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Targeting Metabolic Genes in Drug-Resistant Breast Cancer Cells to Improve Their Drug Response by Using Genome-Scale Metabolic Models

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Adaptive resistance to a drug remains as a critical therapeutic challenge in cancer patients. Metabolic reprogramming in cancer cells is one of the main mechanisms that may result in the drug resistance. The aim of this study is to identify metabolic gene targets that can improve drug response in drug-resistant breast cancer cells upon downregulation. We hypothesized that metabolic perturbation of drug-resistant breast cancer cells would restore the metabolic features of drug-sensitive cells. To identify such genes, we used genome-scale metabolic models (GEMs), which are a computational model that predicts genome-scale metabolic flux distribution based on metabolic network of a cell. By integrating omics data, we can build a cell-specific GEM. In this study, we utilized engineered MCF7 cells, a breast cancer cell line, which were resistant to doxorubicin. First, Proteome data from doxorubicin-resistant cells was used to create GEM representing these drug-resistant. Next, a single-gene knockout simulation was conducted using the drug-resistant GEM. As a result, we obtained a list of metabolic gene targets that could lead to the metabolic features of parental, or drug-sensitive MCF7 upon downregulation of the targets. We performed *in vitro* experiments using inhibitors to validate the predicted metabolic gene targets. The same approach was also applied to the paclitaxel-resistant MCF7. This study shows that metabolic network can serve as a target to improve the drug response of cancer cells. Also, the approach undertaken in this study can be considered for other types of drug-resistant cancer cells.