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Evolutionary dependency of cancer mutations in gene pairs inferred by nonsynonymous-synonymous mutation ratios

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Background

Determining the impact of somatic mutations requires understanding the functional relationship of genes acquiring mutations; however, it is largely unknown how mutations in functionally related genes influence each other.

Methods

We employed non-synonymous-to-synonymous or dNdS ratios to evaluate the evolutionary dependency (ED) of gene pairs, assuming a mutation in one gene of a gene pair can affect the evolutionary fitness of mutations in its partner genes as mutation context. We employed PanCancer- and tumor type-specific mutational profiles to infer the ED of gene pairs and evaluated their biological relevance with respect to gene dependency and drug sensitivity.

Results

We propose that dNdS ratios of gene pairs and their derived cdNS (context-dependent dNdS) scores as measure of ED distinguishing gene pairs either as synergistic (SYN) or antagonistic (ANT). Mutation contexts can induce substantial changes in the evolutionary fitness of mutations in the paired genes, e.g., *IDH1* and *IDH2* mutation contexts lead to substantial increase and decrease of

dNdS ratios of *ATRX* indels and *IDH1* missense mutations corresponding to SYN and ANT relationship with positive and negative cdNS scores, respectively. The impact of gene silencing or knock-outs on cell viability (genetic dependencies) often depends on ED, suggesting that ED can guide the selection of candidates for synthetic lethality such as *TCF7L2-KRAS* mutations. Using cell line-based drug sensitivity data, the effects of targeted agents on cell lines are often associated with mutations of genes exhibiting ED with the target genes, informing drug sensitizing or resistant mutations for targeted inhibitors, e.g., *PRSS1* and *CTCF* mutations as resistant mutations to EGFR and BRAF inhibitors for lung adenocarcinomas and melanomas, respectively.

Conclusions

We propose that the ED of gene pairs evaluated by dNdS ratios can advance our understanding of the functional relationship of genes with potential biological and clinical implications.