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## New Form of Immune System



**Image Title:** None - Laboratory of Max Cooper, published in *Nature*, 08 July 2004, (Vol. 430, No. 6996)

The sea lamprey, best known in North America as an invasive predator of fish in the Great Lakes, possesses a primordial immune system quite unlike that found in higher animals, Howard Hughes Medical Institute researchers have discovered. The finding invites speculation that this ancient immune system might have survived in higher organisms, including humans.

The researchers, led by Howard Hughes Medical Institute investigator Max Cooper, described their findings in the July 8, 2004, issue of the journal *Nature*. Cooper, Zeev Pancer and their colleagues at the University of Alabama at Birmingham collaborated on the studies with Chris Amemiya from Benaroya Institute at Virginia Mason in Seattle.

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Cooper said he and his colleagues were intrigued by the sea lamprey's immune system because it had been reported to have adaptive immune responses and to possess cells that resemble the immune-system lymphocytes of higher organisms. The sea lamprey and the hagfish are jawless vertebrates that are more primitive than jawed vertebrates and are the only surviving descendants from the earliest evolution of vertebrates.

The scientists' initial studies of the lamprey lymphocyte-like cells were somewhat disappointing because they did not reveal any of the immunoglobulin and T-cell receptor genes that underlie the immune systems of higher animals. These genes come in segments that can be rearranged to create a massive number of unique receptor proteins that are expressed on the surface of immune cells and serve to recognize protein antigens on invaders such as bacteria and viruses.

Since the researchers could not find any of the usual immune-system genes in the lamprey lymphocyte-like cells, they proceeded to search for genes that are activated when the lamprey immune system is challenged by a foreign invader.

"Since the earlier studies suggested that lampreys could respond to antigens, we decided if there really were cells in the animals that were capable of specific immune responses, we should try to catch them in the act," said Cooper.

To stimulate the lampreys' immune cells, the researchers exposed lamprey larvae to a "cocktail" of antigens and plant mitogens that could stimulate lymphocyte division. The researchers then found that lamprey cells in the bloodstream responded by enlarging and proliferating much like lymphocytes in higher organisms.

To isolate the genes that were being expressed, the researchers created a library of genes used by the activated lymphocytes, and "subtracted" from that library the genes that were active in red blood cells and non-lymphoid types of white blood cells. What resulted was a set of genes encoding proteins that the researchers named variable lymphocyte receptors (VLRs). Cooper said the VLR proteins consist of various combinations of segments called leucine rich repeats (LRRs), along with a "stalk" region that attaches the arc-shaped protein to the surface of the lamprey lymphocytes.

The researchers next searched for the regions, or loci, on the lamprey chromosomes that harbored the VLR genes. "The second big surprise was that we found only a single VLR locus, not multiple ones," said Cooper. "And this locus contained only one VLR gene that is incomplete." The incomplete gene is surrounded by gene segments for LRR sequences and, in lymphocytes, "these flanking LRR cassettes are somehow stitched into the incomplete VLR gene to make a mature VLR gene," he said. "That's similar

to the way antibody genes and T-cell receptor genes are created in our lymphocytes, but the lamprey VLR gene uses different types of cassettes that are rearranged by a different process. In both cases it's an efficient way of using building blocks to put together a large number of variable lymphocyte receptors, but using very different modular units. Lampreys use LRRs, and we use immunoglobulin segments.”

Cooper noted that both plants and animals use LRRs as components of invariant receptors that recognize common determinants on pathogens, but these receptors are encoded by single non-rearranging genes. The lamprey represents the first animal in which we know that LRR gene rearrangements are used to form adaptive immune system proteins, said Cooper.

“It looks as if nature experimented with different ways to build highly diverse receptors to use for anticipatory systems to recognize potential pathogens,” said Cooper. “And nature invented the LRR rearrangement system before the one that we use was invented.”

One question that intrigues Cooper and his collaborators is whether the lamprey's ancient immune system might have survived in jawed vertebrates, and possibly even humans.

“It seems unlikely that nature would have generated such a complicated system and then quickly thrown it away,” Cooper said. “So, we are looking in higher organisms to see how long this variable system lasted in evolution. It's also possible that these variable lymphocyte receptors could be used for the same practical purposes as antibodies—to recognize a variety of different antigens and pathogens. They could even have advantages over antibodies in that they may be less easily denatured,” he said. A lot of uses for VLRS can be imagined, but these will have to be verified experimentally.