Knowledge-Guided Prioritization of Genes Determinant of Drug Resistance Using ProGENI

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Identification of genes whose basal mRNA expression can predict the sensitivity/resistance of tumor cells to cytotoxic treatments can play an important role in individualized cancer medicine. A pretreatment screening of the expression of genes in the tumor tissue can suggest the best course of chemotherapy or can suggest a combination of drugs to overcome chemoresistance. In this study, we developed a computational method called Prioritization of Genes Enhanced with Network Information (ProGENI), to identify such genes by leveraging both the basal gene expressions and prior knowledge in the form of an experimentally verified network of protein-protein and genetic interactions. This method is based on identifying a small set of genes that a combination of their expression and the activity level of the network module surrounding them shows high correlation with drug response, followed by ranking of the genes based on their relevance to this set using random walk techniques.

Our analysis on a dataset comprised of approximately 300 lymphoblastoid cell lines for 24 cytotoxic treatments revealed a significant improvement in predicting drug sensitivity using ProGENI compared to other methods that do not consider network information. A significant improvement was also observed on another dataset from the Genomics of Drug Sensitivity in Cancer (GDSC) database, containing approximately 600 cell lines from 13 tissue types for 139 drugs. In addition, we used literature evidence in addition to siRNA knockdown experiments to confirm the effect of highly ranked genes on the sensitivity of three drugs: cisplatin, docetaxel and doxorubicin. Our results confirmed the role of more than 73% of the genes (33 out of 45) identified using ProGENI in the sensitivity of cell lines to these three drugs. These results suggest ProGENI to be a powerful computational technique in identifying genes that play a key role in determining the drug response.