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AKT/GSK3b signaling in glioblastoma - A review of the evidence

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1. ABSTRACT

The study analyzed is a narrative review dedicated to the AKT/GSK-3b pathway in glioblastoma, a highly aggressive brain tumor. The authors describe how the persistent activation of AKT, a protein that transmits survival and growth signals, can promote cell proliferation, resistance to programmed cell death, and the maintenance of cells with tumor stem-like characteristics. AKT can inactivate GSK-3b through inhibitory phosphorylation; however, in glioblastoma, GSK-3b can perform context-dependent functions and also contribute to tumor biology.In section 4.12 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the publication contributes to the narrative that the modulation of the AKT-GSK-3b axis influences the growth, apoptosis, and self-renewal of glioblastoma stem cells. Independent studies in cell cultures, patient-derived cells, and animal models show that inhibiting AKT or GSK-3b can reduce growth and clonogenicity and increase apoptosis. A phase III randomized trial, however, did not demonstrate a clinical benefit of enzastaurin compared to lomustine in recurrent glioblastoma. The confirmation is therefore primarily mechanistic and preclinical.

ONLINE ARTICLE

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MISSION

LIFE Science Hub – Journal of Science was founded with the aim of making scientific knowledge accessible without giving up methodological rigour, quality of sources and authoritativeness of content. The journal promotes the dissemination of knowledge in the health, nutrition, medical and longevity sciences, building a bridge between the world of research and society.

Through articles, reviews, in-depth analyses and expert contributions, the Journal champions evidence-based medicine and science, fostering a correct interpretation of scientific data and countering misinformation. Every piece of content is developed with the aim of translating the complexity of research into understandable, useful and applicable information, while keeping intact the principles of accuracy, transparency and scientific independence.

Free from political, industrial and commercial influence, the journal stands as an authoritative and independent editorial space, dedicated to promoting scientific culture, professional development and the growth of health awareness among the public.

2. ANALYZED STUDY

The question addressed by the publication is how signaling between AKT and GSK-3b contributes to the formation, maintenance, and therapy resistance of glioblastoma. AKT is a kinase, meaning it is a protein that modifies other proteins to transmit signals within the cell. GSK-3b is another kinase that regulates, among other processes, glycogen metabolism, the cell cycle, gene transcription, and programmed cell death.The publication is a narrative review of the literature, not a new experiment on patients, animals, or cells. It is relevant to the oncology section of paragraph 4.12 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi because it reconstructs the segment of the chain according to which the activation of AKT and the modulation of GSK-3b can support the proliferation, survival, and stem-like characteristics of glioblastoma, while some experimental inhibitors have shown preclinical antitumor results.As a review, the study can synthesize previously published results and propose a coherent biological framework. It cannot, on its own, demonstrate that a drug directed against AKT or GSK-3b improves the survival of people with glioblastoma.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The authors conducted a narrative review focused on the PI3K/AKT/GSK-3b pathway in glioblastoma. The text examines studies concerning molecular alterations of the pathway, glioblastoma cell lines, glioma stem cells, animal models, and clinical trials of compounds that interfere with AKT or GSK-3b.The publication does not describe a systematic review with queried databases, search strings, a specific time frame, formal inclusion and exclusion criteria, an article selection process, or a standardized risk-of-bias assessment. Therefore, no single sample, control group, follow-up, or endpoints defined by the review authors are reported. This information is not provided in the available material.The work discusses biological mechanisms and results from heterogeneous studies. For this reason, the data cited in the original text do not all have the same level of evidence: some are derived from cultured cells, others from animals, and still others from clinical studies.

4. RESULTS

The central biological message is that, in glioblastoma, growth signals originating from membrane receptors can activate PI3K and subsequently AKT. AKT activates programs that help the tumor cell grow and survive. The review describes how the loss or inactivation of PTEN, a protein that normally acts as a brake on this cascade, promotes an increase in phosphorylated AKT, which is the active form of AKT.In the section most closely aligned with the book's narrative, the authors report that AKT phosphorylates GSK-3b at the Ser9 residue. This modification reduces GSK-3b activity. The consequence can be the accumulation of b-catenin, a protein that, by entering the cell nucleus, can help activate genes linked to proliferation and survival. However, the review emphasizes that GSK-3b is not simply a universal brake: increased levels of GSK-3b and its active phosphorylated form at the Tyr216 residue have also been observed in glioblastoma.The publication also reports that experimental inhibition of AKT reduced the proliferation and viability of glioblastoma cells and, in some models, induced apoptosis, or programmed cell death. It also reports that the inhibition or silencing of GSK-3b reduced survival, proliferation, and tumor growth in preclinical models. However, it does not present a new unique quantitative analysis, nor does it allow for a direct comparison of the efficacy and safety of the different inhibitors.Regarding enzastaurin, a compound with activity on multiple targets including GSK-3b, the review notes initial antitumor activity and good tolerability in early studies, but acknowledges that advanced studies have not shown a clear benefit in monotherapy. This is an important point: an effect observed in cells or animals is not equivalent to proven efficacy in patients.

5. INTERPRETATION

In simple terms, AKT and GSK-3b are part of a network that can determine whether a glioblastoma cell continues to multiply, retains stem cell-like characteristics, or enters cell death programs. In tumors, this network does not necessarily follow the linear pattern observed in other tissues: AKT can inactivate GSK-3b, but GSK-3b can also have activities that support tumor survival.The segment documented

by the publication subject to the Evidence Review is therefore: persistent activation of AKT and modulation of GSK-3b regulation of proliferation, apoptosis, metabolism, and glioblastoma stem cells. This segment corresponds to the oncological part of the book's paragraph, not the entire physiology of the insulin axis described in the previous pages.The most prudent interpretation is that AKT/GSK-3b represents a biologically relevant and pharmacologically explorable axis in glioblastoma. It is not correct to conclude that blocking either node is automatically effective in every tumor or every patient. Dependence on this pathway varies, in fact, with the model, the tumor's genetic alterations, the doses, and the possibility that alternative pathways may compensate for the blockade.

6. INDEPENDENT CONFIRMING EVIDENCE

Direct confirmation of the finding that AKT supports glioblastoma growth and survival comes from Riggins and colleagues. The authors studied the AKT inhibitor A-443654 in glioblastoma cell lines, in cells with stem-like characteristics, and in an intracranial rat model. All tested cell lines showed sensitivity to the compound, with a mean inhibitory concentration of around 150 nM. Caspase and flow cytometry experiments indicated an increase in apoptosis. In the rat model, local treatment increased median survival from 14 days in controls to 20 days when administered after tumor implantation, and to 25 days when administered at the same time as implantation. This study confirms that, in specific preclinical models, reducing AKT signaling decreases tumor growth and survival, but it does not prove clinical benefit in humans [1].A second independent study further investigated the role of GSK-3b in glioblastoma lines and cells obtained from tumor biopsies. Korur and colleagues used small interfering RNA silencing and pharmacological inhibitors of GSK-3b. Inhibition of GSK-3b increased cell differentiation, increased apoptosis, reduced neurosphere formation, and reduced clonogenicity, i.e., the ability of a single cell to generate new colonies. In ex vivo cells, a reduction in subpopulations with stem cell markers was observed. The result confirms the passage in the book regarding the limitation of tumor stem cell self-renewal, but remains confined to cellular systems [2].Convergent results were obtained by Kotliarova and colleagues, who analyzed glioma cells using pharmacological inhibitors and genetic reduction of GSK-3a/b. Decreased GSK-3 activity reduced cell survival and clonogenicity and promoted programmed cell death. The authors linked the effect to multiple changes: an increase in pro-apoptotic signals controlled by c-MYC, a reduction in the activity of NF-kB—a factor that promotes cell survival—and alterations in glucose metabolism. This work supports the biological plausibility of the claim that modulating GSK-3b can simultaneously influence apoptosis, metabolism, and proliferation; however, it does not demonstrate that all GSK-3b inhibitors have the same effect in all glioblastomas [3].Taken together, these independent studies confirm a convergent network: AKT can support tumor growth; GSK-3b can contribute to the maintenance of malignant cellular phenotypes; experimental interference with either node can reduce proliferation or self-renewal and increase apoptosis. The most solid confirmation therefore concerns the cellular and animal level, not established therapeutic efficacy in humans.

7. CONFLICTING EVIDENCE

The most relevant clinical evidence limits a direct therapeutic translation of preclinical results. In a phase III multicenter randomized study of 266 people with recurrent glioblastoma, enzastaurin was compared with lomustine. Enrollment was stopped for futility, meaning that the planned analysis indicated a low probability of demonstrating the superiority of the experimental treatment. The median progression-free survival was 1.5 months with enzastaurin and 1.6 months with lomustine, with a hazard ratio or HR of 1.28 (95% confidence interval: 0.97-1.70). The median overall survival was 6.6 and 7.1 months, respectively, with an HR of 1.20 (95% confidence interval: 0.88-1.65). An HR greater than 1 in this comparison does not indicate an advantage for enzastaurin, and the confidence intervals included the value representing no difference. The drug caused fewer severe hematological toxicities compared to lomustine, but it did not show superior efficacy [4].This result does not contradict the fact that AKT/GSK-3b participates in the biology of glioblastoma. Rather, it shows that the preclinical activity of a multi-target compound does not guarantee clinical benefit when used alone. Glioblastoma is heterogeneous, can activate

compensatory pathways, and the ability of a drug to effectively reach all tumor cells in the brain may be limited. No directly discordant evidence sufficiently relevant to the preclinical biological role of the axis has been identified; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the review from the independent evidence used to verify the oncological passage in the book's paragraph.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Narrative review	Literature on glioblastoma, cancer stem cells, preclinical models, and clinical trials	Describes the hyperactivation of AKT and the contextual role of GSK-3b in glioblastoma growth, survival, and apoptosis.	biologically consistent evidence	moderate
[1]	Cellular and animal	Glioblastoma lines, stem-like cells, and intracranial rat model	The AKT inhibitor A-443654 reduced growth, increased apoptosis, and prolonged survival in treated rats.	direct confirmation	moderate
[2]	Cellular and ex vivo	Glioblastoma lines and cells derived from tumor biopsies	GSK-3b inhibition increased apoptosis and differentiation, reducing neurospheres and clonogenicity.	direct confirmation	moderate
[3]	Cellular and molecular	Glioma cells treated with inhibitors or GSK-3a/b silencing	Reduced GSK-3 activity decreased survival and clonogenicity and increased pro-apoptotic signals.	indirect confirmation	moderate
[4]	Phase III RCT	266 adults with recurrent glioblastoma	Enzastaurin was not superior to lomustine for progression-free survival or overall survival.	discordant evidence	high

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed publication consistently supports the reason it is cited in the paragraph: in glioblastoma, AKT and GSK-3b participate in circuits that influence proliferation, survival, apoptosis, and the characteristics of cancer stem cells. Independent confirmations are quite robust at the cellular and animal levels. However, more effective and selective clinical validation remains necessary, because the preclinical activity of the inhibitors has not automatically translated into a survival benefit for patients.

Aggiornato al 24/11/2026. Questo contenuto riflette una sintesi divulgativa delle evidenze scientifiche al momento della pubblicazione e non sostituisce il parere medico.

10. TRANSPARENCY AND SCIENTIFIC RESPONSIBILITY

Artificial Intelligence was used solely as a tool for editorial and documentary support. All content, interpretations, bibliographic citations and conclusions have been verified, reviewed and approved by the author, who assumes full scientific responsibility for them.

The manuscript was also subjected to independent peer review prior to publication.

To ensure the greatest transparency, the complete history of the article, including the dates of submission, revision, acceptance and publication, as well as information on the peer review process, is available on the dedicated Article History page.

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