Scientists redefine the role of plasma cells in the immune system

November 30 2010

A team of scientists from The Scripps Research Institute have uncovered a previously unknown regulatory mechanism in the body's response to eliminate pathogens, such as bacteria and viruses. The findings challenge a long-held dogma in the field of immunology and have potential implications for far-ranging topics from how vaccines should be administered to the origin of autoimmunity.

The results of the study, led by Scripps Research Professor Michael McHeyzer-Williams, were published in the December issue of the journal Nature Immunology (Volume 11, Number 12).

The new study focuses on plasma cells, which are a component of the immune system known for producing large quantities of antibodies – targeted disease-fighting proteins. The new study, however, shows plasma cells also act in a negative feedback loop, the end result of which affects the function of other higher-ranking immune cells called follicular helper T cells (TFH).

"These plasma cells are not only capable of secreting highly specialized antibodies, but they are also involved in the regulation of the process that generates the mature immune response," said Nadège Pelletier, a research associate in the McHeyzer-Williams lab and first author of the new paper.

Previous to this work, scientists thought of plasma cells as simple soldiers in the fight against the body's foreign invaders and lacking in the

ability to direct the course of future battles.

Protecting Our Body from Foreign Invaders

The immune system is our body's military, and like a real military it detects and eliminates invaders, pathogens such as bacteria or viruses that are responsible for illness. The immune system must also recognize the body's own "self" cells (civilians) so they are not mistaken for invaders. The immune system has an innate (non-specific) component and an adaptive (specific) component. The adaptive immune system provides the body the ability to recognize and remember specific pathogens. In so doing, it provides immunity and is able to mount a stronger defense upon repeat exposure to the pathogen.

In the McHeyzer-Williams lab, scientists have been focusing on understanding the major events that occur during the immune response, especially the communication and regulation processes involving B cells and helper T cells, two key types of cells in our adaptive immune system.

Helper T cells are unable to kill or fight the antigen directly; they are the "generals" of the adaptive immune system, and like a general they give orders in the form of activating or directing other immune cells to do their jobs. B cells are responsible for fighting the infection. Encounters between TFH cells (a subset of helper T cells specialized in B cell responses) and B cells specific for the same pathogen determine the fate of B cells—either becoming plasma cells (antibody producing factories) during the acute phase of the immune response or producing memory of the pathogen so the body will be much more effective at fighting off the pathogen the next time around.

Acute plasma cells are generated a few days after initial infection and fight the pathogen with specific but low-affinity (loosely binding) antibodies. Memory plasma cells are generated later on and their role is

to prevent re-infection: they secrete specific and very high-affinity (tightly binding) antibodies that circulate throughout the body as sentinels, ready to neutralize the pathogen upon reinfection so that the pathogen is eliminated before the symptoms of illness even occur.

Soldiers Calling the Shots

It is the unusual behavior of these highly efficient and specialized antibody-secreting plasma cells that became the focus of the research presented in the recent paper from the McHeyzer-Williams lab.

In the new study, the group shows that plasma cells not only generate antibodies, but also negatively regulate TFH cell program and function and thus are also involved in the regulation of the immune response. The scientists show that plasma cells achieve this function by acting as an antigen-presenting cell: they will present the antigen (small pieces of the pathogen) to the TFH cells, but instead of inducing T cell activation, proliferation, and function like any other antigen-presenting cell, they repress those features in TFH cells so the immune system keeps its response under control, limiting the production of new plasma cells and focusing on the development of an efficient and mature memory.

"What we show is that the plasma cells are capable of presenting the antigen, like the B cells or dendritic cells would do," said Pelletier, "but unlike professional antigen-presenting cells, by doing so, they are shutting down the production of key follicular helper T cell (TFH) growth factors, reducing their number and function, and making them less available to give help… So the plasma cells, which are the final product of the immune response, act as a sensor to keep the immune response under control."

To prove plasma cells were directly or indirectly limiting TFH cell function, the scientists employed knock-out mouse technology, models

lacking the ability to produce a certain protein. Here, the team showed that in the absence of plasma cells, there was an increase of TFH in the germinal center (a microenvironment of the lymph nodes where specific B cells proliferate, mature, and are selected based on their high-affinity for the antigen). Pelletier notes that limiting the number TFH in the germinal center is essential to select the highest affinity mature B cells.

"In that case, you will have the best immune memory possible," emphasized Pelletier.

Thus, the work has larger implications for the field of vaccination.

Other studies suggest that accumulation of TFH in the germinal center causes it to enlarge and this has been associated with autoimmunity. The scientists caution, however, that at this point further study is necessary before drawing conclusions about plasma cells' role in constraining autoreactivity and consequently autoimmune diseases.

More information: www.nature.com/ni/journal/vaop … ent/abs/ni.1954.html

Provided by The Scripps Research Institute