

Big data analysis finds cancer's key vulnerabilities

January 11 2021



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Thousands of different genetic mutations have been implicated in cancer, but a new analysis of almost 10,000 patients found that regardless of the cancer's origin, tumors could be stratified in only 112 subtypes and that, within each subtype, the Master Regulator proteins that control the cancer's transcriptional state were virtually identical, independent of the specific genetic mutations of each patient.

The study, published Jan. 11 in *Cell*, confirms that Master Regulators provide the molecular logic that integrates the effect of many different and patient-specific mutations to implement the transcriptional state of a specific tumor subtype, thus greatly expanding the fraction of patients who may respond to the same treatment.

More specifically, rather than looking for drugs targeting mutated genes associated with increasingly smaller patient subsets, the new study suggests that a much larger fraction of patients may respond to novel drug classes designed to target Master Regulator proteins.

The new analysis of thousands of tumors from all types of cancers also found that the key genetic programs necessary for the survival of [cancer](#) cells are mechanistically controlled by only 24 Master Regulator modules—dubbed MR-Blocks—each one comprising just a handful of such proteins working in concert.

The analysis, which has the potential to streamline and improve [cancer treatment](#) in the future, was led by Andrea Califano, Dr., Cory Abate-Shen, Ph.D., and Mariano Alvarez, Ph.D., at Columbia University's Vagelos College of Physicians and Surgeons and Herbert Irving Comprehensive Cancer Center.

"In today's personalized medicine, we try to identify which one out of thousands of possible genetic mutations or, even worse, mutational patterns may have triggered an individual's disease, and then we hope we have drugs that can target the activity of the related proteins," says Califano, the Clyde and Helen Wu Professor of Chemical and Systems Biology and chair of systems biology at Columbia University Vagelos College of Physicians and Surgeons. "But instead of requiring drugs targeting each different mutation, our study suggests that we may just need a few dozen different drugs that can target MR-Blocks," he adds.

"Identifying the handful of MR-Blocks that are active in each individual's cancer will guide us in selecting the most appropriate drug or drug combination to treat them," Califano says. This hypothesis is already being tested in a number of clinical trials, including in breast cancer, pancreatic cancer, and neuroendocrine tumors, as well as in the Columbia Precision Oncology Initiative, a large-scale program aiming to assess the value of genomic, immunotherapeutic, and Master Regulator-based treatments in 3,000 patients across eight aggressive tumor types.

Personalized Therapy Benefits Only a Few Cancer Patients

Most cancer patients receive the same treatment, which has been tested on thousands and thousands of patients. When those options fail, however, patients may opt for a personalized approach, which involves identifying the genetic mutations in the patient's tumor to guide the selection of drugs that target those mutations.

But few patients actually draw benefit from this approach, Califano says, because most tumors lack druggable mutations and the few that have them often fail to respond or relapse rapidly following an initial response. "Relying solely on the identification of genetic mutations to guide personalized treatment has not turned out to be the slam-dunk that we were all hoping for. Large-scale studies have shown that only to 5% to 10% of patients benefit and most of them eventually progress to a drug-resistant form of the tumor. Additional approaches are thus sorely needed," he explains. "For instance, targeting the oncogene BRAF with inhibitors such as vemurafinib provides extraordinary short-term response in melanoma patients with mutations in this gene. Yet relapse occurs within a few months, such that little if any overall survival benefit is observed."

Califano and his colleagues have focused on a different approach to personalized therapy. Using advanced mathematics and physics-based methodologies to model complicated biological systems, such as the molecular interactions that implement the biological logic of the cell, Califano and his team crunch data from thousands of cancer samples to understand how genetic mutations influence the activity of all of the proteins in a malignant cell. Indeed, genes are important only because they represent the blueprint to make proteins, while the latter are the molecules that preside over specific functions in the cell, including turning a normal cell into a tumor.

"If you model the cell like a complex electronic circuit, it becomes easy to identify the specific components where the aberrant signals arising from mutated genes eventually converge," he says. "Rather than the individual mutations, these components represent the most universal vulnerabilities of the cancer cell."

Many of these points of convergence are proteins that ultimately determine the cell's fate, even though they are rarely affected by mutations.

Califano calls these proteins, which are both necessary and sufficient for cancer cell maintenance across virtually all cancers, "Master Regulators." "You can think of Master Regulators as the narrow opening at the bottom of a funnel," he says. "The top of the funnel collects the effects of all relevant genetic mutations in the cell and 'canalizes' them into that narrow opening.

"We think it will be more effective and efficient to simply plug the end of the funnel, by targeting one or more Master Regulators, than to target all the mutated proteins feeding into it."

Master Regulator Blocks

Though [master regulators](#) have been identified in several specific cancers, the new study looked for Master Regulators across 20 different cancer types, as well as for any overlap they may have across multiple cancers.

To accomplish this goal, Califano's team developed a computational tool called Multi-Omics Master-Regulator Analysis (MOMA) to analyze gene expression and gene alterations in tumors. They used MOMA to analyze 9,738 tissue samples from the Cancer Genome Atlas repository of the National Cancer Institute.

The analysis identified 407 Master Regulators across the various cancers and found that these are organized into only 24 unique and highly interconnected modules, or Master Regulator Blocks (MR-Blocks). Each MR-Block contains only a handful of Master Regulators working in concert to control particular hallmarks of cancer cell behavior. For example, MR-Block:2, the most frequently activated block in the most aggressive cancers, comprises 14 regulators of cell growth, DNA repair, cell division, and cell proliferation. Activation of this block was found to be predictive of poor outcomes in many different types of cancer. In contrast, MR-Block:24 was found to be associated with inflammatory programs and immune response and was thus a predictor of good outcome in melanoma.

On average, between two and six MR-Blocks were activated in each individual tumor.

Targeting MR-Blocks as Therapy

Califano's team also demonstrated that the activity of MR-Blocks in cell lines could be modulated with drugs, favorably affecting cell behavior in several types of cancer.

Targeting MR-blocks, rather than individual mutated proteins, promises to potentially prevent cancer [cells](#) from developing resistance, since individual MR-Blocks capture the effect of an extremely large number of potential [mutations](#) in their upstream pathways, which would otherwise inevitably lead to drug resistance.

"We've shown that if you target MR-Blocks, it's very hard for the cell to go around the blockade," Califano says. "The cell would have to reprogram itself, and that's something that a cell doesn't like to do and most often, albeit with some exceptions, of course, leads to cell death."

Califano envisions that in the future, each patient's cancer may be decomposed into its specific MR-Blocks and be treated with drugs designed to target them, either individually or in combination. The good news is that a tumor needs to aberrantly activate and inactivate many genetic programs to survive. Thus, even targeting just one of several MR-Blocks is likely to induce cancer cell demise, Califano says.

Unfortunately, even though the technology to readily identify which MR-Blocks are active in a patient's cancer already exists, few if any drugs have been developed specifically to target them. As a result, Califano's lab developed algorithms to assess the ability of existing drugs to inhibit or activate individual MR-blocks. For instance, the study shows that four FDA-approved and experimental drugs already exist that are capable of activating MR-Block:14 in prostate cancer, thus dramatically reducing the cell's ability to migrate and metastasize. Drugs designed specifically to target Master Regulators should outperform existing drugs, Califano says. As a result, a number of collaborations are under way to start developing this new class of inhibitors despite the fact that, until very recently, Master Regulators were considered to be largely "undruggable" proteins.

"This is a new concept, so there's been little development of such drugs,"

Califano says. "But we're already testing [drug](#) candidates, and initial validation in both pre-clinical and clinical studies has very much exceeded our expectations."

The study is titled "A Modular Master Regulator Landscape Determines the Impact of Genetic Alterations on the Transcriptional Identity of Cancer Cells."

More information: Evan O. Paull et al. A Modular Master Regulator Landscape Determines the Impact of Genetic Alterations on the Transcriptional Identity of Cancer Cells, (2019). [DOI: 10.1101/758268](https://doi.org/10.1101/758268)

Provided by Columbia University Irving Medical Center

Citation: Big data analysis finds cancer's key vulnerabilities (2021, January 11) retrieved 24 April 2024 from <https://medicalxpress.com/news/2021-01-big-analysis-cancer-key-vulnerabilities.html>

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