Effects of PTEN deficiency in the development of Purkinje cells

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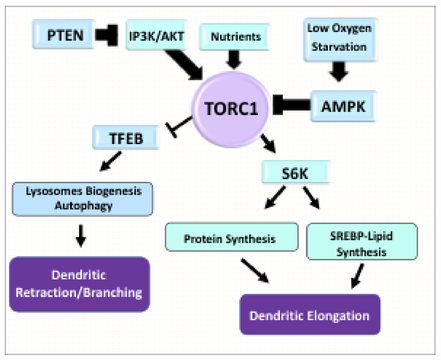
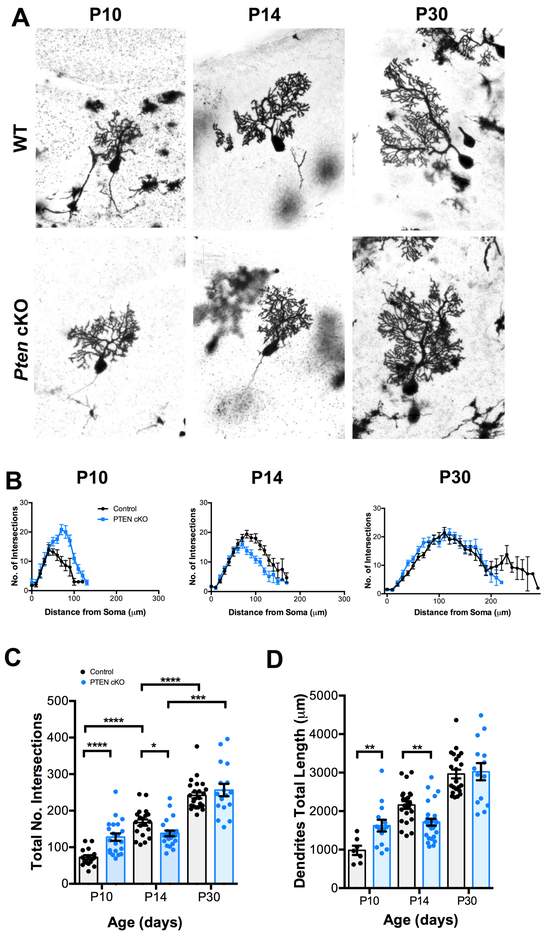
INTRODUCTION

Germline heterozygous mutations in Phosphatase and Tensin Homolog Deleted on Chromosome 10 gene (PTEN) are found in up to 20% of children with autism spectrum disorder (ASD) and macrocephaly. The conditional deletion of the *Pten* gene (*Pten*-cKO) in cerebellar Purkinje cells (PCs) causes cellular hypertrophy and neurodegeneration at adult stages. Interestingly, these mice develop autistic-like behavior including aberrant social interactions and repetitive behaviors even when *Pten* is only deleted in PCs. The effects of PTEN deficiency in the postnatal development of Purkinje cells are unknown. Because PTEN is an inhibitor of the AKT-mTORC1 pathway, which promotes anabolism and inhibits catabolism, we were intrigued on how deficiency of this protein could affect the postnatal development of PCs dendrites and if the effects caused by *Pten* deletion in PCs are driven by metabolic imbalances.

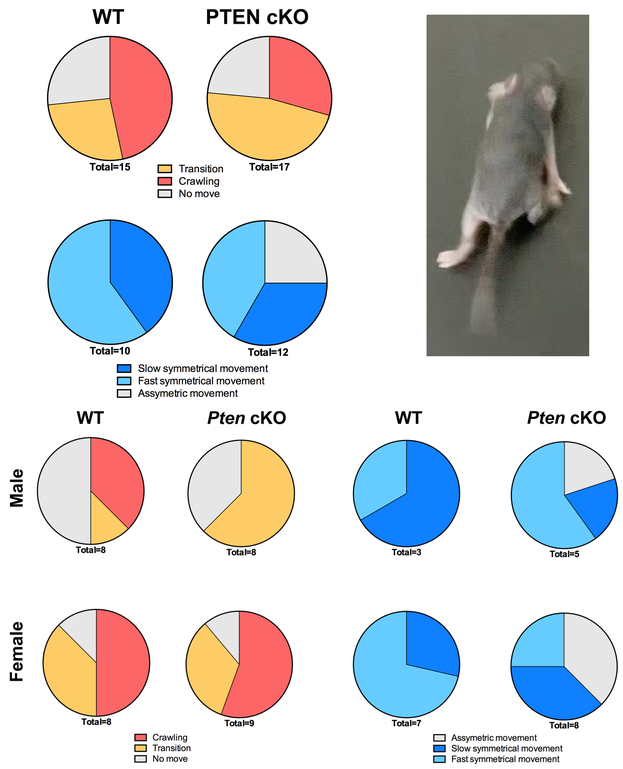
Our hypothesis is that lack of PTEN in PCs during postnatal development could affect the dendritic tree by promoting the overactivation of the mTORC1, which leads to TFEB inhibition (less lysosome biogenesis) and increased activation of S6K (more protein and lipid synthesis). The overactivation of mTORC1 could also lead to energy deficits and changes in AMPK activation. Our results show that this paradigm is more complicated and less predictable.



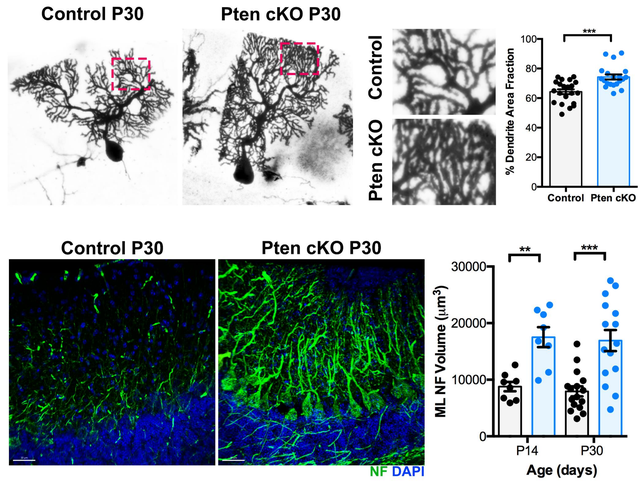
Effects of PTEN deficiency in mouse Purkinje cells dendritic early development



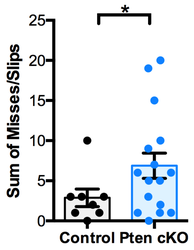
PTEN deficiency in Purkinje cells leads to postnatal motor deficits



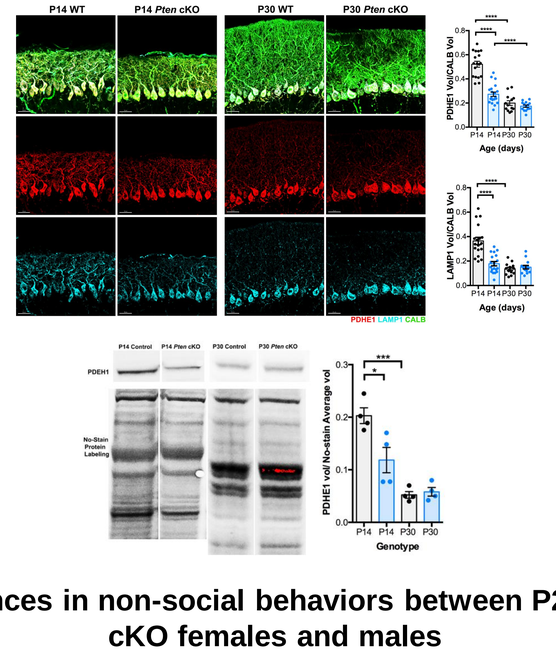
Changes in dendritic structure in *Pten* cKO Purkinje cells are associated with motor deficits at P30



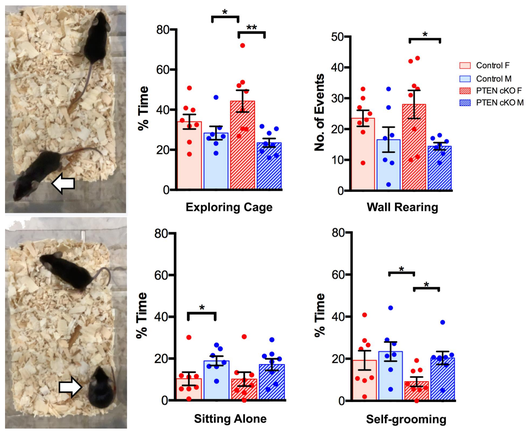
Horizontal Ladder



Changes in dendritic growth occur along changes in mitochondria and lysosomes density in developmental Purkinje cells



Differences in non-social behaviors between P21 *Pten* cKO females and males



CONCLUSION

- Lack of PTEN in PCs caused the overgrowth of dendrites at P10, which seems to be associated with the increased percentage of P8 *Pten* cKO pups going through a transition stage between crawling and walking.
- At P8, *Pten* cKO pups presented also more asymmetrical movement than WT mice, and significant differences were found between females and males.
- At P14, the PC dendritic trees from *Pten* cKO mice were slightly but significantly smaller than WT PC dendritic trees. By P30 the size of the PC dendritic tree was similar between WT and *Pten* cKO mice.
- PTEN deficiency caused changes in the dendritic cytoskeleton, and in mitochondrial and lysosomal density.
- Non-social behaviors are different between *Pten* cKO females and males.

ACKNOWLEDGEMENTS

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