Unraveling how prion proteins move along axons in the brain

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Researchers at the University of California, San Diego School of Medicine have identified the motors that move non-infectious prion proteins (PrPC) - found within many mammalian cells - up and down long, neuronal transport pathways. Identifying normal movement mechanisms of PrPC may help researchers understand the spread of infectious prions within and between neurons to reach the brain, and aid in development of therapies to halt the transport.

Their study is published in the February 18 edition of the journal *Cell*.

The small prion protein is found in the cell membrane of brain neurons. The misfolded or infectious form of this protein (also called "scrapie"), is responsible for "mad cow" disease and has also been implicated in Creutzfeldt-Jakob disease in humans. Non-infectious and scrapie forms interact to produce disease; so, in order to help uncover how the infection is spread within and among neuron cells to the brain, the UCSD scientists studied the movement mechanism of normal PrPC in mouse neuronal cells.

"Our work unraveling the normal mechanism of movement of this prion protein will help us understand how the devastating pathogenic versions found in mad cow disease and other prion diseases are formed and transmitted in the brain. Intriguingly, our work may also shed light on what goes wrong in other neurodegenerative diseases such as Alzheimer's disease," said principal investigator Larry Goldstein, PhD, professor of Cellular and Molecular Medicine, Howard Hughes Medical

Institute investigator and director of the UC San Diego Stem Cell Program.

It is known that normal prion proteins and infectious prions need to interact in order for prion pathogenesis to occur, though not how or why these interactions occur. Discovering the transport mechanisms of prions is one key to the puzzle of how the two types of proteins interact, and an important question in transport regulation has been how motor activity is controlled in cells.

The prion protein cargo travels on long microtubule tracks along the peripheral and central nervous system nerves toward the terminus, or synapse, in membrane-bound sacs called vesicles. Intracellular transport is often bi-directional, because cargoes regularly reverse their course en route to their final destinations.

The researchers identified the motors driving these vesicles as anterograde Kinesin-1 - which moves only toward the synapse - and dynein, which is retrograde, moving away from the synapse. These two motor proteins assemble on the PrPC vesicles to "walk" them back and forth along the microtubules.

Secondly, they discovered that the back and forth cargo movement is modulated by regulatory factors, rather than by any structural changes to the motor-cargo associations. The study data show that the activity of Kinesin-1 and dynein are tightly coupled, with PrPC vesicles moving at different velocities and for varied lengths along axons. However, the type and amounts of these motor assemblies remain stably associated with stationary as well as moving vesicles, and normal retrograde transport by Kinesin-1 is independent of dynein-vesicle attachment.

The UCSD study of the mechanisms behind normal vesicle movement along the axons in mouse cells might also shed light on other

neurodegenerative disease. While Alzheimer's is not generally considered an infectious disease like mad cow disease, emerging data suggest that Tau, amyloid-beta, and alpha-synuclein - proteins implicated in Alzheimer's and Parkinson's disease - have self-propagating fibril structures with prion-like characteristics.

"Whether these toxic molecules spread along neuronal transport pathways in ways similar to the normal prion protein is unknown," said first author Sandra E. Encalada, PhD, of the UCSD Department of Cellular and Molecular Medicine. "But characterization of these normal mechanisms might lead to a way to control movement of intracellular aggregates, and perhaps to therapies for many neurodegenerative diseases."

Provided by University of California - San Diego