Manipulating the immune system to develop 'next-gen' vaccines

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The discovery of how a vital immune cell recognises dead and damaged body cells could modernise vaccine technology by 'tricking' cells into launching an immune response, leading to next-generation vaccines that are more specific, more effective and have fewer side-effects.

Scientists from the Walter and Eliza Hall Institute have identified, for the first time, how a protein found on the surface of immune cells called dendritic cells recognises dangerous damage and trauma that could signify infection.

Dendritic cells are critical for raising the alarm about the presence of foreign invaders in the body such as viruses, bacteria and parasites as well as tumour cells and other dead or damaged cells. Also known as antigen-presenting cells, they digest and present molecules from damaged cells to other immune cells that recognise foreign invaders and launch an immune response.

The research was a collaborative effort that involved a team of immunologists, protein chemists and structural biologists. The research team was led by Dr Mireille Lahoud, Dr Jian-Guo Zhang, Dr Peter Czabotar and Professor Ken Shortman.

Dr Lahoud said the study, published today in the journal *Immunity*, demonstrated that the immune system has evolved a very clever way of detecting damaged and dead cells to help promote an immune response.

"Dr Irina Caminschi and I previously identified a protein called Clec9A (C-type lectin domain family 9A) that sits on the surface of specialised types of dendritic cells and responds to damaged and dying cells," Dr Lahoud said. "In this study we discovered that Clec9A recognises and binds to fibres of actin, internal cell proteins that are found in all cells of the body. Actin is only exposed when the cell membrane is damaged or destroyed, so it is an excellent way of finding cells that could harbour potentially dangerous infections and exposing them to the immune system."

Professor Shortman said that exploiting Clec9A could be used to generate a new, more modern class of vaccines that are more effective and have fewer side-effects. "The Clec9A protein is one of the best targets currently known for improving immune responses," he said. "By creating vaccines that bind to Clec9A, we can trick dendritic cells to think they have encountered a damaged cell and help to launch an immune response to the infectious agent of our choice."

Professor Shortman said targeting Clec9A could decrease the amount of vaccine needed by 100 to 1000 times. "Traditional vaccine technology for generating immunity, such as using inactivated whole viruses or parasites for immune recognition, requires large amounts of vaccine in the hopes it will encounter the correct immune cells, and incorporates other substances (adjuvants) that are needed to signal to the immune system that something foreign is happening. We are proposing a new type of vaccine that we know will head directly to the right cell to help stimulate an immune response, and doesn't cause the same side-effects because it is more specific," Professor Shortman said.

Dr Lahoud said that the finding could develop or increase the efficacy of vaccines for diseases that do not currently have good preventive options, such as malaria, or HIV. "There is also the possibility that the system could be used to develop therapeutic vaccines for treating diseases, such

as some forms of cancer, as well as for preventing them," she said.

Provided by Walter and Eliza Hall Institute