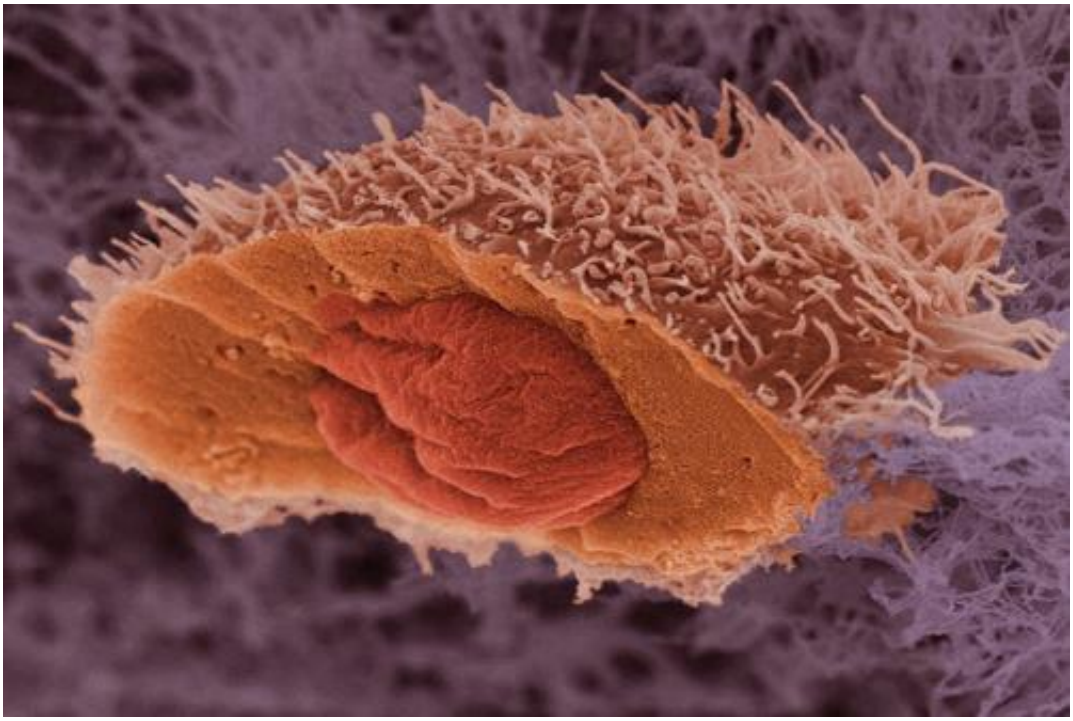
MedicalXpress

Some cancer mutations slow tumor growth

February 4 2013, by Anne Trafton



A scanning electron micrograph of a squamous cell carcinoma, a type of skin cancer. The cell has been frozen and split open to reveal its nucleus. IMAGE: ANNE WESTON, LRI, CRUK. WELLCOME IMAGES

A typical cancer cell has thousands of mutations scattered throughout its genome and hundreds of mutated genes. However, only a handful of those genes, known as drivers, are responsible for cancerous traits such as uncontrolled growth. Cancer biologists have largely ignored the other mutations, believing they had little or no impact on cancer progression.

But a new study from MIT, Harvard University, the Broad Institute and Brigham and Women's Hospital reveals, for the first time, that these so-called passenger mutations are not just along for the ride. When enough of them accumulate, they can slow or even halt tumor growth.

The findings, reported in this week's Proceedings of the National Academy of Sciences, suggest that cancer should be viewed as an evolutionary process whose course is determined by a delicate balance between driver-propelled growth and the gradual buildup of passenger mutations that are damaging to cancer, says Leonid Mirny, an associate professor of physics and health sciences and technology at MIT and senior author of the paper.

Furthermore, drugs that tip the balance in favor of the passenger mutations could offer a new way to treat cancer, the researchers say, beating it with its own weapon—mutations. Although the influence of a single passenger mutation is minuscule, "collectively they can have a profound effect," Mirny says. "If a drug can make them a little bit more deleterious, it's still a tiny effect for each passenger, but collectively this can build up."

Lead author of the paper is Christopher McFarland, a graduate student at Harvard. Other authors are Kirill Korolev, a Pappalardo postdoctoral fellow at MIT, Gregory Kryukov, a senior computational biologist at the Broad Institute, and Shamil Sunyaev, an associate professor at Brigham and Women's.

Power struggle

Cancer can take years or even decades to develop, as cells gradually accumulate the necessary driver mutations. Those mutations usually stimulate oncogenes such as Ras, which promotes cell growth, or turn off tumor-suppressing genes such as p53, which normally restrains growth.

Passenger mutations that arise randomly alongside drivers were believed to be fairly benign: In natural populations, selection weeds out deleterious mutations. However, Mirny and his colleagues suspected that the evolutionary process in cancer can proceed differently, allowing mutations with only a slightly harmful effect to accumulate.

To test this theory, the researchers created a computer model that simulates cancer growth as an evolutionary process during which a cell acquires random mutations. These simulations followed millions of cells: every cell division, mutation and cell death.

They found that during the long periods between acquisition of driver mutations, many passenger mutations arose. When one of the cancerous cells gains a new driver mutation, that cell and its progeny take over the entire population, bringing along all of the original cell's baggage of passenger mutations. "Those mutations otherwise would never spread in the population," Mirny says. "They essentially hitchhike on the driver."

This process repeats five to 10 times during cancer development; each time, a new wave of damaging passengers is accumulated. If enough deleterious passengers are present, their cumulative effects can slow tumor growth, the simulations found. Tumors may become dormant, or even regress, but growth can start up again if new driver mutations are acquired. This matches the cancer growth patterns often seen in human patients.

"Cancer may not be a sequence of inevitable accumulation of driver events, but may be actually a delicate balance between drivers and passengers," Mirny says. "Spontaneous remissions or remissions triggered by drugs may actually be mediated by the load of deleterious passenger mutations."

When they analyzed passenger mutations found in genomic data taken

from cancer patients, the researchers found the same pattern predicted by their model—accumulation of large quantities of slightly deleterious mutations.

Tipping the balance

In computer simulations, the researchers tested the possibility of treating tumors by boosting the impact of deleterious mutations. In their original simulation, each deleterious passenger mutation reduced the cell's fitness by about 0.1 percent. When that was increased to 0.3 percent, tumors shrank under the load of their own mutations.

The same effect could be achieved in real tumors with drugs that interfere with proteins known as chaperones, Mirny suggests. After proteins are synthesized, they need to be folded into the correct shape, and chaperones help with that process. In cancerous cells, chaperones help proteins fold into the correct shape even when they are mutated, helping to suppress the effects of deleterious mutations.

Several potential drugs that inhibit chaperone proteins are now in clinical trials to treat cancer, although researchers had believed that they acted by suppressing the effects of driver mutations, not by enhancing the effects of passengers.

In current studies, the researchers are comparing cancer cell lines that have identical driver mutations but a different load of passenger mutations, to see which grow faster. They are also injecting the cancer cell lines into mice to see which are likeliest to metastasize.

Provided by Massachusetts Institute of Technology