Scientists Map Changes in Genetic Networks Caused By DNA Damage

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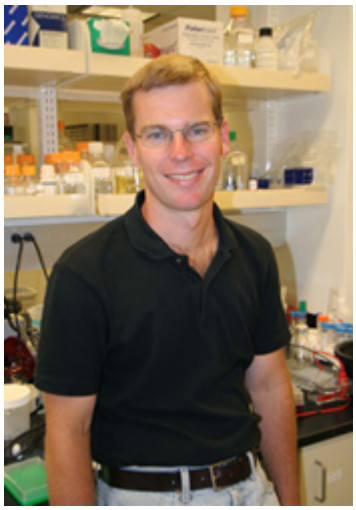
Using a new technology called "differential epistasis maps," an international team of scientists, led by researchers at the University of California, San Diego School of Medicine, has documented for the first time how a cellular genetic network completely rewires itself in response to stress by DNA-damaging agents.

The research – to be published in the December 3 issue of *Science* – is significant because it represents a major technological leap forward from simply compiling lists of genes in an organism to actually describing how these genes actively work together.



Trey Ideker, PhD

"Cell behavior is dynamic, but the genetic networks that govern these behaviors have been studied mostly only under normal, benign laboratory conditions," said Trey Ideker, PhD, professor of medicine and bioengineering, and chief of the Division of Medical Genetics in the UCSD School of Medicine. "This work is the next milestone. It shows that we can map how genetic networks in cells are reprogrammed in response to stimuli, thus revealing functional relationships that would go undetected using other approaches."

Think of it as the difference in the informational value of a photograph versus a video. In the photo, details and data are restricted to what's contained in a single, captured moment. There's no way to determine exactly what occurred before or after, or how players in the picture changed. In a video, on the other hand, whole sequences of events– dynamic processes and responses, interactions and relationships – can be chronicled, identified and studied.

"This study is the first of its kind," said co-author Nevan Krogan, an associate professor of cellular and molecular pharmacology at UC San Francisco. Ideker, who is also principal investigator of the new National Resource for Network Biology, based at UC San Diego, called it "paradigm-shifting."

Epistasis refers to the interaction of genes and how they suppress, amplify or alter each other's functions. To create a differential epistasis map, the researchers focused on 400 or so genes that govern the signaling pathways in a yeast cell. They then created 80,000 double-mutant cell lines in which each line carried mutations in a different pair of the 400 genes. When double-mutant cells grow much more slowly or quickly than expected, these mutant genes are said to interact.

To create the differential map, interactions were identified both before and after exposure to a DNA-damaging compound similar to drugs used in chemotherapy. These two networks were then subtracted, one from the other, to reveal differences. Remarkably, researchers found that most of the interactions identified with the drug were not present without it, and vice versa. In other words, the genetic network was completely reprogrammed by DNA damage.

As researchers progress in mapping these networks, their dynamic nature is both enlightening and depressing, said Ideker. Scientists had hoped cellular networks might not change greatly across different conditions or from cell to cell. That they do so suggests greater challenges and complexities ahead.

"As we look to extend this approach to mammalian systems and ultimately to human cells, new challenges will arise – the ability to selectively control the genetic makeup of cells, the redundancy in genes, transcription factors and other molecules that make more advanced systems more robust, but also more complicated to study," said David Balshaw, program officer for the National Institute of Environmental Health Sciences, which funded the study.

Ideker agreed that there is a lot more work to do. "The Human Genome Project has identified 30,000 genes and their sequence variants across different individuals. However, it leaves completely unanswered how these different genes interact to form the molecular machines that run the cell and govern its various responses. We now have the parts list, but we also need to understand the network connecting all of these parts, and how to fix it during disease."

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