Research discovers novel mechanism for preventing infection via body's mucosal borders

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Researchers at the La Jolla Institute for Allergy & Immunology have identified a previously unknown mechanism that generates protective immune memory cells to fight recurring infections at the body's mucosal linings – which include the mouth, the intestines, the lungs and other areas. These are the main entry points for many viruses and other infectious organisms. The findings were published online today in the journal *Nature Immunology* and open the door to the creation of new and more effective vaccines based on triggering the newly identified mechanism.

The team, led by Hilde Cheroutre, Ph.D., conducted their experiments in mouse models using *Listeria*, the same bacterial agent now suspected in the death of at least 15 U.S. residents, due to exposure to potentially contaminated cantaloupe.

"It is coincidental that our findings are being published at the same time as this tragic outbreak," said Dr. Cheroutre. "Nonetheless, it points out the need to create a vaccine against *Listeria* and other pathogens that enter the body through mucosal linings, primarily via the oral route," she said. "We are hopeful that our findings will open the door to creating strategies to bring stronger immune memory (cells) to the mucosal borders."

Memory cells are important since they can persist for the life of the

individual and will act rapidly upon encountering the same infection later in life to provide immediate protection. The generation of pre-existing immune memory is the basis for successful vaccination, which works by administering non-dangerous, pathogen-like antigens, which trigger the body to develop immune memory cells that will fight the virus or bacteria if seen again.

Specifically, the researchers discovered that the body has a distinct process for establishing strong immunity at the mucosal borders. They also identified a molecule for showing that mucosal protective immune cells are in place, which is a major finding that could significantly aid researchers worldwide in future vaccine design. The molecule is CD8aa.

"We found a specific mechanism that selectively sorts out the best T cells (CD8aa) to become memory T cells at the (mucosal) border," said Dr. Cheroutre. T cells are the body's infection fighting white blood cells. "The immune system has developed a very ingenuous system to make that selection and to ensure that the ones that reside at the (mucosal) border are the fittest T cells."

The mechanism involves interplay between two related molecules, CD8ab and CD8aa expressed by T lymphocytes, and a molecule expressed on interacting cells including the epithelial cells of the intestine. This molecule distinguishes between CD8ab and CD8aa expressing cells and selects the strongest, most effective T cells (CD8aa and CD8ab expressing), by killing off the weaker T cells (CD8ab expressing only).

Dr. Cheroutre noted boosting immune memory cells at the intestines and other mucosal linings could enable the body to stop various pathogens at their primary entry point. "This is very important since many pathogens enter the body through these areas and begin destroying the tissues and the immune system before T cells in other parts of the body can arrive

and begin fighting," she said.

She said the finding could have special implications for researchers working to develop an AIDS vaccine. "The scientific community has thought that to induce immunity to HIV, we have to activate the immune system with an antigen (similar to HIV) and generate pre-existing anti-HIV memory cells," she said. "What we did not know, was that there is a special mechanism required to selectively send the most effective immune cells to the mucosal border, which is often where pathogens such as HIV or *Listeria* enter the body."

Dr. Cheroutre said currently the protective quality of most vaccines is judged by the robust memory T cell response they induce in the blood and lymph nodes. "We judge vaccines on the strength of proliferation of systemic memory T cells," she said. "But this doesn't necessarily mean we are generating protective immunity in the intestines or at other mucosal borders."

She said the reason vaccines are measured this way is logistical. "Researchers can easily take a blood sample and measure T cell numbers in an individual's blood," she said. "However, we cannot, as a practical matter, measure T cells in the intestines of a living person. So although many vaccines induce effective immune protection, we don't know whether a particular vaccine protects us from viruses and bacteria entering through the mucosal linings because up until now, we didn't have a way to measure pre-existing immunity at mucosal interfaces."

The team found a remedy for that situation by showing that the induction of CD8aa on the immune cells in the blood activated by the vaccine warrants protection at the mucosal borders. "This gives us a means of testing potential vaccines for their protective ability at mucosal borders such as the intestine and other pathogen entry-sites," she said. "Basically, the more CD8aa positive immune effector T cells that are

generated by a vaccine, the better the protection at mucosal borders."

Dr. Cheroutre noted that her finding provides information about the mechanism of action for generating mucosal T cell memory, but it remains to be determined how vaccines can be engineered to induce this valuable mucosal immune memory. "This will be the next step for us and for the broader research community," she said. "To provide an effective vaccine, we need to be able to trigger the body to do what the endogenous immune system is doing – induce high affinity effector T cells and selectively sort out those cells to reside at the mucosal borders."

The finding represents Dr. Cheroutre's second major discovery on immune memory. In 2004, she and her team published a study in *Science*, in which she first identified the precursor cells, those T cells that have the capacity to develop into long-lived immune memory cells to fight recurring infections. Her latest finding is a continuation of that work.

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