Reconstruction of integrated maps for drug efficacy assessment

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Background.
Analysis of biological network and signaling pathways is widely used for investigation of cell processes, mechanisms of disease, drug development and analysis of drug repurposing perspectives.
Different scientific groups develop similar conceptions of biological networks and pathways that represent processes in norm , but conceptions of disease-specific pathways and drug mechanism of action pathways can differ significantly amoung researchers. Previously, we've developed the conception of disease-specific pathway maps that show affected normal processes in pathology and some steps that newer have been detected in norm. The disease maps show enhanced and weakened interactions or reactions under pathological conditions resulting from mutations or abberant gene expression.
Another conceptions was compillation of disease-specific pathways with drug, xenobiotic or another enviromental factor action in one mapthat represent both disease-specificity and drug-induced perturbations.
Research objective.
The aim of research was to elucidate mechanisms of acquired or hereditary drug resistance for small group of patients suffering from breast cancer with triple negative phenotype (TNBC).
Materials and methods.
Group of 10 patients suffered from TNBC has been enrolled in study. All patients have got similar antitumor therapy. Whole exome sequencing and whole transcriptome analysis ware performed for the genomic DNA and RNA obtained from tumor samples . DAVID and MetaCorehave been used for functional and integrated analysis. Reconstruction of integrated maps of tumor processes has been performed in Cytoscape APP.
Results.
Whole exome sequence showed high heterogeneity of tumor samples. Several hereditary risk factors (mutations in TP 53/ Li-Fraumeni syndrome, mutation in MSH6 / Lynch syndrome) and damaging mutations in well- known driver genes were detected in patient samples.
Analysis of tumor gene expression data allowed to reveal the concordance of patient data with different subtypes of Lehmann's classification of TNBC. Pathway analysis by MetaCore and David wasn't capable to explain tumor drug resistance in patients. So for the aims of this project we've combined conceptions of disease-specific and drug mechanism of action maps and reconstructed integrated models using Cytoscape. Compilation of different types of data in these maps allowed to clearly define differences between Lehmann's subtype patients and explain possible drug resistance mechanisms in each subtype.
Conclusion.
Compilation of disease-specific pathways and mechanisms of drug action with genetic, farmacogenomic and expression data allows to build comprehensive models that reflect processes of tumor progression and in some cases explain the drug resistance.