Tick-tock: Immune T cells know when their time's up

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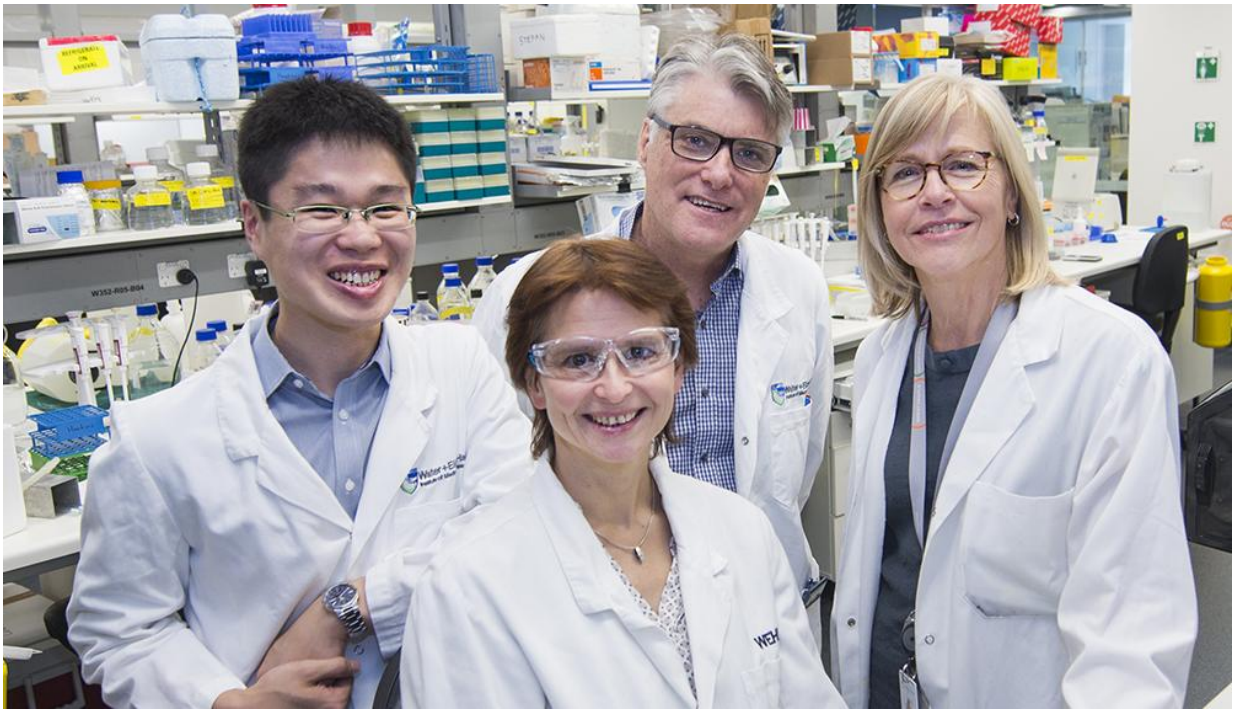

Walter and Eliza Hall Institute researchers Andrew Giang, Dr. SusanneHeinzel, Professor Phil Hodgkin and Professor Lynn Corcoranhave discovered how the size of an immune response is regulated. Credit: Walter and Eliza Hall Institute, Australia

An Australian research team has revealed that two internal 'clocks' control the immune cells enlisted to fight infection. This discovery upends previous theories on how immune responses are regulated.

The team discovered that during an immune response the clocks allocate a certain amount of time in which the cells can divide, as well as prescribing the cells' lifespan. The finding sheds new light on how the body controls immune responses, as well as explaining how immune cell cancers such as leukaemia and lymphoma maybe caused by errors in this system.

Immune T cells are programmed to recognise different microbes that may cause infection. When this happens responding T cells are 'activated', and increase in number by dividing. The number of cells formed and how long they live is tightly controlled to ensure the infection can be successfully fought and any excess immune cells are cleared out of the body.

Dr Susanne Heinzel and Professor Phil Hodgkin led a Walter and Eliza Hall Institute research team that investigated how these two processes - division and clearance - are controlled, in research published today in *Nature Immunology*.

Dr Heinzel said the team discovered activated T cells in an immune response are programmed to divide for a limited time. "We had previously shown the number of cells a 'parent' T cell produces is tightly regulated," she said. "The suspicion was the T cell 'knows' how many times it can divide. We were stunned to find this wasn't the case - the T cell is given an amount of time in which it can divide, like a clock running," she said. "Once this time is up, no more divisions can happen.

"Intriguingly, as well as being allocated a certain amount of time in which to divide, early in an infection, we found T cells separately set their lifespan, how long they and their offspring live. After this time expires, the cells undergo apoptosis, a form of cell suicide," Dr Heinzel said.

Professor Hodgkin said the team built on their discovery of the two-clock system by pinpointing a protein called Myc that acts as the cell division clock. "At the start of an immune response, responding T cells are allocated a certain amount of Myc," he said. "This diminishes over time, and once the cell runs out of Myc, time's up and division stops. The more Myc there is, the more time the cells have to divide.

"We also showed the lifespan clock is controlled by a protein called Bcl-2 - when this time runs out the cells die, whether or not they've come to the end of their division clock," he said.

Dr Heinzel said the research provided new insights into how complex immune responses are controlled, and the fine balance between normal cell division and cancerous cell growth. "The two clocks are an elegant way that our body governs how many responder cells are produced in an immune response, and how long they are retained," she said. "Small changes in each clock combined to substantially alter immune cell numbers.

"It has been known for many years that excess Myc and Bcl-2 are important contributors to cancer formation. Our findings explain how a small series of mutation-driven changes in healthy immune responses could lead to immune cell cancers such as leukaemia and lymphoma," she said.

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