Critical Reviews in Oncology / Hematology 191 (2023) 104142

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Targeting androgen receptor in glioblastoma

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ARTICLE INFO

Keywords:
Glioblastoma
Androgen receptor
5α-Reductase
Epidermal growth factor receptor
Androgen receptor antagonists
5α-Reductase inhibitor

ABSTRACT

Glioblastomas are primary brain tumors that originate from glial stem cells or progenitor cells. There is a large difference in the incidence of glioblastoma between males and females. Studies revealed that the gender differences in the tumor may be attributable to the androgen receptor signaling axis. The incidence rate of glioblastoma in men is higher than that in women. Aberrant activation of the androgen receptor signaling pathway, or interactions between the androgen receptor signaling axis and other signaling axes promote the development of glioblastoma. Therefore, targeting the androgen receptor holds promise as a therapeutic approach for glioblastoma. This review investigates the dynamics of drug research into the treatment of glioblastoma by targeting the androgen receptor. The first finding in line with expectations is that androgen receptor antagonists, represented by enzalutamide, have been studied and shown to have anti-glioblastoma effects. In addition, it was found that the combination of 5-alpha reductase inhibitors and androgen receptor antagonists resulted in better therapeutic outcomes than each of them alone. Similar results were obtained with the combination of an epidermal growth factor receptor inhibitor and an androgen receptor antagonist. In addition, four small molecule compounds have been shown to exert significant anti-glioblastoma effects by directly or indirectly targeting the androgen receptor. Expectantly, one of these small molecules, seviteronel, progressed to the phase II clinical trial stage. These findings suggest that targeting the androgen receptor for glioblastoma may be a promising therapeutic option.

1. Introduction

Gliomas arise from the cancerous transformation of glial cells or precursor cells. According to the fifth edition of the WHO Classification of Tumors of the Central Nervous System in 2021, gliomas were divided into isocitrate dehydrogenase (IDH) mutant type and IDH wild type. IDH mutant type of gliomas include oligodendroglioma and astrocytoma; glioblastoma (GBM) is an IDH wild-type glioma (Berger et al., 2022) (Fig. 1). GBM is the most malignant glioma with the worst prognosis, accounting for 48.6% of malignant central nervous system tumors (Miller et al., 2021; Tan et al., 2020) (Fig. 2A). In the past decades, the incidence rate of primary malignant tumors of the central nervous system has continued to rise (Berger et al., 2022; Porter et al., 2010), in addition, GBM has the highest incidence rate among central nervous system malignant tumors, followed by diffuse astrocytoma and lymphoma (Ostrom et al., 2018a). The incidence of GBM also varies greatly between genders, with the incidence rate in men being 1.6 times higher than that in women (Ostrom et al., 2018a; Thakkar et al., 2014; Ostrom et al., 2018b) (Fig. 2B). Although the incidence rate of low-grade gliomas in men and women is almost the same, malignant brain tumors (including GBM) are more common in men, especially GBM subtypes-primary tumors are more common in men, while secondary tumors are more common in women (Yang et al., 2019a; McKinley et al., 2000). Women and female animals with GBM have longer survival time and better outcomes, even considering the scope of resection, treatment scope and age (Li et al., 2015). These findings suggest that GBM is likely to be a disease with a significant association with sex hormones.

Androgen receptor (AR) is a steroid hormone receptor, which mediates physiological function by combining with its steroid ligands (including dehydroepiandrosterone, testosterone and dihydrotestosterone) (Crona and Whang, 2017; Li et al., 2017). In particular, after ligand-induced conformational changes, AR dissociates from heat shock

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https://doi.org/10.1016/j.critrevonc.2023.104142
Received 24 February 2023; Received in revised form 25 July 2023; Accepted 21 September 2023
Available online 24 September 2023

protein and moves from cytoplasm to nucleus for DNA transcription (Crona and Whang, 2017; Narayanan and Dalton, 2016). Alternatively, AR can be activated independently of androgens. In the case of androgen deficiency, phosphorylation of multiple tyrosine residues can restore AR function (van der Steen et al., 2013). Aberrant activation and disturbed expression of AR have been reported in various types of cancer, such as bladder cancer (Li et al., 2017), prostate cancer (Shen et al., 2021; Herberts et al., 2022), salivary adenocarcinoma (Dalin et al., 2017).

The expression of AR-mRNA and the existence of AR protein in GBM and other brain tumors have been studied for many years (Paoletti et al., 1990; Magrassi et al., 1993). Although the effect of AR on tumor biology has been fully understood in prostate cancer cells, little is known about the regulation of AR on gene expression in GBM (Zalcman et al., 2018). One of the possible reasons for the higher incidence of GBM in men than in women is that men have much higher concentrations of androgens than women (Carrano et al., 2021). Androgen receptor is widely expressed in glioblastomas (Berny et al., 2004; Yague et al., 2004; Batistatou et al., 2004). Carrol et al (Carroll et al., 1995) identified androgen receptor mRNA expression in all of the GBM samples they collected. While according to the study of Paoletti et al., AR expression was detected in 37.5% of glioblastomas, 13.3% of anaplastic astrocytoma and 8.3% of astrocytoma (Paoletti et al., 1990; Batistatou et al., 2004) (Fig. 2C). Referring to the grading criteria for gliomas, it can be found that the higher the AR expression, the more malignant the glioma (Fig. 2D). GBM has the highest AR expression among the three gliomas and is also the most malignant glioma. Although it is not clear what role AR played in the occurrence and development of GBM. One study proposed that androgen receptor signaling promotes GBM by inhibiting TGFβ receptor signaling (Yu et al., 2015). Another study found that circ-ASPH expression was upregulated in GBM specimens and cells, and also found that circ-ASPH promoted GBM cell progression by upregulating the expression of AR. Thus, they concluded that circ-ASPH activated AR, and then AR promoted GBM progression (Qu et al., 2021). Bao et al. found that AR promoted the progression of GBM cells by inhibiting the expression of small VCP/p97-interacting protein and p53 (Bao et al., 2017). By analyzing data from the Cancer Genome Atlas database, Fariña-Jerónimo et al. found that glioblastoma patients with high AR-activity had a worse prognosis, which could be attributed to dysregulated apoptosis due to activation of the AR in glioblastoma cells (Fariña-Jerónimo et al., 2022). Testosterone is an endogenous androgen that has been demonstrated to promote glioblastoma cell proliferation, migration and invasion through activation of the androgen receptor (Rodríguez-Lozano et al., 2019). Dehydroepiandrosterone, another ligand for AR, has been shown to promote the acquisition of drug resistance of glioblastoma to temozolomide (Yang et al., 2019b). The above studies suggest that the initiation, progression, and prognosis of GBM and the development of drug resistance may all be associated with AR (Fig. 3).

According to the latest treatment guidelines of NCCN, the standard care for GBM includes surgery, radiation therapy, and chemotherapy. For newly diagnosed, high-grade GBM patients, maximum surgical resection with preservation of neurological integrity is the first step in treatment. Radiotherapy and temozolomide, are the cornerstones of initial treatment for patients with normal physical status and newly diagnosed GBM. However, the problems of tumor metastasis and drug resistance are currently a huge challenge in the clinical treatment of GBM (Tomar et al., 2021; Gao et al., 2022). Clinicians and scientists are constantly searching for new therapies to treat GBM. Some promising research has focused on identifying abnormal genetic and signal pathways to develop small molecules for targeted therapy. Based on the association of the AR with GBM, the strategy of targeting AR for the treatment of glioblastoma has gained interest and a number of studies have been carried out. This review collects relevant research dynamics and provides an immediate evaluation of progress in targeting androgen receptors for the treatment of GBM, in the hope of informing drug development in this field.

2. Advances in the treatment of glioblastoma with androgen receptor antagonists

Abnormal increases in AR at the DNA, RNA and protein levels have been observed in GBM according to Zalcman et al (Zalcman et al., 2018). When A172, U87MG and T98G (GBM cell lines) cells were treated with the AR antagonists enzalutamide and bicalutamide, both AR antagonists induced cell death in a concentration-dependent manner, with enzalutamide having a more pronounced effect (Zalcman et al., 2018). In addition, oral enzalutamide caused a reduction in tumor volume in vivo in a xenograft glioblastoma model (Zalcman et al., 2018). These studies illustrate that the two AR antagonists, bicalutamide and enzalutamide, can curb the development of GBM in vitro and in vivo. This finding suggests that treating GBM with AR antagonists is a promising strategy.

Zhao et al. found that enzalutamide down-regulated the expression of AR protein and inhibited the growth of U87MG, U138MG, Ln229 and MGPP3 cells. Furthermore, they found that enzalutamide down-regulated the expression of tumor stem cell marker genes Nanog, GATA4 and Oct4 in the homologous in situ GBM mouse model, thereby inhibiting the progression of GBM tumor and significantly prolonging the survival period of mice (Zhao et al., 2021). The results strongly suggest that AR may be involved in the process of GBM formation and act as an important factor in the maintenance and/or proliferation of glioma cancer stem cells, consistent with the findings that androgens/AR promote the proliferation of neural stem cells (Ransome and Boon, 2015).

5α-reductase is a key steroid-producing enzyme. Scientists have demonstrated that 5α-reductase inhibitors can block the synthesis of androgens, thus using them to treat BPH and prostate cancer (Li et al.,

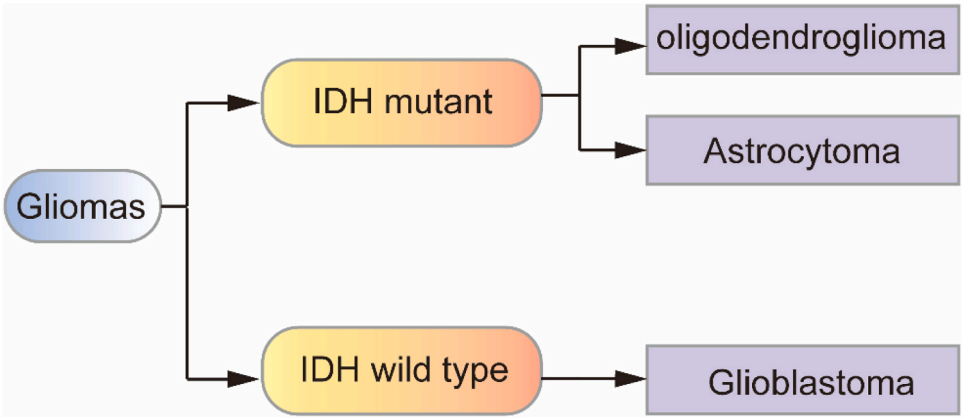

Fig. 1. WHO classification of gliomas in 2021.

2011; McConnell et al., 2003). Dutasteride is a 5α-reductase inhibitor that is often used in clinical practice to treat benign prostatic hyperplasia (Roehrborn et al., 2010; Björnebo et al., 2022). Given that GBM cells express androgen receptors and can synthesize androgens (Mondragón et al., 2021). Thus, interfering with androgen receptor signaling and/or inhibiting androgen synthesis are potential strategies for treating GBM. Orozco et al. examined the effects of the 5α-reductase inhibitor dutasteride, the AR antagonists cyproterone and flutamide, and combinations of these drugs on the metabolism, proliferation and invasive capacity of GBM cells. They found that the addition of dutasteride, cyproterone or flutamide to the culture medium significantly reduced the metabolism and proliferation of GBM cells. In addition, dutasteride significantly reduced the invasive capacity of GBM cells. Moreover, any combination of these drugs enhanced their inhibitory effects, with the combination of dutasteride and flutamide being the most effective in inhibiting GBM cell proliferation. Their study suggests that the combination of an AR antagonist and a 5α-reductase inhibitor may be a more effective option for the treatment of GBM (Orozco et al., 2020).

Epidermal growth factor receptor (EGFR) signal pathway is involved in the activation of AR in glioblastoma (Zalcman et al., 2021; Poisson et al., 1983). Zalcman et al. detected the expression of AR and EGFR in 28 glioblastoma samples by reverse transcription quantitative polymerase chain reaction. They found a positive correlation between AR and EGFR expression levels in the samples ($R=0.47$; $P = 0.00916$) (Zalcman et al., 2021). In addition, the researchers treated A172, U87MG and T98G GBM cells with enzalutamide (AR antagonist) and afatinib (EGFR kinase inhibitor), and then examined AR expression. They found that EGFR overexpression induced AR overexpression and nuclear translocation, and that EGFR kinase inhibitors prevented AR activation in GBM cells. EGFR kinase inhibitors reduced AR nuclear translocation in U87MG cells. This study suggests that AR is involved in the development of GBM by the action of EGFR. Therefore, combining AR antagonists and EGFR kinase inhibitors is also a strategy to treat GBM.

3. Small molecular compounds targeting androgen receptor in the treatment of glioblastoma

Curcumin is a well-known natural compound for tumor suppression and is thought to have therapeutic effects in neurodegenerative diseases because of its ability to cross the blood-brain barrier (Farkhondeh et al., 2019). Curcumin can effectively impede the proliferation and invasion of GBM cells through the WNT/β-catenin and NF-κB pathways (Hesari et al., 2019). The researchers developed a compound named ALZ003, which has a structure similar to that of curcumin and has the characteristic of degrading AR proteins (Bott et al., 2016). ALZ003 significantly inhibited the proliferation of U87MG and U87MG-R cells in a time-dependent and dose-dependent manner. Further research revealed that ALZ003 inhibited the survival of GBM cells by degrading of AR by ubiquitination (Chen et al., 2020). Thus, ALZ003 produces a GBM suppressive effect by targeting and degrading AR.

Cedrol is a sesquiterpenol isolated from the *atlantic cedar*. Cedrol is also the main active ingredient of conifers (Chakraborty et al., 2017; Loizzo et al., 2008). It has anti-inflammatory, anti-fungal and anti-cancer effects (Su et al., 2012; Wang et al., 2019). Chang et al. found that cedrol could inhibit cell proliferation of DBTRG-05MG cells in a dose-dependent manner. Furthermore, cedrol targeted the activation site of AR and then inhibited dihydrotestosterone-induced AR translocation, thereby suppressing the expression of its downstream genes and reducing the proliferation of DBTRG-05MG cells (Chang et al., 2020). These experimental findings suggest that cedrol inhibits GBM cell proliferation by suppressing AR signaling.

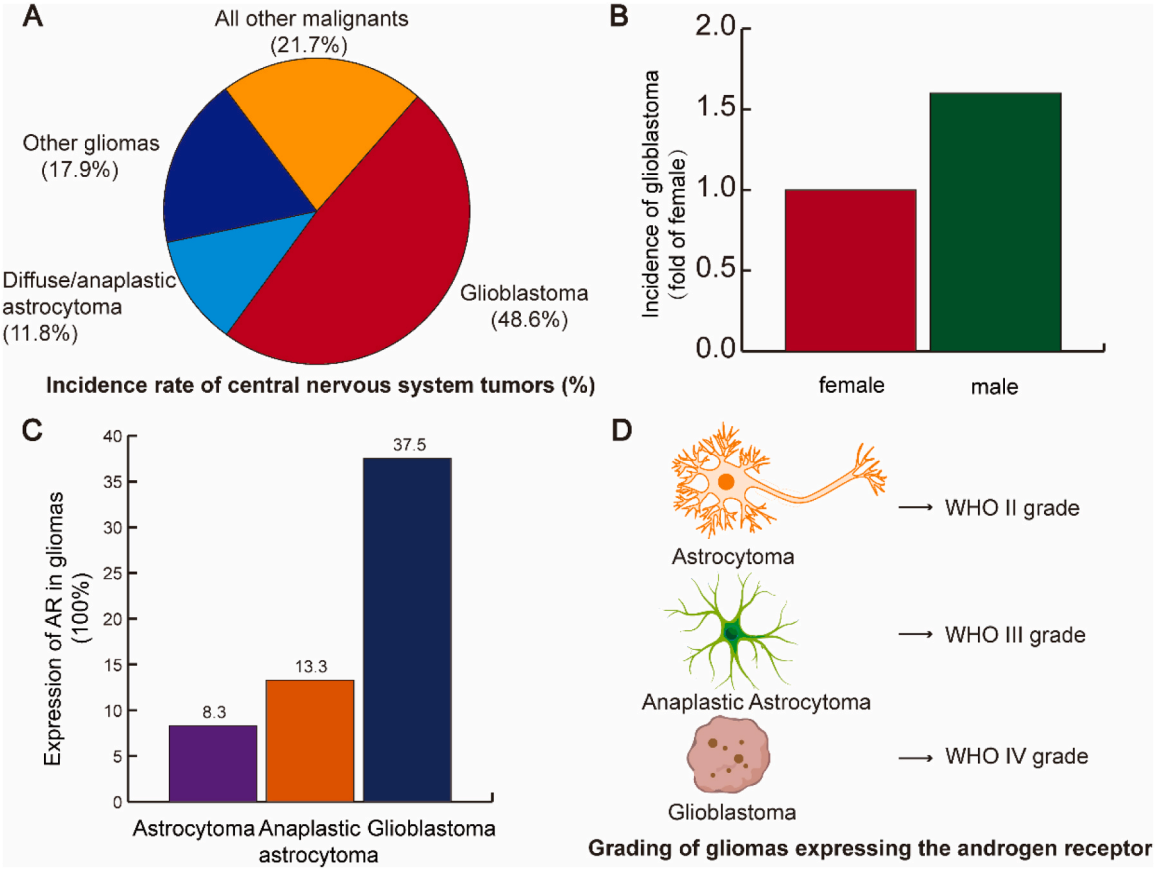

Fig. 2. Incidence of glioblastoma and their androgen receptor expression frequency. (A) Incidence rate of central nervous system tumors; (B) Incidence rate of glioblastoma in men and women; (C) Expression of AR in gliomas; (D) Grading of gliomas.

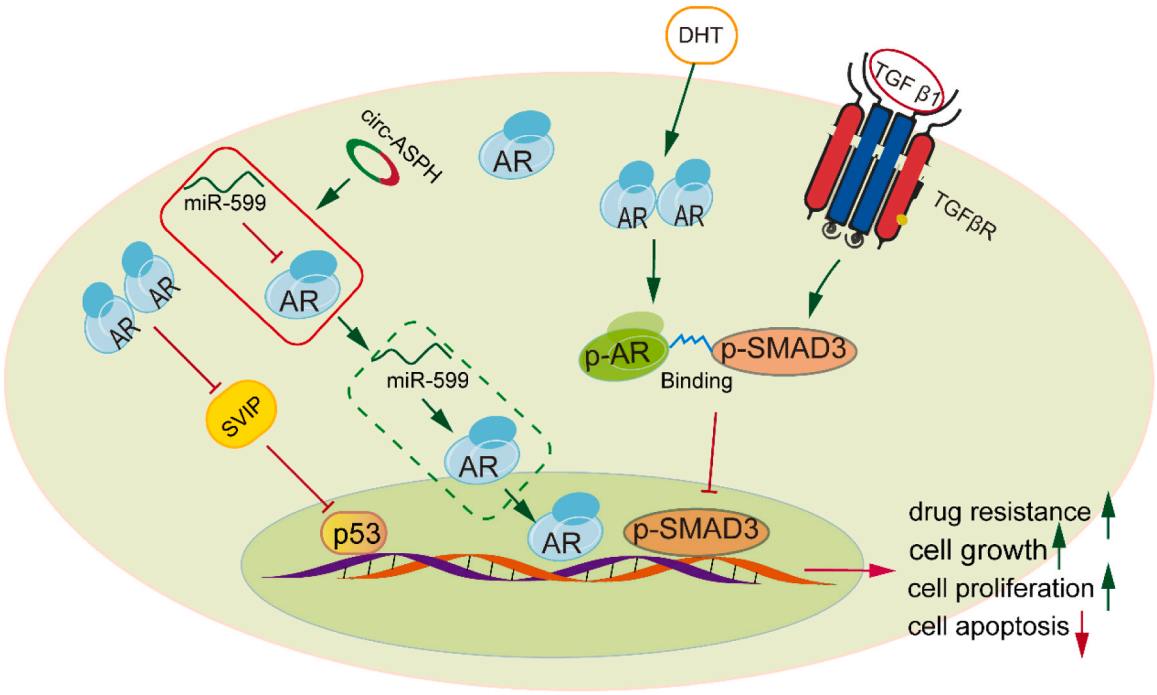

Fig. 3. The role of androgen receptors (AR) in the development and progression of glioblastoma.

Androgens are known to promote the development of GBM, so anti-androgen drugs have the potential to treat GBM (Chang et al., 2022; Pinacho-Garcia et al., 2020). HSP27 (Heat shock 27 kDa protein) is a well-documented chaperone protein that stabilizes AR proteins in the cytoplasm. Regardless of the mutational status of AR, inhibition of HSP27 leads to degradation of AR, which makes HSP27 a good target for eliminating AR in GBM (Gibert et al., 2012). N-(3-((2,5-dimethoxybenzyl) oxy)−4-(methylsulfonamido) phenyl)−4-methoxybenzamide is an inhibitor of HSP27 (Zhong et al., 2013, 2014). It induced AR degradation in GBM cells via the proteasome pathway and selectively inhibited the growth of U87 and T98G cells which overexpressed AR with an IC_{50} of 5 nM. Further studies showed that the compound also significantly inhibited the growth of a xenograft U87 cell tumor model in vivo and had no toxic effect on mice at a dose of 80 mg/kg (Li et al., 2021). This study suggests that N-(3-((2,5-dimethoxybenzyl) oxy)−4-(methylsulfonamido) phenyl)−4-methoxybenzamide also achieves its inhibitory effect on GBM in vitro and in vivo through AR.

Seviteronel is an orally selective CYP17 lyase inhibitor and androgen receptor inhibitor with significant antitumor activity and has completed phase I and phase II clinical trials against prostate cancer (Gupta et al., 2018; Madan et al., 2020). Given that GBM cells express AR and that seviteronel can cross the blood-brain barrier, scientists hypothesized that seviteronel could be used to treat GBM. They conducted studies and found that seviteronel could inhibit the proliferation of GBM cells in vitro and in xenograft models. They also found that seviteronel could enhance the effectiveness of radiotherapy in treating GBM (Sun et al., 2018; Werner et al., 2020). A phase II clinical trial of seviteronel for the treatment of GBM has been conducted (NCT03600467). These studies suggest that sevitronel may be a promising drug for the treatment of GBM.

4. Discussion

GBM is a highly aggressive brain tumor with limited treatment options. Targeted androgen receptor therapy for the treatment of GBM has shown promising research progress. Recent studies have identified the presence of AR in GBM cells, suggesting a potential therapeutic target. It was found that treating GBM cells with AR antagonists inhibited the expression of AR at the gene level and protein level, thereby suppressing the growth of GBM cells (Chang et al., 2022). These evidences then validate that targeting AR can inhibit the growth of glioblastoma. In this review, we have collected a number of studies that have attempted to treat GBM by targeting AR and found that most of this research has yielded positive results.

The AR antagonists bicalutamide, cyproterone, and enzalutamide flutamide are used clinically for the treatment of prostate cancer and or benign prostatic hyperplasia (Fig. 4, Table 1). The current study found that all four drugs can inhibit GBM proliferation in vitro (Chen et al., 2020; Chang et al., 2020; Li et al., 2021; Werner et al., 2020; Simińska et al., 2022). And enzalutamide also inhibits the development of GBM in a xenograft mouse model (Werner et al., 2020). These findings suggest that AR antagonists have promising anti-GBM potential, but clinical trials are needed to validate them. The 5α-reductase inhibitor, dutasteride, is a drug used to treat benign prostatic hyperplasia. When it is used in combination with an AR antagonist against GBM, the approach achieves superior results to each alone. This study opens up ideas for the treatment of GBM. On the one hand, the 5α-reductase inhibitor inhibits the synthesis of androgens; on the other hand, the AR antagonist inhibits the expression of AR; the combination of the two can weaken the promotion of GBM by androgens and AR in two ways. This therapeutic model deserves to be studied in depth and may provide new options for the treatment of GBM. EGFR is widely expressed in GBM cells and studies have demonstrated that EGFR is closely associated with the progression of GBM (Zalcman et al., 2021; Liu et al., 2021; Guo et al., 2022). A positive association between EGFR and AR in GBM cells has also been found, with EGFR promoting the effects of AR (Zalcman et al., 2021). Afatinib, an EGFR inhibitor, has been used in combination with the AR antagonist enzalutamide to combat GBM and has shown significant outcomes, demonstrating the feasibility of this therapeutic idea.

In addition to the six drugs mentioned above, we have collected four small molecule compounds that also inhibit GBM by modulating AR signaling. they are ALZ003, cedrol, N-(3-((2,5-dimethoxybenzyl) oxy)−4-(methylsulfonamido) phenyl)−4-methoxybenzamide and seviteronel (Fig. 5, Table 2). ALZ003 inhibits the proliferation of U87MG and U87MG-R cells and induces their death by suppressing AR protein expression. Cedrol induces DBTRG-05MG cell death by inhibiting AR

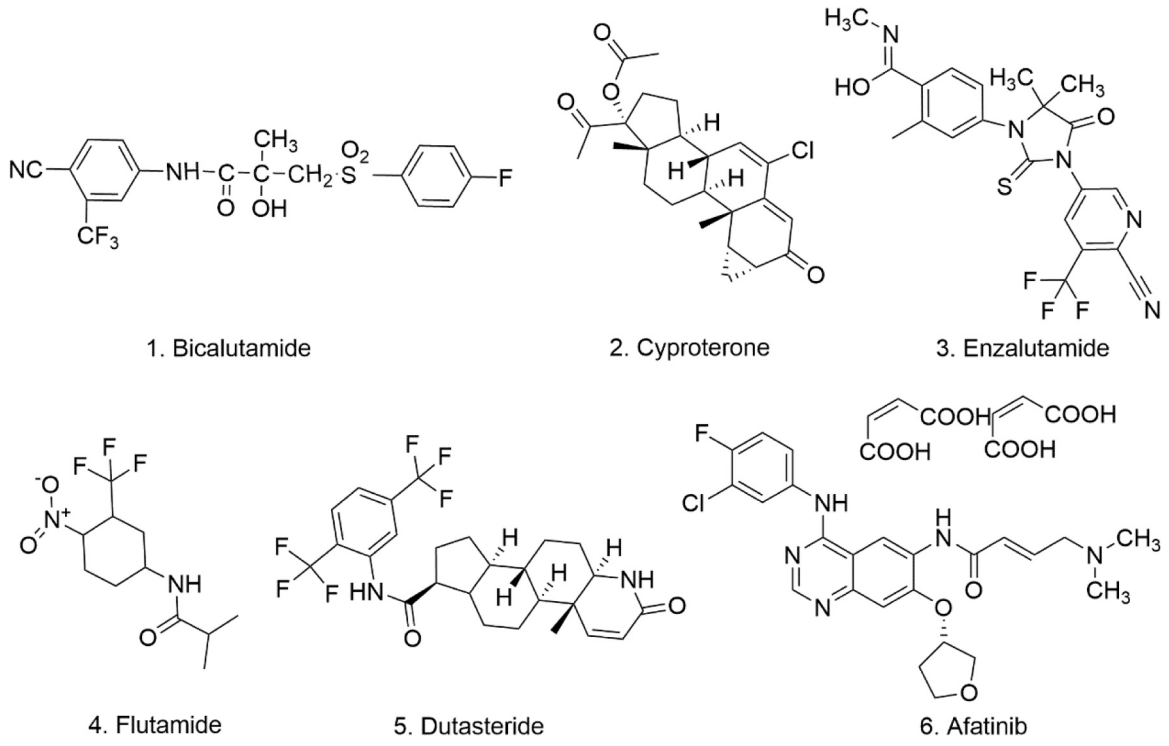

Fig. 4. Chemical structure formulae of the drugs in Table 1.

Table 1
Drugs that exert anti-glioblastoma effects by directly or indirectly modulating the androgen receptor.

No	Agent	Targets	Indications approved by FDA	Cell lines	Concentrations for cellular experiments	Concentrations for animal experiments	Ref.
1	bicalutamide	AR	Advanced prostate cancer	A172, U87MG, U138MG, Ln229, MGPP3 and T98G	20 μM, 40 μM	N.D.	(Zalcman et al., 2018)
2	cyproterone	AR	Prostate cancer	U87	0.1–50 μM	N.D.	(Orozco et al., 2020)
3	enzalutamide	AR	castration-resistant prostate cancer	A172, U87MG, U251MG, U138MG, Ln229, MGPP3 and T98G	10–80 μM	20 mg/kg athymic nude mice	(Zalcman et al., 2018; Zhao et al., 2021; Zalcman et al., 2021)
4	flutamide	AR	Prostate cancer and Benign prostatic hyperplasia	U87	1–100 μM	N.D.	(Orozco et al., 2020)
5	dutasteride	5α-reductase	Benign Prostatic hyperplasia	U87	0.1, 0.5, 1, 10, and 25 μM	N.D.	(Orozco et al., 2020)
6	afatinib	EGFR	Non-small cell lung cancer	172, U87MG and T98G	10–80 μM	N.D.	(Zalcman et al., 2021)

N.D.: No detection.

nuclear translocation, suppressing the expression of downstream genes KLK3/TMPRSS2 and reducing cell proliferation. N-(3-((2,5-dimethoxybenzyl) oxy)−4-(methylsulfonamido) phenyl)−4-methoxybenzamide, an HSP27 protein inhibitor, degraded the AR protein and induced GBM cell death. Seviteronel, a CYP17 enzyme inhibitor and AR antagonist, also inhibited GBM progression by inhibiting AR signaling. Notably, all four of these small molecule compounds have progressed to the animal stage of research on GBM, with seviteronel having progressed to phase II clinical trials.

Both existing drugs and newly discovered small molecule compounds have shown that treatment of GBM can be achieved by modulating AR (Fig. 6). The use of AR as a target for the treatment of GBM deserves more extensive and in-depth research. Screening for drugs with anti-GBM effects from existing drugs may be more efficient, as the existing drugs are those that have undergone rigorous clinical trials and have a guaranteed safety profile. Given that both prostate cancer and GBM are closely related to AR, the search for anti-GBM drugs from anti-prostate cancer drugs may be a shortcut. However, it is also important to note that the anti-GBM effects of these drugs have only progressed to the in vitro and animal testing stage, and clinical trials are necessary to validate them. The search for anti-GBM drugs through chemical synthesis and screening from natural products is also an effective route. The four small molecule drugs mentioned in this review have all progressed to the animal level, and some of them have progressed to the clinical trial stage.

Preclinical studies using AR inhibitors, such as enzalutamide and bicalutamide, have demonstrated significant anti-tumor effects in GBM models. These inhibitors work by blocking the activation of ARs and inhibiting downstream signaling pathways involved in tumor growth and survival.

In addition to AR inhibitors, combination therapies involving AR-targeted agents and other treatment modalities, such as chemotherapy and radiation therapy, have been explored. These combination approaches aim to enhance the efficacy of AR inhibition and overcome potential resistance mechanisms.

Furthermore, ongoing clinical trials are evaluating the safety and

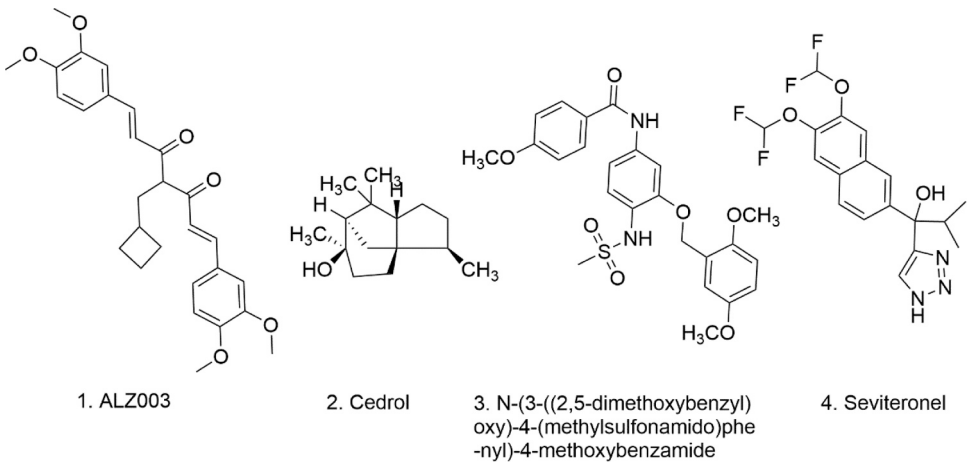

Fig. 5. Chemical structure formulae of the compounds in Table 2.

Table 2
Small molecule compounds against glioblastoma through modulating androgen receptor.

No	Compound	Targets	Source	Cell lines	Concentrations for cellular experiments	Concentrations for animal experiments	Ref.
1	ALZ003	AR	chemical synthesis	U87MG and U87MG-R	50–100 μM	NOD-SCID male mice (8-week-old) 20 mg/kg, 40 mg/kg, 80 mg/kg	(Chen et al., 2020)
2	cedrol	AR	*Atlantic cedar*	DBTRG-05MG	25–200 μM	F344 rats 75 mg/kg, 150 mg/kg	(Chang et al., 2020)
3	N-(3-((2,5-dimethoxybenzyl) oxy)−4-(methylsulfonamido) phenyl)−4-methoxybenzamide	HSP27	chemical synthesis	U87 and T98G	IC_{50} = 5 nM	Male CD-1 mice and nude mice, 20–80 mg/kg	(Li et al., 2021)
4	seviteronel	AR, CYP17	chemical synthesis	LN18 and T98G	2.7–4 μM	150 mg/kg	(Sun et al., 2018, 66)

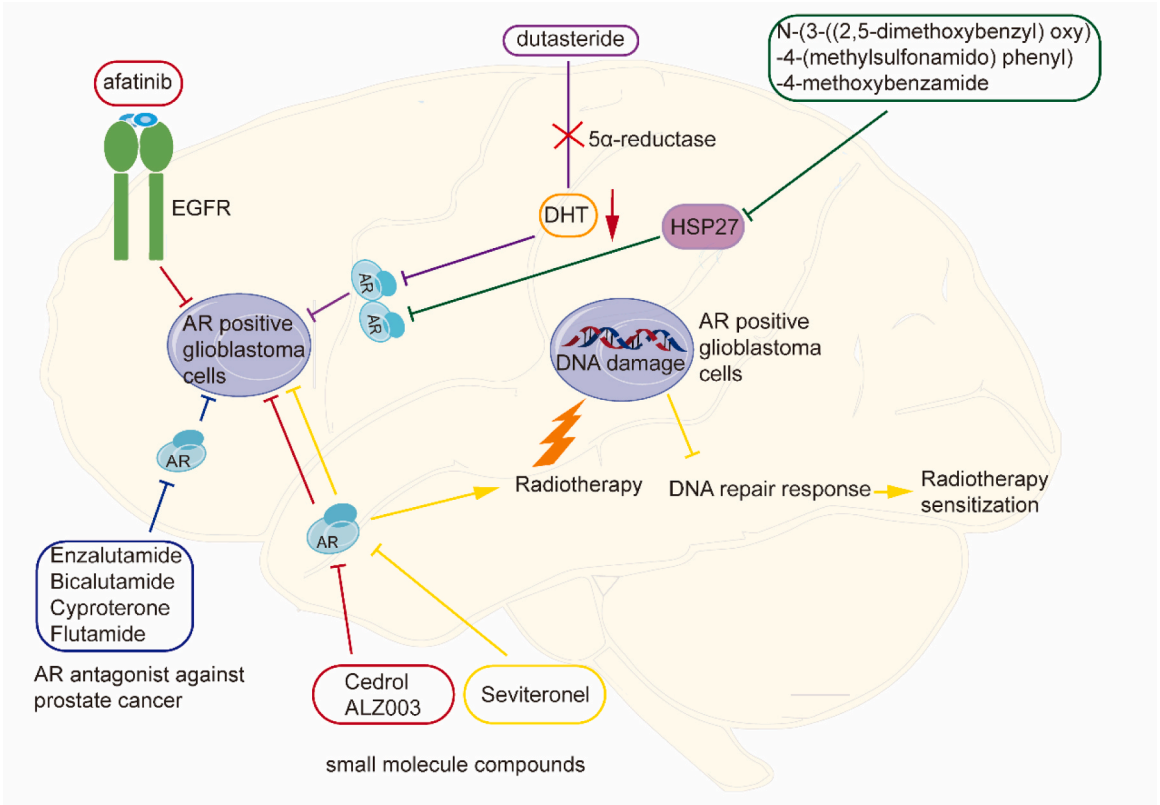

Fig. 6. Overview of drug-targeted AR pathways for the treatment of glioblastoma.

efficacy of AR-targeted therapies in GBM patients. These trials involve the administration of AR inhibitors either as monotherapy or in combination with standard treatments. Preliminary results have shown promising outcomes, including improved progression-free survival and overall survival rates.

Despite these advancements, challenges remain in the development of targeted androgen receptor therapy for GBM. Resistance mechanisms, heterogeneity of GBM tumors, and potential off-target effects of AR inhibitors need to be further investigated and addressed. Overall, the research progress in targeted AR therapy for GBM holds promise for the development of novel treatment strategies.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors have read and agreed to the publication of this manuscript.

Funding

This research was funded by the Special Fund for Bagui Scholars of Guangxi (Y. L), the Opening Foundation of Guangxi Key Laboratory of Chinese Medicine Foundation Research (220655303).

CRediT authorship contribution statement

XG reviewed the literature, **YHL** revised the paper. All the authors approved it; **XNW** designed, and wrote the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Not applicable.

References

Bao, D., Cheng, C., Lan, X., Xing, R., Chen, Z., Zhao, H., Sun, J., Wang, Y., Niu, C., Zhang, B., Fang, S., 2017. Regulation of p53wt glioma cell proliferation by androgen receptor-mediated inhibition of small VCP/p97-interacting protein expression. Oncotarget 8, 23142–23154.

Batistatou, A., Stefanou, D., Goussia, A., Arkoumani, E., Papavassiliou, A.G., Agnantis, N. J., 2004. Estrogen receptor beta (ERbeta) is expressed in brain astrocytic tumors and declines with dedifferentiation of the neoplasm. J. Cancer Res. Clin. Oncol. 130, 405–410.

Berger, T.R., Wen, P.Y., Lang-Orsini, M., Chukwueke, U.N., 2022. World Health Organization 2021 classification of central nervous system tumors and implications for therapy for adult-type gliomas: a review. JAMA Oncol. 8, 1493–1501.

Berny, W., Weiser, A., Jarmundowicz, W., Markowska-Woyciechowska, A., Załuski, R., Zub, W., 2004. Analysis of expression of estrogen (ER) and progesterone receptors (PR) in brain glial tumors and its correlation with expression of p53 protein and proliferating cell nuclear antigen (PCNA). Neurol. I Neurochir. Pol. 38, 367–371.

Björnebo, L., Nordström, T., Discacciati, A., Palsdottir, T., Aly, M., Grönberg, H., Eklund, M., Lantz, A., 2022. Association of 5α-Reductase inhibitors with prostate cancer mortality. JAMA Oncol. 8, 1019–1026.

Bott, L.C., Badders, N.M., Chen, K.-L., Harmison, G.G., Bautista, E., Shih, C.C.Y., Katsuno, M., Sobue, G., Taylor, J.P., Dantuma, N.P., Fischbeck, K.H., Rinaldi, C., 2016. A small-molecule Nrf1 and Nrf2 activator mitigates polyglutamine toxicity in spinal and bulbar muscular atrophy. Hum. Mol. Genet. 25, 1979–1989.

Carrano, A., Juarez, J.J., Incontri, D., Ibarra, A., Guerrero Cazares, H., 2021. Sex-specific differences in glioblastoma. Cells 10, 1783.

Carroll, R.S., Zhang, J., Dashner, K., Sar, M., Black, P.M., 1995. Steroid hormone receptors in astrocytic neoplasms. Neurosurgery 37, 496–503.

Chakraborty, S., Kar, N., Kumari, L., De, A., Bera, T., 2017. Inhibitory effect of a new orally active cedrol-loaded nanostructured lipid carrier on compound 48/80-induced mast cell degranulation and anaphylactic shock in mice. Int. J. Nanomed. 12, 4849–4868.

Chang, C.-Y., Chen, J.-T., Chen, T.-H., Chen, R.-M., 2022. Enzalutamide induces apoptotic insults to human drug-resistant and -Sensitive glioblastoma cells via an intrinsic bax-mitochondrion-cytochrome C caspase cascade activation pathway. Molecules 27, 6666.

Chang, K.-F., Huang, X.-F., Chang, J.T., Huang, Y.-C., Weng, J.-C., Tsai, N.-M., 2020. Cedrol suppresses glioblastoma progression by triggering DNA damage and blocking nuclear translocation of the androgen receptor. Cancer Lett. 495, 180–190.

Chen, T.-C., Chuang, J.-Y., Ko, C.-Y., Kao, T.-J., Yang, P.-Y., Yu, C.-H., Liu, M.-S., Hu, S.-L., Tsai, Y.-T., Chan, H., Chang, W.-C., Hsu, T.-I., 2020. AR ubiquitination induced by the curcumin analog suppresses growth of temozolomide-resistant glioblastoma through disrupting GPX4-Mediated redox homeostasis. Redox Biol. 30, 101413.

Crona, D.J., Whang, Y.E., 2017. Androgen receptor-dependent and -independent mechanisms involved in prostate cancer therapy resistance. Cancers 9, 67.

Dalin, M.G., Watson, P.A., Ho, A.L., Morris, L.G.T., 2017. Androgen receptor signaling in salivary gland cancer. Cancers 9, 17.

Fariña-Jerónimo, H., de Vera, A., Medina, L., Plata-Bello, J., 2022. Androgen receptor activity is associated with worse survival in glioblastoma. J. Integr. Neurosci. 21, 86.

Farkhondeh, T., Samarghandian, S., Pourbagher-Shahri, A.M., Sedaghat, M., 2019. The impact of curcumin and its modified formulations on Alzheimer's disease. J. Cell. Physiol. 234, 16953–16965.

Gao, Z., Xu, J., Fan, Y., Qi, Y., Wang, S., Zhao, S., Guo, X., Xue, H., Deng, L., Zhao, R., Sun, C., Zhang, P., Li, G., 2022. PDIA3P1 promotes Temozolomide resistance in glioblastoma by inhibiting C/EBPβ degradation to facilitate proneural-to-mesenchymal transition. J. Exp. Clin. Cancer Res.: CR 41, 223.

Gibert, B., Eckel, B., Fasquelle, L., Moulin, M., Bouhallier, F., Gonin, V., Mellier, G., Simon, S., Kretz-Remy, C., Arrigo, A.-P., Diaz-Latoud, C., 2012. Knock down of heat shock protein 27 (HspB1) induces degradation of several putative client proteins. PloS One 7, e29719.

Guo, G., Gong, K., Beckley, N., Zhang, Y., Yang, X., Chkheidze, R., Hatanpaa, K.J., Garzon-Muvdi, T., Koduru, P., Nayab, A., Jenks, J., Sathe, A.A., Liu, Y., Xing, C., Wu, S.-Y., Chiang, C.-M., Mukherjee, B., Burma, S., Wohlfeld, B., Patel, T., Mickey, B., Abdullah, K., Youssef, M., Pan, E., Gerber, D.E., Tian, S., Sarkaria, J.N., McBrayer, S.K., Zhao, D., Habib, A.A., 2022. EGFR ligand shifts the role of EGFR from oncogene to tumour suppressor in EGFR-amplified glioblastoma by suppressing invasion through BIN3 upregulation. Nat. Cell Biol. 24, 1291–1305.

Gupta, S., Nordquist, L.T., Fleming, M.T., Berry, W.R., Zhang, J., Ervin, S.L., Eisner, J.R., Baskin-Bey, E.S., Shore, N.D., 2018. Phase I study of Seviteronel, a selective CYP17 lyase and androgen receptor inhibitor, in men with castration-resistant prostate cancer. Clin. Cancer Res 24, 5225–5232.

Herberts, C., Annala, M., Sipola, J., Ng, S.W.S., Chen, X.E., Nurminen, A., Korhonen, O. V., Munzur, A.D., Beja, K., Schönlau, E., Bernales, C.Q., Ritch, E., Bacon, J.V.W., Lack, N.A., Nykter, M., Aggarwal, R., Small, E.J., Gleave, M.E., Quigley, D.A., Feng, F.Y., Chi, K.N., Wyatt, A.W., 2022. Deep whole-genome ctDNA chronology of treatment-resistant prostate cancer. Nature 608, 199–208.

Hesari, A., Rezaei, M., Rezaei, M., Dashtiahangar, M., Fathi, M., Rad, J.G., Momeni, F., Avan, A., Ghasemi, F., 2019. Effect of curcumin on glioblastoma cells. J. Cell. Physiol. 234, 10281–10288.

Li, J., Ding, Z., Wang, Z., Lu, J.-F., Maity, S.N., Navone, N.M., Logothetis, C.J., Mills, G. B., Kim, J., 2011. Androgen regulation of 5α-reductase isoenzymes in prostate cancer: implications for prostate cancer prevention. PloS One 6, e28840.

Li, P., Chen, J., Miyamoto, H., 2017. Androgen receptor signaling in bladder cancer. Cancers 9, 20.

Li, R., Chen, X., You, Y., Wang, X., Liu, Y., Hu, Q., Yan, W., 2015. Comprehensive portrait of recurrent glioblastoma multiforme in molecular and clinical characteristics. Oncotarget 6, 30968–30974.

Li, Y., Orahoske, C.M., Geldenhuys, W.J., Bhattarai, A., Sabbagh, A., Bobba, V., Salem, F. M., Zhang, W., Shukla, G.C., Lathia, J.D., Wang, B., Su, B., 2021. Small-Molecule HSP27 inhibitor abolishes androgen receptors in glioblastoma. J. Med. Chem. 64, 1570–1583.

Liu, Y., Li, Z., Zhang, M., Zhou, H., Wu, X., Zhong, J., Xiao, F., Huang, N., Yang, X., Zeng, R., Yang, L., Xia, Z., Zhang, N., 2021. Rolling-translated EGFR variants sustain EGFR signaling and promote glioblastoma tumorigenicity. Neuro-Oncol. 23, 743–756.

Loizzo, M.R., Tundis, R., Menichini, F., Saab, A.M., Statti, G.A., Menichini, F., 2008. Antiproliferative effects of essential oils and their major constituents in human renal adenocarcinoma and amelanotic melanoma cells. Cell Prolif. 41, 1002–1012.

Madan, R.A., Schmidt, K.T., Karzai, F., Peer, C.J., Cordes, L.M., Chau, C.H., Steinberg, S. M., Owens, H., Eisner, J., Moore, W.R., Dahut, W.L., Gulley, J.L., Figg, W.D., 2020. Phase 2 study of seviteronel (INO-464) in patients with metastatic castration-resistant prostate cancer after enzalutamide treatment. Clin. Genitourin. Cancer 18, 258–267 e1.

Magrassi, L., Butti, G., Silini, E., Bono, F., Paoletti, P., Milanesi, G., 1993. The expression of genes of the steroid-thyroid hormone receptor superfamily in central nervous system tumors. Anticancer Res. 13, 859–866.

McConnell, J.D., Roehrborn, C.G., Bautista, O.M., Andriole, G.L., Dixon, C.M., Kusek, J. W., Lepor, H., McVary, K.T., Nyberg, L.M., Clarke, H.S., Crawford, E.D., Diokno, A., Foley, J.P., Foster, H.E., Jacobs, S.C., Kaplan, S.A., Kreder, K.J., Lieber, M.M., Lucia, M.S., Miller, G.J., Menon, M., Milam, D.F., Ramsdell, J.W., Schenkman, N.S., Slawin, K.M., Smith, J.A., 2003. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. New Engl. J. Med. 349, 2387–2398.

McKinley, B.P., Michalek, A.M., Fenstermaker, R.A., Plunkett, R.J., 2000. The impact of age and sex on the incidence of glial tumors in New York state from 1976 to 1995. J. Neurosurg. 93, 932–939.

Miller, K.D., Ostrom, Q.T., Kruchko, C., Patil, N., Tihan, T., Cioffi, G., Fuchs, H.E., Waite, K.A., Jemal, A., Siegel, R.L., Barnholtz-Sloan, J.S., 2021. Brain and other central nervous system tumor statistics, 2021. CA: a Cancer J. Clin. 71, 381–406.
Mondragón, J.A., Serrano, Y., Torres, A., Orozco, M., Segovia, J., Manjarrez, G., Romano, M.C., 2021. Glioblastoma cells express crucial enzymes involved in androgen synthesis: 3β-hydroxysteroid dehydrogenase, 17-20α-hydroxylase, 17β-hydroxysteroid dehydrogenase and 5α-reductase. Endocrinol. Diabetes Metab. 4, e00289.
Narayanan, R., Dalton, J.T., 2016. Androgen receptor: a complex therapeutic target for breast cancer. Cancers 8, 108.
Orozco, M., Valdez, R.A., Ramos, L., Cabeza, M., Segovia, J., Romano, M.C., 2020. Dutasteride combined with androgen receptor antagonists inhibit glioblastoma U87 cell metabolism, proliferation, and invasion capacity: androgen regulation. Steroids 164, 108733.
Ostrom, Q.T., Gittleman, H., Truitt, G., Boscia, A., Kruchko, C., Barnholtz-Sloan, J.S., 2018a. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2011-2015. Neuro-Oncol. 20 (suppl_4), iv1–iv86.
Ostrom, Q.T., Cote, D.J., Ascha, M., Kruchko, C., Barnholtz-Sloan, J.S., 2018b. Adult glioma incidence and survival by race or ethnicity in the United States From 2000 to 2014. JAMA Oncol. 4, 1254–1262.
Paoletti, P., Butti, G., Zibera, C., Scerrati, M., Gibelli, N., Roselli, R., Magrassi, L., Sica, G., Rossi, G., Robustelli della Cuna, G., 1990. Characteristics and biological role of steroid hormone receptors in neuroepithelial tumors. J. Neurosurg. 73, 736–742.
Pinacho-Garcia, L.M., Valdez, R.A., Navarrete, A., Cabeza, M., Segovia, J., Romano, M.C., 2020. The effect of finasteride and dutasteride on the synthesis of neurosteroids by glioblastoma cells. Steroids 155, 108556.
Poisson, M., Pertuiset, B.F., Hauw, J.J., Philippon, J., Buge, A., Moguilewsky, M., Philibert, D., 1983. Steroid hormone receptors in human meningiomas, gliomas and brain metastases. J. Neuro-Oncol. 1, 179–189.
Porter, K.R., McCarthy, B.J., Freels, S., Kim, Y., Davis, F.G., 2010. Prevalence estimates for primary brain tumors in the United States by age, gender, behavior, and histology. Neuro-Oncol. 12, 520–527.
Qu, Y., Qi, L., Hao, L., Zhu, J., 2021. Upregulation of circ-ASPH contributes to glioma cell proliferation and aggressiveness by targeting the miR-599/AR/SOCS2-AS1 signaling pathway. Oncol. Lett. 21, 388.
Ransome, M.I., Boon, W.C., 2015. Testosterone-induced adult neurosphere growth is mediated by sexually-dimorphic aromatase expression. Front. Cell. Neurosci. 9, 253.
Rodríguez-Lozano, D.C., Piña-Medina, A.G., Hansberg-Pastor, V., Bello-Alvarez, C., Camacho-Arroyo, I., 2019. Testosterone promotes glioblastoma cell proliferation, migration, and invasion through androgen receptor activation. Front. Endocrinol. 10, 16.
Roehrborn, C.G., Siami, P., Barkin, J., Damião, R., Major-Walker, K., Nandy, I., Morrill, B.B., Gagnier, R.P., Montorsi, F., 2010. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study. Eur. Urol. 57, 123–131.
Shen, T., Wang, W., Zhou, W., Coleman, I., Cai, Q., Dong, B., Ittmann, M.M., Creighton, C.J., Bian, Y., Meng, Y., Rowley, D.R., Nelson, P.S., Moore, D.D., Yang, F., 2021. MAPK4 promotes prostate cancer by concerted activation of androgen receptor and AKT. J. Clin. Investig. 131, e135465.
Simińska, D., Korbecki, J., Kojder, K., Jeżewski, D., Tarnowski, M., Tomasiak, P., Piotrowska, K., Masztalewicz, M., Kolasa, A., Chlubek, D., Baranowska-Bosiacka, I., 2022. Androgen receptor expression in the various regions of resected glioblastoma multiforme tumors and in an in vitro model. Int. J. Mol. Sci. 23, 13004.
Su, Y.-C., Hsu, K.-P., Wang, E.I.C., Ho, C.-L., 2012. Composition, anticancer, and antimicrobial activities in vitro of the heartwood essential oil of Cunninghamia lanceolata var. konishii from Taiwan. Nat. Prod. Commun. 7, 1245–1247.
Sun, H.S., Werner, C., Dresser, J., Wilder-Romans, K., Baskin-Bey, E., Eisner, J., Lawrence, T., Spratt, D., Speers, C., Wahl, D., 2018. Targeting androgen signaling in glioblastoma (GBM) using seviteronel (SEVI), A CYP17 lyase and androgen receptor (AR) INHIBITOR, alone and in combination with radiation (RT). Neuro-Oncol. 20, 88-88.
Tan, A.C., Ashley, D.M., López, G.Y., Malinzak, M., Friedman, H.S., Khasraw, M., 2020. Management of glioblastoma: state of the art and future directions. CA: a Cancer J. Clin. 70, 299–312.
Thakkar, J.P., Dolecek, T.A., Horbinski, C., Ostrom, Q.T., Lightner, D.D., Barnholtz-Sloan, J.S., Villano, J.L., 2014. Epidemiologic and molecular prognostic review of glioblastoma. cancer epidemiology, biomarkers & prevention: a publication of the american association for cancer research. Cosponsored Am. Soc. Prev. Oncol. 23, 1985–1996.
Tomar, M.S., Kumar, A., Srivastava, C., Shrivastava, A., 2021. Elucidating the mechanisms of Temozolomide resistance in gliomas and the strategies to overcome the resistance. Biochim. Et. Biophys. Acta Rev. Cancer 1876, 188616.
van der Steen, T., Tindall, D.J., Huang, H., 2013. Posttranslational modification of the androgen receptor in prostate cancer. Int. J. Mol. Sci. 14, 14833–14859.
Wang, J.-W., Chen, S.-S., Zhang, Y.-M., Guan, J., Su, G.-Y., Ding, M., Li, W., Zhao, Y.-Q., 2019. Anti-inflammatory and analgesic activity based on polymorphism of cedrol in mice. Environ. Toxicol. Pharmacol. 68, 13–18.
Werner, C.K., Nna, U.J., Sun, H., Wilder-Romans, K., Dresser, J., Kothari, A.U., Zhou, W., Yao, Y., Rao, A., Stallard, S., Koschmann, C., Bor, T., Debinski, W., Hegedus, A.M., Morgan, M.A., Venneti, S., Baskin-Bey, E., Spratt, D.E., Colman, H., Sarkaria, J.N., Chinnaiyan, A.M., Eisner, J.R., Speers, C., Lawrence, T.S., Strowd, R.E., Wahl, D.R., 2020. Expression of the androgen receptor governs radiation resistance in a subset of glioblastomas vulnerable to antiandrogen therapy. Mol. Cancer Ther. 19, 2163–2174.
Yague, J.G., Lavaque, E., Carretero, J., Azcoitia, I., Garcia-Segura, L.M., 2004. Aromatase, the enzyme responsible for estrogen biosynthesis, is expressed by human and rat glioblastomas. Neurosci. Lett. 368, 279–284.
Yang, W., Warrington, N.M., Taylor, S.J., Whitmire, P., Carrasco, E., Singleton, K.W., Wu, N., Lathia, J.D., Berens, M.E., Kim, A.H., Barnholtz-Sloan, J.S., Swanson, K.R., Luo, J., Rubin, J.B., 2019a. Sex differences in GBM revealed by analysis of patient imaging, transcriptome, and survival data. Sci. Transl. Med. 11, eaao5253.
Yang, W.-B., Chuang, J.-Y., Ko, C.-Y., Chang, W.-C., Hsu, T.-I., 2019b. Dehydroepiandrosterone induces temozolomide resistance through modulating phosphorylation and acetylation of Sp1 in Glioblastoma. Mol. Neurobiol. 56, 2301–2313.
Yu, X., Jiang, Y., Wei, W., Cong, P., Ding, Y., Xiang, L., Wu, K., 2015. Androgen receptor signaling regulates growth of glioblastoma multiforme in men. Tumour Biol.: J. Int. Soc. Oncodev. Biol. Med. 36, 967–972.
Zalcman, N., Canello, T., Ovadia, H., Charbit, H., Zelikovitch, B., Mordechai, A., Fellig, Y., Rabani, S., Shahar, T., Lossos, A., Lavon, I., 2018. Androgen receptor: a potential therapeutic target for glioblastoma. Oncotarget 9, 19980–19993.
Zalcman, N., Gutreiman, M., Shahar, T., Weller, M., Lavon, I., 2021. Androgen receptor activation in glioblastoma can be achieved by ligand-independent signaling through EGFR-A potential therapeutic target. Int. J. Mol. Sci. 22, 10954.
Zhao, N., Wang, F., Ahmed, S., Liu, K., Zhang, C., Cathcart, S.J., DiMaio, D.J., Punsoni, M., Guan, B., Zhou, P., Wang, S., Batra, S.K., Bronich, T., Hei, T.K., Lin, C., Zhang, C., 2021. Androgen receptor, although not a specific marker for, is a novel target to suppress glioma stem cells as a therapeutic strategy for glioblastoma. Front. Oncol. 11, 616625.
Zhong, B., Chennamaneni, S., Lama, R., Yi, X., Geldenhuys, W.J., Pink, J.J., Dowlati, A., Xu, Y., Zhou, A., Su, B., 2013. Synthesis and anticancer mechanism investigation of dual Hsp27 and tubulin inhibitors. J. Med. Chem. 56, 5306–5320.
Zhong, B., Lama, R., Kulman, D.G., Li, B., Su, B., 2014. Lead optimization of dual tubulin and Hsp27 inhibitors. Eur. J. Med. Chem. 80, 243–253.

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