'Performance-enhancing' boost helps to fight infection

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Dr Axel Kallies (left) and Mr Kevin Man have discovered how immune system performance is enhanced.

(Medical Xpress)—Melbourne researchers have found that even our immune system is subject to performance enhancement, giving immune cells the boost they need to ensure the best team is selected to fight infections.

The discovery could help in developing new treatments for blood diseases such as leukaemia and autoimmune diseases in which the body attacks its own tissues, such as diabetes or rheumatoid arthritis. It could also be used to enhance immune response to HIV and other chronic infections.

The finding, by researchers at the Walter and Eliza Hall Institute, builds on the 55-year-old theory of 'clonal selection' proposed by Australian Nobel Laureate and former institute director Sir Macfarlane Burnet. The theory revolutionised scientists' understanding of the immune system and how it functioned.

Dr Axel Kallies, Mr Kevin Man and colleagues from the institute's Molecular Immunology division led the research, which was published today in the journal *Nature Immunology*.

Burnet's theory of clonal selection proposed a new model of how the immune system recognised and fought foreign invaders, stating that each immune cell was programmed to recognise a specific infectious agent. Only when the right cell came into contact with an invader would it be activated and stimulated to 'clone' itself, generating large numbers of identical cells to fight the infection."

Studying a type of immune cell called killer T cells, Dr Kallies and his research team showed how the body identified which cells were the most capable of fighting a particular infection. Killer T cells are responsible for killing virus- or bacteria-infected cells, tumour cells and other damaged cells in the body.

"We found that a protein called IRF4 is activated in killer T cell 'clones' that are best equipped to recognise and fight an infection," Dr Kallies said. "Burnet's clonal selection theory tells us that the best T cell clones are selected by the immune system and produced in large numbers but, until now, we didn't know how this was regulated and what happened at the molecular level. We discovered that IRF4 controls the mass production of 'elite' killer T cells, as well as ensuring their survival and enhancing their performance by allowing them to take up large amounts of sugar and other nutrients."

The research team found that IRF4 was produced at different levels depending on how well the killer T cell recognised and bound infected cells. "IRF4 was produced at the highest levels in cells that were the best at recognising the foreign invader," Dr Kallies said. "This is how the immune system guarantees that the best killer T cells survive, producing an 'army of clones' that maintain their killer function to fight the infection. Without sufficient IRF4, the immune system fails to mount a productive immune response."

Dr Kallies said IRF4 was already being investigated by pharmaceutical companies as a potential therapeutic target. "We are slowly peeling back the layers of how immune cells develop, become activated and function," Dr Kallies said. "Targeting the IRF4 pathway could help us to control immune cells. For example, blocking the pathway to diminish proliferation of immune cells when they are out of control, as happens in blood cancers such as leukaemia or in autoimmunity. We could also enhance the activation of IRF4 to rescue T cell clones that are not functional, as a way of boosting the immune response to overwhelming infections such as HIV."

Provided by Walter and Eliza Hall Institute of Medical Research