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Evolution of innate immunity

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A new type of highly variable lymphocyte receptor discovered in the lamprey suggests two distinct evolutionary strategies to generate receptor diversity in vertebrates, according to a Nature paper this week (*Nature* 2004, **430:**174-180).

The discovery, by Zeev Pancer and Max D. Cooper at the University of Alabama at Birmingham, shows that evolutionarily diverse vertebrates have a similar fundamental strategy of somatic rearrangement of germline receptor units to combat infectious disease.

The fundamentals are similar across species, but in jawed vertebrates, diversity is generated by joining gene segments in the immunoglobulin and T-cell receptor gene loci, while in the sea lamprey *Petromyzon marinus* (a jawless vertebrate), the Alabama team found a completely different set of molecules that mediate adaptive immunity - with a completely different molecular structure and molecular architecture.

"After more than 40 years of evidence of adaptive immunity in agnathans [jawless fish], we found the molecules," Pancer told us. "It's no wonder that for so many years it was a big mystery," he added, "because everyone until now more or less linked adaptive immunity with rearranging immunoglobulin genes, as it is from sharks up to man."

Experts are uncertain whether the findings illustrate convergent evolution. Pancer believes that at the lamprey level, this is not yet convergent evolution but merely a continuation of the usage of a very ancient motif - the leucine rich repeat - that is conserved in man, invertebrates, and plants.

Max D. Cooper, coauthor of the paper, also believes in the common ancestor idea. "I think the strategy of using the kind of building blocks like toll and toll-like receptors and other innate immune receptors was used by many different organisms, but with a single gene," Cooper told us.

Cooper fully anticipates that the mechanism will be present in hagfish as well, and the authors had 'hints' that it will still be present going forward into the jawed vertebrates, although he did not know how far. "I would imagine that since every living thing on the planet uses this kind of building block, these leucine rich repeat sequences, for defense, that having the ability to vary them within an individual would give that individual a huge advantage in going into different environments and dealing with different pathogens. That's our speculation."

Martin F. Flajnik, who wrote an accompanying News and Views article, believes there may be evidence for convergent evolution. "I think they [Pancer et al.] would like to say the genes that were used, and the mechanism, [evolved] by convergence; but maybe the transcriptional control - the way that you only express one per lymphocyte - that may be something that goes back to the common ancestor," Flajnik, professor in the Department of Microbiology and Immunology at the University of Maryland, explained.

"If you want to resolve that issue, you need to have information from other species," Masanori Kasahara, at the Graduate University for Advanced Studies (Sokendai) Japan told us. The question of the switch in jawed vertebrates to a novel receptor that uses immunoglobulin-like domains can also only

be answered by acquiring information from other animals, said Kasahara, who wasn't involved in the study.

"In order to have a system like this where you just express one type of receptor per cell, you've got to have millions of lymphocytes to make it worthwhile, and lampreys are big, I guess... but for a small animal, it wouldn't make any sense to have this type of adaptive immune system," said Flajnik. "I think any animal that lives for a long time, or is complex, is going to try to come up with an adaptive immune system."

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