Identifying Collateral and Synthetic Lethal Vulnerabilities within the DNA-damage Response

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Genomic deletion in DNA-damage response (DDR) genes is an important driver of tumorigenesis, frequently accompanied by collateral heterozygous deletion of chromosomally neighbouring passenger genes. While deletion of these passenger genes is typically tolerated due to functional redundancy, cancer cells can become selectively vulnerable to inhibition of the remaining copies of these genes. Such *collateral vulnerability* can be exploited in synergy with *synthetic lethality* (SL) wherein the inhibition of genes that functionally compensate the DDR loss induces lethality.

We developed a computational method to identify genes inducing collateral vulnerability (genes *co-deleted* with DDR genes) and/or SL (genes deleted in a *mutually exclusive* manner to DDR and its co-deleted genes). Using AffinityPropagation, we identified gene clusters that are collaterally deleted ('CD clusters') with eight DDR genes (ATM, BRCA1, BRCA2, CDH1, MSH2, MSH3, PTEN and TP53) across >6,000 tumours from TCGA. We developed an edge-swapping method to identify genes that are deleted in mutually exclusive fashion to these clusters. We identified >600 CD clusters that formed 425 cluster pairs containing at least one SL gene pair. Of these, 125 pairs were validated using gene-essentiality (GARP) scores from siRNA-based knockdown screens on breast cancer cell lines [1]. We found FXR2 within the TP53 CD-cluster in agreement with existing literature [2], and BCL2 was predicted SL to the TP53-cluster. Inhibition of either BCL2 or TP53 in cell lines lacking the other showed the lowest GARP scores (highest cell death) compared to cells wild type for at least one of the genes (median $BCL2^{-/-}$ $TP53^{-/-}$ < -1.0, but median $BCL2^{+/+}$ $TP53^{+/+}$, $BCL2^{+/+}$ $TP53^{-/-}$ or $BCL2^{-/-}$ $TP53^{+/+}$ > 0). We found similar GARP evidence for PTEN-DYNC1L1 and PTEN-WDR48. Our method thus identifies novel vulnerabilities with potential therapeutic implications for DDR-defective cancers.

[1] Marcotte *et al*. Nucl Acids Res 2014, 42(10):6106-27

[2] Fan *et al.* eLife 2017, 6:e26129.