Molecular Neuropathology of HACE1 Deficiency

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Introduction
Spastic Paraplegia and Psychomotor Retardation with or without Seizures (SPPRS – OMIM #616756) is caused by mutations in the gene HACE1 (HECT Domain and Ankyrin Repeat Containing E3 Ubiquitin Ligase). Symptoms include severe developmental delay and intellectual disability. Hace1 KO mice phenocopy SPPRS patients:

Mouse Primary Culture Model of SPPRS Shows Morphological Abnormalities

Hace1 KO Cell Lines Have Increased ROS, DNA Damage and Perturbed Morphology

In Vivo Effects of HACE1-Deficiency

RAC1 is the Main Effector of HACE1-Deficiency

Left: Primary hippocampal cultures from Hace1 WT (left) and Hace1 KO (right) mice, cultured for 14 days and stained against MAP2 (red) and DAPI (blue)

Below: Quantification of mean dendritic branch points and dendritic trunks of the Hace1 WT and KO neurons (Student’s two-tailed t-test). N (mice) = 2 (WT); 2 (KO);
N (pups) = 10 (WT); 9 (KO).

Outlook:
1. Confirm increased levels of RAC1 in primary culture model and in iNs
2. Develop cell line model of SPPRS (in neuroblastoma?)
3. Inhibit RAC1, NADPH oxidase complex, HACE1 ubiquitination and scavenge ROS for rescue of disease phenotype
4. Explore contribution of microglia to SPPRS pathology in primary culture model

References: