# Immune cells lose 'killer instinct' in cancerous tumors, but functionality can be re-awakened

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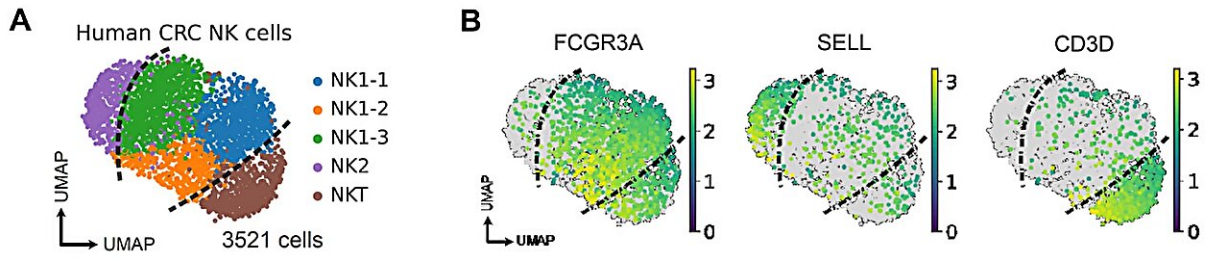


Evidence for dysfunctional NK cells within human CRC was sought through bioinformatics analysis of publicly available data sets alongside flowcytometric analysis of primary human CRC samples. A UMAP of 3521 NK cells from scRNA-seq of 62 human CRC samples, from GSE178341. B Expression of selected marker genes for clusters shown in "A." Credit: *Nature Communications* (2024). DOI: 10.1038/s41467-024-44789-z

Some immune cells in our bodies see their "killer instinct" restricted after entering solid tumors, according to new research.

In a new paper published in *Nature Communications*, a team led by researchers from the University of Birmingham and the University of Cambridge found how immune cells called natural killer cells (NK cells) rapidly lose their functionality when entering and residing in tumors.

Using tumor cells grown from mice models, the team established that NK cells adopt a dormant state when entering solid tumors through the loss of production of key effector mechanisms used to promote immune responses including chemokines, cytokines, and granzymes. Further studies including cells taken from human colon cancers confirmed that the loss of function of natural killer cells happens in people too.

The team further tested whether the loss of function experienced by NK cells upon entering tumor environments could be reversed. Targeting the IL-15 pathway, which is currently being trialed in patients, resulted in significantly more NK cell activity and in the mice models, better tumor control.

David Withers, professor of immune regulation at the University of Birmingham and co-lead author of the study said, "Natural killer cells are an exciting prospective field in the world of cancer treatment, using the body's own immune system in the fight against cancer growth. Up until now though, we have seen that NK cells have the innate capacity to slow cancers but often seem to lie dormant within tumor cells.

"Using a mice model, we have been able to specifically see what happens to Natural killer cells after entering solid tumor environments—which seemingly blunts their killer instinct.

"Crucially, the team also found that treating with Interleukin-15 could re-awaken the dormant killer instinct in the NK cells. This is a hugely exciting discovery that allays some of the fears we may have about how natural killer cells behave in tumor environments, and could pave the way for new types of treatment to add to the arsenal to tackle solid tumor cancers."

## Immune orchestrators stuck in cancers become

## 'exhausted'

In a closely related study also published in *Nature Communications*, the research team led by Professor David Withers and Professor Menna Clatworthy also found that some dendritic cells (DCs), immune cell that play a key role in orchestrating anti-tumor immune response, get stuck within cancers.

The normal function of DCs is to capture material from cancer cells and deliver this to lymph nodes where they stimulate anti-tumor immune responses.

The team discovered that rather than trafficking to lymph nodes, some DCs stay in the tumor, where they become "exhausted," with reduced ability to stimulate anti-tumor immune responses, and upregulation of cues that could even reduce anti-tumor immune cell function.

Identifying why these cells become trapped and how to overcome this impairment to normal DC behavior has the potential to boost anti-tumor responses.

Menna Clatworthy, NIHR research professor and professor of translational immunology at the University of Cambridge and co lead-author of the two studies said, "We found that exhausted dendritic cells stuck in the tumor were located next to a type of tumor killer immune cell, CD8 T cells, potentially preventing them from doing their job. Remarkably, these dysfunctional tumor DCs could be revived using a cancer immunotherapy that's used in the clinic.

"Our work helps develop our understanding of how cancers can disrupt the immune system, and crucially, how we can rescue this to improve anti-cancer immune responses."

**More information:** Isaac Dean et al, Rapid functional impairment of natural killer cells following tumor entry limits anti-tumor immunity, *Nature Communications* (2024). DOI: 10.1038/s41467-024-44789-z

Colin Y. C. Lee et al, Tumour-retained activated CCR7+ dendritic cells are heterogeneous and regulate local anti-tumour cytolytic activity, *Nature Communications* (2024). DOI: 10.1038/s41467-024-44787-1