Uncovering synthetic lethal interactions for colorectal cancer therapeutics via an integrated approach

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Abstract

Using synthetic lethality-based methods to develop cancer-specific therapeutics has been rapidly adapted due to its translational impact. Various scaled RNAi-based experimental strategies have driven identification of synthetic lethal (SL) interactions in cancer. As an alternative, we present an integrated computational and experimental approach to uncovering SL pairs in colorectal cancer (CRC). Certain verified SL pairs were simultaneously differentially-expressed in high percentages of cancerous tissues, for example, CRC. Protein levels of ~20 selected genes were evaluated using immunohistochemistry in 171 CRC patients, and their pairwise combinations (169 in total) were correlated to clinicopathological features, for example, tumor size. This resulted in 11 predicted SL pairs, including the previously verified (*MSH2*, *POLB*) and (*CSNK1E*, *MYC*). Additionally, we validated two novel SL pairs using RNAi (*CSNK1E* and *CTNNB1* with *TP53*) and small-molecule inhibitor (*CSNK1E* with *TP53*) in isogenic *TP53* HCT-116 cell lines, indicating that these SL pairs can be readily translated to pre-clinical studies in treating *TP53*-mutant CRC patients.