Viral evasion gene reveals new targets for eliminating chronic infections

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Dr. Gabrielle Belz's team from the Walter and Eliza Hall Institute in Melbourne, Australia, has discovered how a key viral gene helps viruses evade early detection by the immune system. Their finding is providing new insights into how viruses are able to establish chronic infections, leading scientists to reevaluate their approaches to viral vaccine development. Credit: Czesia Markiewicz, Walter and Eliza Hall Institute

Walter and Eliza Hall Institute researchers in Melbourne, Australia, have discovered how a key viral gene helps viruses evade early detection by the immune system. Their finding is providing new insights into how viruses are able to establish chronic infections, leading scientists to reevaluate their approaches to viral vaccine development.

Researchers from the institute's Immunology division together with collaborators at the University of Cambridge (UK) have been studying

how the immune system responds to viruses that cause persistent or chronic infections and why the immune system is unable to eliminate these infections.

Dr Gabrielle Belz, Dr Adele Mount and colleagues are particularly interested in immune system cells called dendritic cells and their interaction with viruses that cause chronic infections.

"Chronic infections are one of the greatest health challenges for the Western world, but currently we have very few ways of dealing with them," Dr Belz said. "They require ongoing medical care and support due to an inability to treat infection effectively.

"We are trying to understand how chronic infections sneak past the usually highly effective immune armoury and covertly establish disease. If we can stop these infections establishing then we can eliminate, or substantially reduce, that societal burden."

Dendritic cells, which are studied by Dr Belz, Dr Mount and colleagues, act as 'sentinels' of the immune system; they are critical for the early detection of invading bacteria and viruses and are one of the first cells to trigger the immune response. "Dendritic cells are called 'antigen presenting cells'; they digest infectious agents into small fragments and shuttle these fragments to the outside of the cell where they are displayed to virus-specific killer T cells, helping to launch a full-blown immune response," Dr Belz said.

The team has been investigating a virus called gamma herpesvirus-68, which establishes chronic infections in mice and provides a model of the workings of the human gamma herpesvirus Epstein-Barr Virus, commonly known to cause infectious mononucleosis, or 'kissing disease'. Their results, which have been published in the *Journal of Immunology* show that a viral gene called K3 rapidly disables the antigen-processing

machinery normally used by dendritic cells to alert the immune system to infections.

"This gene quickly helps the virus to hide from the immune system by subverting normal antigen presentation to T cells, which have the critical task of destroying virally-infected cells," Dr Belz said. "The virus carries out a top-secret operation. It shuts down the normal mechanisms that allow the immune system to recognise an infection and then boards the antigen-presenting cells which ferry the virus through the blood and tissues, allowing it to spread throughout the body and establish system infection."

Dr Belz said the study could change conventional views on the best way to generate an immune response to combat chronic infections.

"Our research shows that viral evasion of the immune system in chronic infections happens incredibly early," Dr Belz said. "Dendritic cells are compromised long before they have the chance to interact with T cells for the next phase of the immune response, so the T cells are never really activated properly. If we want to make an effective vaccine, we need to look at these early escape points used by the virus as the first target for trying to generate a more efficient immune response that will contain the virus and prevent it establishing a systemic infection."

Provided by Walter and Eliza Hall Institute

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