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# UNDERSTANDING PROPERTIES OF NEURAL STEM CELLS ISOLATED FROM A MONOGENIC MOUSE MODEL OF AUTISM EXPRESSING THE R451C NLGN3 MUTATION

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Adult neurogenesis takes place mainly in two niches, the sub-granular zone (SGZ) in the hippocampus and the sub--ventricular zone in the cerebral cortex, tightly regulated through the proliferation and self-renewal of neural stem cells (NSCs). Alterations of these processes have been reported in several neurodevelopmental disorder animal models, including autism spectrum disorders (ASDs).

Neuroligin-3 (Nlgn3) is a postsynaptic transmembrane protein involved in the assembly of excitatory and inhibitory synapses. Mutations in the Nlgn3 gene have been associated with monogenic forms of ASD. Specifically, the R451C substitution causes Nlgn3 misfolding and retention in the endoplasmic reticulum, which activates the unfolded protein response and reduces Nlgn3 protein levels in several brain regions.

We previously showed that Nlgn3-R451C knock-in (KI) mice have impaired adult hippocampal neurogenesis, and that prolonged fluoxetine treatment rescues both neurogenesis and social behavior. Starting from this observation, we asked whether the R451C mutation also affects NSCs directly. NSC lines were derived from the SGZ of KI and wild-type (WT) mice and compared using BrdU incorporation, XTT assay and neurosphere assays. KI NSCs showed higher proliferation than WT cells in all three assays.

We are now investigating whether the PI3K/AKT/mTOR pathway is involved in this phenotype, as it is a master regulator of NSC proliferation and has been reported to be altered by Nlgn3 loss. To this aim, we are measuring the phosphorylated and total levels of AKT and mTOR in KI and WT NSCs by western blot. Additionally, we are evaluating proliferation in Nlgn3-knockout (KO) cells following the exogenous expression of either the mutant or WT forms of the protein. These experiments aim to clarify whether Nlgn3 plays a direct role in NSC biology, independent of its established synaptic functions