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Licensing to Kill

Marauding immune cells called natural killer (NK) cells, which attack and kill invaders and spew inflammatory substances called cytokines, need to be “licensed” to properly carry out their work, researchers have found. Ironically, they said that their discovery of how these cells mature explains how they are trained not to attack the body's own tissues.

The researchers, including Howard Hughes Medical Institute investigator Wayne M. Yokoyama, published their findings in the August 4, 2005, issue of the journal *Nature*. The other senior author was Ted Hansen, Yokoyama's colleague at the Washington University School of Medicine in St. Louis.

A major question in immunology, said Yokoyama, has been how NK cells develop their tolerance for the body's own tissues, known simply as “self.” It was known that proteins on the surface of self cells prevent NK cells from attacking them. These proteins, known as major histocompatibility complex (MHC) class I molecules, plug into inhibitory receptors on the surface of NK cells, rendering them unable to attack self. Molecules that plug into receptors in this way are known as ligands.

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- Wayne M. Yokoyama

The genes for the MHC proteins and the NK cell receptors are inherited independently from one another, and can vary widely. Until now, researchers had not understood how coordination of the two sets of highly variable, or polymorphic, components developed as NK cells became functional. “The conundrum was, how is it possible that you have receptors that are highly polymorphic recognizing highly polymorphic ligands?” said Yokoyama.

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Even stranger, said Yokoyama, is that mice bred to lack MHC class I molecules do not behave as if NK cells had “gone wild,” destroying tissues as might be expected. Such destruction also does not occur in the rare humans who lack MHC molecules.

To explore the possibility of a matching process that enables NK cells to become functional, Yokoyama and his colleagues studied a mouse developed by the Hansen laboratory. Normally, individuals express many different MHC class I molecules consisting of conglomerations of multiple proteins produced by multiple genes. To simplify their studies, Hansen and his colleagues produced the functional equivalent of a complete MHC class I molecule using only a single gene. This enabled them to engineer entire MHC class I molecules into mouse cells by inserting only that gene. Since the mouse cells had been engineered to otherwise lack expression of all other MHC class I genes, this allowed them to precisely test how a single MHC class I molecule affected the development of NK cells.

The researchers' studies yielded the surprising finding that developing NK cells are induced to become functional by a “two-faced” receptor on their surface. In mature, functioning NK cells, this receptor, called Ly49, is an inhibitory receptor. But this same receptor plays an activating, or licensing, role in enabling immature NK cells to develop into functioning, self-tolerant cells. “So, paradoxically, this inhibitory receptor confers a positive result with respect to maturation into functional NK cells,” said Yokoyama.

The licensing concept might explain differences in response among human patients with hepatitis C infections, explained Yokoyama. “This virus in many individuals causes a chronic long-lasting infection of several decades,” he said. “In other individuals, though, the virus seems to be controlled and eradicated.” The difference, he said, could be that people who clear the virus have “better licensed” NK cells that mount a better response to the virus. Findings of some immunological and genetic studies in humans with hepatitis C have been consistent with such a concept, he noted.

Licensing might also explain why donor NK cells given to leukemia patients during bone marrow transplantation as treatment do not always have an anti-tumor effect, said Yokoyama. While clinicians have expected that the donor NK cells would attack leukemic cells as being “non-self,” in some situations the outcome does not come out as expected, “perhaps because licensing needs to be considered,” he said.

According to Yokoyama, further studies in his laboratory aim not only at understanding the molecular details of licensing, but also developing immunological tests to determine if licensing can be used to predict successful eradication of viral infections or anti-leukemia effects.