Dora Clara TARLUNGEANU

Thesis supervisor: Dr. Gaia Novarino
MolTag Associate Student, IST Austria

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Title: The Branched Chain Amino Acids in Autism Spectrum Disorders

Abstract in English:
Autism spectrum disorders (ASD) are a group of genetic disorders often overlapping with other neurological conditions. Despite the remarkable number of scientific breakthroughs of the last 100 years, the treatment of neurodevelopmental disorders (e.g. autism spectrum disorder, intellectual disability, epilepsy) remains a great challenge. Recent advancements in genomics, like whole-exome or whole-genome sequencing, have enabled scientists to identify numerous mutations underlying neurodevelopmental disorders. Given the few hundred risk genes that were discovered, the etiological variability and the heterogeneous phenotypic outcomes, the need for genotype- along with phenotype-based diagnosis of individual patients becomes a requisite.

Driven by this rationale, in a previous study our group described mutations, identified via whole-exome sequencing, in the gene *BCKDK* – encoding for a key regulator of branched chain amino acid (BCAA) catabolism - as a cause of ASD. Following up on the role of BCAAs, in the study described here we show that the *solute carrier transporter 7a5* (*SLC7A5*), a large neutral amino acid transporter localized mainly at the blood brain barrier (BBB), has an essential role in maintaining normal levels of brain BCAAs. In mice, deletion of *Slc7a5* from the endothelial cells of the BBB leads to atypical brain amino acid profile, abnormal mRNA translation and severe neurological abnormalities. Additionally, deletion of *Slc7a5* from the neural progenitor cell population leads to microcephaly. Interestingly, we demonstrate that BCAA intracerebroventricular administration ameliorates abnormal behaviors in adult mutant mice. Furthermore, whole-exome sequencing of patients diagnosed with neurological disorders helped us identify several patients with autistic traits, microcephaly and motor delay carrying deleterious homozygous mutations in the *SLC7A5* gene.

In conclusion, our data elucidate a neurological syndrome defined by *SLC7A5* mutations and support an essential role for the BCAAs in human brain function. Together with recent studies (described in chapter two) that have successfully made the transition into clinical practice, our findings on the role of BCAAs might have a crucial impact on the development of novel individualized therapeutic strategies for ASD.