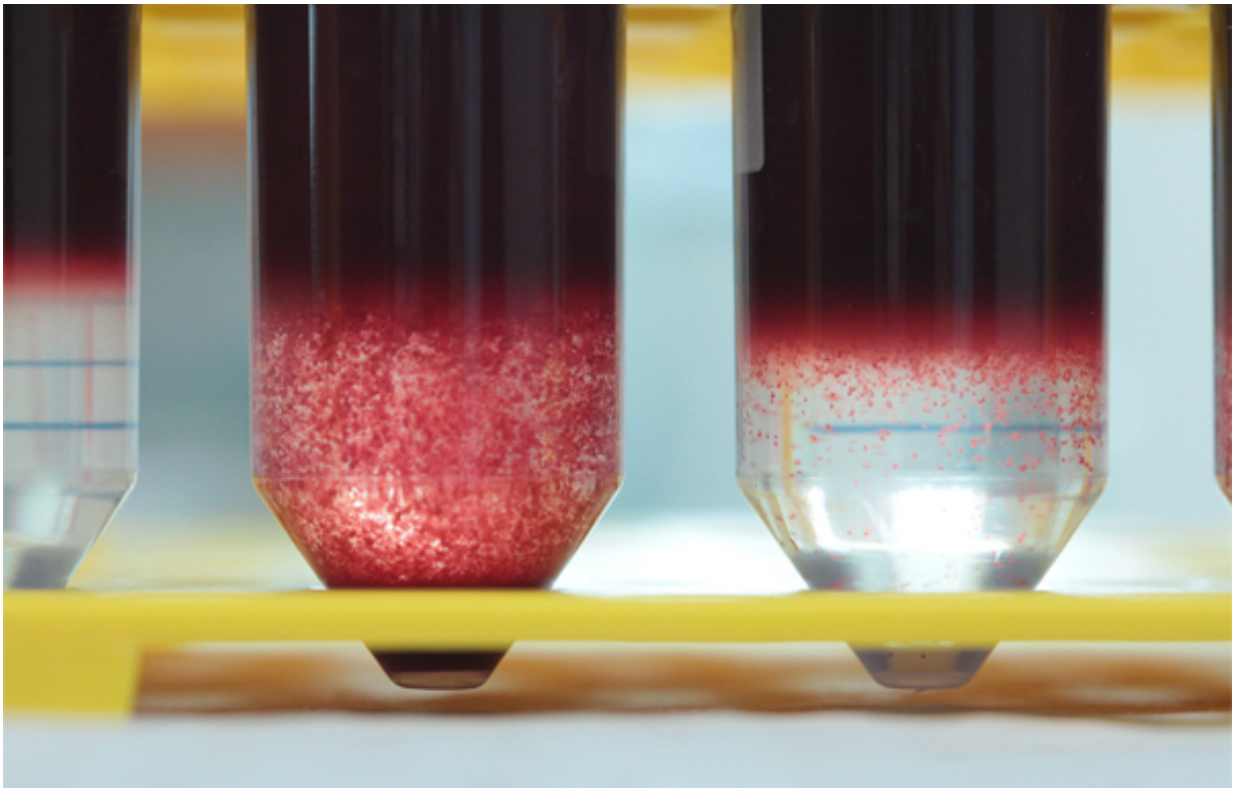


# Insight into how we protect ourselves from certain bacteria and fungi

May 4 2015

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Australian scientists have shown that a specific gene determines the development and function of important cells that bridge the gap between our fast-acting 'innate', and slower-acting 'adaptive', immune systems.

STAT3, as it's known, helps shield us against a variety of fungal and bacterial infections, and understanding its role may help in finding ways to boost our defenses.

Most of us barely give our [immune system](#) a thought, unless we are struck down by disease, or are born with an immunodeficiency that leaves us susceptible to constant attack.

'Primary immunodeficiencies', caused by single gene mutations, allow new insights into the immune system because the symptoms produced suggest specific irregularities in the gene's function and effects.

People with mutations in the STAT3 gene, for example, are prone to bacterial and [fungal infections](#), particularly *Staphylococcus aureus* and *Candida albicans*.

While studying patients with STAT3 mutations, Dr Elissa Deenick and Associate Professor Stuart Tangye from Sydney's Garvan Institute of Medical Research detected fewer numbers of two specific cell types. Next, they determined that the ability of those cells to function properly is greatly impaired.

The cells in question, natural killer T (NKT) cells and mucosal-associated invariant T (MAIT) cells, are unconventional T cells that do not behave like the specialist cells of our 'adaptive' immune system. Instead, these innate-like T cells have evolved to recognise specific pathogens and respond against them very rapidly.

NKT cells have evolved to recognise certain glycolipids, which are present in bacteria such as *Sphingomonas* and *Ehrlichia*.

MAIT cells have evolved to recognise part of a vitamin B metabolite produced by a range of bacteria and fungi.

In healthy people, MAIT cells can produce a very efficient response against any organism that produces the metabolite. They do this by pumping out messaging chemicals known as 'cytokines'. In particular, they produce high levels of Interleukin 17 (IL-17), a cytokine known to be important in dealing with fungal infections.

Patients with STAT3 mutations not only produce considerably fewer MAIT cells than normal, the production of IL-17 by those cells is much reduced. This helps explain why these patients have recurrent candida infections.

Dr Deenick and Associate Professor Tangye not only discovered that mutations in STAT3 reduce the number and quality of MAIT and NKT cells, they also established that the requirement for the gene is intrinsic to those cells.

Remarkably, the researchers were able to investigate parents of STAT3 patients, both of whom had a mixture of normal and mutated cells. In each parent, the normal MAIT and NKT cells survived, but the [mutant cells](#) did not. This demonstrated the cell-intrinsic effect of STAT3. The pioneering discovery is published online today in the prestigious *Journal of Experimental Medicine*.

"The chances of us finding those parents, and therefore being able to demonstrate this cell-intrinsic effect in a human study, are almost ridiculously slim," said Dr Elissa Deenick.

"In immunological terms, MAIT cells represent virgin territory, as so little is known about them. It was only three years ago that groups from Monash and Melbourne Universities discovered the metabolite they recognise."

"This is the first report to identify the STAT3 signaling pathway as non-

redundant for maintenance of NKT and MAIT [cells](#) in healthy people," said Associate Professor Tangye.

"Our next step will be to study them in the context of other infectious diseases.

"In addition to being an important basic science finding, this knowledge expands the disease profile of patients with STAT 3 mutations, and will help in the development of better treatments."

**More information:** MR1 presents microbial vitamin B metabolites to MAIT cells, *Nature* 491, 717–723 (29 November 2012) [DOI: 10.1038/nature11605](#)

Provided by Garvan Institute of Medical Research

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