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RESEARCH NEWS

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Researchers Identify Avian Counterpart to Mammalian Antibody Receptor

Howard Hughes Medical Institute (HHMI) researchers have isolated a protein receptor in chickens that is responsible for transferring antibodies from mother to offspring - a function critical to bestowing a temporary immunity that protects the young against infection until their own immune systems begin functioning.

The receptor molecule is a functional counterpart to one found in mammals, including humans, that also attaches to antibodies and transfers them to offspring. In the case of humans, the antibodies pass through the placenta before birth. In chickens, they are passed to embryos across the yolk sac membrane of the egg.

> "Studies investigating these questions could yield insights into the evolution of the vertebrate adaptive immune system."
> **— Pamela J. Bjorkman**

The researchers were surprised to find, however, that although the mammalian and chicken receptors play the same basic role, their structures were unique, revealing different evolutionary routes to the same function. According to the researchers, the discovery raises intriguing questions about how the chicken receptor functions and its relationship to similar proteins in mammals.

Led by HHMI investigator Pamela J. Bjorkman at the California Institute of Technology, the researchers published their findings in the May 2004 issue of the journal *Immunity* .

In their studies, the researchers sought to isolate the avian counterpart of the receptor called FcRn (the neonatal Fc receptor), which in mammals transfers the antibody immunoglobulin G (IgG) from mother to offspring. FcRn bears an intriguing structural resemblance to molecules called major histocompatibility complex (MHC) proteins, which function in the vertebrate adaptive immune response by presenting antigenic peptides to T cells.

Previous studies had indicated that the avian antibody immunoglobulin Y (IgY) was transferred from hens to chicks by a receptor, but its relationship to MHC molecules had not been investigated.

“In the sense that this receptor was moving IgY, which is the counterpart of IgG in mammals, it sounded like it was the avian equivalent of FcRn,” said Bjorkman. “But all that had been shown previously was that there was an IgY binding activity on yolk sacs. Nobody had purified or characterized the protein.”

To isolate the avian receptor, the researchers exploited the fact that, as is also the case for IgG binding to FcRn, the IgY antibody tends to attach to its receptor under slightly acidic conditions, and to release from the receptor under slightly basic conditions. The researchers knew they could carry out a relatively straightforward isolation of the FcRY receptor by passing a solution of yolk sacs through a separation column containing IgY under acid conditions—causing the receptor to stick to the IgY. Then they could use a flow of more basic liquid to flush out only the IgY-binding protein.

“When we did that, it was absolutely pure and clean,” said Bjorkman. “There was nothing else there.” Thus, she said, they knew immediately that they had likely identified the receptor responsible for IgY transport to chicks. Further studies of the protein showed that it had the appropriate binding properties to IgY.

According to Bjorkman, the newly isolated chicken receptor protein, which she and her colleagues have named FcRY, has raised more questions than it has answered. For example, their studies showed that avian FcRY, unlike mammalian FcRn, uses multiple domains to bind to its antibody, changing its conformation in the process. “The fact that you need all of these binding domains is something we still don't quite understand, and the observed pH-dependent conformational change is quite different from what happens in mammalian FcRn, where a chemical titration controls binding,” said Bjorkman.

Another mystery, said Bjorkman, is that the FcRY receptor does not resemble FcRn structurally, but more closely resembles an entirely different, poorly understood mammalian protein called the phospholipase A2 receptor, which is found in muscle. “This is something we don't understand at all,” said Bjorkman. “It's completely unexpected.” Nor is it certain that chickens also have a functional counterpart to the phospholipase A2 receptor, she said.

More research will be needed to understand the significance of the relationship of FcRY and FcRn to their respective homologs: phospholipase receptors and MHC molecules. MHC molecules recognize and present foreign proteins, such as those from invading bacteria, to immune system T cells to trigger their action. “Although molecules such as FcRn do function in the immune system, in that they transport immunoglobulin, they certainly don't present antigens to T cell receptors, the primary function of MHC proteins,” said Bjorkman. She said studies investigating these questions could yield insights into the evolution of the vertebrate adaptive immune system.