Neuroimmunology Sits on Broad Research Base

"Until recently neuroimmunology was just a series of little clubs," says Cedric Raine of Albert Einstein College of Medicine in New York. "There were the myasthenia gravis people, the developmental neurobiology people, the multiple sclerosis people, the geneticists, the peripheral nerve group, and so on. They all went their own ways without much cross-talk." Then in 1981 the Journal of Neuroimmunology *came into existence, and in 1982 neuroimmunologists held their first international conference with 150 attendees. At a recent meeting in Philadelphia* the group numbered more than 600, and participants voted to form their own society with Raine as the first president.*

Today many neuroimmunologists study how cells of the nervous and immune system interact by using tissue culture and animals as experimental systems and are just beginning to define these phenomena in humans. New results on genetics, cell-cell interactions, and cellular responses to factors and antibodies—interactions that are biologically intertwined—dominated the recent meeting.

Linking Immune Response Genes to Disease

Researchers who study genetics and its relation to neuroimmunological disease focus on genes of the major histocompatibility complex (MHC) that control immune responses. MHC genes code for sugar-containing protein molecules known as class I and class II antigens. Most cells outside the central nervous system (CNS) express class I antigens on their surface, but only a small group of cells found mostly in the blood express class II antigens. These proteins are important for immune system function because most T lymphocytes respond only to foreign antigens—from a virus, for example—if another cell presents the MHC and foreign antigen together.

Jay Berzofsky of the National Cancer Institute in Bethesda, Maryland, has new evidence that cells that present foreign antigens to T lymphocytes do so in a particular way. After the presenting cell takes a foreign antigen inside itself, processing enzymes often cut the protein into pieces. But the purpose of this processing is not simply to make the protein smaller as researchers once thought. Instead, antigen is processed so that the resulting peptide has two faces. According to Berzofsky, this molecular dual nature, or amphipathicity, may allow one half of the peptide to interact with the MHC antigen of the presenting cell and the other half to interact with the appropriate antigen receptor on responding T lymphocytes.

In a related discussion, Lawrence Samelson of the National Institute of Child Health and Human Development in Bethesda reported that the membrane receptors on T cells that bind to processed antigen are even more complex than had been realized previously. He finds that about 90% of mouse T cell receptors, which are very similar to their human counterparts, are composed of seven different subunits and the other 10% have nine subcomponents. Furthermore, when antigen binds to this receptor complex, certain protein chains are phosphorylated at different amino acids—serine residues on the *gamma* subunit and tyrosine residues on the *eta* subunit—by different enzymes. What all of this means in terms of T cell antigen receptor function still remains to be determined.

Samelson also notes that the structure of the T lymphocyte antigen receptor is somewhat reminiscent of the structure of the acetylcholine receptor found on some nerve and muscle cells. If this structural analogy translates into similar function, then some subunits of the T cell receptor may help to form a membrane pore that allows ions to pass into the lymphocyte and activate it.

Other researchers are studying the relation between MHC genes and susceptibility to certain neuroimmunological diseases such as multiple sclerosis and myasthenia gravis. But many are intrigued by a recently described link between MHC genes and narcolepsy, an abnormal sleeping behavior.

According to Takeo Juji of the Tokyo University School of Medicine in Japan, narcoleptics spontaneously nap during the day, typically for about 20-minute periods. They can be easily awakened by touching or speaking, and amphetamine-derived stimulants can prevent their daytime sleeping.

What researchers now find especially interesting is that genes of the MHC locus are in some way associated with a human behavior. Just how that occurs is something that Juji and his colleagues are trying to understand. In 1983 they reported that two class II gene loci, DR2 and DQW1, are associated with narcolepsy. Other researchers have since identified narcolepsy patients who lack the DR2 gene, which calls into question how often the MHC genes and the abnormal sleeping behavior are really associated. Now, however, Juji says he has identified another genetic marker located within the MHC region that occurs in 100% of narcoleptic patients tested.

Juji qualifies the relation of MHC genes to narcolepsy. "The hypothesis that class II antigens *cause* narcolepsy is unreasonable," he says. "But a gene that is closely linked to DR2 and DQW1 may cause the disorder." Such a gene has yet to be identified.

Varying Influences on Cell-Cell Interactions

Many cell-cell interactions, a second research area in neuroimmunology, depend on immune response genes. But other factors often modify cellular interactions within the nervous system.

Alain Prochiantz of the Collége de France in Paris and his co-workers find that astrocytes, nonneuronal cells of the CNS, regulate the kind of fiberlike process that a growing nerve cell sends out. Astrocytes cultured from the rodent mesencephalon (midbrain) cause neurons obtained from the same brain region to extend two kinds of processes—dendrites and axons. But astrocytes from a different part of the brain, the striatum, do not support dendritic outgrowth from midbrain neurons.

The brain origin of the astrocytes seems to control "the speed of dendritic outgrowth," rather than the presence or absence of new dendrites, says Prochiantz. Astrocytes from the mesencephalon secrete a specific glycoprotein that he believes may affect the initiation sites for dendrites and somehow control their rate of outgrowth.

Other researchers investigate how cell-cell interactions and MHC antigens participate in diseases such as multiple sclerosis (MS). In an interview with *Science*, Raine said that under certain conditions brain endothelial cells, which line blood vessels and make up the walls of capillaries, express Ia antigens, a category of class II antigens. "Endothelial cells do not normally express Ia antigens," Raine says. "But in multiple sclerosis they

*The "Second International Congress of Neuroimmunology," held in Philadelphia, Pennsylvania, from 8 to 11 September, was sponsored by the New York Academy of Sciences.

do." This may help to explain why patients with MS show periods of remission and worsening disease.

In MS, cells of the immune system invade the CNS—both the brain and spinal cord—and destroy myelin, a white fatty material that surrounds nerve fibers. As a result, MS patients may experience double vision, numbness or weakness in the arms and legs, and bladder control problems.

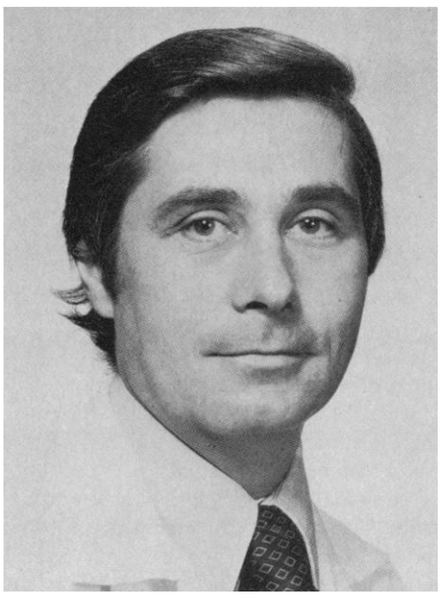
Normally, blood cells do no enter the CNS. But in MS the blood-brain barrier becomes leaky and lymphocytes may enter the brain and spinal cord and trigger a complex series of reactions. "Activated T cells release factors, including histamine-like substances, which may open up the blood-brain barrier and allow the T cells to pass through," says Ute Traugott, also of Albert Einstein. Then, astrocytes, which lie close to capillary endothelial cells, can also be activated to express Ia antigens.

Astrocyte and endothelial cell expression of Ia antigen can further enhance the immune response and draw macrophages into the brain. "Macrophages attack the myelin," Traugott says. "And as soon as you have myelin damage, you have release of myelin components such as myelin basic protein. Then you can have a second wave of disease and progressive growth of the demyelinating lesion." Researchers have observed these events in mice and rats with a disease that resembles MS, and they propose that similar phenomena occur in patients with multiple sclerosis.

Chemical Factors May Alter Disease Course

Still unanswered is why the immune response rages unchecked in patients with severe MS. Barry Arnason of the University of Chicago in Illinois and his colleagues utilize a third approach in neuroimmunology—namely, studies of factors that are secreted from cells—to study MS. Their new data point to a possible defect in nervous system regulation of immune responses.

Many neurologists believe that patients with MS progress to severe disease after a major stress. Normally stress activates nerve cells of the sympathetic nervous system (SNS), which are linearly arranged outside the spinal cord and which control many vital body functions such as heart rate, blood vessel diameter, and glandular secretion. The sympathetic nervous system also seems to regulate the activity of T suppressor lymphocytes, which normally dampen immune responses and keep them in check. But in MS patients the immune system attacks CNS tissue, which can be fatal.



Barry Arnason *reports changes in sympathetic nervous system function and T suppressor cells in patients with severe multiple sclerosis.*

This presents a paradox, however. Normally stress activates T suppressor cells and dampens the immune response. But in MS patients the opposite seems to occur. Arnason's new data extend the findings of others and indicate that the sympathetic nervous system is biologically linked to the activity of T suppressor cells through β receptors. Neurobiologists have known for many years that β receptors are on neurons and other types of cells types that are stimulated by the sympathetic nervous system, and more recent data indicate that T suppressor cells have similar receptors.

Other researchers showed that destruction of the SNS in animals causes an increased number of β receptors on lymphocytes. And in their previous work, Arnason and his colleagues found that T suppressor cells have about three times as many β receptors as other kinds of T cells. Now, Arnason, Anthony Reder, Margaret Brown, and Ricardo Maselli, also of the University of Chicago, find that the number of β receptors on T suppressor cells is increased in patients with MS.

Arnason is cautious about interpreting these data and also his group's observation that patients with MS often show abnormal sympathetic nervous system function. His working hypothesis is that a specific region of demyelination that affects sympathetic neurons may act as "a strategic hit in the nervous system" in patients with MS. This might lead to a decreased stimulation of T suppressor cells and an overactive immmune response that then leads to more demyelination and worse disease, says Arnason.

Adriano Fontana of University Hospital in Zurich, Switzerland, describes another kind of interaction between the nervous and immune systems that is controlled, at least in part, by a soluble factor. He and Erhart Hofer of Sandoz find that glioblastoma cells in culture release a factor that blocks T cell responses. "We first reported in 1984 that these brain tumors release a factor that inhibits interleukin-2 effects," he says.

Normally, interleukin-2 (IL-2), which is secreted by activated T cells, stimulates T lymphocytes to multiply and express specific marker proteins. But in the presence of the glioblastoma factor, T cells do not respond to IL-2 that researchers add to the culture. Whether similar events occur in vivo has not yet been determined. Fontana and his coworkers have now cloned and sequenced the entire T cell suppressive factor, which resembles transforming growth factor β, and they should be able to determine whether it is present in patients with brain tumors who are also immunosuppressed.

Only recently have T cells themselves been found to secrete factors that affect nervous system function. "The role of T cell secretion has been underemphasized," says Raine.

New results presented at the recent meeting indicate that researchers are now trying to identify specific effects that T cell products have on the nervous system. It is an area of some controversy. For example, Robert Knobler of Jefferson Medical College in Philadelphia, Pennsylvania, and his coworkers find that IL-2 decreases the proliferation of rat oligodendrocytes, the cells in the brain and spinal cord that make myelin. In contrast, Jean Merril of the University of California at Los Angeles and her co-workers have reported that IL-2 increases oligodendrocyte proliferation. Nevertheless, Knobler thinks that IL-2 suppression of oligodendrocyte proliferation may help to explain why these cells fail to remyelinate nerve fibers in patients with MS. Raine says that there are many articles citing oligodendrocyte proliferation around areas of demyelination in MS patients, but the permanence and functional significance of these areas is not known.

Raine and Krzysztof Selmaj of the Medical Academy of Lodz in Poland report that another factor from cells of the immune system also affects CNS tissue. Tumor necrosis factor (TNF), which is secreted from macrophages in vivo, causes specific structural changes in myelin when the researchers add it to myelinated nerve fibers in vitro. The in vivo action of TNF on myelin remains to be determined. ■

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