Dozens of New Genes That Create T Cell-Resistant Cancer Discovered With Innovative ‘Two-Cell Type’ CRISPR Screen

Large-Scale Gene Editing Study Provides New Insights Into Why Immunotherapy Fails in Majority of Cancer Patients

New York, NY (August 7, 2017) — To better understand why some cancers are resistant to immunotherapy, researchers at the New York Genome Center, New York University, the Broad Institute and the National Cancer Institute collaborated on a large-scale CRISPR cancer study published today in Nature. The investigators developed a novel use of a gene editing technique, a ‘two-cell type’ CRISPR assay system (2CT CRISPR) that specifically examines how genetic mutations in one cell can affect the interaction between two different cell types. The study, “Identification of Essential Genes for Cancer Immunotherapy,” uncovered dozens of novel genes involved in resistance to therapies that harness the immune system to fight cancer.

“We cast a wide, deep net and conducted an unbiased survey of all of the 19,000 genes in the cancer’s genome — not just the genes that are known to be involved in creating immunotherapy-resistant tumors,” explained the study’s senior author, Dr. Nicholas P. Restifo, a senior investigator at the National Cancer Institute. The Restifo Lab has pioneered the use of T cell-based immunotherapies. "The big surprise was that we found many new genes that we never suspected could potentially be involved in preventing the immune system from killing cancer cells."

The study was aimed at linking the loss of the ability to kill tumor cells with the failure of immunotherapy. The researchers reported that the large gene list uncovered by 2CT CRISPR could serve as a “blueprint” to study the emergence of tumor resistance, and eventually lead to more effective immunotherapy treatments for patients.

The innovative 2CT CRISPR screen consisted of human T cells, often referred to as ‘the executioners’ because of the key role they play in attacking cancer, as effectors and human melanoma tumor cells as targets. The melanoma cells were modified by CRISPR and then tested for resistance by applying T cells. Researchers were able to identify which loss-of-function mutations in melanoma reduced the effectiveness of the T cells and led to immunotherapy-resistant tumors.

The researchers knocked out — one by one — each of the approximately 19,000 genes in the tumor cell’s genome, and then tested whether tumor cells with specific gene knock-outs were now resistant to the T cells. This was done in a pooled manner, enabling a single investigator to simultaneously visualize more than 123,000 distinct cuts or edits to the tumor’s genome. This approach led them to discover which genes — when knocked out in cancer cells — create T cell-resistant cancer cells.

“We were very encouraged by the hits from the 2CT CRISPR screen in pinpointing which genes are involved in immunotherapy resistance, as well as revealing so many novel genes. For example, the top two hits — HLA and B2M — form a complex that is required for antigen presentation and thus required for the T cells to see and attack the cancer. Seeing these genes at the top of the list is a really nice sign that the genetic screen yielded meaningful data,” said co-first author, Dr. Neville Sanjana, Core Faculty Member at the New York Genome Center, Assistant Professor of Biology, New York University, and Assistant Professor of Neuroscience and Physiology at NYU School of Medicine. Dr. Sanjana noted, “It has been really wonderful to collaborate with the Restifo Lab. This kind of project is only possible with a team with diverse expertise in gene editing, functional genomics and cancer immunotherapy.”

The research team correlated the genes uncovered by the 2CT CRISPR screen with a large dataset from the Cancer Genome Atlas (TCGA), containing more than 11,000 tumors from 36 cancer types. Analysis of the TCGA data suggested that across cancer types there is a core set of genes important for effective immune response to cancer and this same core set was found in the 2CT CRISPR screen.

One of the genes without a previously established role in cancer immunotherapy that the investigators identified was APLNR. The product of this gene is a protein called the apelin receptor, and the study demonstrated for the first time its connection to the JAK-STAT pathway, known to be important for immune response. The Nature
study demonstrates that loss of APLNR in a mouse cancer model results in poor prognosis and blocks effective treatment through immunotherapy.

Co-first author Shashankkumar Patel, a predoctoral fellow in the Restifo Lab, explained, “We did an in-depth study – a study within a study – on this particular gene, demonstrating a model for digging deep to uncover more genetic insights. Our team performed experiments to elucidate its biological significance in cancer immunotherapy resistance.” The researchers validated their finding in vivo, in a mouse model. “This proof of concept study with the apelin receptor demonstrates that the large majority of the new genes we found, if also validated, may help explain the mechanisms behind cancer resistance,” said Patel.

The researchers also validated their findings using multiple methods: in genetically distinct melanomas (distinct from the melanoma used in the CRISPR screen); in other immunogenic cancers like renal cell carcinoma; using other antigens (distinct from the one recognized by the T cells in the CRISPR screen); and through bioinformatic analyses of mutations found in patients that do not respond to immunotherapy.

The 2CT CRISPR assay establishes a successful model for researchers to interrogate other immune cell types, including dendritic cells and macrophages, and other diseases where interactions between multiple cells is important. “This is the first step for systematically identifying the reasons immunotherapy is not working for many cancer patients,” said Dr. Restifo. “The hope is to help scientists and clinicians find a way around the obstacles so that more patients can benefit from this promising treatment modality.”

The study’s findings, if validated in a clinical setting, would enable physicians to stratify patients, and personalize their treatment in order to achieve better response rates to immunotherapy.

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