Development of New Molecular Strategies for the Treatment of Rett Syndrome in mutant mice

Sujet proposé par

PANAYOTIS Nicolas / nicolas.panayotis@u-paris.fr

SPPIN, CNRS UMR 8003
Molecular Biology of Neuronal Transport

M2 Research project title

Development of New Molecular Strategies for the Treatment of Rett Syndrome in mutant mice

Keywords

Molecular Neurobiology, Neurodevelopmental Disorders, Mouse Models, Nuclear Transport, MeCP2, Importins

Description of the project

Introduction. Rett syndrome (RTT) is a neurodevelopmental disorder caused by mutations in the MECP2 gene, affecting 1 in 10,000 girls. In RTT girls, normal growth is followed by regression of milestones between 6 to 18 months, leading to various neurological symptoms. Among all MECP2 mutations, T158M, which affects MeCP2's DNA binding domain, is both frequent and severe. While RTT is incurable, it could be reversed in adult mice after rescuing MeCP2 expression. As of now, gene replacement therapies showed promise but failed to rescue optimal MeCP2 levels. MeCP2 regulates gene expression in the nucleus, but its transport mechanisms in MeCP2 disorders were never targeted. Importins are crucial for the transport of proteins and we discovered their roles in anxiety via control of MeCP2 nuclear shuttling, and of other importins and signaling cargos in pain and memory. Hypothesis and aims. MeCP2 gene therapies are challenged by poor brain penetration of viral vectors, suboptimal brain cell's transduction, and difficulty in fine-tuning MeCP2 expression to avoid adverse effects associated with overexpression. Clinical trials are ongoing, but there is no universal solution for the diverse mutations in RTT girls. Thus, developing new therapies with efficacy on severe MeCP2 variants is urgent. We are testing if 1) Combination of MeCP2 gene therapy with focal ultrasound (fUS) can boost MeCP2 brain penetration, cell transduction, and ameliorate RTT symptoms in T158M mice. 2) Manipulating importin pathways can adjust MeCP2 nuclear levels and improve behavioral, cellular, and transcriptional outcomes of the gene therapy. Methods. We bridge expertises in molecular neurobiology, Rett syndrome models, and neuronal subcellular transport with collaborations with experts in neurophotonics, and in vivo brain imaging. The research is organized around 3 levels, from i) the evaluation of behavioral & physiological changes upon modulation of MeCP2's expression and nuclear shuttling to ii) the study of neuronal morphology, and iii) gene expression. Conclusion. Our research will enable the development of a new MeCP2 gene therapy in a severe clinical context. The research question is driven by solid published works showing that manipulation of specific importin ?'s helps to control the shuttling of MeCP2 in the nucleus of specific neuronal subsets. Given the difficulty to design efficient gene therapy in all RTT girls, optimizations based on maximizing viral vector delivery (fUS) and titration of MeCP2 nuclear transport should increase the potency of the treatment.

Methods and techniques

- Mouse Behavioral Profiling (longitudinal scoring, anxiety-related behaviors, sensorimotor coordination, social interactions) - Immunofluorescence, imaging, and image analyses (cell counting, subcellular fluorescence intensity measurements, neuronal morphology, colocalization studies) - Gene therapy (preparation and systemic administration of AAV vectors, study of AAV localization, brain cell's transduction, MeCP2 expression levels) - Mouse brain dissection and preparation of RNA for transcriptomics (RNA-seq) - Possibility to apply fUS technology (focused ultrasound) in collaboration with experts in the field to boost AAV brain delivery and perform in vivo

imaging of brain activity.

References (at least 3)

References about Rett syndrome and current therapeutic options: - M. J. Lyst, A. Bird, Rett syndrome: a complex disorder with simple roots. Nat Rev Genet 16, 261-275 (2015). - K. Brown et al., The molecular basis of variable phenotypic severity among common missense mutations causing Rett syndrome. Hum Mol Genet 25, 558-570 (2016). - I. Jagadeeswaran, J. Oh, S. E. Sinnett, Preclinical Milestones in MECP2 Gene Transfer for Treating Rett Syndrome. Dev Neurosci, 1-10 (2024). - N. Panayotis, et al., State-of-the-art therapies for Rett syndrome. Dev Med Child Neurol, (2022). References about subcellular transport, importin-based nuclear shuttling in neuronal functions: - N. Panayotis, et al., Macromolecular transport in synapse to nucleus communication. Trends Neurosci 38, 108-116 (2015). - N. Panayotis, et al., Importin alpha5 Regulates Anxiety through MeCP2 and Sphingosine Kinase 1. Cell Rep 25, 3169-3179 e3167 (2018). - N. Panayotis, et al., beta-sitosterol reduces anxiety and synergizes with established anxiolytic drugs in mice. Cell Rep Med 2, 100281 (2021). - L. Marvaldi, N. Panayotis, et al., Importin alpha3 regulates chronic pain pathways in peripheral sensory neurons. Science 369, 842-846 (2020).

Ecole doctorale de rattachement

ED3C

Aurez-vous la possibilité de présenter l'étudiant à une école doctorale ?

Oui