Acidic nanoparticles prevent neurodegeneration in LB-induced Parkinson's disease mouse model

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Résumé

Parkinson's disease (PD) is a neurodegenerative disease characterized by accumulation of α-synuclein protein enclaved in neuronal intracytoplasmic inclusions called Lewy Bodies. Increasingly, genetic and neuropathological evidence indicate an alteration of the autophagy-lysosomal pathway at different levels, and a likely mechanism linking these data relates to a lysosomal impairment, making it a point of particular vulnerability. In particular, the lysosomes, responsible for cargo degradation in acidic conditions by specific enzymes called cathepsins, are responsible for the clearance of α-synuclein among others, and for the removal of old or damaged organelles, such as mitochondria. Both α-synuclein aggregation and mitochondrial dysfunction are considered major pathogenic events in PD. Impairment of lysosomal function is associated with impaired lysosomal acidification, decreased proteolytic processing of lysosomal enzymes, reduced degradation of lysosomal substrates, including α-synuclein.
In order to restore the autophagy-lysosomal pathway function, we chose to target the lysosomal compartment using acidic nanoparticles aiming to reestablish the appropriate and functional lysosomal pH in a PD mouse model. We produced acidic nanoparticle (aNP) made of biodegradable poly(lactic-co-glycolic acidic) (PLGA) polymers, previously shown to be efficient to target lysosomal compartment and reestablish proper lysosomal pH *in vitro*. We hypothesized that the restoration of the lysosomal pH through aNP injection in a α-synuclein-related mouse model of PD might induce beneficial effects.

To test this hypothesis, we used the LB-mouse model of PD which consist of mice receiving human-derived LB containing fractions into the substantia nigra, previously described and characterized by our laboratory as a relevant model for PD pathology. We then injected acidic nanoparticles (aNPs) or non-acidic nanoparticles (NPs) in the substantia nigra of LB-injected or control mice.

Four months post-injection, we evaluated the extent of the nigrostriatal lesions in the different experimental groups and demonstrated an attenuation of dopaminergic neurodegeneration in these animals, both at the level of nigral dopaminergic neuron cell bodies and striatal dopaminergic terminals in aNPs - LB injected group compared to controls. Furthermore,

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we assessed the synucleinopathy in those animals and showed decreased levels of total, PK-resistant and S129-phosphorylated α-synuclein in the substantia nigra of aNPs - LB injected mice. Further work will evaluate whether restoration of proper lysosomal function will occur through increased numbers and appropriate relocalization of lysosomes and increased levels of cathepsins activity.
In conclusion, we demonstrated that acidic nanoparticles, after intracerebral injection into a α-synuclein-based mouse model of PD, attenuated PD-related neurodegeneration and synucleinopathy by mechanisms involving a rescue of compromised lysosomes. By combining a wide range and unique set of tools at the interface between chemistry and biology, this study demonstrated that strategies enhancing or restoring lysosomal-mediated degradation thus appear as tantalizing neuroprotective/disease-modifying therapeutic strategies and would be of major therapeutic interest for PD.

Mots-Clés: Parkinson's disease, alpha synuclein, acidic nanoparticle, autophagy, lysosomal pathway