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SYSTEMS BIOLOGY

Lethal weaknesses

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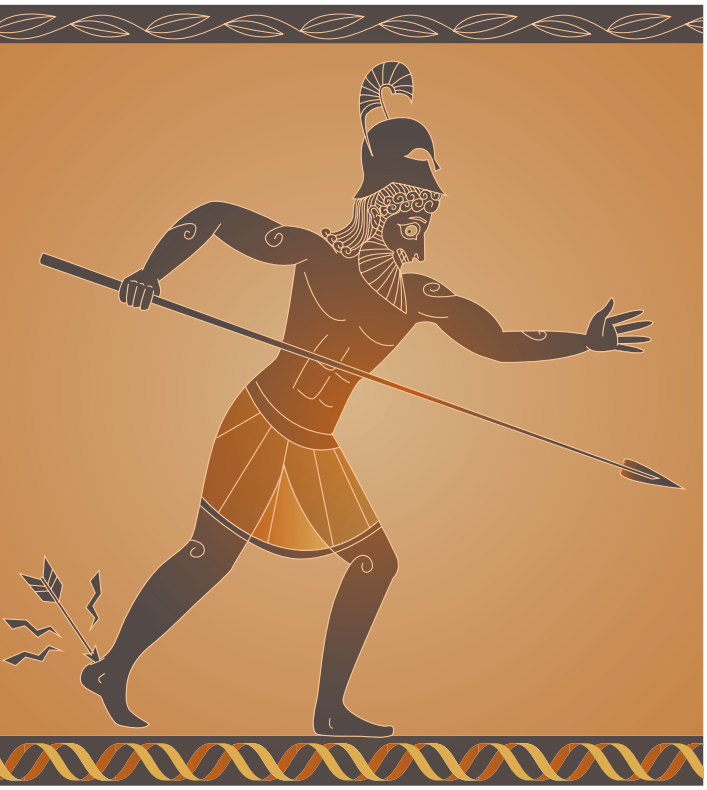

We often tend to think of metabolic changes in isolation. However, what is important in metabolomics is the flux through the reaction cycles, as the dynamics of the system show both its strengths and its weaknesses. Eytan Ruppin, Tomer Shlomi and colleagues have constructed a genomic-scale network model of cancer metabolism and have used it to identify potential synthetic lethal interactions.

The authors combined data from a recently constructed human metabolic network with cancer gene expression data from the NCI-60 cancer cell lines. They initially used 197 genes encoding metabolic enzymes that were highly expressed in 90% of the cell lines, and then used the human metabolic network data to add additional enzymes that are required to produce the reactions associated with the proteins encoded by these 197 genes. To this model of 772 reactions and 683 genes they applied flux balance analysis, a constraint-based modelling approach that assumes that a cell is under selective pressure and which searches for the reactions that produce essential biomass precursors at high rates. This enables the model to be used to assess the effect of knocking down specific genes or of applying drugs that target specific reactions.

The authors used this model to ask an important set of therapeutic questions. First, they identified 199 genes that are predicted to be growth supporting and found that 52 were likely to induce substantial cytostatic effects in cancer cells. However, 49 of the 52 genes would probably affect the proliferation of normal cells, making them similar targets to those of current cytostatic drugs. In a bid to identify cancer-specific targets, the authors used their model to hunt for synthetic lethal interactions in the cancer metabolome. To do this they simulated double-gene knockdowns in their cancer model and assigned each pair a synergy score that reflected an additional drop in proliferation below the minimum rate that is achieved with knockdown of each gene alone. They identified 342 synthetic lethal pairs, 99 of which are predicted not to have adverse effects on normal cells. Interestingly, 45% of the gene pairs had at least one gene that functions either in the pentose phosphate pathway (PPP) or in pyruvate metabolism, two pathways that are known to be perturbed in cancer.

Finally, the authors used genomic and transcriptomic data sets to identify cancers in which one of the genes in a synthetic lethal gene pair is mutated and inactive. In theory, knockdown of the remaining gene in the synthetic lethal pair should be toxic to the cancer cells alone. The authors found several examples in their data sets, including succinate dehydrogenase (SDH), the function of which is lost in paragangliomas and pheochromocytomas. The model predicts that loss of SDH is synthetic lethal with inhibition of pyruvate carboxylase and that knockdown of pyruvate carboxylase would have little effect on normal cells. Several preclinical drugs that target pyruvate carboxylase have been described and might be of use in the treatment of these cancers. Similarly, fumarate hydratase, which is mutated in leiomyomas, leiomyosarcomas and renal cell carcinoma, is predicted to be synthetic lethal with the loss of pyruvate carboxylase and nine other genes.

These findings clearly underscore the importance of assessing the dynamics of the cancer metabolome. The value of such models should increase as more tissue-specific and cancer type-specific metabolic data are produced and validated.

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ORIGINAL RESEARCH PAPER Folger, O. *et al.* Predicting selective drug targets in cancer through metabolic networks. *Mol. Sys. Biol.* **7**:501 (2011)