Systematic discovery of mutation-specific synthetic lethals by mining pan-cancer human primary tumor data.

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Public Summary:
Two genes are synthetically lethal (SL) when defects in both are lethal to a cell but a single defect is non-lethal. SL partners of cancer mutations are of great interest as pharmacological targets; however, identifying them by cell line-based methods is challenging. Here we develop MiSL (Mining Synthetic Lethals), an algorithm that mines pan-cancer human primary tumour data to identify mutation-specific SL partners for specific cancers. We apply MiSL to 12 different cancers and predict 145,891 SL partners for 3,120 mutations, including known mutation-specific SL partners. Comparisons with functional screens show that MiSL predictions are enriched for SLs in multiple cancers. We extensively validate a SL interaction identified by MiSL between the IDH1 mutation and ACACA in leukaemia using gene targeting and patient-derived xenografts. Furthermore, we apply MiSL to pinpoint genetic biomarkers for drug sensitivity. These results demonstrate that MiSL can accelerate precision oncology by identifying mutation-specific targets and biomarkers.

Scientific Abstract:
Two genes are synthetically lethal (SL) when defects in both are lethal to a cell but a single defect is non-lethal. SL partners of cancer mutations are of great interest as pharmacological targets; however, identifying them by cell line-based methods is challenging. Here we develop MiSL (Mining Synthetic Lethals), an algorithm that mines pan-cancer human primary tumour data to identify mutation-specific SL partners for specific cancers. We apply MiSL to 12 different cancers and predict 145,891 SL partners for 3,120 mutations, including known mutation-specific SL partners. Comparisons with functional screens show that MiSL predictions are enriched for SLs in multiple cancers. We extensively validate a SL interaction identified by MiSL between the IDH1 mutation and ACACA in leukaemia using gene targeting and patient-derived xenografts. Furthermore, we apply MiSL to pinpoint genetic biomarkers for drug sensitivity. These results demonstrate that MiSL can accelerate precision oncology by identifying mutation-specific targets and biomarkers.