Epidermal growth factor receptor in glioblastoma

- Bufalin enhanced temozolomide efficacy by promoting EGFR protein degradation in glioblastoma
- EGFRvIII-positive glioblastoma contributes to immune escape and malignant progression via the c-Fos-MDK-LRP1 axis
- Nanobodies targeting EGFR provide insight into conformations stabilized by glioblastoma mutations
- Resolving spatial subclonal genomic heterogeneity of loss of heterozygosity and extrachromosomal DNA in gliomas
- EGFRvIII-driven microenvironmental fibroblast activation and transformation accelerate oral cancer progression via lipocalin-2/STAT3 axis
- Imaging the effects of treatment with TERT and EGFR inhibitors on glioblastoma: An MR study
- Intracerebroventricular bivalent CAR T cells targeting EGFR and IL-13Ralpha2 in recurrent glioblastoma: a phase 1 trial
- Innovating Glioma Therapy Using Secretions from Umbilical Cord Mesenchymal Stem Cells to Target Homeobox and Growth Factor Genes

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Epidermal Growth Factor Receptor (EGFR) plays a significant role in glioblastoma, a highly aggressive and malignant form of brain cancer. Here are some key points about the involvement of EGFR in glioblastoma:

EGFR Amplification and Mutation: One of the hallmark features of glioblastoma is the overexpression of EGFR. This often results from gene amplification, leading to an increased number of EGFR receptors on the surface of tumor cells. Additionally, mutations in the EGFR gene, such as the EGFRvIII mutation, are common in glioblastoma.

EGFR Signaling Pathways: EGFR is a receptor tyrosine kinase, meaning it activates various signaling pathways when bound by its ligand, epidermal growth factor (EGF). These pathways include the MAPK (Mitogen-Activated Protein Kinase) and PI3K/AKT pathways, which are critical for cell proliferation, survival, and migration. Dysregulation of these pathways due to EGFR overexpression contributes to the uncontrolled growth of glioblastoma cells.

Resistance to Therapy: The presence of EGFR amplification and mutations can make glioblastomas resistant to certain treatments. For example, some targeted therapies aimed at inhibiting EGFR signaling may initially show promise but can ultimately fail due to the development of resistance mechanisms within the tumor.

Tumor Heterogeneity: Glioblastoma tumors are highly heterogeneous, meaning they consist of various cell populations with different genetic and molecular characteristics. This heterogeneity extends to EGFR expression and mutations. Some regions of the tumor may have high EGFR expression and mutations, while others may not. This poses challenges for targeted therapies that rely on a uniform target.

Therapeutic Target: Despite the complexities associated with EGFR in glioblastoma, it remains an

attractive therapeutic target. Researchers are actively studying ways to target EGFR and its downstream signaling pathways to inhibit tumor growth. This includes the development of small molecule inhibitors and monoclonal antibodies.

Clinical Trials: Clinical trials are ongoing to assess the effectiveness of EGFR-targeted therapies, either as standalone treatments or in combination with other therapies like radiation and chemotherapy. These trials aim to improve outcomes for glioblastoma patients.

Personalized Medicine: Given the heterogeneity of glioblastoma tumors, there is growing interest in personalized medicine approaches. This involves characterizing the molecular profile of an individual patient's tumor, including EGFR status, to tailor treatment strategies for better outcomes.

In summary, EGFR plays a pivotal role in the development and progression of glioblastoma. Its overexpression and mutations drive critical signaling pathways that promote tumor growth and resistance to therapy. Targeting EGFR and its associated pathways is an active area of research and clinical investigation in the quest to improve treatments for glioblastoma patients.

Patients with pathologically confirmed glioblastoma, IDH wildtype, from January 2015 to December 2020, with an EGFR amplification status, were included. Patients who did not undergo DCE or conventional brain MRI were excluded. Patients were categorized into training and test sets by a ratio of 7:3. DCE MRI data were used to generate volume transfer constant (Ktrans) and extracellular volume fraction (Ve) maps. Ktrans, Ve, and conventional MRI were then used to extract the radiomics features, from which the prediction models for EGFR amplification status were developed and validated.

Results: A total of 190 patients (mean age, 59.9; male, 55.3%), divided into training (n = 133) and test (n = 57) sets, were enrolled. In the test set, the radiomics model using the Ktrans map exhibited the highest area under the receiver operating characteristic curve (AUROC), 0.80 (95% confidence interval [CI], 0.65-0.95). The AUROC for the Ve map-based and conventional MRI-based models were 0.74 (95% CI, 0.58-0.90) and 0.76 (95% CI, 0.61-0.91).

Conclusion: The DCE MRI-based radiomics model that predicts EGFR amplification in glioblastoma, IDH wildtype, was developed and validated. The MRI-based radiomics model using the Ktrans map has higher AUROC than conventional MRI [1].

There are ongoing clinical trials exploring the efficacy of dopamine receptor 2 (DRD2) inhibition against glioblastomas. He et al. examined potential molecular determinants of this efficacy.

The Cancer Genome Atlas (TCGA) glioblastoma database and other published mRNA profiles were used to analyze the DRD2 and EGFR expression pattern. In vitro and in vivo responses to DRD2 inhibitors were determined using patient derived xenograft (PDX) glioblastoma models. Immunohistochemical studies were performed on clinically annotated glioblastoma samples derived from patients treated with ONC201.

Analysis of clinical glioblastoma specimens derived from independent patient cohorts revealed an inverse correlation between EGFR and DRD2 mRNA expression, with implication that signaling mediated by these proteins shares overlapping functions. In independent panels of PDX glioblastoma

lines, high EGFR expression was associated with poor in vitro and in vivo response to DRD2 inhibitors, including haloperidol and ONC201. Moreover, ectopic expression of a constitutively active EGFR, EGFRvIII, suppressed glioblastoma sensitivity to ONC201. DRD2 expression positively correlated with expression of rate-limiting enzymes for dopamine synthesis as well as dopamine secretion, suggesting contribution of autocrine DRD2 signaling. Analysis of specimens from patients treated with ONC201 (n = 15) showed an inverse correlation between the intensity of EGFR staining and clinical response. The median overall survival for patients with high and low EGFR staining was 162 and 373 days, respectively (p = 0.037).

High EGFR expression is a determinant of poor glioblastoma response to DRD2. This finding should inform future clinical trial designs [2].

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2)
He Y, Li J, Koga T, et al. Epidermal Growth Factor Receptor (EGFR) as a molecular determinant of glioblastoma response to dopamine receptor 2 (DRD2) inhibitors [published online ahead of print, 2020 Aug 24]. Neuro Oncol. 2020;noaa188. doi:10.1093/neuonc/noaa188