MedicalXpress

Team finds connection in pathogenesis of neurological diseases, HIV

February 4 2014

A new study by George Washington University (GW) researcher Michael Bukrinsky, M.D., Ph.D., shows similarities in the pathogenesis of prion disease—misfolded proteins that can lead to neurological diseases—and the HIV virus.

The research, published in the *Journal of Biological Chemistry*, looks at the relationship between cholesterol metabolism and prion infection as a follow-up to previous research on the relationship between cholesterol metabolism and HIV. Bukrinsky, a professor of microbiology, immunology, and tropical medicine at the GW School of Medicine and Health Sciences, and his research team found a striking relationship between impairment of cellular cholesterol transporter ABCA1 and the conversion of prion into the pathological form, which occurs in lipid rafts – the membrane domains of neuronal cells.

"The effect of prions on ABCA1 and lipid rafts is very similar to what we found with HIV before, suggesting that while prions and viruses are very different, they seem to target the same cellular mechanism of cholesterol metabolism," said Bukrinsky. "This mechanism may be key to controlling many different diseases. It may be that drugs that stimulate ABCA1 can help not only to target prions and HIV, but also a number of other pathogens."

Under normal circumstances, an abundance of ABCA1 limits the number of lipid rafts – and vice versa. With prions, the opposite effect takes place. During the conversion of prions into a pathogenic form, an

abundance of ABCA1 in cells increases, but so does the amount of lipid rafts. The reason for this paradox is that ABCA1 in prion-infected cells is non-functional. The researchers found that ABCA1 was displaced from the plasma membrane and from lipid rafts by prions and was internalized, inhibiting its function. Stimulation of ABCA1 with drugs inhibited conversion of prions from non-pathogenic to pathogenic form, reducing the number of lipid rafts in the cell, and opening the possibility of treating prion disease with these drugs.

Bukrinsky and his research team also found that when cells are loaded with cholesterol, it likewise counteracts this effect of prions on ABCA1 and lipid metabolism in a cell. While in most circumstances having lots of lipids and fats in one's diet is not recommended, this finding suggests that being loaded with fat actually stops the conversion of prions from the non-pathogenic to pathogenic form. Neuronal cells loaded with lipids are actually less prone to becoming susceptible to prion disease. "This isn't a recommendation as we are talking about a very specific cell type and under special circumstances," said Bukrinsky, "but it's an interesting possibility."

More information: The paper, titled "Prion Infection Impairs Cholesterol Metabolism in Neuronal Cells" is available online at www.jbc.org/content/early/2013 … M113.535807.abstract

Provided by George Washington University