Moving ahead on harnessing synthetic lethality to fight cancer

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As cancer cells often harbor genomic alternations, one promising avenue to selectively and effectively target cancer is based on synthetic lethality (SL). SL occurs when the perturbation of 2 nonessential genes is lethal. Hence, targeting a gene whose SL partner(s) are inactive exclusively in the tumor is more likely to selectively kill the cancer cells without harming the normal cells. One can also aim to selectively eradicate cancer cells harboring overactive genes based on synthetic dosage lethality (SDL), a state in which a certain gene is essential as a result of the over-activity of another gene. Genome-scale SL and SDL networks can therefore greatly advance our understanding of cancerous mechanisms and susceptibilities, and provide a platform for various translational applications. Although several technologies have been developed to identify SL interactions in cancer, they currently cannot encompass the large combinatorial search space that these interactions span. Additionally, such technologies are usually implemented in vitro, and the in vivo setting is especially prohibitive.

In light of these observations we developed a data-driven approach that identifies SL and SDL interactions in cancer by analyzing large cohorts of cancer molecular profiles (Fig. 1). This approach, termed DAISY (Data-mining Synthetic lethality identification pipeline), is based on 3 fundamental properties that characterize SL pairs. If two genes, A and B, are SL, the following apply: (1) the inactivation of A and the inactivation of B are mutually exclusive; (2) inhibiting A is selectively deleterious to cancer cells with an inactive form of B; and (3) A and B are likely to have a similar function and hence their expression is overall correlated. Analogous associations characterize SDL interactions. Accordingly, given somatic copy-number alteration (SCNA), gene expression, somatic mutations, and gene essentiality data, DAISY has detected gene pairs that show these 3 associations in a highly statistically significant manner across thousands of cancer samples.

DAISY was tested and validated based on more than 7,000 gene pairs that have been previously tested for SL in cancer, and the novel SL interactions that it identified for the tumor suppressor von Hippel–Lindau (VHL) were validated. Subsequently, DAISY was applied to generate genome-scale SL and SDL networks. The integration of these networks with the genomic and transcriptomic profiles of a given cancer cell line enabled prediction of the response of this cell line to gene inhibition and drug administration (Fig. 1). Such predictions were generated for hundreds of cancer cell lines and tested based on genome-scale siRNA and pharmacological screens, obtaining a strong predictive signal. The SL-network was also examined in a clinical setting based on the assumption that co-underexpression of 2 SL-paired genes increases tumor vulnerability and results in higher survival rates. Indeed, according to the analysis of breast cancer data, the number of SL-pairs that the tumor co-underexpresses is a highly predictive marker of improved patient survival.

DAISY and the networks that it generates demonstrate the value embedded in the rapidly accumulating cancer databases. In the future, DAISY and its improved versions could be further applied to exploit such data and explore SL in cancer. In the current implementation, DAISY has been used to analyze data derived from various cancer types with the aim of identifying the core set of SL-interactions that are common across cancer types. However, DAISY can also be applied to generate cancer type-specific SL-networks. To test the predictive power of the SL-network we have previously used clinical survival data, although one can also go the other way and identify SL-interactions based on the integrative analysis of survival data along with the molecular profiles of the tumors. Such an approach, first
presented by Szczurek et al.,\textsuperscript{10} can pinpoint the strongest and most clinically relevant SL-interactions. As DAISY is based on the identification of gene inactivation, additional mechanisms of gene inactivation, such as epigenetic and post-transcriptional regulation, can be accounted for in the future. Lastly, DAISY can potentially be used to identify high-order SL-interactions involving more than 2 genes. To this end, 2 main hurdles should be overcome: (1) the combinatorial space would be challenging to explore in such cases even via computational means, and (2) multiple hypotheses correction may obstruct the detection of statistically significant interactions.

SL-based therapeutic strategies could carry unique translational benefits. As previously indicated,\textsuperscript{3} they are especially promising for the treatment of aggressive genetically unstable tumors that harbor many gene deletions and amplifications. They may enable killing of a broad array of genomically heterogeneous cells, each sensitive to the drug applied as a result of the inactivity or over-activity of a different subset of its SL- or SDL-partners, respectively. Furthermore, targeting a gene with many inactive SL- and/or overactive SDL-partners may be less prone to the emergence of drug resistance, as this would require various genomic and regulatory alterations. In line with these observations, SL-based treatment could be developed such that the resistance mechanism itself would be deleterious to cancer cells, for example by developing a drug that targets a gene whose SL-partners are inactive tumor suppressors or overactive oncogenes—in this case, cancer cells that evolve resistance to the drug may reactivate these tumor suppressors or inactivate these oncogenes, thus hindering their survival. In closing, if nothing else, one simple factor that would considerably help to realize the noteworthy translational potential of SL-based therapies was recently highlighted by Ryan et al.\textsuperscript{4} “As the number of patient and cell line samples with such data available is increasing exponentially, we can expect significant improvements in the accuracy and coverage of the predicted SL networks.”

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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