Mucosal-surface immune function discoveries could boost vaccine research

14 June 2007

In a finding that could have important implications for HIV vaccine research, new research at Weill Cornell Medical College illuminates the ways in which the body prevents its mucosal surfaces from being overwhelmed by bacteria.

Bacteria, most of them "friendly," appear in huge quantities along the intestinal wall, the mouth, nose and throat, and the anal and urogenital tracts. Now, groundbreaking research at Weill Cornell shows that the epithelial cells that line these mucosal surfaces help guide the immune system's efforts to keep bacteria in check.

"That's a wholly new finding, since most biologists think of epithelial cells as a barrier cell -- not as a highly active player in immune function," explains senior researcher Dr. Andrea Cerutti, associate professor in the Department of Pathology and Laboratory Medicine at Weill Cornell Medical College.

"Armed with this knowledge, perhaps we can harness the mechanisms we've discovered to ward off more dangerous pathogens that use mucosal surfaces as their point of entry into the body -- viruses such as HIV, or rotavirus, the diarrhea pathogen that kills millions of children in poor countries each year," he explains.

His team published their findings in the June issue of *Immunity*.

The new research focused on a type of protective immune system antigen called immunoglobulin A (IgA), which is produced by immune system B cells. In humans, IgA takes two forms -- IgA1 and IgA2.

IgA2, especially, is found in high concentrations along mucosal sites wherever friendly, "commensal" bacteria abound, such as in the intestine where these germs aid in digestion. "Of course, left unchecked, even these bacteria could overrun the gut and cause harm," Dr. Cerutti says. "But somehow the immune system keeps them in balance, giving us the bacteria's benefits with no dangers."

IgA2 is a key player in this balancing act, but since there are many types of IgA antigens, how do local B cells know to produce this variety"

The new cell-culture experiments performed at Weill Cornell solve that riddle. "The answer lies in a surprising place -- the billions of epithelial cells that line the gut, urogenital tract and respiratory mucosa," explains co-lead author Dr. Bing He, an investigator in the Department of Pathology and Laboratory Medicine. Up to now, biologists have typically thought of epithelial cells as merely a tight wall or barrier shielding the body from outside invaders.

"However, our work suggests that these cells also act in an immunological way in the presence of commensal bacteria," Dr. He says. "Using specific receptors on their surface, epithelial cells sense the presence of abundant bacteria and start producing a factor called APRIL. APRIL, a cytokine-signaling chemical, essentially tells nearby B-cells to start producing the IgA2 antigen."

IgA2 helps the immune system keep mucosal bacteria in check. So, as bacteria levels rise, so too do levels of IgA2, dampening the excessive growth of these otherwise helpful bugs.

And there is one more twist to the story.

"We have also discovered that epithelial cells cross-talk with another big immune system player called dendritic cells," says co-first author Dr. Weifeng Xu, another researcher in the Department of Pathology and Laboratory Medicine. Dendritic cells are the body's key immune "sensors" dedicated to spotting possible threats.

"Using another signaling route, epithelial cells in the mucosal lining tell dendritic cells to boost their own production of APRIL. That ratchets up IgA2 production even more," Dr. Xu says.

The bottom line: Epithelial cells in the mucosa appear to be a major new player in the immune defense of these vulnerable surfaces.

"That's really important, because we now want to know how crucial IgA is to the neutralization of HIV, rotavirus or other pathogens," adds Dr. Daniel Knowles, a study co-author and chairman of the Department of Pathology and Laboratory Medicine at Weill Cornell.

Dr. Cerutti agrees that these discoveries are probably just the beginning.

"A better understanding of how the body fights off mucosal pathogens helps us immensely when we try and develop vaccines that target these areas," he explains. "By taking advantages of these mechanisms, we should move that much closer to interventions that shield millions against potentially lethal infections."

Source: New York- Presbyterian Hospital

APA citation: Mucosal-surface immune function discoveries could boost vaccine research (2007, June 14) retrieved 11 October 2022 from https://medicalxpress.com/news/2007-06-mucosal-surface-immune-function-discoveries-boost.html

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