New cancer immunotherapy targeting myeloid cells slows tumor growth

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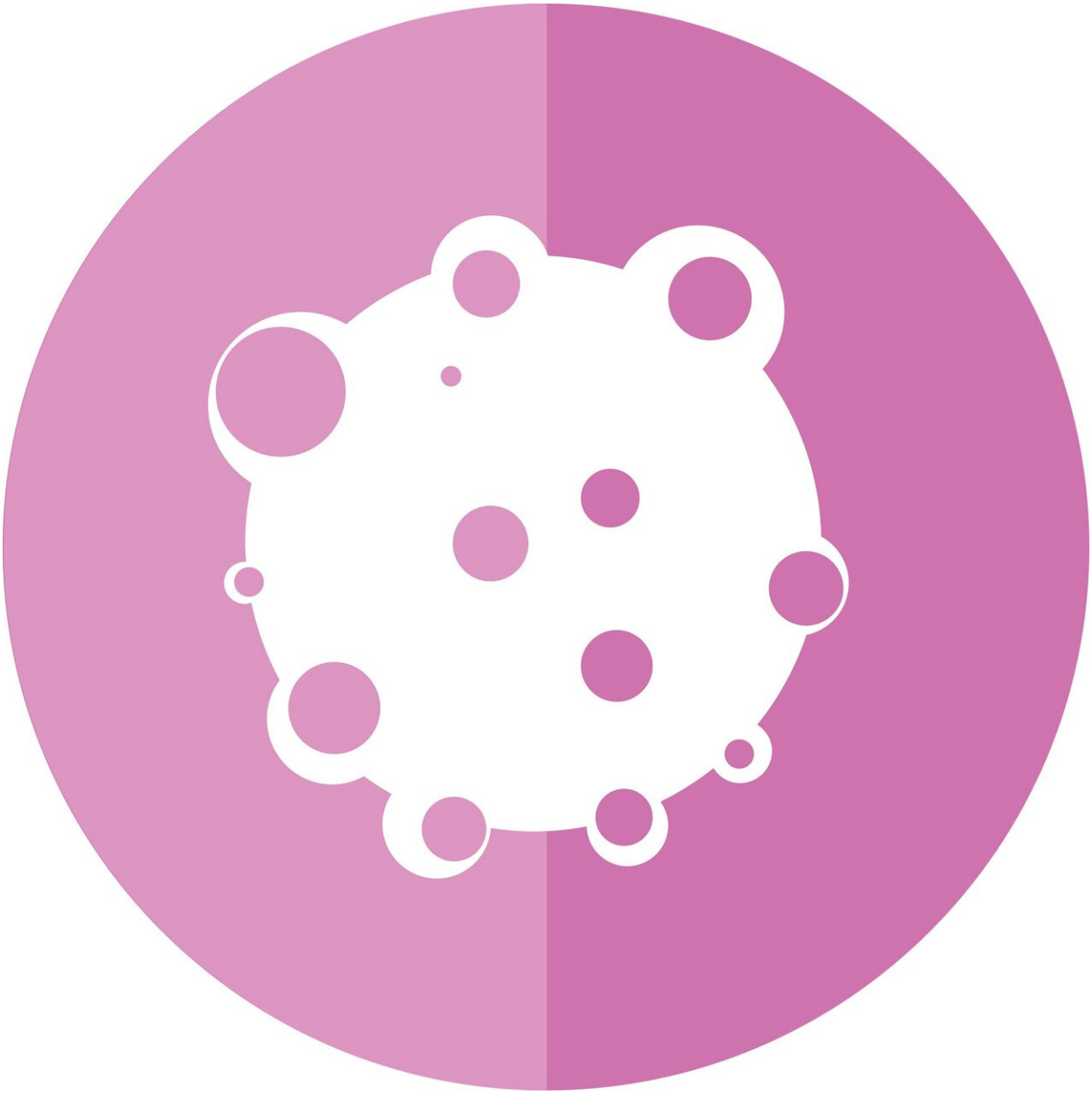

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Checkpoint inhibitors, a type of immunotherapy, that target myeloid immune cells and slow tumor growth were discovered by a team from the Perelman School of Medicine at the University of Pennsylvania and other institutions. Reporting in *Nature Cancer*, the researchers showed for the first time in human cells and a mouse model that inhibiting the c-Rel molecule in myeloid cells—as opposed to lymphoid cells that today's immunotherapies target—blocked the production of immune suppressor cells and significantly shrank tumors.

Checkpoint inhibitors blocks proteins, called checkpoints, that are made by some types of immune system cells, such as T-cells. These checkpoints help keep immune responses from being too strong, but they often keep T-cells from killing cancer cells. These therapies have changed the cancer landscape by showing survival benefits where traditional therapies, like chemotherapy, may have failed. However, the number of patients who respond to these types of therapies remains limited, pushing researchers to explore a new class of inhibitors.

The team showed that in c-Rel-deficient mice tumor size and weight were reduced by up to 80 percent, and that administering the c-Rel inhibitor drug in another set of mice shrank tumors by up to 70 percent, compared to controls.

The findings not only show the potential of this new immunotherapy, but also point to a previously unknown pathway of cancer's assault on the body involving what are known as myeloid-derived suppressor cells (MDSCs). Cunning tumor cells, the authors found, hijack c-Rel to produce MDSCs that keep the immune system from attacking the cancer. The Penn-developed inhibitor releases that break.

"c-Rel is generally considered to be a promotor of immune responses, not a suppressor. That's why this discovery is surprising and unexpected," said senior author Youhai H. Chen, MD, Ph.D., a professor of Pathology and Laboratory Medicine in the Perelman School of Medicine. "There are two big takeaways: conceptually, this is a new pathway of cancer development that wasn't known before. And we have shown that a new drug inhibitor targeting this pathway works as well, if not better, than the first generation of checkpoint blockers."

The discovery of c-Rel's role in cancer was serendipitous. Chen's lab was studying c-Rel's role in inflammation and autoimmune diseases when they observed a relationship with MDSCs. Already equipped with a c-Rel mouse model, they decided to follow the thread and investigate whether c-Rel played a role in cancer growth, too, given the known function of MDSCs.

The results, said Chen, whose lab has been studying c-Rel for nearly two decades, were striking.

Beyond significant shrinkage of tumors in mice, in another experiment, the researchers deleted the REL gene, which blocked tumor growth and reduced MDSCs in mice, suggesting c-Rel is required to generate MDSCs. Follow-up genetic sequencing also showed how c-Rel turns on pro-tumor gene signatures that suppress functions of the immune system in MDSCs.

The researchers then tested their c-Rel inhibitor drug in mice and found that it not only reduced tumor growth, but also enhanced the effects of anti-PD-L1 therapy, another checkpoint inhibitor, when given in combination with the c-Rel drug. That one-two punch approach had the strongest suppression of tumor growth.

Combination therapy has become a popular approach for treating cancer

patients, especially for those who do not respond well to other treatments. "In patients who respond to anti-PD-L1 treatments, many of them still die after two years," Chen said. "If you could extend lives by adding another effective approach, that would be a big advance."

Using human cells, the team also showed that its c-Rel inhibitor drug blocked the development of MDSCs in vitro, suggesting that inhibition might help eliminate cancer in patients, according to the authors.

Now that the efficacy of the inhibitor has been demonstrated in the preclinical setting, Chen said, the next step will be studies to assess the safety of the drug, before moving on to further studies and clinical trials.

"This represents a new class of checkpoints belonging to a different type of cell in the immune system that could move the field of immunotherapy even further along," Chen said.

More information: Ting Li et al. c-Rel is a myeloid checkpoint for cancer immunotherapy, *Nature Cancer* (2020). DOI: 10.1038/s43018-020-0061-3

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