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Cancer cells' immune weak spot revealed

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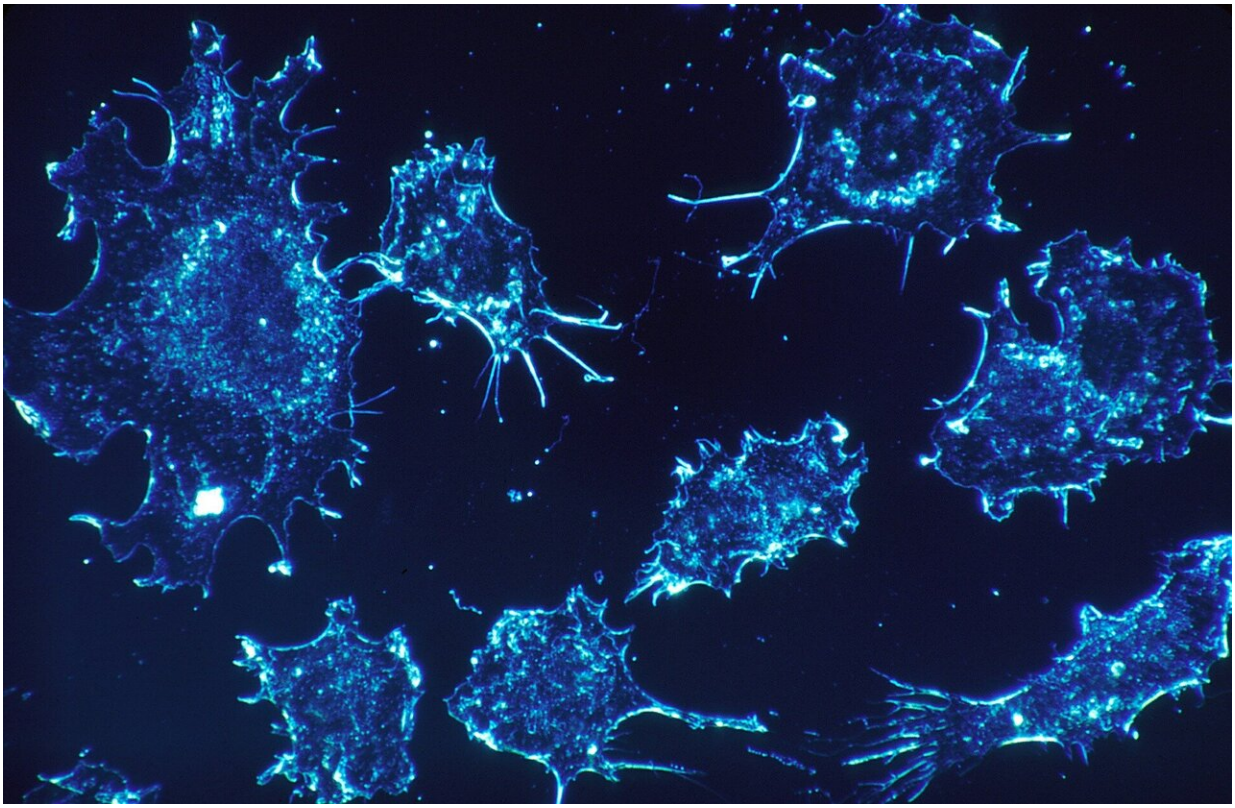

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Scientists have found a vulnerability in cancer cells that could make them more susceptible to being destroyed by the immune system, according to a new report in *eLife*.

The discovery could make it possible to circumvent the resistance

starting to be seen with a new generation of immunotherapy treatments called checkpoint inhibitors.

Scientists have been heralding immunotherapy treatments as breakthroughs in cancer research as they have prolonged life in some people with previously untreatable cancers. However, not everyone responds to immunotherapy and recent studies suggest that some cancers are able to escape the effects of checkpoint inhibitor drugs. As a result, there is considerable interest in finding ways to amplify the body's immune response to cancer.

"Anti-tumour immunity is not solely mediated by the adaptive immune system, but also by innate immune cells, most notably natural killer, or NK, cells," explains lead author Matthew Pech, a scientist in cancer immunology at Calico Life Sciences, South San Francisco, US. "In this study, we used genetic screening in a modified leukaemia cell line to find molecules in cancer cells that determine their response to NK cells."

The team used a gene-editing technique called CRISPR to tweak all the genes in the leukaemia cells, and then studied how this affected their interaction with NK cells. They were particularly interested in an important molecule called interferon-gamma (IFNγ), which immunotherapy-resistant tumour cells are often insensitive to. They found two broad classes of 'hits': genes involved in the tumour-NK cell interaction and components of the IFNγ signalling pathway. Among them was a novel molecule called DCAF15—part of a family of 'adaptors' that provide specificity to the ubiquitination machinery. Ubiquitination controls many processes within cells, including protein turnover, proliferation and DNA repair.

To explore this molecule further, the team deleted DCAF15 from leukaemia cells and looked at how they responded to NK cells. They found that the absence of DCAF15 sensitised the leukaemia cells to the

NK cells.

Having identified DCAF15 as a potential molecule that could sensitise cancer cells to the innate immune system, the team looked at whether an experimental anti-leukaemia drug called indisulam, which modulates the activity of DCAF15, would also affect the immune response.

As they hoped, they found in a range of blood cancer cells that indisulam caused a similar increase in a molecule called CD80, which provides important signals that amplify the immune response, as had been seen in the cells without DCAF15. This raised the possibility that drugs of this type could be used to boost the immune response towards cancer cells. Moreover, an analysis of data from patients with leukaemia found that reduced DCAF15 levels were linked to better survival of acute myeloid leukaemia (AML).

"We have identified DCAF15 as an important molecule in controlling the body's immune response to tumours," concludes senior author Jeff Settleman, who was Head of Oncology Research at Calico Life Sciences, South San Francisco, at the time the study was carried out. "The finding that an existing drug, indisulam, was able to reproduce the immune-promoting effects of deleting DCAF15, alongside our observation that AML patients with lower levels of DCAF15 had better clinical outcomes, suggest that blocking this molecule may be a beneficial strategy in the treatment of blood cancers."

More information: Matthew Pech et al, Systematic identification of cancer cell vulnerabilities to natural killer cell-mediated immune surveillance, *eLife* (2019). DOI: 10.7554/eLife.47362

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