Impact of a Costello Syndrome-Causing Mutation on Learning and Myelin-Producing Cells

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Background:

Costello Syndrome (CS) is a rare genetic disorder caused by hyperactivating mutations in the *HRAS* gene, which controls the RAS/MAPK intracellular pathway. Symptoms of CS typically include neurocognitive developmental delays, increased risk of autism spectrum disorder, intellectual disabilities, and other neurological issues. Additionally, most CS patients present with white matter (WM) abnormalities. WM has been proposed to regulate learning due to its roles in increasing/synchronizing action potentials and protecting neuronal axons. Females of a myelin-focused mouse model of CS (*PlpCre;HRasG12V*; *pHRas*) show learning deficits in a myelin-regulated test (the complex running wheel; CW) that resolve with time. To shed light onto the mechanisms of these learning deficits, the goal of our study is to describe changes in oligodendrocyte (OL; myelin-producing cells) lineage cells in *pHRas* mice.

Methods:

To correlate the cellular and functional impact of *HRas* mutation on OL lineage (OLL) cells, *HRas* mutation was induced in mature OLs (mOL) using a tamoxifen-inducible system. Four months after recombination, mice were subjected to the voluntary CW test (a wheel with unevenly spaced rungs), and learning curves were analyzed. An acquisition phase of 14 days was followed by a break from CWs of 3 weeks and a second CW phase of 7 days (memory of skills acquired). After the second exposure to the CW, mice were euthanized, and brain sections were collected for staining with DAPI (nucleated cells), GFP (recombinant cells), PDGFRα (oligodendrocyte precursor cells; OPCs), and Sox10 (OLL cells). Then, cell quantification was performed after conducting confocal imaging. Seven regions of the corpus callosum, across 4 coronal sections, were analyzed for regional differences in the numbers of PDGFRα$^+$ OPCs and Sox10$^+$ OLL cells.

Results:

Our antecedents show that at 2 weeks and 2 months post-mutation, there were significant decreases in distance, average speed, and max speed ran, as well as activity in mutant mice compared to WTs (defective learning curves). However, at 4 months post-mutation, there were no significant differences in learning curves between mutant and WT mice. We then wondered how OPC populations remained at 4 months post-tamoxifen when differences in behavioral phenotypes were no longer detected. We observed that the number of PDGFRα$^+$ OPCs decreased in the lateral region of the most anterior coronal section of the corpus callosum, suggesting non-cell-autonomous effects of *pHRas* on proliferation and/or differentiation of OPCs.

Conclusion:

Taken together, our results shed light on the role of the *HRas* mutation on CS mouse models that show transient learning deficits on the CW after the induction of the mutation. Our working hypothesis is that decreased number of OPCs may be a result of an increase in their differentiation into mOLs (to form myelin that restores learning) but lead to a proliferative exhaustion state. We propose an immediate impact (weeks) of *HRas* mutation on learning that is ameliorated by OPC differentiation < 4 months post-injection. Finding the mechanism of these events can aid in the understanding of this disease and in designing therapeutic treatments based on restoration of myelin function.