Characterizing the Role of the Endosomal/ Lysosomal system in beta-Amyloid Production and Secretion in Alzheimer’s disease

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Characterizing the Role of the Endosomal/ Lysosomal system in beta-Amyloid Production and Secretion in Alzheimer's disease

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Research Abstract

Alzheimer’s Disease is the most common neurodegenerative disease in adults. Currently there are more than 750,000 Canadians with Alzheimer’s disease, and this number will to rise to over 1 million. Alzheimer’s disease is characterized by a buildup of beta-amyloid in the brain. Beta-amyloid is produce by cutting up a protein called the Amyloid Precursor Protein (APP), which is performed by 2 enzymes called a beta-secretase and a gamma-secretase. Many laboratories

have shown that the cleavage of APP to make beta-amyloid is tightly linked to APP’s movement inside the cell. We have found that APP and the gamma-secretase enzyme are present in a compartment in the cell called a lysosome, and we believe this is an important site for making beta-amyloid. Recently, we have discovered 3 completely new ways for APP to be transported with nerve cells. One of these pathways is called macropinocytosis and is able to transport APP directly from the cell surface to lysosome. Another pathway transports APP directly from a sorting organelle called the Golgi to the lysosome, and a third pathway transports proteins from lysosomes back to the cell surface. Inhibition of each of these pathways dramatically reduces the amount of amyloid secreted, suggesting that the lysosome is an important source of beta-amyloid. Here we propose to learn how these pathways are regulated. We have cloned APP and attached a fluorescent protein tag that allow us to directly see this protein moving in live cells under the microscope. We will use Laser Scanning Confocal Microscopy and Total Internal Fluorescence Microscopy to study where APP resides and how it is transported inside the cell. We will examine each of these pathways to identify proteins and drugs that inhibit APP transport and test them to see if they can reduce beta-amyloid production. This work will help us understand the biology of APP and beta-amyloid production, and provide targets for treatment in Alzheimer’s disease.

Further information available at:

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