Elucidating the role of Neuregulin 1 on the neuroinflammatory and behavioral profile in the early-life immune activation mouse model of autism: focus on the brain-gut axis

Autism spectrum disorder (ASD) is a highly heterogeneous neurodevelopmental disorder, involving the early onset of behavioral abnormalities, social impairments, and communication deficits. Inflammatory and immune changes are recognized as pivotal mechanisms in ASD. Moreover, gastrointestinal disorders, microbiota-gut immune response and enteric nervous system dysfunction have also been described in ASD.
Several studies have confirmed that there is a strong genetic component in ASD disorders: the disease preferentially affects males over females (4:1) and currently about 1000 genes have been associated with the onset of autism spectrum disorders (Dias et al. 2020). Most of the genes associated with ASD control the development of the nervous system and the mechanisms of cellular communication between neurons.
Recently, Neuregulin 1 (NRG1), a candidate gene for schizophrenia, has been involved in the pathogenesis of ASD (Prata et al., 2017). NRG1, the best characterized member within the family of neuregulins (NRGs), is a trophic factor involved in neural development, neurotransmission, synaptic plasticity and neuron-glia communication. Beside its role in development, NRG-1 has been shown to have neuroprotective and anti-inflammatory effects (Kataria et al., 2019).
In both ASD children and mouse models, NRG1 level (in peripheral blood monocytes and brain, respectively) has been found altered and associated with behavioural deficits. Studies on NRG1 haploinsufficient mice reveal that interaction between NRG1 and environmental factors may lead to pathophysiological processes that underlie neurodevelopmental disorders. Despite this evidence, the global impact of a dysfunctional NRG1signalling on neuroinflammation, behaviour, gut immune response and microbiota is largely unexplored.
The main objectives of the project are:

I) to study the consequences of NRG1 haploinsufficiency, using transmembrane domain Neuregulin1 mutant (Nrg1 TM HET) mouse, in the pathophysiology of the "Early Immune Activation (EIA)" mouse model of ASD.

EIA is a variant of the more common MIA paradigm, consists of a “two-hit” regimen involving prenatal treatment mimicking a maternal viral infection (polyinosinic:polycytidylic acid, Poly I:C) followed by a treatment mimicking a postnatal bacterial infection with lipopolysaccharide (LPS) on postnatal day 9.

II) to test the effects of the modulation of the brain-intestinal axis by the intestinal anti-inflammatory drug mesalamine (a drug used to treat human inflammatory Bowel disease), to identify the contribution of gut inflammation on behavioural and neuroinflammatory profile, as well as on intestinal permeability and microbiota composition in the EIA model and its role in the partial loss of function of NRG1.

Early immune activation (EIA) will be induced in heterozygous NRG1 KO and WT pregnant dams and in their offspring at postnatal day 9. The effects of EIA, alone or in combination with mesalamine treatment (at 6-7 post-natal week), will be evaluated on behaviour, neuroinflammatory, gut immune response and microbiota composition.

The results will clarify the role of NRG1 in the pathogenesis of ASD and the contribution of bidirectional communication between gut and brain in ASD.