Bad antibodies made good: The immune system's secret weapon uncovered

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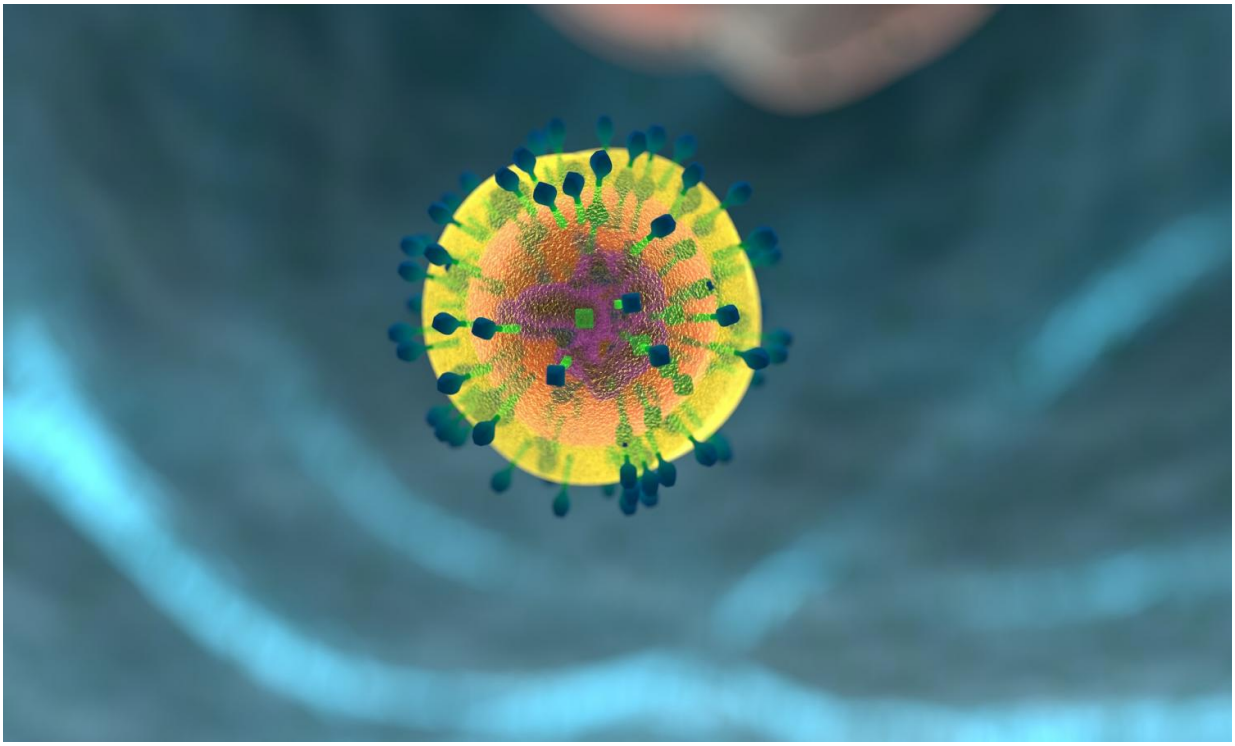

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The 'bad apples' of the immune system are also its secret weapon, according to major Australian research published today in the world-leading journal *Science*.

In a world first, scientists from Sydney's Garvan Institute of Medical

Research have revealed how a population of 'bad' antibodies in the immune system - which are usually 'silenced' because they can harm the body - can provide crucial protection against invading microbes. The research was carried out in mice.

The 'bad' antibodies are known to react against the body's own tissues and can cause autoimmune disease. For this reason, it was once thought that they were discarded by the immune system or that they were made inactive in the long term. However, the new findings show for the first time that 'bad' antibodies go through a rapid 'redemption' process and are activated when the body is faced with a disease threat that other antibodies cannot tackle.

As a result, the 'redeemed' antibodies no longer threaten the body, but instead become powerful weapons to fight disease - and particularly diseases that evade the immune system by disguising themselves to look like normal body tissue.

Professor Chris Goodnow, who co-led the new research with A/Prof Daniel Christ (both Immunology Division, Garvan), says the new findings will fundamentally change thinking about how the immune system protects us.

"We once thought that harmful antibodies were discarded by the body - like a few bad apples in the barrel - and no one had any idea that you could start with a 'bad' antibody and make it good.

"From these new findings, we now know that every antibody is precious when it comes to fighting invading microbes - and this new understanding means that 'bad' antibodies are a valuable resource for the development of vaccines for HIV, and for other diseases that go undercover in the body."

This study was made possible by the generosity of The Bill and Patricia Ritchie Foundation, and through funding from the National Health and Medical Research Council (Australia).

Carrying out the immune system's toughest task

The new research appears to solve an enduring mystery that has puzzled scientists for decades: How does the immune system attack invading microbes that look almost identical to the body's own molecules, without mounting an attack on the body at the same time?

Campylobacter, HIV and others are particularly problematic targets for the immune system because they have evolved to appear almost identical to the body's own molecules; they are 'wolves in sheep's clothing'. This makes it difficult for the immune system to attack them, because it systematically avoids using antibodies that can attack 'self'.

To understand how the immune system recognises these 'wolves in sheep's clothing', scientists from the Garvan Institute zeroed in on a mysterious army of immune cells in the bloodstream.

'Bad' antibodies are hiding inside silenced B cells

The silenced cell army contains millions of immune cells known as B cells - which produce antibodies to fight diseases. Unlike other B cells, though, the cells of this army pose a danger to the body. This is because they can make 'bad' antibodies, which can attack 'self' and cause autoimmune disease. For this reason, they are kept in a long-term silenced state (known as anergy).

Professor Chris Goodnow discovered the silenced cells 30 years ago - and has been working to understand their function ever since.

"The big question about these cells has been why they are there at all, and in such large numbers," says Prof Goodnow. "Why does the body keep these cells, whose antibodies pose a genuine risk to health, instead of destroying them completely, as we once thought?"

The new findings appear to answer that question, showing that selected cells in the army can be reawakened to fight invaders - but only once their 'bad' antibodies are made good.

"We've shown that these silenced cells do have a crucial purpose, says Deborah Burnett, a PhD student at Garvan whose work forms the basis of the study. "Far from 'clogging up' the immune system for no good reason, they're providing weapons—bad apples made good—to fight off invaders whose 'wolf in sheep's clothing tactics make it almost impossible for the other cells of the immune system to fight them."

Three tiny DNA changes turn bad into brilliant

Working with a sophisticated preclinical mouse model, which was developed at Garvan by Prof Rob Brink (Immunology Division) and his team, the researchers showed that the silenced cells can produce antibodies when they encounter an invader that appears highly similar to 'self'.

Crucially, before the cells attack, the antibodies they make are first redeemed through tiny alterations to their DNA sequence. This ensures the antibody that each cell makes no longer attacks 'self', but rapidly becomes a 5000 times more potent weapon against the invading foreigner.

Remarkably, in the model system tested, only three DNA changes were needed to transform antibodies from dangerous cells to effective weapons against disease: a first change to stop the antibody from binding

to 'self', and a further two changes to increase their ability to specifically bind the invader.

At the atomic level, a dimple makes the difference

In experiments conducted at the Australian Synchrotron, the research team showed how the three DNA changes rearrange the tips of the antibody in defined ways, so that it becomes much better at recognising the foreign molecule and worse at recognising 'self'. In particular, the redeemed antibody fits neatly around a nanoscale 'dimple' that is present on the foreign molecule but is absent on self.

"This research has taken us on an exciting journey," says A/Prof Christ. "Not only have we uncovered a new kind of immunity, we've been able to confirm precisely how a bad antibody can be made good.

"Crucially, these redeemed antibodies are by no means a fall-back option. In fact, our findings show the opposite - that antibodies made by tweaking 'bad' antibodies can be even better than those developed through established pathways."

Towards better vaccines

Our findings indicate that theres a whole class of B cells out there - the silenced B cells - that might be accessible for vaccine development, and that we have so far largely ignored, A/Prof Christ says.

Dr Burnett adds, "We're hoping that, instead of ignoring this population of silenced B cells, researchers will in the future consider targeting these cells when they're developing vaccines, particularly against targets such as HIV, which disguise themselves as 'self'."

More information: "Germinal center antibody mutation trajectories are determined by rapid self/foreign discrimination" *Science* (2018). science.sciencemag.org/cgi/doi … 1126/science.aao3859

Provided by Garvan Institute of Medical Research