Panel 45

Genetic Substrate Reduction Therapy for Mucopolysaccharidoses type III: toward a siRNA-containing nanoparticle targeted to brain cells

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The classical therapeutic approach for LSD, enzyme replacement therapy, would hardly rise as a potentially successful tool to reduce the disease burden in MPS III patients, as it is long known to have no impact on neuropathology. A tempting alternative, however, would be to block substrate accumulation upstream, by decreasing its synthesis. That concept is known as substrate reduction therapy (SRT).

Having this in mind, we designed an RNA-based strategy based upon the selective downregulation of one gene involved in the very early stages of the glycosaminoglycans' (GAG) biosynthethic cascade. Our goal is to promote an effective reduction of the accumulating substrate, ultimately decreasing or delaying MPS' symptoms. As tools to achieve substrate reduction, we are evaluating a specific type of antisense oligonucleotides, able to trigger a naturally-occurring post-transcriptional gene silencing process called RNA interference: the small interfering RNAs (siRNAs). So far, the obtained results are quite promising with marked decreases of the target mRNA levels in all tested cell lines (MPS IIIA, IIIC and IIID patients' fibroblasts). Currently, we are evaluating the effect of that decrease on the overall storage of GAGs 7 days post-transfection, also with promising results.

Here we present an overview on the current results of this project, while discussing its next steps, namely the development and evaluation of vectors for *in vivo* delivery. Our goal is to develop targeted stable nucleic acid lipid particles (t-SNALPs) coupled with different ligands, which promote cell uptake of the 'anti-GAG' siRNAs in a variety of cells, including neurons.

Acknowledgments: This work was partially supported by the Portuguese Society for Metabolic Disorders (*Sociedade Portuguesa de Doenças Metabólicas*, SPDM - *Bolsa SPDM de apoio à investigação Dr. Aguinaldo Cabral 2018*).