Medical Xpress

Link found between environment, genetics in triggering multiple sclerosis

May 31 2011

Environmental and inherited risk factors associated with multiple sclerosis – previously poorly understood and not known to be connected – converge to alter a critical cellular function linked to the chronic neurologic disease, researchers with the UC Irvine Multiple Sclerosis Research Center have discovered.

The findings, which appear in the online, open-access journal *Nature Communications*, suggest that a unifying mechanism may be responsible for multiple sclerosis and point to therapies personalized according to genetic factors.

"MS results from complex interactions between an individual's genetics and his or her environment," said study leader Dr. Michael Demetriou, a UCI neurologist and associate director of the Multiple Sclerosis Research Center. "Defining how these come together to induce the disease is critical for developing a cure. We've taken a giant first step toward understanding this."

Using blood samples from about 13,000 people, Demetriou and colleagues identified the way environmental factors – including metabolism and vitamin D3, obtained through either sunlight exposure or diet – interact with four genes (interleukin-7 receptor-alpha, interleukin-2 receptor-alpha, MGAT1 and CTLA-4) to affect how specific sugars are added to proteins regulating the disease.

Earlier work on mice by Demetriou revealed that changes in the addition

of these specific sugars to proteins engender a spontaneous MS-like disease. They also found that N-acetylglucosamine (GlcNAc), a dietary supplement and simple sugar related to glucosamine, is able to suppress this process.

The current research shows that both vitamin D3 and GlcNAc can reverse the effects of four human MS genetic factors and restore the normal addition of sugars to proteins. "This suggests that oral vitamin D3 and GlcNAc may serve as the first therapy for MS that directly targets an underlying defect promoting disease," Demetriou said.

Virtually all proteins on the surface of cells, including immune and nervous system cells, are modified with complex sugars of variable lengths and composition. This adds information to proteins separate from that directly defined by the genome. The sugars interact with specific sugar-binding proteins on the cell, forming a molecular lattice that controls the clustering, signaling and surface expression of critical receptors and transporters, such as the T cell receptor and CTLA-4. Reducing sugar modification weakens the lattice and enhances growth and activity of immune system T cells in such a way that they increase neural degeneration – a hallmark of MS.

Production of the complex sugars is regulated by both metabolic and enzymatic functions, the latter altered by genetic MS risk factors and vitamin D3. Demetriou pointed out that the MGAT1 genetic variant linked to MS increases or decreases the sugars attached to proteins depending on metabolism – one possible explanation for why people with the same genetic risk factor may or may not develop MS.

These sugars have also been implicated in many other chronic diseases, such as diabetes and cancer, Demetriou added, so this work could open up entirely new areas of medicine.