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Cancer susceptibilities revealed through a map of negative genetic interactions in isogenic cancer cells

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Abstract

Improved efforts are necessary to define the functional product of cancer mutations currently being revealed through large-scale sequencing efforts. Using genome-scale pooled shRNA screening technology, we mapped negative genetic interactions across a set of isogenic cancer cell lines and confirmed hundreds of these interactions in orthogonal co-culture competition assays to generate a high-confidence genetic interaction network of differentially essential or DiE genes. The network uncovered examples of conserved genetic interactions, densely connected functional modules derived from comparative genomics with model systems data, functions for uncharacterized genes in the human genome, targetable vulnerabilities, and DiE genes through differential expression. Interestingly, the *PTEN*$^{-/-}$ DiE genes reveal a signature that can preferentially classify *PTEN*-dependent genotypes across a series of non-isogenic cell lines derived from breast, pancreas and ovarian cancers. Our reference network suggests that many cancer vulnerabilities remain to be discovered through systematic derivation of a network of differentially essential genes in an isogenic cancer cell model.