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REVIEW

## Adenosine triphosphate induced cell death: Mechanisms and implications in cancer biology and therapy

Hao-Ling Zhang, Doblin Sandai, Zhong-Wen Zhang, Zhi-Jing Song, Dinesh Babu, Yasser Tabana, Sabbar Saad Dahham, Mowaffaq Adam Ahmed Adam, Yong Wang, Wei Wang, Hao-Long Zhang, Rui Zhao, Khaled Barakat, Mohammad Syamsul Reza Harun, Siti Nurfatimah Mohd Shapudin, Bronwyn Lok

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#### Abstract

Adenosine triphosphate (ATP) induced cell death (AICD) is a critical cellular process that has garnered substantial scientific interest for its profound relevance to cancer biology and to therapeutic interventions. This comprehensive review unveils the intricate web of AICD mechanisms and their intricate connections with cancer biology. This review offers a comprehensive framework for comprehending the multifaceted role of AICD in the context of cancer. This is achieved by elucidating the dynamic interplay between systemic and cellular ATP



homeostasis, deciphering the intricate mechanisms governing AICD, elucidating its intricate involvement in cancer signaling pathways, and scrutinizing validated key genes. Moreover, the exploration of AICD as a potential avenue for cancer treatment underscores its essential role in shaping the future landscape of cancer therapeutics.

Key Words: Adenosine triphosphate induced cell death; Adenosine triphosphate homeostasis; Mechanism; Cancer signaling pathways; Prognosis and clinical values; Cancer treatment

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Core Tip: The research delves deeply into the pivotal realm of adenosine triphosphate (ATP)-induced cell death (AICD), a fundamental cellular phenomenon that has captured significant scholarly interest owing to its pertinence in cancer biology and therapeutic strategies. Our review is dedicated to delivering an all-encompassing grasp of the intricate mechanisms underpinning AICD and its far-reaching ramifications within the cancer context. By meticulously dissecting the dynamic interplay between systemic and cellular ATP homeostasis, unraveling the governing mechanisms steering AICD, and probing its intricate entanglement with cancer signaling pathways, we present an exhaustive framework that illuminates the multifaceted role of AICD in the realm of cancer.

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#### INTRODUCTION

In recent years, adenosine triphosphate (ATP) induced cell death (AICD) has emerged as a discernible mode of cell death triggered by elevated extracellular ATP (eATP) levels, exhibiting intimate association with the progression of various cancer types[1-3]. ATP, or adenosine triphosphate, a nucleotide crucial for cellular energy metabolism, assumes a pivotal role in multiple tumor-related signaling pathways and biological processes[4,5]. Nonetheless, the precise mechanisms and modalities underlying AICD have long remained elusive. Subsequent investigations have unveiled the distinctive features and regulatory mechanisms of AICD, setting it apart from other forms of cell demise such as apoptosis and necrosis. This review provides a concise summary of key discoveries in the field of AICD that have propelled advancements (Figure 1)[5-12].

The identification of AICD represents a significant milestone in the realm of cell biology. Initially, researchers noted that the addition of exogenous ATP to cells resulted in cell death, thereby generating considerable interest and instigating extensive investigations[1]. AICD, being an inevitable facet of the cell's life cycle, assumes a pivotal role in maintaining tissue homeostasis and functionality, holding profound significance for tissue development, as well as the etiology and progression of various diseases. The mechanisms and specific manifestations of AICD remain unknown.

In the realm of oncology, aberrant regulation of AICD is a crucial determinant in tumor initiation and progression. It exerts direct influence on the fate of tumor cells, impeding their proliferation, invasion, and metastasis, while also indirectly suppressing tumor development through immune system activation[13-15]. Furthermore, AICD elicits transformative changes in the tumor microenvironment, having an impact on the proliferative, invasive, and migratory capabilities of tumor cells. Consequently, an extensive exploration of the interconnections and correlations between AICD and cancer provides novel targets and strategies for cancer therapy, facilitating a profound comprehension of the mechanisms underlying cancer onset and progression.

This paper presents a comprehensive review of the mechanisms underlying AICD and its association with cancer. The primary objective is to outline potential avenues for future research, investigating various aspects related to AICD and its relevance to cancer. Through an in-depth exploration of these mechanisms and their functions, this paper aspires to unveil novel breakthroughs in cancer treatment development and to enhance our comprehension of the occurrence and progression of cancer.

#### SYSTEMIC AND CELLULAR ATP HOMEOSTASIS

ATP homeostasis in biological systems and cells is a dynamic state of balance that involves the precise regulation of ATP concentration within a specific range. This is achieved through intricate processes including ATP synthesis, degradation, transport, and exchange both within and outside the cell, as well as regulation by the intracellular environment. Maintaining ATP homeostasis is crucial for sustaining cellular energy metabolism and overall physiological function. Various external factors can impact ATP production and stability, thereby perturbing ATP homeostasis.





Figure 1 Chronological depiction of key milestones in the exploration of adenosine triphosphate induced cell death. ATP: Adenosine triphosphate.

These factors encompass fluctuations in oxygen levels, alterations in nutrient availability, exposure to toxins and pharmacological agents, variations in temperature and thermal stress, changes in potential of hydrogen (pH), activation of inflammatory and immune responses, oxidative stress resulting from the accumulation of reactive oxygen species, infections and pathogen invasions, exposure to environmental toxins, as well as prolonged or intense physical and psychological stressors. Internally, several factors participate in the regulation of ATP homeostasis. This includes the coordinated regulation of ATP synthesis pathways, ATP consumption pathways, ATP transport pathways, and ATP hydrolase activity. Additionally, ATP homeostasis can be affected by disruptions in intracellular ATP leakage, alterations in eATP transport pathways, and dysregulation of eATP metabolic pathways (Figure 2).

#### EXTERNAL FACTORS THAT AFFECT ATP HOMEOSTASIS IN SYSTEMS AND CELLS

Hypoxia induces an elevation in eATP levels, which can be attenuated by the administration of L-type Ca<sup>2+</sup> channel blockers and reduced by the activity of a nucleoside hydrolase such as apyrase. Furthermore, the application of iberiotoxin (100 nM), a specific blocker of O<sup>2</sup> sensitive Ca<sup>2+</sup>-dependent K<sup>+</sup> channels, has been shown to enhance the release of ATP[16]. Nutrient deficiency also affects ATP synthesis and metabolism[17].

Chemotherapeutic agents trigger the release of ATP through two main mechanisms: Caspase-gated pannexin-1 (Panx1) channels and caspase/Panx1-independent pathways. Various pro-apoptotic drugs, such as topoisomerase II inhibitors, kinase inhibitors, and proteomic inhibitors, induce the functional activation of Panx1 channels by inhibiting the Cterminal cleavage of Panx1 mediated by caspase-3. The activation of caspase-activated Panx1 channels facilitates the efflux of ATP, as well as adenosine diphosphate (ADP) and adenosine monophosphate (AMP), which collectively constitute over 90% of the adenine nucleotide pool released during the transition from early to late apoptosis[18].

Blood flow undergoes a substantial increase in response to elevated temperatures, most likely attributed to physiological mechanisms governed by temperature-sensitive regulatory processes. ATP exhibits sensitivity to physiological temperature elevations observed both *in vitro* and in vivo, potentially as a result of the activation of cystic fibrosis transmembrane conductance regulator (CFTR)-like channels that disrupt ATP synthesis and stability[19]. Brainstem astrocytes possess the capacity to directly perceive alterations in blood and brain carbon dioxide and pH levels, and potentially govern the function of respiratory neuronal networks to modulate respiration. The reduction in extracellular pH triggers the release of ATP, which results in the depolarization of neighboring astrocytes and neurons. Perturbations in acid-base equilibrium can impede the regular progression of intracellular energy metabolism and impact ATP synthesis and stability[20]. Clodronate, as a highly effective and specific inhibitor of vesicular ATP release, represents a distinctive therapeutic approach to the management of chronic pain. Its inhibitory action on vesicular ATP release implicates its potential efficacy in the treatment of various purinergic-mediated disorders, such as inflammatory conditions, diabetes, and neurological ailments.

These discoveries underscore the contribution of chronic inflammation and immune responses to the dysregulation of cellular ATP homeostasis<sup>[21]</sup>. These findings imply that hydrogen peroxide triggers the release of ATP from intracellular compartments into the extracellular milieu via lysosomal exocytosis. The generation of reactive oxygen species during





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Figure 2 The process of adenosine triphosphate production necessitates the sequential progression through a series of reactions encompassing glycolysis, pyruvate decarboxylation, the krebs cycle, and the respiratory chain. Cellular entities harness carbon sources to generate adenosine triphosphate (ATP) *via* glycolysis and the respiratory chain. Engineered cellular systems, when designed along specific pathways to facilitate targeted product synthesis, incur heightened ATP consumption for processes such as sugar uptake, cellular proliferation, biosynthesis, product efflux, and the acquisition of tolerance to cytotoxic agents. Furthermore, the equilibrium of ATP is influenced by a range of factors, including pH levels and oxygen availability. Perturbations in these dynamics can result in the overproduction of intracellular ATP, leading to its efflux through membrane-associated signaling channels or extracellular vesicles. Subsequent activation of cell membrane-associated P2 receptors by extracellular ATP triggers the influx of intracellular calcium ions, culminating in apoptotic cell demise. ATP: Adenosine triphosphate.

oxidative stress disrupts the delicate balance of ATP homeostasis[22]. Accumulating evidence suggests that the ATP/ P2X7 signaling pathway confers extensive protection against viral infections in the host. The eATP exerts inhibitory effects on the replication of various viruses, including vesicular stomatitis virus, Newcastle disease virus, mouse leukemia virus, and herpes simplex virus, both *in vivo* and *in vitro*, by activating P2X7 receptors [P2X7R/purinergic receptor P2X7 (P2X7Rs)]. Concurrently, ATP administration leads to a significant upregulation of interferon-beta (IFN- $\beta$ ) expression in a concentration- and time-dependent manner. Mechanistically, ATP stimulates the secretion of IFN- $\beta$ through the activation of the (p38 mitogen-activated protein kinase/c-jun n-terminal kinase/activating transcription factor 2) P38/JNK signaling pathway, which plays a crucial role in facilitating antiviral immune responses[23]. Furthermore, cellular energy homeostasis, particularly ATP production and stability, can be disrupted by environmental toxins (*e.g.*, heavy metals, organic pollutants) and prolonged or heightened stress. These external factors can disrupt the delicate balance of energy metabolism within cells, leading to alterations in ATP synthesis and stability[24,25].

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#### INTERNAL FACTORS AFFECTING ATP HOMEOSTASIS IN SYSTEMS AND CELLS

The ATP synthesis pathway exerts a considerable influence on the cellular release of ATP. Oxidative phosphorylation and photophosphorylation, catalyzed by F1F0-ATP synthetase, represent the fundamental mechanisms by which cells generate energy through ATP synthesis<sup>[26]</sup>. Enhanced enzymatic activity of F1F0-ATP synthetase results in increased ATP production. Mitochondrial exposure to shear stress induces mitochondrial ATP production via the involvement of a specific protein called fossa or fossa protein-1, thereby converting the mechanical shear stress into a novel modulator of ATP production. This process leads to the release of ATP from vesicles and initiates purinergic Ca<sup>2+</sup> signaling[25]. These findings indicate that under conditions of metabolic activity or stress, the ATP synthesis pathway can be activated in response to mitochondrial dysfunction, resulting in an upregulation of ATP production. Additionally, aberrant ion channels<sup>[27]</sup>, transporters, and membrane vesicles can also contribute to augmented ATP synthesis in cells, thereby increasing the pool of available ATP for subsequent release.

Furthermore, the ATP-consuming pathway plays a crucial role in the release of ATP by cells. Cell proliferation, for instance, is associated with heightened ATP consumption [28]. In muscle protein synthesis, citrulline has been shown to induce ATP redistribution, resulting in increased ATP consumption during the process<sup>[29]</sup>. As a consequence, cells release more ATP to fulfill their heightened energy demands. Similarly, during the shortening of rabbit psoas muscle skin fibers, ATP consumption is elevated[30]. Studies have also demonstrated that certain abused drugs, such as degeneration of optic atrophy, exhibit increased ATP consumption during their transport across filter-grown CACO-2-monolayers[31]. ATPase and ATP-dependent enzyme reactions are implicated in this increased ATP consumption, which subsequently affects the quantity of ATP released by cells. These findings underscore the significance of the ATP-consuming pathway in modulating ATP release dynamics in cellular processes.

ATP transport channels play a vital role in cellular ATP release. Notably, the opening of the Panx1 half-channel is modulated by the activity of P2X7Rs. Evidence suggests that P2X7Rs are activated under pathological conditions like ischemia, leading to the opening of the PANX1 half-channel. This allows substantial Ca<sup>2+</sup> influx from the extracellular space and the release of ATP from the cytoplasm, ultimately triggering cell death[32]. These findings indicate that activated Pannexin channels facilitate ATP release from the intracellular space through the cell membrane to the extracellular environment.

CFTR also promote ATP release by stimulating independent ATP release channels, thus governing cellular autocrine signaling[27]. Studies have demonstrated that CFTR forms pores in the cell membrane, enhancing the efflux of ATP from the cytoplasm to the extracellular milieu. Furthermore, eATP plays a regulatory role in various signaling systems, including the propagation of intercellular Ca<sup>2+</sup> signaling (ICS). Nexin semi-channels, P2X7Rs, pannexin channels, anion channels, vesicles, and transporters are recognized as potential ATP-released channels; however, their precise contributions to ICS remain subject to debate. In the inner ear, these connexins play a dual and crucial role in Ca<sup>2+</sup> signaling: serving as semi-channels, they promote ATP release and sustain long-range ICS propagation; acting as gap junction channels, as well as facilitating the diffusion of Ca<sup>2+</sup>-mobilized second messengers among coupled cells[33]. Additionally, the binding of ATP facilitates the release of substrates by multidrug resistant protein [34]. Simultaneously, multidrugresistant protein participates in intracellular substance transport and excretion, contributing to the transport of ATP from the cytoplasm to the extracellular space, thus promoting ATP release.

Cells can regulate the balance of ATP concentration inside and outside the cell by modulating the activity of ATP hydrolase. Among the ATP hydrolases, exonucleoside triphosphate diphosphate hydrolases form a significant enzyme family, with members including ectonucleoside triphosphate diphosphohydrolase 1 (CD39) and ENTPD3. These enzymes are capable of catalyzing the hydrolysis of ATP to ADP, leading to the degradation and subsequent release of ATP[35]. Moreover, the ectonucleotide pyrophosphatase/phosphodiesterase family includes members such as ectonucleotide pyrophosphatase/phosphodiesterase 1 and ectonucleotide pyrophosphatase/phosphodiesterase 2, which are also involved in ATP hydrolysis. These enzymes catalyze the hydrolysis of ATP to AMP and two inorganic phosphate ions. The impact of eATP on the release of ATP from cells is a multifaceted and intricately regulated process that entails the interplay of various cell surface receptors, channels, and enzymes.

#### AICD MECHANISMS

The complexity of AICD can vary depending on the specific cell type and the surrounding microenvironment. Nevertheless, several general mechanisms have been elucidated. One of these mechanisms involves the activation of purinergic receptors, particularly the P2X7R, which can initiate a cascade of events leading to cell death. Another mechanism is associated with the elevation of intracellular calcium ion concentration. Moreover, ATP-triggered cell death may also contribute to the activation of inflammatory responses. Lastly, AICD is linked to the perturbation of mitochondrial function, with the release of cytochrome c being strongly associated with the activation of apoptosis signaling pathways (Figure 3).

EATP stimulates the activation of the P2X7R, leading to inflammasome activation and the release of pro-inflammatory cytokines in monocytes. Native-like T cells effectively respond to innate stimuli by secreting a multitude of pro-inflammatory cytokines, and human T cell compartments exhibit the highest expression of the P2X7R. Within the innate lymphoid population, Ty $\delta$  cells demonstrate heightened sensitivity to P2X7R activation compared to conventional T cells, influencing fundamental cellular mechanisms such as calcium signaling and AICD[36]. Neuroinflammation is positively linked to P2X7R activation through risk-associated molecular patterns, with eATP being the most prominent among them. The P2X7R is expressed in various retinal cells, including retinal endothelial cells, and ATP serves as the sole



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**Figure 3 Illustration of the mechanism of adenosine triphosphate induced cell death, which involves several interconnected pathways.** Upon binding to the purinergic receptor P2X7 (P2X7R), extracellular adenosine triphosphate (ATP) induces a surge in intracellular calcium levels, leading to caspase activation and subsequent cell death. Additionally, ATP activates the NOD-like receptor family pyrin domain containing 3 inflammasome by releasing High Mobility Group Box 1/Toll-Like Receptor 4, triggering caspase-1 activation and promoting cell apoptosis. The interaction between ATP and P2X7Rs also activates the Nuclear Factor-kappa B and Phosphatidylinositol 3-kinase-protein kinase B/hypoxia-inducible factor pathways, resulting in DNA damage and cell death. Simultaneously, the continuous accumulation of intracellular Ca<sup>2+</sup> stimulates the opening of the mitochondrial permeability transition pore, leading to DNA damage and ultimately cell necrosis. Ca<sup>2+</sup> induces mitochondria to release cytochrome c, further contributing to the apoptotic process. Moreover, ATP-triggered cellular demise instigates a transformative shift within the extracellular microenvironment, concurrently unleashing a plethora of cytokines. Lastly, apart from elucidating the fundamental underpinnings of ATP induced cell death, this Figure also encapsulates a synthesized appraisal of the plausible mechanisms governing microenvironmental equilibrium, as extrapolated from relevant literature. ATP: Adenosine triphosphate; NF-κB: Nuclear Factor-kappa B; NLRP3: NOD-like receptor family pyrin domain containing 3; Pl3K-AKT: Phosphatidylinositol 3-kinase-protein kinase B; ROS: Reactive oxygen species; TNF-α: Tumor necrosis factor-alpha; IL: Interleukin; ASC: Apoptosis-related speckle-like protein; STAT: Signal transducer and activator of transcription.

physiological agonist for P2X7. High glucose induces periretinal cell death by activating P2X7R, and the ATP released by the deceased cells functions as a "danger signal," further amplifying the inflammatory response caused by glucoseinduced injury[37]. Research has demonstrated that brief (1-4 min) stimulation of mouse macrophages with high eATP leads to delayed (hourly) cell death, as evidenced by DEVDase (caspase-3 and caspase-7) activity. "Transient" P2X7R activation and Ca<sup>2+</sup> overload have been identified as triggers for death in native mouse macrophages, independent of Panx1 and pro-inflammatory caspase-1 and toll-like receptor (TLR) signaling[38]. Furthermore, knockdown of chloride intracellular channel protein 4 enhances ATP-induced apoptosis of HN4 cells through mitochondrial and endoplasmic reticulum pathways[39].

#### AICD AND CANCER SIGNALING PATHWAYS

AICD is directly associated with multiple signaling pathways in tumor cells, achieved through the binding and activation of key molecules in these pathways. Among them, a correlation exists between the mitochondrial pathway and AICD. Upon eATP activation of the P2X7R, intracellular mitochondrial Ca<sup>2+</sup> levels increase, leading to the formation of Bcl-2associated X /Bcl-2 homologous antagonist/killer oligomer complexes that insert into the outer membrane pores of mitochondria. This causes changes in mitochondrial osmotic pressure and transmembrane potential loss, subsequently facilitating the release of cytochrome c from mitochondria into the cytoplasm and activating the caspase-9 precursor.

Consequently, caspase-3 and caspase-7 are activated, triggering a Caspase cascade reaction, and ultimately inducing cell apoptosis [40-47]. ATP promotes apoptosis by activating extracellular P2X7Rs. The apoptosis of tumor cells can induce apoptosis in surrounding cells, resulting in proliferative necrosis, providing an environment favorable for cancer spread. P2X7R activation leads to tumor necrosis factor (TNF) activation, stimulating Caspase activation, and initiating the execution phase of apoptosis[48,49]. Simultaneously, P2X7R activation alters membrane permeability, leading to an outflow of intracellular ions, cell swelling, and rupture, ultimately causing cell necrosis[50,51]. Necrosis is an internal tumor death that creates an ideal environment for cancer dissemination. ATP activates immune cell membrane P2X7Rs, triggering the release of necrosis factors, and activating serine-threonine kinases such as receptor-interacting protein kinase 1 and receptor-interacting protein kinase 3 after TNF receptor 1 or TLR stimulation, ultimately inducing necrosis [50-54].

The autophagy pathway plays a crucial role in recycling metabolic waste in tumor cells, ensuring their energy requirements are met, or facilitating evasion of apoptosis, ultimately leading to tumor cell proliferation. ATP can promote autophagy initiation by activating the AMP-activated protein kinase (AMPK) signaling pathway [55,56]. When intracellular ATP levels decrease, AMPK becomes phosphorylated and activated, subsequently activating the unc-51-like autophagy activating kinase 1 complex and initiating the autophagy process.

Nuclear factor kappaB (NF-κB) assumes a critical role in numerous biological processes of tumor cells, encompassing inflammation, proliferation, survival, apoptosis, angiogenesis, epithelial-mesenchymal transition (EMT), metastasis, stemcell characteristics, metabolism, and therapeutic resistance. Prior investigations have established that NF-KB activation leads to DNA damage and initiates the signaling pathway of NF-κB[57]. The Wnt signaling pathway holds paramount significance in embryonic development by preserving stem cell properties and dictating cell fate. When ATP binds to the P2 purinergic receptor, it activates protein kinase C and phosphoinositide 3-kinase (PI3K) signaling pathways, thereby inhibiting the activity of glycogen synthesis kinase- $3\beta$  (GSK- $3\beta$ )[57-60].

Consequently, β-catenin is no longer phosphorylated and degraded by GSK-3β, which regulates cell growth and differentiation. Several studies have indicated that ATP can promote the activation of the PI3K/ protein kinase B (Akt) pathway through P2 purinergic receptor activation. This process results in PI3K catalyzing the transformation of phosphatidylinositol diphosphate into phosphatidylinositol triphosphate (PIP3). Subsequently, PIP3 attracts Akt kinase to the cell membrane, resulting in its phosphorylation and activation. Activated Akt kinase modulates cancer development by phosphorylating a diverse array of downstream effector proteins.

MAPK comprises a cluster of evolutionarily conserved serine-threonine kinases, encompassing extracellular signalregulated kinase (ERK), p38, JNK, and big mitogen-activated protein kinase 1, with each representing distinct classical MAPK pathways. ATP phosphorylates and activates MAPK protein kinases (such as ERK, JNK, and p38) by engaging P2 purinergic receptors[61].

Research has revealed that AICD may incite DNA damage, consequently activating tumor protein 53 (p53) expression and function. Activated p53 effectively regulates multiple target genes, including cyclin-dependent kinase inhibitor 1 (p21), Bax, p53 upregulated modulator of apoptosis, etc., which are closely associated with cancer development[62,63]. The induction of AICD exerts a direct or indirect impact on cancer signaling pathways and cancer characteristics, thus further underscoring its vital role in cancer.

#### VALIDATED KEY GENES IN AICD KEY GENES: FUNCTIONS, PROGNOSIS, AND CLINICAL VALUES

The underlying mechanism of AICD remains incompletely understood. However, several overarching mechanisms have been revealed. Among them, a pivotal pathway involves the activation of the P2 receptor family, specifically the P2X7R, by eATP. Perturbation or activation of these genes may modify susceptibility to AICD. Furthermore, investigations into ATP homeostasis have highlighted the regulatory role of PANX1 protein in intracellular ATP concentration, thus influencing AICD. Also, activation of P2X7R triggers an elevation in intracellular calcium levels, which is balanced by the calcium release-activated calcium channel protein 1 (ORAI1) and stromal interaction molecule (STIM) 1 proteins to maintain intracellular calcium homeostasis. Besides these mechanisms, apoptotic and mitochondrial pathways also participate in AICD. Consequently, 37 genes have been identified as crucial players in the AICD mechanism. As the concept of AICD gains prominence, researchers are increasingly focusing on its role in diverse tumor types, implying that the expression levels and clinical significance of AICD may hold significant relevance across different tumors.

Therefore, this paper will discuss prevalent cancer types globally. Table 1 below enumerates the functions and subcellular localizations of these genes during AICD. Due to the limited availability of cancer prognosis-related information regarding AICD genes, an extensive analysis was conducted using clinical data from the database provided by the American Cancer Letters and Biology Institute (https://www.aclbi.com/static/index.html/). Table 1, establishes a comprehensive gene prognosis model centered on AICD, aiming to assess the prognostic significance of individual genes across several types of cancer.

#### Table 1 List of adenosine triphosphate induced cell death core genes and their relationship with tumors

Gene	Full name	Risk factor	Protective factor	Clinical prognostic value	Role in ATP induced cell death	Ref.
P2RX7	Purinergic receptor P2X7	NA	NA	HNSC, KIRC, LAML, SARC	Activates inflammatory mediators and increases calcium ions	Tamajusuku et al [ <mark>89</mark> ]
CASP3	Caspase-3	DPG, HNSC, MESO	OV, THYM	ACC, COAD, LGG, LIHC, LUSC, PAAD	Caspase-3 cleavage by caspase-1/4/5/11 forms pores, releasing pro- inflammatory cytokines	Souza et al[90]
PANX1	Pannexin-1	NSCLC, BRCA, RCA, SARC, MESO		LUAD, MESO, PAAD, STAD	P2X7 activation opens PANX1 channels, releasing ATP and triggering cell death pathways	Shoji <i>et al</i> [ <mark>91</mark> ]
NLRP3	NOD-like receptor family pyrin domain-containing protein 3	SARC, TGCT	PAAD	LAML, SKCM	NLRP3 activated by stimuli forms inflam- masome, triggers caspase-1 activation, releases cytokines, induces apoptosis	Sadatomi <i>et et al</i> [92]
CASP1	Caspase-1	DPG, HNSC, PAAD, LAML, THYM	BRCA, MESO	BRCA, LAML, LGG, MESO, SARC, THYM	Caspase-1 induces cytokine processing, pyrosis, and inflam- mation	Sadatomi <i>et al</i> [92]
P2RY1	P2Y purinoceptor 1	DPG, PAAD	NA	BLCA, KIRC	P2RY1 can increase calcium ions in the Golgi apparatus	Ohishi et al[93]
P2RY11	P2Y purinoceptor 11	NA	HNSC,PAAD,UCEC, Rb, TGCT	ACC, BLCA, LGG, UCEC, UVM	Involved in immune inflammatory mechanisms	Yoon et al[94]
ORAI1	Calcium release- activated calcium channel protein 1	RCA, SARC, MESO	HNSC	ACC, BLCA, KIRP, LGG, MESO,	Increased intracellular calcium ions	Peng et al[95]
STIM1	Stromal interaction molecule 1	HNSC, PCPG	SARC	KIRP, PAAD, UVM	STIM1 responds to ATP- induced calcium influx, activating ORAI1 and promoting cell death	Peng et al[95]
CASP8	Caspase-8	CESC, RCA	DPG, BRCA, OV, SKCM, SARC	LGG, PAAD, SKCM	CASP8 causes apoptosis	Zeng et al[96]
CASP9	Caspase-9	DPG, NSCLC, ACC, THYM	PAAD,BRCA, Rb, MESO	ACC, BLCA, BRCA, LAML, LGG, MESO	CASP9 causes apoptosis	Zeng et al[96]
CASP7	Caspase-7	НСС, ТНҮМ	BRCA, MESO	ACC, KIRC, LGG, LIHC, STAD	CASP7 causes apoptosis	Zeng et al[96]
P2RX3	Purinergic receptor P2X3	DPG	PAAD,NSCLC, CESC, Rb	KIRC, KIRP, LUAD	NA	Ohishi et al[93]
NLRP1	NLR family pyrin domain-containing protein 1	RCA, MESO, THYM	HNSC, NSCLC, SARC	LGG, LUAD, SKCM	NLRP1 activates caspase-1, induces pyrodeath, and releases IL-1β and IL-18	Zhao et al[97]
P2RX4	P2X purinoceptor 4	HNSC, HCC, RCA, Rb, MESO	DPG, UCEC	LGG, LIHC, MESO, UCEC, UVM	P2RX4 contributes to AICD (pyroptosis) by activating the NLRP3 inflammasome, leading to IL-1 $\beta$ and IL-18 production	Ohishi et al[93]
P2RX5	P2X purinoceptor 5	RCA, ACC	HNSC	ACC, KIRC, LGG, SKCM	NA	Ohishi et al[93]
SAPK	Stress-Activated Protein Kinase	NA	NA	NA	ATP induces cell death via SAPK pathways, regulating apoptosis, necrosis, and stress	Humphreys <i>et al</i> [98]



					signaling	
p38 MAPK	p38 mitogen- activated protein kinases (p38 MAPK)	NA	NA	NA	ATP activates p38 MAPK, which leads to cell death through apoptosis and necrosis	Noguchi <i>et al</i> [99]
ASK1	Apoptosis Signal- Regulating Kinase 1	OV, THYM	DPG, HNSC, RCA	KIRC, LAML, LGG, MESO, PAAD, READ, SKCM	Excessive ATP induces cellular stress, activating ASK1 and downstream pathways for cell death	Noguchi <i>et al</i> [99]
NOX2	NADPH oxidase 2	NA	NA	CESC, KIRC, LIHC, LUAD, SKCM	ATP activates NOX2, generating ROS causing oxidative stress and potential cell death	Noguchi <i>et al</i> [99]
bax	BCL2 Associated X	NA	PAAD, BRCA, CESC, RCA	LGG, LIHC, MESO, SKCM, UVM	Excessive ATP triggers BAX activation, mitochondrial dysfunction, and apoptotic cell deat	Wen <i>et a</i> l[100]
MLC	Myosin Light Chain	UCEC, MESO	HNSC, PAAD, BRCA, CESC, RCA, PCPG	CESC, KIRC	ATP depletion hampers muscle contraction, affecting myosin function and cellular viability	Hwang <i>et al</i> [101]
ROCK I	Rho-associated, coiled-coil containing protein kinase 1	ТНҮМ	BRCA, RCA	KIRC, LGG, PAAD	ATP activates P2X7 receptors, inducing apoptosis <i>via</i> the Rho/ROCK pathway, potentially involving ROCK I	Hwang <i>et al</i> [101]
ERK1/2	Extracellular Signal- Regulated Kinase 1 and 2	NA	NA	NA	ERK1/2 promotes cell survival or antagonizes apoptosis, but prolonged activation may lead to cell death. Activates the ERK1/2 pathway, affecting cell fate	Tsukimoto <i>et al</i> [102]
P2X6	P2X purinoceptor 6	DPG, HNSC, BRCA, OV, UCEC, RCA, MESO	SARC, ACC	ACC, HNSC, KIRC, LGG, OV, UVM	Activation may raise calcium levels, potentially triggering cell death	Banfi <i>et al</i> [103]
СҮТС	Cytochrome c	HNSC, NSCLC, Rb, MESO, THYM	DPG, RCA	ACC, BRCA, COAD, HNSC, KIRP, LAML, LGG, LUAD, MESO, UCEC	Cytochrome c released by mitochondria during cell stress triggers cell apoptosis	Sadatomi <i>et al</i> [92]
TNF-α	Tumor necrosis factor alpha	CESC, Rb, MESO	HNSC, PAAD, RCA, SARC	SKCM, THYM	ATP induces cell death, activating TNF- $\alpha$ and triggering apoptosis or necroptosis pathways. Immune cells produce TNF- $\alpha$ in response to ATP, amplifying the cellular response	Hide et al[5]
P2RY5	P2R purinoceptor 5	NA	NA	NA	NA	Yoon et al[94]
P2RY14	P2R purinoceptor14	RCA	HNSC, HCC, OV, UCEC MESO	HNSC, KIRP, LUAD, SKCM, UCEC	NA	Ohishi et al[93]
P2RY13	P2R purinoceptor 13	NA	PAAD, NSCLC, CESC, SKCM, RCA, SARC	ACC, CESC, KIRC, LUAD, SARC, SKCM, UCEC	P2Y13 may play a role in ADP receptors, mainly involved in ATP homeostasis	Ohishi et al[93]
P2RY12	P2R purinoceptor 12	DPG,PAAD,OV, SARC, MESO, THYM,	NSCLC	LAML, LUAD, SKCM	P2Y12 may play a role in ADP receptors, mainly involved in ATP homeostasis	Ohishi et al[93]
P2RY6	P2R purinoceptor 6	DPG, HNSC, PAAD, HCC, BRCA, RCA	SARC,	KIRC, LGG, SKCM, UVM	P2Y6 may be involved in calcium signaling	Ohishi et al[93]

					leading to cell death	
P2RY4	P2R purinoceptor 4	HCC, SARC	HNSC, PAAD, RCA	PRAD	P2Y6 may be involved in calcium signaling leading to cell death	Ohishi et al[ <mark>93</mark> ]
P2RY2	P2R purinoceptor 2	DPG, UCEC, BRCA, OV	RCA, SARC	BLCA, GBM, LAML, LGG, MESO, OV, PAAD, UCEC, UVM	ATP binding triggers intracellular signaling pathways that may lead to cell death	Ohishi et al[93]
ANO6	Anoctamin-6	HNSC, PAAD, OV, NSCLC, BRCA, CESC		BRCA, CESC, KIRC, LGG, MESO, OV, PAAD	As a calcium-activating channel and superburning enzyme, it may influence cell death pathways	Ousingsawat <i>et al</i> [104]
cyclinE2	cyclinE2	DPG, HCC, UCEC, RCA, SARC, Rb, ACC, MESO	HNSC	ACC, BRCA, KICH, KIRP, LGG, LIHC, LUAD, MESO, THYM	NA	Wang et al[105]
cyclinD2	Cyclin D2	HNSC	PAAD, NSCLC, BRCA, LAML, MESO, PCPG	LAML, LGG, LUSC, MESO, PAAD, SKCM, THCA, UCEC	NA	Wang <i>et al</i> [105]

ACC: Adrenocortical carcinoma; BLCA: Bladder urothelial carcinoma; BRCA: Breast invasive carcinoma; CESC: Cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL: Cholangiocarcinoma; COAD: Colon adenocarcinoma; COADREAD: Colon adenocarcinoma/rectum adenocarcinoma esophageal carcinoma; DLBC: Lymphoid neoplasm diffuse large B-cell lymphoma; ESCA: Esophageal carcinoma; GBM: Glioblastoma multiforme; GBMLGG: Glioma; HNSC: Head and neck squamous cell carcinoma; KICH: Kidney chromophobe; KIPAN: Pan-kidney cohort (KICH + KIRC + KIRP); KIRC: Kidney renal clear cell carcinoma; KIRP: Kidney renal papillary cell carcinoma; LAML: Acute myeloid leukemia; LGG: Brain lower grade glioma; LIHC: Liver hepatocellular carcinoma; LUAD: Lung adenocarcinoma; LUSC: Lung squamous cell carcinoma; MESO: Mesothelioma; OV: Ovarian serous cystadenocarcinoma; SARC: Sarcomay; SKCM: Skin cutaneous melanoma; STAD: Stomach adenocarcinoma; STES: Stomach and esophageal carcinoma; GCT: Testicular germ cell tumors; THCA: Thyroid carcinoma; THYM: Thymoma; UCEC: Uterine corpus endometrial carcinoma; UCS: Uterine carcinosarcoma; UVM: Uveal melanoma.

#### AICD IN GLOBALLY-PREVALENT CANCER TYPES

#### Breast cancer

Breast cancer is the predominant malignancy among women globally, holding the foremost position in cancer-related mortalities. Emerging investigations have revealed a significant elevation of P2X7Rs in breast cancer, implicating their involvement in mediating crucial cellular processes. Specifically, P2X7Rs have been associated with the activation of the Akt signaling pathway, the calcium-activated small conductance calcium-activated potassium channel 3 potassium channel, and the induction of EMT. Additionally, they play a regulatory role in the secretion of extracellular vesicles, thereby fostering breast cancer invasion and migration. These mechanisms are influenced by factors such as hypoxia and ATP exposure[64]. In T47D cells, the silencing of the P2X7R remarkably hindered the invasion and migration induced by ATP stimulation. Moreover, the activation of P2X7Rs by ATP led to a down-regulation of E-cadherin protein levels and an up-regulation of matrix metalloproteinase-13 (MMP-13) production[65]. This suggests that ATP-induced activation of P2X7Rs may facilitate breast cancer cell invasion and migration through the activation of the Akt pathway and the regulation of E-cadherin and MMP-13 expression. Furthermore, the glycoprotein PANX1 has emerged as a key player in breast cancer metastases, bearing similarities in structure and function to connexins and contributing to cell-environment communication. Elevated PANX1 expression has been associated with a shift towards an EMT phenotype and has been implicated in the tumor-promoting role of breast cancer, correlating with unfavorable clinical outcomes in breast cancer patients[66].

The expression levels of ORAI1 were also found to be upregulated in breast cancer cell lines. Employing ORAI1 small interfering RNA (siRNA) interference in breast cancer cells resulted in reduced calcium ion entry related to storage operations and altered calcium inflow linked to invasive stimulation. Microarray data analysis of 295 breast cancer cases indicated that the transcriptional breast cancer subtype with the worst prognosis (basal type) exhibited alterations in the relationship between ORAI1 regulatory factors, namely STIM1 and STIM2. Notably, breast cancer patients with tumors expressing high levels of STIM1 and low levels of STIM2 had significantly worse prognoses[67]. *In vitro* investigations have further validated the pivotal role of STIM1 in the proliferation and metastasis of breast cancer. STIM1 was found to be expressed in 66.1% of breast cancer cases, a significantly higher proportion than in adjacent non-tumor tissues. Moreover, STIM1 overexpression demonstrated positive associations with larger tumors, lymph node metastasis, and negative estrogen receptor status. Additionally, in breast cancer patients, increased STIM1 expression was significantly linked to poorer disease-free survival but did not exhibit a significant correlation with overall survival[68].

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The P2Y2 receptor plays a pivotal role in the progression of various tumor types. It exhibits high expression levels in MCF7 and Hs578T breast cancer cells. Targeting the P2Y2 receptor with siRNA leads to a significant attenuation of ATPor uridine 5'-triphosphate-driven migration and invasion of breast cancer cells, along with down-regulation of the EMTrelated genes snail family transcriptional repressor 1 and E-cadherin. Consistent with *in vitro* findings, the expression of the P2Y2 receptor was markedly higher at the tumor infiltrating margin, invasive tumor cells within breast adipose tissue, and/or cancer embolus of lymphatic sinus compared to the tumor core[69]. Abnormal expression and mutations of the P2Y6 receptor have been observed in most tumor types and strongly correlated with poor prognosis in breast cancer patients. Additionally, uridine diphosphate significantly enhances the migration and invasion of breast cancer cells, and this effect can be blocked by P2Y6 receptor-specific inhibitors MRS2578 and P2Y6 short hairpin RNA (shRNA)[70]. Furthermore, the expression of P2Y12 is significantly up-regulated in cisplatin-treated 4T1 breast cancer cells [71]. Notably, a certain relationship exists between AICD and breast cancer. Being an intracellular energy molecule, ATP plays critical biological functions within the cell. Therefore, further investigations are warranted to elucidate the mechanism of action and potential therapeutic value of ATP in breast cancer.

#### Lung cancer

Lung cancer, one of the most prevalent cancer types globally, is directly associated with smoking, but it can also affect non-smokers. It involves the uncontrolled proliferation of lung cells, leading to the formation of malignant tumors. Recent research has demonstrated a significant relationship between the dysregulated expression of the P2X7R and the occurrence and progression of lung cancer. Particularly, the P2X7R is prominently expressed in tumor-associated macrophages (TAMs), and its deficiency impairs the "M2-like" polarization of TAM by reducing the phosphorylation of signal transducer and activator of transcription 6 and interferon regulatory factor 4. Consequently, P2X7 deficiency curtails lung cancer and Lewis lung cancer progression by inhibiting tumor cell proliferation and angiogenesis, promoting T cell mobilization, and reverting M2-like TAM polarization[72]. Furthermore, relevant data has verified the functional presence of P2X1, P2X4, and P2X7Rs in laboratory of allergic disease 2 cells and HLMC[73].

Overexpression of ORAI1/calcium release activated calcium modulator 1 (CRACM1) has a suppressive effect on extracellular signal-regulated kinase 1/2 (ERK1/2) and Akt phosphorylation. This overexpression induces the expression of the cell cycle regulator p21 while reducing the expression of cyclin D3. As a result, cell cycle arrest occurs in the G0/G1 phase. Of particular significance is that the heightened expression of ORAI1/CRACM1 significantly diminishes epidermal growth factor-triggered calcium influx[74]. In non-small cell lung cancer (NSCLC), the expression of STIM1 is substantially elevated compared to benign lesions and is positively correlated with advanced T stages of NSCLC. STIM1 knockdown in NSCLC cell lines A549 and lung cancer (SK-MES-1) Leads to significant inhibition of cell proliferation and arrests A549 and SK-MES-1 cells in the G2/M and S phases of the cell cycle. Moreover, STIM1 knockdown markedly reduces the growth of xenografted tumors in nude mice[74,75].

While some studies have indicated the potential involvement of ATP in the regulation of lung cancer occurrence and development, further research is needed to confirm and clarify whether ATP acts as an independent risk factor for lung cancer. Additionally, exploring how ATP-related mechanisms can be applied for clinical intervention remains an essential area of investigation.

#### Colorectal cancer (CRC)

CRC stands as a prominent contributor to cancer-related mortality on a global scale. In CRC patients, distinct phenotypes characterized by high and low P2X7R expressions have been identified. Those exhibiting high P2X7R expression displayed shorter survival, elevated serum carcinoembryonic antigen levels, and more advanced tumor stages. Moreover, P2X7R expression showed significant upregulation in metastatic CRC and metastatic CRC cell lines, indicating a positive correlation between P2X7R expression and metastasis[75,76]. P2X7R, through inducing glucose transporter protein 1 (GLUT-1) expression, aids in tumor cells' resistance to unfavorable conditions. GLUT1, a principal glucose transporter in CRC cells, serves as a prognostic marker for adverse outcomes in CRC patients. Recent investigations have identified P2X7R and GLUT-1 as potential prognostic biomarkers for the development of novel treatment strategies. Higher P2X7R expression was found in patients with poorly differentiated tumors, and those with GLUT-1 overexpression experienced reduced overall survival and disease-free survival. Therefore, P2X7R and GLUT-1 may independently serve as prognostic markers, offering a novel avenue for targeted therapy in CRC patients[77].

Purinergic receptors, particularly P2Y2 receptors, have been identified to exert an anti-apoptotic effect in ursolic acidinduced CRC HT-29 and prostate cancer DU145 cells. P2Y2 receptor activation leads to Src activation, subsequently phosphorylating p38, resulting in cyclooxygenase-2 (COX-2) overexpression and thereby inducing resistance to apoptosis in HT-29 and DU145 cells[78]. Current investigations indicate that sustained activation of P2Y6R may contribute to the development of intestinal tumors by inhibiting the apoptotic process and promoting chemotherapy resistance, which poses a critical challenge in the management of CRC patients[79].

STIM1 overexpression is prevalent in CRC patients. Notably, elevated STIM1 expression is significantly associated with tumor size, depth of invasion, lymph node metastasis, and serum carcinoembryonic antigen levels in CRC. Furthermore, ectopic STIM1 expression enhances the motility of CRC cells, while STIM1 depletion through shRNA inhibits CRC cell migration[80]. Additionally, ORAI1 is upregulated in human CRC tissues, and its high expression is closely linked to tumor invasion depth, lymph node metastasis, and peri-nerve invasion. Patients with high ORAI1 expression experience shortened overall survival. CRC cell lines also exhibit upregulated ORAI1 expression. Although ORAI1 downregulation suppresses cell proliferation, this growth inhibition is not attributed to augmented apoptosis, and STIM1 does not participate in the regulation of CRC cell proliferation[81].

#### Prostate cancer

Prostate cancer, one of the most prevalent malignancies in men, is characterized by the aberrant proliferation and propagation of malignant cells within prostate tissue. In the context of prostate cancer, the expression profile of P2X7R exhibits a distinctive stage-specific pattern, initially appearing in the nucleus, progressing to the cytoplasm, and ultimately localizing to the apical membrane of epithelial cells. Early biopsy findings revealed that all 114 prostate tissues examined exhibited positive P2X7 staining, indicating the presence of P2X7 at the early stage of prostate cancer[82]. Subsequent investigations demonstrated that the downregulation of P2X7 by siRNA substantially attenuated the in vitro migration and invasion of prostate cancer cells driven by ATP or 2',3'-O-(Benzoyl-4-benzoyl)-adenosine 5'-triphosphate, while also suppressing tumor invasion and metastasis in nude mice. Additionally, the silencing of P2X7 significantly reduced the expression of EMT/invasion-related genes, namely Snail, e-cadherin, claudin-1, interleukin (IL)-8, and matrix metalloproteinase-3, along with dampening the phosphorylation of PI3K/AKT and ERK1/2[83].

Moreover, P2X4 protein exhibits expression in prostate epithelial cells, a specific subset of CD66+ neutrophils, and the majority of CD68+ macrophages. Elevated P2X4 expression in prostate cancer has been associated with post-radical prostatectomy metastasis. Depletion of the P2X4 gene leads to a reduction in the growth, migration, and invasion of prostate cancer cells. Furthermore, knockout of P2X4 in Myc-CaP cells results in a significant decrease in the subcutaneous growth of allografts in FVB/NJ mice[84]. Additionally, other investigations have demonstrated that indoline derivatives can activate the P2Y1R receptor and induce mitochondrial apoptosis signaling[85]. In prostate cancer cells, the P2Y2 receptor shows a notable expression. Suppression of the P2Y2 receptor inhibits cell invasion and metastasis. Moreover, ATP presence promotes the expression of IL-8 and Snail genes while inhibiting the expression of E-cadherin and Claudin-1. Consequently, knockdown of the P2Y2 receptor affects the expression of these EMT/invasion-related genes both *in vitro* and *in vivo*[86].

The functional interplay between STIM1 and ORAI1, as well as the calcium channel selectivity of ORAI1, are crucial for its pro-apoptotic effect. Furthermore, it was observed that resistance to apoptosis in androgen-independent prostate cancer cells was associated with the down-regulation of ORAI1 expression and store-operated calcium entry. Upon ORAI1 restoration, steroid-deprived cells transfected with ORAI1 exhibited reestablished channel currents for calcium storage operations, leading to the restoration of normal apoptosis rates. Therefore, irrespective of the stimulus inducing apoptosis, ORAI1 plays a vital role in initiating apoptosis and establishing an anti-apoptotic phenotype in prostate cancer cells[87].

Concurrently, STIM1 and ORAI1 have been demonstrated to hinder cell growth by arresting human prostate cancer cells in the G<sub>0</sub>/G<sub>1</sub> phase and promoting cell senescence. Additionally, STIM1 and ORAI1 inhibit the NF-κB signaling pathway and remodel the tumor microenvironment by reducing the formation of M2-type macrophages, potentially creating an unfavorable milieu for tumor growth inhibition. However, STIM1 can also promote cell migration and EMT through the activation of transforming growth factor-beta, Snail, and Wnt/ $\beta$ -Catenin pathways[88]. These findings collectively indicate that STIM1 and ORAI1 play a multifaceted and vital regulatory role in prostate cancer development, encompassing crucial biological processes such as cancer cell growth, apoptosis, and metastasis.

Therefore, this paper discussed prevalent cancer types globally. Table 1 below enumerates the functions and subcellular localizations of these genes during AICD[89-105]. Due to the limited availability of cancer prognosis-related information regarding AICD genes, an extensive analysis was conducted using clinical data from the database provided by the American Cancer Letters and Biology Institute (https://www.aclbi.com/static/index.html/). Table 1, establishes a comprehensive gene prognosis model centered on AICD, aiming to assess the prognostic significance of individual genes across several types of cancer.

#### AICD AS POTENTIAL CANCER TREATMENT

The elucidation of the AICD mechanism has offered valuable insights into prospective drug investigations, underscoring its promising potential in cancer treatment. In recent years, there has been a notable surge of interest within the scientific community towards harnessing the AICD mechanisms for cancer therapy. This intricate mechanism involves the engagement of eATP with the P2X7R located on the cell membrane's surface, culminating in heightened intracellular calcium ion levels and concurrent activation of the PI3K/Akt signaling cascade, which impacts molecules including NF-KB, toll-like receptor 4, and tumor necrosis factor-alpha (TNF- $\alpha$ ), ultimately triggering cell death. This comprehensive exploration into the molecular intricacies furnishes a robust scientific foundation for the future development of novel therapeutics targeting this pathway.

Caffeine exerts its impact by facilitating the degradation of intracellular adenylate (AMP), thereby intensifying the cellular consumption of ATP. In the context of the rat brain, a notable interplay emerged between chronic high-intensity interval training (HIIT) and caffeine consumption, revealing a linkage to the activity of Na+-K+-ATPase and antioxidant enzymes within the brain, alongside the manifestation of anti-anxiety behaviors. Notably, caffeine administration was observed to amplify anxiety-related behaviors, while concurrently mitigating alterations induced by HIIT in the antioxidant system and Na<sup>+</sup>-K<sup>+</sup>-ATPase activity [106]. This implies that caffeine could potentially heighten AMP degradation through the modulation of ATPase activity. Notably, a mitochondrial reverse transport inhibitor, atractyloside, perturbs adenylate transport within mitochondria, thus precipitating intracellular ATP degradation.

Furthermore, recent investigations have revealed a spectrum of novel P2X7R inhibitors, including emodin, which have demonstrated substantial efficacy in suppressing P2X7R-mediated breast cancer invasion, signifying their promising potential for prospective clinical applications[64]. A notable example is brilliant blue G (BBG), a P2X7R inhibitor, crucial in addressing bone cancer pain. Noteworthy findings have indicated that BBG-mediated inhibition of P2X7R or



utilization of small interfering RNA directed against P2X7 in RVM distinctly diminishes spinal cord 5-HT levels and Fos expression[107]. Additionally, it is noteworthy that P2Y12 receptor selective antagonists play a vital role in diverse malignancies. Clopidogrel, for instance, has been identified as an efficacious selective P2Y12 receptor antagonist, pivotal in orchestrating platelet function regulation and eliciting positive effects in the context of cancer[108].

Furthermore, the dose-dependent attenuation of ATP-induced intracellular calcium concentration signaling  $[(Ca^{2+})i]$ through the phospholipase C inhibitor U73122 underscores its important role. These pharmacological attributes compellingly underscore the functional expression of G-protein-coupled P2Y2 receptors in esophageal squamous cell cells[109]. To encapsulate, P2 receptor-associated inhibitors confer potent suppression of tumor cell proliferation, invasion, immune modulation, angiogenesis, and tumor microenvironment regulation, as well as influencing drug targets and enhancing chemotherapy sensitization. Moreover, these inhibitors may fortify immune cell-mediated tumor assaults, thus augmenting therapeutic outcomes.

Suppression of PANX1 protein levels through shRNA-mediated downregulation or application of channel-blocking agents such as carbenoxolone and probenecid has robustly attenuated cell proliferation and migration, concurrently stimulating melanin synthesis. Intriguingly, cell surface biotin labeling analysis revealed an intracellular reservoir of PANX1 within melanoma cells. Notably, PANX1's potential modulation of signal transduction via the Wnt/β-catenin pathway is underscored by the significant reduction in  $\beta$ -catenin levels following PANX1 silencing[110]. Concurrently, berberine (BBR) exhibited notable effects on MDA-MB-231 cell viability, fostering dose-dependent lactate dehydrogenase release, while effectively curtailing colony formation and migratory potential. BBR further exhibited marked suppression of pro-inflammatory cytokine secretion, including IL-1 $\alpha$ , IL-1 $\beta$ , IL-6, and TNF- $\alpha$ [11]. Subsequent investigations revealed downregulated expressions of P2X P2X7, NOD-like receptor family pyrin domain containing 3 (NLRP3), pre-Caspase-1, apoptosis-related speckle-like protein (ASC) encompassing caspase activation and recruitment domains, Caspase-1 p20, IL-18, and IL-1β in the NLRP3 inflammatory body pathway. Moreover, decreased mRNA levels of NLRP3, caspase-1, and ASC further corroborated these findings[111].

The concept of AICD mechanism has garnered significant interest within the realm of cancer therapy, emerging as a focal point for exploration within innovative anti-cancer therapeutic avenues. Serving as a fundamental underpinning of cell demise, the AICD mechanism is intrinsically intertwined, either directly or indirectly, with diverse modes of cell death. This interplay holds the potential to reveal intricate associations among distinct cell death modalities. Recent investigations underscore the promise of harnessing AICD as a catalyst for novel therapeutic approaches, potentially encompassing novel drug development and synergistic utilization with established treatments to enhance therapeutic efficacy. Nevertheless, while the appeal of the AICD mechanism is compelling, its practical application necessitates further comprehensive scrutiny, aimed at elucidating intricate molecular underpinnings, refining its applicability spectrum, and addressing safety parameters. Furthermore, this study made use of the ClinicalTrials.gov website (https:// clinicaltrials.gov/), a comprehensive repository of clinical trial information, to compile a list of AICD-associated genes that have undergone completed clinical trials (Table 2).

#### REFLECTIONS ON ATP AND AICD

The intricate interplay between ATP and AICD within the tumor microenvironment, its intersection with anti-tumor immunity, and the nuanced impact of individual variances on cancer progression and therapeutic responsiveness pose an interesting challenge for scientific research. Firstly, while the pivotal role of ATP in instigating apoptotic cascades within neoplastic cells is acknowledged, the precise orchestration of its regulatory mechanisms remains unknown.

Immunological integrity serves as a robust "fortification" to the human body. However, the link between extrinsic factors and unhealthy lifestyles may affect the strength of immune cells over time, leading to gradual weakness and an eventual breach in the body's protective barrier. Consequently, the body becomes susceptible to infections and ailments. AICD has demonstrated its potential to galvanize the immune system. However, the specific recognition and response mechanisms of immune cells against antigens liberated by AICD remain shrouded in mystery. The elevated metabolic activity of tumor cells and their heightened demise in the TME lead to an augmented ATP concentration. Remarkably, ATP undergoes gradual enzymatic transformation into adenosine through the sequential CD39→Ecto-5'-Nucleotidase  $\rightarrow$  and rogen receptor pathway. Consequently, the dynamic distribution and concentration of ATP in the tumor microenvironment represents an unsolved conundrum that warrants closer investigation.

The notion of a specific immune response pertains to the targeted immune reaction directed against a particular pathogenic entity. Molecules intricately linked with immunological responses possess the capacity to instigate cell death, often paralleled by the demise of infected cellular hosts. However, the induction of cell death through ATP activation may yield diverse outcomes in distinct immune cell types. Heterogeneous immune cell populations exhibit varying sensitivities to ATP-triggered cell death, thereby influencing the vigor and efficiency of immune functionalities. Interventions targeting the adenosine pathway not only counteract immunosuppression but also amplify ATP accumulation within the tumor microenvironment through the CD39 blockade. Abundant ATP receptors in immune cells, including dendritic cells, macrophages, and neutrophils, foster heightened immune activity upon exposure to eATP.

Furthermore, the intricate role of ATP in modulating immunosuppressive dynamics within the tumor microenvironment remains partially veiled. Often characterized by immunosuppressive traits, the tumor microenvironment's potential for immune subversion, and whether ATP release can serve as a countermeasure to revert this suppressive state, warrant further exploration. Remarkably, individual responsiveness to ATP stimulation may exhibit substantial variation, potentially rendering certain individuals more predisposed to heightened susceptibility to AICD, while others may manifest attenuated responses. Genetic idiosyncrasies among individuals underpin a broad spectrum of cancer treatment



#### Table 2 Clinical trials for adenosine triphosphate induced cell death

NCT number	Conditions	Drugs	Brief summary
NCT02587819	Carcinoma, basal cell	Treatment with BSCT	This phase 1 clinical trial assesses the safety of BSCT (anti-nf-P2X7) 10% Ointment in basal cell Carcinoma patients
NCT03088644	Healthy	Drug: JNJ-54175446; Drug: 18F- JNJ-64413739	Open-label trial investigates P2X7R occupancy using PET tracer 18F-JNJ- 64413739 for P2X7R with JNJ-54175446
NCT03437590	Healthy	Drug: JNJ-55308942; Drug: [18F]-JNJ-64413739	The primary objective of this investigation is to quantify the inhibition of [18F]- JNJ-64413739 uptake in the brain upon achieving peak plasma concentration (Tmax) and at 24 hours after administering a single dose of JNJ-55308942. Additionally, this study aims to establish a comprehensive model for understanding the interplay between JNJ-55308942 exposure and its receptor interactions
NCT01664000	Solid tumors	Drug: Thioureidobutyronitrile	A phase 1 open-label trial with dose escalation is being conducted to explore the safety, pharmacokinetics, and pharmacodynamics of intravenous kevetrin (thioureidobutyronitrile) in advanced solid tumor patients
NCT00899158	Pancreatic cancer	Other: Immunologic techniques; Other: Laboratory biomarker analysis; procedure: Biopsy	The study seeks to clarify how caspase-3, phosphatidylinositol-3 kinase, and 3- methylhistidine contribute to skeletal muscle wasting in weight loss among pancreatic cancer patients
NCT04972188	Healthy	ZYIL1 capsule	This phase I study investigates the safety, tolerability, pharmacokinetics, and pharmacodynamics of orally administered ZYIL1 in healthy adult subjects through a prospective, open-label, multiple-dose approach
NCT04015076	Healthy	Drug: Inzomelid; Drug: Placebo	This phase 1 study aims to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and food effects of Inzomelid in healthy adults through a randomized, double-blind, placebo-controlled design. An open-label cohort will also verify the safety, pharmacokinetics, and pharmacodynamics of Inzomelid in adult patients with cryopyrin-associated periodic syndromes
NCT04938414	Subarachnoid hemorrhage, aneurysmal	Diagnostic test: Lumbar puncture	Caspase-1 inhibition mitigates pyroptotic neuroinflammation and alleviates cerebrospinal fluid circulation impairment post subarachnoid hemorrhage
NCT02872818	Apoptotic signal pathways in endometrial hyperplasia	Drug: 17β estradiol hemihydrate; Drug: Metformin; Drug: Medroxyprogesterone acetate	This study aims to clarify apoptotic signaling pathways involving Survivin, Bcl-2, Bax, c-Myc, and caspase-9 in a rat model of iatrogenic endometrial hyperplasia treated with metformin and medroxyprogesterone acetate
NCT02466516	Non-alcoholic steato- hepatitis	Drug: SEL; Biological: SIM	This phase 2 randomized, open-label trial evaluates the safety, tolerability, and efficacy of GS-4997 alone or combined with simtuzumab (SIM) in non-alcoholic steatohepatitis subjects with F2-F3 fibrosis stages
NCT00169130	Lymphoma, large-cell, diffuse	Drug: Doxorubicin; Drug: Cyclophosphamide; Procedure: Autologous stem cell transplantation	This prospective study investigates the ACVBP regimen followed by autologous stem cell transplantation in treatment-naive patients aged 60 or below with low-intermediate risk diffuse large B-cell lymphoma and BCL-2 overexpression
NCT02582879	Chronic Lymphocytic Leukemia (CLL)	NA	This multicenter, prospective, observational registry examines CLL/SLL patients initiating approved oral kinase inhibitors, BCL-2 inhibitors, or other anti-CLL therapies. The study aims to comprehensively analyze treatment patterns, including patient characteristics, resource use, clinical outcomes, and patient-reported outcomes
NCT02226965	Lymphoma, diffuse large B-Cell	Drug: PNT2258	A phase II trial investigates PNT2258 in patients with relapsed or refractory diffuse large B-cell lymphoma
NCT00005032	Lung cancer	Biological: Oblimersen sodium; Drug: Paclitaxel	A Phase I/II trial explores the combination of G3139, a BCL-2 antisense oligonucleotide, with paclitaxel for treating recurrent small cell lung cancer
NCT02419560	Lymphoma, mantle- cell recurrent lymphoma, mantle- cell	Drug: ABT-199 and ibrutinib combination	This study aims to determine the optimal dosing regimen for combining ibrutinib with ABT-199 to treat relapsed or refractory mantle cell lymphoma
NCT00085228	Prostate cancer	Biological: Oblimersen sodium; Drug: docetaxel	Docetaxel and similar agents block tumor cell division through diverse mechanisms, while oblimersen may boost docetaxel's impact by sensitizing tumor cells to enhance its efficacy
NCT03255096	Diffuse large B-cell lymphoma high-grade B-cell lymphoma	Drug: RO6870810; Drug: Venetoclax; Drug: Rituximab	An open-label Phase Ib study assessing the safety, pharmacokinetics, and clinical effects of RO6870810 and Venetoclax in patients with relapsed/refractory DLBCL and/or high-grade B-cell lymphoma carrying gene rearrangements (MYC and/or BCL2 and/or BCL6), with or without Rituximab
NCT00001572	B Cell lymphoma follicular lymphoma	Drug: Id-KLH Vaccine; Drug: QS-21 (Stimulation-QS-21) Drug	To evaluate new vaccine formulations for viability and adverse effects, as well as analyze immune responses targeting the patient's lymphoma-specific



	neoplasm		idiotype
NCT00062010	Lung cancer	Biological: Interferon alpha; Drug: 13-cis-retinoic acid; Drug: Paclitaxel	In patients with recurrent small cell lung cancer undergoing interferon alfa, isotretinoin, and paclitaxel treatment, the investigation aims to determine treatment response frequency and duration, evaluate regimen toxicity, assess overall survival duration, and explore potential links between bcl-2 levels in peripheral blood monocytes and treatment outcomes
NCT00039481	Cardiac toxicity; unspecified childhood solid tumor, protocol specific	Biological: Oblimersen sodium; Drug: dexrazoxane hydrochloride; Drug: Doxorubicin hydrochloride	In this phase I trial, oblimersen's effectiveness, combined with chemotherapy and dexrazoxane, is assessed for treating relapsed or refractory solid tumors in youth. Chemotherapeutic agents inhibit tumor cell division through diverse mechanisms, impeding growth or triggering cell death. Oblimersen is anticipated to heighten the potency of doxorubicin and cyclophosphamide by increasing tumor cell sensitivity. Dexrazoxane, a chemoprotective agent, may also shield normal cells from chemotherapy's adverse effects
NCT006666666	Adenocarcinoma of the prostate stage iv prostate cancer	Drug: AT-101; Drug: Bicalutamide; Other: LHRH agent	In this phase II trial, gossypol's potential to hinder tumor cell growth by blocking blood flow is studied when combined with androgen ablation therapy for newly diagnosed metastatic prostate cancer. Androgens stimulate prostate tumor cell proliferation, which can be reduced by luteinizing hormone- releasing hormone agonists and drugs such as bicalutamide. The simultaneous use of gossypol and androgen ablation therapy appears to hold potential as a viable treatment approach for prostate cancer
NCT00003103	Bladder cancer breast cancer colorectal cancer	Biological: Oblimersen sodium; Drug: Docetaxel	This phase I/II trial evaluates oblimersen's effectiveness in treating solid tumors that have not responded to previous therapies, utilizing various mechanisms to halt tumor cell division, leading to growth arrest or cell death
NCT03080311	Small cell lung cancer; solid tumor	Drug: APG-1252	In this Phase I trial, the safety, pharmacokinetic, and pharmacodynamic profiles of intravenously administered APG-1252 are examined in patients with small cell lung cancer or other solid tumors
NCT00016263	Melanoma (skin)	Biological: Oblimersen sodium; Drug: Dacarbazine	This randomized study compares Dacarbazine alone to Dacarbazine combined with G3139 (Bcl-2 Antisense Oligonucleotide) in patients with advanced malignant melanoma
NCT00169000	Metastatic breast cancer	Drug: Capecitabine; Drug: Docetaxel	Phase I study using accelerated titration design to determine MTD of capecitabine (days 1-14) combined with fixed dose docetaxel (75 mg/m2 IV, day 8). Nine patients will be treated at MTD, evaluating pharmacokinetics, Bax: Bcl-2 ratios, and antitumor response
NCT02997423	Glioblastoma		This multi-institutional, consortium-based, non-interventional study aims to assess if high cytochrome c oxidase activity in newly diagnosed primary GBM tumor specimens is linked to reduced overall survival (primary outcome) and progression-free survival (secondary outcome) times
NCT01205503	Breast cancer non-hodgkin's lymphoma	Drug: Mesna; Drug: Saline; Drug: Doxorubicin	This study aims to investigate if mesna can inhibit specific chemical alterations in the blood of doxorubicin-treated patients. Researchers hypothesize that these changes may be associated with "chemobrain," a cognitive impairment reported by some chemotherapy recipients
NCT01037790	Adult solid tumor adenocarcinoma of the colon adenocarcinoma of the rectum	Drug: PD-0332991	PD 0332991 has the potential to hinder tumor cell growth by blocking key enzymes vital for cell proliferation. This phase II trial evaluates PD 0332991's effectiveness and side effects in treating patients with resistant solid tumors
NCT02154490	Recurrent squamous cell lung carcinoma stage iv squamous cell lung carcinoma AJCC v7	Drug: Docetaxel; biological: Durvalumab; Drug: Erlotinib hydrochloride	Create a National Clinical Trials Network for screening sizable yet homogeneous cancer populations, assigning them to a multi-sub-study "Master Protocol." Assess the screen success rate, defined as the percentage of screened patients enrolling in a therapeutic sub-study

outcomes and their efficacy. The profound impact of individual variations in ATP responsiveness on cancer progression and therapeutic response underscores a pressing inquiry, necessitating thorough investigation into the underpinning mechanisms and conceivable implications.

Additionally, the intricate interplay between the complex and diversified tumor microenvironment and individualized patterns of ATP responsiveness can engender pronounced dissimilarities in cell death incidence and severity. Such variances may closely interlink with the tempo of tumor evolution, aggressiveness, and treatment susceptibility. Nonetheless, a comprehensive resolution to this enigma remains elusive, with further research needed to unravel the intricate relationships between ATP responsiveness, individual differences, and the multifaceted intricacies of the tumor microenvironment.

#### LIMITATIONS AND FUTURE

ATP, an essential extracellular signaling molecule, has been recognized as a cause of cell death induced by high eATP concentrations. It can trigger cell death through diverse mechanisms and directly impact tumor cells to inhibit their



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proliferation, invasion, and metastasis. Additionally, ATP can hinder tumor development by activating the immune system. However, the precise mechanisms and occurrence of AICD have been the subject of debate and remain unclear until now, despite preliminary insights into the relationship between AICD and cancer having been gained. Further investigation is warranted to elucidate the intricate mechanisms underlying AICD, particularly at the cellular and molecular levels There also needs to be a comprehensive characterization of the distinctive changes associated with this process. Additionally, a comprehensive understanding of the interplay and relative significance of AICD in relation to other cell death pathways in diverse disease contexts is crucial. Moreover, investigating the varied responses of different cell types to AICD and exploring potential cell-specific mechanisms are important avenues for future research. These endeavors will enhance our understanding of the molecular mechanisms governing AICD, facilitate the identification of novel regulators, and offer new targets and strategies for the development of cancer therapies and other related diseases.

The introduction of the concept of AICD has sparked increasing interest among researchers regarding its association with tumors. Investigations into this relationship have encompassed numerous prevalent cancer types, examining the correlation between AICD and various tumor characteristics. However, due to insufficient biological evidence and experimental verification, these studies have offered indirect evidence of the connection between AICD and cancer. The precise role of genes in the direct or indirect interplay between AICD and tumors remains unclear. Consequently, these studies have been unable to identify the genes and features that may exert a more significant influence on the relationship between AICD and cancer. Consequently, further research is imperative to comprehensively explore and validate the intricate association between AICD and cancer, ultimately identifying the pivotal factors involved in this interplay.

Moving forward, it is crucial to validate the potential of AICD in clinical applications and advance the development of therapeutic strategies that induce AICD with high efficiency and selectivity. Additionally, synergistic combinations with immunotherapy should be further explored. In summary, AICD represents an autonomous and innovative cell death paradigm. However, comprehensive investigations are needed to elucidate the precise mechanisms underlying AICD and establish the intricate connections between AICD and cancer.

#### CONCLUSION

ATP serves as a vital extracellular signaling molecule for cell survival, yet excessive ATP can induce cell death. With the introduction of the concept of AICD, extensive literature has emerged focusing on its investigation and elucidation. Researchers have made discoveries regarding ATP-activated proteins and provided comprehensive reviews on the topic. However, a comprehensive synthesis of the literature remains lacking, especially an overview of the mechanisms underlying AICD. Further investigation is needed to explore the intricate details of AICD, particularly in terms of its cross-regulation and mutual influence with other cell death pathways, as well as its relative importance in various disease conditions. Moreover, the distinctive changes occurring at the cellular and molecular levels during AICD have yet to be fully described.

This paper provides an in-depth exploration of the multifaceted mechanisms through which AICD. It delineates how ATP serves as a mediator of apoptosis via diverse pathways, encompassing the activation of caspases within the cysteine protease family, the regulation of mitochondrial membrane potential, and the modulation of apoptosis-related protein expression. Additionally, ATP exerts a profound impact on cancer cells by instigating various forms of cell necrosis, including necrotic apoptosis and necrotic tumor cell death. The involvement of ATP in orchestrating the delicate balance between cell survival and death is underscored through its regulation of the autophagy process.

In the realm of cancer biology, ATP emerges as a pivotal regulator influencing tumor cell proliferation, invasion, and metastasis. The article underscores ATP's role in impeding tumor growth by activating apoptosis pathways and enhancing immune-mediated tumor clearance through the induction of tumor cell necrosis. Furthermore, ATP's contribution extends to the modulation of the tumor microenvironment, influencing factors such as inflammation and immune responses, thereby exerting a significant impact on tumor development.

On the therapeutic front, the study accentuates the potential of ATP as a therapeutic agent for inducing cell death. By precisely adjusting ATP levels and subsequently activating core pathways involved in cell death, targeted induction of tumor cell death becomes achievable, offering promising prospects for therapeutic intervention. This comprehensive exploration establishes a crucial theoretical foundation for future research endeavors and clinical applications.

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#### FOOTNOTES

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Lok B collected and collated the data and produced a visual atlas; Sandai D presents the conceptualization and methodology, revises manuscripts, conducts reviews and edits, and is responsible for project management; Zhang HL presented the conceptualization and methodology, analyzed the data, and wrote the first draft; Zhang ZW, Song ZJ, Babu D, Tabana Y, Dahham SS, Adam Ahmed Adam M, Wang Y, and Wang W presented the conceptualization and methodology, analyzed the data, and conducted the review and editing; Zhang HL, Zhao R, Barakat K, Harun MSR, Shapudin SNM and Lok B collected and collated the data and produced a visual atlas; Sandai D presents the conceptualization and methodology, revises manuscripts, conducts reviews and edits, and is responsible for project management; both Sandai D and Song ZJ give detailed guidance to this paper, which is of great significance. Therefore, as a cocorresponding author; all authors have read and approve the final manuscript.

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#### REFERENCES

- Jun DJ, Kim J, Jung SY, Song R, Noh JH, Park YS, Ryu SH, Kim JH, Kong YY, Chung JM, Kim KT. Extracellular ATP mediates necrotic 1 cell swelling in SN4741 dopaminergic neurons through P2X7 receptors. J Biol Chem 2007; 282: 37350-37358 [PMID: 17962183 DOI: 10.1074/jbc.M707915200]
- Mello Pde A, Filippi-Chiela EC, Nascimento J, Beckenkamp A, Santana DB, Kipper F, Casali EA, Nejar Bruno A, Paccez JD, Zerbini LF, 2 Wink MR, Lenz G, Buffon A. Adenosine uptake is the major effector of extracellular ATP toxicity in human cervical cancer cells. Mol Biol Cell 2014; 25: 2905-2918 [PMID: 25103241 DOI: 10.1091/mbc.E14-01-0042]
- Song S, Jacobson KN, McDermott KM, Reddy SP, Cress AE, Tang H, Dudek SM, Black SM, Garcia JG, Makino A, Yuan JX. ATP promotes 3 cell survival via regulation of cytosolic [Ca2+] and Bcl-2/Bax ratio in lung cancer cells. Am J Physiol Cell Physiol 2016; 310: C99-114 [PMID: 26491047 DOI: 10.1152/ajpcell.00092.2015]
- Prahoveanu E, Petrescu A, Moisa I. The effect of ATP on lactic dehydrogenase (LDH) activity and influenza B virus multiplication. Virologie 4 1975; 26: 51-55 [PMID: 1216689]
- Hide I, Tanaka M, Inoue A, Nakajima K, Kohsaka S, Inoue K, Nakata Y. Extracellular ATP triggers tumor necrosis factor-alpha release from 5 rat microglia. J Neurochem 2000; 75: 965-972 [PMID: 10936177 DOI: 10.1046/j.1471-4159.2000.0750965.x]
- 6 Grinwald PM. Positive feedback in the living process: the role of ATP in ischaemic cell death. Med Hypotheses 1977; 3: 138-143 [PMID: 895588 DOI: 10.1016/0306-9877(77)90061-5]
- 7 Nagelkerke JF, Dogterom P, De Bont HJ, Mulder GJ. Prolonged high intracellular free calcium concentrations induced by ATP are not immediately cytotoxic in isolated rat hepatocytes. Changes in biochemical parameters implicated in cell toxicity. Biochem J 1989; 263: 347-353 [PMID: 2597107 DOI: 10.1042/bj2630347]
- Zheng LM, Zychlinsky A, Liu CC, Ojcius DM, Young JD. Extracellular ATP as a trigger for apoptosis or programmed cell death. J Cell Biol 8 1991; 112: 279-288 [PMID: 1988462 DOI: 10.1083/jcb.112.2.279]
- 9 Vandewalle B, Hornez L, Revillion F, Lefebvre J. Effect of extracellular ATP on breast tumor cell growth, implication of intracellular calcium. Cancer Lett 1994; 85: 47-54 [PMID: 7923101 DOI: 10.1016/0304-3835(94)90237-2]
- 10 Ferrari D, Stroh C, Schulze-Osthoff K. P2X7/P2Z purinoreceptor-mediated activation of transcription factor NFAT in microglial cells. J Biol Chem 1999; 274: 13205-13210 [PMID: 10224077 DOI: 10.1074/jbc.274.19.13205]
- Brough D, Le Feuvre RA, Iwakura Y, Rothwell NJ. Purinergic (P2X7) receptor activation of microglia induces cell death via an interleukin-1-11 independent mechanism. Mol Cell Neurosci 2002; 19: 272-280 [PMID: 11860279 DOI: 10.1006/mcne.2001.1054]
- Seki S, Tsukimoto M, Suzuki A, Hattori F, Takai Erina, Oshima Y., Kajima S. Anti-angiogenic effect of P2X7 receptor antagonist oxidized 12 ATP as a mechanism of anti-tumor growth. Pharmaceut Anal Acta 2012; 3 . Available from: https://www.researchgate.net/publication/290487342 Anti

angiogenic\_effect\_of\_P2X7\_receptor\_antagonist\_oxidized\_ATP\_as\_a\_mechanism\_of\_anti-tumor\_growth

- 13 Wang X, Li L, Guan R, Zhu D, Song N, Shen L. Emodin Inhibits ATP-Induced Proliferation and Migration by Suppressing P2Y Receptors in Human Lung Adenocarcinoma Cells. Cell Physiol Biochem 2017; 44: 1337-1351 [PMID: 29183030 DOI: 10.1159/000485495]
- 14 Trautmann A. Extracellular ATP in the immune system: more than just a "danger signal". Sci Signal 2009; 2: pe6 [PMID: 19193605 DOI: 10.1126/scisignal.256pe6]



- Ryoden Y, Nagata S. The XK plasma membrane scramblase and the VPS13A cytosolic lipid transporter for ATP-induced cell death. Bioessays 15 2022; 44: e2200106 [PMID: 35996795 DOI: 10.1002/bies.202200106]
- Buttigieg J, Nurse CA. Detection of hypoxia-evoked ATP release from chemoreceptor cells of the rat carotid body. Biochem Biophys Res 16 Commun 2004; 322: 82-87 [PMID: 15313176 DOI: 10.1016/j.bbrc.2004.07.081]
- 17 Davidson AL, Dassa E, Orelle C, Chen J. Structure, function, and evolution of bacterial ATP-binding cassette systems. Microbiol Mol Biol Rev 2008; 72: 317-364, table of contents [PMID: 18535149 DOI: 10.1128/MMBR.00031-07]
- Boyd-Tressler A, Penuela S, Laird DW, Dubyak GR. Chemotherapeutic drugs induce ATP release via caspase-gated pannexin-1 channels and 18 a caspase/pannexin-1-independent mechanism. J Biol Chem 2014; 289: 27246-27263 [PMID: 25112874 DOI: 10.1074/jbc.M114.590240]
- Kalsi KK, González-Alonso J. Temperature-dependent release of ATP from human erythrocytes: mechanism for the control of local tissue 19 perfusion. Exp Physiol 2012; 97: 419-432 [PMID: 22227202 DOI: 10.1113/expphysiol.2011.064238]
- Gourine AV, Kasymov V, Marina N, Tang F, Figueiredo MF, Lane S, Teschemacher AG, Spyer KM, Deisseroth K, Kasparov S. Astrocytes 20 control breathing through pH-dependent release of ATP. Science 2010; 329: 571-575 [PMID: 20647426 DOI: 10.1126/science.1190721]
- 21 Kato Y, Hiasa M, Ichikawa R, Hasuzawa N, Kadowaki A, Iwatsuki K, Shima K, Endo Y, Kitahara Y, Inoue T, Nomura M, Omote H, Moriyama Y, Miyaji T. Identification of a vesicular ATP release inhibitor for the treatment of neuropathic and inflammatory pain. Proc Natl Acad Sci U S A 2017; 114: E6297-E6305 [PMID: 28720702 DOI: 10.1073/pnas.1704847114]
- Li Z, Gu Y, Wen R, Shen F, Tian HL, Yang GY, Zhang Z. Lysosome exocytosis is involved in astrocyte ATP release after oxidative stress 22 induced by H(2)O(2). Neurosci Lett 2019; 705: 251-258 [PMID: 30928480 DOI: 10.1016/j.neulet.2019.03.046]
- 23 Zhang C, He H, Wang L, Zhang N, Huang H, Xiong Q, Yan Y, Wu N, Ren H, Han H, Liu M, Qian M, Du B. Virus-Triggered ATP Release Limits Viral Replication through Facilitating IFN-β Production in a P2X7-Dependent Manner. J Immunol 2017; 199: 1372-1381 [PMID: 28687662 DOI: 10.4049/jimmunol.1700187]
- Skals M, Bjaelde RG, Reinholdt J, Poulsen K, Vad BS, Otzen DE, Leipziger J, Praetorius HA. Bacterial RTX toxins allow acute ATP release 24 from human erythrocytes directly through the toxin pore. J Biol Chem 2014; 289: 19098-19109 [PMID: 24860098 DOI: 10.1074/jbc.M114.571414]
- Yamamoto K, Imamura H, Ando J. Shear stress augments mitochondrial ATP generation that triggers ATP release and Ca(2+) signaling in 25 vascular endothelial cells. Am J Physiol Heart Circ Physiol 2018; 315: H1477-H1485 [PMID: 30141983 DOI: 10.1152/ajpheart.00204.2018]
- Senior AE, Nadanaciva S, Weber J. The molecular mechanism of ATP synthesis by F1F0-ATP synthase. Biochim Biophys Acta 2002; 1553: 26 188-211 [PMID: 11997128 DOI: 10.1016/s0005-2728(02)00185-8]
- Braunstein GM, Roman RM, Clancy JP, Kudlow BA, Taylor AL, Shylonsky VG, Jovov B, Peter K, Jilling T, Ismailov II, Benos DJ, 27 Schwiebert LM, Fitz JG, Schwiebert EM. Cystic fibrosis transmembrane conductance regulator facilitates ATP release by stimulating a separate ATP release channel for autocrine control of cell volume regulation. J Biol Chem 2001; 276: 6621-6630 [PMID: 11110786 DOI: 10.1074/jbc.M005893200]
- Vander Heiden MG, Lunt SY, Dayton TL, Fiske BP, Israelsen WJ, Mattaini KR, Vokes NI, Stephanopoulos G, Cantley LC, Metallo CM, 28 Locasale JW. Metabolic pathway alterations that support cell proliferation. Cold Spring Harb Symp Quant Biol 2011; 76: 325-334 [PMID: 22262476 DOI: 10.1101/sqb.2012.76.010900]
- 29 Goron A, Lamarche F, Blanchet S, Delangle P, Schlattner U, Fontaine E, Moinard C. Citrulline stimulates muscle protein synthesis, by reallocating ATP consumption to muscle protein synthesis. J Cachexia Sarcopenia Muscle 2019; 10: 919-928 [PMID: 31070021 DOI: 10.1002/icsm.12435]
- Potma EJ, Stienen GJ. Increase in ATP consumption during shortening in skinned fibres from rabbit psoas muscle: effects of inorganic 30 phosphate. J Physiol 1996; 496 ( Pt 1): 1-12 [PMID: 8910191 DOI: 10.1113/jphysiol.1996.sp021660]
- Meyer MR, Wagmann L, Schneider-Daum N, Loretz B, de Souza Carvalho C, Lehr CM, Maurer HH. P-glycoprotein interactions of novel 31 psychoactive substances - stimulation of ATP consumption and transport across Caco-2 monolayers. Biochem Pharmacol 2015; 94: 220-226 [PMID: 25637762 DOI: 10.1016/j.bcp.2015.01.008]
- 32 Iwabuchi S, Kawahara K. Functional significance of the negative-feedback regulation of ATP release via pannexin-1 hemichannels under ischemic stress in astrocytes. Neurochem Int 2011; 58: 376-384 [PMID: 21185900 DOI: 10.1016/j.neuint.2010.12.013]
- Anselmi F, Hernandez VH, Crispino G, Seydel A, Ortolano S, Roper SD, Kessaris N, Richardson W, Rickheit G, Filippov MA, Monyer H, 33 Mammano F. ATP release through connexin hemichannels and gap junction transfer of second messengers propagate Ca2+ signals across the inner ear. Proc Natl Acad Sci USA 2008; 105: 18770-18775 [PMID: 19047635 DOI: 10.1073/pnas.0800793105]
- Johnson ZL, Chen J. ATP Binding Enables Substrate Release from Multidrug Resistance Protein 1. Cell 2018; 172: 81-89.e10 [PMID: 34 29290467 DOI: 10.1016/j.cell.2017.12.005]
- Zhou Q, Yan J, Putheti P, Wu Y, Sun X, Toxavidis V, Tigges J, Kassam N, Enjyoji K, Robson SC, Strom TB, Gao W. Isolated CD39 35 expression on CD4+ T cells denotes both regulatory and memory populations. Am J Transplant 2009; 9: 2303-2311 [PMID: 19656134 DOI: 10.1111/j.1600-6143.2009.02777.x
- Winzer R, Serracant-Prat A, Brock VJ, Pinto-Espinoza C, Rissiek B, Amadi M, Eich N, Rissiek A, Schneider E, Magnus T, Guse AH, Diercks 36 BP, Koch-Nolte F, Tolosa E. P2X7 is expressed on human innate-like T lymphocytes and mediates susceptibility to ATP-induced cell death. Eur J Immunol 2022; 52: 1805-1818 [PMID: 36178227 DOI: 10.1002/eji.202249932]
- 37 Kong H, Zhao H, Chen T, Song Y, Cui Y. Targeted P2X7/NLRP3 signaling pathway against inflammation, apoptosis, and pyroptosis of retinal endothelial cells in diabetic retinopathy. Cell Death Dis 2022; 13: 336 [PMID: 35410316 DOI: 10.1038/s41419-022-04786-w]
- Hanley PJ, Kronlage M, Kirschning C, Del Rey A, Di Virgilio F, Leipziger J, Chessell IP, Sargin S, Filippov MA, Lindemann O, Mohr S, 38 Königs V, Schillers H, Bähler M, Schwab A. Transient P2X7 receptor activation triggers macrophage death independent of Toll-like receptors 2 and 4, caspase-1, and pannexin-1 proteins. J Biol Chem 2012; 287: 10650-10663 [PMID: 22235111 DOI: 10.1074/jbc.M111.332676]
- Xue H, Lu J, Yuan R, Liu J, Liu Y, Wu K, Wu J, Du J, Shen B. Knockdown of CLIC4 enhances ATP-induced HN4 cell apoptosis through 39 mitochondrial and endoplasmic reticulum pathways. Cell Biosci 2016; 6: 5 [PMID: 26816615 DOI: 10.1186/s13578-016-0070-1]
- Lépine S, Le Stunff H, Lakatos B, Sulpice JC, Giraud F. ATP-induced apoptosis of thymocytes is mediated by activation of P2 X 7 receptor 40 and involves de novo ceramide synthesis and mitochondria. Biochim Biophys Acta 2006; 1761: 73-82 [PMID: 16325464 DOI: 10.1016/j.bbalip.2005.10.001]
- Sekar P, Huang DY, Hsieh SL, Chang SF, Lin WW. AMPK-dependent and independent actions of P2X7 in regulation of mitochondrial and 41 lysosomal functions in microglia. Cell Commun Signal 2018; 16: 83 [PMID: 30458799 DOI: 10.1186/s12964-018-0293-3]
- Sarti AC, Vultaggio-Poma V, Falzoni S, Missiroli S, Giuliani AL, Boldrini P, Bonora M, Faita F, Di Lascio N, Kusmic C, Solini A, Novello S, 42 Morari M, Rossato M, Wieckowski MR, Giorgi C, Pinton P, Di Virgilio F. Mitochondrial P2X7 Receptor Localization Modulates Energy



Metabolism Enhancing Physical Performance. Function (Oxf) 2021; 2: zqab005 [PMID: 35330818 DOI: 10.1093/function/zqab005]

- Kerkhofs M, La Rovere R, Welkenhuysen K, Janssens A, Vandenberghe P, Madesh M, Parys JB, Bultynck G. BIRD-2, a BH4-domain-43 targeting peptide of Bcl-2, provokes Bax/Bak-independent cell death in B-cell cancers through mitochondrial Ca(2+)-dependent mPTP opening. Cell Calcium 2021; 94: 102333 [PMID: 33450506 DOI: 10.1016/j.ceca.2020.102333]
- 44 Wiley JS, Sluyter R, Gu BJ, Stokes L, Fuller SJ. The human P2X7 receptor and its role in innate immunity. Tissue Antigens 2011; 78: 321-332 [PMID: 21988719 DOI: 10.1111/j.1399-0039.2011.01780.x]
- Garrido C, Galluzzi L, Brunet M, Puig PE, Didelot C, Kroemer G. Mechanisms of cytochrome c release from mitochondria. Cell Death Differ 45 2006; 13: 1423-1433 [PMID: 16676004 DOI: 10.1038/sj.cdd.4401950]
- Slee EA, Harte MT, Kluck RM, Wolf BB, Casiano CA, Newmeyer DD, Wang HG, Reed JC, Nicholson DW, Alnemri ES, Green DR, Martin 46 SJ. Ordering the cytochrome c-initiated caspase cascade: hierarchical activation of caspases-2, -3, -6, -7, -8, and -10 in a caspase-9-dependent manner. J Cell Biol 1999; 144: 281-292 [PMID: 9922454 DOI: 10.1083/jcb.144.2.281]
- Kuida K, Haydar TF, Kuan CY, Gu Y, Taya C, Karasuyama H, Su MS, Rakic P, Flavell RA. Reduced apoptosis and cytochrome c-mediated 47 caspase activation in mice lacking caspase 9. Cell 1998; 94: 325-337 [PMID: 9708735 DOI: 10.1016/s0092-8674(00)81476-2]
- 48 Barberà-Cremades M, Gómez AI, Baroja-Mazo A, Martínez-Alarcón L, Martínez CM, de Torre-Minguela C, Pelegrín P. P2X7 Receptor Induces Tumor Necrosis Factor-α Converting Enzyme Activation and Release to Boost TNF-α Production. Front Immunol 2017; 8: 862 [PMID: 28791020 DOI: 10.3389/fimmu.2017.00862]
- Wang Q, Wang L, Feng YH, Li X, Zeng R, Gorodeski GI. P2X7 receptor-mediated apoptosis of human cervical epithelial cells. Am J Physiol 49 Cell Physiol 2004; 287: C1349-C1358 [PMID: 15269006 DOI: 10.1152/ajpcell.00256.2004]
- Harada K, Hide I, Seki T, Tanaka S, Nakata Y, Sakai N. Extracellular ATP differentially modulates Toll-like receptor 4-mediated cell survival 50 and death of microglia. J Neurochem 2011; 116: 1138-1147 [PMID: 21210814 DOI: 10.1111/j.1471-4159.2011.07170.x]
- Schulze-Lohoff E, Hugo C, Rost S, Arnold S, Gruber A, Brüne B, Sterzel RB. Extracellular ATP causes apoptosis and necrosis of cultured 51 mesangial cells via P2Z/P2X7 receptors. Am J Physiol 1998; 275: F962-F971 [PMID: 9843914 DOI: 10.1152/ajprenal.1998.275.6.F962]
- 52 Ramírez K T R, Calzaferri F, Rios C D L, Manuel Vidal-Sanz, Marta Agudo-Barriuso. P2X7R and TNFR1 antagonism neuroprotects rodent retinal ganglion cells in a sepsis model. Acta Ophthalmologica 2022; 100 [DOI: 10.1111/j.1755-3768.2022.0676]
- Adriouch S, Dox C, Welge V, Seman M, Koch-Nolte F, Haag F. Cutting edge: a natural P451L mutation in the cytoplasmic domain impairs 53 the function of the mouse P2X7 receptor. J Immunol 2002; 169: 4108-4112 [PMID: 12370338 DOI: 10.4049/jimmunol.169.8.4108]
- 54 Li X, Zhang M, Huang X, Liang W, Li G, Lu X, Li Y, Pan H, Shi L, Zhu H, Qian L, Shan B, Yuan J. Ubiquitination of RIPK1 regulates its activation mediated by TNFR1 and TLRs signaling in distinct manners. Nat Commun 2020; 11: 6364 [PMID: 33311474 DOI: 10.1038/s41467-020-19935-y
- Lu Y, Yuan T, Min X, Yuan Z, Cai Z. AMPK: Potential Therapeutic Target for Vascular Calcification. Front Cardiovasc Med 2021; 8: 670222 55 [PMID: 34046440 DOI: 10.3389/fcvm.2021.670222]
- Li FJ, Xu ZS, Soo AD, Lun ZR, He CY. ATP-driven and AMPK-independent autophagy in an early branching eukaryotic parasite. Autophagy 56 2017; 13: 715-729 [PMID: 28121493 DOI: 10.1080/15548627.2017.1280218]
- Schmitt AM, Crawley CD, Kang S, Raleigh DR, Yu X, Wahlstrom JS, Voce DJ, Darga TE, Weichselbaum RR, Yamini B. p50 (NF-KB1) is an 57 effector protein in the cytotoxic response to DNA methylation damage. Mol Cell 2011; 44: 785-796 [PMID: 22152481 DOI: 10.1016/j.molcel.2011.09.026
- 58 Jacques-Silva MC, Bernardi A, Rodnight R, Lenz G. ERK, PKC and PI3K/Akt pathways mediate extracellular ATP and adenosine-induced proliferation of U138-MG human glioma cell line. Oncology 2004; 67: 450-459 [PMID: 15714002 DOI: 10.1159/000082930]
- 59 Maharati A, Moghbeli M. PI3K/AKT signaling pathway as a critical regulator of epithelial-mesenchymal transition in colorectal tumor cells. Cell Commun Signal 2023; 21: 201 [PMID: 37580737 DOI: 10.1186/s12964-023-01225-x]
- Zhang WJ, Luo C, Huang C, Pu FQ, Zhu JF, Zhu ZM. PI3K/Akt/GSK-3β signal pathway is involved in P2X7 receptor-induced proliferation 60 and EMT of colorectal cancer cells. Eur J Pharmacol 2021; 899: 174041 [PMID: 33737010 DOI: 10.1016/j.ejphar.2021.174041]
- Shiratori M, Tozaki-Saitoh H, Yoshitake M, Tsuda M, Inoue K. P2X7 receptor activation induces CXCL2 production in microglia through 61 NFAT and PKC/MAPK pathways. J Neurochem 2010; 114: 810-819 [PMID: 20477948 DOI: 10.1111/j.1471-4159.2010.06809.x]
- 62 Kitabatake K, Kaji T, Tsukimoto M. ATP and ADP enhance DNA damage repair in y-irradiated BEAS-2B human bronchial epithelial cells through activation of P2X7 and P2Y12 receptors. Toxicol Appl Pharmacol 2020; 407: 115240 [PMID: 32941855 DOI: 10.1016/j.taap.2020.115240
- Sakaguchi K, Herrera JE, Saito S, Miki T, Bustin M, Vassilev A, Anderson CW, Appella E. DNA damage activates p53 through a 63 phosphorylation-acetylation cascade. Genes Dev 1998; 12: 2831-2841 [PMID: 9744860 DOI: 10.1101/gad.12.18.2831]
- Zhu X, Li Q, Song W, Peng X, Zhao R. P2X7 receptor: a critical regulator and potential target for breast cancer. J Mol Med (Berl) 2021; 99: 64 349-358 [PMID: 33486566 DOI: 10.1007/s00109-021-02041-x]
- Xia J, Yu X, Tang L, Li G, He T. P2X7 receptor stimulates breast cancer cell invasion and migration via the AKT pathway. Oncol Rep 2015; 65 34: 103-110 [PMID: 25976617 DOI: 10.3892/or.2015.3979]
- Jalaleddine N, El-Hajjar L, Dakik H, Shaito A, Saliba J, Safi R, Zibara K, El-Sabban M. Pannexin1 Is Associated with Enhanced Epithelial-66 To-Mesenchymal Transition in Human Patient Breast Cancer Tissues and in Breast Cancer Cell Lines. Cancers (Basel) 2019; 11 [PMID: 31817827 DOI: 10.3390/cancers11121967]
- McAndrew D, Grice DM, Peters AA, Davis FM, Stewart T, Rice M, Smart CE, Brown MA, Kenny PA, Roberts-Thomson SJ, Monteith GR. 67 ORAI1-mediated calcium influx in lactation and in breast cancer. Mol Cancer Ther 2011; 10: 448-460 [PMID: 21224390 DOI: 10.1158/1535-7163.MCT-10-0923
- Yang Y, Jiang Z, Wang B, Chang L, Liu J, Zhang L, Gu L. Expression of STIM1 is associated with tumor aggressiveness and poor prognosis 68 in breast cancer. Pathol Res Pract 2017; 213: 1043-1047 [PMID: 28869106 DOI: 10.1016/j.prp.2017.08.006]
- Qiu Y, Liu Y, Li WH, Zhang HQ, Tian XX, Fang WG. P2Y2 receptor promotes the migration and invasion of breast cancer cells via EMT-69 related genes Snail and E-cadherin. Oncol Rep 2018; 39: 138-150 [PMID: 29115551 DOI: 10.3892/or.2017.6081]
- Ma X, Pan X, Wei Y, Tan B, Yang L, Ren H, Qian M, Du B. Chemotherapy-induced uridine diphosphate release promotes breast cancer 70 metastasis through P2Y6 activation. Oncotarget 2016; 7: 29036-29050 [PMID: 27074554 DOI: 10.18632/oncotarget.8664]
- 71 Sarangi S, Pandey A, Papa AL, Sengupta P, Kopparam J, Dadwal U, Basu S, Sengupta S. P2Y12 receptor inhibition augments cytotoxic effects of cisplatin in breast cancer. Med Oncol 2013; 30: 567 [PMID: 23568163 DOI: 10.1007/s12032-013-0567-y]
- 72 Qin J, Zhang X, Tan B, Zhang S, Yin C, Xue Q, Zhang Z, Ren H, Chen J, Liu M, Qian M, Du B. Blocking P2X7-Mediated Macrophage



Polarization Overcomes Treatment Resistance in Lung Cancer. Cancer Immunol Res 2020; 8: 1426-1439 [PMID: 32933967 DOI: 10.1158/2326-6066.CIR-20-0123]

- Wareham K, Vial C, Wykes RC, Bradding P, Seward EP. Functional evidence for the expression of P2X1, P2X4 and P2X7 receptors in 73 human lung mast cells. Br J Pharmacol 2009; 157: 1215-1224 [PMID: 19552691 DOI: 10.1111/j.1476-5381.2009.00287.x]
- Hou MF, Kuo HC, Li JH, Wang YS, Chang CC, Chen KC, Chen WC, Chiu CC, Yang S, Chang WC. Orail/CRACM1 overexpression 74 suppresses cell proliferation via attenuation of the store-operated calcium influx-mediated signalling pathway in A549 lung cancer cells. Biochim Biophys Acta 2011; 1810: 1278-1284 [PMID: 21782006 DOI: 10.1016/j.bbagen.2011.07.001]
- Ge C, Zeng B, Li R, Li Z, Fu Q, Wang W, Wang Z, Dong S, Lai Z, Wang Y, Xue Y, Guo J, Di T, Song X. Knockdown of STIM1 expression 75 inhibits non-small-cell lung cancer cell proliferation in vitro and in nude mouse xenografts. Bioengineered 2019; 10: 425-436 [PMID: 31564210 DOI: 10.1080/21655979.2019.1669518]
- 76 Zhang Y, Ding J, Wang L. The role of P2X7 receptor in prognosis and metastasis of colorectal cancer. Adv Med Sci 2019; 64: 388-394 [PMID: 31276917 DOI: 10.1016/j.advms.2019.05.002]
- Calik I, Calik M, Turken G, Ozercan IH. A promising independent prognostic biomarker in colorectal cancer: P2X7 receptor. Int J Clin Exp 77 Pathol 2020; 13: 107-121 [PMID: 32211091]
- Limami Y, Pinon A, Leger DY, Pinault E, Delage C, Beneytout JL, Simon A, Liagre B. The P2Y2/Src/p38/COX-2 pathway is involved in the 78 resistance to ursolic acid-induced apoptosis in colorectal and prostate cancer cells. Biochimie 2012; 94: 1754-1763 [PMID: 22521508 DOI: 10.1016/j.biochi.2012.04.006]
- Placet M, Arguin G, Molle CM, Babeu JP, Jones C, Carrier JC, Robaye B, Geha S, Boudreau F, Gendron FP. The G protein-coupled P2Y6 79 receptor promotes colorectal cancer tumorigenesis by inhibiting apoptosis. Biochim Biophys Acta Mol Basis Dis 2018; 1864: 1539-1551 [PMID: 29454075 DOI: 10.1016/j.bbadis.2018.02.008]
- Wang JY, Sun J, Huang MY, Wang YS, Hou MF, Sun Y, He H, Krishna N, Chiu SJ, Lin S, Yang S, Chang WC. STIM1 overexpression 80 promotes colorectal cancer progression, cell motility and COX-2 expression. Oncogene 2015; 34: 4358-4367 [PMID: 25381814 DOI: 10.1038/onc.2014.366]
- 81 Gui L, Wang Z, Han J, Ma H, Li Z. High Expression of Orail Enhances Cell Proliferation and is Associated with Poor Prognosis in Human Colorectal Cancer. Clin Lab 2016; 62: 1689-1698 [PMID: 28164587 DOI: 10.7754/Clin.Lab.2016.160131]
- Slater M, Danieletto S, Gidley-Baird A, Teh LC, Barden JA. Early prostate cancer detected using expression of non-functional cytolytic P2X7 82 receptors. *Histopathology* 2004; 44: 206-215 [PMID: 14987223 DOI: 10.1111/j.0309-0167.2004.01798.x]
- Qiu Y, Li WH, Zhang HQ, Liu Y, Tian XX, Fang WG. P2X7 mediates ATP-driven invasiveness in prostate cancer cells. PLoS One 2014; 9: 83 e114371 [PMID: 25486274 DOI: 10.1371/journal.pone.0114371]
- Maynard JP, Lu J, Vidal I, Hicks J, Mummert L, Ali T, Kempski R, Carter AM, Sosa RY, Peiffer LB, Joshu CE, Lotan TL, De Marzo AM, 84 Sfanos KS. P2X4 purinergic receptors offer a therapeutic target for aggressive prostate cancer. J Pathol 2022; 256: 149-163 [PMID: 34652816 DOI: 10.1002/path.5815]
- 85 Le HTT, Murugesan A, Ramesh T, Yli-Harja O, Konda Mani S, Kandhavelu M. Molecular interaction of HIC, an agonist of P2Y1 receptor, and its role in prostate cancer apoptosis. Int J Biol Macromol 2021; 189: 142-150 [PMID: 34425116 DOI: 10.1016/j.ijbiomac.2021.08.103]
- Li WH, Qiu Y, Zhang HQ, Liu Y, You JF, Tian XX, Fang WG. P2Y2 receptor promotes cell invasion and metastasis in prostate cancer cells. 86 Br J Cancer 2013; 109: 1666-1675 [PMID: 23969730 DOI: 10.1038/bjc.2013.484]
- Flourakis M, Lehen'kyi V, Beck B, Raphaël M, Vandenberghe M, Abeele FV, Roudbaraki M, Lepage G, Mauroy B, Romanin C, Shuba Y, 87 Skryma R, Prevarskaya N. Orail contributes to the establishment of an apoptosis-resistant phenotype in prostate cancer cells. Cell Death Dis 2010; 1: e75 [PMID: 21364678 DOI: 10.1038/cddis.2010.52]
- Xu Y, Zhang S, Niu H, Ye Y, Hu F, Chen S, Li X, Luo X, Jiang S, Liu Y, Chen Y, Li J, Xiang R, Li N. STIM1 accelerates cell senescence in a 88 remodeled microenvironment but enhances the epithelial-to-mesenchymal transition in prostate cancer. Sci Rep 2015; 5: 11754 [PMID: 26257076 DOI: 10.1038/srep11754]
- 89 Tamajusuku AS, Villodre ES, Paulus R, Coutinho-Silva R, Battasstini AM, Wink MR, Lenz G. Characterization of ATP-induced cell death in the GL261 mouse glioma. J Cell Biochem 2010; 109: 983-991 [PMID: 20069573 DOI: 10.1002/jcb.22478]
- Souza CO, Santoro GF, Figliuolo VR, Nanini HF, de Souza HS, Castelo-Branco MT, Abalo AA, Paiva MM, Coutinho CM, Coutinho-Silva R. 90 Extracellular ATP induces cell death in human intestinal epithelial cells. Biochim Biophys Acta 2012; 1820: 1867-1878 [PMID: 22951220 DOI: 10.1016/j.bbagen.2012.08.013]
- Shoji KF, Sáez PJ, Harcha PA, Aguila HL, Sáez JC. Pannexin1 channels act downstream of P2X 7 receptors in ATP-induced murine T-cell 91 death. Channels (Austin) 2014; 8: 142-156 [PMID: 24590064 DOI: 10.4161/chan.28122]
- Sadatomi D, Nakashioya K, Mamiya S, Honda S, Kameyama Y, Yamamura Y, Tanimura S, Takeda K. Mitochondrial function is required for 92 extracellular ATP-induced NLRP3 inflammasome activation. J Biochem 2017; 161: 503-512 [PMID: 28096454 DOI: 10.1093/jb/mvw098]
- Ohishi A, Keno Y, Marumiya A, Sudo Y, Uda Y, Matsuda K, Morita Y, Furuta T, Nishida K, Nagasawa K. Expression level of P2X7 receptor 93 is a determinant of ATP-induced death of mouse cultured neurons. Neuroscience 2016; 319: 35-45 [PMID: 26812038 DOI: 10.1016/j.neuroscience.2016.01.048]
- 94 Yoon MJ, Lee HJ, Kim JH, Kim DK. Extracellular ATP induces apoptotic signaling in human monocyte leukemic cells, HL-60 and F-36P. Arch Pharm Res 2006; 29: 1032-1041 [PMID: 17146973 DOI: 10.1007/BF02969288]
- Peng H, Hao Y, Mousawi F, Roger S, Li J, Sim JA, Ponnambalam S, Yang X, Jiang LH. Purinergic and Store-Operated Ca(2+) Signaling 95 Mechanisms in Mesenchymal Stem Cells and Their Roles in ATP-Induced Stimulation of Cell Migration. Stem Cells 2016; 34: 2102-2114 [PMID: 27038239 DOI: 10.1002/stem.2370]
- Zeng CY, Li CG, Shu JX, Xu LH, Ouyang DY, Mai FY, Zeng QZ, Zhang CC, Li RM, He XH. ATP induces caspase-3/gasdermin E-mediated 96 pyroptosis in NLRP3 pathway-blocked murine macrophages. Apoptosis 2019; 24: 703-717 [PMID: 31175486 DOI: 10.1007/s10495-019-01551-x]
- Zhao LR, Xing RL, Wang PM, Zhang NS, Yin SJ, Li XC, Zhang L. NLRP1 and NLRP3 inflammasomes mediate LPS/ATP-induced 97 pyroptosis in knee osteoarthritis. Mol Med Rep 2018; 17: 5463-5469 [PMID: 29393464 DOI: 10.3892/mmr.2018.8520]
- Humphreys BD, Rice J, Kertesy SB, Dubyak GR. Stress-activated protein kinase/JNK activation and apoptotic induction by the macrophage 98 P2X7 nucleotide receptor. J Biol Chem 2000; 275: 26792-26798 [PMID: 10854431 DOI: 10.1074/jbc.M002770200]
- 99 Noguchi T, Ishii K, Fukutomi H, Naguro I, Matsuzawa A, Takeda K, Ichijo H. Requirement of reactive oxygen species-dependent activation of ASK1-p38 MAPK pathway for extracellular ATP-induced apoptosis in macrophage. J Biol Chem 2008; 283: 7657-7665 [PMID: 18211888 DOI: 10.1074/jbc.M708402200]



- Wen LT, Caldwell CC, Knowles AF. Poly(ADP-ribose) polymerase activation and changes in Bax protein expression associated with 100 extracellular ATP-mediated apoptosis in human embryonic kidney 293-P2X7 cells. Mol Pharmacol 2003; 63: 706-713 [PMID: 12606781 DOI: 10.1124/mol.63.3.706]
- 101 Hwang SM, Koo NY, Choi SY, Chun GS, Kim JS, Park K. P2X7 Receptor-mediated Membrane Blebbing in Salivary Epithelial Cells. Korean J Physiol Pharmacol 2009; 13: 175-179 [PMID: 19885034 DOI: 10.4196/kjpp.2009.13.3.175]
- Tsukimoto M, Maehata M, Harada H, Ikari A, Takagi K, Degawa M. P2X7 receptor-dependent cell death is modulated during murine T cell maturation and mediated by dual signaling pathways. J Immunol 2006; 177: 2842-2850 [PMID: 16920919 DOI: 10.4049/jimmunol.177.5.2842]
- 103 Banfi C, Ferrario S, De Vincenti O, Ceruti S, Fumagalli M, Mazzola A, D' Ambrosi N, Volontè C, Fratto P, Vitali E, Burnstock G, Beltrami E, Parolari A, Polvani G, Biglioli P, Tremoli E, Abbracchio MP. P2 receptors in human heart: upregulation of P2X6 in patients undergoing heart transplantation, interaction with TNFalpha and potential role in myocardial cell death. J Mol Cell Cardiol 2005; 39: 929-939 [PMID: 16242142 DOI: 10.1016/j.yjmcc.2005.09.002]
- Ousingsawat J, Wanitchakool P, Kmit A, Romao AM, Jantarajit W, Schreiber R, Kunzelmann K. Anoctamin 6 mediates effects essential for 104 innate immunity downstream of P2X7 receptors in macrophages. Nat Commun 2015; 6: 6245 [PMID: 25651887 DOI: 10.1038/ncomms7245]
- Wang J, Liu S, Nie Y, Wu B, Wu Q, Song M, Tang M, Xiao L, Xu P, Tan X, Zhang L, Li G, Liang S, Zhang C. Activation of P2X7 receptors 105 decreases the proliferation of murine luteal cells. Reprod Fertil Dev 2015; 27: 1262-1271 [PMID: 25782073 DOI: 10.1071/RD14381]
- Vieira JM, Carvalho FB, Gutierres JM, Soares MSP, Oliveira PS, Rubin MA, Morsch VM, Schetinger MR, Spanevello RM. Caffeine prevents 106 high-intensity exercise-induced increase in enzymatic antioxidant and Na(+)-K(+)-ATPase activities and reduction of anxiolytic like-behaviour in rats. Redox Rep 2017; 22: 493-500 [PMID: 28482759 DOI: 10.1080/13510002.2017.1322739]
- 107 Huang ZX, Lu ZJ, Ma WQ, Wu FX, Zhang YQ, Yu WF, Zhao ZQ. Involvement of RVM-expressed P2X7 receptor in bone cancer pain: mechanism of descending facilitation. Pain 2014; 155: 783-791 [PMID: 24447511 DOI: 10.1016/j.pain.2014.01.011]
- Wang Z, Zhu S, Tan S, Zeng Y, Zeng H. The P2 purinoceptors in prostate cancer. Purinergic Signal 2023; 19: 255-263 [PMID: 35771310 108 DOI: 10.1007/s11302-022-09874-2]
- Maaser K, Höpfner M, Kap H, Sutter AP, Barthel B, von Lampe B, Zeitz M, Scherübl H. Extracellular nucleotides inhibit growth of human 109 oesophageal cancer cells via P2Y(2)-receptors. Br J Cancer 2002; 86: 636-644 [PMID: 11870549 DOI: 10.1038/sj.bjc.6600100]
- 110 Freeman TJ, Sayedyahossein S, Johnston D, Sanchez-Pupo RE, O'Donnell B, Huang K, Lakhani Z, Nouri-Nejad D, Barr KJ, Harland L, Latosinsky S, Grant A, Dagnino L, Penuela S. Inhibition of Pannexin 1 Reduces the Tumorigenic Properties of Human Melanoma Cells. Cancers (Basel) 2019; 11 [PMID: 30654593 DOI: 10.3390/cancers11010102]
- Yao M, Fan X, Yuan B, Takagi N, Liu S, Han X, Ren J, Liu J. Berberine inhibits NLRP3 Inflammasome pathway in human triple-negative 111 breast cancer MDA-MB-231 cell. BMC Complement Altern Med 2019; 19: 216 [PMID: 31412862 DOI: 10.1186/s12906-019-2615-4]





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