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GENETIC SCREEN

A network to guide precision cancer therapy

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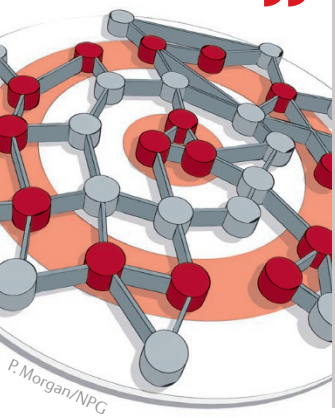

P. Morgan/NPG

A novel comprehensive map of synthetic-lethal interactions between genes that are mutated in cancer may have great clinical potential. The network resource was obtained using a cross-species approach, revealing interactions that are conserved between yeast and humans, making it potentially a useful source of targets to design new precision cancer therapies.

The ideal cancer drug will efficiently eliminate tumour cells without harming healthy cells. One emerging approach exploits the phenomenon of synthetic-lethal interactions. These genetic interactions between two mutations result in cell death only when both mutations are present, whereas the presence of either mutation alone has no effect on cell viability. If one of these mutations is found in cancer cells but not in normal cells, targeted therapy can be used to mimic the effect of the second genetic mutation, thereby selectively killing the cancer cells.

Although some synthetic-lethal combinations are well-known and even US Food and Drug Administration (FDA)-approved, there are potentially thousands of such interactions that could be clinically relevant. A team led by Trey Ideker (University of California San Diego) therefore set out to map these interactions systematically using a cross-species network mapping approach. “We first leveraged the ultra-high-throughput mapping platform of yeast, targeting the right sets of genes and conditions (that is, those that are mutated in cancer or those that are druggable),” explains Ideker, whose team screened approximately 169,000 potential interactions among orthologues of tumour suppressor genes and genes encoding druggable targets. On the basis of strong synthetic-lethal hits, the researchers then designed a parallel assay to evaluate combinations of tumour suppressor genes and drugs in HeLa cells. “The current ability to map these interactions in humans is not as high-throughput as yeast, but fast enough that we could still survey several thousands of potential interactions,” recounts Ideker.

One of the major findings relates to the degree of conservation of interactions across species. For a given interaction that was observed in the yeast network, the equivalent human interaction was only about four times as likely to occur as any randomly chosen gene mutation–drug pair. However, yeast interactions that were stable across many different conditions, and for which the gene mutation and drug target had similar functions, were much more likely to be conserved in humans (about 20-fold). “This finding should be useful in the future for predicting whether an interaction reported in basic research is likely to translate to humans and ultimately to the clinic,” concludes Ideker. In accordance, the authors were able to prioritize more than 105 human tumour suppressor gene–drug combinations for future follow-up.

This study provides a central resource that will help to functionally interpret the vast number of mutations identified in cancer genome sequencing studies. Hopefully, it will also help in identifying new therapeutic combinations of gene mutations and drugs in humans.

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