Alpha-synuclein conformational strains spread, seed and target neuronal cells differentially after injection into the olfactory bulb

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Résumé

Alpha-synuclein inclusions, the hallmarks of synucleinopathies, are believed to spread in the brain of patients following a stereotypical pattern along brain neuronal connections. There is substantial evidence that pathological forms of alpha-synuclein can seed and propagate in cell culture models and *in vivo*. However, we still do not know why the same pathological protein, propagating in a prion-like manner, leads to a variety of diseases (synucleinopathies). Each synucleinopathy presents with distinct clinical features, different cellular populations are targeted and alpha-synuclein propagates with different kinetics in each disease. Our lab has demonstrated that alpha-synuclein can assemble into different polymorphs that are characterized by distinct biochemical properties. Moreover, those polymorphs can imprint their structural characteristics to newly recruited proteins. We therefore hypothesized that the clinical heterogeneity observed in synucleinopathies might be explained by distinct pathological alpha-synuclein strains.
We produced and characterized 5 different strains of recombinant human alpha-synuclein fibrils to investigate their pathological effects *in vivo*, following injection into the brain of wild-type mice. We demonstrate that 5 different alpha-synuclein strains (fibrils, ribbons, P65, P91, P110) are able to seed and propagate in the WT mouse brain after several months post injection. The strains seed alpha-synuclein pathology to various extents, and propagate differently depending on their identity. Strain-induced inclusions are thioflavin S positive, and are mainly neuritic, or both neuritic and somatic inclusions, depending on the conformational strain; somatic inclusions being predominantly localized within neurons.
In conclusion, conformational strains are capable of seeding and transneuronal spreading to different extents and this leads to diverse aggregation patterns in WT mice. This data supports the idea that diverse polymorphs could underlie the heterogeneity of anatomopathological features observed in synucleinopathies.

Mots-Clés: Alpha, synuclein, strains, fibrils, prion, like spreading, olfactory bulb

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