Structural, physical and functional properties of alpha-synuclein fibrils and their propagations in synucleinopathies

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Résumé

Protein intracellular inclusions within the central nervous system are hallmarks of several progressive neurodegenerative disorders in man. The protein constituents of those deposits and the affected regions within the brain differ from one neurodegenerative disorder to another. Until recently, the vicious circle consisting of spread, seeded assembly and accumulation over time within the central nervous system of misfolded proteins aggregates was thought to be restricted to the prion protein PrP. Recent reports suggest that other protein aggregates, among which alpha-synuclein, spread and amplify within the central nervous system leading to distinct diseases.
I will present data illustrating the propagation propensities of alpha-synuclein assemblies. I will show how they bind to the cell membranes, what they bind to and the cellular consequences of binding. I will present a quantitative assessment of their uptake, transport and export. I will show data demonstrating that pathogenic protein assemblies disrupt the endo-lysosomal membranes to reach the cytosol where they amplify. Finally, I will describe how and why different alpha-synuclein polymorphs cause distinct diseases.

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Mots-Clés: Parkinson's disease, alphasynuclein, prion, like

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