MedicalXpress

Molecular interplay explains many immunodeficiencies

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Australian scientists have described an exquisitely balanced interplay of four molecules that trigger and govern antibody production in immune cells. As well as being an important basic science discovery, it helps explain why people with mutations in any one of the associated genes cannot fight infection effectively, and develop rare and crippling immunodeficiency disorders.

Our immune system is made of a number of different types of cells that undertake specific functions. Those that make antibodies are known as 'B cells', and they become active after infection. Once a B cell is activated, it can proliferate into thousands of clones, known as 'plasma cells', which patrol the body and secrete large amounts of antibody to destroy the invader.

Dr Lucinda Berglund and Associate Professor Stuart Tangye, from Sydney's Garvan Institute of Medical Research, are the first to describe a specific molecular process that controls the activation and differentiation of B cells. They used human blood and tissue samples to show that the chemical messaging molecule interleukin 21 (IL-21) activates the STAT3 gene in B cells, which in turn triggers the expression of a molecule known as 'CD25', a cell surface receptor that attracts a second messaging molecule, interleukin 2 (IL-2). IL-21 and IL-2 then work co-operatively to induce plasma cell development and antibody production. Their findings are published in the international journal *Blood*.

"The interesting and informative aspect of this finding for me is that

some people have mutations in the IL-21 receptor, some have mutations in STAT3, while others have mutations in CD25, and they all have B cell defects," said Associate Professor Tangye.

"By examining B cells from people with specific genetic mutations, we revealed that both components of the IL-21 receptor are critical for B cell function – and people can have mutations in either, with equally debilitating effects. We see these effects in patients with X-linked severe combined immunodeficiency, whose impaired response to IL-21 causes severe antibody deficiency."

"Patients with mutations in the STAT3 gene develop Hyper IgE Syndrome, another rare immunodeficiency that manifests as compromised antibody production and greatly depleted immune defences."

Immunodeficiencies arising from mutations in single genes give scientists a unique opportunity to understand B cell signaling, and reveal potential targets for modulating B cell responses in immunodeficiency and autoimmunity.

The current study arose from analysing global gene expression in B cells from healthy people and people with STAT3 deficiency – which immediately highlighted genes that were poorly expressed in disease. The Tangye lab plans to investigate other genes that impact the function of B cells.

More information: bloodjournal.hematologylibrary …
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Provided by Garvan Institute of Medical Research