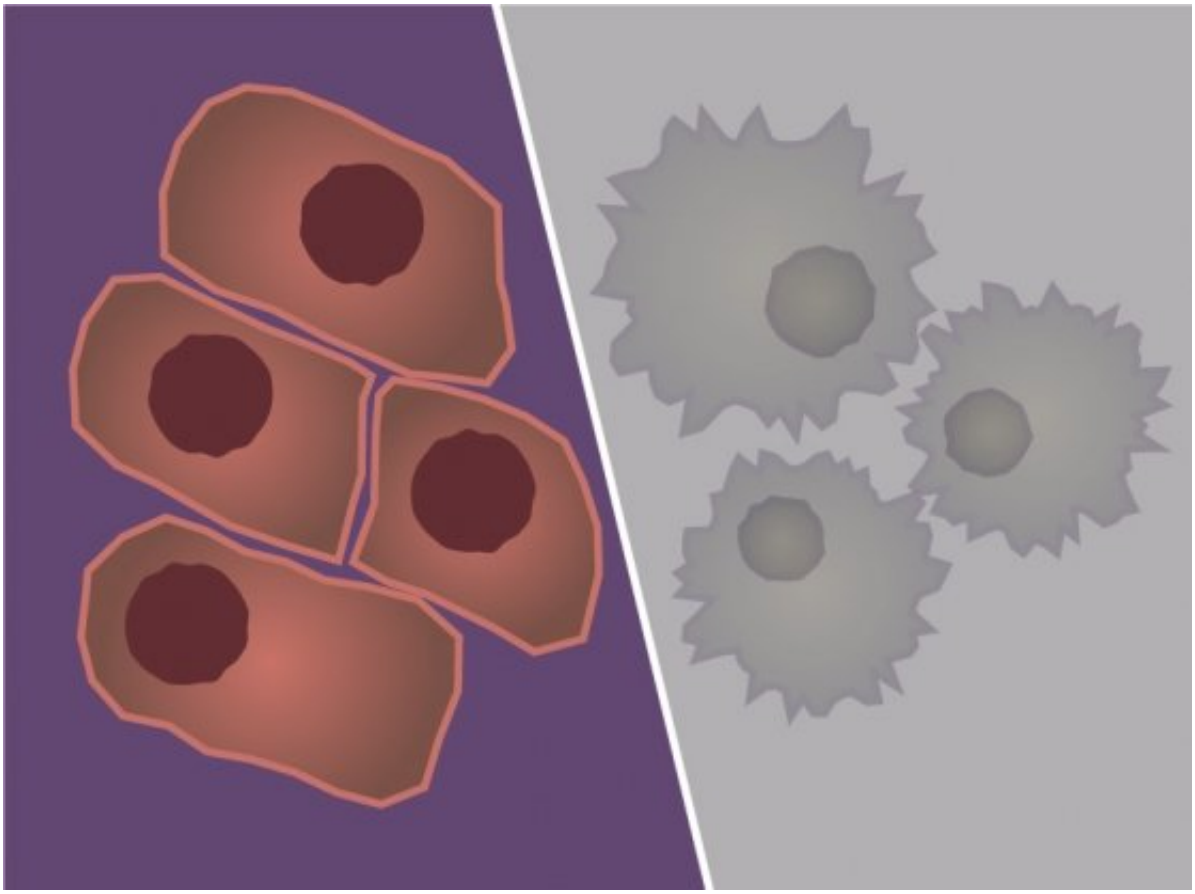
MedicalXpress

Single-cell analysis reveals how melanoma cells resist immunotherapy

November 2 2018, by Karen Zusi



Credit: Broad Institute of MIT and Harvard

Unleashing the immune system to fight tumors—an approach enabled by immunotherapy—has led to remarkable outcomes in some cancer patients, but in many more, cancer cells evade the treatment and

continue to spread. Now, a team led by researchers from Broad Institute of MIT and Harvard and Dana-Farber Cancer Institute has identified a gene expression pattern that human melanoma cells use to resist immunotherapy, and demonstrated a combination therapy approach that could overcome this resistance.

The paper, published today in *Cell*, appears alongside a companion immunotherapy study led by a separate research team from Broad Institute and Massachusetts General Hospital.

"With additional data, we hope that the methods and specific combination therapy identified in our study could have a real benefit for patients," said co-senior author Benjamin Izar, an instructor in medicine and melanoma oncologist at Dana-Farber Cancer Institute and postdoctoral fellow at the Broad Institute. He and Aviv Regev, director of the Klarman Cell Observatory at the Broad Institute, professor of biology at MIT, and an HHMI investigator, are co-senior authors on the paper.

"Our team has mapped out a high-resolution landscape of immunotherapy-resistant melanoma," added Regev. "We've discovered a gene expression program that can help predict resistance to immunotherapy before treatment even begins, and a potential way to reverse this program in order to delay or counter that resistance."

Using single-cell RNA sequencing data, the researchers analyzed thousands of melanoma cells from more than 30 melanoma patients, half of which had exhibited resistance to immunotherapies. The team identified a distinct gene expression pattern that correlated with reduced T cell presence in the tumor and other features of immunotherapy resistance.

By measuring the levels of this "resistance program" before treatment,

the team could predict how tumors would respond to immunotherapy—thereby addressing a major clinical challenge in the field of immuno-oncology. This analysis was done in larger independent cohorts of melanoma patients, assembled in collaboration with colleagues at Massachusetts General Hospital and the University of Essen in Germany. And in another patient cohort, the group showed that cancer cells further amplify this program when exposed to immunotherapy.

The resistance program included signals that are hallmarks of immune system evasion. Abnormal cells typically have substances on their surfaces, called antigens, that enable T cells to home in and destroy them. But the resistant tumor cells are able to reduce their antigen levels and hide from the immune system. They also reduce the enzymes attacked by the T cells, rendering an assault ineffective if it does occur. Other genes expressed in this program include those that cause cells to unduly proliferate.

"We found that multiple immune evasion mechanisms, and other hallmarks of cancer growth, are strongly co-regulated with each other in this resistance program," said Livnat Jerby, a postdoctoral fellow in Regev's lab and first author on the paper. "Certain mutations in these pathways have already been reported to confer immunotherapy resistance, but here we show that there is a shared regulatory program controlling their expression."

Once the researchers understood this molecular strategy, they began exploring ways to suppress it and sensitize melanoma tumor cells to immunotherapy. Mining data across hundreds of human cell lines, the team predicted that a class of cancer drugs called CDK4/6 inhibitors, which are already known to suppress cell proliferation, could in part reverse the resistance program in cells.

In a mouse model of extremely immunotherapy-resistant melanoma—which expressed the newly discovered resistance program at high levels—the CDK4/6 inhibitors dramatically improved responses to immunotherapy, and the combination approach significantly slowed or eradicated tumors in roughly half the mice.

"It's unclear what all of CDK4's activities might actually be, but our data indicate that it could be a 'master regulator' of this resistance program," said Jerby.

Based on this work, the researchers are pursuing a clinical trial to further test their findings. "Our work, along with that of colleagues studying the effects of CDK4/6 inhibitors in breast cancer and other diseases, provides a rationale for exploring combination therapy with immune checkpoint inhibitors," said Izar. "It's exciting to see that our work may actually translate back into the clinic and make a difference for patients with resistant melanoma."

More information: Livnat Jerby-Arnon et al. A Cancer Cell Program Promotes T Cell Exclusion and Resistance to Checkpoint Blockade, *Cell* (2018). DOI: 10.1016/j.cell.2018.09.006

Provided by Broad Institute of MIT and Harvard