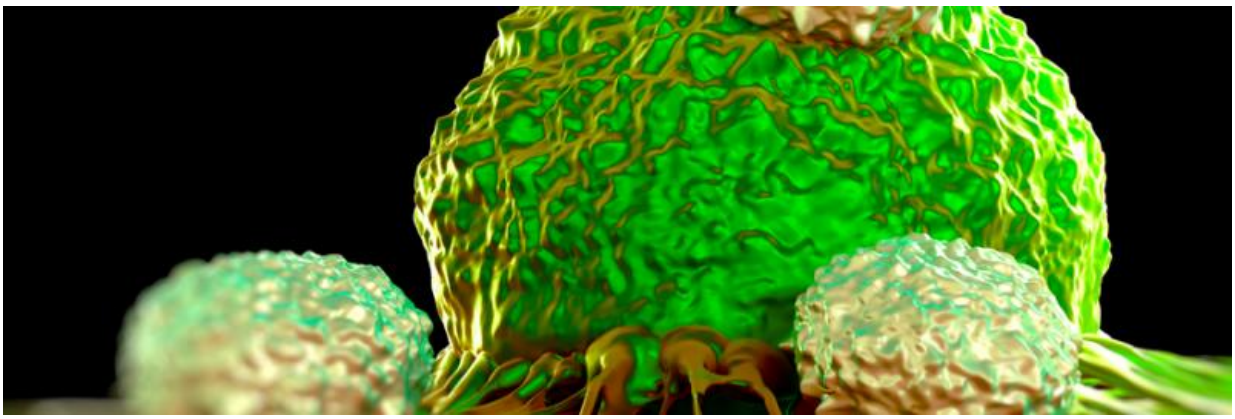
Dying tumour cells release intracellular ions in a last-ditch attempt to block the immune system

September 15 2016



Credit: Babraham Institute

Researchers at the National Cancer Institute in the USA and the Babraham Institute, UK, have discovered how a mineral ion leaked from tumour tissue as it dies acts to stop the work of anti-tumour immune cells. This discovery provides a new approach in the development of treatments to engage the immune system in the fight against cancer.

Tumours consist of a mix of actively multiplying cells and areas of dead tissue. Previous research has found that tumours can repress the immune cells that act against them but until now, it wasn't known how. New

research, published online today in *Nature*, found that cells within tumours release potassium into the extracellular space upon dying. Potassium is an ion that is usually found at high concentrations within cells and not outside them. The increased level of potassium in the extracellular tumour environment dulled the activity of T cells, a specialised effector cell of the immune system, preventing their anti-tumour function.

The researchers molecularly engineered tumour-specific T cells to increase their capacity to remove potassium from the cell. This created T cells which could effectively function to stimulate an anti-tumour immune response despite the elevated potassium environment surrounding them. The cells were engineered to express more molecular pumps specifically to deport excess potassium from the cell. Boosting the cells' 'potassium export' capabilities prevented the high levels of intracellular potassium accumulation responsible for cellular dysfunction.

Modifying the T cells in this way enhanced the clearance of tumours and survival rates in mice with skin cancer.

Dr Rahul Roychoudhuri, group leader in the Lymphocyte Signalling and Development programme at the Babraham Institute and an author on the paper, said: "While ions such as calcium are known to play critical roles in the activation of T cells when they encounter foreign invaders and cancer cells, very little was known about how extracellular potassium might affect this. Surprisingly, we found that high levels of potassium, which was released by dying cells in tumours, had very little effect on calcium but blocked activation of a cellular signalling pathway called the PI3K pathway when T cells encountered tumour antigens. We have a lot of experience studying the PI3K pathway at the Institute so were well positioned to help understand the mechanisms by which potassium was blocking T cell activation."

This research uncovers a new mechanism by which tumours act to block anti-tumour function and identifies new target points for the design of new immune-based therapies for cancer. Dr Nicholas Restifo, lead author from the National Cancer Institute, said: "The findings provide new insights into how ionic imbalances in the tumour microenvironment can powerfully impede the functions of immune cells infiltrating tumours. We're particularly excited about how this may help us to develop new therapies to activate immune function in cancer patients."

More information: Robert Eil et al. Ionic immune suppression within the tumour microenvironment limits T cell effector function, *Nature* (2016). DOI: 10.1038/nature19364

Provided by Babraham Institute

Citation: Dying tumour cells release intracellular ions in a last-ditch attempt to block the immune system (2016, September 15) retrieved 23 April 2024 from https://medicalxpress.com/news/2016-09-dying-tumour-cells-intracellular-ions.html

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