NEWS

Rewriting the Mathematics of Tumor Growth

By Mike Martin

A new theory about tumor growth makes oncology look a little like cosmology. Just as the universe accelerates as it expands, tumors become malignant at an accelerating speed, according to a team of scientists who have been probing the mathematics of tumor growth.

Specifically, the researchers have discovered that tumor-driving mutations characteristic of nearly all cancer cells have a surprisingly small selective growth advantage of 0.4%. That advantage isn't large enough to sustain tumor growth, which calls into question the long-held belief that tumors result from one or two mutations.

"The most important take-away message from this research is that relying on genome studies to identify one wrong component is not the right approach," said surgical oncologist Steven Libutti, M.D., director of the Montefiore–Einstein Center for Cancer Care at the Albert Einstein College of Medicine in New York. "Any individual mutation makes only a small contribution to the overall appearance of a cancer, and early mutations alone are probably not the only story."

Bert Vogelstein, M.D., a Howard Hughes Medical Institute investigator, led the team of researchers from six institutions around the world who mapped tumor growth rates. In a model best described as a sequential driver mutation theory, they suggest mutations that drive tumor growth—called driver mutations—multiply sequentially over time, each one slightly increasing the tumor growth rate through a process that depends on the average of three factors: driver mutation rate, the 0.4% average selective growth advantage, and cell division time. Other models describe tumor dynamics as an exponential

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function or according to a Gompertz curve that shows how tumor growth gradually rises and levels off over time.

But this theory "is unique because it shows, for the first time, that a cancer cell with only one driver mutation will grow to only a certain size and then stop until another mutation happens," said Iuliana Shapira, M.D., director of the cancer genetics department at North Shore University Hospital in Manhasset, N.Y., and was not part of the research team.

With a combination of experimental data and computer simulations, the group applied their theory to hypothetical patients with glioblastoma multiforme, pancreatic adenocarcinoma, and familial adenomatous polyposis (FAP), which can become malignant. In computational tests of both the brain and pancreatic cancers, a second driver mutation appeared 8.3 years after the first. But the mutation rate accelerated, with only 4.5 more years passing until the third driver mutation emerged. Malignant progression in FAP follows a similar scenario.

"For years, a benign tumor may grow slowly," said team member Tibor Antal, Ph.D., a lecturer at Scotland's University of Edinburgh School of Mathematics. "But when it starts gathering new mutations, the growth process speeds up and leads to a malignant cancer fast."

The idea that cancerous mutations progress with the disease, thereby creating cumulative damage—rather than simply being a one-time force that pushes a boulder down a hill—makes sense to Libutti, who was not a member of the research team. "Their research agrees with data showing that cancer is a long, complicated problem that can change with time and conditions," Libutti explained.

The sequential driver mutation theory may also help efforts to "personalize" cancer genomics, Shapira explained. "One could foresee the capability to estimate how many driver mutations fuel specific types of cancer, and how long a specific type of cancer was present in someone."

Behind the Numbers

The researchers first demonstrated their ideas in six hypothetical patients with either glioma or pancreatic adenocarcinoma, finding "enormous variation in the times required for disease progression," explained research team member Kenneth Kinzler, Ph.D., an oncological geneticist at Johns Hopkins Kimmel Cancer Center.

Steven Libutti, M.D.

They used data from the *Catalog of Somatic Mutations in Cancer* (COSMIC) and a software program called CHASM, short for "Cancer-specific High-throughput Annotation of Somatic Mutations," that sorts and highlights DNA changes most likely to promote cancer.

"A goal of CHASM is to provide cancer researchers important mutations for functional testing from thousands of candidates," explained the program's co-inventor Rachel Karchin, Ph.D., a research team member and biomedical engineering professor at the Johns Hopkins University Institute for Computational Medicine.

CHASM examined 713 mutations sequenced from 14 glioma patients and 562 mutations in nine pancreatic adenocarcinoma patients. Using this information, the researchers estimated that roughly 100 tumor suppressor genes, 100 oncogenes, and 21,000 positions on the human genome can become driver mutations. Experimental evidence added the last variable: cell division time. For a report published in the March 2008 *Proceedings of the National Academy of*

Sciences, Vogelstein and colleagues showed that tumor cells in glioma divide about once every 3 days. Selected driver mutations, tumor growth rates, and the estimated 0.4% selective growth advantage were plugged into the computer simulation model, a statistically driven mathematical program called the Galton–Watson process that described cancer growth in the hypothetical patients.

"In this process, cells divide or die with a probability that depends on the number of driver mutations they have," said Ivana Bozic, a graduate student in the department of mathematics and the Program for Evolutionary Dynamics at Harvard University. "The result is a branching that shows how cancers can develop for decades."

The simulated decades of branching mutations returned the frustratingly heterogeneous scenarios oncologists observe in the clinic. In glioblastoma patient 1, a second driver mutation had not occurred within 20 years after tumor initiation, and the tumor remained microgram size. In glioblastoma patient 6, a second driver mutation occurred after only 2 years. At 20 years, the tumor would weigh in the kilograms. Patients 2–5 had progression rates between these two extremes. The team found similar results for the six pancreatic adenocarcinoma patients, confirming that "the model helps provide an understanding of the heterogeneity in tumor sizes and development times observed by epidemiologists and clinicians," explained team member Martin Nowak, Ph.D., a Harvard University biology and mathematics professor and director of the school's Program for Evolutionary Dynamics.

Metastases, too, find some explanation in the model, Libutti explained. "Many cancer patients live for 10–15 years without developing metastatic disease," he said. "Other patients live only months. Reducing such vastly different outcomes to mathematics is an important tool."

Homing in on FAP

The team applied its model to clinical studies on FAP published in the *New England Journal of Medicine* in 1993 and 2002 by Johns Hopkins University gastroenterologist Francis Giardiello, M.D. FAP patients can develop three types of tumors: benign polyps, adenomas, and malignant colon carcinoma. A mutation in one copy of the adenomatous polyposis coli (APC) gene causes FAP. Inactivation of the second copy of the APC gene initiates formation of a benign colonic adenoma. Carcinoma formation is a longer-term process involving many more mutations. With Giardiello's data, the sequential driver mutation model predicted the age distribution of FAP patients, number and size of visible polyps, and polyp growth rate better than existing models. It predicted that 43% of FAP patients who had not yet developed polyps would develop at least one polyp with an average diameter of 0.8 mm within 4 years. Giardiello's actual results were 49% of patients and a 0.9-mm average polyp size.

The team also discovered that the number of polyps in patients influences the probability that they will develop a tumor. More polyps can mean more driver mutations, and according to the team's theory, more driver mutations means higher probability of tumor growth. Specifically, that probability increases from 0.001 with only one polyp to 0.63, or 63%, with 1,000 polyps. This number takes time to develop and helps explain why FAP patients usually do not become colon cancer patients until their forties or fifties, even with their extreme genetic predispositions toward polyposis.

The findings are in line with colorectal cancer research published in a July 2011 *Cancer Research* article by a University of Texas Southwestern Medical Center group led by cell biology professor Jerry Shay, Ph.D. Just 18 months ago, Shay said he was convinced that only a few driver mutations would be enough to cause malignancy. "Then we decided to test all 151 colorectal cancer candidate genes," Shay explained. To his team's surprise, nearly 45%, or 65 mutations, drove malignant proliferation. What's more, some 700 mutations previously thought to be of the passenger variety—with no direct influence on tumor formation—contribute as well.

"The question is, how do all these mutated genes work together in a coordinated set?" said Shay. "Carcinogenesis may indeed require a continuum of steps, which would help explain why malignancies like colon cancer take so long to evolve."

Too Simple To Be True?

A study of cancer's most complex progression mechanisms with acronyms that spell COSMIC and CHASM may not sound simple. But according to Antal, "The main virtue of the model is its simplicity. It describes the onset of subsequent driver mutations in the simplest possible way."

However, other experts say the model's simplicity may also be its main limitation. Many assumptions designed to simplify the model still need experimental confirmation, explained Marc Chamberlain, M.D., chief of neuro-oncology at the University of Washington, who was not involved in the research. Although the team's findings "probably will stimulate laboratory interest in confirming their model, I do not believe it will change clinical management," he said.

The study is also narrowly focused on mutations, explained Libutti. "It does not take into consideration host and tissue context, and epigenetic factors that also turn on oncogenes or shut off tumor suppressors, such as methylation and acetylation."

Host and tissue context appear important, for instance, in multiple endocrine neoplasia type 1 (MEN-1) tumors, Libutti added. Although MEN-1 patients are born with one mutated copy of the MEN-1 gene in each cell, "the tumors develop only in certain organs like the pancreas and certain tissues in the endocrine system. The tumors are specific, but their mutations are general, which points to other factors at work."

Despite these considerations, the study, its guiding theory, and findings "are telling us that we may be better off developing genetic algorithms that explain cancer as a long-term, incremental process," said Shay. Sixty-nine percent of cancers appear in people older than 65 years, he added, a statistic that supports the idea that cancers gestate and evolve for years.

"Focusing on long-term progression," Shay explained, "should give us more pathways we can go after that are potentially druggable and, therefore, potentially treatable."