Immune cell health discovery could optimise cancer therapies

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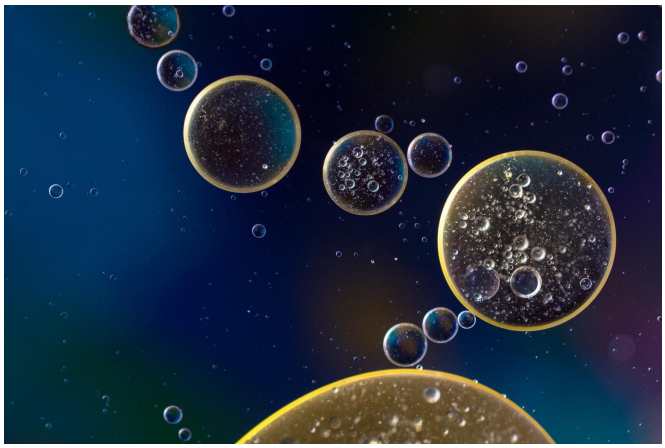

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Scientists at UCL have discovered how immune cells, essential for tackling life-threatening infections and cancers, are able to 'recycle' material within themselves in order to stay healthy and function, a breakthrough finding which could lead to more effective immunotherapies.

In the study, published in *Cell Reports*, researchers investigated how 'autophagy' - the natural physiological process of 'self-eating' which allows intracellular components, such as mitochondria, to be degraded and replaced—takes place in liver-based T cells.

T cells are a subset of lymphocytes (white blood cells) that play a key role in protecting against chronic liver infection and tumours.

Researchers discovered that T cells in the liver had an enhanced rate of autophagy and that this is enabled by the presence and action of a soluble messenger protein found in the liver: the cytokine 'interleukin-15' (IL-15).

This is the first study to identify that IL-15 can boost autophagy in human T cells and researchers believe this new understanding could enable emerging immunotherapies, such as CAR T cell therapy, to be positively manipulated to boost T cell health and survival.

Corresponding author, Dr. Leo Swadling (UCL Infection & Immunity), said: "The liver is a common site for chronic viral infection and tumours and T cells play a key role in protecting against these.

"T cells living within the liver must adapt to the stressful microenvironment, with low levels of oxygen and an abundance of inhibitory signals, to find ways of maintaining prolonged survival and functionality.

"We discovered that a population of T cells able to live exclusively within the human liver can switch on autophagy to maintain nutrient supply and renew organelles like mitochondria to maintain their fitness. We could imprint this same adaptation on T cells taken from blood by exposing them to the cytokine IL-15."

The research team were assisted by surgeons and the Tissue Access for Patient Benefit project (TAPb) at The Royal Free Hospital, London, and gained rare access to live immune cells from human liver samples.

Several cutting-edge single cell technologies were used to compare autophagy in the T cells from these liver samples to T cells in the blood.

Lead author, Professor Mala Maini (UCL Infection & Immunity), said: "Understanding how human T cells are adapted for autophagy opens up the possibility of manipulating this dynamic process, which could enable a wide range of new and effective therapeutic possibilities.

"For instance, we can now investigate whether modulating autophagy rates can be used to

improve emerging immunotherapies for cancer and chronic viral infection (such as TCR-redirected T cells and CAR T cells), where T cells must persist and function in diverse tumour and tissue microenvironments."

More information: Leo Swadling et al, Human Liver Memory CD8+ T Cells Use Autophagy for Tissue Residence, *Cell Reports* (2020). DOI: 10.1016/j.celrep.2019.12.050

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