ann Oncol 2016; 27. [http://dx.doi.org/10.1093/annonc/mdw378.58]

[131] Phase 1/1b Study to Evaluate the Safety and Tolerability of CPI-444 Alone and in Combination With Atezolizumab in Advanced Cancers. ClinicalTrials.gov. [cited 30 Nov 2018]. Available from: https://clinicaltrials.gov/ct2/show/record/NCT02655822

[132] Ohta A, Sitkovsky M. Caveats and cautions for the therapeutic targeting of the anti-inflammatory A2 adenosine receptors [http://dx.doi.org/10.1038/nrd1983-c1]

[133] Hatfield SM, Sitkovsky M. A2A adenosine receptor antagonists to weaken the hypoxia-HIF-1α driven immunosuppression and improve immunotherapies of cancer. Curr Opin Pharmacol 2016; 29: 90-6. [http://dx.doi.org/10.1016/j.coph.2016.06.009] [PMID: 27429212]

[134] Panjehpour M, Castro M, Klotz K-N. Human breast cancer cell line MDA-MB-231 expresses endogenous A2B adenosine receptors mediating a Ca2+ signal. Br J Pharmacol 2005; 145(2): 211-8. [http://dx.doi.org/10.1038/sj.bjp.0706180] [PMID: 15753948]

[135] Koussémou M, Lorenz K, Klotz K-N. Human breast cancer cell line MDA-MB-231 expresses endogenous A 2B adenosine receptors mediating a Ca 2+ signal. Br J Pharmacol 2018; 145: 211-8.

[136] Mittal D, Sinha D, Barkauskas D, *et al.* Adenosine 2B Receptor Expression on Cancer Cells Promotes Metastasis. Cancer Res 2016; 76(15): 4372-82. [http://dx.doi.org/10.1158/0008-5472.CAN-16-0544] [PMID: 27221704]

[137] Mølck C, Ryall J, Failla LM, *et al.* The A_{2b} adenosine receptor antagonist PSB-603 promotes oxidative phosphorylation and ROS production in colorectal cancer cells via adenosine receptor-independent mechanism. Cancer Lett 2016; 383(1): 135-43. [http://dx.doi.org/10.1016/j.canlet.2016.09.018] [PMID: 27693637]

[138] Galezowski M, Wegrzyn P, Bobowska A, Commandeur C, Dziedzic K, Nowogrodzki M, *et al.* Characterization of novel dual A 2A /A 2B adenosine receptor antagonists for cancer immunotherapy. Cancer Res 2018; 78: 3770-0.

[139] Gessi S, Merighi S, Borea PA, Cohen S, Fishman P. Adenosine Receptors and Current Opportunities to Treat Cancer. The Adenosine Receptors 2018; 543-55. [http://dx.doi.org/10.1007/978-3-319-90808-3_23]

[140] Varani K, Maniero S, Vincenzi F, *et al.* Aɜ receptors are overexpressed in pleura from patients with mesothelioma and reduce cell growth via Akt/nuclear factor-κB pathway. Am J Respir Crit Care Med 2011; 183(4): 522-30. [http://dx.doi.org/10.1164/rccm.201006-0980OC] [PMID: 20870754]

[141] Varani K, Vincenzi F, Targa M, *et al.* The stimulation of A(3) adenosine receptors reduces bone-residing breast cancer in a rat preclinical model. Eur J Cancer 2013; 49(2): 482-91. [http://dx.doi.org/10.1016/j.ejca.2012.06.005] [PMID: 22770890]

[142] Gessi S, Fogli E, Sacchetto V, *et al.* Adenosine modulates HIF-1α, VEGF, IL-8, and foam cell formation in a human model of hypoxic foam cells. Arterioscler Thromb Vasc Biol 2010; 30(1): 90-7. [http://dx.doi.org/10.1161/ATVBAHA.109.194902] [PMID: 19834107]

[143] Fishman P, Bar-Yehuda S, Ohana G, *et al.* Adenosine acts as an inhibitor of lymphoma cell growth: a major role for the A3 adenosine receptor. Eur J Cancer 2000; 36(11): 1452-8. [http://dx.doi.org/10.1016/S0959-8049(00)00130-1] [PMID: 10899660]

[144] Vincenzi F, Targa M, Corciulo C, Gessi S, Merighi S, Setti S, *et al.* The Anti-Tumor Effect of A3 Adenosine Receptors Is Potentiated by Pulsed Electromagnetic Fields in Cultured Neural Cancer Cells.PLoS One 2012; 7: e39317.. [http://dx.doi.org/10.1371/journal.pone.0039317]

[145] Ohana G, Bar-Yehuda S, Barer F, Fishman P. Differential effect of adenosine on tumor and normal cell growth: focus on the A3 adenosine receptor. J Cell Physiol 2001; 186(1): 19-23. [http://dx.doi.org/10.1002/1097-4652(200101)186:1<19::AID-JCP1011>3.0.CO;2-3] [PMID: 11147810]

[146] Hofer M, Pospísil M, Vacek A, *et al.* Effects of adenosine A(3) receptor agonist on bone marrow granulocytic system in 5-fluorouracil-treated mice. Eur J Pharmacol 2006; 538(1-3): 163-7. [http://dx.doi.org/10.1016/j.ejphar.2006.03.042] [PMID: 16643889]

[147] Merimsky O, Bar-Yehuda S, Madi L, Fishman P. Modulation of the A3 adenosine receptor by low agonist concentration induces antitumor and myelostimulatory effects. Drug Dev Res 2003; 58: 386-9. [http://dx.doi.org/10.1002/ddr.10182]

[148] Bar-Yehuda S, Madi L, Barak D, *et al.* Agonists to the A3 adenosine receptor induce G-CSF production via NF-kappaB activation: a new class of myeloprotective agents. Exp Hematol 2002; 30(12): 1390-8. [http://dx.doi.org/10.1016/S0301-472X(02)00962-1] [PMID: 12482500]

[149] Ohana G, Bar-Yehuda S, Arich A, *et al.* Inhibition of primary colon carcinoma growth and liver metastasis by the A3 adenosine receptor agonist CF101. Br J Cancer 2003; 89(8): 1552-8. [http://dx.doi.org/10.1038/sj.bjc.6601315] [PMID: 14562031]

[150] Harish A, Hohana G, Fishman P, Arnon O, Bar-Yehuda S. A3 adenosine receptor agonist potentiates natural killer cell activity. Int J Oncol 2003; 23(4): 1245-9. [http://dx.doi.org/10.3892/ijo.23.4.1245] [PMID: 12964011]

[151] Montinaro A, Forte G, Sorrentino R, *et al.* Adoptive immunotherapy with Cl-IB-MECA-treated CD8+ T cells reduces melanoma growth in mice. PLoS One 2012; 7(9)e45401 [http://dx.doi.org/10.1371/journal.pone.0045401] [PMID: 23028986]

[152] Jacobson KA, Merighi S, Varani K, *et al.* A 3 adenosine receptors as modulators of inflammation: from medicinal chemistry to therapy. Med Res Rev 2018; 38(4): 1031-72. [http://dx.doi.org/10.1002/med.21456] [PMID: 28682469]

[153] van Troostenburg AR, Clark EV, Carey WDH, *et al.* Tolerability, pharmacokinetics and concentration-dependent hemodynamic effects of oral CF101, an A3 adenosine receptor agonist, in healthy young men. Int J Clin Pharmacol Ther 2004; 42(10): 534-42. [http://dx.doi.org/10.5414/CPP42534] [PMID: 15516022]

[154] Bar-Yehuda S, Madi L, Silberman D, Gery S, Shkapenuk M, Fishman P. CF101, an agonist to the A3 adenosine receptor, enhances the chemotherapeutic effect of 5-fluorouracil in a colon carcinoma murine model. Neoplasia 2005; 7(1): 85-90. [http://dx.doi.org/10.1593/neo.04364] [PMID: 15720820]

[155] Bar-Yehuda S, Stemmer SM, Madi L, *et al.* The A3 adenosine receptor agonist CF102 induces apoptosis of hepatocellular carcinoma via de-regulation of the Wnt and NF-kappaB signal transduction pathways. Int J Oncol 2008; 33(2): 287-95. [PMID: 18636149]

[156] Stemmer SM, Benjaminov O, Medalia G, *et al.* CF102 for the treatment of hepatocellular carcinoma: a phase I/II, open-label, dose-escalation study. Oncologist 2013; 18(1): 25-6.

[http://dx.doi.org/10.1634/theoncologist.2012-0211] [PMID: 23299770]

[157] Phase 2, Randomized, Double-Blind, Placebo-Controlled of the Efficacy and Safety of CF102 in Hepatocellular Carcinoma (HCC). ClinicalTrials.gov. [cited 30 Nov 2018]. Available from: https://clinicaltrials.gov/ct2/show/NCT02128958

[158] Zhao Z, Yaar R, Ladd D, Cataldo LM, Ravid K. Overexpression of A3 adenosine receptors in smooth, cardiac, and skeletal muscle is lethal to embryos. Microvasc Res 2002; 63(1): 61-9. [http://dx.doi.org/10.1006/mvre.2001.2366] [PMID: 11749073]

[159] Kim SG, Ravi G, Hoffmann C, *et al.* p53-Independent induction of Fas and apoptosis in leukemic cells by an adenosine derivative, Cl-IB-MECA. Biochem Pharmacol 2002; 63(5): 871-80. [http://dx.doi.org/10.1016/S0006-2952(02)00839-0] [PMID: 11911839]

[160] Gao Z, Li BS, Day YJ, Linden J. A3 adenosine receptor activation triggers phosphorylation of protein kinase B and protects rat basophilic leukemia 2H3 mast cells from apoptosis. Mol Pharmacol 2001; 59(1): 76-82. [http://dx.doi.org/10.1124/mol.59.1.76] [PMID: 11125027]

[161] Lu J, Pierron A, Ravid K. An adenosine analogue, IB-MECA, down-regulates estrogen receptor α and suppresses human breast cancer cell proliferation. Cancer Res 2003; 63(19): 6413-23. [PMID: 14559831]

[162] Kim SJ, Min HY, Chung HJ, *et al.* Inhibition of cell proliferation through cell cycle arrest and apoptosis by thio-Cl-IB-MECA, a novel A3 adenosine receptor agonist, in human lung cancer cells. Cancer Lett 2008; 264(2): 309-15. [http://dx.doi.org/10.1016/j.canlet.2008.01.037] [PMID: 18321638]

[163] Deb PK. Recent Updates in the Computer Aided Drug Design Strategies for the Discovery of Agonists and Antagonists of Adenosine Receptors. Curr Pharm Des 252019; (7): 747-9. [http://dx.doi.org/10.2174/1381612825999190515120510] [PMID: 31232230]

[164] Samanta PN, Kar S, Leszczynski J. Recent Advances of In-Silico Modeling of Potent Antagonists for the Adenosine Receptors. Curr Pharm Des 2019; 25(7): 750-73. [http://dx.doi.org/10.2174/1381612825666190304123545] [PMID: 30836910]

[165] Al-Shar'i NA, Al-Balas QA. Molecular Dynamics Simulations of Adenosine Receptors: Advances, Applications and Trends. Curr Pharm Des 2019; 25(7): 783-816. [http://dx.doi.org/10.2174/1381612825666190304123414] [PMID: 30834825]

[166] Mahmod Al-Qattan MN, Mordi MN. Molecular basis of modulating adenosine receptors activities. Curr Pharm Des 2019; 25(7): 817-31. [http://dx.doi.org/10.2174/1381612825666190304122624] [PMID: 30834826]

[167] Agrawal N, Chandrasekaran B, Al-Aboudi A. Recent advances in the in-silico structure-based and ligand-based approaches for the design and discovery of agonists and antagonists of A2A adenosine receptor. Curr Pharm Des 2019; 25(7): 774-82. [http://dx.doi.org/10.2174/1381612825666190306162006] [PMID: 30848185]

[168] Deb PK, Chandrasekaran B, Mailavaram R, Tekade RK, Jaber AMY. Molecular modeling approaches for the discovery of adenosine A_{2B} receptor antagonists: current status and future perspectives. Drug Discov Today 2019.S1359-6446(19)30045-5 [http://dx.doi.org/10.1016/j.drudis.2019.05.011] [PMID: 31103731]