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Researchers discover new target for vaccine development in abundant immune cells

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White blood cells called neutrophils, which are the first line of defense against infection, play an unexpected role by boosting antibody production, according to research led by Mount Sinai School of Medicine. The findings suggest neutrophils have multiple roles within the immune system and function at levels previously unknown to the scientific community. The research, published in *Nature Immunology*, provides groundbreaking insight into possible new approaches in vaccine development for blood-borne infections and HIV.

Neutrophils are part of the so-called innate immune system—the immune system encoded at birth that remains unchanged—and are at the front lines defending against infection and inflammation. The research was led by Andrea Cerutti, MD, Professor of Medicine at Mount Sinai School of Medicine, and included an international team of investigators that also involved Irene Puga, PhD, of IMIM-Hospital del Mar in Barcelona, Spain, and Montserrat Cols, PhD, of Mount Sinai.

Researchers evaluated healthy human tissues key to the immune system to assess the abundance of neutrophils in the lymph nodes, tonsils, lymphoid tissue in the intestine, and the spleen. They found very few neutrophils in all areas but one—the region of the spleen called the marginal zone. The spleen is an organ whose primary role is as a filtration system for agents that cause infection and inflammation in the body. Looking more closely at these cells, they found that their role spanned beyond the innate immune system.

According to the study, neutrophils in the marginal zone express two molecules called BAFF and APRIL, which then activate immune cells called B-cells in the adaptive immune system, which is more sophisticated and dynamic than the innate immune system. Neutrophils signal BAFF and APRIL to reprogram B-cells to create different classes of antibodies, allowing the immune system to mount a more potent antibody response.

"Our study is important because we discovered a completely new function in an immune cell that has been studied since immunology research began," said Dr. Cerutti. "The interactivity of the neutrophils in the innate immune system with the B-cells of the more sophisticated adaptive immune system shows that neutrophils operate at a much higher level than previously thought and play a very critical role in mounting a robust response to infection."

Dr. Cerutti's team also evaluated the spleens of people with a condition called neutropenia, which is characterized by a shortage in neutrophils and a compromised immune system, and found that the marginal zones in the spleens of these patients had fewer B-cells and antibodies. This demonstrates the necessity of having neutrophils interact with marginal zone B-cells to generate an innate layer of antibody defense. The fact that the research team found an abundance of neutrophils and marginal zone B-cells in the spleens from healthy individuals, but not neutropenic patients, indicates that these cells are primed and prepared to launch multi-level antibody production in healthy humans, even in the absence of a pathogen.

"Since neutrophils boost and reprogram B-cells to strengthen the immune system regardless of whether there is an infection, we may be able to harness them in vaccine development to enhance immune protection," said Dr. Cerutti. "This has significant promise in vaccinating against blood-borne infections, as B-cells are the first line of defense to

antigens in the circulatory system. If we can improve vaccines with neutrophil-activating agents, we may have a chance to boost B-cell antibody production, and improve immune protection."

With this new knowledge, Dr. Cerutti and his collaborator Meimei Shan, PhD, from Mount Sinai, are evaluating neutrophil activation and B-cell antibody production in rhesus monkeys vaccinated against Simian Immunodeficiency Virus (SIV), or HIV as it occurs in monkeys, using a vaccine that includes a chemical that activates neutrophils.

"Now that we know that neutrophils are important in the release of powerful antibody-inducing molecules, such as BAFF and APRIL, neutrophils become a potential target for protective vaccines against HIV and other infectious agents," said Dr. Cerutti. "The initial results of this SIV study are encouraging and demonstrate the enormous untapped potential of neutrophils in vaccine development."

Ongoing experiments are testing the generation of antibodies to SIV and the activation of neutrophils and B-cells in the blood, spleen, and intestinal and urogenital tracts, which are major sites of SIV/HIV entry. These measurements are conducted in animals vaccinated in the presence or absence of an agent that stimulates neutrophils. Ultimately, the ability of this vaccine to generate protection against SIV will be tested after challenging the vaccinated animals with a live virus.

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