Methods of Resistance to Epidermal Growth Factor Receptor Inhibition in Glioblastoma Multiforme

Although there have been many advances in the understanding of the pathogenesis of glioblastoma multiforme (GBM), there has been little change in overall survival. Despite various interventions, there is universal recurrence and poor outcome. This may be due, in part, to the fact that there are sub-divisions of GBM that require individual treatment. The major limitation of these conventional modalities is their lack of specificity and inherent morbidities. Considering that a number of genes are altered in gliomas, including P53, PTEN, CDKN2A, and EGFR, as well as the fact that a number of allelic losses and alterations have been shown to be predictive of outcome and treatment response, therapy centered at tumor-specific mutations holds the promise of more precise tumor treatment. To this end, investigations have focused on mutated EGFR.

Recently, a number of GBM subgroups have been classified according to genetic alterations, gene expression-based molecular classification, and signaling profiles. The Classical, Mesenchymal, and Proneural subtypes have been divided based on alterations and gene expression of EGFR, NF1, and PDGFRA/IDH1 respectively, but the neural category is currently less well defined.\(^1\)\(^-\)\(^3\) The large array of genomic abnormalities found in GBMs and the fact that genetic alterations results in heterogeneous treatment response, provides further support that mutation specific immunotherapy may be necessary to provide improved therapies. Neoplasm directed vaccines have shown promise in targeting GBM subgroups.\(^1\)\(^-\)\(^9\)

Recent trials have been aimed at GBMs with mutations in epidermal growth factor receptor, which are observed in one third of cases. A phase II study showed promise in the treatment of patients with GBM, but failed to provide a universal or overwhelming benefit upon subset analysis.\(^1\) Eligible patients for this multicenter, prospective trial included adults with EGFR-\(vIII\)-positive GBM and a Karnofsky performance status (KPS) greater than 80 who underwent a gross total resection and demonstrated no radiographic evidence of progression after external beam radiation therapy and concurrent temozolomide (TMZ). The results were as follows. The median progression-free survival (PFS) from time of histologic diagnosis for the 18 patients receiving the vaccine was 14.2 months as compared to 6.3 months in the 17 patients within the matched cohort. Similarly, overall survival (OS) was greater in patients receiving the vaccine, and after adjustment for age and KPS, the survival of vaccinated patients was significantly better than that observed in the matched control group (HR = 5.1). Notably, in patients who received the vaccine and eventual reoperation for recurrence, reoperative pathology revealed that 82% had lost EGFR-\(vIII\) expression. In 14 patients had serum samples demonstrating an EGFR-\(vIII\)-specific humoral response. This subset of patients with a humoral response lived significantly longer than those that did not.

Alterations in MGMT methylation status may explain some of the heterogeneity in outcomes, but further mutations and methods of resistance are likely, as PFS and OS were unexpectedly longer in vaccinated patients with unmethylated MGMT. Moreover, in multivariate analysis after adjusting for age and KPS,
patients with unmethylated MGMT had a significantly longer PFS from vaccination and histologic diagnosis than patients with methylated MGMT who did not receive the vaccine. A major limitation of the study is that overall survival may not be significantly different from recent studies using different forms of immunotherapy. In addition, considering that only one third of patients with GBM express EGFRvIII (10, 30), the overall target population is restricted.

Recently, Jun et al. developed a genetically engineered mouse model of EGFR associated gliomagenesis based on activation of EGFR in coalition with deletions in the Ink4a/Arf and PTEN genes.11 They found chronic activation of wild-type EGFR with a ligand is necessary. These tumors are resistant to EGFR tyrosine kinase inhibition. EGFR inhibition causes an alteration in gene expression of GBM tumor cells including activation of the MET tyrosine kinase. This MET activity causes activation of downstream signaling pathways resulting in survival of GBM cells, supporting the importance of transcriptional activation of the MET receptor tyrosine kinase. Most importantly, targeted pharmacological inhibition of MET reversed this function and overcame the resistance to EGFR inhibition in these cells. These results elucidate mechanisms of resistance to EGFR inhibition and provide further evidence that multi-targeted therapy will likely be necessary in the treatment of GBM. Despite advances, further knowledge of GBM subtypes and gene expression, along with their methods of resistance, will be essential.

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REFERENCES

Surface Topography Can Be Used to Instruct Stem Cell Fate

Biomaterials have become integral components in tissue engineering applications. Numerous investigations have established the ability to direct cellular behavior by manipulating the specific characteristics of biomaterials including their physical features and chemical structure. The instructive properties of biomaterials can be manipulated for improved integration after surgical implantation with the functionality being highly dependent on proper cell-material interactions.1 Optimizing cell-material interactions is critical to enhance the therapeutic performance of biomaterials, yet the interplay between surface topographies and cell behavior is complex and still incompletely understood.

It is well recognized that growth factors are chemical cues that interact with cells to signal their molecular function. But more recently, surface topography of the biomaterials have been shown to have the capability of influencing cellular behavior without the presence of chemical signals.2 Optimizing the interactions between cells and biomaterials has proved to be challenging on 3 levels. First, the exact mechanism in which cells