

Featured Article

Natural killer cells are made, not born First evidence of immune cell's activation potential in infection, tumor control

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Call it the immune system's version of nature versus nurture.

For years, scientists regarded natural killer cells as a blunt instrument of the body's immune defense system. Born to kill, these cells were thought to travel straight from the bone marrow, where they are manufactured, to the blood, circulating there and infiltrating the sites of early tumors or infectious agents in the body.

Now, Rockefeller University scientists, led by Christian Münz, Ph.D., have learned otherwise. Natural killer cells, Münz and his colleagues say, have to be nurtured. Their ability to destroy tumor and infected cells is not present at birth.

This new insight paves the road to changes in bone marrow and stem cell transplant procedures and will enable scientists to pursue research into activating natural killer cells to help the body fight emerging infections and tumors.

In two separate papers in the February issue of *The Journal of Immunology*, Münz, postdoctoral associate Guido Ferlazzo, Ph.D., and their colleagues show that natural killer cells accumulate mostly in "secondary lymphoid tissues" - the tonsils, lymph nodes and spleen - after emerging from the bone marrow. There, the natural killer cells await activation (probably after stimulation by sentinel dendritic cells) before they react in two distinct modes. In one mode, they promptly secrete cytokines, chemical messenger proteins, which modulate emerging T and B immune cell responses. In the other, they become potent killers of tumors and virus-infected cells. While natural killer cells do provide a crucial first defense against many infectious agents and tumor cells, they do so with more discrimination than raw determination.

"Natural killer cells burst forth from the the tonsils, lymph nodes and spleen, and destroy infected and cancerous cells while the immune system's T and B cells are still mobilizing," says Münz. "Without natural killer cells, threatening conditions can get a strong foothold before the adaptive immune response kicks in."

Leading oncologists treating human leukemias and lymphomas already track natural killer cell activities after bone marrow and stem cell transplants. James Young, M.D., a researcher at Rockefeller's neighboring Memorial Sloan-Kettering Cancer Center's Allogeneic Bone Marrow and Stem Cell Transplant Service, is one of them. "The emerging data on the activation of natural killer cells, their distinct functions in the body and their cellular targets, are helping to move the study of natural killer cells in transplantation and cancer from conjecture to sound hypotheses," he says.

The findings by Münz and his colleagues not only explain why a natural killer burst is important - the burst likely results from mobilization of natural killer cells from lymphoid tissues, and these activated immune cells are discriminating enough to recognize, through a full repertoire of surface receptors, virus-infected and tumor cells - it also affirms a potential strategic change in bone marrow or stem cell donor matching.

Bone marrow donors are selected based on the similarity of their white blood cell profiles: the closer the match to the patient, the better. But that's likely less important when doctors can harness the donor's natural killer cells to fight both residual cancer cells and residual immune system cells of the patient. Certain mismatches between donor and recipient can actually encourage the donor's natural killer cells to deliver an extra punch to the cancer and the threatening graft-versus-host disease, the updated logic goes.

Münz and his colleagues did not develop the bone marrow donor match strategy, but part of their aim in understanding where and how natural killers hang out, was to determine how the cells are recruited to combat cancer and other emerging diseases in the body. The Rockefeller scientists are in close contact with clinicians interested in tailoring immune cells - such as natural killers - in treating human leukemias.

The current Journal of Immunology publications also contribute to strategies for dealing with the viral menace known as Epstein-Barr virus, a member of the herpes family of viruses. Though most infections are latent, active Epstein-Barr is the source of infectious mononucleosis in many teenagers.

Epstein-Barr also is a human cancer-causing virus. The virus hijacks the immune system's B cells in an elaborate chemical signaling mimicry of normal B cells. The result often is B cell tumors like Hodgkin's disease and Burkitt's lymphoma. Münz and his colleagues know that the natural killer cell response, or burst, is important in establishing immune control against the cancer causing Epstein-Barr virus.

"We have seen that Epstein-Barr virus transformation of B cells can be delayed by a strong natural killer cell burst," says Münz. "Now we are studying how this herpes virus may be targeted by natural killer cell responses." By learning both what molecular signals activate natural killer cells in their dialogue with dendritic cells and how viruses can be targeted by natural killer cells, Münz and his colleagues may be able to artificially stimulate natural killer cells to heighten their effect and ward off emerging Epstein-Barr virus associated malignancies.

"We're trying to get a sum of all signals that activate natural killer cells against viruses and tumors and do not cause harm to healthy human tissues," says Münz. "In the past five years, we've learned enough about these cells to extend hopes of their eventual usefulness in medical treatments."

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