Analyzing how cancer mutations interact may improve targeted therapies

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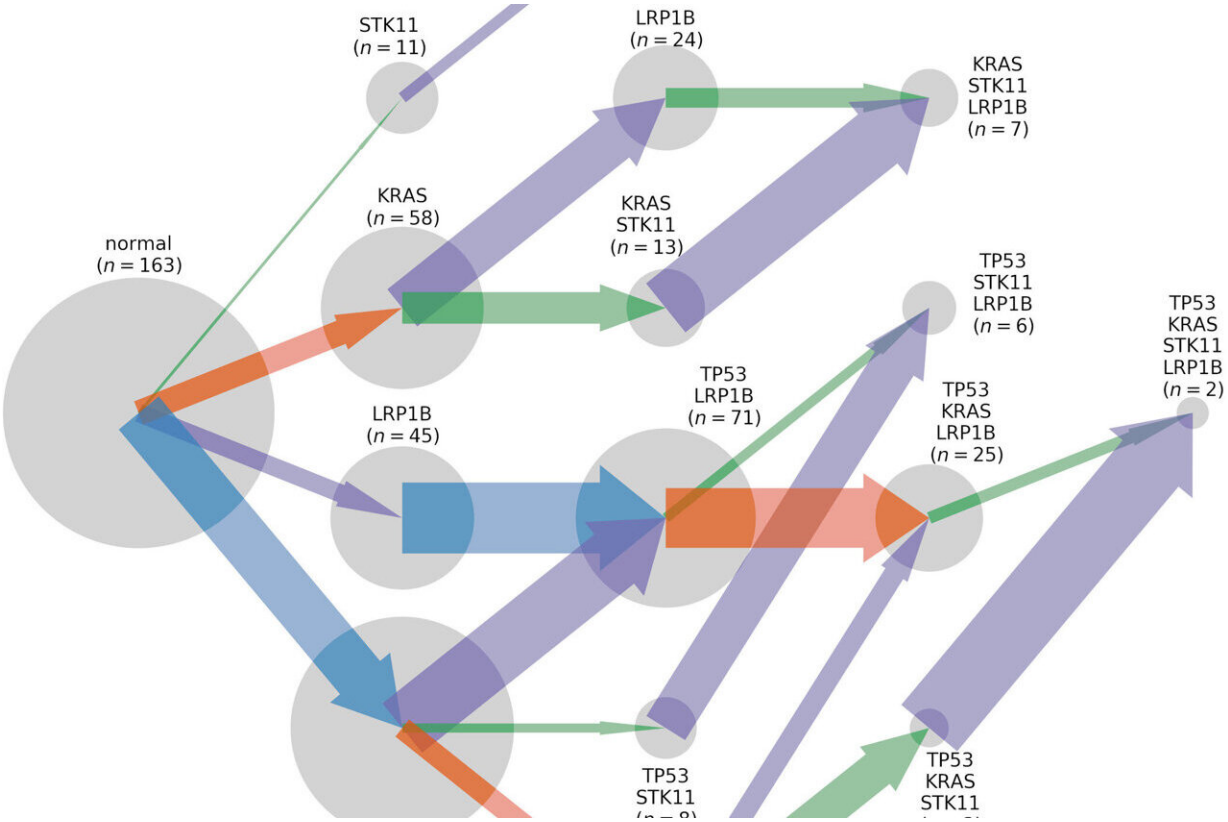

Trajectories of the somatic evolution by mutation of TP53, KRAS, LRP1B, and STK11, inferred from a total of 565 whole-exome sequenced lung adenocarcinoma tumors. Somatic genotypes (gray circles; areas are proportional to observed n for the somatic genotype) evolve at (A) fluxes, (B) mutation rates, and (C) scaled selection coefficients that are proportional to the width of arrows pointing from one somatic genotype to another, colored by the gene in which the mutation occurs (TP53, blue; KRAS, orange; STK11, green; LRP1B: purple). Credit: *Mathematical Biosciences* (2023). DOI: 10.1016/j.mbs.2023.109091

Cancer arises when multiple mutations result in relentless, inappropriate cell growth. But these mutations don't act in isolation. Instead, mutations can influence each other in ways that affect cancer evolution. Researchers have long struggled to get a handle on these interactions, often by making assumptions that oversimplify the complex reality.

A new method from the Yale School of Public Health (YSPH) offers a way to analyze how mutations interact with each other to alter tumor development. The innovation should make it easier to develop targeted therapies that anticipate the evolutionary path of a cancer, then corner and eradicate it.

"We can now characterize where, on its genetic trajectory in a given patient, cancer is," said lead author Jeffrey P. Townsend, the Elihu Professor of Biostatistics at the Yale School of Public Health and professor of ecology and evolutionary biology at Yale. "That information can be very helpful for determining appropriate treatments, especially as we obtain more and more options for precision treatment of tumors."

The results are published in Mathematical Biosciences.

How much blame to assign each mutation

To become cancerous, cells mutate and evolve traits called hallmarks of cancer. These hallmarks include abilities to generate growth signals or ignore signals to stop growing, to metastasize, to generate new blood vessels to serve the tumor(s), to dodge immune cells that can spot and kill an aberrant cell, and so on. Cancer cells can mutate in a variety of ways to acquire these hallmarks. Once a cancer cell, they keep evolving.

This continual adaptation to their environment makes cancer hard to

treat in a targeted way. A targeted drug creates evolutionary pressure—cells that survive it quickly come to predominate in the tumor, eventually rendering that drug ineffective. A way to predict what mutations are likely to happen next could help clinicians work out ways to forestall resistance.

Some years ago, Townsend and his colleagues devised a way to estimate how important each mutation is to a cancer by looking at the frequency of each individual mutation in a large number of tumors as well as the underlying rate at which that mutation appears.

"It was a breakthrough, because before that everyone was just calling mutations 'cancer-causing' or not, but not quantifying how much each mutation contributed," said Townsend, who is also affiliated with the Program in Computational Biology and Bioinformatics at Yale.

Cancers exhibit multiple mutations. The next step was to characterize not just each mutation's average effect, but how each one interacts with the next one that occurs.

The term for these interactions is epistasis: that is, how one mutation affects the degree to which another mutation allows a cancer to grow and survive. Untangling epistasis is complex, especially when considering the relationships between three or more mutations.

For the current project, Townsend began by deriving a mathematical approach to estimate epistasis for pairs of point mutations. Then he teamed up with Jorge Alfaro-Murillo, an associate research scientist in biostatistics at YSPH, who is the study's first author.

Alfaro-Murillo derived a mathematical approach that, with enough data, will provide estimates of epistatic interactions among three, four, or even more mutations.

Mutation order matters

Researchers have long noticed that some mutations always seem to co-occur in a given cancer, while others appear mutually exclusive. Because of this, many previous studies have assumed that certain mutations either work together or antagonize each other.

But that isn't necessarily the case, because not all co-occurrences are actual biological interactions. For example, some could occur because a certain exposure, such as tobacco smoke, tends to result in characteristic mutations, each one arising independently due to the smoke itself.

"There are tons of approaches out there for looking at mutual exclusivity and co-occurrence and trying to figure out how often they're occurring in sets of tumors. But mutual exclusivity and co-occurrence are simply not the best way of figuring out the answer," Townsend said. "Our method gives a better answer to the question of which genes are interacting."

In addition to accounting for underlying mutation rates, "it does so in part by taking into account the order in which mutations occur," Alfaro-Murillo explained.

For example, say gene A's job is to cause a dangerously mutated cell to self-destruct, while gene B's job is to cause a cell to multiply.

If a cell develops a mutation in gene B first, then a normal gene A will ensure the cell dies before it divides uncontrollably. But if gene A mutates first, followed by gene B, the cell can survive and start multiplying. Order matters.

"If first mutation A occurs, then mutation B, that might be more important than B occurring before A," Alfaro-Murillo said. "That's a major difference from just examining mutual exclusivity."

Translating the results to cancer care

In an important limitation, the authors considered only tumors that had not been exposed to treatments. They plan next to examine tumors responding to treatment, and also to look past point mutations and consider those mutations that result in larger changes, such as copy number changes in the genome or chromosomal alterations. Copy number alterations, also known as CNAs, are somatic changes to chromosome structure that result in a gain or loss in copies of sections of DNA and are prevalent in many types of cancer.

These analytical methods should help make cancer trials, and ultimately treatments involving multiple cancer drugs, more efficient.

"If your tumor has a certain composition of mutations, and if you know a therapy makes it more likely that you will get certain mutations, then if there are drugs targeted for those mutations, you could perhaps apply them right away," Alfaro-Murillo said. "If you can see what is more likely to happen next, then you can prepare for it."

More information: Jorge A. Alfaro-Murillo et al, Pairwise and higher-order epistatic effects among somatic cancer mutations across oncogenesis, *Mathematical Biosciences* (2023). DOI: 10.1016/j.mbs.2023.109091

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