MOLECULAR AND CELLULAR UNDERPINNINGS OF AUTISTIC PHENOTYPES

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Autism Spectrum Disorders (ASD) are characterized by impairments in social interaction, communication and repetitive/stereotypic behaviours. Involvement of synaptic and synapse regulating genes has been consistently observed across several ASD genomic screenings as well as in 'monogenic' forms of autism, suggesting a central role for defects in synaptic structure and function in the pathogenesis of ASD.

Autophagy is an evolutionarily conserved catabolic process that provides a primary route for turnover of cellular proteins. We hypothesized that an imbalance in the autophagy cascade might be related with impairments in the maintenance of synaptic homeostasis. Ambra1 is strongly expressed in cortex, hippocampus and striatum and a positive regulator of Beclin1, a principal player in autophagosome formation. While homozygosity of the *Ambra1* null mutation causes embryonic lethality, heterozygous mice are viable and reproduce normally. Behavioral characterization revealed an autism-like phenotype exclusive for *Ambra1+/-* females and MRI analysis showed a significant brain enlargement at puberty.

Aiming at a translational approach to the cellular and molecular mechanisms that underlie the aetiology of ASD, the present project proposes (1) to characterize, at the cellular level, neurons derived from autistic versus non-autistic patients with a known and specifically contrasting genetic background. (2) To clarify how an autophagy-related gene, *Ambra1*, might contribute to autism and autistic phenotypes, namely early brain enlargement, and to uncover the cellular substrates thereof in our *Ambra1* mutant mouse model.