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Defining the Therapeutic Window of P2X7R Targeting: An eATP-Driven Functional Zoning Model for Precision Immunotherapy

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Abstract. The P2X7 receptor (P2X7R) is an ATP-gated cation channel whose effects on tumour progression depend on extracellular ATP (eATP) exposure and cellular context. P2X7R activation can support proliferative and immunosuppressive signalling, whereas sustained stimulation can induce cell death under permissive conditions. To examine these contrasting responses, this review proposes an original eATP-driven functional zoning model. Let $C(x)$ denote tumour burden at a common observation time and x denote local effective eATP concentration. The paper defines $F(x) = -\frac{\mathrm{d}c(x)}{\mathrm{d}x}$ to describe the direction and magnitude of the marginal concentration response. Under an assumed profile in which $F(x)$ decreases to a negative minimum and subsequently rises through zero, the model distinguishes an absolute pro-tumour zone, a relative anti-tumour zone and an absolute anti-tumour zone. The relative zone denotes weakening marginal tumour promotion, while positive $F(x)$ denotes a tumour-suppressive concentration response. The minimum and zero crossing specify testable mathematical conditions rather than established treatment thresholds. Validation requires concentration-response measurements, receptor-specific controls and assessment of tumour and immune-cell contributions. The framework provides hypotheses for investigating P2X7R-targeted interventions; its value for patient stratification and combination immunotherapy remains to be established.

Keywords: P2X7 receptor, extracellular ATP, tumour microenvironment, pyroptosis, precision immunotherapy

1. Introduction

The P2X7 receptor (P2X7R) is a trimeric ATP-gated, non-selective cation channel involved in inflammatory and immune responses [1, 2]. Compared with several other P2X receptors, it has relatively low sensitivity to ATP. Extracellular ATP (eATP) released by stressed or dying cells can therefore become an important regulator of P2X7R activity in the tumour microenvironment (TME) [1, 3]. The consequences of receptor activation depend on exposure conditions and the responding cell population, creating opportunities for therapeutic intervention but also complicating the interpretation of experimental results.

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Evidence from tumour models links P2X7R to pathways supporting proliferation, invasion and angiogenesis [4-6]. PI3K–Akt–GSK-3β signalling and HIF–VEGF regulation provide possible connections between receptor activity and these tumour-promoting processes. P2X7R can also influence the immune compartment. In an ovarian cancer co-culture study, silencing P2X7R in macrophages reduced STAT6 phosphorylation and M2-associated markers and relieved macrophage-mediated suppression of CAR-T activity [7]. These findings identify distinct routes through which tumour-cell and myeloid-cell responses may support tumour progression, without establishing that the same mechanisms operate across all cancers.

Other responses to P2X7R activation may contribute to tumour control. In appropriately primed macrophages, receptor-mediated K^+ efflux can promote NLRP3 inflammasome activation, followed by caspase-1 activation and gasdermin D-mediated pyroptosis [3]. Sustained stimulation can also increase membrane permeability and lead to cell death under permissive conditions. These processes may release inflammatory mediators and cellular material that influence surrounding immune cells. Their contribution to anti-tumour immunity, however, depends on which cells are affected and how the resulting signals alter the tissue response [3].

The distinction between tumour-cell and host responses is illustrated by apparently opposing experimental observations. P2X7R inhibition can suppress tumour-promoting behaviour in gastric cancer models, whereas deletion of P2X7R in the host has been associated with accelerated growth of transplanted B16 melanoma and CT26 colon carcinoma [5-9]. These interventions act on different biological compartments and should not be interpreted as equivalent tests of receptor function. Local eATP availability may contribute to the divergent outcomes, alongside receptor expression, exposure duration and immune composition. A concentration-based framework must therefore retain these contextual limits rather than treating eATP as a sufficient predictor of treatment response.

This paper examines the mechanisms underlying these contrasting effects and proposes an original eATP-driven functional zoning model. Let $C(x)$ represent tumour burden at a common observation time and x represent local effective eATP concentration. The paper defines $F(x) = -\frac{\mathrm{d}C(x)}{\mathrm{d}x}$ to describe the marginal change in tumour burden across concentrations. Within an explicitly assumed response profile, the minimum of $F(x)$ identifies the strongest marginal tumour-promoting response, while a subsequent negative-to-positive zero crossing marks a reversal towards a tumour-suppressive concentration response. The framework organizes these relationships into testable hypotheses for P2X7R-targeted interventions. Numerical thresholds and their relevance to patient stratification or combination immunotherapy remain to be established.

2. Structural and functional basis of P2X7R activation

P2X7R is a trimeric ATP-gated ion channel, with three subunits arranged around a central ion-conducting pore [2, 10]. Compared with several other P2X receptors, it is relatively insensitive to ATP. The micromolar-to-millimolar agonist concentrations associated with its activation must therefore be interpreted in relation to the agonist used and the experimental conditions. Low extracellular ATP availability limits receptor activation, whereas ATP accumulation near damaged or necrotic tumour tissue can increase P2X7R engagement [2, 11]. This concentration dependence provides a biological basis for examining how local eATP availability influences receptor-associated tumour responses.

Activated P2X7R conducts Na^+, K^+ and Ca^{2+}. Sustained stimulation can also increase membrane permeability to larger molecules, including molecules up to approximately 900 Da [2, 3]. This large-molecule-permeable phenotype is often described as macropore formation. However, increased

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permeability should be distinguished from a specific structural explanation: it does not, by itself, establish that the receptor pore progressively dilates. The extent of permeabilization and its relationship to cell death depend on the duration and intensity of stimulation, the cell type and the surrounding biochemical conditions [3, 11].

These permeability changes have different signalling consequences. Ca^{2+} entry can activate calcium-sensitive signalling pathways, while K^+ efflux contributes to NLRP3 inflammasome activation and inflammatory cytokine processing [3]. Neither response alone determines the effect on tumour burden. P2X7R is expressed in tumour cells and in several immune populations, including macrophages, dendritic cells, natural killer cells and T-cell subsets [3, 10]. Its overall effect therefore depends on which populations respond and how their responses interact. An eATP-based model must account for this cellular context when relating receptor activation to tumour promotion or suppression.

3. Pro-tumour signalling pathways under low eATP concentrations

At basal or low-level activation, P2X7R promotes tumour progression through at least three mechanistically distinct signalling axes: the PI3K-Akt-GSK-3β proliferative cascade, the HIF-VEGF angiogenic programme, and the induction of immunosuppressive M2-like macrophage polarization.

3.1. The PI3K-Akt-GSK-3β axis and tumour proliferation

Within the TME, eATP can activate P2X7R under conditions that favour proliferative signalling without inducing overt cell death. P2X7R activation permits Ca^{2+} entry and raises intracellular Ca^{2+} levels. In tumour models exhibiting P2X7R-dependent PI3K–Akt signalling, receptor activation can couple this ionic response to pathways regulating proliferation and survival. PI3K converts PIP_2 to PIP_3, which recruits Akt to the plasma membrane and facilitates its activation. Activated Akt then phosphorylates GSK-3β at Ser9, reducing its kinase activity. This inhibitory phosphorylation links Akt signalling to the regulation of downstream proteins involved in tumour progression. In the β-catenin degradation pathway, GSK-3β contributes to the phosphorylation events that target β-catenin for ubiquitin-dependent proteasomal degradation. Once GSK-3β is inhibited, β-catenin accumulates in the cytoplasm and, upon reaching a sufficient level, translocates into the nucleus to initiate the transcription of pro-proliferative genes such as CCND1 and MYC. Meanwhile, EMT-related transcription factors, including Snail (SNAI1), Slug (SNAI2), and ZEB1, are stabilized as a result of GSK-3β inhibition by phosphorylation, leading to the disassembly of intercellular adherens junctions and cytoskeletal rearrangement, thereby increasing the risk of tumour proliferation and metastasis.

3.2. The HIF-VEGF axis and tumour angiogenesis

Akt signalling can influence HIF-1α abundance through pathways regulating both protein synthesis and degradation. Activation of mTORC1 promotes translation through downstream effectors, including 4E-BP1 and S6K1, and can increase HIF-1α synthesis. Akt-mediated phosphorylation of GSK-3β at Ser9 can also reduce GSK-3β-dependent HIF-1α degradation in settings where this regulatory pathway is active. These mechanisms provide a possible connection between P2X7R-associated Akt signalling and HIF-1α accumulation. Their contribution under normoxic or mildly hypoxic conditions, however, must be established in the relevant tumour model.

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HIF-1α associates with ARNT (HIF-1β) to form the HIF-1 transcriptional complex, which binds hypoxia response elements containing the core sequence 5′-RCGTG-3′. Activation of targets such as VEGFA can increase VEGF production and support angiogenic responses. As a tumour expands, local hypoxia may further stimulate this pathway. P2X7R-associated signalling and oxygen availability could therefore converge on HIF-1 activity, although increased HIF-1α or VEGF expression alone does not establish improved tumour perfusion or demonstrate that the angiogenic response is P2X7R-dependent.

3.3. Induction of immunosuppressive M2-like macrophage polarization

P2X7R has been linked to STAT6-associated macrophage polarization in an ovarian cancer co-culture model. Silencing P2X7R in macrophages reduced STAT6 phosphorylation and the expression of M2-associated markers, including CD206 and IL-10. STAT6 overexpression reversed these changes, supporting a functional relationship between P2X7R signalling and the macrophage phenotype [7]. These findings connect receptor activity to STAT6-associated regulation, although they do not by themselves define every upstream signalling step.

The same study examined the consequences for CAR-T activity against ovarian cancer cells. M2 macrophages suppressed CAR-T-mediated cytotoxicity, whereas P2X7R silencing in macrophages relieved this suppression [7]. This provides a specific example of how P2X7R activity in the myeloid compartment can influence an anti-tumour response. Its relevance to other tumour settings should be assessed alongside macrophage state, local cytokine conditions and the immune intervention being tested.

4. Anti-tumour effector mechanisms under high eATP concentrations

Sustained exposure to high eATP concentrations can shift P2X7R-associated responses from signalling that supports cell survival towards membrane permeabilization and cell death. The following sections examine inflammasome-dependent pyroptosis, lytic responses associated with increased membrane permeability, and their possible immune consequences. Whether these events contribute to tumour control depends on the responding cell population and the resulting tissue response.

4.1. NLRP3 inflammasome assembly and pyroptotic cell death

In the canonical macrophage response, NLRP3 inflammasome activation is commonly described in terms of priming and activation signals. During transcriptional priming, stimuli such as bacterial lipopolysaccharide activate NF-κB signalling and increase the expression of NLRP3 and pro-IL-1β [3]. Priming is not restricted to Toll-like receptor ligands; cytokine receptor signalling can also prepare macrophages for a subsequent ATP response. The source of this signal should therefore be established in the tumour setting under study, rather than inferred from experimental protocols that use microbial products.

P2X7R-mediated K^+ efflux provides an activation signal that can promote NLRP3 inflammasome assembly [4]. NLRP3 recruits ASC and pro-caspase-1, supporting caspase-1 activation. Active caspase-1 processes pro-IL-1β and pro-IL-18 and cleaves gasdermin D (GSDMD). The released GSDMD N-terminal fragment forms membrane pores, enabling inflammatory mediator release and, under conditions that overcome membrane repair, progression to pyroptotic lysis [3, 10]. This

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sequence distinguishes receptor-mediated ion flux from gasdermin-mediated pore formation. The resulting inflammatory response must then be evaluated separately from its effect on tumour burden.

Pyroptosis can connect inflammatory cell death with anti-tumour immune responses. IL-1β and IL-18 released during inflammasome-associated pyroptosis can contribute to immune activation, including responses involving dendritic cells, $CD8^+$ T cells and NK cells [3]. Dying cells also release damage-associated molecular patterns that can stimulate antigen-presenting cells. These events provide possible links between local cell death and subsequent immune responses, but cytokine release alone does not establish effective tumour control. The proposed anti-tumour role of P2X7R-associated pyroptosis therefore requires evidence connecting the affected cell population, the inflammatory response and the tumour outcome.

4.2. Macropore formation and lytic cell death

Prolonged stimulation with high eATP concentrations can increase P2X7R-associated membrane permeability, allowing the passage of larger molecules, reported to reach approximately 900 Da [2, 3]. This phenomenon is commonly described as macropore formation. Increased large-molecule permeability, however, should be distinguished from progressive structural dilation of the receptor pore. Its extent and consequences depend on stimulation conditions, the responding cell type and the extracellular environment [3, 11]. The relevant functional distinction is therefore between ion conduction, increased permeability to larger molecules and the eventual loss of membrane integrity, rather than an assumed sequence of progressively enlarged receptor conformations.

Macropore opening disrupts transmembrane ionic homeostasis, driving K^+ loss and Na^+/Ca^{2+} influx, osmotic swelling, phosphatidylserine externalisation, membrane blebbing and microvesicle shedding, culminating in irreversible loss of membrane integrity and lytic cell death [3, 10]. The temporal relationship between membrane permeabilization, inflammasome activation and terminal cell lysis must be established in the experimental system under study. Although macropore closure can reverse membrane permeability in some cell types once the agonist is withdrawn, complete membrane rupture and cell death constitute an irreversible terminal event [3, 10]. P2X7R-associated membrane permeabilization and pyroptosis may occur in the same experimental system, but they should not be treated as interchangeable processes. In appropriately primed macrophages, receptor-mediated K^+ efflux can promote NLRP3 inflammasome activation and subsequent GSDMD-dependent pyroptosis [3]. Increased membrane permeability during sustained stimulation may also involve processes that are not explained by this pathway alone. Their contributions therefore require evaluation in the relevant cell type and stimulation conditions [3, 10]. Likewise, the immune consequences cannot be inferred solely from a lytic phenotype: they must be assessed in relation to the released mediators and the responses of surrounding immune cells.

4.3. Cell-type-specific divergence of P2X7R responses

The cellular source of a P2X7R response is essential to its interpretation. In tumour cells, receptor activation may support proliferative signalling or, under conditions that induce cell death, release material available for uptake by antigen-presenting cells. In immune cells, activation can affect inflammatory cytokine release and effector responses [3, 10]. These outcomes should be evaluated separately before attributing an overall tumour-promoting or tumour-suppressive effect to P2X7R. Claims of NLRP3-independent pyroptosis additionally require identification of the alternative death pathway and evidence for its operation in the tumour cells being studied.

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This distinction also matters when evaluating P2X7R-targeted treatment. Receptor expression alone does not establish whether an agonist or antagonist will be beneficial. The relevant questions are which cells respond, whether activation promotes their survival or death, and how those changes affect immune activity and tumour burden. Predominantly proliferative signalling in tumour cells provides a different rationale for intervention from immune-cell activation that supports tumour control. Local eATP concentration is therefore one component of the biological context, rather than a sufficient predictor of treatment outcome. This provides a rationale for the conceptual model developed below, while defining the cellular information needed to interpret its predictions.

5. An eATP-driven functional zoning model for P2X7R targeting

The mechanisms discussed above motivate a concentration-based description of tumour responses to eATP. The paper proposes an original conceptual model that relates local effective eATP concentration to tumour burden and uses the slope of this relationship to distinguish functional zones. The model specifies mathematical conditions for changes in the marginal response; it does not assign numerical ATP thresholds or establish treatment efficacy.

5.1. Conceptual framework and mathematical formalization

Let x denote local effective eATP concentration and $C(x)$ denote tumour burden at a common observation time under specified biological conditions. Following the definition in the abstract, it is defined as

$$F(x) = -\frac{\mathrm{d}C(x)}{\mathrm{d}x}$$

Its units are therefore tumour burden per unit eATP concentration. When $F(x)$ is negative, an incremental increase in eATP corresponds to greater tumour burden. When $F(x)$ is positive, the same increment corresponds to lower tumour burden. Its magnitude describes the steepness of the local concentration response. These comparisons concern variation across concentrations at a fixed observation time, rather than changes in tumour burden over time.

The formulation is motivated by P2X7R signalling, but a response to eATP cannot automatically be attributed to this receptor alone. Receptor-specific perturbations and suitable controls would be needed to identify the P2X7R-dependent component of $C(x)$. The biological conditions represented by each curve must also be specified before curves from different tumour models can be compared.

5.2. Functional zones and clinical translation

A three-zone representation requires an additional assumption about the shape of $F(x)$. It is considered a concentration range in which $F(x)$ is initially negative, decreases to a minimum at x_m, and then increases through a negative-to-positive zero crossing at x_0, where $x_m < x_0$. This assumed profile yields the following functional zones. In the absolute pro-tumour zone, $F(x) < 0$ and $F'(x) < 0$. Tumour burden increases with eATP, and the marginal tumour-promoting response becomes stronger as concentration rises.

In the relative anti-tumour zone, $F(x) < 0$ and $F'(x) > 0$. Tumour burden still increases with eATP, but the marginal increase becomes smaller. "Relative anti-tumour" thus denotes attenuation of the preceding tumour-promoting trend, rather than demonstrated tumour suppression. In the absolute

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anti-tumour zone, $F(x) > 0$. Increasing eATP corresponds to decreasing tumour burden within the conditions represented by $C(x)$. The term "absolute" describes the direction of this marginal response; it does not establish tumour elimination or a reduction relative to an untreated control.

The minimum and zero crossing answer different questions. At x_m, $F(x)$ is most negative, identifying the strongest marginal tumour-promoting response within the specified domain. For a smooth interior minimum, $F'(x_m) = 0$ is necessary but insufficient; the surrounding behaviour must establish a minimum. A global-minimum claim additionally requires comparison across the full domain. At x_0, $F(x_0) = 0$, with $F(x)$ changing from negative to positive as x passes through x_0, marking a reversal in the direction of the concentration response.

Neither point alone identifies an optimal intervention. The minimum of $F(x)$ is not necessarily the maximum of $C(x)$, and changing eATP concentration is not equivalent to administering a P2X7R agonist or antagonist. A therapeutic window would require intervention-specific efficacy and safety measurements. Likewise, these zones cannot directly be assigned to clinical stable disease or objective response.

5.3. Model assumptions and limitations

The model represents eATP exposure by a single effective concentration. In the TME, ATP release and extracellular nucleotide metabolism vary across space and time [11]. A concentration measured at one location or time may therefore inadequately describe exposure across a tumour. The formulation also assumes a sufficiently smooth $C(x)$ and the response profile specified above. Other profiles may contain multiple minima or zero crossings, or none within the observed concentration range. Estimating $F(x)$ from experimental data would require adequate concentration sampling and an analysis of uncertainty; no numerical transition concentrations are estimated here.

Cellular composition further limits generalization. P2X7R responses in tumour cells and immune populations may contribute differently to the observed tumour burden [3, 10]. A single curve does not resolve those contributions or describe delayed immune effects. The model should therefore be tested in defined biological settings, with measurements that distinguish receptor-dependent responses from other effects of eATP. Its present contribution is a set of explicit hypotheses linking concentration, tumour burden and the direction of the marginal response.

6. Therapeutic implications for precision immunotherapy

The functional zoning model provides a way to examine how local eATP conditions might influence responses to P2X7R-targeted interventions. Its immediate application is to experimental design. Measuring $C(x)$ across a defined concentration range would allow estimation of $F(x)$ and assessment of whether the proposed zones occur in a given tumour setting. A single eATP measurement would not establish the local slope of $C(x)$ or reliably assign a tumour to a functional zone.

Intervention studies could then test whether the observed concentration response depends on P2X7R. Where receptor-specific controls show that P2X7R contributes to tumour-promoting signalling, antagonism would have a mechanistic rationale. Where receptor activation induces tumour-cell death or supports an immune response that reduces tumour burden, agonism could be investigated. Neither strategy follows from the sign of $F(x)$ alone: changing extracellular ATP availability and directly modulating P2X7R can produce different effects. The identity and

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functional state of responding tumour and immune cells must therefore be considered alongside receptor expression [3, 10].

The same distinction applies to combination therapy. Interventions targeting extracellular nucleotide metabolism can affect both ATP availability and downstream adenosine signalling [8, 11]. Their effects should be measured separately rather than assumed to move a tumour into a favourable zone. Combinations with P2X7R modulators or immune checkpoint inhibitors could be evaluated by comparing tumour burden and immune responses with those produced by each component alone. Such comparisons would test whether the proposed interaction occurs under the conditions represented by the model.

Clinical stratification remains a longer-term application. It would require reproducible measures of local eATP exposure and evidence that the resulting response profiles predict treatment outcomes beyond receptor expression and cellular composition. Safety assessment must also remain independent of the zoning classification. A concentration associated with lower tumour burden does not, by itself, demonstrate an acceptable effect on immune cells or other tissues. These studies would establish whether the model can inform treatment selection, rather than presuming that its mathematical boundaries already define a usable therapeutic window.

7. Conclusion

P2X7R-associated tumour responses vary with eATP exposure and cellular context. This review proposes an original functional zoning model that defines $F(x)$ as the negative derivative of tumour burden with respect to local effective eATP concentration. The formulation describes a marginal concentration response at a common observation time, rather than tumour growth over time. Under the assumed response profile, the minimum of $F(x)$ identifies the strongest marginal tumour-promoting response, while a subsequent negative-to-positive zero crossing marks a reversal towards a tumour-suppressive concentration response. The three-zone interpretation distinguishes an increasingly tumour-promoting response, attenuation of that trend and a tumour-suppressive response. These relationships provide hypotheses for testing how eATP availability and P2X7R activity jointly influence tumour burden. Their evaluation requires defined exposure conditions, receptor-specific controls and assessment of tumour and immune-cell contributions. Numerical thresholds, treatment-selection rules and safety boundaries remain to be established. The model offers a basis for investigating P2X7R-targeted strategies, with its clinical relevance contingent on experimental and prospective validation.

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