Network Biology Methods for Improved Drug Discovery in Brain Cancers

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Targeted therapies for glioblastoma multiforme (GBM) have low success rates in clinical trials and fail to target specific disease-causing mutations, partially due to the exclusive use of genomic data in current drug discovery methods. In this study, multiomics data, network integration methods, and rigorous drug screening trials were used to identify new and significant targets and lead compounds. First, multiomics datasets of GBM patients were obtained from TCGA, NCBI GEO, and Broad GDAC and analyzed to determine significance. Next, the data was integrated using correlation networks; and a final rank of genes was obtained using rank aggregation functions. A target was then modeled, validated, and screened with compounds (n>10,000) to identify leads. The p values obtained from the top differentially expressed genes (n=2320) indicated that the expression patterns were statistically significant ($p<0.001$). YWHAE was identified as the top gene; and was linked with apoptosis, cell cycle control, and cell division. It was also influential in the prognosis of seven cancers. The gene's produced protein, 14-3-3 epsilon protein was modeled, and its structure was validated using the QMEAN scoring function. The protein had a global score of 0.87, indicating a high model quality. Additionally, compound libraries were obtained and tested for binding affinity to 14-3-3 epsilon protein using a drug screening tool to identify lead compounds. The top ten leads were ranked based on z-score and their docking results were deemed to be significant ($z>6$). This study showed that network integration methods and multiomics data identified new and significant drug targets and leads for GBM. Further experimentation will confirm YWHAE, the leads, and the methods used.

Awards Won: