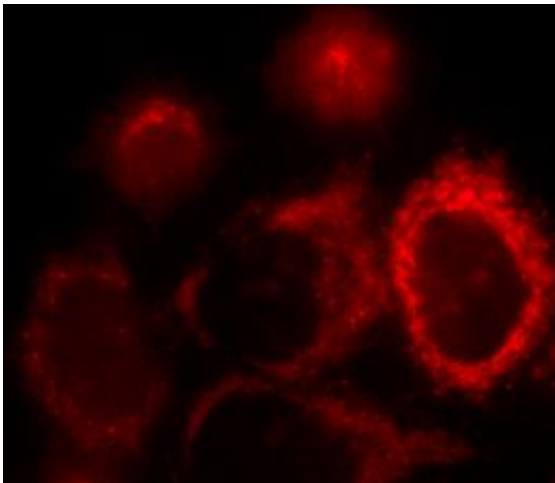


## For cancer cells, genetics alone is poor indicator for drug response (w/Video)

April 12 2009, by David Cameron

---



These six cancer cells are genetically identical. The two cells on the left and the one at the top have slightly different levels of a particular protein - the product of pure chance. After administration of a new cancer drug, the cell on top and the two on the left begin to die, as you can see in the enlarged image.

In certain respects, cells are less like machines and more like people. True, they have lots of components, but they also have lots of personality. For example, when specific groups of people are studied in aggregate (conservatives, liberals, atheists, evangelicals), they appear to be fairly uniform and predictable. But when looked at one person at a time, individuals often break the preconceptions.

Same with cells.

Researchers tend to identify characteristics of particular cells by looking at millions at a time. As a result, they'll find that, say, "group A" responds very well to a particular [cancer treatment](#), whereas "group B" does not. They will then often compare group A to group B to find out why.

But often ignored is that not every cell in either group behaves in ways that the aggregate indicates. In a group of cells shown to be vulnerable to a particular cancer treatment, perhaps 10 percent resist it while 90 percent succumb. While researchers have offered various explanations for this, few have studied it.

Now a group of scientists in the lab of Harvard Medical School Professor of Systems Biology Peter Sorger have studied such "outlier" cells in the context of a new and highly touted cancer drug. They have found that vastly disparate reactions occur within genetically homogeneous cell groups. These discrepancies result from protein levels that vary from cell to cell, even among cells that are identical [genetic](#) twins. What's more, these protein levels and their subsequent traits can be passed down to daughter cells—a heritability that has nothing to do with genetics.

"Genetics are permanently heritable, while these protein levels are temporarily heritable," says Sorger. "But this temporary [inheritance](#) can make all the difference in the world when it comes to the effectiveness of certain medications."

These findings are published April 12 online in *Nature*.

In order to investigate this disparate behavior among cells, graduate student Sabrina Spencer and postdoctoral researcher Suzanne Gaudet, both in Sorger's lab, looked at a molecule called TRAIL, a protein that causes cells to, literally, commit suicide—a process scientists call

apoptosis. While TRAIL is a natural cell product, drug makers have been investigating ways to harness its power so that it can directly target cancer cells.

While TRAIL continues to be a promising drug candidate, its success rate isn't 100 percent, and the researchers wanted to figure out why.

The researchers took both cancerous and non-cancerous cells and exposed them to varying doses of TRAIL. Although these cell lines were known to be vulnerable to the molecule, a fraction always managed to survive.

The researchers noticed that when this outlier group was isolated and once again exposed to TRAIL, the cells and their immediate progeny continued to remain highly resistant for a short time. An immediate explanation might be that this group had developed some sort of genetic defense. However, when this new "resistant" group was given several days to reproduce, the pattern soon reset to the original: 90 percent died, ten percent survived.

"We knew that there were clearly factors at work here that were not genetic," says Spencer. "Genetic resistance would remain uniform in subsequent generations. But the factors at work here were clearly more dynamic."

Using a variety of imaging techniques, the researchers soon discovered that even though these cells were genetically identical —the same cell in the same tissue doing the same thing, the actual numbers of proteins in each cell varied. Specifically, proteins involved in the cell-suicide mechanism triggered by TRAIL were affected. These protein levels altered the dynamics of the entire mechanism, sometimes making cells, for all intents and purposes, immune to TRAIL. While these protein levels were initially passed on to progeny, the heritability was transient.

The scientists describe it as an extra layer of inheritance, one that is superimposed onto genetic inheritance.

As for what actually causes these protein levels to vary between identical cells, the researchers cited a simple explanation: It's completely random.

"For decades biologists have had this notion that cells produce proteins in orderly, uniform ways, like an assembly line, but they don't," says Sorger. "Rather, cells produce proteins in fits and starts, and the timing and degree varies from one cell to the next—even cells that are identical in every way. This randomness is something that we're just beginning to appreciate."

These findings also offer an alternative to the cancer stem-cell hypothesis. For that, scientists have posited that certain cancers survive standard treatments because a population of tumor-specific stem cells evades chemotherapy or radiation. This paper, however, offers an alternative explanation, namely, that purely through chance, certain [cells](#) produce quantities of proteins that fundamentally alter the cell's response to treatment.

Ultimately, Sorger and his group think that this new insight will make it possible to design anti-cancer treatments that are more effective than those available today.

More information: *Nature*, early online publication, April 12, 2009, "Non-genetic origins of cell-to-cell variability in TRAIL-induced apoptosis," Sabrina L. Spencer, Suzanne Gaudet, John G. Albeck, John M. Burke & Peter K. Sorger

Source: Harvard Medical School

Citation: For cancer cells, genetics alone is poor indicator for drug response (w/Video) (2009, April 12) retrieved 2 May 2024 from <https://medicalxpress.com/news/2009-04-cancer-cells-genetics-poor-indicator.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.