B cells school gut microbes

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Your immune system's B cells can respond to an amazing number of pathogens—viruses, bacteria, etc.—without ever having encountered them. That's because, as they develop, your B cells reshuffle their antibody-producing genes into an amazing number of possible combinations—more than 100 million—to produce what's called your primary pre-immune B cell repertoire.

It's long been thought that in people and in mice this reshuffling process—called V(D)J recombination, after the B cells' antibody-coding V, D and J gene segments—occurs in two places: the bone marrow and

the spleen.

But new research from a team led by Fredrick Alt and Duane Wesemann at Harvard Medical School and Boston Children's Hospital suggests that there may be one more place B cells go to undergo recombination: the gut. What's more, that reshuffling in the gut may be influenced by the microbes that live there.

Early B cell programming in the gut isn't unheard of; it happens in species as diverse as sheep, rabbits and chickens.

"The B cell gets its name from the fact that it was discovered in chickens in an organ called the bursa," said Alt, HMS Charles A. Janeway Professor of Pediatrics and professor of genetics at Boston Children's. "That organ is in the chicken's gut and is an important training site for the chicken's B cells."

In fact, the presence of B cells in the gut is perfectly normal as well. The lamina propia, a layer of loose connective tissue just underneath the gut surface, is chock-full of mature B cells ready to grab pathogens that try to cross into the bloodstream.

However, while working on the origins of a kind of B cell lymphoma, Alt and Wesemann noticed immature B cells in the lamina propia of young mice. That came as a surprise, as typically only mature, fully grown B cells would be found in the gut.

"They're not mature, they're not producing antibody, why were they there?" Alt asked.

When examined, those immature cells showed evidence of active V(D)J recombination, a sign that their antibody repertoire was becoming more diverse; the cells were gaining the capability to react to more potential

pathogens. What's more, as Alt and Wesemann reported in *Nature*, the repertoire in the lamina propia of these mice differed markedly from that in the bone marrow, suggesting that cells in the two locations were under different influences.

To better understand these influences, Wesemann took young mice that had been raised germ-free and housed some of them with mice from a regular, nonsterile animal facility, allowing their guts to be colonized by microbes from their cage mates. The researchers then compared the level of antibody gene reshuffling in gut B cells from the colonized mice versus the mice that stayed germ-free.

The results: Immature B cells from the colonized mice showed evidence of much more gene reshuffling than those from their germ-free peers, suggesting some kind of interaction between the gut microbes and the young B cells. In addition, the colonized mice had more reshuffling activity in immature B cells in the spleen and bone marrow, reinforcing the notion that gut microbes influence immune cell development throughout the body.

How and why this is happening is still unclear. What signals are the microbes producing? What roles do particular species of bacteria play? No one yet knows the answers to these or other questions, but the age of the mice may be a factor.

"It appears to happen only in a narrow window of time, when young mice are weaning," said Wesemann, who was a senior postdoctoral fellow in the Alt lab and recently became HMS assistant professor of medicine at Brigham and Women's Hospital. "It's a time period when environmental influences could help shape an animal's antibody repertoire."

"There also may be a relationship to allergies or food tolerance,"

Wesemann added.

Since immature B cells also exist in the lamina propia of humans, the same training process he and Alt found in mice could be taking place in us, he said.

The gut microbiome's sway over the immune system—its capability to train immune cells and dampen overreactions—has been a hot topic in recent years. But as Alt explained, much of that work has focused on T cells.

"The findings bring B cells into the picture of how gut microflora influence immune development," Alt said, "but they raise more questions than they answer."

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