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Abstract

Background

Two genes are called synthetic lethal (SL) if their simultaneous mutations lead to cell death, but each individual mutation does not. Targeting SL partners of mutated cancer genes can kill cancer cells specifically, but leave normal cells intact. Therefore, synthetic lethality strategy offers an elegant alternative to killing cancer cells with non-druggable mutant tumor suppressor genes and stability genes, for example, TP53, by targeting its SL partners. We present a computational approach to identifying SL gene pairs for novel therapeutics in lung adenocarcinoma (LADC).

Methods

We first identified functionally relevant (simultaneously differentially expressed) gene pairs by screening the collected 668 SL pairs, which were verified in various cancers, using microarray gene expression data of paired lung cancerous and non-cancerous tissues. From the top-ranked pairs, 21 genes were chosen for immunohistochemistry (IHC) staining at multiple cellular locations using tissues dissected from 131 LADC patients in Taiwan. To find novel SL pairs, we combined the 24 IHC of individual proteins to result in 273 IHC pairs. Next, we tested each of these IHC pairs for the two proposed synergistic effects with clinical features to identify tumor-cell-dependent pairs, which are our predicted SL pairs.

Results

Of the 19 predicted SL pairs, FEN1-RAD54B, BRCA1-TP53 and BRCA2-TP53 have been verified in colorectal cancer (by siRNA knockdown) and cervical cancer cells (by both genomewide screen and siRNA knockdown) in literature, respectively. IHC of FEN1(N)-RAD54B$(\uparrow,\uparrow)$*, BRCA1(C)-RAD54B*$(\downarrow,\uparrow)$ *and PARP1-RAD54B*$(\uparrow,\uparrow)$ *were shown to correlate with poor overall survival of 131 LADC patients. Thus, they may serve as prognosis markers.*

Conclusions

In addition to FEN1-RAD54B, our method uncovered two previously validated SL pairs BRCA1-TP53 and BRCA2-TP53, and predicted some promising pairs such as EGFR-RB1. After future in vitro and in vivo validations, BRCA1 and RB1, may be promising targets for TP53-mutant and EGFR-mutant LADC patients, while to date safety regarding inhibition of TP53 is controversial and EGFR is often mutated in Asian LADC patients. This suggests that the proposed approach is useful in revealing novel drug targets for Asian

LADC.