New tools in fight against virus that attacks the brain

November 18 2014, by Mark Michaud

Credit: Human Brain Project

Researchers have developed new insight into a rare but deadly brain infection, called progressive multifocal leukoencephalopathy (PML). This disease – which is caused by the JC virus – is most frequently found in people with suppressed immune systems and, until now, scientists have had no effective way to study it or test new

treatments.

"The JC virus is an example of an infection that specifically targets glia, the brain's support cells," said neurologist Steve Goldman, M.D., Ph.D., co-director of University of Rochester Center for Translational Neuromedicine and senior author of the paper. "Because this virus only infects human glia and not brain cells in other species, it has eluded our efforts to better understand this disease. To get around this problem, we have developed a new mouse model that allows us to study human glia in live animals."

The JC virus is so common that it is estimated that 70 to 90 percent of all Americans have been exposed to it, and may carry it in a dormant form. For the vast majority of these people, the virus will never become infective or trigger any disease in their lifetimes.

However, in some individuals with compromised immune systems – either because of a disease or from taking immunosuppressive drugs – the virus can become active and eventually make its way into the brain. Once there, the virus can trigger PML, an almost uniformly fatal infection of the white matter of the brain.

PML was first seen in leukemia and lymphoma patients in the 1950's and 1960's, but became more common during the AIDS epidemic in the 1980's, prior to the widespread use of antiretroviral treatments. More recently, it has been increasingly observed in individuals undergoing long-term immunosuppressive treatments for autoimmune diseases like multiple sclerosis.

Until now, it has been almost impossible to study the progression of disease or test new therapies, because the virus only attacks a specific human brain cell type called glia. It does not affect glia cells in mice or in any other animals commonly used to investigate disease mechanisms,

making its study difficult.

Glia consists of two main categories of cells: astrocytes, the brain's primary support cells, and oligodendrocytes, the source of myelin, the fatty tissue of the white matter that insulates nerve fibers in the brain.

The new discovery – which appears today in the *Journal of Clinical Investigation* – was the result of research using a new tool developed at the University of Rochester. Last year, Goldman and Maiken Nedergaard, M.D., D.M.Sc., reported that they had created a mouse model whose brains consisted of both animal neurons and human glia cells. While the previous study focused on the fact that the human cells essentially made the mice smarter, at the same time it created a powerful new platform for researchers to study human glial cells in live adult animals, including diseases that impact these cells.

Previously, scientists believed that the JC virus attacked and killed oligodendrocytes, thereby destroying the brain's ability to produce myelin. This conclusion had been reached because autopsies and MRI scans of people with PML revealed loss of the brain's white matter, which is primarily comprised of myelin.

Using the new animal model, Goldman and his team were able to track the impact of the JC virus infection as it unfolded in real time. They observed that the initial target of the virus was, in fact, astrocytes and, to a lesser extent, glial progenitor cells, the cells that give rise to astrocytes and oligodendrocytes. The astrocytes serve as hosts for the virus to replicate and mutate, to the point where the cells literally explode and spread the infection in a chain reaction-like pattern.

Because astrocytes play an important support role, as they die off other cells – including oligodendrocytes – are affected. The virus does eventually infect and kill oligodendrocytes once the viral load in the

brain reaches a tipping point, but these cells are not responsible for spreading the disease in the brain. Once oligodendrocytes begin to die off, myelin is lost, and since glial progenitor cells are also targeted by the virus, the brain loses its ability to replenish the lost myelin.

"We have been looking at the wrong cell population," said Goldman. "Astrocytes seem to be the main target of the virus, and oligodendrocytes are essentially innocent bystanders caught in the crossfire."

These findings now enable researchers to focus on potential new ways to identify the early symptoms of the disease, as well as to develop new therapies. For example, patients who develop PML often complain of confusion and other cognitive problems, long before white matter loss prompts a clinical diagnosis. Goldman speculates that this may be the result of the early loss of astrocytes, which are known to help coordinate signal transmission in the brain. The new mouse model also allows researchers to test new therapies that specifically target infected astrocytes, while protecting their uninfected neighbors.

Provided by University of Rochester Medical Center