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The Role of the P2X7 Receptor in Cancer Development and Progression

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1. INTRODUCTION

Cancer, a complex and heterogeneous group of diseases, is characterized by the uncontrolled proliferation and spread of abnormal cells. The tumor microenvironment (TME), a dynamic ecosystem surrounding tumor cells, is now recognized as a critical determinant of cancer progression. This intricate milieu comprises cancer cells, immune cells, stromal cells, the extracellular matrix, and a variety of soluble factors, including adenosine triphosphate (ATP)[1].Understanding the molecular interactions within the TME is paramount for the development of effective cancer therapies. Notably, the concentration of ATP in the TME is significantly elevated compared to normal physiological conditions [2]. This abundance of extracellular ATP suggests a prominent role for ATP-sensitive receptors, such as the P2X7 receptor, in the context of cancer biology. The heightened ATP levels in the tumor environment, often resulting from cellular stress, damage, and death associated with rapid tumor growth, can selectively activate receptors with lower ATP affinity, such as P2X7.

The P2X7 receptor is an ATP-gated cation channel belonging to the P2X receptor family [1]. Structurally, it is a trimeric protein composed of subunits each featuring intracellular N- and C-termini, two transmembrane domains, and an extracellular loop that harbors the ATP-binding site [7]. Activation of P2X7 occurs upon binding of high concentrations of extracellular ATP (eATP) [1]. This activation triggers a dual functionality: short-term stimulation leads to the opening of a non-selective cation channel, permitting the influx of sodium (Na+) and calcium (Ca2+) ions and the efflux of potassium (K+) ions, while prolonged stimulation results in the formation of a large, non-selective macropore [1]. In normal physiology, the P2X7 receptor is involved in diverse processes, including neuron-glia signaling within the central nervous system (CNS)[6],

modulation of immune responses[1], regulation of neurotransmitter release[6], and the orchestration of inflammatory responses. The signaling pathways activated by P2X7 involve ion fluxes, the activation of various kinases (e.g., MAPKs, PI3K/Akt), transcription factors (e.g., NF-κB, NFAT), and the assembly of the NLRP3 inflammasome. This dual gating mechanism, where different cellular outcomes are dictated by the duration and concentration of ATP stimulation, suggests a complex role for P2X7 in cancer, a disease where ATP levels can fluctuate considerably within the tumor environment. Cancer cells might exploit these varying ATP levels or manipulate P2X7 function to their advantage [9].

Given the altered expression of P2X7 observed across a spectrum of cancer types and its involvement in fundamental cancer-related processes such as proliferation, apoptosis, migration, invasion, angiogenesis, and immune modulation, the receptor has emerged as a potential diagnostic marker and therapeutic target [2]. This article aims to provide a comprehensive review of the current scientific literature concerning the role of the P2X7 receptor across various types of cancer, with a focus on its molecular mechanisms, therapeutic potential, and the controversies surrounding its involvement[10]..

2. THE P2X7 RECEPTOR: A KEY PLAYER IN CELLULAR PROCESSES

The P2X7 receptor, a member of the P2X family of ATP-gated ion channels, exhibits a unique structure that distinguishes it from its counterparts. Each subunit of the trimeric receptor possesses a dolphin-like architecture, characterized by two transmembrane domains forming the "fluke" and a large extracellular domain representing the "body," along with several loop domains acting as the "head," "dorsal fin," and "flippers"[13]. A distinctive feature of the P2X7 receptor is its long intracellular C-terminus, which constitutes approximately 40% of the entire protein and is considered crucial for its diverse signaling capabilities beyond simple ion channel function [8]. This extended domain serves as a platform for interactions with numerous intracellular proteins, enabling P2X7 to trigger a wider range of downstream effects[14].

Activation of the P2X7 receptor is initiated by the binding of extracellular ATP to sites located between the extracellular loops of the receptor subunits, inducing conformational changes that lead to the opening of the ion channel [7]. Notably, P2X7 exhibits a lower affinity for ATP compared to other P2X receptors, suggesting its role as a detector of high ATP concentrations that are typically present at sites of tissue damage or within the tumor microenvironment [8]. Upon initial activation, P2X7 functions as a non-selective cation channel, allowing the passage of sodium, potassium, and calcium ions across the cell membrane[16]. However, sustained exposure to high concentrations of ATP triggers a time-dependent transition, leading to the formation of a large, non-selective macropore permeable to molecules with a molecular weight up to 900 Da [1]. The long C-terminus of the P2X7 receptor is essential for this macropore formation [2]. The transition from ion channel to macropore provides a mechanism for both subtle signaling changes, mediated by ion fluxes, and drastic cellular events, such as cell death due to the disruption of intracellular homeostasis. This biphasic response enables P2X7 to play diverse roles in cancer, depending on the local ATP concentration and the duration of exposure[17]. The precise mechanism of macropore formation remains a subject of investigation, with hypotheses including pore dilation of the P2X7 channel itself or its interaction with other pore-forming proteins like Pannexin 1[3].

Beyond its ion channel and pore-forming activities, the P2X7 receptor is involved in a wide array of normal physiological functions and signaling pathways. Within the CNS, P2X7 plays a crucial role in neuron-glia communication and the modulation of neurotransmitter release, including monoamines, glutamate, gamma-aminobutyric acid (GABA), and nitric oxide (NO). It is also implicated in neuroplasticity, the brain's ability to adapt and change[6]. In the immune system, P2X7 is a key regulator of immune cell activation, triggering the release of cytokines such as interleukin-1β (IL-1β) and IL-18, activating the inflammasome, and influencing antigen presentation[1]. In other tissues, P2X7 contributes to skin homeostasis [7], pain transduction [2], and various other physiological processes. The signaling pathways downstream of P2X7 activation involve the activation of kinases like MAPK and PI3K/Akt, as well as transcription factors such as NF-κB and NFAT, ultimately leading to diverse cellular responses, including cytokine production, cell proliferation, and apoptosis[1]. P2X7's involvement in both the nervous and immune systems highlights its potential to influence the complex interplay between cancer cells and the host immune response. P2X7 on immune cells can either promote anti-tumor immunity or contribute to tumor-promoting inflammation, depending on the specific context[18].

3. GENERAL INVOLVEMENT OF P2X7 IN CANCER DEVELOPMENT AND PROGRESSION

The P2X7 receptor exhibits altered expression and activity in cancer cells and the tumor microenvironment. Notably, it is frequently upregulated in a wide range of solid and hematological malignancies[20]. The high extracellular ATP concentrations prevalent in the TME are sufficient to activate the P2X7 receptor [2]. This altered expression and the unique conditions of the TME contribute to the multifaceted roles of P2X7 in cancer, with the potential for both pro- and anti-tumorigenic effects depending on the specific context [1]. The consistent upregulation of P2X7 in many cancers suggests a broad role in cancer biology, potentially providing cancer cells with a survival or proliferative advantage in the ATP-rich TME[21].

The P2X7 receptor plays a multifaceted role in cancer development and progression, contributing to tumor growth, metastasis, and influencing the immune response. It can promote tumor growth and survival through its ion channel activity

and the activation of pro-survival signaling pathways[22]. Furthermore, P2X7 contributes to metastasis by promoting cancer cell invasion, migration, and the epithelial-mesenchymal transition (EMT)[25]. The receptor also plays a complex role in the immune response, exhibiting the potential for both anti-tumor immunity and immunosuppression. P2X7 appears to be a central regulator within the TME, influencing not only the behavior of cancer cells but also the surrounding immune and stromal components. This broad influence makes it a compelling, yet potentially challenging, therapeutic target[26]. Initial research has provided insights into the potential of P2X7 as a therapeutic target, with preclinical studies demonstrating anti-tumor effects through the use of both agonists and antagonists. The fact that both agonists and antagonists show promise underscores the complexity of P2X7's role and suggests the need for a nuanced therapeutic approach tailored to the specific cancer type and context[27]. Agonists might be beneficial for inducing cell death via macropore formation in certain cancers, while antagonists could be more effective in blocking pro-tumorigenic signaling in others [2].

4. P2X7'S ROLE IN SPECIFIC CANCER TYPES

4.1. Breast Cancer

In breast cancer, the P2X7 receptor exhibits altered expression patterns, with higher levels observed in tumor tissue compared to adjacent normal tissue [33]. It is also upregulated in several breast cancer malignancies [3], particularly in aggressive basal-like and triple-negative subtypes[33]. Activation of P2X7 by ATP promotes breast cancer cell invasion and migration through the AKT signaling pathway. This process involves the downregulation of E-cadherin, a protein crucial for cell-cell adhesion, and the upregulation of MMP-13, an enzyme involved in extracellular matrix degradation [32]. Furthermore, P2X7 activation induces changes in cell morphology by reorganizing the actin cytoskeleton and promoting the formation of filopodia in triple-negative breast cancer cells. Higher P2RX7 expression has been linked to reduced distant-metastasis free survival, suggesting a role in metastasis. Notably, P2X7 inhibition has been shown to reduce breast cancer-induced osteolytic lesions, indicating implications for bone metastasis. P2X7 activation also facilitates the secretion of extracellular vesicles (EVs) from breast cancer cells, potentially contributing to the formation of a pre-metastatic niche in bone[33]. Therapeutically, blockade of P2X7 has been shown to inhibit the growth of breast cancer in mice via the NLRP3/caspase 1 pathway [23]. The multikinase inhibitor regorafenib reduces P2X7 receptor protein expression and subsequently inhibits VEGF and PI3K/AKT expression, suggesting a potential therapeutic mechanism [34]. Overall, P2X7 appears to primarily promote tumor progression in breast cancer, especially invasion and metastasis, making it a potential target in advanced disease [32].

4.2. Lung Cancer

The P2X7 receptor is expressed at higher levels in lung cancer tissue compared to normal lung tissue [35] and is considered aberrantly expressed in this disease. However, one study reported that overexpression of P2X7R was associated with improved overall survival in non-small cell lung cancer [37], highlighting the complexity of its role. P2X7 plays a critical regulatory function in lung cancer invasion and migration through multiple mechanisms of action and affects the proliferation and apoptosis of cancer cells in the lung. Antagonists of P2X7R can block its function, leading to a significant inhibitory effect on lung cancer cell development and progression [35]. Targeting P2X7R with inhibitors has been shown to effectively suppress the growth and metastasis of lung cancer cells [36]. Furthermore, inhibiting P2X7R has been proposed as a potential targeted therapy for COVID-19-associated lung cancer progression [24]. Mechanistically, P2X7R activation regulates lung cancer cell function by activating multiple intracellular signaling pathways, such as the JNK, Rho, HMGB1-RAGE, and EMT pathways, thereby affecting cell survival, growth, invasion, and metastasis. It can also activate the PI3K/AKT signaling pathway, decrease GSK3b activity, activate Wnt/β-catenin, increase VEGF levels, and increase MMP2 expression, all of which are involved in tumor cell migration and invasion [36]. The role of P2X7 in lung cancer appears intricate, with evidence suggesting a tumor-promoting role [24] alongside a contradictory finding of improved survival with overexpression in a specific context [37]. This discrepancy might stem from different subtypes of lung cancer or the stage of the disease, necessitating further research to clarify its context-dependent involvement[43].

4.3. Colorectal Cancer (CRC)

The P2X7 receptor plays a significant role in promoting colorectal inflammation and tumorigenesis by modulating the gut microbiota and the inflammasome[49]. Persistent activation of P2X7 underlies chronic inflammation and carcinogenic changes in the intestine. Regulatory mechanisms downstream of P2X7, in combination with signals from a dysbiotic microbiota, intensify inflammation and foster the development of colitis-associated CRC [19]. Irregular expression of P2X7 in CRC can indirectly affect its occurrence and development by promoting inflammatory bowel disease, and it can also directly influence the proliferation and metastasis of CRC cells [39]. Overexpression of P2X7 has been correlated with worsened overall survival in CRC patients. Both P2X7R and GLUT-1 may serve as independent prognostic markers and offer new options for targeted therapies in CRC [38]. Mechanistically, P2X7 promotes CRC cell invasion and migration by activating STAT3. It increases the levels of CD31 and VEGF, thereby stimulating tumor angiogenesis through the VEGF-VEGFR signaling pathway. P2X7 also activates PI3K/Akt phosphorylation, upregulates MMP expression, and mediates the

invasion and metastasis of CRC cells. Furthermore, it triggers the expression of cyclin D1, promoting the proliferation of CRC cells by activating the Akt and NF-κB signaling pathways and can modulate EMT [39]. P2X7 also supports tumor cells in resisting unfavorable conditions by stimulating GLUT-1 expression [38]. In essence, P2X7 appears to be significantly involved in the inflammatory processes driving colorectal cancer[19], and its overexpression is associated with a poorer prognosis [38], suggesting that targeting P2X7 in CRC might be a beneficial therapeutic strategy, particularly in the context of inflammation-driven tumorigenesis[51].

4.4. Melanoma

In melanoma, the P2X7 receptor is overexpressed in metastatic malignant melanoma, and its expression closely correlates with reduced overall survival [4]. Antagonism of melanoma cell-expressed P2X7 receptor inhibits in vitro anchorage-independent growth and migration, as well as in vivo dissemination and lung metastasis formation [40]. Stimulation of P2X7 triggers the release of miRNA-containing microvesicles and exosomes from melanoma cells, profoundly altering their miRNA content, size, and quantity, and promoting growth or migration [4]. In P2X7 null mice bearing melanoma, a decrease in pro-inflammatory cytokines (IL1-β, TNF-α, IL-6, IL-12, IL-17, IFN-γ) and an increase in the immunosuppressive cytokine TGF-β were observed, along with an upregulation of tumor-associated and splenic A2AR, suggesting a novel correlation between P2X7R and A2AR in oncogenesis [28]. Host P2X7R expression is critical for supporting an anti-tumor immune response and restricting tumor growth and metastatic diffusion [29]. Additionally, a P2X7 receptor antagonist has been shown to enhance radiation-induced cytotoxicity in melanoma cells both in vitro and in vivo [41]. Thus, in melanoma, P2X7 appears to be a key driver of metastasis and significantly influences the tumor-immune microenvironment, indicating that targeting P2X7 could be a promising strategy to inhibit melanoma progression and potentially enhance the efficacy of other therapies like radiation and immunotherapy [1].

4.5. Leukemia

The P2X7 receptor exhibits high expression levels in acute myeloid leukemia (AML) and chronic lymphocytic leukemia (CLL), while its expression is lower in acute B-cell lymphoblastic leukemia (B-ALL) and chronic myelogenous leukemia (CML) compared to normal controls [44]. High-level expression of P2X7 has also been reported in leukemia patients, particularly in relapsed cases, and is upregulated in lymphocytes from patients with aggressive variants of B-CLL [30]. High ATP levels have been shown to exert direct cytotoxic effects on several leukemia cell types by activating P2X7R. Specifically, P2X7R activation with high-dose ATP induces apoptosis in AML blast cells and leukemic stem/progenitor cells [42]. P2X7 promotes the progression of MLL-AF9 induced AML by upregulating Pbx3, thereby promoting cell proliferation and increasing leukemia stem cell levels [44]. Therapeutically, P2X7 antagonists or silencing can reduce AML growth in vivo. The ATP/P2X7 axis is recognized as a crucial regulator of leukemic initiating cell proliferation and homing, representing an emerging therapeutic target in AML[46]. Therefore, P2X7 plays a complex role in leukemia, with evidence suggesting both pro- and anti-leukemic effects depending on the ATP concentration and the specific leukemia subtype[56]. High ATP might induce cell death through P2X7, whereas in other contexts, P2X7 promotes proliferation and disease progression. This duality requires careful consideration when considering P2X7 as a therapeutic target in leukemia [30].

4.6. Other Cancer Types

In prostate cancer, P2X7 promotes cell growth by increasing calcium influx or through mitochondrial involvement[11]. It is involved in invasiveness and metastasis through the PI3K/Akt and ERK1/2 signaling pathways and by influencing specific EMT/invasion-related genes. P2X7 may also aid in the early detection of prostate cancer and represents a potential therapeutic target[47]. A genetic interaction between P2X7 and VEGFR-2 polymorphisms has been associated with overall survival in prostate cancer patients [70]. Downregulation of P2X7 reduces HIF-1α and VEGF levels, thereby inhibiting angiogenesis. Overall, P2X7 appears to be largely pro-tumorigenic in prostate cancer [11], promoting growth, invasion, and angiogenesis.

In ovarian cancer, P2X7 exhibits higher expression in metastatic tissues[60]. It promotes cell migration and maintains a mesenchymal phenotype, contributing to the aggressive nature of the disease. The ATP/P2X7 axis is a regulatory axis of migration in ovarian carcinoma-derived cells, making P2X7 a potential drug target for inhibiting migration and invasion. Thus, P2X7 seems to play a significant role in promoting the aggressive, metastatic phenotype of ovarian cancer [50].

In pancreatic cancer, activation of P2X7 increases proliferation of cancer cells via the ERK1/2 and JNK pathways [48]. P2X7 is expressed in both pancreatic cancer cells and pancreatic stellate cells (PSCs) [53]. It is involved in IL-6 release from PSCs, which subsequently promotes cancer cell migration [54]. P2X7 can support both survival and death in PSCs [55]. However, P2X7R inhibition failed to show chemopreventive effects in a mouse model of pancreatic cancer [57]. The role of P2X7 in pancreatic cancer is complex, with evidence for promoting proliferation and influencing the tumor microenvironment through stellate cell interactions, but its therapeutic targeting might be challenging [48].

In glioma, stimulation of P2X7 boosts cell proliferation and increases cell viability[62]. It also promotes cell adhesion, mitochondria depolarization, and reactive oxygen species overproduction. P2X7 influences glioma tumor growth in vivo via

the activation of pro-survival signaling pathways and ATP release [59]. It may promote the growth of glioblastoma multiforme (GBM) [58]. Stimulation of glioblastoma stem cells (GSCs) leads to changes in the proteome of extracellular vesicles, potentially increasing the aggressiveness of the tumor [61]. Generally, P2X7 appears to promote glioma growth and aggressiveness [58], making it a potential therapeutic target in this cancer type[63].

5. MOLECULAR MECHANISMS UNDERLYING P2X7'S INFLUENCE ON CANCER

The P2X7 receptor exerts its influence on cancer through a variety of molecular mechanisms, significantly impacting inflammation, immune cell dynamics, and fundamental cancer cell behaviors[64]. A key mechanism involves the activation of the NLRP3 inflammasome, a multiprotein complex that leads to the maturation and release of pro-inflammatory cytokines such as IL-1β and IL-18. This inflammatory signaling can have both tumor-promoting and tumor-suppressing effects depending on the specific cytokines and immune cells involved, highlighting the context-dependent nature of P2X7's role[65]. P2X7 also modulates the recruitment and polarization of immune cells within the TME, influencing processes such as dendritic cell maturation, T helper cell differentiation, and the function of myeloid-derived suppressor cells (MDSCs) [3]. Activation of P2X7 can lead to the release of various pro-inflammatory mediators and growth factors [7], as well as influencing the production of a wide range of cytokines and chemokines that shape the tumor microenvironment [5].

Beyond its role in inflammation and immunity, P2X7 significantly impacts cancer cell proliferation, apoptosis, and angiogenesis. It promotes proliferation through the activation of several signaling pathways, including ERK1/2, JNK, PI3K/Akt, NFATc1, and others [5]. Conversely, prolonged activation of P2X7 can induce apoptosis through macropore formation, caspase activation, and the induction of mitochondrial stress [1]. P2X7 also contributes to angiogenesis, the formation of new blood vessels, by increasing the production of vascular endothelial growth factor (VEGF) and activating hypoxia-inducible factor-1α (HIF-1α) signaling.[5] The ability of P2X7 to both promote proliferation and induce apoptosis highlights the critical role of its activation state, determined by ATP concentration and duration of exposure, in dictating its net effect on cancer cells. Cancer cells might develop mechanisms to evade P2X7-mediated apoptosis by modulating receptor signaling or the local ATP concentration.

Furthermore, P2X7 is involved in other crucial cancer-related processes such as metabolic reprogramming and epithelial-mesenchymal transition (EMT). It participates in metabolic reprogramming by affecting mitochondrial function, glycolysis, glycogen storage, and oxidative phosphorylation, enabling cancer cells to adapt to the nutrient-poor conditions within tumors[31]. P2X7 also induces EMT, a process that allows cancer cells to become more mobile and invasive, by regulating the expression of E-cadherin, matrix metalloproteinases (MMPs), Snail, and other EMT-related proteins [5]. Additionally, P2X7 influences the maintenance of cancer stem cells, a subpopulation of cancer cells with self-renewal and differentiation capabilities that contribute to tumor initiation, progression, and recurrence. The involvement of P2X7 in metabolic reprogramming and EMT further solidifies its role as a key player in cancer progression beyond just proliferation and survival, as these processes are critical for metastasis, drug resistance, and tumor recurrence, making P2X7 a potentially valuable target to disrupt these aspects of cancer[31].

6. TARGETING THE P2X7 RECEPTOR: THERAPEUTIC POTENTIAL AND CHALLENGES

Research has extensively investigated the effects of targeting the P2X7 receptor using both agonists and antagonists in preclinical cancer models. In some cancers, such as leukemia and pancreatic cancer, P2X7 agonists like high concentrations of ATP or its analog BzATP have shown the ability to induce cell death. Conversely, P2X7 antagonists, including compounds such as A438079, AZD9056, BBG, and oxidized ATP, have demonstrated promise in inhibiting tumor growth, metastasis, and inflammation across various preclinical models of cancers like breast, lung, colorectal, melanoma, leukemia, glioma, and pancreatic cancer. These preclinical findings strongly suggest the therapeutic potential of targeting P2X7. However, the choice between using agonists and antagonists appears to be highly dependent on the specific cancer type and the desired therapeutic outcome, whether it's direct cytotoxicity or blocking pro-tumorigenic signaling pathways. A personalized therapeutic approach might be necessary, given the dual roles of P2X7 in cancer [2].

Despite the encouraging results from preclinical studies, relatively few P2X7R modulators have progressed to clinical testing in cancer patients [15]. Some antagonists, such as BIL010t and BIL06v, have been evaluated in Phase 1 clinical trials for cancer [68]. Notably, early clinical trials of P2X7R-targeted therapies for inflammatory diseases yielded unsatisfactory results, which has somewhat reduced the interest of the pharmaceutical and biotechnology industries in pursuing their clinical development for other indications, including cancer [70]. This limited progress in clinical trials suggests potential challenges in translating the success observed in preclinical models to human efficacy. These challenges could arise from various factors, including drug delivery limitations, off-target effects of the modulators, or the inherent complexity of P2X7's role in different cancer types and stages in humans.

Developing effective P2X7-targeted cancer treatments requires careful consideration of the dual role of the receptor, necessitating a tailored therapeutic strategy based on the specific cancer type and context [1]. Future research should focus on the development of highly selective and potent P2X7 modulators with favorable pharmacokinetic and pharmacodynamic

properties [12]. It is also crucial to gain a deeper understanding of the role of different P2X7 splice variants and genetic polymorphisms in cancer susceptibility and treatment response. The potential for combination therapies that target P2X7 along with other anticancer agents or immunotherapies also warrants further exploration. Finally, research into the development of P2X7-targeted diagnostics and biomarkers could aid in patient stratification and monitoring of treatment response, ultimately guiding the clinical application of P2X7-targeted therapies [2].

7. CONTRADICTORY FINDINGS AND CONTROVERSIES IN P2X7 RESEARCH

The research landscape concerning the role of the P2X7 receptor in cancer is marked by several contradictory findings and ongoing debates, highlighting the complexity and context-dependent nature of its involvement. For instance, studies have described opposing roles for P2X7R in regulating immune responses against tumors, with some suggesting a promotion of anti-tumor immunity while others indicate a contribution to immunosuppression [15]. In the context of glioma, conflicting data exist regarding the effect of P2X7R blockade on tumor growth, with some studies reporting inhibition and others showing increased growth [58]. Furthermore, the P2X7 receptor itself is recognized as having both pro- and anti-tumor potential, depending on the specific cellular context and experimental conditions [1]. Notably, one study in non-small cell lung cancer found that overexpression of P2X7R was associated with improved overall survival, a result that seemingly contradicts findings in other cancer types where P2X7 upregulation often correlates with poorer prognosis [37]. These discrepancies likely arise from a multitude of factors. Variations in experimental models, including in vitro versus in vivo studies and the use of different cell lines and animal models, can contribute to divergent results. The inherent heterogeneity of cancer, with its diverse subtypes and specific molecular profiles, is another significant factor. The existence of multiple P2X7 splice variants, each with potentially differing functions, adds another layer of complexity. The composition of the tumor microenvironment and the specific concentrations and durations of ATP exposure can also influence P2X7 signaling and its downstream effects. Finally, genetic polymorphisms within the *P2RX7* gene, which can affect receptor function, might contribute to the variability observed in different studies and patient populations [2]. Addressing these complexities through well-designed studies that account for these variables will be crucial for a more unified understanding of P2X7's role in cancer.

8. CONCLUSION: CURRENT UNDERSTANDING AND FUTURE PERSPECTIVES

The current understanding of the P2X7 receptor's involvement in cancer reveals a complex and multifaceted landscape. Frequently overexpressed across a wide spectrum of cancers, P2X7 plays a significant role in various aspects of cancer progression, including cell proliferation, survival, invasion, migration, metastasis, angiogenesis, and the modulation of the immune response. The receptor exhibits a dual nature, demonstrating both pro- and anti-tumorigenic potential depending on the specific cellular and microenvironmental context. While P2X7's influence can vary considerably across different cancer types, its frequent upregulation and involvement in key oncogenic processes highlight its importance in cancer biology[66].

Future research on P2X7 in cancer should focus on elucidating its precise roles in specific cancer subtypes and stages to inform targeted therapeutic strategies. The development of highly selective and effective P2X7 agonists and antagonists is crucial for translating preclinical promise into clinical success[67]. Further investigation into P2X7 as a potential diagnostic and prognostic biomarker could aid in patient stratification and treatment monitoring. Exploring combination therapies that target P2X7 in conjunction with other anticancer treatments, including immunotherapies, holds significant potential. Understanding the functional implications of different P2X7 splice variants and genetic polymorphisms in cancer susceptibility and treatment response is also essential. Ultimately, well-designed clinical trials are needed to evaluate the efficacy and safety of P2X7 modulators in cancer patients, paving the way for new therapeutic interventions that leverage the complex role of this receptor in the fight against cancer[69].

Table: Summary of P2X7 Receptor Involvement in Different Cancer Types

Cancer Type	P2X7 Expression	Main Effects on Cancer Cells	Role in Tumor Microenvironment	Therapeutic Potential
Breast Cancer	Upregulated	Promotes invasion, migration (via AKT), downregulates E-cadherin, upregulates MMP-13, induces morphological changes, linked to bone metastasis, facilitates EV	Influences pre-metastatic niche formation in bone.	P2X7 blockade inhibits growth (NLRP3/caspase 1), regorafenib reduces expression, potential therapeutic target.

		secretion.		
Lung Cancer	Upregulated	Regulates invasion, migration, proliferation, apoptosis (complex), activates JNK, Rho, HMGB1-RAGE, EMT, PI3K/AKT, increases VEGF, MMP2.		P2X7R antagonists inhibit growth and metastasis, potential for COVID-19-associated progression.
Colorectal Cancer	Upregulated	Promotes inflammation, tumorigenesis, invasion, migration (via STAT3), increases CD31, VEGF, upregulates MMP, cyclin D1, modulates EMT, stimulates GLUT-1.	Modulates gut microbiota, activates inflammasome.	Biomarker, potential therapeutic target, antagonists inhibit growth, metastasis.
Melanoma	Upregulated	Promotes metastatic spreading, inhibits anchorage-independent growth, migration, dissemination, lung metastasis, triggers miRNA-containing EV release, enhances radiosensitivity.	Influences immune response (decreases pro-inflammatory cytokines, increases TGF-β, upregulates A2AR), host P2X7R critical for anti-tumor immunity.	P2X7 antagonism inhibits growth and metastasis, potential for combination with radiation and immunotherapy.
Leukemia	Variable	High ATP induces apoptosis (AML, LSCs), promotes proliferation (MLL-AF9), increases LSC levels, upregulates Pbx3.		P2X7 antagonists/silencing reduce AML growth, ATP/P2X7 axis therapeutic target in AML.
Prostate Cancer	Upregulated	Promotes cell growth (Ca^{2+} influx, mitochondria), invasiveness, metastasis (PI3K/Akt, ERK1/2, EMT genes), increases VEGF, reduces apoptosis in CRPC.		Potential therapeutic target, statins may counteract effects, aids in early detection.
Ovarian Cancer	Upregulated	Promotes cell migration, maintains mesenchymal phenotype, increases migration via BzATP, decreases with antagonists, knockout reduces migration, in vivo inhibition impedes tumor growth/displacement.		Potential drug target for migration/invasion.

Pancreatic Cancer	Upregulated	Increases proliferation (ERK1/2, JNK), involved in IL-6 release from stellate cells (promotes migration), supports both life and death in stellate cells.	Influences tumor microenvironment through stellate cell interactions.	P2 receptor antagonist reduces proliferation, P2X7R inhibition in vivo showed mixed results.
Glioma	Upregulated	Boosts proliferation, increases viability, promotes cell adhesion, mitochondria depolarization, ROS overproduction, influences tumor growth in vivo (pro-survival), may promote GBM growth, stimulation of GSCs changes EV proteome (increased aggressiveness).	Shapes tumor microenvironment through inflammation markers, EMT components, eATP release.	Potential therapeutic target, P2X7 antagonist inhibits tumor development in vivo.

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