Team uses evolutionary principles to model cancer mutations

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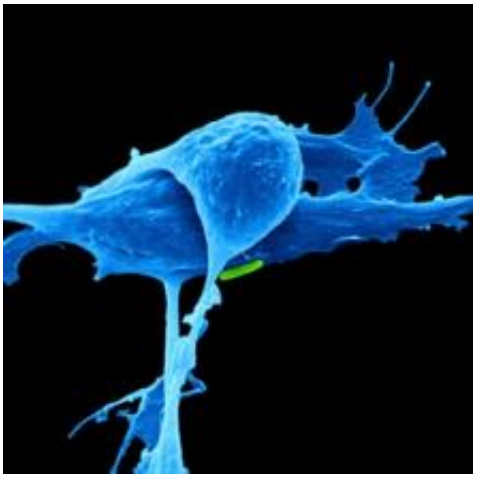

Moffitt Cancer Center researchers are taking a unique approach to understanding and investigating cancer by utilizing evolutionary principles and computational modeling to examine the role of specific genetic mutations in the Darwinian struggle among tumor and normal cells during cancer growth.

Cells become malignant by acquiring genetic mutations that lead to increased survival and reproduction. Many researchers in the past have viewed cancer progression as the result of unlimited accumulation of these genetic mutations. However, Moffitt researchers model cancer progression on the premise that cancer cells live in an environment that

has limited resources, such as space and nutrients and, like all living organisms, must obey the laws of evolution. These laws include trade-offs between proliferation and survival.

For example, elephants use their available resources primarily to maximize survival so that they have relatively long lives and few offspring. Rabbits, on the other hand, produce many offspring but survive in the wild for less than two years. Similarly, cells that evolve to form cancers can do so by either increasing longevity or increasing the number of offspring. But like elephants and rabbits, they can only move down one evolutionary path at a time, so the mutations observed in cancer cells are limited to this evolutionary trade-off. With this in mind, cancer cells can invest available resources in maximizing their defenses against attacks by the normal tissue or accept a high rate of mortality and overcome it through very rapid proliferation. The cells cannot do both.

Moffitt researchers performed computer simulations based on these concepts. They found that the frequency with which any genetic mutation is observed depends on its ability to increase the cell's fitness, its ability to survive and reproduce. The researched called this process "evolutionary triage."

"Genes that increase fitness are observed more frequently than those that do not," explained Robert A. Gatenby, M.D., chair of the Department of Diagnostic Imaging and co-director of the Cancer Biology and Evolution Program at Moffitt. "However, the effect of any mutation on cell fitness can change drastically depending on environmental factors such as blood flow, past genetic mutations, and the properties of competing cells. Currently, cancer biologists divide mutations into 'drivers,' which promote tumor growth and 'passengers,' which have no effect on growth. In the computer simulations, it was clear that many mutations could be drivers in one environment, but passengers in another."

Since driver mutations are common targets for cancer therapy, the scientists also simulated therapies that seek to disable driver genes. Similar to what is found in clinical settings, they observed that targeted therapies can kill the mutated cells and decrease the tumor size. However, the diversity of tumor environments produces many mutational pathways to formation of a malignant cell. As result, cancer cells that lack the driver mutation and are resistant to therapy were almost invariably present and caused the tumor to recur.

The investigators were startled to find that some genes were actually never observed to be mutated in cancers. It turned out that mutations in these genes always reduced the tumor cell's ability to survive or reproduce. As a result, even when they occurred, evolutionary triage eliminated them because they were less fit than their competitors. According to Gatenby, "our computer simulations demonstrate an unexpected result - genes that are never observed to be mutated might actually be the best targets for therapy. This is because up or down regulation of these genes unconditionally reduces cell fitness."

The researchers showed that targeting genes that are never mutated, particularly when followed by treatment that targeted cancer driver mutations, was a highly effective treatment strategy. The final question was: "Do 'never mutations' exist in human cancer?" Fortunately, large databases that list all of the mutations in clinical cancers have been developed by the National Cancer Institute. With the help of Mohammad Fallahi-Sichani, Ph.D., a bioinformatics expert from the Scripps Research Institute, 1,100 genes that are never mutated in human cancers were identified. The research group, which included Moffitt Physicist Jessica Cunningham and Joel S. Brown, an evolutionary biologist at University of Illinois, is now working with John Cleveland, Ph.D., associate center director of Basic Science at Moffitt, to investigate the possibility of targeting "never" genes for therapy.

More information: This study was published in the Nov. 19 issue of *Nature Communications*. www.nature.com/ncomms/2014/141 … full/ncomms6499.html

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