Lysosomal stress triggers exosome release and transfer of proteins

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USA

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Research Abstract
? DESCRIPTION (provided by applicant): Autophagic-Lysosomal Stress Promotes Exosomal Release and Transfer of Proteins Autophagic-lysosomal dysfunction has been linked to neurodegenerative diseases like Parkinson’s and Alzheimer’s disease with strong evidence indicating that in aging and disease, this major protein/lipid quality control pathway is inefficiet. There is increasing association with genetic mutations that may contribute to lysosomal stress, including reduction in glucocerebrosidase (GC) function in Parkinson’s and related disorders.

The net effect is reduced lysosomal activity that may contribute to the accumulation of redundant proteins and dysfunctional organelles. While most proteins are retained internally and sequestered as aggregates, recent work has shown that proteins like a-synuclein and tau can spread from one cell to another, or from one region to another. The transmission of pathology may be an opportunity for neurons to enhance self- preservation mechanisms extruding potentially toxic proteins into the extracellular milieu. We have evidence that chemically-induced lysosomal stress can increase the extracellular release in the form of exosomes and may contain proteotoxic elements. Exosomes are intracellular vesicles released from most cells that are readily taken into recipient cells and may represent a medium for pathological transfer of proteins. Further, it is likely that exosomal release is significantly increased versus free protein release when there is lysosomal stress. In this project we examine the role of lysosomal stress in exosomal production and transfer of cargo to nearby cells as a model linking lysosomal dysfunction seen in neurodegeneration and the transmission of pathology. We employ complimentary cell, animal and human substrates to characterize this biological and putatively neuropathological event.

Further information available at:

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