



Promising step towards controlling autoimmune diseases

28 July, 2009

When the body's immune response is too robust, it does not stop at attacking invading microbes such as bacteria and viruses. It goes on to attack itself, leading to autoimmune diseases such as rheumatoid arthritis and lupus.

Australian scientists believe they may have identified a master regulator that tips our bodies into autoimmunity when our immune systems overreact, and into immunodeficiency when they underreact.

Understanding the mechanisms involved is a promising step in the development of drugs to dampen a range of autoimmune diseases, which affect about 3% of the population.

Dr Di Yu and Professor Charles Mackay from Sydney's Garvan Institute of Medical Research, in collaboration with Dr Carola Vinuesa from Canberra's John Curtin School of Medical Research, have demonstrated in mice that the gene transcription factor BCL6 determines the body's immune response. Their findings are now published online in the international journal *Immunity*.

The body's B cells make high quality antibodies by mutating in microenvironments known as 'germinal centres' until they produce an antibody that matches an invader, much like a key fits a lock.

But B cells do not act alone. They need the help of another kind of immune cells, T follicular helper (Tfh) cells, which essentially tell them, through chemical signals, whether or not they are heading in the right direction, making the right kind of key to fit the lock.

Postdoctoral researcher Di Yu, who has spent the last few years studying Tfh cells, published two *Nature* papers (2005 and 2007) that showed their hyperactivation can induce autoimmunity.

"We've shown in this study that without BCL6, which modulates the expression of a whole suite of genes, you can't generate Tfh cells," he said.

"Of course, without Tfh cells, B cells can't do their job properly, so can't produce memory cells that protect you against future infections."

"We already know that people who can't produce Tfh cells develop immunodeficiency such as Common Variable Immunodeficiency (CVID). Without Tfh cells, those patients can't produce high affinity antibody-secreting B cells. As a result, they suffer recurrent infections."

"When I was doing my PhD in Canberra, I was working with mice with too many Tfh cells. These mice generated lots of antibodies, but because there were too many T helper cells, any kind of B cell mutation got help, including destructive mutations."

"That resulted in antibodies being produced against the body's own tissue, otherwise known as self-reactive antibodies, or autoantibodies."

"I suspect that the same will apply in humans as in mice, so I am currently collaborating with people working on rheumatoid arthritis and lupus. It will be interesting to see whether the patients with these autoimmune diseases have an aberrant Tfh function."

"If the Tfh cells are hyperactive in humans with autoimmune diseases, it ought to be possible to develop drugs to dampen their activity."

"You would do this by stemming the migration of Tfh cells to germinal centres, by targeting soluble chemical 'factors' or cell surface receptors."

"Scientists have known of the existence of the body's T cells and their various subsets (killer T cells and helper T cells) for over 50 years. This is a major breakthrough that pinpoints the way T cells differentiate into follicular helper T cells."

"We know that these cells can trigger autoimmune diseases, and believe this finding may be instrumental in harnessing them."

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.

MEDIA ENQUIRIES

Alison Heather
Science Communications Manager
Garvan Institute of Medical Research
+61 2 9295 8128
+61 434 071 326
a.heather "at" garvan.org.au