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Cell membrane proteins could provide targets for broader vaccines

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Vaccines with broader reach might be made by stimulating specialized immune cells to recognize foreign cell membrane proteins that are shared across bacterial species, say researchers from Children's Hospital of Pittsburgh of UPMC and the University of Pittsburgh School of Medicine in a report published online today in *Immunity*. The approach could be particularly beneficial in preventing infection by multi-drug resistant organisms.

The genetic heritage of organisms such as oysters, frogs and fish indicate that a family of cell-signaling molecules called interleukin-17 (IL-17) arose in evolution before the advent of T cells, one of the main arms of the immune system in humans. The human IL-17 gene is turned on in a specialized group of immune cells in the T helper-cell lineage, known as Th17 cells, explained senior author Jay K. Kolls, M.D., professor of pediatrics and immunology, Pitt School of Medicine, and vice chair for translational research, Department of Pediatrics, and director, Richard King Mellon Foundation Institute for Pediatric Research, Children's Hospital of Pittsburgh of UPMC.

"That development led us to think that perhaps Th17 cells confer some immunological advantage for eliminating infectious organisms beyond the antibody strategy that we typically employ when we make vaccines," he explained. "We wanted to better understand what role Th17 cells play."

The research team exposed mice to Klebsiella pneumoniae bacteria, a

common cause of lung infection, and re-exposed them several weeks after they recovered from the first pneumonia. They found that the presence of the germ in both instances led to increased numbers of Th17 cells in the lungs and spleen. But when they blocked IL-17, they found the mice still developed immunity to infection. The antibody response, which is controlled by B cells, did not require IL-17 to become established.

Next, they infected mice bred to lack B cells, which make antibodies, with the bacteria. They found that the animals could become immunized against repeat infection as long as IL-17 was unblocked, allowing Th17 cells to develop an immunological memory of the Klebsiella bacteria.

The researchers determined also that while antibodies react to sugar complexes called polysaccharides in the bacterial coat or capsule, Th17 cells respond to protein complexes in the cell membrane. Those proteins, which are integral to the structure of the cell membrane, tend to be similar across bacterial strains, unlike the capsular polysaccharides, which are variable, Dr. Kolls said.

"Some current vaccines require generating a response to a number of these capsular sugars for effective immunization," he said. "An approach that harnesses the stability of the Th17 cell response to common proteins has the potential to simplify vaccination and provide a broader spectrum of coverage. This strategy may be particularly useful against bacteria that have diverse capsular sugars or multi-drug resistant organisms."

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