

Some of your body's cells have a 'license to kill'

February 22 2009, By Robert S. Boyd

Millions of "natural killer cells" -- nature's first line of defense against cancer, viruses and other infectious microbes --- are on constant patrol inside your body.

These tiny assassins, the immune system's rapid-response team, can quickly spot a dangerous cell, poke holes in its outer wall and release poisons to destroy it. They also alert other immune cells to join the attack.

Despite their forbidding name, natural killer cells are the good guys in the never-ending war against disease.

Like some espionage agents, NK cells have a "license to kill," according to Wayne Yokoyama, an immunologist with the Howard Hughes Medical Institute at Washington University in St. Louis. The "license" is a molecular tag that allows a killer cell to whack a bad cell.

Although NK cells were discovered more than 30 years ago, they're still not well understood, and they remain an active field of research. Scientists are trying to figure out how killer cells "see" a target cell, how they tell whether it's infected or healthy and how they carry out their lethal task.

"We remain puzzled about where and when NK cells develop," James Di Santo, the director of the immunology department at the Institut Pasteur in Paris, acknowledged in the journal *Nature Immunology*. "We still have

many questions."

"We have gained only a partial understanding of how NK cells recognize a target cell as friend or foe," Michael Caligiuri, a professor of cancer research at Ohio State University, wrote in the journal *Blood*.

Caligiuri said researchers hope "the immune system can be engineered to cure some forms of cancer." Other potential targets for possible vaccines, treatments or cures are HIV, viruses that cause hepatitis and herpes, and various bacteria, fungi and parasites.

Some patients received NK cells in preliminary clinical trials in the 1980s, but the tests were abandoned, partly because of toxic side effects.

"We're still in early stages," Yokoyama said. "As we know more about how they work, we'll do better."

Recent advances in NK research include:

- The discovery by Yokoyama and other scientists that NK cells can "remember" a previous infection and respond more rapidly to a second attack.

"Once they've been activated, they can respond more easily and effectively to the next call for activation," Yokoyama wrote in the Jan. 30 issue of the *Proceedings of the National Academy of Sciences*.

- A possible method to make NK cells even more deadly executioners.

Andre Veillette, a cancer researcher at the Clinical Research Institute of Montreal, has identified a molecule, named CRACC, on the surface of NK cells that he said "augments their ability to kill abnormal cells."

A drug that stimulates CRACC would "increase their killer function," Veillette said.

NK cells are being generated constantly in bone marrow. They prowl through the blood and lymph systems, searching for signs of infected or cancerous cells. When they find one, they latch on to it and attempt to execute it, leaving nearby healthy cells alone.

If an NK cell can't find a certain protein complex, called MHC-1, which is normally on the surface of a target cell, the target is doomed. If the protein is present, however, the diseased cell is spared.

This ability to distinguish between friend and enemy "ensures that NK cells effectively carry out their surveillance function by leaving most cells undisturbed while being ready to destroy cells that are diseased," Di Santo said.

Another strength of NK cells is their quickness. "NK cells are able to deliver a response immediately after recognizing specific signals from molecules of foreign origin," said Jordan Orange, an immunologist at the University of Pennsylvania.

Other parts of the immune system, so-called B and T cells, are more numerous and powerful than NK cells but slower to react to an infection.

"It takes many days for that to happen," Yokoyama said. "NK cells, though there are less of them, can initiate a large response very early."

"More work is required to realize the dream of harnessing NK cell-based therapies in the clinic," Di Santo said. "Ultimately, we can hope that unraveling the mysteries of how these (NK cells) function will have an impact on human disease therapies."

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