Heal thyself: Systems biology model reveals how cells avoid becoming cancerous

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Researchers at the University of California, San Diego and three other institutions have described for the first time a web of inter-related responses that cells use to avoid becoming diseased or cancerous after being exposed to a powerful chemical mutagen. The group led by UCSD bioengineering professor Trey Ideker describe in the May 19 issue of *Science* an elaborate system of gene control that is triggered by chemical damage to DNA.

"This research sheds light on the complexity of DNA repair, and offers an example of how the cellular process stimulates other pathways," said David Schwartz, director of the National Institute of Environmental Health Sciences (NIEHS), one of the agencies which funded the study. "This new knowledge has great potential for the development of new therapeutic agents to combat a broad spectrum of diseases, including cancer, neurodegenerative diseases, and premature aging."

Researchers involved in the study agreed that their findings could eventually be used to develop drugs to boost DNA repair in response to environmental toxins and possibly treat inherited degenerative diseases such as xeroderma pigmentosum, a disease in which the body's ability to repair DNA damage caused by ultraviolet light is disabled, ataxia telangiectasia, a progressive, neurodegenerative childhood disease, Werner syndrome, a premature aging disorder, and others.

"DNA damage is a basic physiological process that is important to coping with environmental toxins and a number of congenital diseases,"

said Ideker, the senior author of the paper. "Over the past several decades, scientists have discovered many parts of the DNA-damage-repair machinery, but what has been missing until now is a 'systems biology' approach that explains how all the parts function together to enable a cell to repair its DNA while under routine assault."

UCSD post-doctoral fellow Christopher T. Workman, Ph.D. candidate Craig Mak, and technicians Scott McCuine and Maya Agarwal analyzed the effect of exposure of yeast cells to MMS (methyl-methanesulfonate), a chemical known to cause DNA damage in a manner similar to that of certain mutagens in tobacco smoke. The alkylation injury caused by MMS results in small kinks in the otherwise smoothly curving double helix of DNA. Cells rapidly identify the damage, stop dividing, excise the damaged DNA, and use several alternate methods to substitute a clean copy of genetic material.

"It's almost as if cells have something akin to a computer program that becomes activated by DNA damage, and that program enables the cells to respond very quickly," said Mak. "And this program is easily recognizable as operating in everything from yeasts to humans and mice to fruit flies."

Researchers have previously identified hundreds of genes involved in repairing MMS damage. However, they have been mystified by another group of genes whose expression is sharply affected by DNA damage, but which appear to play no role in repairing the damage itself.

Ideker's team uncovered a tangled network of interactions of 30 transcription factors with more than 5,000 yeast genes. A transcription factor is a protein that, either alone or in combination with other transcription factors, binds to one or more genes to affect the expression of that gene or genes. The discovery by Ideker's group of a huge network of transcription factor-gene interactions was made possible by new

biotechnology tools that provide comprehensive analysis of cells, like a passerby suddenly being able to monitor all the telephone calls made within a city.

The team discovered that part of the interaction network was involved, as expected, in repairing damaged DNA. However, they were surprised to find that a much larger part of the network is involved in modulating the expression of genes not directly related to DNA repair, such as genes involved in cell growth and division, protein degradation, responses to stress, and other metabolic functions. Ideker and others have theorized that when a cell's DNA is damaged, the cell may be programmed to also stop dividing and perform a variety of housekeeping chores while it repairs its DNA. If true, the model may demystify the long-standing question of why DNA damage influences the expression of hundreds of genes not involved in the actual repair process.

"What we quickly realized is that we had uncovered not just a model of DNA repair, but a blueprint of how the initial event of DNA damage is transmitted by these transcription factors to repair processes and all the other important functions of the cell," said Ideker. "With this model now in hand, we'd like to take a much closer look at the cell's response to environmental toxins. We'd like to understand what goes wrong in certain congenital diseases involving DNA repair, and we'd also like to understand how the model plays a role in various cancers."

Source: University of California - San Diego

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