COASY-associated diseases in mouse: not just a matter of neurodegeneration

COASY protein-associated neurodegeneration (CoPAN), a form of neurodegeneration with brain iron accumulation (NBIA), and pontocerebellar hypoplasia type 12 (PCH12) are two extremely rare autosomal recessive disorders that have been linked to *COASY*, the gene encoding the bifunctional enzyme CoA synthase, which catalyzes the last two reactions of cellular de novo coenzyme A (CoA) biosynthesis. Understanding why the different symptoms emerge in these disorders and what determines the development of one syndrome over the other is still not achieved.

To unravel the contribution of different brain cell types to the pathogenesis of these diseases, as well as to elucidate the mechanisms linking CoA metabolism, iron dyshomeostasis, and neurodegeneration, we generated conditional, tissue-specific mouse models lacking Coasy gene in neurons or in astrocytic lineage, using the Cre-loxP system.

Neuronal-specific Coasy null mice showed a clinical phenotype similar to those of CoPAN patients, characterized by neurological impairment, progressive sensorimotor defects, dystonia-like movements, and reduced lifespan. Interestingly, besides the alteration of iron homeostasis neurodegenerative neuropathology, we also found a broad neuroinflammation, characterized by microglial activation, astrocytes hyper-proliferation, and higher expression of pro-inflammatory cytokines in the brain of ko mice.

Likewise, the ablation of the Coasy gene in the astrocytic lineage induces a similar clinical phenotype and astrogliosis, but histological analysis also reveals severe congenital cerebral and cerebellar cortical hypoplasia, indicating a crucial role of Coasy during neurodevelopment.

All together, these data suggest that neuroinflammation could play an important role in the pathogenesis of the human disease, representing a potential target for future therapeutic interventions. Moreover, *Coasy* ablation in specific cell types triggers abnormal neuronal development, offering new insights into disease mechanisms.