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HARNESSING ADRENERGIC RECEPTOR PATHWAYS IN GLIOMAS: FROM TUMOR BIOLOGY TO TARGETED THERAPIES

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Abstract. Brain tumor biology, characterized by aberrant tumorigenesis, relentless invasiveness and a dynamic tumor microenvironment, drives the aggressive progression of gliomas, necessitating novel therapeutic strategies. Gliomas, aggressive brain tumors with dismal survival rates, pose a significant therapeutic challenge despite multimodal treatments. Adrenergic receptors (ARs), including α- and β-subtypes, are increasingly recognized as pivotal drivers of glioma biology, orchestrating tumorigenesis through dysregulated signaling pathways like cAMP/PKA, MAPK and PI3K/AKT. These pathways fuel proliferation, invasion and angiogenesis, while AR crosstalk with receptors such as EGFR and P2Y12 modulates the tumor microenvironment. This review integrates cutting-edge insights into ARs' multifaceted roles in glioma progression, emphasizing their potential as diagnostic biomarkers and therapeutic targets. We explore innovative strategies, including β-AR blockade with agents like propranolol and synergistic receptor-targeted therapies, to overcome treatment resistance and enhance patient outcomes. By decoding AR signaling in gliomas, this work highlights new avenues for precision medicine in neuro-oncology.

Keywords: *Tumor biology, glioma, adrenergic receptors, tumorigenesis, tumor progression, therapeutic targets.*

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1. Introduction

Gliomas are the most prevalent primary intracranial tumors, accounting for approximately 16% of all primary brain tumors. Epidemiological data reveal a higher incidence in males than in females, with most cases occurring in individuals over the age of 50 (Wu *et al*., 2022; Lu *et al*., 2022). Among these tumors, approximately 10% harbor mutations in the isocitrate dehydrogenase (IDH) gene, which are associated with a distinct clinical course. Indeed, the American Brain Tumor Association reports that patients with IDH-mutant gliomas exhibit extended survival times - 27 to 31 months, compared to only 11 to 15 months for patients with IDH wild-type tumors. Although the five-year survival

rate for most glioma patients is less than 5%, those with IDH-mutant gliomas tend to have comparatively better prognoses.

Beyond their survival impact, IDH mutations are increasingly recognized for influencing the tumor's epigenetic landscape through the accumulation of the oncometabolite 2-hydroxyglutarate. This altered epigenetic state can affect gene expression patterns involved in diverse pathways, potentially including adrenergic receptor (AR) signaling. Although direct links between IDH mutation status and AR expression in gliomas are still under investigation, emerging evidence suggests that IDH-mutant gliomas may demonstrate altered microenvironmental and immunological profiles that could intersect with AR-mediated signaling. Better defining these mechanistic connections - whether through epigenetic remodeling, metabolic changes, or modifications in the tumor microenvironment - may offer new opportunities to refine AR-targeted strategies for different glioma subtypes.

Malignant gliomas are particularly challenging to treat, as they are highly vascularized and exhibit a propensity to invade surrounding brain tissues via neural networks, forming abnormal vascular structures. Their aggressive, infiltrative nature and high recurrence rates result in limited treatment efficacy even with maximal surgical resection and multimodal adjuvant therapies (Al-Khatib *et al*., 2024; Shams & Patel, 2022). Standard approaches - such as surgical resection, radiotherapy, chemotherapy, immunotherapy and tumor treating fields (TTF) - provide variable success and can be hampered by adverse effects, resistance or high costs (Zhu & Zhu, 2017). These realities underscore the necessity of developing new treatment modalities.

In recent years, molecular targeted therapies have garnered attention for their specificity, safety and reduced toxicity. ARs, which mediate the body's stress response via catecholamines, have gained prominence due to their involvement in tumorigenesis and progression in various cancers (Zhang *et al*., 2024; Huang *et al*., 2018). β-AR antagonists (β-blockers), widely used for cardiovascular conditions, have shown antitumor activity in multiple malignancies - including lung, colon and melanoma - by inhibiting proliferative and invasive signaling cascades (Eng *et al*., 2014; Coelho *et al*., 2017; Schuster *et al*., 2023). Chronic stress, which heightens sympathetic nervous system activity and elevates circulating catecholamines, further implies the role of ARs in tumor development (Cooper *et al*., 2023; Han *et al*., 2022). Norepinephrine, a key catecholamine released under stress, fosters tumorigenesis and metastasis through β-AR signaling (Barbieri *et al*., 2015). By contrast, epinephrine's tumor-promoting effects remain less clear and may involve interactions with immune cells such as natural killer (NK) cells (Idorn & Hojman, 2016). Notably, some studies indicate that tricyclic antidepressants, which sharply increase systemic norepinephrine levels, are associated with higher tumor risk (Fitzgerald, 2012). Within the central nervous system, aberrant AR expression has been implicated in astrocytomas and other gliomas (Yoshioka *et al*., 2016; Kraboth & Kalman, 2023).

Taken together, these findings highlight the critical role of ARs in glioma pathobiology and their potential as therapeutic targets. This review provides an overview of recent progress in elucidating how ARs drive glioma tumorigenesis and progression and discusses emerging strategies to harness AR signaling for more effective glioma treatments.

This review integrates peer-reviewed studies published primarily between 2015 and 2024, sourced from PubMed, Scopus and Web of Science. Keywords used included "glioma", "adrenergic receptor", "β2-AR", "stress signaling", "propranolol", "EGFR

crosstalk" and "GPR55". Priority was given to original studies elucidating AR signaling pathways, therapeutic modulation or receptor crosstalk in glioma models. Review articles were used for background synthesis or context comparison only.

2. Structure and Function of ARs

ARs are integral members of the G protein-coupled receptor (GPCR) family, characterized by their complex structure comprising an extracellular domain, a seven-transmembrane helical domain and an intracellular domain. The structural attributes of GPCRs, combined with their crucial role in signal transduction, make them ideal drug targets. Indeed, approximately 40% of the drugs on the global pharmaceutical market are designed to target GPCRs, highlighting their significant importance and widespread application in therapeutics (Keri & Barth, 2018). ARs are broadly categorized into two main types: alpha (α) and beta (β), each further subdivided into several subtypes. The α receptors are divided into three α1 subtypes (α1A, α1B, α1D) and three α2 subtypes (α2A, α2B, α2C), whereas the β receptors are divided into three subtypes (β1, β2, β3). The α1 receptors primarily function through the activation of phospholipase C-β (PLC-β) via Gq proteins, leading to the hydrolysis of phosphatidylinositol-4,5-biphosphate (PIP2) into second messengers' inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG). This hydrolysis results in an increase in intracellular calcium (Ca^{2+}) levels, triggering a cascade of downstream signaling pathways that convert extracellular stimuli into intracellular responses. In contrast, α2 receptors are coupled with Gi proteins, which inhibit adenylate cyclase activity, thereby reducing intracellular cyclic adenosine monophosphate (cAMP) levels. This reduction subsequently inhibits protein kinase A (PKA)-mediated downstream signaling pathways, illustrating a different mechanism of intracellular signaling regulation (Figure 1).

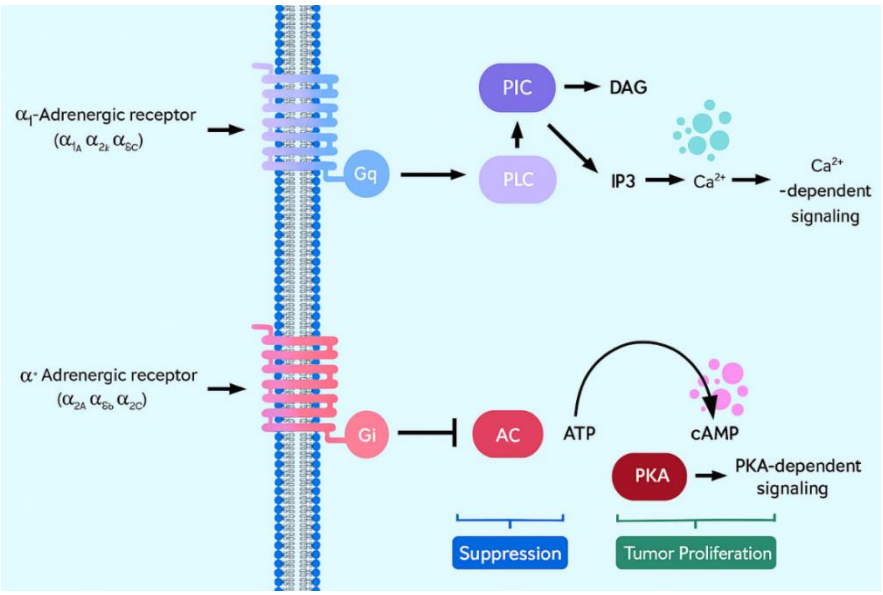

Figure 1. Presents a schematic overview of the α-AR subtypes and their corresponding downstream signaling pathways. The α1-AR subtype, linked to the Gq G-protein, activates phospholipase C (PLC), which catalyzes the breakdown of phosphatidylinositol-4,5-bisphosphate (PIP2) into inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG). This, in turn, initiates further signaling cascades. In contrast, the α2-AR subtype, associated with the Gi G-protein, inhibits adenylyl cyclase (AC), leading to reduced intracellular cAMP levels and suppression of the cAMP/PKA signaling pathway

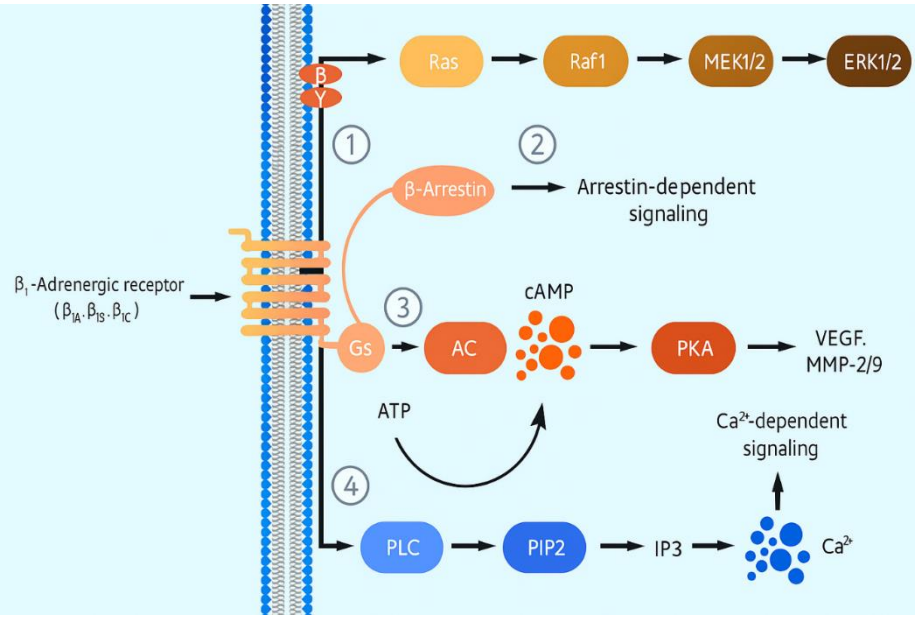

Figure 2. Provides a schematic depiction of the β-AR subtypes and their associated downstream signaling pathways. β-ARs signal through Gβγ and Gs G-proteins, activating two key pathways: The Ras→Raf1→MEK1/2→ERK1/2 cascade and the cAMP/PKA pathway (①②). In addition, β-ARs can trigger G protein-independent signaling, including β-arrestin-dependent pathways and phospholipase C (PLC)/IP3/Ca2+ signaling (③④). Abbreviations include AC for adenylyl cyclase, PIP2 for phosphatidylinositol-4,5-bisphosphate and IP3 for inositol 1,4,5-triphosphate

The ability of ARs to activate diverse downstream signaling pathways underlies their functional complexity. For instance, specific activation of ARs has been linked to the promotion of cell proliferation in various cancers, including lung cancer (Hu *et al*., 2016), ovarian cancer (Wang & Jiang, 2021), liver cancer (Jiang *et al*., 2019), pancreatic cancer (Lin *et al*., 2023), prostate cancer (Cardoner *et al*., 2024) and gastric cancer (Deshpande *et al*., 2020). Conversely, in breast cancer cells, AR activation has been found to inhibit the proliferation of MDA-MB-231 cells, suggesting a more nuanced role depending on the cancer type and cellular context (Silva *et al*., 2022). The adrenergic system also plays a pivotal role in regulating tumor biology beyond cell proliferation. In prostate cancer, a higher density of adrenergic nerve fibers correlates with a poorer prognosis, indicating a role in promoting tumor aggressiveness (Fernandez *et al*., 2013). Inhibition of β-AR signaling in prostate cancer has been shown to disrupt endothelial cell metabolism, thereby impeding angiogenesis and tumor growth in aggressive cancer forms (Hondermarck & Jobling, 2018). Moreover, research by Renz and colleagues has demonstrated that chronic stress can enhance the secretion of nerve growth factors such as nerve growth factor (NGF) or brain-derived neurotrophic factor (BDNF), which in turn promotes the growth of adrenergic nerve fibers. Blocking β2-AR signaling has been shown to counteract stress-induced nerve growth and inhibit the development of pancreatic tumors (Benzaquen *et al*., 2024). Additionally, monoamine oxidases, which degrade catecholamines like epinephrine and norepinephrine, have been found to inhibit α1-AR and β2-AR-mediated invasion of liver cancer cells and promote anoikis, a form of programmed cell death induced by detachment (Zou *et al*., 2024). These studies collectively underscore the multifaceted role of ARs in regulating tumor cell survival, invasion, apoptosis and angiogenesis. The newly formed adrenergic nerve fibers also

contribute to shaping the tumor microenvironment, thereby further influencing tumor progression and highlighting ARs as critical components in cancer biology and potential therapeutic targets.

3. The role of AR in the occurrence and development of brain glioma

3.1. α-AR and brain glioma

α-Adrenergic receptors (α-ARs) play an essential role in the tumorigenesis and progression of various cancers. For example, α2-AR activation has been shown to enhance the proliferation of breast and pancreatic cancer cells, highlighting its importance in cancer biology (Yaniv *et al*., 2024; Li *et al*., 2023). However, research on α-ARs in gliomas remains relatively limited. One study investigated the effects of prazosin - a non-selective α1-AR antagonist and a selective α2B-AR antagonist - on glioblastoma-initiating cells (GICs) and their differentiated progeny in vitro. Prazosin not only induced apoptosis in these cells but also inhibited the growth of brain gliomas in an orthotopic mouse model transplanted with human GICs (Assad Kahn *et al*., 2016).

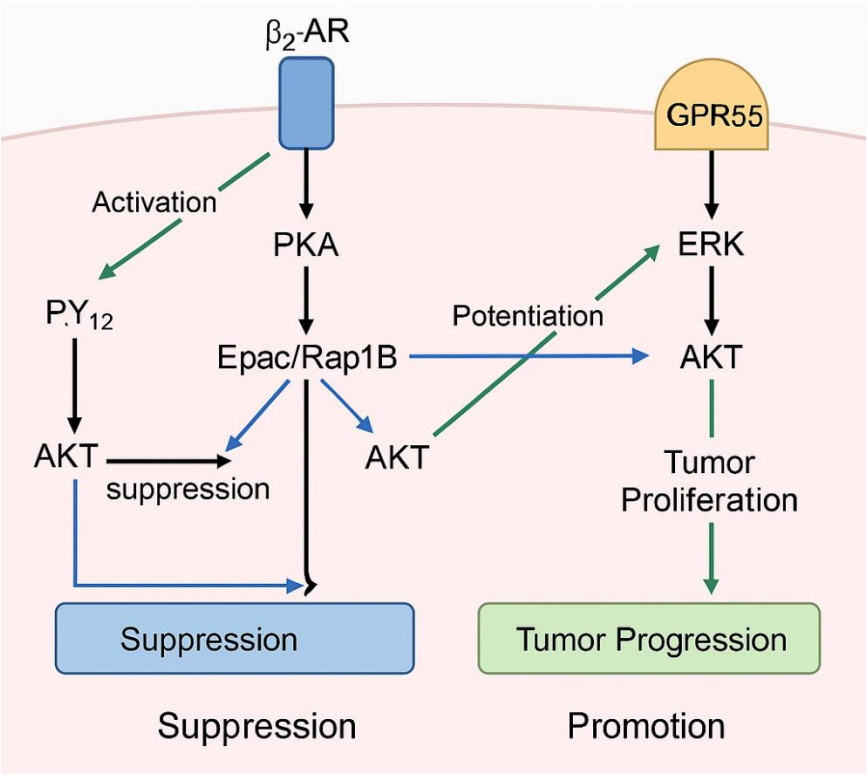

Figure 3. AR Signaling Crosstalk in Gliomas. This schematic illustrates the complex signaling interplay between β_2-adrenergic receptors (β_2-AR), purinergic $P2Y_{12}$ receptors and G protein-coupled receptor 55 (GPR55) in glioma cells. Activation of β_2-AR stimulates the PKA and Epac/Rap1B pathways, which in certain contexts suppress AKT signaling and glioma proliferation. However, $P2Y_{12}$ activation can reverse this suppression by reactivating AKT, thereby promoting tumor growth. In parallel, GPR55 activation enhances ERK and AKT phosphorylation, leading to increased tumor proliferation and invasiveness. Crosstalk between β_2-AR and GPR55 signaling may potentiate oncogenic outputs depending on the intracellular context. This network highlights potential therapeutic strategies involving simultaneous β_2-AR activation and inhibition of $P2Y_{12}$ or GPR55 to suppress glioma progression

Further analysis showed that prazosin's pro-apoptotic effect was significantly reduced when the expression of protein kinase C delta (PKCδ) was knocked down. Under these conditions, prazosin's suppression of AKT phosphorylation was also diminished, suggesting that its antitumor effects are largely mediated by PKCδ activation and AKT inhibition. Interestingly, prazosin-binding sites could not be identified in membrane extracts of GICs, indicating that prazosin's antitumor action may not be directly associated with α-AR antagonism. Additionally, prazosin treatment did not affect AKT phosphorylation or induced apoptosis in neural stem cells (NSCs), nor was any notable brain damage observed in prazosin-treated mice. These findings imply that prazosin exerts a relatively selective cytotoxic effect on GICs, likely by activating PKCδ, which subsequently inhibits the AKT pathway and activates caspase-3, leading to GIC apoptosis. However, the precise molecular mechanisms underlying prazosin's anti-important effects require further exploration (Assad Kahn *et al*., 2016).

There is also evidence that doxazosin, another α1-AR antagonist, modulates the bioactivity of angiotensin peptides, thereby inhibiting glioma cell proliferation (Tan *et al*., 2019). Taken together, these findings underscore the potential of α-AR antagonists as therapeutic agents against gliomas, although additional research is warranted to fully elucidate the mechanisms and clinical implications of targeting α-ARs in glioma treatment (Figure 3).

3.2. β-AR and brain glioma

β-ARs) play a key role in mediating the physiological effects of catecholamines, such as epinephrine and norepinephrine, in the sympathetic nervous system. Upon activation, β-ARs predominantly increase intracellular cyclic AMP (cAMP), which subsequently activates protein kinase A (PKA). This signaling cascade triggers downstream events that can boost tumor cell proliferation, invasiveness and angiogenesis, often through the upregulation of factors such as vascular endothelial growth factor (VEGF). Among adrenergic receptors, β-ARs have been the most extensively studied in the context of brain gliomas, underscoring their critical involvement in glioma pathogenesis and progression (Prenner *et al*., 2007).

Recent work from our research group underscores the heterogeneous expression of β-AR subtypes in various glioma cell lines, revealing that their expression levels may correlate with tumor aggressiveness. For instance, in the less malignant U87-MG cell line, neither β1-AR nor β2-AR was detected, whereas the more aggressive U251-MG line expressed both subtypes, with β2-AR being especially prominent (Kraboth & Kalman, 2023). Other highly malignant human astrocytoma cell lines, such as 1321N1 and U118-MG, also exhibit β2-AR expression, though at different levels; notably, U118-MG cells have significantly lower β2-AR than 1321N1 cells (Wang *et al*., 2024; D'Alessandro *et al*., 2021). Complementing these findings, Sardi et al. reported broad β1-AR and β2-AR expression in pediatric malignant primary brain tumor tissues and across several glioma lines, including U87-MG, T98G and Daoy, while β3-AR was undetectable (Sardi *et al*., 2013).

Conversely, Annabi et al. provided evidence that patient-derived glioma tissues can express β1-, β2- and β3-AR subtypes, yet none of these subtypes were expressed in cultured U87-MG cells under standard laboratory conditions (Annabi *et al*., 2009). Intriguingly, when U87-MG cells were implanted orthotopically into mouse brains, they re-expressed all three β-AR subtypes within the resulting tumor tissue. Such observations

suggest that tumor cells may adapt to their microenvironment in vivo by activating β-AR expression, particularly in response to angiogenesis-related cues. External factors in the tumor microenvironment, including growth factors, hypoxic conditions and stress-related molecules, could potentially stimulate β-AR upregulation as the tumor progresses and becomes more vascularized.

Functionally, β-AR signaling in gliomas can vary dramatically depending on the specific cellular context. In certain astrocytoma lines (e.g., 1321N1 and U118-MG), β2-AR agonists significantly inhibit proliferation, an effect reversed by the non-selective β-AR antagonist propranolol (D'Alessandro *et al*., 2021). In U87-MG cells, which do not express β2-AR, agonists targeting β2-AR fail to increase proliferation - consistent with the absence of β2-AR (Kraboth & Kalman, 2023; D'Alessandro *et al*., 2021). By contrast, our group discovered that the β-AR agonist isoproterenol (ISO) markedly increases proliferation in U251-MG cells (Kraboth & Kalman, 2023). Although the precise basis for these opposite responses remains unclear, one hypothesis is that β-AR signaling can differentially regulate downstream effector pathways depending on the molecular milieu of a particular cell line.

In astrocytoma cells, the β2-AR agonist (R,R')-4'-methoxy-1-naphthylfenoterol (*R,R*')−*MNF* (R,R')−MNF increases intracellular cAMP concentrations, thereby suppressing growth factor-driven ERK1/2 and PI3K signaling, key pathways that ordinarily facilitate cell proliferation and survival (D'Alessandro *et al*., 2021). This modulation is further supported by the upregulation of the cell cycle inhibitors p21^cip1 and p27^kip1 and the downregulation of cyclin D1, promoting G1 phase arrest. In contrast, in U251-MG cells, β-AR activation appears to boost ERK1/2 phosphorylation, possibly elevating matrix metalloproteinase (MMP) expression and promoting both migration and proliferation (Kraboth & Kalman, 2023). These differences highlight the nuanced role of β-ARs in gliomas, where the net effect on cell fate - proliferation or inhibition - may depend on which downstream branches of the cAMP/PKA signaling network are activated, along with the relative influence of co-activated or opposing pathways such as ERK, PI3K and others.

Additional complexity arises when considering β-AR signaling's impact on cell migration. One study reported that ISO suppresses glioma cell migration via the β2-AR/cAMP/Epac/Rap1B pathway, leading to downregulation of Rac1 (Manzano *et al*., 2021). This demonstrates that β-AR activation can either promote or inhibit key malignant behaviors (e.g., proliferation, migration) depending on the receptor subtype expressed, the specific agonist involved and the cell type's underlying signaling architecture.

Investigations into the role of β-ARs in rat C6 glioma cells further reinforce this concept. Activation of β2-AR by (R,R')-MNF inhibits C6 proliferation, a finding consistent with results in some human astrocytoma cells (Wnorowski *et al*., 2017). Interestingly, (R,R')-MNF was later found to also antagonize GPR55, another G protein-coupled receptor implicated in cell growth. Thus, the reduction in C6 proliferation may be the cumulative outcome of modulating both β2-AR and GPR55 activity (Wnorowski *et al*., 2017). Studies examining natural compounds have shown similarly intricate effects. Extracts from Hypericum perforatum L. - specifically hyperforin and hyperoside - induce β1-AR internalization in rat C6 cells, lowering β1-AR density on the cell membrane and suppressing downstream PKA-dependent pathways by reducing cAMP levels (Keksel *et al*., 2019). These extracts also decrease the affinity of β2-AR for its

ligands, yet their net influence on proliferation, migration and additional malignancy-related processes has yet to be thoroughly evaluated (Prenner *et al*., 2007).

Overall, the existing evidence underscores the complex, context-dependent nature of β-AR signaling in gliomas. This variability suggests that β-ARs could serve as critical modulators of glioma growth and progression, making them attractive, albeit challenging, therapeutic targets. Further elucidation of how different β-AR subtypes interact with key intracellular pathways - including ERK, PI3K/AKT, Epac/Rap1B and MMP-related networks - will be crucial for developing targeted interventions. Understanding how the tumor microenvironment, epigenetic factors and stress-related molecules influence β-AR expression in vivo is equally important, as these insights may guide the rational design of β-AR-directed therapies. Ultimately, integrating β-AR modulators with existing treatment modalities, such as chemotherapy, radiation or immunotherapy, could lead to more effective strategies for combating gliomas. Continued research is needed to clarify the precise mechanisms of β-AR-driven tumor progression and to determine optimal ways to exploit these receptors for therapeutic benefit (Table 1).

Table 1. α-AR and β-AR involvement in brain gliomas

Receptor Type	Key Insights	Therapeutic Potential	Research Opportunities	Ref.
α2-AR	Prazosin induces apoptosis in GICs via PKCδ activation and AKT inhibition, possibly through off-target effects. No prazosin binding sites detected in GIC	Prazosin shows promise for selective glioma cell apoptosis, without harming neural stem cells. Could be a glioma-specific treatment.	Clarify the mechanism behind prazosin's off-target effects and explore other α2-AR antagonists for glioma therapy.	(Assad Kahn *et al*., 2016)
α1-AR	Doxazosin inhibits glioma proliferation by modulating angiotensin peptides, which are involved in tumorigenesis and angiogenesis.	Doxazosin may inhibit glioma growth by disrupting angiotensin-mediated pathways, potentially combined with ACE inhibitors.	Investigate the molecular interaction between α1-AR and angiotensin peptides in gliomas to optimize therapeutic targeting.	(Tan *et al*., 2019)
β1-AR	Detected in glioma tissues and cell lines. Absent in cultured U87-MG cells but present in orthotopic brain tumors in mice. Potential adaptive response during tumor formation.	Potential target for glioma therapies focusing on β1-AR expression in malignant gliomas.	Further studies to elucidate adaptive mechanisms leading to β1-AR expression in tumors.	(Annabi *et al*., 2009)
β2-AR	Expressed in aggressive gliomas. β2-AR agonists modulate cell proliferation and inhibition based on pathways (ERK1/2, PI3K). Can stimulate or inhibit depending on context.	Agonists/antagonists could be tailored for glioma subtypes. Propranolol (β-blocker) shows potential in reversing tumor-promoting effects of β2-AR	Explore β2-AR pathways and cell-context dependency to develop targeted therapies. Clarify the role of signaling pathways like ERK1/2, PI3K and cAMP.	(Kraboth & Kalman, 2023)
β3-AR	Detected in glioma tissues but absent in vitro. Upregulated in vivo during tumor growth and angiogenesis.	Exploring β3-AR's role in angiogenesis and tumor progression could provide new therapeutic targets.	Investigate the specific contribution of β3-AR to tumor angiogenesis and growth in gliomas, both in vitro and in vivo.	(Annabi *et al*., 2009)

4. Exploring interactions between AR and other membrane receptors in brain glioma development

The interplay between AR and other membrane receptors has emerged as a crucial factor in the development and progression of brain glioma. This crosstalk between different signaling pathways not only influences tumor cell behavior but also presents potential therapeutic targets. Recent studies have shown that certain compounds, such as (R,R')-MNF, serve dual roles by acting both as a β2-AR agonist and as an antagonist of the orphan G protein-coupled receptor GPR55 (Wnorowski *et al*., 2017; Plazinska *et al*., 2014; He *et al*., 2024). GPR55 is implicated in tumorigenesis due to its pro-tumor characteristics, with elevated levels of GPR55 expression correlating with increased tumor invasiveness in several cancers, including brain glioma, pancreatic cancer and breast cancer. Upon activation, GPR55 enhances the phosphorylation of signaling molecules such as ERK1/2 and AKT, promoting tumor cell proliferation and migration. On the other hand, β2-AR activation is associated with an inhibitory effect on glioma cell proliferation. This suggests a potential therapeutic approach that combines the activation of β2-AR with the inhibition of GPR55 to effectively target glioma growth and invasiveness (Wnorowski *et al*., 2017; He *et al*., 2024). In addition, studies in rat C6 glioma cells have demonstrated that β-AR activation results in an increase in intracellular cAMP levels, which subsequently inhibits protein kinase B (PKB, also known as AKT) activity (Tsygankova *et al*., 2001). However, this inhibitory effect can be reversed through the activation of the purinergic receptor P2Y12, which not only negates the effects of β-AR activation but also enhances the PI3K/PKB signaling pathway, thereby promoting the proliferation of C6 glioma cells (Morrone *et al*., 2021). These findings highlight the complex nature of AR signaling and its interactions with other membrane receptors, suggesting that the crosstalk between ARs and other receptors could be pivotal in modulating glioma progression and could serve as an important consideration in the development of targeted therapies (Table 2). Notably, although references (Quesnel *et al*., 2022; Garramona *et al*., 2023; Schuller *et al*., 2008) demonstrate AR–EGFR interactions in lung, breast and pancreatic cancer models, respectively, their direct validation in glioma models remains unclear. Thus, additional research is warranted to establish whether similar mechanisms operate in gliomas.

Table 2. Crosstalk between ARs and other membrane receptors in glioma

AR Type	Interacting Receptor	Interaction Effect	Outcome on Cancer Cells	Ref.
β2-AR	GPR55	β2-AR activation inhibits proliferation; GPR55 activation promotes proliferation via ERK1/2 and AKT phosphorylation	Potential therapeutic approach: Activate β2-AR and inhibit GPR55 to target glioma growth	(Wnorowski *et al*., 2017; He *et al*., 2024)
β-AR	P2Y12 receptor	P2Y12 activation reverses β-AR-induced inhibition of AKT, enhancing PI3K/PKB signaling pathway	Promote proliferation of C6 glioma cells	(Morrone *et al*., 2021)
α1-AR	EGFR	Inhibition of α1-AR reduces EGFR-mediated ERK1/2 phosphorylation	Suppresses proliferation and induces apoptosis in breast cancer cells	(Quesnel *et al*., 2022)
β-AR	EGFR	β-AR activation transactivates EGFR via PKA-dependent mechanism, increasing AKT and ERK1/2 phosphorylation	Promotes lung cancer development	(Garramona *et al*., 2023)
β-AR	GABAB receptor	Activation of GABAB receptor counteracts β-AR-induced proliferation and migration	Inhibits proliferation and migration of pancreatic cancer cells	(Schuller *et al*., 2008)

There is accumulating evidence that ARs do not function in isolation but interact with various other membrane receptors to collectively regulate tumor initiation and progression. One of the most studied interactions is the transactivation of the epidermal growth factor receptor (EGFR) by ARs. For example, inhibition of α1-AR has been shown to reduce EGFR-mediated ERK1/2 phosphorylation, thereby suppressing the proliferation of breast cancer cells and inducing apoptosis (Quesnel *et al*., 2022). Conversely, β-AR activation has been found to transactivate EGFR via a PKA-dependent mechanism, leading to increased phosphorylation of AKT and ERK1/2, which subsequently promotes lung cancer development (Garramona *et al*., 2023). This bidirectional regulation underscores the multifaceted role of ARs in modulating cancer cell signaling networks. ARs also exhibit crosstalk with other G protein-coupled receptors (GPCRs), further complicating their signaling dynamics. Schuller et al. reported that isoproterenol (ISO)-induced β-AR activation could enhance the proliferation and migration of pancreatic cancer cells, effects that were counteracted by the activation of the metabotropic γ-aminobutyric acid (GABAB) receptor with the agonist baclofen (Schuller *et al*., 2008). This inhibitory effect suggests a potential therapeutic strategy that involves modulating multiple GPCR pathways to control tumor growth and spread. These findings indicate that the interactions between ARs and other membrane receptors contribute significantly to the regulatory mechanisms underlying glioma development. Understanding these complexes signaling networks is essential for identifying novel therapeutic targets and developing more effective treatment strategies for brain glioma. The dynamic crosstalk between ARs and various membrane receptors could provide new insights into the pathophysiology of gliomas and pave the way for innovative approaches to cancer therapy. Future research should focus on delineating these interactions in greater detail to fully exploit their potential in clinical applications (Table 3).

Table 3. Potential therapeutic strategies involving AR and other receptors

Strategy	Mechanism	Potential Benefit	Ref.
Combine β2-AR activation with GPR55 inhibition	β2-AR activation inhibits glioma proliferation; GPR55 inhibition reduces pro-tumor signaling	Effectively target glioma growth and invasiveness	(Wnorowski *et al*., 2017; He *et al*., 2024)
Inhibit P2Y12 receptor	Prevents reversal of β-AR-mediated inhibition of AKT, maintaining suppression of proliferation	Maintains inhibitory effect on glioma cell proliferation	(Morrone *et al*., 2021)
Modulate AR and EGFR interaction	Inhibit α1-AR to reduce EGFR signaling or modulate β-AR to affect EGFR transactivation	Suppress proliferation and induce apoptosis in cancer cells	(Quesnel *et al*., 2022; Garramona *et al*., 2023)
Activate GABAB receptor	Counteracts β-AR-induced proliferation and migration through GPCR pathways	Controls tumor growth and spread	(Schuller *et al*., 2008)

5. Discussion

ARs, particularly β-ARs, have emerged as crucial regulators of glioma pathogenesis and progression. These receptors are involved in an array of tumor-related processes, including glioma cell survival, apoptosis, proliferation, invasion, angiogenesis and metastasis. Their multifaceted roles underscore the complexity of glioma biology and highlight the therapeutic potential of ARs as targets for intervention. However, the function of β-ARs is not uniform across different glioma subtypes; rather, it varies considerably depending on the cellular and molecular context.

As discussed earlier, β-ARs engage in multiple signaling pathways that may either promote or inhibit glioma progression. These pathways include: (1) activation of the PKA signaling pathway through Gs protein coupling, leading to increased intracellular cAMP levels and subsequent modulation of downstream targets; (2) inhibition of PKA signaling via Gi protein coupling, which can attenuate cAMP signaling in certain cellular contexts; (3) activation of G protein-independent pathways, such as those mediated by β-arrestin and MAPK cascades, which are implicated in cell proliferation and survival and (4) interactions with other membrane receptors, such as EGFRs and purinergic receptors, resulting in the co-regulation of signaling networks.

This diversity in β-AR signaling is likely influenced by the distinct protein expression profiles of different glioma cells, leading to the selective activation of specific downstream pathways or the concurrent activation of multiple pathways with potential synergistic or antagonistic effects. Such variability in signaling responses can lead to highly context-dependent functional outcomes, influencing cell behavior, glioma aggressiveness and treatment responsiveness. This heterogeneity may explain why β-AR-targeted therapies yield variable clinical outcomes across different glioma subtypes and individual patients. Understanding these differences is essential for designing more personalized and effective therapeutic strategies for glioma management.

A critical aspect of β-AR-mediated signaling in gliomas is its capacity to integrate with other key oncogenic pathways. One of the most well-characterized interactions is between β-ARs and EGFRs, a family of receptor tyrosine kinases that play a central role in GBM progression. EGFR mutations and amplifications are among the most common genetic alterations in GBM, making EGFR a major therapeutic target. Recent studies suggest that β-ARs can either enhance or inhibit EGFR-driven signaling, depending on the specific cellular context. In some tumors, β-AR inhibition reduces EGFR-mediated activation of the PI3K/AKT and MAPK pathways, leading to decreased proliferation and increased apoptosis. Conversely, β-AR activation can potentiate EGFR signaling via PKA-dependent mechanisms, further promoting glioma growth and invasiveness.

Beyond EGFR, β-ARs also interact with other membrane receptors, including purinergic P2Y receptors, cannabinoid receptors and serotonin receptors, which influence glioma cell migration, invasion and resistance to therapy. For instance, in glioma models, β-ARs have been shown to modulate the expression and activity of MMPs, enzymes that degrade the extracellular matrix and facilitate tumor cell invasion. Additionally, β-AR-mediated signaling can regulate the HIF-1α pathway, which plays a key role in glioma adaptation to hypoxic conditions and resistance to anti-angiogenic therapy. Given the intricate crosstalk between β-ARs and other oncogenic pathways, understanding the precise conditions under which β-AR signaling promotes or inhibits tumor growth is critical. These insights could inform the development of novel combination therapies that simultaneously target β-ARs and other key signaling molecules to maximize therapeutic efficacy.

The potential for AR-targeted therapies in glioma treatment is promising but remains largely underexplored. Preclinical studies have demonstrated that β-AR antagonists, such as propranolol, can suppress glioma proliferation, angiogenesis and invasion. Propranolol has been shown to inhibit β-AR-mediated cAMP signaling, reduce VEGF expression and impair glioma cell migration, suggesting that β-AR blockade could serve as an effective therapeutic strategy. Furthermore, studies in other cancers, including breast and lung cancer, have indicated that β-AR inhibition may enhance the efficacy of chemotherapy and radiotherapy by sensitizing tumor cells to treatment-induced apoptosis.

Given these findings, combining β-AR-targeted therapies with standard glioma treatments - such as temozolomide chemotherapy, radiotherapy and immunotherapy - could yield synergistic effects. For example, β-AR inhibition may counteract the immunosuppressive effects of chronic stress-mediated catecholamine release, thereby enhancing the efficacy of immune checkpoint inhibitors. Additionally, β-AR antagonists may reduce tumor vasculature abnormalities and improve drug delivery by modulating angiogenesis, potentially overcoming one of the major limitations of current glioma therapies.

However, several challenges must be addressed before β-AR-targeted therapies can be widely implemented in clinical practice. One major obstacle is the heterogeneity of β-AR expression in gliomas, which varies across different tumor subtypes and stages. This variability suggests that not all glioma patients would benefit equally from β-AR blockade, emphasizing the need for biomarkers that can predict treatment responsiveness. Future research should focus on identifying molecular signatures that correlate with β-AR dependency in gliomas, allowing for the stratification of patients who are most likely to respond to β-AR-targeted interventions. Another challenge lies in the potential systemic effects of β-AR antagonists. Because β-ARs are widely expressed in normal tissues, prolonged β-AR inhibition could lead to off-target effects, including cardiovascular and metabolic disturbances. Therefore, the development of selective β-AR modulators that specifically target glioma cells while sparing normal brain tissue represents an important area of future research. Advances in drug delivery systems, such as nanoparticle-based formulations or blood-brain barrier (BBB)-penetrant small molecules, may also improve the efficacy and safety profile of β-AR-targeted therapies in glioma patients.

Compared to previous reviews on adrenergic signaling in cancer, our study offers several novel perspectives specific to gliomas. While Choy et al. (2016) and Simińska et al. (2022) reviewed β-AR expression in various cancers, they did not explore the differential β-AR expression in glioma subtypes or its modulation by the tumor microenvironment. Our manuscript systematically compares AR expression across glioma models (e.g., U87, U251, C6), highlighting context-dependent signaling outcomes. Additionally, the inclusion of receptor crosstalk - specifically AR interactions with GPR55, EGFR and P2Y12 - in gliomas provides mechanistic insight not previously synthesized in a unified framework. These dimensions distinguish our review from existing literature and advance the field by proposing specific therapeutic pairings grounded in signaling convergence.

6. Future Directions and Clinical Implications

Given the complexity of AR signaling and its implications for glioma progression, future research should focus on delineating the precise molecular mechanisms by which ARs regulate glioma biology. Determining the role of β-AR subtypes in glioma progression - understanding whether specific β-AR subtypes (β1, β2, β3) have distinct or overlapping roles in glioma pathophysiology could help refine targeted therapeutic approaches. Elucidating the interaction between β-ARs and other oncogenic pathways - investigating how β-ARs modulate EGFR, HIF-1α and MMP activity may reveal novel combination therapy strategies. Exploring the impact of chronic stress and the tumor microenvironment on β-AR signaling - assessing how systemic factors, such as stress-induced catecholamine release, influence glioma behavior could provide insights into

how lifestyle factors affect glioma progression and treatment response. Developing clinically relevant β-AR-targeted therapies - translating preclinical findings into effective clinical interventions requires rigorous testing of β-AR inhibitors, agonists and modulators in glioma models and clinical trials. Several β-blockers, including propranolol, are currently being investigated for oncological applications. For example, clinical trials such as NCT03384836 and NCT04583756 are assessing the antitumor effects of β-blockade in glioblastoma and other cancers. These studies underscore the translational potential of our review's core findings. The feasibility of β-AR modulation in glioma could be improved by advanced delivery technologies, including nanoparticle-based formulations and BBB-penetrant small molecules. Moreover, molecular profiling of tumors to determine β2-AR expression or AR/GPR55 interaction patterns may serve as predictive biomarkers for patient stratification. Integrating AR antagonists with chemotherapy, radiation or immune checkpoint inhibitors holds promise in counteracting stress-induced immunosuppression and therapy resistance.

7. Conclusion

The dynamic and multifaceted role of ARs in glioma pathogenesis presents both challenges and opportunities for therapeutic intervention. By further exploring the diverse signaling pathways and interactions associated with ARs, researchers can develop more sophisticated strategies for targeting these receptors in glioma and potentially other cancers. As this field evolves, ARs may become a cornerstone of precision oncology, providing new avenues for personalized glioma treatment. Integrating AR-targeted therapies with existing treatment modalities holds promise for improving patient outcomes and overcoming the limitations of current glioma therapies. Continued advancements in this area may ultimately transform ARs into a key component of multimodal glioma treatment strategies, offering new hope for patients with this devastating disease.

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