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A FRET-based method to measure seeding activity of misfolded protein species in complex biological samples

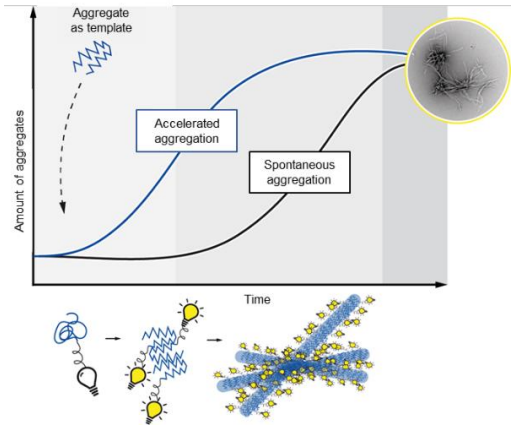
Keywords: Huntington´s disease, Huntingtin, protein-misfolding, FRET

INVENTION NOVELTY

Self-propagating protein aggregates are a pathological hallmark of a large number of neurodegenerative diseases including Huntington's disease (HD). A remaining question in protein-misfolding related diseases is whether misfolded protein aggregates are responsible for pathogenesis. To tackle this question, researchers of the Max Delbrück Center established a FRET-based aggregate seeding (FRASE) biosensor assay that enables the quantification of mutant huntingtin protein (mHTT) seeding activity (HSA) in complex biosamples from HD patients and various disease models.

VALUE PROPOSITION

HD is a monogenic neurodegenerative disorder resulting from a mutation in the huntingtin gene. This leads to the expression of the mHTT which provokes pathological changes in both the central nervous system and periphery. The relationship between the early emergence of aggregates that may act as seeds for the conversion of healthy protein into disease-causing protein species is highly understudied, since sensitive and easy to handle assays for complex biological samples are missing. Establishing this relationship might facilitate tracking and prediction of disease. The proposed invention has the potential to fill this diagnostic gap by providing an assay for the determination of the seeding activity of pathogenic protein species from biological material within an excellent dynamic range and outstanding sensitivity.



The FRASE assay allows to monitor the aggregation of sensor proteins using a FRET-based readout.

TECHNOLOGY DESCRIPTION

The proposed invention provides a FRET-based assay for the quantification of seeding activity (Δt50) of amyloidogenic proteins like mHTT in complex biosamples. The innovative set-up enables the detection of femtomolar amounts of misfolded protein species by amplifying oligomers that are present in cell and tissue samples in a one-step procedure with tissue homogenate and labelled probe proteins. The assay was validated in mice and human brain homogenates and in cellular, *C. elegans* and *Drosophila* models.
This technology has the potential to be developed towards a diagnostic tool for assessing the risk for development, predicting the onset or assessing the progression of a polyQ disease.
Furthermore, it can be applied as screening tool for identifying compounds that inhibit mHTT seeding activity *in vitro*.

COMMERCIAL OPPORTUNITY

This opportunity is available for co-development and for in-licensing.

DEVELOPMENT STATUS

Protocols for the assay have been established and validated in various biological samples in manifold academic collaborations.

PATENT SITUATION

Patent pending in US (US20210302442A1) with priority of 2018.

FURTHER READING

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