Conformational epitopes exposed on misfolded toxic forms of amyloid-beta, tau and alpha-synuclein directly contribute to their seeding activity

POSTER 55254

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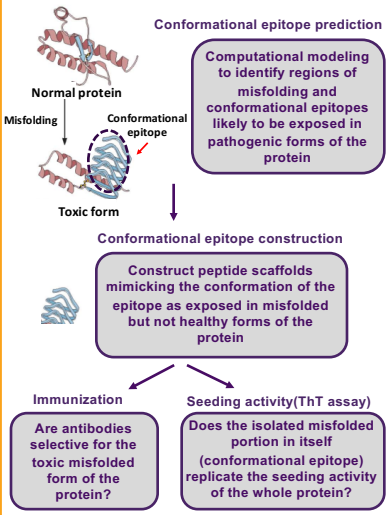
Conformational surface epitopes on misfolded, pathogenic proteins mediate seeding activity and represent unique targets for therapeutic antibodies

INTRODUCTION

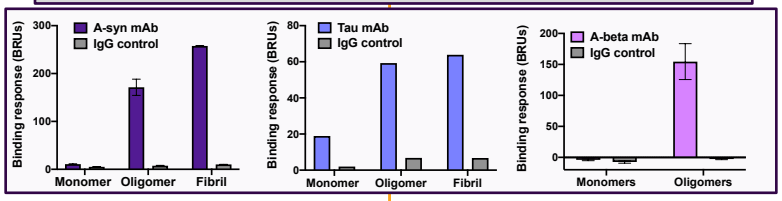
- Misfolding of proteins into toxic aggregates capable of prion-like propagation has been implicated in the pathogenesis of neurodegenerative disorders
  - Amyloid-beta oligomers -> Alzheimer's disease (AD)
  - Tau oligomers & small soluble fibrils -> AD, tauopathies (FTLD, PSP)
  - Alpha-synuclein oligomers & small soluble fibrils -> Synucleinopathies (Parkinson's, Lewy body dementia, multiple system atrophy)
- Misfolding of proteins into toxic forms leads to the exposure of conformational epitopes not normally present on the healthy form of the protein
- Question: Do these small misfolded regions directly contribute to the pathogenic seeding activity of misfolded proteins and represent a unique target for therapeutic antibodies?

METHODS



RESULTS

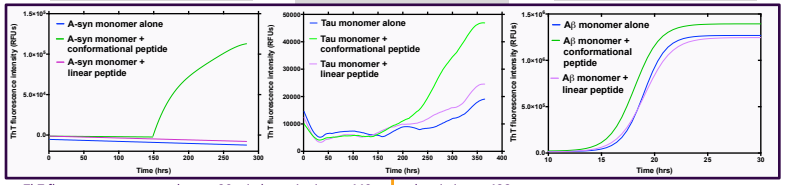
Antibodies raised against conformational epitopes of misfolded A-syn, tau and Aβ are selective for pathogenic forms (oligomers, soluble fibrils) vs physiologic forms (monomers) of the proteins (SPR binding assay)



SPR binding response measured 30s into the dissociation phase

Conformational peptide epitopes of misfolded A-syn, tau and Aβ possess seeding activity and promote aggregation of monomers (ThT assay)

A-syn – Induction of aggregation | Tau – Enhancement of aggregation | Aβ – Acceleration of aggregation



ThT fluorescence measured every 30 min by excitation at 440 nm and emission at 486 nm

CONCLUSIONS

- Small misfolded regions (conformational epitopes) exposed on misfolded toxic A-syn, tau and Aβ are sufficient to replicate the seeding activity of the full-length protein suggesting that they directly contribute to prion-like pathogenicity
- The results also indicate that these conformational epitopes represent a biologically relevant and disease-selective target for therapeutic antibodies

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