Epidermal growth factor receptor 3 in glioblastoma

The mutant Type III variant of epidermal growth factor receptor (EGFRvIII) is present in approximately one-third of glioblastoma (GBM) patients. It is never found in normal tissues; therefore, it represents a candidate target for glioblastoma immunotherapy, because it is a tumor-specific receptor expressed only in tumors.

Data indicate that EGFRvIII does not alter radiosensitivity with or without anti-EGFR treatment [1].

Epidermal growth factor receptor (EGFR) gene amplification and overexpression are a striking feature of glioblastoma multiforme (Glioblastoma) but are rare in Low-grade gliomas, suggesting a causal role for aberrant EGFR signaling in the pathogenesis of Glioblastoma. The most common EGFR mutant is named EGFRvIII (EGFR type III, EGFRvIII, de2-7, ΔEGFR) [2] [3].

This mutant is generated from a deletion of exons 2 to 7 of the EGFR gene, which results in an in-frame deletion of 267 amino acids from the extracellular domain of the receptor. EGFRvIII is unable to bind ligand, and it signals constitutively. It is important to note that EGFRvIII is usually coexpressed with the wild type (wt) receptor in Glioblastoma [4] [5].

Despite the long-known enigmatic epidermal growth factor receptor (EGFR) gene amplification and protein overexpression in glioblastoma, the potential of EGFR as a target for this tumor type has been unfulfilled [6].

This is in sharp contrast with the observations in EGFR-mutant lung cancer.

Overexpression of epidermal growth factor receptor (EGFR) in glioblastoma multiforme (Glioblastoma) secondary to EGFR gene amplification is associated with a more aggressive tumor phenotype and a worse clinical outcome.

Epidermal growth factor receptor (EGFR), pMAPK, 4E-BP1, p4E-BP1, pS6, eIF4E, and peIF4E expression levels were evaluated using immunohistochemistry. Expression levels were semiquantitatively evaluated using a histoscore. Immunohistochemistry and PCR were used for IDH1 mutations. Statistical analysis was based on the following tests: chi-square, Student's t, Pearson correlation, Spearman's rho, and Mann-Whitney; ROC and Kaplan-Meier curves were constructed. A significant increase was observed between grades for expression of total and phosphorylated 4E-BP1 and for eIF4E, Ki67, EGFR, and cyclin D1. Although expression of EGFR, eIF4E, and Ki67 correlated with survival, only peIF4E was an independent predictor of survival in the multivariate analysis. Combining

the evaluation of different proteins enables us to generate helpful diagnostic nomograms. In conclusion, cell signaling pathways are activated in DIAs; peIF4E is an independent prognostic factor and a promising therapeutic target. Joint analysis of the expression of 4E-BP1 and peIF4E could be helpful in the diagnosis of glioblastoma multiforme in small biopsy samples [7].

Ren et al., analyzed the microarray and proteomics profiles of tumor tissues from glioblastoma patients (N = 180), and identified potential RNA regulators of the Kininogen 1 (KNG1). Validation experiments in U87 glioblastoma cells showed that the regulation of KNG1 by CTU1, KIAA1274, and RAX was mediated by miR 138. The siRNA-mediated knockdown of CTU1, KIAA1274, or RAX in U87 cells and immortalized human endothelial cells (iHECs) significantly reduced KNG1 expression ($P < 0.05$ for all), which resulted in the upregulation of oncogenic EGFR signaling in both cell lines, and stimulated angiogenic processes in cultured iHECs and zebrafish and mouse xenograft models of glioblastoma-induced angiogenesis. Angiogenic transduction of iHECs occurred via the uptake of U87-derived exosomes enriched in miR-138, with the siRNA-mediated knockdown of KNG1, CTU1, KIAA1274, or RAX increasing the level of miR-138 enrichment to varying extents and enhancing the angiogenic effects of the U87-derived exosomes on iHECs. The competing endogenous RNA network of KNG1 represents potential targets for the development of novel therapeutic strategies for glioblastoma [8].

Fluorophore/nanoparticle labeled with anti-EGFR antibodies

Senders et al., systematically review all clinically tested fluorescent agents for application in fluorescence guided surgery (FGS) for glioma and all preclinically tested agents with the potential for FGS for glioma.

They searched the PubMed and Embase databases for all potentially relevant studies through March 2016.

They assessed fluorescent agents by the following outcomes: rate of gross total resection (GTR), overall and progression free survival, sensitivity and specificity in discriminating tumor and healthy brain tissue, tumor-to-normal ratio of fluorescent signal, and incidence of adverse events.

The search strategy resulted in 2155 articles that were screened by titles and abstracts. After full-text screening, 105 articles fulfilled the inclusion criteria evaluating the following fluorescent agents: 5-aminolevulinic acid (5-ALA) (44 studies, including three randomized control trials), fluorescein (11), indocyanine green (five), hypericin (two), 5-aminofluorescein-human serum albumin (one), endogenous fluorophores (nine) and fluorescent agents in a pre-clinical testing phase (30). Three meta-analyses were also identified.

5-ALA is the only fluorescent agent that has been tested in a randomized controlled trial and results in an improvement of GTR and progression-free survival in high-grade gliomas. Observational cohort studies and case series suggest similar outcomes for FGS using fluorescein. Molecular targeting agents (e.g., fluorophore/nanoparticle labeled with anti-EGFR antibodies) are still in the pre-clinical phase, but offer promising results and may be valuable future alternatives. [9].

References

PEPvIII, a peptide sequence from EGFRvIII, was designed to represent a target of glioma and is presented by MHC I/II complexes. Dendritic cells (DCs) have great potential to sensitize CD4+ T and CD8+ T cells to precisely target and eradicate GBM. Here, we show that PEPvIII could be loaded by DCs and presented to T lymphocytes, especially PEPvIII-specific CTLs, to precisely kill U87-EGFRvIII cells. In addition to inhibiting proliferation and inducing the apoptosis of U87-EGFRvIII cells, miR-326 also reduced the expression of TGF-β1 in the tumour environment, resulting in improved efficacy of T cell activation and killing via suppressing the SMO/Gli2 axis, which at least partially reversed the immunosuppressive environment. Furthermore, combining the EGFRvIII-DC vaccine with miR-326 was more effective in killing U87-EGFRvIII cells compared with the administration of either one alone. This finding suggested that a DC-based vaccine combined with miR-326 may induce more powerful anti-tumour immunity against GBM cells that express a relevant antigen, which provides a promising approach for GBM immunotherapy [10].

Expression of EGFRvIII correlates with increased tumorigenicity in mouse models and poor long term survival in clinical studies of glioblastoma patients. In addition, EGFRvIII positive cells are believed to stimulate proliferation of non-EGFRvIII cells through IL-6 cell-to-cell signaling and to release microvesicles containing EGFRvIII , which can merge with neighboring cells, transferring tumor-promoting activity.

EGFRvIII expression may also be associated with tumor stem cells that have been identified in GBM. These stem cells contribute to resistance to cytotoxic therapy and tumor recurrence. EGFRvIII is expressed in tumors in about 30% of glioblastoma patients. It has not been detected at a significant level in normal tissues; therefore, targeting of this tumor-specific molecule is not likely to impact healthy tissues.

The variant III mutation of the epidermal growth factor receptor (EGFRvIII) results from an in-frame deletion of a portion of the extracellular domain, creating a neoepitope.

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