Talk title:

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

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Two genes are said to have synthetic lethal (SL) interaction if their simultaneous mutations lead to cell death, but each individual mutation does not. Using synthetic lethality-based methods to develop cancer-specific therapeutics has been rapidly adapted due to its translational impact. Here, we present an integrated computational and experimental approach to uncovering SL pairs in colorectal cancer (CRC). Our pilot study showed that certain verified SL pairs were simultaneously differentially-expressed in high percentages of cancerous tissues. Thus, we hypothesized that cancer cells depend on some of these gene pairs for survival and/or proliferation. Protein levels of ~20 selected genes were evaluated by immunohistochemistry using 171 CRC patients, and their pairwise combination were correlated to clinicopathological features. This resulted in 11 predicted SL pairs, including the previously verified (*MSH2*, *POLB*) and (*CSNK1E*, *MYC*). Additionally we validated two novel SL pairs of *TP53* using RNAi, small-molecule inhibitor and mouse model, indicating that these SL pairs can be readily translated to preclinical studies in treating *TP53*-mutant CRC patients. Kaplan-Meier estimates demonstrated that four IHC pairs were correlated with poor survival. Finally, multivariate Cox regression analysis showed that these four protein pairs and stage can predict CRC patient overall survival, suggesting their clinical application in decisions for adjuvant treatment. Our approach is readily accessible and applicable to other cancers.