Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

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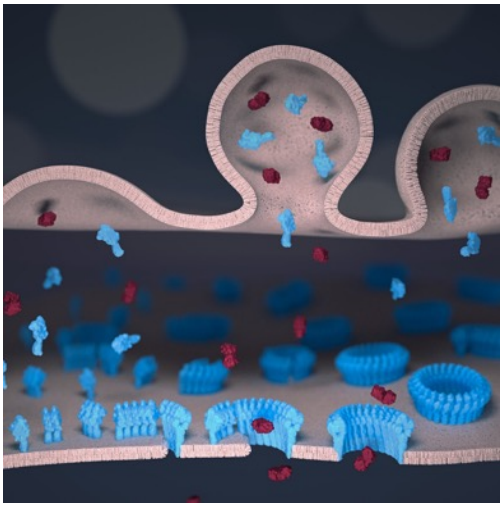
Media release

Immune system defence force captured in action on microscopic CCTV

An international scientific collaboration involving Peter MacCallum Cancer Centre, University College London, Birkbeck College (London) and Monash University has visualised in microscopic detail how the natural defence force within our immune system attacks and destroys harmful invaders such as virus-infected and cancerous cells.



Schematic view of the immune synapse
Perforin (blue) and granzyme (red) are delivered to the synapse by cytotoxic granule fusion with the lymphocyte membrane (top). Perforin binds to the target membrane (bottom) and, following a 'growing pore' mechanism, forms transmembrane pores. The pores allow granzymes to pass the target membrane, and trigger cell death by apoptosis.

***Image courtesy of Adrian Hodel, University College London**

The research, published today in *Nature Nanotechnology*, deepens understanding of the critical role of the protein called 'perforin' in a functioning immune system, bringing us one step closer to new therapies with the potential to boost or inhibit its impact when required.

As part of the research, Profs. Hoogenboom and Saibil in the United Kingdom used atomic force microscopy and electron microscopy to reveal precisely how a subset of white blood cells, called cytotoxic lymphocytes (or Killer T Cells), show remarkable efficiency in first perforating their victims and next injecting poisonous enzymes to rid the body of disease.

Using a form of microscopic CCTV, it was shown how perforin binds to the protective membrane that surrounds harmful cells. After binding, the perforin self-assembles into ring-like structures. These structures each contain multiple perforin molecules that together puncture the target cells, leaving tiny holes - just tens of nanometres in diameter.

A/Prof Ilia Voskoboinik, a lead co-author of the research and Head of Peter Mac's Killer Cell Biology lab, highlights the medical and the fundamental importance of the findings.

"To kill virus-infected or cancerous cells, perforin must be quick and efficient.

“Our experiments in Melbourne show that patients who are born with impaired perforin may present with fatal failure of the immune system and also have a higher risk of developing blood cancers.

“This was entirely consistent with the microscopic data obtained in London, which shows that the effectiveness of perforin is greatly hampered even if only a small number of the perforin molecules are abnormal.

“This new understanding brings us one step closer to targeted therapies that can strengthen the body’s perforin-producing power to ward off disease. We could also inhibit its function to prevent the rejection of organ transplants, when accepting foreign tissue or cells can be instead life-saving.

Background

To film perforin in action, the scientists used atomic force microscopy, in Bart Hoogenboom’s lab at the London Centre for Nanotechnology at UCL. This type of microscopy uses an ultrafine needle to feel rather than see perforin on a target membrane, similar to a blind person reading Braille. The needle repeatedly scans the surface to produce an image that refreshes fast enough to track how perforin molecules get together and cut holes in the membrane.

Initially, perforin appeared as a blur on these images. However, once a few perforin molecules together inserted into the membrane, they could be more clearly identified and shown to recruit more perforin to thus growing transmembrane pores.

By also recording static snapshots at higher resolution by using electron microscopy, Helen Saibil’s team at Birkbeck succeeded in estimating, for each perforin assembly, the number of molecules at each stage of the process. This confirmed a change from loosely packed small perforin assemblies on the membrane to larger and more tightly bound transmembrane pores.

Journal link: Carl Leung, Adrian W. Hodel, Amelia J. Brennan, Natalya Lukoyanova, Sharon Tran, Colin M. House, Stephanie C. Kondos, James C. Whisstock, Michelle A. Dunstone, Joseph A. Trapani, Ilia Voskoboinik*, Helen R. Saibil*, & Bart W. Hoogenboom*, *Real-time visualization of perforin nanopore assembly*, Nature Nanotechnology (2017), in press (* co-lead authors).

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Contacts:

For more information or to arrange an interview with Associate Professor Ilia Voskoboinik please contact the Peter Mac Communications team on 0417 123 048.

About Peter Mac’s Immunology program

Peter Mac’s Cancer Immunology Program was established in 1991 at the Austin Hospital and moved to Peter Mac with 25 staff members in 2000. Its outcomes have benefited from the support of continuous National Health and Medical Research Council Program Grant funding since 2003, international grants from US Department of Defence, US Komen Foundation, Wellcome Trust UK, multiple international industry sources and multiple grants and fellowships from the Peter MacCallum Cancer Foundation, Cancer Council Victoria and the National Breast Cancer Foundation.

Key Australian research partners include The University of Melbourne, Monash University, Ludwig Institute for Cancer Research and the Walter and Eliza Hall Institute of Medical Research.

About Peter Mac
Peter MacCallum Cancer Centre is one of the world's leading cancer research, education and treatment centres globally and is Australia's only public hospital solely dedicated to caring for people affected by cancer. We have over 2,500 staff, including more than 580 laboratory and clinical researchers, all focused on providing better treatments, better care and potential cures for cancer.