Protein behind development of immune system sentinels identified

September 20 2010

A protein called PU.1 is essential for the development of dendritic cells, the sentinels of the immune system, Walter and Eliza Hall Institute researchers in Melbourne, Australia, have shown.

Dendritic cells (DC) are immune cells that present proteins from foreign invaders, such as viruses, to the killer T cells of the immune system, allowing a full immune response to be mounted against the invaders.

Researchers from the Immunology division have been studying dendritic cells and how different molecules regulate their development.

Dr Li Wu said one of the molecules that is known to be important to this development is a protein called Flt3 which is a cytokine receptor found on the surface of blood stem cells and the parent cells that give rise to DC.

"Despite its importance in early blood cell development and dendritic cell development, there is surprisingly little known about how Flt3 expression is controlled," Dr Wu said.

The team of Dr Sebastian Carotta, Dr Aleksandar Dakic, Ms Angela D'Amico, Mr Milon Pang and Dr Kylie Greig, led by Dr Stephen Nutt and Dr Li Wu, has shown the transcription factor PU.1 can directly bind to the Flt3 gene to regulate its expression. "PU.1 can therefore control DC development through regulating Flt3," Dr Wu said.

Dr Carotta said PU.1 was already known to be important to the development of blood cells and immune cells. "If PU.1 is poorly regulated there is a deficiency in the development of blood cells and leukaemia can result," he said.

"To study the role of PU.1 and look at how it's regulated we developed an animal model and a new in vitro system for tracing DC development from their precursors. These systems make it possible to switch off PU.1 in the precursor cells to DC. From that we determined that loss of PU.1 completely abolished DC development," Dr Carotta said.

Dr Wu said this study revealed PU.1 to be a master regulator of DC development. "Although a growing number of transcription factors have been implicated in the development of specific dendritic cell populations, this is the first time a single transcription factor has been shown to be required for all DC lineages," she said.

The study has been published in the journal *Immunity*.

Dr Wu said the findings had potential to improve DC-based therapies, such as those given to cancer patients who have suppressed DC function. "The problem is people don't know how to develop good DC for these therapies," she said. "By understanding how DC development is regulated it should be possible to create different types of DC populations for therapeutic use."

Provided by Walter and Eliza Hall Institute