Team uncovers important process for immune system development

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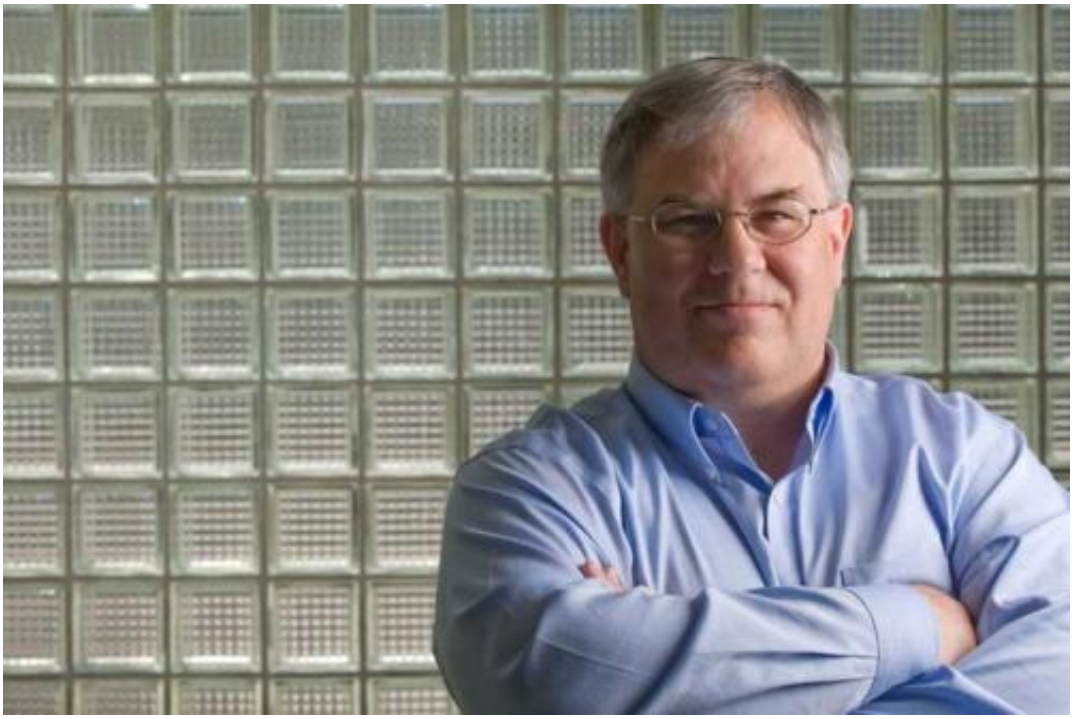

"Understanding how T cells are selected for antigen reactivity has been an enigma, and here we have made a major advance in understanding how this selection works," UCI's Dr. Michael Demetriou said.

Research by UC Irvine immunologists reveals new information about how our immune system functions, shedding light on a vital process that determines how the body's ability to fight infection develops.

In the online version of *Nature Immunology*, neurology professor Dr.

Michael Demetriou, postdoctoral scholar Raymond Zhou and other Institute for Immunology colleagues describe a critical mechanism underlying how T cells are created, selected and released into the bloodstream.

A T cell is a type of blood cell called a lymphocyte that protects the body from infection. T cell precursors called thymocytes are created in the bone marrow and migrate to the thymus – a walnut-sized organ at the base of the neck – where they turn into T cells.

However, very few thymocytes become fully functional T cells, and in the current study, the Demetriou team gained important new insights into why.

As they transform into T cells, thymocytes grow receptors that react to an antigen (any substance provoking an immune response) that's bound to a small molecule called MHC. If this reaction is too strong or too weak, the thymocyte does not mature into a T cell.

Demetriou and the others found that the delicate balance determining the proper reactive ability is controlled by glycosylation, a process in which a sugar attaches to a target protein to give the protein stability and form. They saw that changes in the addition of sugars to receptors – including the blocking of glycosylation – during T cell development profoundly influenced how thymocytes reacted to the MHC-bound antigens and whether they became mature T cells.

Glycosylation also may help explain the creation of self-reactive T cells that escape from the thymus and can go on to attack the body's own antigens, a process called autoimmunity that's the basis of immune system disorders such as multiple sclerosis.

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an enigma, and here we have made a major advance in understanding how this selection works," Demetriou said.

The work, he added, represents a breakthrough in basic research and facilitates further discoveries about T cell processes that could someday yield new therapeutic approaches to infection and autoimmune diseases.

More information: N-glycosylation bidirectionally extends the boundaries of thymocyte positive selection by decoupling Lck from Ca2+ signaling, *Nature Immunology* (2014) DOI: 10.1038/ni.3007

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