Prediction of Repurposed Drug Compound For Astrocytoma

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Background and Motivations

The fields of medicine, biotechnology and pharmacology have all witnessed great progress in recent years, yet new drug discovery is still a long, expensive, difficult, and inefficient process. Adverse side effects of successful drugs remain a series issue. Repurposed drug discovery is a promising low-cost, time-saving approach to drug discovery. Cancer is a complex disease and its curing calls for a systems treatment. In 2011, the World Health Organization (WHO) suggested that mobile phone radiation could be a risk of brain cancer. Among brain cancers glioma has the poorest prognosis, with the highest percentage of patients dying within one year.

Proposed Approaches

A brain tumor is an intracranial solid tumor within the brain or the central spinal canal. The largest group of primary brain tumors is gliomas. The main type of gliomas is astrocytoma. The WHO grading system established a four-tiered histologic grading guideline for astrocytomas that assigns a grade from 1 to 4, with 1 being the least aggressive and 4 being the most aggressive. The WHO-grading scheme is based on the appearance of certain characteristics: atypia, mitosis, endothelial proliferation, and necrosis.

Microarray data were derived from GEO database (GEO accn. GSE4290). Expression data were handled using Affymetrix Human Genome U133 Plus 2.0 Array. Samples were collected from patients with brain tumor. 103 brain tumor samples include 19 anaplastic astrocytomas and 77 glioblastomas. 23 samples from epilepsy patients were used as non-tumor samples.

In this project, we demonstrated a low-cost and fast-speed procedure for discovery of repurposed drug compounds with minimal intracellular side effects for the systems treatment of complex diseases, and applied it on astrocytoma. We used "gene set enrichment analysis" (GSEA) [5] and the Connectivity Map (CMap) [2] to find repurposed candidate drug compounds for the purpose of curing astrocytoma, the most common glioma. The drug discovery procedure integrated gene expression data of astrocytoma patient cohorts, Gene Ontology [1] database, and the CMap. Sets of gene expression microarray data of grade specific astrocytoma patient cohorts were used to obtain differentially expressed genes (DEGs). The DEGs were used to construct modules of functional genes according to the "hallmarks of cancer" oncogenesis system [3] and KEGG pathways in cancer [4]. Candidate repurposed drugs were identified by separately querying the CMap with the functional modules. GSEA were used for scoring the drugs. A candidate drug compound was composed of a minimum set of candidate drugs that combined would have beneficial effects to all the hallmark of cancer functions. Furthermore, none of drugs in a compound were allowed to have an adverse effect on any of the functions.

Conclusions

We found several repo-drug compounds that satisfied our selection criterion for the systems treatment of grade specific astrocytoma. A five-drug compound for (the treatment of) astrocytoma in grade IV was composed of chlorphenesin, enilconazole, Prestwick-1084, tridihexethyl, and parthenolide; a two-drug compound for anaplastic astrocytoma in grade II was composed of parthenolide and zoxazolamine; a two-drug compound for anaplastic astrocytoma in grade III was composed of doxazosin and fluvoxamine. Parthenolide in recent years has been used in research as a potential cancer drug. Cell model validation of our drug compounds are under way, animal model validation and being planned. We believe our procedure can be usefully applied to the discovery of repurposed drug compounds for the systems treatment of grade specific cancers other than glioma, and for other types of complex diseases.

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Results

Table 1. Significantly drugs list within effective function datasets without any side effects.

Drug Name	Grade Type	ATC code	Disease
chlorphenesin	**grade 4 vs. non-tumor**	**D01AE07**	
cyproterone	grade 3 vs. non-tumor	G03HA01	Prostate cancer
enilconazole	**grade 4 vs. non-tumor**		
fenspiride	grade 4 vs. non-tumor	R03BX01, R03DX03	
parthenolide	**grade 3 vs. non-tumor** **grade 4 vs. non-tumor**		**Cancer, unspecific**
Prestwick-1084	grade 4 vs. non-tumor		
tridihexethyl	**grade 4 vs. non-tumor**	**A03AB08**	**Alzheimer's disease**
zoxazolamine	grade 3 vs. non-tumor		

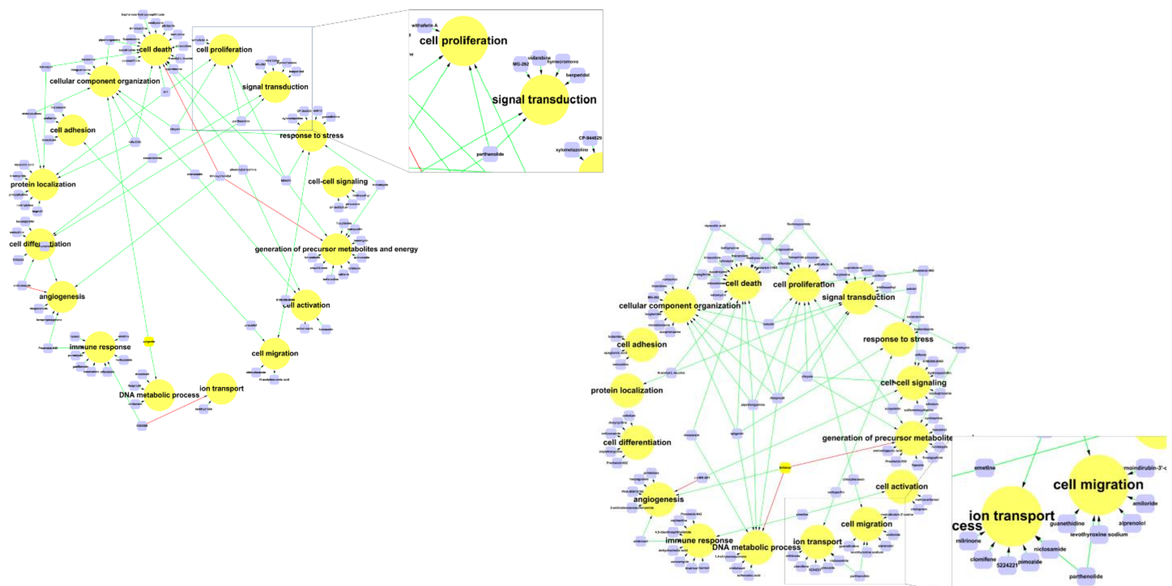

Figure 1. Drug-functional association network. Beneficial links (green edges) have p-value < 0.01 and enrichment score (ES) < -0.75; adverse links (red edges) have p-value < 0.01 and ES > 0. The left network was determined by Grade III vs. Non-tumor data and the right, by Grade IV vs. Non-tumor samples.

Table 2. Significantly drug complexs list within effective function datasets without any side effects.

Drug Name	GO Grade Type	Functional GO term
parthenolide zoxazolamine	grade 3 vs. non-tumor	cell differentiation, cell proliferation, protein localization, signal transduction.
chlorphenesin enilconazole Prestwick-1084 tridihexethyl **parthenolide**	grade 4 vs. non-tumor	cell death, cell migration, cell proliferation, ion transport, signal transduction.

References

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