Recent News

Increasing Protein Synthesis by Leucine Ameliorates Synaptopathy Caused by Dementia, ALS and Autism

Dr. Yi-Ping Hsueh, Research Fellow at the Institute of Molecular Biology, Academia Sinica, has found that increasing protein synthesis has a beneficial effect on synapses, the information exchange sites between neurons. Increasing protein synthesis by adding leucine supplement ameliorates synapse defects, they found. Such supplementation may be a simple and safe method for potential therapies for this novel pathogenic mechanism that is involved in multiple neurological disorders, including dementia, amyotrophic lateral sclerosis (Lou Gehrigs disease), autism and spastic paraplegia. The work was published in Nature Communications on March 17, 2016.

Synapses are subcellular neuronal structures through which neurons communicate with other neurons or target cells. They are critical for neural functions. Many neurological disorders result in synaptic defects and thus impair brain activities. Dr. Hsueh's previous work published in the Journal of Clinical Investigation (2011) demonstrated that valosin-containing protein (VCP), encoded by a causative gene for frontotemporal dementia, amyotrophic lateral sclerosis and autism, controls the synapse density of neurons. However, how VCP controls synapse formation and density was unclear. In the current study, Dr. Hsueh and her student found that endoplasmic reticulum (ER) formation is the critical event downstream of VCP in controlling synapse formation. The ER is a fine mesh membrane structure that is distributed over entire cells. It is a key structure for protein synthesis, including membrane, secreted and cytosolic proteins. In VCP-deficient neurons, protein synthesis efficiency is significantly impaired. Since proper protein synthesis is needed for synaptic growth, turnover and activity, reduced protein synthesis efficiency caused by VCP deficiency thus results in synaptic defects. This "ER-protein synthesis" model explains the pathogenic mechanism of VCP-related disorders.

To further evaluate the “ER-protein synthesis” model, Dr. Hsueh and her student further performed two sets of experiments. First, in addition to VCP, other ER regulators also control protein synthesis. One of them is Atlastin 1, a causative gene in Spastic paraplegia. Therefore the “ER-protein synthesis” model seems to apply to multiple neurological disorders. Second, adding extra leucine to the culture medium that is known to enhance protein synthesis effectively increases synapse density of neurons carrying VCP and Atlastin 1 mutations. This study reveals a novel pathogenic mechanism of neurological disorders and suggests a simple and safe therapy for these disorders.

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The full article entitled “VCP and ATL1 regulate endoplasmic reticulum and protein synthesis for dendritic spine formation” is available at Nature Communications website at: http://www.nature.com/ncomms/2016/160317/ncomms11020/full/ncomms11020.html