Team decodes evolution of skin and ovarian cancer cells

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A team of researchers led by scientists at the University of California, San Francisco has developed a way to uncover the evolution of human cancer cells, determining the order in which mutations emerge in them as they wend their way from a normal, healthy state into invasive, malignant masses.

The work may give doctors a new way to design diagnostics for detecting the signs of early cancers, when they are generally more treatable than in their later stages.

This approach relies on teasing apart the DNA of cancer cells, and it is something like genetic archeology. Just as archeologists sometimes date objects found at an excavation site by the age of the objects found around them, the new technique allows scientists to dig into the DNA of cancer cells and determine which genetic mutations came first by looking at surrounding genetic material.

Using the new technique, the researchers were able to identify not just the mutations that differentiate two types of human cancer from normal cells, but the actual order in which some of the most key mutations occurred.

"You can tell which mutations come really early and which come late," said UCSF dermatologist Raymond Cho, MD, PhD.

Cho and his UCSF colleagues developed the technique in collaboration

with researchers led by Paul Spellman and Joe Gray at Oregon Health & Science University, Elizabeth Purdom at the University of California, Berkeley and scientists at Samsung Advanced Institute of Technology. The work appears this week in the journal *Cancer Discovery*.

Mutations Lead to Cancer

Cancer is a profoundly heterogeneous disease, making it more like thousands of diseases than just one. Different types of cancer differ in terms of the organs they affect, how they behave in the body, how they respond to treatment and even how they look under the microscope. And most fundamentally, they differ genetically.

Cancer emerges because of mutations in the DNA of cells. Any number of things can cause these mutations – for instance, family genetics, infections, toxins, radioactivity, sunlight or some combination of each. Over time these mutations shut down some genes, crank up the production of others and lead in the end to the cell's proliferation, growth, spread and all the other ominous hallmarks of cancer.

Interested in finding which mutations come first, Cho and his colleagues developed a way of teasing them apart by virtue of the fact that long pieces of DNA in cancers often abnormally double in number. The technique relies on determining the sequence of the cancer [DNA](#) to see which mutations are also doubled, indicting they occurred before the duplication.

They worked with a type of skin cancer known as cutaneous squamous cell carcinoma, which has among the highest numbers of mutations of any cancer, and also with a common type of ovarian cancer. By examining the accumulation of copies of TP53, a gene known to be involved with these forms of cancer, they found that complex changes in TP53 occurred earlier in most cases, rather than later, as had been

previously believed.

The results are significant, said Cho, because the ability to identify the actual sequence of mutations will help scientists determine which [mutations](#) lead to precancerous lesions and which produce invasive carcinomas.

More information: The article, "Temporal Dissection of Tumorigenesis in Primary cancers" is authored by Steffen Durinck, Christine Ho, Nicholas J. Wang, Wilson Liao, Lakshmi R. Jakkula, Eric A. Collisson, Jennifer Pons, Sai-Wing Chan, Ernest T. Lam, Catherine Chu, Kyunghee Park, Sung-woo Hong, Joe S. Hur, Nam Huh, Isaac M. Neuhaus, Siegrid S. Yu, Roy C. Grekin, Theodora M. Mauro, James E. Cleaver, Pui-Yan Kwok, Philip E. LeBoit, Gad Getz, Kristian Cibulskis, Jon C. Aster, Haiyan Huang, Elizabeth Purdom, Jian Li, Lars Bolund, Sarah T. Arron, Joe W. Gray, Paul T. Spellman, and Raymond J. Cho. It appears in the July 2011 issue of the journal *Cancer Discovery*. See: dx.doi.org/10.1158/2159-8290.CD-11-0028

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