Novel genetic screens provide panoramic views of cellular systems

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Despite the rise of systems biology, many geneticists continue to probe genes in isolation. They even use cutting-edge RNA interference (RNAi) technology to knock down one gene at a time. This approach often yields a narrow view of cellular systems.

Now, researchers at Harvard Medical School, the Institute for Cancer Research, and the Institut de Biologia Molecular de Barcelona have widened the lens, using RNAi to systematically knock down pairs of genes in fruit fly cells. The findings appear in the Oct. 17 issue of *Science*.

"Data from our novel double RNAi screens provide panoramic views of cellular processes," says senior author Norbert Perrimon, who is an HMS professor of genetics and an investigator with Howard Hughes Medical Institute. "By using this approach to expose interactions between genes, researchers may accelerate the pace of discovery in systems biology and advance personalized medicine."

In a typical RNAi screen, researchers begin with a library of short interfering RNAs (siRNAs) targeting specific genes. Each siRNA disrupts the gene's ability to produce a particular protein. Scientists place the siRNAs on thousands of cells, with just one gene being targeted in each well of cells. Then they watch the cells and record changes.

But this approach fails to capture some key players because many genes are redundant. Thus, cells can mask their distress when they lose a single

gene by turning to fail-safes with the same function. Perrimon's approach overcomes this obstacle.

"If you take one part out of a plane engine, it still works, but if you take out that part plus its fail-safe, then you're in trouble," explains corresponding author Chris Bakal, a postdoctoral research in the Perrimon lab.

Bakal began with a traditional RNAi screen for genes that play a role in a cell's stress response, generating a list of genes that help the cell decide whether to die, move, or take some other action in a stressful environment. But Bakal noticed that some key players—genes identified by other labs via a different method—were missing from the list.

He selected 12 of these "suspects," including a tumor-suppressor gene called PTEN, for further study. Bakal knocked down PTEN and used the resulting cells to perform another massive RNAi screen. Thus, he performed the screen in the context of a defective tumor suppressor. The stress response results were very different from the original screen. He performed similar double-knock-down screens with the 11 other suspects. In total, he tested 17,724 different combinations in the same cell type.

"A given gene behaved differently, depending on the genetic context," says Bakal. "Our approach highlights the connections between genes, telling a more complete story."

His data indicate how specific genes interact and how they influence each other. Bakal says researchers can use this approach to map cellular systems and make predictions about the behavior of particular genes, which has direct implications for personalized medicine. Clinicians must understand a patient's genetic context before making medical decisions based on his or her DNA sequence. In the future, physicians may turn to

double RNAi screen results when reading genomes.

Source: Harvard Medical School