

Resistance mechanisms in glioblastoma

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Glioblastoma (GBM) is the most frequent and aggressive malignant brain tumor. The current standard treatment for this tumor is surgical resection followed by concurrent radiation and temozolomide (TMZ) therapy. However, most of the patient do not respond to TMZ treatment. Understanding dysregulated pathways that lead to resistance to this alkylating drug is of the utmost importance to develop new therapeutic strategies and improve GBM patients' prognosis.

The first part of this study was focused on the characterization of a selected list of candidate genes potentially associated with TMZ resistance that were identified by perturbation screens. Survival analysis, mutational frequency and differential expression analysis were employed in order to assess the relevance of the candidate genes for GBM biology.

These investigations were carried out with the help of open access data available from The Cancer Genome Atlas (TCGA) project (Tomczak et al., 2015). Survival analysis indicated that PIM1 could be regarded as a potential prognostic marker for GBM patients. Differential expression analysis unveiled a correlation between PIM1 and the mesenchymal subtype, the most aggressive and multitherapy-resistant GBM subtype.

In the second part the focus shifted to pathway analysis. The results of three different CRISPR screens (CRISPR knockout, CRISPR interference and CRISPR activation) were used in order to identify potential pathways related to TMZ resistance. Both Gene Set Enrichment Analysis and Over-Representation Analysis approaches were employed. Nonetheless, this type of analysis conducted on these CRISPR screen data showed a lack of statistical power, thus limiting the identification of dysregulated pathways.

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