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Computer modeling of glioblastoma gene network and hub genes analysis

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Motivation and Aim: Glioblastoma is the most aggressive type of brain tumors resistant to a number of antitumor drugs. The problem of therapy and drug treatment course is complicated by extremely high heterogeneity in the benign cell populations, the random arrangement of tumor cells, and polymorphism of their nuclei. The pathogenesis of gliomas needs to be studied using modern technologies to find new therapy targets. For an object such as gliomas, it is necessary to conduct new studies based on modern cellular technologies, genome-wide technologies for high-throughput sequencing, and the integration of available information from international databases and genomic projects [2].

Methods and Algorithms: There are open international databases on gene expression including glioblastoma (microarrays and sequencing data of GEO NCBI, http://www.ncbi.nlm.nih.gov/geoprofiles/), expression in various types of tumor cells (The Cancer Gene Atlas, cancergenome.nih.gov), gene expression for brain compartments (Allen Brain Atlas), protein interactions databases such as HPRD (http://hprd.org/), KEGG biochemical reactions (http://www.genome.jp/kegg/), Interactome (http://interactome.org/), sequenced tumor genomes, including gliomas and glioblastomas (https://cghub.ucsc.edu/). The Allen Institute has developed the Ivy Glioblastoma Atlas Project database (http://glioblastoma.alleninstitute.org/) according to patients with glioma. We demonstrate that these publicly available online bioinformatics tools can give helpful information for annotation of gene list for glioblastoma, reconstruction of gene network and comparative analysis of the related diseases. This approach for gene network analysis of list of gene names using online bioinformatics tools presents application of bioinformatics methods to annotation of complex human diseases. We used DAVID (Database for Annotation, Visualization and Integrated Discovery) tool (https://david.ncifcrf.gov/summary.jsp) and the PANTHER (Protein ANalysis THrough Evolutionary Relationships) (http://pantherdb.org/) resource for gene ontology analysis. Then we applied gene network reconstruction tools. Prioritization of genes was performed using the resource ToppGene: Candidate gene prioritization (https://toppgene.cchmc.org).

Results, the most significant GO categories for glioblastoma genes are protein binding, positive regulation of protein phosphorylation, membrane location (according to cellular compartments – GOTERM_CC classification), and kinase activity. In general, according to the categories from the table, membrane proteins and kinases play an important role, apparently associated with signal transduction into the cell. UP_KEYWORD (terms from UniProt (https://www.uniprot.org/) shows associations with tumors and kinase activity. The categories of processes related to the development of the nervous system are also presented. The hub genes for glioblastoma were identified by the Cytoscape tool (https://cytoscape.org/), and pathway enrichment analysis of the genes was performed using Database for Annotation, Visualization and Integrated Discovery (DAVID) following [4].

Yang and Yang (2021) recently analyzed glioma genes by GSEA, and the significantly enriched KEGG pathways involved in synapse signaling and oxytocin signaling pathways [5]. The core molecules of GBM and the DrugBank database were assessed to identify 10 drugs included tetrachlorodecaoxide related to cancer and neuropsychiatric diseases. The study of the structure of the gene network shows a high connectivity of genes and their products. Glioma progression is strongly connected with different types of epigenetic phenomena, such as histone modifications, DNA methylation, chromatin remodeling, and aberrant microRNA

Conclusion: Overall, online bioinformatics tools allow to model main parameters of gene network related to given disease [3]. Zhu and colleagues (Zhu et al., 2021) provided a framework of workflow for potential therapeutic drug discovery and predicted 10 potential drugs for glioblastoma therapy. Integration of the results obtained by online bioinformatics tools and genetics data leads to novel knowledge in the study of complex oncological diseases. Note recent thematic journal issues on the chronic disease markers (https://www.frontiersin.org/research-topics/21036/high-throughput-sequencing-based-investigation-of-chronic-disease-markers-and-mechanisms) in *Frontiers in Genetics* and related works highlighting importance of new drug targets search [1].

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