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## Ancient "Jumping DNA" May Have Evolved into Key Component of Human Immune System

The human immune system, an elegant and intricate biological defense system unmatched in most life forms, may have evolved from a mobile piece of DNA that inserted itself into the mammalian genome more than 450 million years ago.

A team of researchers led by David G. Schatz at the Howard Hughes Medical Institute at Yale University has found evidence that tiny gene particles vital to the task of producing millions of different kinds of antibodies act like a gene segment that can "jump" into foreign DNA. Although there are many examples of such genes in lower organisms, it is the first cut-and-paste "transposase" ever found in humans.

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An adaptive immune system relies on two lines of defense to detect and destroy invaders. Both parts of the immune system belong to a class of white blood cells called lymphocytes, found in the blood and lymphoid organs. B lymphocytes produce antibodies that bind tightly to a foreign molecule, inactivating it or marking it for destruction by other cells in the immune system. T lymphocytes detect the presence of foreign molecules inside special "processing" cells once those cells have displayed a fragment of the foreign molecule—those pieces are called antigens—on the processing cell's

surface. So-called T-cell receptors on the surface of the T lymphocyte bind strongly to the antigen.

Although they perform different functions, both B and T lymphocytes use the same unique genetic mechanism to economically generate an almost unlimited number of antibodies and T-cell receptors. Indeed, the human immune system is capable of producing a larger number of different antibodies and receptors than there are numbers of genes in the entire human genome. To accomplish this feat, the immune system uses a smaller number of gene segments that can be shuffled and joined to one another to produce many distinct combinations. Each recombination essentially produces a new gene, and provides an almost infinite database of genetic information from which to generate antibodies and T-cell receptors.

This system of genetic recombination is at the heart of Schatz's study. Two closely linked genes, RAG1 and RAG2 (for recombination-activating genes 1 and 2), code for proteins that promote this genetic recombination. The Schatz team has found that RAG1 and RAG2 work together as a transposase, an enzyme that snips pieces of DNA out of one location in a chromosome and transposes these pieces elsewhere. This ability to slice and recombine genes accounts for the "split nature" of antibody and T-cell receptor gene DNA, allowing vertebrates to create millions of different antibodies and T-cell receptors from a limited number of genes, Schatz believes.

Schatz's team and other research groups have explored the genomes of a variety of vertebrates for the presence of RAG1 and RAG2 and have found these two genes in all jawed vertebrates examined thus far. All of these species possess immune systems that use genetic recombination. However, jawless hagfish and lamprey, which lie just below the jawed vertebrates on the evolutionary tree and do not possess the system of B and T lymphocytes, lack RAG1 and RAG2 or any close relatives of these genes. Based on these findings, Schatz and his colleagues suggest that the RAG transposase must have acted something like a virus, inserting itself into the genome of jawed vertebrates after that lineage split from its jawless relatives approximately 450 million years ago.

"No other genes in mammals are split up like this and then recombined at the DNA level," Schatz says. He cautions, however, that although the researchers have shown transpositional activity *in vitro*, they have not proven it works that way in the human body. The RAG genes now may just work to slice and connect pieces of genes without inserting the excised piece of DNA in a different location.

"One question we are interested in now is to understand why RAG1 and RAG2 may have once functioned as a [more general] transposase, but don't now. What has changed?" Schatz says. "Has the body found a way of suppressing their ability to insert genes elsewhere in the genome? That would make sense, because moving your DNA around that way randomly could kill you."