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# Role of renin angiotensin system inhibitors and metformin in Glioblastoma Therapy: a review

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## Abstract

Glioblastoma multiforme (GBM) is a highly aggressive and incurable disease accounting for about 10,000 deaths in the USA each year. Despite the current treatment approach which includes surgery with chemotherapy and radiation therapy, there remains a high prevalence of recurrence. Notable improvements have been observed in persons receiving concurrent antihypertensive drugs such as renin angiotensin inhibitors (RAS) or the antidiabetic drug metformin with standard therapy. Anti-tumoral effects of RAS inhibitors and metformin have been observed in in vitro and in vivo studies. Although clinical trials have shown mixed results, the potential for the use of RAS inhibitors and metformin as adjuvant GBM therapy remains promising. Nevertheless, evidence suggest that these drugs exert multimodal antitumor actions; by particularly targeting several cancer hallmarks. In this review, we highlight the results of clinical studies using multidrug cocktails containing RAS inhibitors and or metformin added to standard therapy for GBM. In addition, we highlight the possible molecular mechanisms by which these repurposed drugs with an excellent safety profile might elicit their anti-tumoral effects. RAS inhibition elicits anti-inflammatory, anti-angiogenic, and immune sensitivity effects in GBM. However, metformin promotes anti-migratory, anti-proliferative and pro-apoptotic effects mainly through the activation of AMP-activated protein kinase. Also, we discussed metformin's potential in targeting both GBM cells as well as GBM associated-stem cells. Finally, we summarize a few drug interactions that may cause an additive or antagonistic effect that may lead to adverse effects and influence treatment outcome.

**Keywords:** Glioblastoma; Metformin; Renin angiotensin system inhibitors; Therapeutics.