Mechanistic study on the interaction between PtX and neural stem cells cellular membranes

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Stimulating the differentiation of endogenous neural stem cells is a promising therapeutic approach for the treatment of neurodegenerative diseases. On the other hand, allogenic cellular transplantation is limited by the accessibility to the cells, immunoreaction, death of the transplanted cells and ethical issues. **Therefore, we hypothesized that the stimulation of endogenous neural stem cells (located in specific regions of the organism) via a targeted nano-vector delivery system charged in retinoic acid could contribute to the replacement of non-functioning neurons**.

We have previously shown that nanovector (NV) decorated with a peptide (PtX*) specifically penetrates in neural stem cells (NSC) of the subventricular zone of the brain (SVZ) and do not in neurons or astrocytes. However, the interactions between PtX-NV (and PtX alone) with NSC of the SVZ remain to be elucidated.

In the present work we compared the interactions of our drug delivery system with NSC of the SVZ and with NSC of spinal cord (SC). NSC were isolated from newborn rats and grown as neurospheres. We observed that depending on their origin, PtX-NV interactions with NSC were different (e.g. pharmacokinetic curbs not overlapping, different degree of internalization at specific conditions, etc). To explain these differences, PtX-NV interactions with NSC membrane were studied. We first measured the variation of the organization state of the cell membranes by performing a Laurdan assay. Laurdan is a lipophilic probe able to penetrate into the membrane and to change its emission wavelength according to its organizational state. General polarization (GP) is the mathematical synthesis of these wavelength variations. NSC SVZ and NSC SC GP values were significantly different at a resting stage (GP 0.31 and GP 0.39 respectively) and were differently impacted when incubated with PtX (GP decrease was stronger for NSC SVZ) or NV (GP -0.03 and GP +0.03 respectively) or PtX-NV. The effect on cell membrane permeability was then assessed by FITC-Dextran and propidium iodide (PI) incubation after the treatment with PtX. Membrane permeabilization was less increased when NSC from SC were incubated with PtX (few cells were $FITC^+$) compared to NSC from SVZ. However, whatever the NSC origin, PtX was not able to modify nuclear membrane permeability (no cells were PI^+).

The information obtained in this study will contribute to the optimization and to the fine tuning of our drug delivery system depending on the localization of NSC and thus of neurodegenerative disease pathology.

*patent pending