Hunting for the Complicated Mechanisms Behind Multiple Sclerosis

by Joel Schwarz

Like in so many medical mysteries, all of the suspects that may be involved in causing multiple sclerosis (MS) have yet to be identified leaving potential points of therapeutic interventions undiscovered. Among the investigators doggedly pursuing many of these avenues is Joan Goverman, Ph.D., whose recent work suggests how a common virus could trigger an autoimmune response in a subset of people genetically predisposed to develop MS. Goverman, who is chair and professor of the Department of Immunology at the University of Washington and a Center on Human Development and Disability research affiliate, and her colleagues also have discovered that there are critical differences in how inflammation is regulated in different regions of the central nervous system. “Where a lesion occurs is important because the locations have different clinical effects. The brain, spinal cord and optical nerve also have different environments so the treatment varies with the location of the injury,” she said.

More than a million people around the world have MS, and it primarily affects young adults between the ages of 20 and 45. However, children as young as three and adults in their 70s have contracted the disease. MS is caused when immune cells attack the layer of lipid, or fat, called myelin that functions as insulation for axons that connect neurons to each other. Axons protrude from the ends of neurons and transmit electrical impulses from one neuron to the next. Myelin sheaths these axons and allows the electrical impulses to travel quickly, essentially “jumping” along the axon. In MS, the breakdown of myelin causes the transmission of these impulses to slow down and be blocked, which causes the neurological disability seen in MS patients. Axons that are stripped of their myelin for long periods of time become broken, and this damage cannot be repaired. “As myelin is destroyed and broken axons accumulate, the brain begins to atrophy and the damage is irreversible,” said Goverman. What triggers these processes and finding ways of preventing and treating them are the medical questions that she and other researchers are trying to answer.

In a recently published study, Goverman’s lab proposed a novel mechanism for how a common virus may help trigger MS in at least a subset of patients. “There are clearly environmental factors, possibly including pathogens, for which people have been hunting for decades. Most recently, the Epstein Barr virus has been implicated in susceptibility to MS. But 90 percent of people have been infected with this virus, so it is hard to explain why only a small number of people get MS. We know that there is a collection of genes that confer susceptibility to MS, and our hypothesis is that a small number of people...”
carrying these genes also have the bad luck of having T lymphocytes that can recognize a virus and also recognize a part of the myelin sheath. T lymphocytes are cells that recognize pieces of pathogens called antigens and initiate an immune response that neutralizes or kills the pathogen. Usually, T cells express only one T cell receptor (called a TCR) that recognizes only one antigen. However, some T cells can express two TCRs and recognize two different antigens. If one of these antigens is derived from a virus and one from the myelin sheath, then the viral infection could activate a T cell by triggering one TCR and the T cells could then attack myelin using the other TCR and inadvertently trigger MS.

The low probability that a T cell will express a TCR specific for a pathogen and for a myelin antigen could be what makes MS rare,” she said. The “dual TCR” T cells that the Goverman lab discovered using an animal model of MS are expressed on T cells that exhibit killing activity and express a protein called CD8. Other T cells help orchestrate the immune response and are called “helper T cells” and express a protein called CD4. Both types of cells are found in MS, and in the future Goverman wants to find out if CD4+ cells attract CD8+ cells and if the presence of CD4+ cells makes MS worse.

This research is the first to report a mechanism for triggering an autoimmune disease that depends on the expression of dual TCRs. “This could explain the element of chance that seems to be part of the environmental influence that contributes to developing autoimmunity, and gives us a novel research direction in which to go,” said Goverman. “With MS we need to look at how many T cells can be found that recognize two antigens.”

In the long run, Goverman wants to look at MS patients and see if there are multiple pathways leading to the disease. “MS is a heterogeneous disease both clinically and pathologically, and we need to define the different pathogenic pathways that ultimately lead to demyelination and axonal loss. There may be 10 different pathways to get MS and each pathway may have five different steps. There also might be different combinations of pathways that are linked. Ultimately we need a way of stratifying patients so we can find a way to match up damage, clinical signs and the biomarkers that fit each pathway to MS,” she said.

Stratification of patients also could lead to more effective, targeted therapies. “The cost of testing new drugs is becoming prohibitive because so many drugs fail in clinical trials. Interferon-beta is a frontline treatment for MS, yet less than 50 percent of patients respond to this treatment. Many drugs fail in trials because patients are grouped together as all having the same disease when in reality different pathways are leading to similar symptoms. Even though a new drug might be very effective in one subset of patients, if it is not effective in most patients that were grouped together, it looks like it failed. We have no way of finding the appropriate population to test unless we know how to stratify patients." In addition, Goverman believes some therapies developed to treat other autoimmune conditions might be useful with MS. “In the last five years some medicines developed to treat cancer have also been effective in multiple autoimmune diseases, including MS. The reason for this is that different autoimmune diseases may share common immune mechanisms and these commonalities allow drugs to be effective in different diseases,” she said.