

Systems biology

# DiscoverSL: an R package for multi-omic data driven prediction of synthetic lethality in cancers

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Associate Editor: Russell Schwartz

Received on May 7, 2018; revised on July 9, 2018; editorial decision on July 24, 2018; accepted on July 26, 2018

## Abstract

**Summary:** Synthetic lethality is a state when simultaneous loss of two genes is lethal to a cancer cell, while the loss of the individual genes is not. We developed an R package *DiscoverSL* to predict and visualize synthetic lethality in cancers using multi-omic cancer data. Mutation, copy number alteration and gene expression data from The Cancer Genome Atlas project were combined to develop a multi-parametric Random Forest classifier. The effects of selectively targeting the predicted synthetic lethal genes is tested *in silico* using shRNA and drug screening data from cancer cell line databases. The clinical outcome in patients with mutation in primary gene and over/under-expression in the synthetic lethal gene is evaluated using Kaplan–Meier analysis. The method helps to identify new therapeutic approaches by exploiting the concept of synthetic lethality.

**Availability and implementation:** DiscoverSL package with user manual and sample workflow is available for download from github url: <https://github.com/shaoli86/DiscoverSL/releases/tag/V1.0> under GNU GPL-3.

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**Supplementary information:** [Supplementary data](#) are available at *Bioinformatics* online.

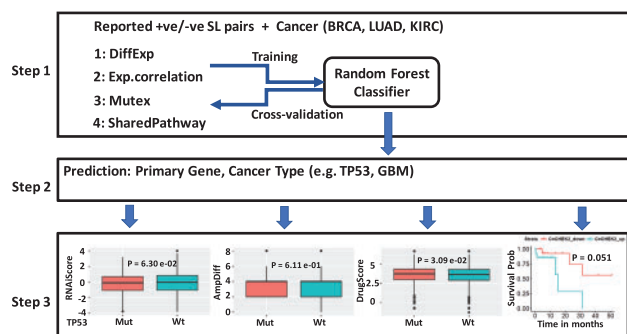
## 1 Introduction

In synthetic lethality, the mutant tumor cells are dependent upon their synthetic lethal (SL) interactors for survival. So, in tumors where the driver or oncogenes cannot be targeted, SL interactors can potentially serve as a drug target (Ashworth, 2008). Some recently published algorithms use cancer genomic data for prediction of SL interactions (Jerby-Arnon *et al.*, 2014; Sinha *et al.*, 2017; Srihari *et al.*, 2015), still the problem of identifying clinically relevant SL interactors persists. Cancers are driven by mutations and, there is a need for an integrative resource that identifies targetable and clinically relevant SL interactions based on cancer gene mutations, along with potential drugs for targeting them. Here we present an integrative R package ‘DiscoverSL’ that predicts cancer-specific SL interactions of any given susceptibility gene using a machine learning approach. The clinical relevance of the predictions was assessed *in silico* using cell line and patient data using the functional modules

provided, to estimate the relative sensitivity to shRNA silencing, copy number changes, drugs and Kaplan–Meier (KM) analysis. The package also includes additional plot modules for intuitive visualization. Together, *DiscoverSL* R package offers an integrative approach to discover mutation-specific SL interactions in cancers.

## 2 The algorithm and modules

The potential SL interactions were predicted using a Random Forest (RF) model trained on positive and negative SL genes collected from published screens and applied to cancer data (see [Supplementary Methods](#)). As shown in [Figure 1](#), the training model includes, reported SL interactions and select cancer types. Four features were estimated using the following modules as shown in Step1: *DiffExp* (differential expression of Gene2 +/- mutation in Gene1), *ExpCorrelation* (correlation of expression), *Mutex* (mutual



**Fig. 1.** The workflow of the DiscoverSL showing the trained RF model on combined multiple data types (Step1), applied to new data for prediction (Step 2) and validation (Step 3)

exclusivity) and *SharedPathway* (association with common pathways) derived from mutation, gene expression, copy number alteration (CNA) profiles from The Cancer Genome Atlas (TCGA) patient samples and associated gene-pathway information using the MsigDB (Subramanian *et al.*, 2005). The predictive power is tested using cross-validation and an independent test set from SynLethDB (Guo *et al.*, 2015) (Supplementary Fig. S1 and Supplementary Table S1) (Step 2). To reinforce the importance of patient-specific SL interactions in making therapeutic decisions, *in-silico* validation was provided as shown in Step3. These include, (i) conditional essentiality calculated from shRNA screens using module *DiffRNAi* (visualization: *plotRNAi*), (ii) relative targetability calculated from TCGA CNA data using module *TTestMutAmp* (visualization: *plotAmplificationDiff*), (iii) drug sensitivity from cell line data using module *DrugSensitivity* (visualization: *plotSensitivitybyDrug*) and (iv) KM curve to show the effect of change in expression of SL interactor gene in patient samples carrying mutation in the primary gene which is available as *plotSurvivalCurveSL*. Detailed description of the dataset and calculation of all functions are available in Supplementary Material.

### 3 Case study

The utility of *DiscoverSL* is demonstrated with a case study on the SL interactions for the known tumor suppressor gene TP53 in Glioblastoma Multiforme (GBM). The model predicted 313 potential SL interactors for TP53 in GBM, filtered for conditional essentiality or drug sensitivity ( $P$ -value < 0.1). The predicted SL genes included previously reported SL interactors Checkpoint Kinase 1 and 2 (CHEK1/CHEK2) (Origanti *et al.*, 2013) (Supplementary Fig. S2). KM analysis of disease-free survival for CHEK1 and CHEK2 under-expression versus over-expression in the presence of TP53 mutation was shown in GBM ( $P = 0.06$  and  $P = 0.05$ ) (Supplementary Fig. S2e–f). Drug Sensitivity for targeting CHEK1/CHEK2 could not be tested in TP53 mutated cells due to unavailability of data. However, the predicted SL interactors of TP53 included cancer-related genes, targeted by drugs Ponatinib (FGFR2, FGFR3, FGFR4, FLT3, RET), Pazopanib (FGFR3, FLT1, FLT4),

Axitinib (FLT1, FLT4) and Olaparib (PARP1) that show relative sensitivity in presence of TP53 mutation in GDSC cancer cell lines (Yang *et al.*, 2013) (Supplementary Fig. S3a–d). Pathway enrichment analysis showed that the predicted SL interactors of TP53 in GBM were associated with PI3k-Akt signaling, Rap1 signaling, RAF/MAP kinase cascade and Ras signaling pathways (Supplementary Table S2). A recent publication reported that inhibition of PI3K/Akt pathway selectively radiosensitized p53 mutant GBM cell lines compared to cells with wild-type p53 (Palanichamy *et al.*, 2018). These observations show that *DiscoverSL* can be used to identify SL candidates with potential clinical relevance.

### 4 Conclusion

Investigating cancer-specific SL interactions offers immense potential for targeted drug treatment for patients based on their mutation profiles. *DiscoverSL* offers an integrative computational pipeline for prediction and *in-silico* validation of SL interactions derived from patient-specific mutations in cancer. It can be an excellent resource for discovering clinically relevant and targetable synthetic lethal interactions in cancer.

### Funding

This work was funded by the Intramural Research Program of the National Institutes of Health, National Cancer Institute.

*Conflict of Interest:* none declared.

### References

- Ashworth, A. (2008) A synthetic lethal therapeutic approach: poly(ADP) ribose polymerase inhibitors for the treatment of cancers deficient in DNA double-strand break repair. *J. Clin. Oncol.*, **26**, 3785–3790.
- Guo, J. et al. (2015) SynLethDB: synthetic lethality database toward discovery of selective and sensitive anticancer drug targets. *Nucleic Acids Res.*, **43**, gkv1108.
- Jerby-Arnon, L. et al. (2014) Predicting cancer-specific vulnerability via data-driven detection of synthetic lethality. *Cell*, **158**, 1199–1209.
- Origanti, S. et al. (2013) Synthetic lethality of Chk1 inhibition combined with p53 and/or p21 loss during a DNA damage response in normal and tumor cells. *Oncogene*, **32**, 577–588.
- Palanichamy, K. et al. (2018) Lack of Constitutively Active DNA Repair Sensitizes Glioblastomas to Akt Inhibition and Induces Synthetic Lethality with Radiation Treatment in a p53-Dependent Manner. *Mol. Cancer Ther.*, **17**, 336–346.
- Sinha, S. et al. (2017) Systematic discovery of mutation-specific synthetic lethals by mining pan-cancer human primary tumor data. *Nat. Commun.*, **8**, 15580.
- Srihari, S. et al. (2015) Inferring synthetic lethal interactions from mutual exclusivity of genetic events in cancer. *Biol. Direct.*, **10**, 57.
- Subramanian, A. et al. (2005) Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proc. Natl. Acad. Sci. USA*, **102**, 15545–15550.
- Yang, W. et al. (2013) Genomics of Drug Sensitivity in Cancer (GDSC): a resource for therapeutic biomarker discovery in cancer cells. *Nucleic Acids Res.*, **41**, D955–D961.