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GARVAN INSTITUTE

How a single molecule gives our immune systems their memory

While most of us are able to protect ourselves against recurrent infections by making antibodies that will recognise the same invader in the future, people with Hyper IgE Syndrome, a rare immunodeficiency disorder, cannot.

They have what's called a 'functional antibody deficiency', meaning while you can detect antibodies in their blood, those antibodies are not very good at fighting specific diseases, such as tetanus or measles or diphtheria.

It was known that Hyper IgE Syndrome is caused by mutations in the STAT3 gene. By studying the blood cells of people with this disease, Australian scientists have now been able to identify exactly how STAT3 functions inside B cells, the immune cells that make antibodies.

Danielle Avery with Drs Elissa Deenick, Cindy Ma and Stuart Tangye from Sydney's Garvan Institute of Medical Research detail the mechanisms behind STAT3's action in a paper published in the prestigious *Journal of Experimental Medicine*, now online.

"For some time, we've been trying to work out how mutations in STAT3 compromises this important arm of the immune system," said Dr Tangye.

"When you're healthy and you have an immune response, your B cells form two populations of cells to protect you in the future. One population, known as 'plasma cells', are like little antibody factories. They migrate to the bone marrow and pump out antibody. The other population, known as 'memory B cells', circulate around the body, seeking out invaders they recognise."

"You need STAT3 for B cells to become plasma cells or memory B cells – and when you don't have it, you can't respond to vaccinations and you become very vulnerable to infection."

"STAT3 is what's known as a 'transcription factor'. It sits inside a B cell and is activated when a particular molecule binds to its receptor on the cell surface. We have shown in tissue culture that the molecule that drives the action of STAT3 is interleukin 21, or IL-21, which is known to be very efficient at inducing antibody production. Once IL-21 binds to its receptor, STAT3 becomes activated and triggers a cascade of other responses inside the cell."

"This is a very important immune pathway, and understanding exactly how it functions has broad implications for our understanding of the immune system. Too little STAT3 leads to immunodeficiency, while too much probably leads to the development of autoimmune diseases such as lupus, as well as some cancers."

“The dream, of course, for people with Hyper IgE Syndrome and other immunodeficiency disorders, would be to restore the function of STAT3.”
“For those with autoimmune conditions, where the immune system is over activated and the body attacks itself, the goal would be to turn down its function.”

The good news is that drugs are at least in the pipeline to target STAT3.

ABOUT GARVAN

The Garvan Institute of Medical Research was founded in 1963. Initially a research department of St Vincent's Hospital in Sydney, it is now one of Australia's largest medical research institutions with nearly 500 scientists, students and support staff. Garvan’s main research programs are: Cancer, Diabetes & Obesity, Immunology and Inflammation, Osteoporosis and Bone Biology, and Neuroscience. The Garvan’s mission is to make significant contributions to medical science that will change the directions of science and medicine and have major impacts on human health. The outcome of Garvan’s discoveries is the development of better methods of diagnosis, treatment, and ultimately, prevention of disease.

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