Natural Born Killers: NK Cells Drafted Into the Cancer Fight

Once thought of as foot soldiers in the body’s fight against cancer, natural killer (NK) cells are more akin to special forces in bolstering the immune system to respond to foreign invaders. New studies are revealing that rather than randomly killing cells—as was thought for many years—NK cells are programmed to seek out specific targets on cancer cells.

“For the past 25 years, we have been so preoccupied with understanding B and T cells. We thought the other cells were nonspecific,” said Lewis Lanier, Ph.D., professor of microbiology and immunology at the University of California at San Francisco. “That was extremely naive and an oversimplification. … We are finding out natural killer cells are not so nonspecific, but quite sophisticated.”

The immune system is made up of a series of highly choreographed white blood cells that interact with each other to mount an attack against invaders, such as viruses and tumors. B cells secrete antibodies or proteins that recognize and attach to foreign substances, such as a virus or bacterium, or antigens on cancer cells. Each type of B cell makes one specific antibody that attaches to one specific antigen, marking it for destruction by other immune cells. T cells directly attack infected, foreign, or cancerous cells. They too have to recognize a specific antigen before attacking.

In contrast, NK cells produce powerful chemical substances that bind to and kill target cells. B and T cells
could not do their jobs as efficiently if it weren’t for the NK cells. NK cells can immediately spot faulty cells and kill them or at least can keep them at bay until the B cells and T cells can finish the job.

“Natural killer cells are the first protection,” said Porunelloor A. Mathew, Ph.D., associate professor of molecular biology and immunology at the University of North Texas Health Science Center in Fort Worth. “In order for cancer to grow, it has to escape the first defense. We have been focusing on natural killer cells because the actual mechanisms of how they work are not yet known completely. We believe once we have complete knowledge of how natural killer cells function, we will be able use them more efficiently.”

**Many Receptors**

The sophistication of NK cells lies in the fact that they have numerous surface receptors that bind to molecules on the surface of cancer cells. It is the interplay between the receptors and the ligands, or molecules they recognize, on target cells that determines whether NK cells will be activated to kill that cell.

“NK cells have a number of different receptors that are capable of recognizing a number of different targets,” said Wayne M. Yokoyama, M.D., a Howard Hughes Medical Institute investigator and chief of rheumatology at Washington University in St. Louis. “What appears to happen is, because NK cells have so many different receptors, it means larger portions of the NK cell pool can respond to any given insult or target ligand. They are poised to respond very quickly.”

Scientists have identified the role of a few such receptors, but researchers suspect there could be many more, Yokoyama said. What they respond to and how they differentiate between tumor and normal cells remains a mystery.

Researchers do know that these receptors can be classified in two groups: activation and inhibitory receptors. Whether NK cells are activated to kill or not depends on the molecule major histocompatibility complex I (MHC-I), which is present on most normal cells. When a virus infects a cell or when it becomes cancerous, the MHC-I molecule will present a small peptide on its surface that signals the T cell, another crucial weapon in the body’s immune response, to kill it. But some cancer cells have craftily developed a way to downregulate the expression of MHC-I so that it does not show the peptide on its surface. Viruses can also do this to infected cells. “In either case, the peptide cannot be presented, so the T cell is blind to the tumor cell or virus infection,” Yokoyama said.

This is when the NK cells bounce into action. It “sees” that MHC-I has been downregulated, but if the cell also expresses ligands for the activation receptor, it is still activated to kill the cancer or virus-infected cell. But some cancer cells have evolved to get around this, too. For example, they may secrete a molecule called a transforming growth factor (TGF), which inhibits the function of T cells and NK cells, Mathew said.

“In those people who get cancer, there is nothing wrong with their natural killer cells or T cells,” he said. “The reason they get cancer is because the cancer cells have found some trick to escape killing from natural killer cells and T cells.”

**Harnessing the Response**

Because of this versatility of the NK cells, researchers are focused on understanding NK cell signaling and figuring out how to harness their unique killing power to treat cancer.

A recent study found that NK cells accumulate in two different locations, secondary lymphoid tissues—such as the tonsils, lymph nodes and spleen—and peripheral blood. The NK cells in the secondary lymphoid tissue behave differently from the ones in the blood in that they are activated by dendritic cells and then secrete cytokines such as interferon. Cytokines are proteins that act as chemical messengers, signaling other immune cells to respond. These particular NK cell–secreted cytokines stimulate a more efficient killing response by the T cells. The NK cells in the blood attack tumors there, such as leukemia and lymphomas, explained Christian Münz, Ph.D., assistant professor of viral immunobiology at Rockefeller University in New York, who published these results in the February issue of the *Journal of Immunology*.

“We want to identify the exact mechanistic signals that allow natural killer cells to help make a better T-cell response,” he said. This is critical because, as quick and determined as they are, NK cells often cannot kill all cancer cells in a body. They become overwhelmed and need the T and B cells to go after the cancer.

**NK Cells on Trial**

Scientists hope that understanding these signals will lead to therapies that can use the body’s immune system to kill cancer cells. That was the theory behind a recent clinical trial of a combination of the laboratory-manufactured version of the cytokine interleukin 2 (IL-2) and the monoclonal antibody rituximab. Researchers at Chiron Corp. in Emeryville, Calif., were trying to determine if IL-2 could increase the population of NK cells available to kill rituximab-coated cancer cells.

Patients with advanced-stage non-Hodgkin lymphoma who were treated with IL-2 and rituximab had a rapid increase in their NK cell numbers. The NK cells recognized the antibody-coated cancer cells and destroyed them. Some patients’ tumors shrank 25% to 50% percent, and some tumors disappeared completely.

Researchers also found that in some patients, the binding between the NK receptor and the antibody was less efficient because the receptor was mutated. Most likely, this hampered the NK cells’ ability to kill the cancer and...
meant these patients needed more NK cells, explained Stephen Dilly, M.D., senior vice president for biopharmaceutical development at Chiron.

Chiron’s next trial will include 300 patients with early-stage non-Hodgkin lymphoma, comparing those who receive rituximab alone with those who receive rituximab with IL-2. This trial builds upon research conducted in the 1980s that found if human blood was mixed with IL-2 in the test tube, activated NK cells grew out. When IL-2 was injected back into the patient, tumors disappeared in some cases, Yokoyama said. This looked like a promising therapy, but IL-2 was too toxic at the doses used.

“But in principle, it showed the proof of concept,” he said. “We now know more about receptors. It is possible that we could arm the natural killer cells better, come up with some other agent to stimulate the natural killer cells that wouldn’t be so toxic, and downregulate MHC-I on the tumor, or enhance the expression of ligands on cancer cells so that the natural killer activation receptors could be turned on.”

Mathew envisions using NK cells as part of an integrated approach to cancer therapy—particularly relapse caused by metastasis. Surgery, chemotherapy, and radiation are often used to destroy cancer cells, but some of the cells escape and start growing in different parts of the body. NK cells could be employed to stop this spread, Mathew explained.

“NK cells have so many receptors,” he said. “Eventually, we would like to target all of these receptors on NK cells. We believe by targeting all receptors, we will be able to kill cancer 100%. But this is … a long-term objective.”

—Leslie Harris O’Hanlon