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Certain diseases, birth defects may be linked to failure of protein recycling system

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A group of signaling proteins known as Wnt - which help build the human body's skin, bone, muscle and other tissues - depend on a complex delivery and recycling system to ensure their transport to tissue-building cell sites, according to a study at Cincinnati Children's Hospital Medical Center. When the recycling system - the Retromer Complex - breaks down, the delivery of this specialized family of signaling proteins fails as their transport vehicle, a cargo receptor called Wntless (Wls) becomes unstable and is degraded. This important finding provides new insight into what may be a mechanism behind cancer, heart disease or birth defects related to Wnt proteins, researchers said.

Writing for the January 15, 2008 edition of *Developmental Cell*, researchers at Cincinnati Children's studied the critical role that a trafficking protein (called Vps35) has as the central assembly platform of the Retromer Complex. This complex is made up of trafficking proteins that act like cellular postmen to return a cargo receptor, Wls, from cellular compartments called endosomes to the Trans-Golgi Network. The network acts like a molecular clearing house - packaging and sorting proteins for targeted delivery - and the job of Wls is to deliver Wnt signaling proteins from Trans Golgi to their intended tissue-building sites. If the Retromer Complex fails to recycle Wls back to the Trans Golgi to do their job, it thwarts stable delivery of Wnt signaling proteins.

"We know secreted Wnt proteins play essential roles in many biological processes, including the development of diseases, but very little is known

about the mechanisms by which Wnt processing and secretion are regulated," said Xinhua Lin, Ph.D., a researcher in the Division of Development Biology at Cincinnati Children's and senior author of the study. "Our main finding in this study is that the Retromer Complex is required for stable Wnt secretion, providing new insights into how certain diseases work."

In a series of experiments with genetically engineered cells from the fruit fly Drosophila, mice and humans, Dr. Lin and his colleagues mutated the Vps35 trafficking protein to compromise its central assembly role in the Retromer Complex, then observed the delivery cycle of Wnt proteins between the Trans-Golgi Network and targeted cell sites. In all three series, the compromised Retromer Complex resulted in Wnt protein accumulating in the Trans-Golgi Network and Wls cargo receptors being degraded instead of returning to the network and their job of delivering Wnt proteins.

"Although we propose that the Wls protein acts as a cargo receptor for Wnt signaling proteins, we need to conduct more experiments to further our understanding of this process, including how the Wls delivers Wnt from the Trans-Golgi," Dr. Lin said.

In their study, the researchers proposed a delivery cycle model where Wnt initially enters the Trans-Golgi Network and binds with the Wls cargo receptor, which then transports Wnt to targeted cell surfaces. Once Wls has delivered Wnt proteins, one of two things occurs, depending on whether the Retromer Complex is functioning normally. When working as designed, the Retromer Complex retrieves the spent Wls protein for return to the Trans-Golgi. When Retromer Complex breaks down, Wls cargo receptor is absorbed into the cell's lysosome, where it is digested and destroyed.

Source: Cincinnati Children's Hospital Medical Center