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Dual blockade of STAT3 and EGFR: a key to unlock drug resistance in glioblastoma?

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See the article by Fan and An et al in this issue, pp. 457–469.

The lack of effective therapy against glioblastoma (GBM) is largely linked to tumor heterogeneity and high drug resistance. Primary resistance to chemotherapy stems from intrinsic properties of cancer cells to induce adaptive signaling cascades. On the other hand, drug resistance may develop during treatment through the selection of unresponsive clones. Epidermal growth factor receptor (EGFR) is the most frequent altered gene in GBM by gene amplification, accompanied in a subset of tumors by somatic mutation, the most frequent variant being EGFR variant (v)III.[1] So far, monotherapies against EGFR have failed to provide sustainable tumor growth inhibition, and a rationale for combinatorial therapy is an important clinical need. Among the prominent oncogenic pathways in GBM, the Weiss laboratory previously reported that EGFR and EGFRvIII cooperate to activate the transcription factor signal transducer and activator of transcription 3 (STAT3).[2] Nuclear STAT3 modulates the expression of genes relevant to cell proliferation, stemness, migration, and angiogenesis. Additionally, in the GBM microenvironment, STAT3 activity promotes the accumulation of anti-inflammatory macrophages which contribute to immune evasion.[3] Hence, several oncogenic pathways converge to STAT3, which appears as a molecular hub in GBM, making it an ideal therapeutic target. Yet, GBM exhibits primary resistance to STAT3 inhibition.[2]

In this issue of *Neuro-Oncology*, the paper by Fan et al[4] elucidates the underlying mechanism of primary resistance to STAT3 impairment in GBM cells. The authors find that in response to the STAT3 inhibitor Stattic,[5] GBM cells induce cytokine expression, in particular the pro-inflammatory cytokine interleukin-6. They further show that nuclear factor-kappa B (NF-κB) activation is responsible for the induced cytokine expression upon STAT3 blockade or downregulation. Unexpectedly they found that STAT3 inhibition leads to EGFR activation, which drives NF-κB activity. This was independent of EGFR overexpression and phosphatase and tensin homolog (PTEN) mutation. To understand the molecular crosstalk between STAT3, EGFR, and NF-κB, they performed subcellular fractionation and demonstrated phosphorylated EGFR and NF-κB signal in the nucleus after STAT3 inhibition, supporting the existence of a transcriptional regulatory mechanism.

To provide mechanistic insight on EGFR activation upon STAT3 inhibition, the authors[4] asked whether STAT3 expression correlated with differential expression of various EGFR ligands in GBM patients. Interestingly, the EGFR ligands betacellulin (BTC) and epiregulin were negatively correlated with STAT3 expression in patient samples, and in vitro STAT3 depletion induced BTC expression and secretion, leading to EGFR activation. While EGFR-STAT3 forward signaling is a known mechanism in cancer resistance to EGFR targeted therapeutics,[6] these results show that STAT3 blockade induces a STAT3-EGFR feedback loop involving BTC, thereby promoting resistance to STAT3 inhibition. These molecular findings were applied for functional experiments on GBM cells. The authors show that Stattic treatment in combination with a BTC-blocking antibody reduced GBM growth and induced apoptosis in vitro. They corroborate their findings in orthotopic GBM patient-derived xenografts, using osimertinib,[7] a third-generation EGFR tyrosine kinase inhibitor known to cross the blood brain barrier. While single inhibition of STAT3 or EGFR did not impair GBM growth in vivo, dual blockade improved overall survival of tumor bearing mice.

Altogether, the study by Fan et al[4] highlights the potential of dual targeting of EGFR and STAT3, which act as partners in crime for sustaining tumor growth, and represents a conceptual advance for combinatorial therapy in GBM. However, a number of important questions remain unsolved:

1. Among 49 receptor tyrosine kinases tested and 6 different EGFR ligands, the effect of STAT3 blockade seems specific to EGFR and its ligand BTC, although BTC was reported to increase ErbB3 phosphorylation and biases the EGFR to dimerize with ErbB3.[8] It is unclear why other EGFR ligands are not induced, and how they would modulate the effect if expressed in the tumor microenvironment. As BTC displays low expression in normal brain[9] and is involved in neural stem cell proliferation,[10] it would be interesting to assess if BTC has a role in STAT3-mediated regulation of stemness genes and proneural-mesenchymal transition in GBM.
2. STAT3 activation in GBM influences the tumor microenvironment through release of cytokines, which leads to immune cell tolerance, immunosuppression, and regulation of angiogenesis.[3] STAT3 targeting shows promise as immunotherapy, yet it may not be sufficient to counteract immunosuppression.[11] Hence, targeting the STAT3-EGFR feedback loop may impair not only tumor cells but also the ability of the tumor microenvironment to sustain malignant progression.
3. The results of Fan et al[4] are in line with recent findings,[12] which demonstrate upon STAT3 inhibition the induction of a feedback loop involving STAT3 insulin-like growth factor type 1 receptor (IGF-1R) crosstalk in GBM. That study further identified[12] a STAT3 gene signature that prior treatment allowed the prediction of STAT3-resistant GBMs. It would be interesting to determine if this signature also predicts the response to osimertinib-STAT3 blockade.
4. The authors indicate that EGFR overexpression does not influence the induction of BTC-EGFR signaling upon STAT3 blockade. This is surprising also in view of their earlier results indicating that EGFR and EGFRvIII act synergistically to induce STAT3 activation, thereby promoting GBM growth.[2] Therefore, it would be important to assess the extent of BTC, STAT3, and EGFR induction as well as the impact of dual STAT3-EGFR blockade in EGFRvIII-expressing cells. Recently, the efficacy of osimertinib was reported in a case of multifocal EGFR mutant-GBM that show partial response.[13] Clinical trials using the STAT3 inhibitor WP1066 (phase I, NCT01904123) or osimertinib (phase II, NCT03732352) as monotherapy are ongoing for recurrent GBMs. Altogether, the understanding of drug regulatory mechanisms and the identification of novel molecular dependencies will pave the way for the rationale design of novel combinatorial treatments in GBM and probably in other tumor entities (ie, EGFR-mutated non-small-cell lung cancer where osimertinib is already approved.[14]

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