Defining the mechanistic basis of a prion disaggregase

https://neurodegenerationresearch.eu/survey/defining-the-mechanistic-basis-of-a-prion-disaggregase-2/

Principal Investigators

SHORTER, JAMES

Institution

UNIVERSITY OF PENNSYLVANIA

Contact information of lead PI
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1

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Research Abstract
DESCRIPTION (provided by applicant): The research objective of this proposal is to define the mechanistic basis of Hsp104 a prion disaggregase, which is unknown. Hsp104 is a hexameric AAA+ (ATPases Associated with diverse Activities) protein from yeast, which is the only cellular factor known to rapidly disassemble amyloid or prion fibrils as well as their toxic soluble oligomeric precursors. This catalytic amyloid-disaggregase activity is remarkable because cross-? amyloid is one of the most stable protein-based structures in nature. Moreover, this activity is

unique to Hsp104 and is not achieved by any other (AAA+) protein, including ClpX. Even the bacterial Hsp104 homologue, ClpB, which can disaggregate environmentally denatured protein aggregates (like Hsp104), cannot disaggregate amyloids or prions. This Hsp104 activity has enabled yeast to harness multiple prions for beneficial purposes. By contrast, in humans (which curiously lack a direct Hsp104 homologue) prions, amyloids and toxic soluble oligomers cause several fatal neurodegenerative disorders, including Parkinson's disease (PD). Protein aggregation and amyloid formation also plague the purification of recombinant proteins for basic studies and therapeutic purposes. Thus, Hsp104 offers an unparalleled opportunity to: eradicate amyloid (and toxic soluble oligomers)~ understand how amyloid (and toxic soluble oligomers) can be disaggregated~ and understand how AAA+ architecture has been adapted for this modality. Hsp104 could even be specifically enhanced and developed as: (a) an agent to increase protein solubility in diverse expression systems to enable facile purification of recalcitrant proteins for structural and mechanistic studies, and valuable therapeutic proteins for patients~ and (b) a potential therapeutic agent and mechanistic probe for diverse protein-misfolding disorders. Indeed, we have established Hsp104 as the only cellular factor known to dissociate ?-synuclein (?-syn) oligomers and amyloids and rescue ?-syn-induced neurodegeneration in the substantia nigra of a rat PD model. To develop these potential Hsp104 utilities further, it is critical to understand Hsp104 mechanism, which despite intense investigation remains poorly defined. It is unknown how Hsp104 monomers collaborate within the hexamer to promote prion or protein disaggregation or how Hsp104 engages and eradicates prions. It is also unknown how conformational changes in Hsp104 hexamers facilitate function. We have established key assays and collaborations with leading experts to meet these challenges. Based on our preliminary data, we hypothesize that hexamer plasticity enables Hsp104 to adapt distinct mechanisms to dissolve diverse aggregated structures, including prions. Here, we will combine pure protein biochemistry, biophysics and yeast biology to define the mechanistic basis of Hsp104's amyloid- disaggregase activity via three specific aims: (1) Define how individual subunits of Hsp104 hexamers collaborate to enable protein disaggregation~ (2) Define how Hsp104 engages and deconstructs Sup35 and Ure2 prions~ and (3) Define conformational changes of the Hsp104 hexamer during its ATPase cycle.

Further information available at:

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