New weapon identified in arsenal against disease

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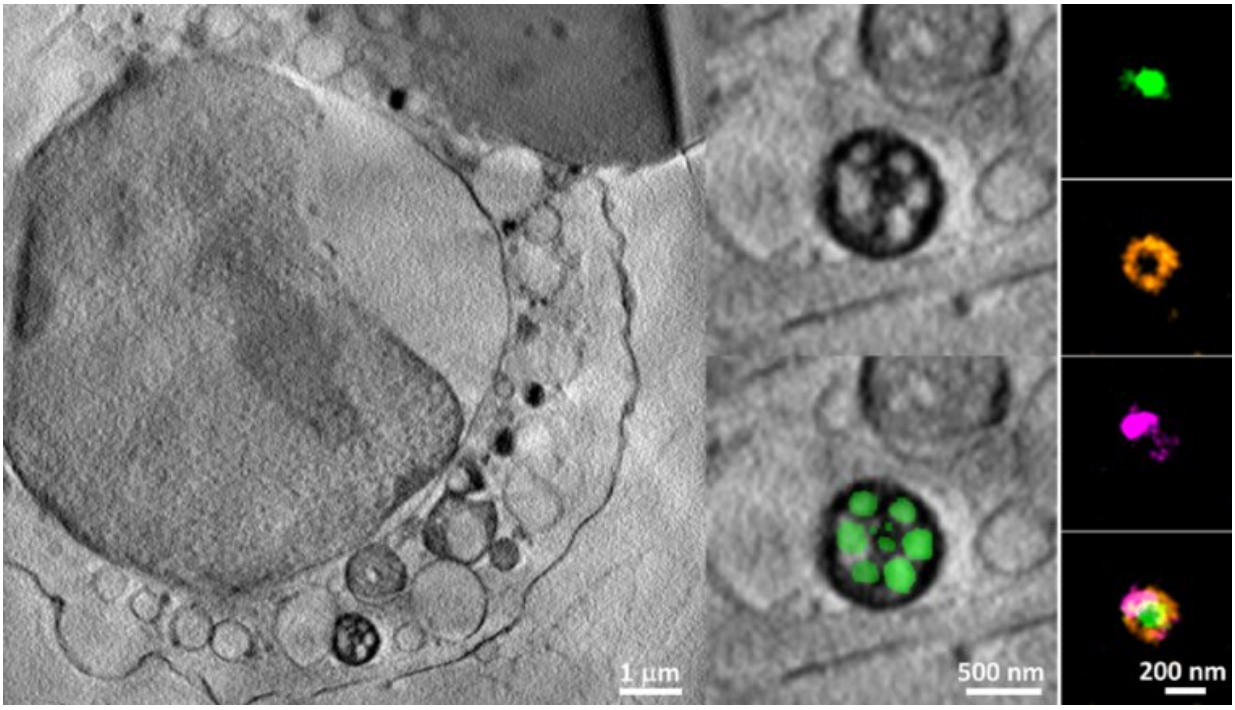

Cryo-soft-x-ray tomography projection of a CD8+ T cell interacting with a carbon coated EM grid containing ICAM-1 and anti-CD3e (left). SMAPs (middle) can be observed within the multicore granules inside the cell. dSTORM images of an individual SMAP positive for perforin (green), WGA (orange) and granzyme B (magenta) released by CD8+ T cells (right). Credit: University of Oxford

Scientists at the Kennedy Institute of Rheumatology in the Nuffield

Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences have discovered a new way for T cells to attack cells infected by viruses or deranged by cancer.

Published online by the journal *Science* on Thursday 7 May 2020, the new research from the Dustin Group describes the structure and composition of supramolecular attack particles (SMAPs) and their role in killing targeted cells.

Cytotoxic T lymphocytes (CTLs) are essential components in the immune response against viruses and cancer. CTLs are known to recognise infected or damaged cells and release soluble protein molecules, which create perforations in the membrane of the targeted cell. These holes allow toxic enzymes to enter and initiate a self-destruct program, killing the targeted cell (cytotoxicity).

The new study reveals a complementary mechanism of cytotoxicity in the CTLs. The team identified SMAPs, ~120 nm diameter protein particles released by CTLs to kill other cells, for example, if virally infected or cancerous. SMAPs have a core of cytotoxic proteins surrounded by a glycoprotein shell.

The core-shell structure was demonstrated in collaboration with the B24 beam line at the Diamond Light Source at the Harwell Science and Innovation Campus using cryo-soft-X-ray tomography. "Using this national resource we were able to determine the physical nature of the particles. This confirmed and extended our observations with super-resolution fluorescence microscopy," said Stefan Balint, Postdoctoral research assistant in molecular immunology who spearheaded the work at the Kennedy Institute.

The core-shell structure of the SMAPs allowed for the whole unit to be released from the CTL and immediately attach to a target to kill it. The

study also showed the potential for SMAPs to exist independently and autonomously from the CTL. "The CTL could leave it in the environment like a land mine," said Mike Dustin, Director of Research of the Kennedy Institute. "If the cytotoxic proteins are like bullets in the CTL's arsenal then the SMAP is a bomb."

A better understanding of SMAPs could be useful to develop new strategies to reinforce CTL activity in anti-viral immunity, cancer immunotherapy, regulation of the immune response and many other settings. SMAPs have been discovered in CTL and natural killer cells, but proteinaceous particles with core-shell structures may have wider implications for physiology and disease. "We are particularly excited about the potential for engineering SMAPs to very specific targeting of tumours and other patient specific treatments," added Mike Dustin.

More information: Š. Balint et al, Supramolecular attack particles are autonomous killing entities released from cytotoxic T cells, *Science* (2020). DOI: 10.1126/science.aay9207

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