Personalized anti-cancer drug treatment choice using RNA-seq and network analysis.

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The development of omics technologies and emerging of targeted therapies have opened a new era in the medicine of 21st century - the era of personalized medicine based on identification of the precise molecular mechanism of a certain pathology in a concrete patient. Personalized medicine and targeted therapy play a very special role in cancer diseases as it has been widely shown in multiple studies that the same types of cancer in two different patients can appear to be very different in their origins and mechanisms and therefore responding differently to the same treatment. Development of personalized drug target identification algorithm based on the patient omics data analysis would solve this problem of optimal therapy selection and would bring the cancer treatment strategy to a completely new level. Our work aims to introduce an algorithm for reconstruction of the molecular mechanism of a certain pathology and selection of effective therapies based on the personalized model of the disease. The drug target identification algorithm introduced in this work can be applied for various types of omics data. For illustrating the algorithm in the current study, we will show its application example on the basis of RNA-seq data of colorectal cancer tumor sequencing. We analyzed RNA-seq data of the patients with the good and pure response to standard therapy and revealed differentially expressed genes (DEGs) in the tumor compared to normal surrounding tissue. We applied *Upstream Analysis* algorithm [1] for identification of key master-regulators responsible for pathologic gene regulation in cancer cells of the studied cases. The analysis comprised of three main steps: 1) AI-based algorithm to scan promoters of DEGs using TRANSFAC database and to identify complexes of transcription factors (TF), which regulate DEGs; 2) a graph search algorithm using TRANSPATH database to identify common regulators of the TFs selected on the previous step as potential drug targets; 3) effective treatments are then selected for the identified drug targets, on the basis of HumanPSD database, containing the information about the approved drugs, as well as the therapies under development, and their targets. This algorithm is available at the Genome Enhancer web site (ge.genexplain.com).

The performed analysis revealed that the studied patient cases had rather different mechanism of carcinogenesis that involve fairly different although partially overlapping sets of master regulators in the molecular circuits that control activity of the gene expression in these tumors. Based on the revealed master regulators our algorithm proposed highly tuned personalized prospective drug treatment prognosis for the different patients with various cancer progression. We have shown that the predicted by GE sensitivity to the anti VEGFA therapy highly correlated with observed response in the studied patients. The target-oriented approach towards treatment prescription accelerates the off-label drug usage and enables effective treatment selection for clinically complicated cases with no obvious treatment options.

1. Kel A., et.al. Walking pathways with positive feedback loops reveal DNA methylation biomarkers of colorectal cancer // BMC Bioinformatics. 2019. V. 20 (Suppl 4)