P2X7 receptor: An emerging therapeutic target in acute myeloid leukemia (Review)

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Abstract. The P2X7 receptor (P2X7R) is a ligand-gated ion channel that exhibits bifunctional properties, switching between a cation-permeable channel and a large cytolytic pore. In acute myeloid leukemia (AML), P2X7R is aberrantly overexpressed, particularly in leukemia stem cells (LSCs) and AML blasts. Within the bone marrow niche of AML, P2X7R binding by extracellular adenosine triphosphate not only contributes to a profound immunosuppressive niche that protects the AML cells from immune surveillance, but also drives LSC proliferation, survival, homing, and self-renewal through downstream signaling cascades, including the cAMP response element-binding protein/phosphoglycerate dehydrogenase/serine metabolic axis, PBX homeobox 3, Wnt/β-catenin, and c-Myc. Elevated P2X7R expression is associated with poor prognosis, chemoresistance, and disease recurrence of AML. The central role of P2X7R in AML pathophysiology makes it a potential biomarker for prognostic stratification and a promising therapeutic target. Several targeting strategies are currently under investigation, including the small molecule antagonists and specific anti-P2X7R antibodies. Furthermore, a therapeutic approach involves combining P2X7R inhibition with conventional chemotherapy. In conclusion, targeting the P2X7R pathway represents a potential novel and multi-faceted strategy to improve outcomes for patients with AML by remodeling its protective microenvironment and directly attacking the leukemia cells.

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Contents

1. Introduction

Acute myeloid meukemia (AML) is an aggressive, heterogeneous malignancy defined by the clonal expansion of immature myeloid blasts. Despite therapeutic advances, relapse remains a huge challenge due to a reservoir of therapy-resistant leukemic stem cells (LSCs) (1-3). The bone marrow (BM) microenvironment, or niche, plays a crucial role in nurturing these LSCs and promoting chemoresistance (4).

Purinergic signaling, mediated by extracellular nucleotides such as adenosine triphosphate (ATP) and their receptors (P2X and P2Y families), is increasingly recognized as a key regulator within the BM niche. Among these receptors, P2X7 receptor (P2X7R) is particularly notable due to its high sensitivity to elevated extracellular adenosine triphosphate (eATP), a common feature of tumor microenvironments (TME). As a ligand-gated ion channel, its activation induces rapid Na^+ and Ca^{2+} influx and K^+ efflux, which promote cancer cell proliferation and migration (5,6). Beyond the formation of non-selective ion channel pores, P2X7R can form macropores in the cell membrane, particularly under sustained high

eATP concentrations. The formation of these macropores permits the passage of large molecules and ultimately results in cell death (6). The dual nature of P2X7R, facilitating both pro-tumorigenic responses and cell death, is often critically dysregulated in cancers.

P2X7R is highly expressed on hematopoietic cells, where it functions as a key sensor of eATP, a ubiquitous 'danger signal' released during cellular stress, injury, or death. The role of P2X7R in hematopoiesis and immune regulation is multifaceted and context-dependent. In hematopoietic stem and progenitor cells (HSPCs), P2X7R signaling influences survival, proliferation, and differentiation (7). In mature immune cells, the effects of P2X7R activation are diverse. P2X7R activation modulates macrophage polarization, enhances inflammatory responses, and promotes antigen presentation (8,9). In dendritic cells (DCs), it promotes cell maturation, proinflammatory cytokine release, and antigen presentation (10). In addition, it can mediate cluster of differentiation (CD)8^+ T-cell activation and apoptosis (11).

In AML, the concentration of eATP is significantly higher in the endosteal niche than in the vascular niche. Moreover, LSCs preferentially localize to the endosteal region, a distribution characteristic that provides crucial support for maintaining the functional activity of LSCs (12). P2X7R is frequently overexpressed on LSCs and AML blasts (13), which constitute the self-renewing population responsible for disease initiation, relapse, and chemoresistance. Within the unique BM niche of AML, elevated eATP provides a persistent activation signal for P2X7R. This signaling contributes to the maintenance of LSCs, and supports the survival and proliferation of AML blasts (5,12). Furthermore, by regulating the metabolic status of LSCs, the P2X7R signaling pathway modulates their homing and self-renewal, thereby driving disease progression (12).

Given the central role in AML pathophysiology, P2X7R has emerged as a promising biomarker for prognosis and a potential therapeutic target. Small-molecule antagonists that block the ATP-binding site to inhibit downstream signaling, and anti-P2X7R antibodies that specifically eliminate P2X7R-expressing leukemia cells, have been designed and are under investigation (7,13,14). The other promising avenue may involve combining P2X7R inhibitors with conventional chemotherapy (15). However, P2X7R targeted therapy is still in the early research stage. It is speculated that the main reason is the failure to achieve ideal therapeutic effects and ensure the *in vivo* safety, indicating that further exploration and improvement are still needed.

While recent reviews have discussed eATP and P2X7R signaling across various cancers, the present review systematically and comprehensively summarizes the roles of eATP and P2X7R in AML, including the context-dependent duality of P2X7R in hematopoietic cells, LSCs, and AML blasts, and the potential for targeting P2X7R in AML therapy.

2. Structure and function of P2X7R

Structure of P2X7R. Human P2X7R is encoded by the *P2X7R* gene located at chromosome 12q24.31. It typically assembles as a homotrimer of three identical subunits, although heterotrimeric assemblies also exist (16-20). Each subunit comprises ~595 amino acids, contains a short intracellular N-terminus (26 amino acids), two transmembrane helices (~24 amino acids each), a large extracellular ligand-binding loop (282 amino acids), and a characteristically long intracellular C-terminal tail. P2X7R possesses the longest C-terminal intracellular domain (239 amino acids) among all the P2X family members and mediates a bifunctional response on stimulation (21,22). The 'dolphin anatomy' is commonly adopted to identify specific regions in the tertiary structure of P2X subunits and to describe P2X7R architecture. Each subunit resembles the shape of a dolphin, with the transmembrane helices corresponding to the flukes and the extracellular region forming the body (Fig. 1) (21).

Dual functional characteristics of P2X7R. Differences in ATP concentration and duration of action can switch P2X7R between ion channel and large-pore conformations, thereby mediating the dual biological effects of cell survival or cell death. Receptor activation initiates when a low concentration of ATP ligand (≥100 μM, sub-millimolar range) binds to the orthosteric site of P2X7R (11) or non-nucleotide agonists engage allosteric sites. Ligand binding induces conformational changes within the extracellular domain that propagate to the transmembrane helices (23). This rearrangement specifically alters the position of the second transmembrane helices (TM2), widening the central pore to permit rapid cation flux (Na^+ and Ca^{2+} influx, K^+ efflux) within milliseconds, representing its canonical ion channel function (Fig. 1) (24). Among these, the calcium channel activity of P2X7R plays a central role in promoting proliferation (6). Sustained activation, particularly under high concentrations of eATP (≥0.3-0.5 mM) (23), induces a conformational change in P2X7R, and the ion channel gradually transforms into large membrane pores (25,26). This large conductance pore permits the passage of molecules up to ~900 Da (27,28), mediating cell death by disrupting intracellular homeostasis and inducing necrotic cell lysis (6). The extended C-terminal tail is indispensable for this pore dilation (21,29), likely through interactions with membrane lipids (such as phosphatidylinositol 4,5-bisphosphate (PIP_2)] and cytosolic proteins that relay conformational signals. However, the precise mechanism of macropore formation remains actively debated, potentially involving: i) Intrinsic dilation of the P2X7R pore itself; ii) recruitment of an accessory protein (such as pannexin-1 hemichannels) to form the conduit; or iii) oligomerization of additional P2X7R subunits (30).

Differences in P2X7R variants also play an important role in regulating its function. Human P2X7R exhibits significant polymorphism, with at least nine splice variants identified. The full-length variant (P2X7RA) requires its intact C-terminus for macropore function, as truncation abolishes large solute uptake. P2X7RB, a common splice variant lacking the final 249 C-terminal amino acids, retains ion channel capability but cannot form functional macropores independently (Fig. 1) (31-36). This is mainly manifested in AML as distinct sensitivity to daunorubicin (DNR). AML blasts with high P2X7RA expression are more prone to cell death upon exposure to DNR due to its large pore formation. By contrast, cells highly expressing P2X7RB can only form ion channels, leading to strong cell viability and even resistance to the cytotoxic effect of DNR (37). Notably, co-expression of P2X7RB with P2X7RA generates heterotrimers that exhibit enhanced ATP affinity, amplified macropore activity, and increased

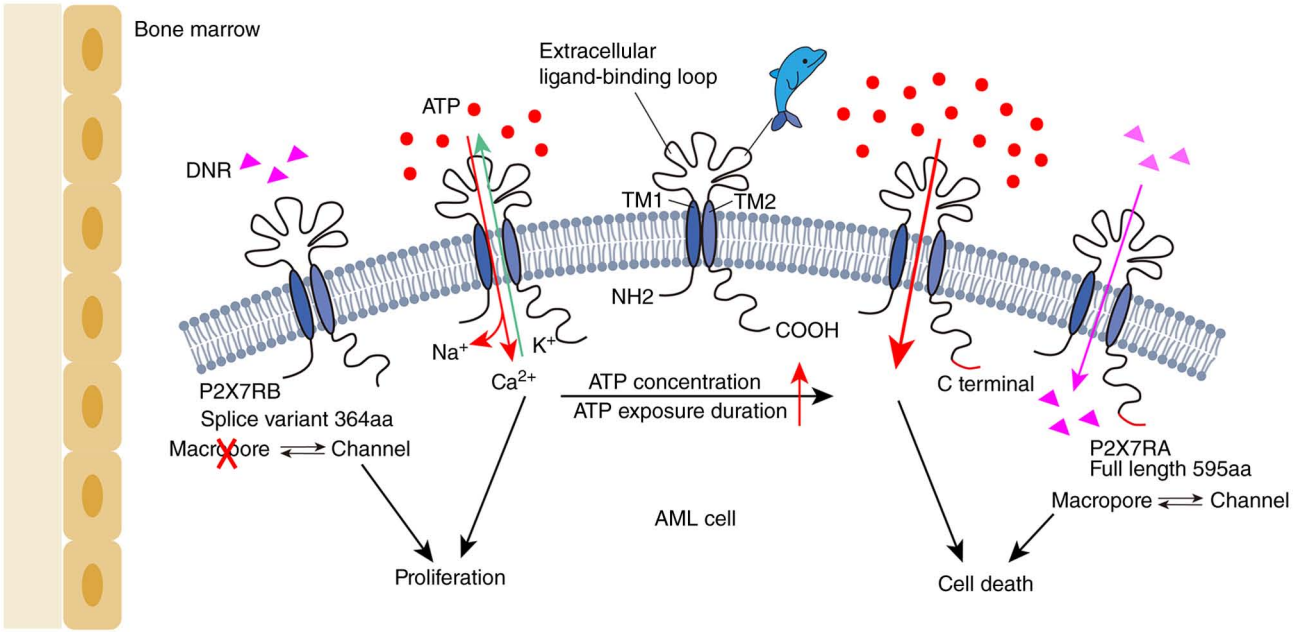

Figure 1. Structure and function of P2X7R. P2X7R presents a typical dolphin-like structural conformation (21). Low concentrations of ATP stimulation rapidly open P2X7R as an ion channel, while sustained activation, particularly under high concentrations of eATP, gradually opens macropores (24-26). In AML, the full-length of P2X7RA mediates both ion channel activation and macropore formation, while the P2X7RB variant only retains basic channel activity due to the lack of the C-terminal domain. The macropores formed by P2X7RA permit the passage of DNR, thereby promoting the chemosensitivity of AML cells (37). P2X7R, P2X7 receptor; ATP, adenosine triphosphate; eATP, extracellular adenosine triphosphate; AML, acute myeloid leukemia; DNR, daunorubicin; TM2, second transmembrane helices.

support for cellular energy metabolism and proliferation compared with P2X7RA homotrimers (23).

Another variant, nfP2X7R (potentially arising from alternative splicing or mutations), primarily resides intracellularly but translocates to the plasma membrane under high eATP conditions. Similar to P2X7RB, nfP2X7R functions as a small ion channel that promotes tumor survival and proliferation but lacks ethidium-permeable macropore capability. Under stimulation by high concentrations of eATP in the TME, nfP2X7R expression is upregulated while the expression of functional P2X7R is downregulated, thereby protecting tumor cells (38). These variant-specific functional differences highlight the complex regulation of P2X7R in physiological and disease conditions.

The human *P2X7R* gene also exhibits a high degree of polymorphism. Notably, >13,000 single nucleotide polymorphisms (SNPs) associated with *P2X7R* have been identified in the human genome (39). These SNPs can affect receptor function by causing amino acid substitutions or altering the eATP-binding sites, ultimately leading to the loss of the original channel function or large-pore function of P2X7R (40-42). Previous research on *P2X7R* SNPs in leukemia has mainly focused on chronic lymphocytic leukemia (CLL). Researchers analyzed the 1513 A>C polymorphism in populations of different geographic origins, but no association between this SNP and the progression of CLL was found (39).

Dynamic alterations in the TME, particularly eATP fluctuations induced by chemotherapy, can directly regulate the activation of P2X7R. In AML, certain chemotherapeutic agents, such as DNR, can induce immunogenic cell death of cancer cells, thereby triggering effective antitumor T-cell immune responses (43). The eATP then acts on P2X7R to further activate downstream signaling pathways.

3. Expression and function of P2X7R in hematopoietic cells in AML

P2X7R is widely expressed in human hematopoietic cells, encompassing HSPCs as well as differentiated lineages such as monocytes/macrophages, DCs, and lymphocytes (8,44). Its function exhibits significanT cell specificity and context dependence, especially in AML (Fig. 2).

P2X7R and HSPCs in AML. HSPCs in AML display multiple abnormalities, including suppression of normal hematopoiesis, disrupted phenotypic differentiation, epigenetic and metabolic reprogramming, and drug resistance, giving rise to a unique subset of HSPC-like LSCs (45,46). Additionally, HSPCs in AML show enhanced mitochondrial function, imbalanced fatty acid oxidation and glycolysis, and reduced ROS levels. Aberrant activation of stemness-related pathways in HSPCs mediates chemotherapy resistance and relapse of AML (47).

P2X7R plays an important role in regulating the functions of HSPCs (Fig. 2A). P2X7R facilitates the mobilization of HSPCs. Upon P2X7R activation by ATP, the NLR family pyrin domain-containing 3 (NLRP3) inflammasome is assembled and activated, leading to the release of pro-inflammatory cytokines such as interleukin (IL)-1β and IL-18, which in turn trigger complement system activation, thereby promoting the egress and mobilization of BM-derived stem and progenitor cells into the peripheral blood. In *P2x7r*$^{-/-}$ mice, granulocyte colony-stimulating factor (CSF)-triggered mobilization of HSPCs is notably impaired (48). Overexpression of P2X7R also impaired the colony-forming ability of HSPCs *in vitro*. In addition, HSPCs with P2X7R overexpression exhibited a significant

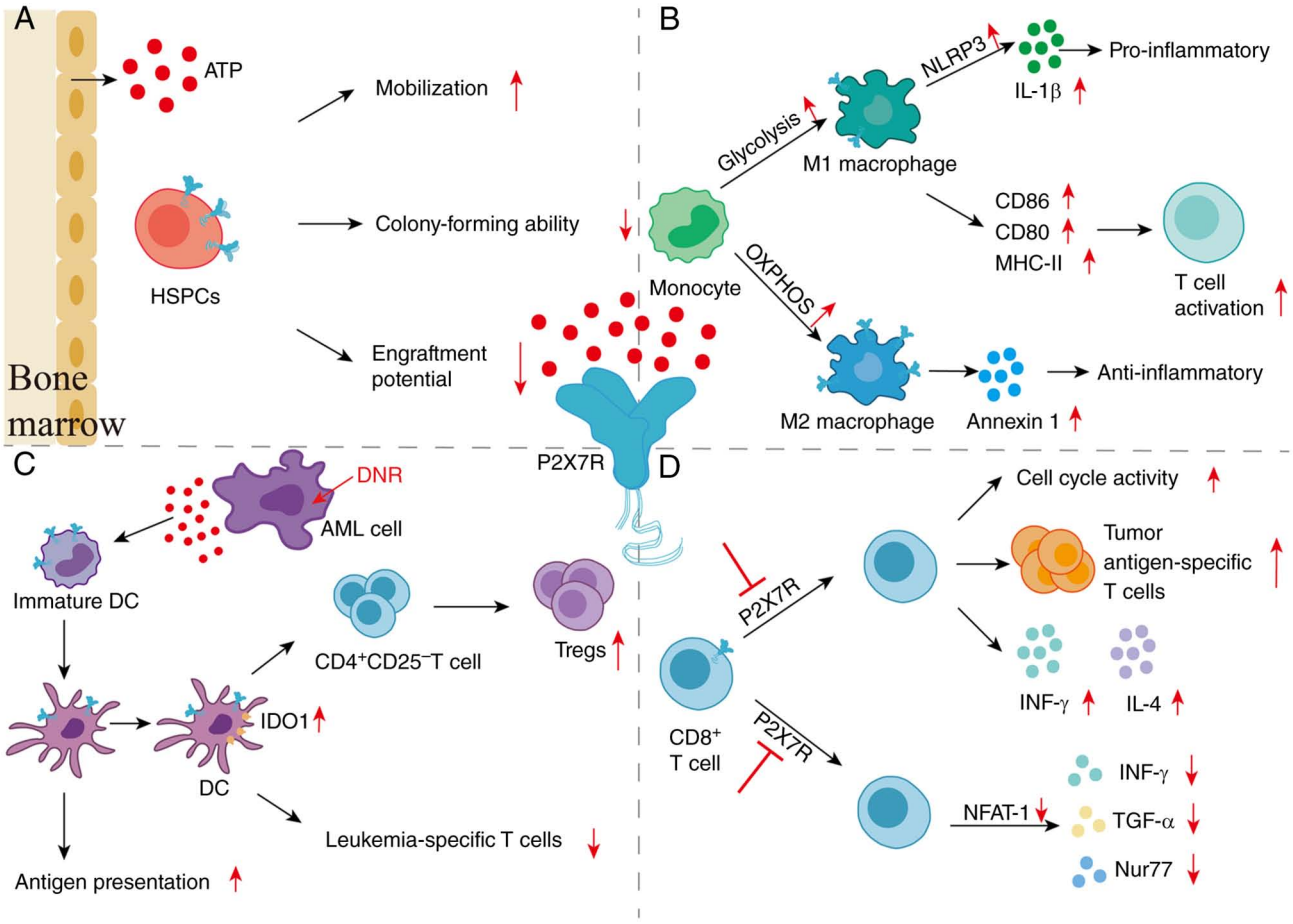

Figure 2. Effects of P2X7R on HSPCs, macrophages, DCs, and $CD8^+$ T cells in the BM niche of AML. (A) ATP released into the BM niche of AML activates P2X7R on HSPCs, promoting mobilization, inhibiting colony-forming ability and engraftment potential (49). (B) P2X7R activation drives monocyte differentiation into M1 macrophages by enhancing glycolysis, while promoting differentiation into immunosuppressive M2 macrophages through enhancement of OXPHOS (53). (C) DNR induces apoptosis of AML cells and triggers substantial ATP release, thereby facilitating DC maturation and enhancing antigen presentation. Elevated eATP upregulates IDO-1 expression in DCs, which promotes the differentiation of $CD4^+CD25^-$ T cells into Tregs, and restrains the immune response of leukemia-specific T cells (43). (D) In $CD8^+$ T cells, P2X7R inhibition enhances T-cell function by promoting cell cycle activity, tumor antigen-specific T cells, and secretion of IFN-γ and IL-4 (64-66). On the other hand, P2X7R inhibition inhibits T-cell activity via the downregulation of NFAT-1, which in turn reduces the secretion of IFN-γ, TGF-α and Nur77 (66). P2X7R, P2X7 receptor; HSPCs, hematopoietic stem and progenitor cells; DCs, dendritic cells; BM, bone marrow; AML, acute myeloid leukemia; ATP, adenosine triphosphate; OXPHOS, oxidative phosphorylation; DNR, daunorubicin; eATP, extracellular adenosine triphosphate; IDO-1, indoleamine 2,3-dioxygenase 1; Tregs, regulatory T cells; IFN-γ, interferon-γ; IL-4, interleukin 4; NFAT-1, nuclear factor of activated T cells 1; TGF-α, transforming growth factor-α.

reduction in their engraftment potential (49). P2X7R also plays an important role in HSPC response to acute genotoxic stress. Under such stressful conditions, P2X7R is a direct transcriptional target of p53 in HSPCs. The expression of P2X7R in HSPCs is upregulated through a p53-dependent mechanism after whole-body irradiation. *P2x7r* deficiency was shown not only to significantly prolong the survival of mice with irradiation-induced hematopoietic failure but also to enhance regenerative capacity (50). These findings suggest that abnormal enhanced P2X7R signaling on HSPCs in AML may persistently suppress normal hematopoiesis and exacerbate BM failure. Under genotoxic stress such as chemotherapy, P2X7R was shown to further impair HSPC regenerative potential and worsen therapy-related myelosuppression and hematopoietic reconstitution defects.

P2X7R and macrophages in AML. The expression level of P2X7R in human monocytes and monocyte-derived macrophages is significantly higher than in other immune cells. P2X7R is the most abundant purinergic receptor in macrophages, with an expression rate of ~90%. Furthermore, P2X7R expression on monocytes is 4-5 times higher than on B cells, T cells, and NKT cells, and its intracellular expression level of P2X7R is much higher than that on the cell surface (51).

P2X7R was found to be involved in macrophage function and polarization (Fig. 2B). Immediate stimulation with ATP or the P2X7R agonist benzoylbenzoyl-ATP reduced C-C motif chemokine ligand 18 release in a dose-dependent manner, whereas delayed stimulation had no such effect (52). P2X7R has also been shown to modulate macrophage polarization by influencing both oxidative phosphorylation and glycolysis. Enhanced oxidative metabolism was demonstrated to support M2 differentiation, while increased glycolytic activity was reported to promote M1 polarization (53). In M1 macrophages, P2X7R was revealed to promote pro-inflammatory responses (9,54-56), which were shown to exhibit antitumor effects by mediating the activation

of the NLRP3 inflammasome, releasing IL-1β, and inducing pyroptosis (57). In M2 macrophages, P2X7R was observed to stimulate the secretion of anti-inflammatory mediators such as Annexin 1 (9).

Macrophages in AML were shown to be reprogrammed into an M2-like pro-leukemic phenotype through the CSF-1/IL-10/STAT3 axis, accompanied by increased expression of CD163 and CD206, which was observed to be correlated with poor prognosis and chemotherapy resistance (58). M2-like alternatively activated macrophages were shown to be markedly enriched in the BM of patients with AML, and their high infiltration was associated with enhanced stemness of LSCs and chemoresistance. Experiments have validated that M2 macrophages directly promote leukemia progression *in vitro* and *in vivo* (59). Furthermore, M2 macrophages have been shown to sustain LSC survival via IL-10/TGF-β secretion and modulation of angiogenesis (60). The role of P2X7R in M2 macrophage function was demonstrated to further contribute to leukemia development by enhancing the immunosuppressive effects of M2-like macrophages within the BM microenvironment in AML.

In the AML BM niche, the high expression of P2X7R on monocytes and macrophages, together with its role in modulating M2 polarization, may promote the reprogramming of tumor-associated macrophages toward a pro-leukemic M2-like phenotype. By enhancing the immunosuppressive functions of M2-like macrophages, P2X7R has been shown to contribute to the survival of LSCs, chemoresistance, and leukemia progression, making it a potential immunotherapeutic target within the AML BM microenvironment.

P2X7R and DCs in AML. Extracellular ATP was shown to promote DC maturation by activating P2X7R and induce the release of pro-inflammatory cytokines such as IFN-γ and IL-12 via the NF-κB pathway (61). In addition, P2X7R was demonstrated to regulate the secretion of IL-12, IL-6 and IL-23 in DCs through the NLRP3 inflammasome (62) and to upregulate the expression of CD80 and CD86 (11). In addition, ATP released from immunogenic cell death can also activate P2X7R (63), further strengthening antigen presentation and ultimately enhancing T-cell activation.

However, the expression of P2X7R on DCs exhibits the opposite effect in AML. ATP released from leukemic cells induced by chemotherapy was shown to trigger potent anti-leukemia immune responses by activating P2X7R on the surface of DCs, driving DCs to fully mature and acquire efficient antigen-presenting capacity. Subsequently, ATP was demonstrated to upregulate indoleamine 2,3-dioxygenase 1 (IDO1) expression in DCs through a P2X7R-dependent pathway. IDO1 was revealed to mediate the conversion of naive $CD4^+CD25^-$ T cells into functional regulatory T cells (Tregs). In addition, leukemia-derived DCs were shown to suppress the generation of leukemia-specific T cells via IDO1 (Fig. 2C). Such DCs can effectively induce the generation of Tregs, which in turn further inhibit specific T-cell immune responses against leukemia (43).

P2X7R activation on DCs by eATP released from leukemic cells exerts dual effects in the AML BM niche. While it promotes DC maturation and antigen presentation, it also induces a P2X7R-dependent upregulation of IDO1, leading to the generation of Tregs that suppress anti-leukemia immune responses. This P2X7R-IDO1-Treg axis in AML-associated DCs may therefore represent a critical immunosuppressive mechanism within the BM microenvironment, contributing to immune evasion and limiting the efficacy of chemotherapy-induced anti-leukemia immunity.

P2X7R and $CD8^+$ T cells in AML. P2X7R also exhibits dual functions in $CD8^+$ T cells (Fig. 2D). Knockout or inhibition of P2X7R in $CD8^+$ T cells was shown to enhance their antitumor activity. For instance, *P2x7r* knockout in effector memory T cells increased cell cycle activity upon stimulation (64,65). Adoptive transfer of $P2x7r^{-/-}$ $CD8^+$ T cells promoted T-cell infiltration into tumors and elevated the proportion of tumor antigen-specific T cells, thereby significantly suppressing tumor growth (64). Inhibition of P2X7R in γδ T cells not only markedly reduced apoptosis and improved survival of unconventional T cells *in vitro*, but also increased the number of cells secreting IFN-γ and IL-4 (66). Additionally, activation of P2X7R induced T-cell senescence and limited its antitumor function (64). On the other hand, *P2x7r* deficiency impaired the antitumor capacity of T cells. In $P2x7r^{-/-}$ $CD8^+$ T cells, the formation rate of initial calcium microdomains and the nuclear translocation of nuclear factor of activated T cells 1 (NFAT-1) were significantly reduced, a key transcription factor in T-cell activation. These changes further led to downregulated expression of INF-γ, TNF-α and nuclear receptor Nur77, ultimately resulting in impaired cell proliferation (67).

T cells in AML are characterized by exhaustion, aberrant differentiation, functional suppression and elevated Treg proportions. Specifically, $CD8^+$ T cells in AML highly express exhaustion markers including PD-1, TIM-3, LAG-3 and CD244, with decreased secretion of cytotoxic molecules and IFN-γ, leading to impaired proliferation and cytolytic capacity (68). In addition, the $CD8^+$ T-cell subsets from newly diagnosed and relapsed patients with AML exhibit strong heterogeneity (69). At the initial diagnosis, the proportion of terminally differentiated effector T cells ($CCR7^-CD45RA^+$, $CD27^-CD45RA^+$) is markedly elevated, while the percentages of naive T cells ($CCR7^+CD45RA^+$) and naive-like T cells ($CD27^+CD45RA^+$) are decreased. Terminal differentiation as well as excessive clonal expansion are commonly observed in relapsed cases. Notably, persistently elevated Treg levels during disease remission also indicate a significantly higher long-term risk of leukemia relapse (70). However, the expression pattern and functional mechanisms of P2X7R in $CD8^+$ T cell within AML still require further investigations.

P2X7R plays a complex and context-dependent role in $CD8^+$ T-cell function in the AML BM niche. Although P2X7R activation can promote T-cell senescence and limit antitumor immunity, its deficiency may also impair T-cell activation and proliferation. Given that $CD8^+$ T cells in AML exhibit exhaustion, terminal differentiation, and functional suppression, the effect of P2X7R signaling in this setting remains to be determined. Understanding how P2X7R modulates the balance between T-cell activation and exhaustion within the AML BM microenvironment could suggest strategies to restore effective antitumor immunity while avoiding the pro-leukemic immunosuppressive effects.

4. Expression and function of P2X7R in LSCs and AML blasts

Expression of P2X7R in patients with AML. Compared with normal HSPCs, expression of P2X7R was shown to be significantly elevated in AML, particularly in LSCs. Overexpression of P2X7R was also observed in established human AML cell lines and blasT cells derived from patients with AML (12,71,72). In patients with AML, the expression levels of P2X7R were revealed to differ among various subtypes, with higher levels in M4, M5, and M6 groups, but not in M1 or M2 groups (13,72). Furthermore, P2X7R expression was demonstrated to be associated with the malignant progression and development of AML. In children with acute leukemia, P2X1R, P2X4R, P2X5R, and P2X7R were simultaneously highly expressed, among which the expression of P2X7R was reported to be even higher in relapsed patients. However, the expression of P2X7R was shown to be significantly decreased after chemotherapy upon reaching the complete remission (CR) stage (73). These findings indicate the heterogenous expression pattern of P2X7R in patients with AML.

The expression of P2X7R isoforms also varies among patients with AML. It has been reported that P2X7RA and P2X7RB are markedly upregulated in *de novo* patients with AML. However, patients with relapsed or refractory AML were shown to exhibit different expression patterns from *de novo* patients. P2X7RA mRNA was demonstrated to be significantly decreased and P2X7RB mRNA was reported to be substantially increased in patients with relapsed AML, and the reason was revealed to be chemotherapy-related positive selection of P2X7RB. In patients in remission, both P2X7RA and P2X7RB expression were significantly decreased compared with *de novo* patients with AML. These findings suggest that high P2X7RB expression may confer chemotherapy resistance (37). It was verified by the formation of large pores by P2X7RA under high ATP conditions, while P2X7RB was unable to form cytotoxic pores *in vivo* (39).

P2X7R and LSCs/AML blasts. The expression of P2X7R in LSCs serves as a crucial regulator in sustaining their functions, including proliferation, survival and homing. High levels of eATP in AML BM microenvironment and ATP/P2X7R-mediated signal were shown to be important for the leukemogenic activities of LSCs (71). ATP/P2X7R signaling was revealed to be essential for the homing of LSCs to their supportive BM niches and for maintaining their self-renewal capacity, both of which contribute to leukemogenesis. Moreover, ATP/P2X7R signaling was demonstrated to directly stimulate the proliferation and enhance the survival of LSCs (12).

Although P2X7R is expressed in both LSCs and normal HSPCs, the biological roles in these two stem cell populations are significantly different. Multiple subsets of LSCs express P2X7R, including $CD34^-CD38^-$, $CD34^+CD38^-$, $CD34^+CD38^+$, and $CD34^-CD38^+$ subsets. Expression of P2X7R in HSPCs was shown to be significantly lower than that in LSCs. Studies have shown that high concentrations of eATP can induce LSC apoptosis, while having little effect on the survival rate of normal $CD34^+$ HSPCs. P2X7RB isoform expressed on normal HSPCs was also reported to lack the biological function of inducing apoptosis (12,49,74). The differences of P2X7R may be attributed to variations in the expression level or isoforms of P2X7R between LSCs and HSPCs.

The expression of P2X7R on AML cells is also involved in cell proliferation. P2X7R can maintain the activity and quantity of mitochondria in leukemia cells by sensing high levels of eATP, thereby promoting the proliferation of these cells. Inhibition of P2X7R in AML cells or blockade of ATP release can reduce leukemic cell proliferation (75).

Upstream and downstream signaling pathways of P2X7R in AML. In the AML BM niche, multiple mechanisms have been shown to drive the release of ATP and thereby activate P2X7R, which in turn promotes AML progression (Fig. 3A). Osteoblasts in AML were revealed to exhibit upregulated expression of pannexin 1 and connexin-43, which facilitates ATP release (12). DNR treatment was demonstrated to promote the release of ATP from dying leukemic cells, which subsequently activates P2X7R (43). Extracellular nucleotide levels were shown to be tightly regulated by extracellular nucleotidases such as CD39 and CD73 (11,76), which were reported to hydrolyze eATP into immunosuppressive adenosine (76), thereby limiting the activation of P2X7R.

An ATP-rich BM microenvironment in AML provides sufficient conditions for robust activation of P2X7R, which then triggers a series of downstream signaling cascades, including the cAMP response element-binding protein (CREB)/phosphoglycerate dehydrogenase (Phgdh)/serine metabolic axis (12), PBX homeobox 3 (Pbx3) (13), Wnt/β-catenin (77), and c-Myc (37) (Fig. 3B). Activation of P2X7R was shown to facilitate Ca^{2+} influx, which in turn promoted calcium-mediated phosphorylation of CREB, upregulated Phgdh, and sustained serine metabolism, ultimately enhancing the homing and self-renewal of LSCs (12). In MLL-rearranged AML, overexpression of P2X7R was demonstrated to upregulate Pbx3, thereby promoting the proliferation of MLL-AF9-driven leukemic cells and increasing the population of LSCs, ultimately exerting a leukemogenic effect (13). A previous study also revealed that the P2X7R-mediated Wnt/β-catenin signaling pathway can promote the progression of AML (77). Combination treatment with DNR and a P2X7R inhibitor prevented the downregulation of the proto-oncogene c-Myc, which was not observed with DNR treatment alone (37).

5. P2X7R as a prognosis marker and therapeutic target in AML

Potential role of P2X7R as a biomarker for AML prognosis. Elevated P2X7R expression has been found to be linked to chemotherapy resistance and poor prognosis in AML (78). The CR rate after one induction therapy course was significantly lower in patients with AML and high P2X7R than in those with low or negative P2X7R (72). In AML mice with MLL-rearrangements, peripheral blood leukemia cell counts rebound more rapidly in the $P2X7R^{high}$ group, and the reason was that P2X7R accelerated the progression of AML by promoting cell proliferation and increasing the number of LSCs (13). The overexpression of P2X7R also enhanced the proliferative capacity of leukemic blasts, which play a critical role in the recurrence and decreased survival rates

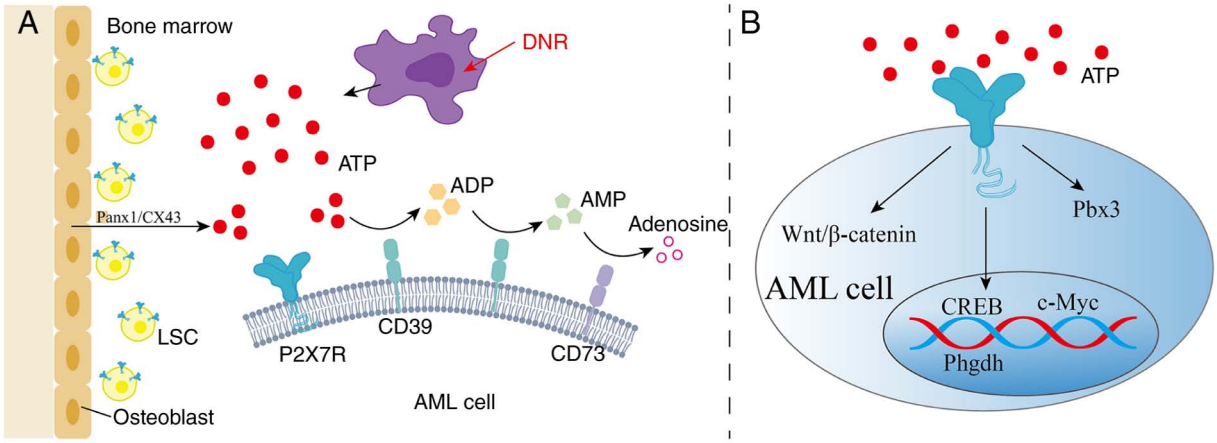

Figure 3. Upstream and downstream signaling pathways of P2X7R in AML. (A) ATP released into the BM niche from osteoblasts and dying AML cells can be sequentially hydrolyzed into ADP, AMP and adenosine by CD39 and CD73 (43). (B) P2X7R promotes AML progression by activating multiple downstream pathways, including the CREB/Phgdh/serine metabolic axis (12), Pbx3 (13), Wnt/β-catenin (77) and c-Myc (37). P2X7R, P2X7 receptor; AML, acute myeloid leukemia; ATP, adenosine triphosphate; BM, bone marrow; ADP, adenosine diphosphate; AMP, adenosine monophosphate; CREB, cAMP response element-binding protein; Phgdh, phosphoglycerate dehydrogenase; Pbx3, PBX homeobox 3; Panx1, pannexin 1; CX43, connexin-43; LSC, leukemia stem cell; DNR, daunorubicin; CREB, cAMP response element-binding protein.

of AML (12,13,78). By contrast, when P2X7R was knocked down, the survival of mice recipients transplanted with human AML cell lines or primary leukemic cells was significantly prolonged (12). Further studies have shown that individuals with high P2X7RB frequently exhibit chemoresistance and a higher risk of disease recurrence, suggesting that P2X7RB may serve as a potential novel therapeutic target (37). The key role of P2X7R in the development of AML drug resistance and disease recurrence provides the possibility for P2X7R to serve as a biomarker for AML prognosis.

P2X7R blockade in AML therapy. Brilliant Blue G (BBG) and oxidized ATP are first-generation P2X7R inhibitors that also exhibit inhibitory activity against P2X1R and P2X4R (79). Their limited specificity has led to the development of a second generation of P2X7R inhibitors, which have optimized pharmacological properties, such as A438079, AZ10606120, A740003, AZ11645373, JNJ-47965567 and ZINC 58368839 (80-83).

A740003 has been widely studied in AML and has demonstrated anti-AML effects (13,78,84). A740003 is a highly selective P2X7R antagonist that can block BzATP-induced intracellular calcium concentration changes, P2X7R-mediated pore formation, and has similar blocking activities in rats and humans (85,86). A740003 can inhibit the proliferation of human and murine AML cells both *in vitro* and *in vivo*, and impair the colony-forming ability of human AML cells (12). Intratumoral administration of A740003 reduced tumor formation in nude mouse xenograft models (13). Previous research also showed the anti-leukemia effects of A740003 in a TIB-49 murine AML model (77). Mechanistically, A740003 significantly reduced the levels of phosphorylated CREB, CREB, and Phgdh proteins in wild-type AML cells but not in *P2x7r*$^{-/-}$ cells. Treatment with A740003 also significantly reduced CREB phosphorylation and Phgdh levels in human AML samples (12).

4-Aminopyrazine (4-AP), one of the most commonly used K^+ channel inhibitors, can suppress the proliferation of various types of cancer cells and induce cell apoptosis, including AML cells (87,88). It has been proposed that 4-AP may promote ATP release from apoptotic AML cells, and the released ATP acts on P2X7R in an autocrine or paracrine manner, increasing the intracellular Ca^{2+} concentration and thereby participating in the regulation of the cell apoptosis (87).

P2X7R antagonists have also been shown to play a critical role in graft-vs.-host disease (GVHD). In patients with AML who had undergone allogeneic hematopoietic stem cell transplantation, the combination of the P2X7R antagonist BBG with cyclophosphamide not only significantly reduced the incidence of hepatic GVHD but also did not impair graft-vs.-leukemia (GVL) immune function (89).

Combination strategy targeting P2X7R and chemotherapy. The association between P2X7R expression and chemoresistance suggests that conventional chemotherapy may fail to completely eradicate P2X7R^{high} LSCs (13), which provides a rationale for combination therapy targeting P2X7R together with conventional chemotherapy.

P2X7R antagonists combined with chemotherapeutic agents have demonstrated synergistic antileukemic effects. P2X7R antagonists and 6-mercaptopurine significantly enhanced the antiproliferative response of leukemic cells *in vitro* (75). Similarly, the combination of P2X7R antagonist AZ10606120 with DNR effectively inhibited leukemia growth by blocking the oncogenic c-Myc pathway (37). A more nuanced strategy involves targeting specific P2X7R isoforms. The P2X7RA isoform was shown to facilitate DNR uptake, increasing cellular sensitivity to chemotherapy, whereas the P2X7RB isoform was demonstrated to be highly expressed in relapsed AML cells. This differential expression suggests a sequential combination strategy: Initial administration of DNR to eliminate P2X7RA-expressing cells, followed by the use of a P2X7RB-specific inhibitor to eradicate the residual, resistant population (37,90).

Beyond antagonists, ATP itself can enhance chemosensitivity in AML treatment. For instance, ATP administration has

been shown to increase the cytotoxicity of cytarabine against AML cells (74). Furthermore, the frequent co-expression of P2X7R and P2X4R offers another promising strategy for combination therapy. Simultaneous targeting of these receptors and their associated pathways holds promise for treating a wider range of diseases driven by their dysfunction in the future (91).

Research progress and limitations of targeting P2X7R in AML. Considerable progress has been made in the development of P2X7R inhibitors. Researchers constructed a 3D pharmacophore model based on known antagonists (A740003, A804598, and JNJ47965567) to screen for novel compounds targeting the negative allosteric pocket of human P2X7R. This approach identified three promising candidates (compounds 2, 2g, and 9), among which the compound 2 family demonstrated significantly higher inhibitory activity than the others (92). Another design strategy stems from in-depth analysis of the P2X7R structure. Using high-resolution cryo-electron microscopy to resolve the full-length human P2X7R structure, researchers successfully designed UB-MBX-46, a potent and selective antagonist with a unique polycyclic scaffold. UB-MBX-46 not only exhibited subnanomolar potency and near-irreversible binding capacity but also had high selectivity for P2X7R (93). These advances provide critical insights and a foundation for the development of inhibitors with improved efficacy, specificity, and therapeutic potential. The safety and efficacy of a variety of small-molecule inhibitors targeting P2X7R have been preliminarily verified, such as A740003, AZD9056 and A438079 (12,94-98).

Research has also expanded to anti-P2X7R antibodies and nanobodies with superior specificity and efficacy (83,99). Specific antibodies targeting P2X7R have been designed using gene fusion technology. Adeno-associated viral vectors can also be used to express P2X7R-specific antibodies with long-lasting biological effects (100). However, the specific applications and detailed mechanisms of these antibodies in AML treatment require further investigation.

The antibodies targeting nfP2X7R offer new potential for cancer therapy. Antibodies against the E200 sequence of P2X7R, such as BIL03s and BPM09, can specifically bind to nfP2X7R without interacting with functional P2X7R (38). BIL010t, a first-in-class antibody targeting nfP2X7R, has been tested in a phase I clinical trial for basal cell carcinoma and has demonstrated a favorable safety profile (14).

However, targeting P2X7R in AML therapy still has multiple challenges. Although activation of P2X7R is generally associated with poor prognosis in tumors, this receptor is neither a simple oncogenic nor a tumor-suppressive molecule. A more detailed understanding of its roles in distinct disease contexts still needs to be explored. The expression profile of P2X7R in distincT cell types within the BM microenvironment under physiological conditions and in the pathological context of AML still need to be systematically characterized (26). Another important aspect is to characterize the functional diversity of P2X7R isoforms. P2X7R antagonists/antibodies have also not reached approval for clinical use due to poor pharmacokinetic properties, insufficient selectivity, species differences, tissue distribution, and limited clinical efficacy (92). Further clinical trials are still required to validate the long-term safety and efficacy of P2X7R-targeted approaches.

6. Conclusions

As an ATP-gated ion channel, P2X7R plays a critical and dualistic role in AML pathogenesis and the immunosuppressive BM niche. The formation of ion channels and large pores confers its functional properties of promoting cell survival or inducing cell death, which are significantly modulated by ATP concentration and duration of action, P2X7R subtypes, and the TME. P2X7R is highly expressed on LSCs, AML blasts, and multiple immune cells in AML. Sustained activation by eATP in the BM niche promotes AML blast survival, LSC maintenance, and suppresses anti-leukemic immunity via downstream signaling pathways. The pathophysiological role of P2X7R establishes it as a prognosis marker and potential therapeutic target. Current strategies include small molecule antagonists, specific antibodies, and combination with conventional chemotherapy. Despite the rationale for targeting P2X7R in AML, bridging the promising preclinical data to established clinical therapy requires further extensive investigation.

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Authors' contributions

LF conceived the study. YL wrote the original draft. HX, HM, TS and ZL wrote, reviewed and edited the manuscript. LF and NW designed the scope and structure of the review. LF supervised the study and was responsible for funding acquisition, LF. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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