Getting turned on: Scientists discover switch mechanism for controlling traffic in cells

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Scientists have identified a mechanism that switches on an extremely important process for the proper functioning and survival of our body's cells. Specifically, the fast-track transportation pathway of 'cargo' to and from the surface of the cell. Defects in this trafficking pathway can have severe consequences, leading to numerous diseases such as high cholesterol, neuropathies, sterility and complications in immune response. Understanding the mechanisms underlying these disorders is crucial to developing possible treatments and new therapeutic strategies.

Dr. Peter McPherson and Dr. Brigitte Ritter and their colleagues have discovered how a molecule called Rab35, which acts as a switch is turned on in order to activate the fast-track recycling pathway - in which cargo that needs to be recycled back to the surface of the cell is rapidly selected and transported. The new study, published in the prestigious journal *Molecular Cell*, was conducted at The Montreal Neurological Institute and Hospital - The Neuro, McGill University.

"The cells that make up our bodies are like a busy city," says Dr. McPherson, neuroscientist at The Neuro and the co-principal investigator for the study. "The cell surface is defined by a membrane that separates its interior from the external world, like the walls or borders of a city. Within this environment, there are simultaneous trafficking pathways that transport vital nutrients, receptors and other components required for cells to function, within cargo vehicles called 'vesicles.' Like traffic in a city, these 'cargo' vesicles travel at different speeds to numerous destinations within the cell with different purposes.

For example, the receptors on the cell surface that bind to cholesterol are on the fast track pathway, so that once they deliver the cholesterol inside the cell, they move back to the surface quickly so that they can pick up some more. It is therefore crucial to understand the controls and switching mechanisms of trafficking inside cells, as this system is of vital importance to the proper functioning of the body."

The Rab35 molecule is the trafficking switch for the fast-track or high-priority recycling pathway signaling the quick return of cargo to the cell surface membrane. It is known that Rab35 exists in two forms, 'on' (GTP- bound) or off (GDP- bound). When Rab35 is turned 'on', it allows the cargo to go back up to the cell surface. What Dr. McPherson and Dr. Ritter and colleagues have discovered is the switch that turns Rab35 on.

"In this study we identified that a particular region of the vesicle-bound protein connecden, , called the DENN domain, is the 'finger' that flips the switch," says Dr. Ritter. "The DENN domain connects with the Rab35 molecule and through enzymatic activity converts Rab35 from the inactive to the active form, in essence, turning on the switch."

DENN domains are found in multiple protein products encoded by 16 human genes. Mutations in the DENN domain cause humans diseases such as sterility and Charcot-Marie-Tooth neuropathy, yet until now the function of this common module has been unknown. The DENN domain is evolutionarily ancient and bioinformatics studies suggest that it is present in all eukaryotic, or multi-compartmental cells, indicating that the DENN domain has mediated crucial functions throughout evolution.

"If the finger or the switch itself is mutated or missing, cargo can't recycle, which has dire consequences," adds Dr. McPherson. "For example a very important cargo transported by this specific fast track recycling pathway, controlled by Rab35 is the MHC class I receptor

involved in the immune system response. If a cell becomes infected by a virus, the MHC receptor is loaded with fragments of the virus that have infected the inside of a cell. The MHC receptor needs to be taken back to the cell surface quickly so that so that it can act as a signpost indicating to circulating immune cells that this particular cell has been infected by a virus and needs to be destroyed, preventing viral infection to other cells."

This critical new insight into the control mechanisms for the cells' trafficking system provide a deeper understanding of diseases that result from complications in trafficking, as well as provide new therapeutic targets for the development of treatments.

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