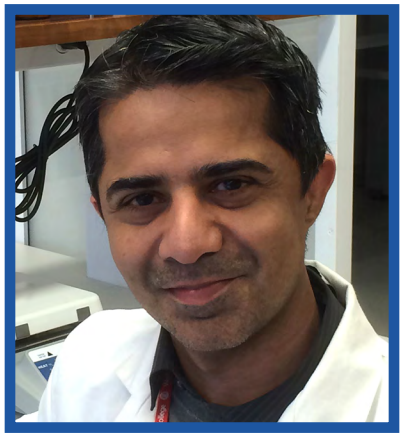
Lysosomal Exocytosis as a Route for Clearance of Degradation-Resistant Materials in Neurons

May 20

Tuesday, 12:30 pm

Billings Building—Rosedale Room

SPEAKER:



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Host: Gary E. Gibson, Ph.D.

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Abstract

Two studies will be discussed: 1) Considerable evidence supports the release of pathogenic aggregates of the neuronal protein tau into the extracellular space. While this release is proposed to instigate the neuron-to-neuron transmission and spread of tau pathology in tauopathies including Alzheimer's disease, the molecular-cellular mechanism(s) remain unclear. We have found that neuronally generated pathogenic species of tau accumulate within neuronal lysosomes in mouse brains and primary neurons. We then find that neurons release these pathogenic tau species via SNARE-dependent lysosomal exocytosis. Additionally, we find that this release is dependent on neuronal activity and cytosolic Ca2+. These results propose lysosomal exocytosis as a central mechanism for the release of aggregated and degradation-resistant proteins from neurons. 2) In a separate study we have found that if lysosomal exocytosis is reduced by pathogenic mutations in the SNARE-chaperone protein cysteine string protein-α (CSPα), lysosomes accumulate in neurons resulting in a lysosomal storage disorder—adult-onset neuronal ceroid lipofuscinosis (ANCL). From a screen of FDA-approved neuroactive drugs, we have identified immunomodulatory imide drugs (IMiDs), Thalidomide, Lenalidomide, and Pomalidomide, which are now being tested for enhancing lysosomal exocytosis, and thus relieving the lysosomal storage defect in ANCL.

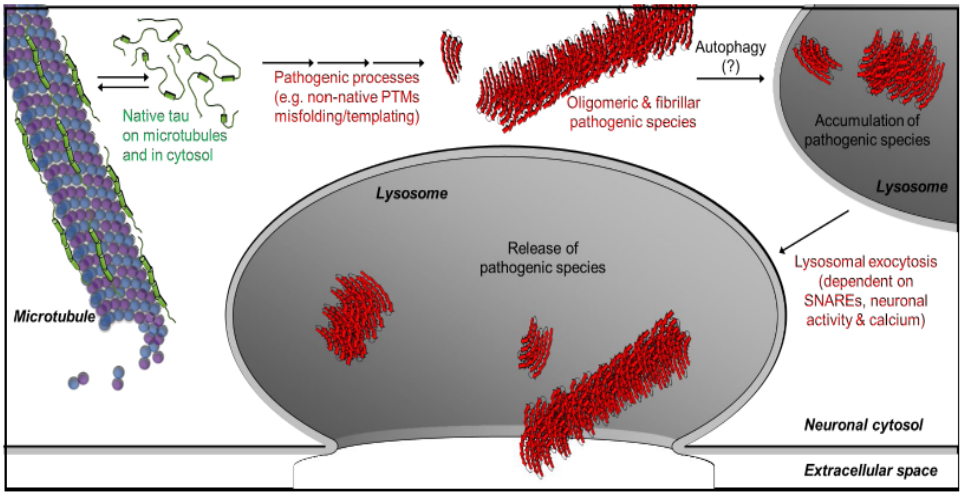

Figure 6 | Model of our findings: Lysosomal exocytosis releases pathogenic tau species from neurons. Native tau is expressed as a largely-unstructured monomer in the cytosol, in equilibrium with the microtubule-bound conformer(s). Pathogenic processes oligomerize tau into β-sheet-rich amyloid-type aggregates of various sizes. We demonstrate here that these larger pathogenic species, generated in the neuronal cytosol, accumulate in neuronal lysosomes over time, possibly due to their high structural and metabolic stability. SNARE-dependent lysosomal exocytosis releases these non-membrane enveloped aggregates, and this release is upregulated by neuronal activity and cytosolic Ca^{2+}.

Publications

1. Naseri NN, Ergel B, Kharel P, Na Y, Huang Q, Huang R, Dolzhanskaya N, Burré J, Velinov MT, Sharma M. *Aggregation of mutant cysteine string protein-α via Fe-S cluster binding is mitigated by iron chelators.* Nature Structural & Molecular Biology, 2020; 27(2):192-201. [PMID: 32042150; PMCID: PMC7021000]

2. Xie YX, Naseri NN, Fels J, Kharel P, Na Y, Lane D, Burré J, Sharma M. *Lysosomal exocytosis releases pathogenic α-synuclein species from neurons in synucleinopathy models,* Nature Communications, 2022; 13(1):4918. [PMID: 35995799; PMCID: PMC9395532]

3. Xie YX, Xie YX, McDonough S, Rao A, McAleer J, Haller J, Naseri NN, Na Y, Luo W, Burré J, Sharma M. *Lysosomal exocytosis releases pathogenic tau species from neurons, under review* (Unpublished data from this study will be included in the talk)

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