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Genetic Disruption of Metabolic Balance in Mouse Cerebellar Neurons Causes Deficits in the Postnatal Development of Their Dendritic Tree and Mouse Motor Skills

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Genetic disruption of metabolic balance in mouse cerebellar neurons causes deficits in the postnatal development of their dendritic tree and mouse motor skills

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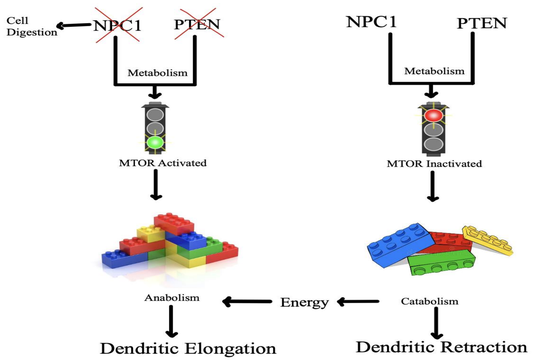
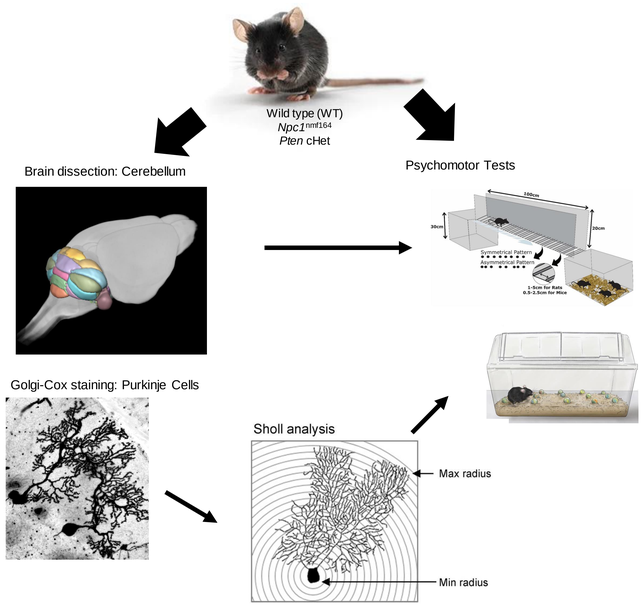
INTRODUCTION

The Npc1^{nmf164} mutant mouse is an animal model for the human disease Niemann-Pick type C (NPC). NPC is a lysosomal storage disease that is acquired by autosomal recessive inheritance. It is mostly caused by mutations in NPC1, a protein that transports cholesterol out of the lysosomes, therefore abnormal accumulation of cholesterol in lysosomes is a hallmark of NPC. Cerebellar Purkinje cells (PCs) are severely affected by NPC, in fact PCs degenerate first and to a larger extent at childhood stages. Therefore, we have been studying how the Npc1^{nmf164} mutation affects PC development during cerebellar postnatal development, a stage that precedes the degeneration of these cells in NPC.

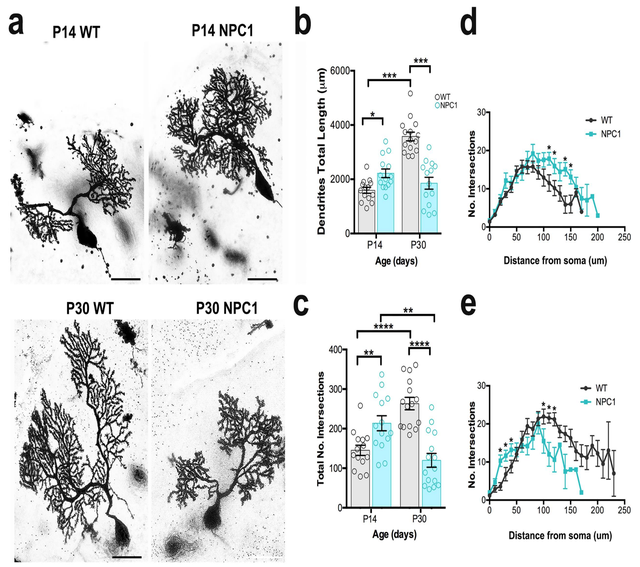
For the purpose of these experiments, Npc1^{nmf164} mice are used to examine changes in PCs using histological methods, microscopy, and imaging analysis. Our results suggest that lack of NPC1 alters the development of dendrites and synapses in PC by altering metabolic pathways. It has been shown that lack of lysosomal NPC1 causes the hyperactivation of the anabolic mTORC1 pathway, which also inhibits the production of lysosomes and catabolic processes such as autophagy. This disruption of metabolic pathways during the development of PCs may lead to developmental defects and predisposition to degeneration.



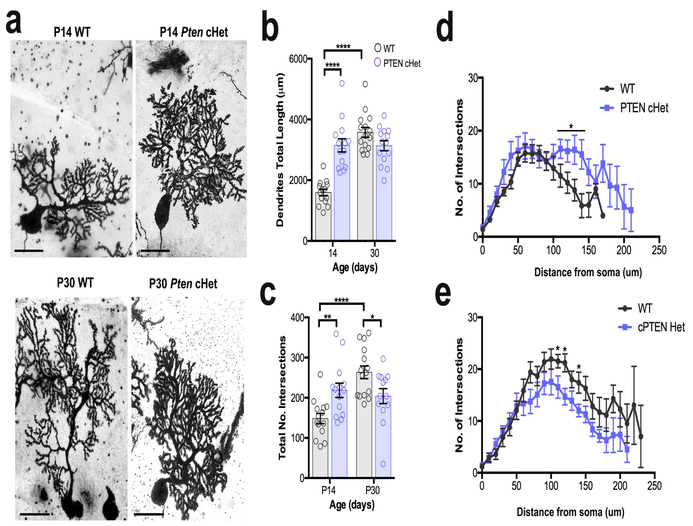
Experimental Strategy



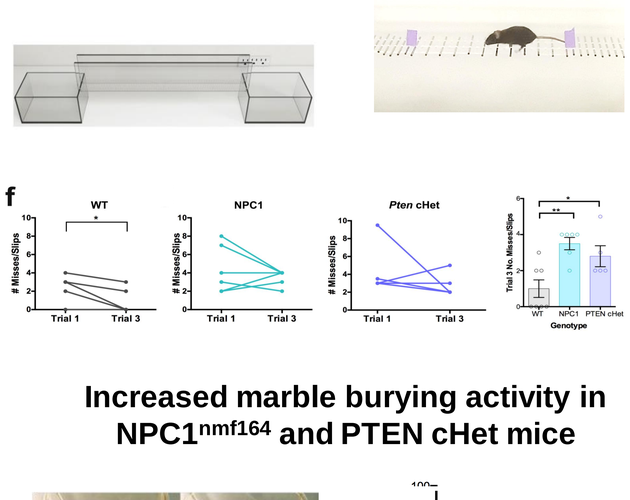
Developmental defects in Purkinje Cell dendrites from NPC1^{nmf164} mice



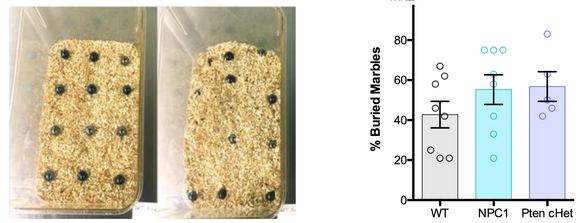
Developmental defects in Purkinje Cell dendrites from PTEN cHet mice



Ladder rung walking task reveals motor deficits in NPC1^{nmf164} and PTEN cHet mice



Increased marble burying activity in NPC1^{nmf164} and PTEN cHet mice



CONCLUSION

- NPC1 deficiency alters the postnatal development of Purkinje cell dendrites in Npc1^{nmf164} mice.
- Similarly, haploinsufficiency of PTEN in Purkinje cell alters the postnatal development of dendrites, suggesting that mTOR hyperactivation drives the deficits in dendritic development.
- Pathological changes in Purkinje cells are accompanied by deficits in psychomotor behavioral tests.
- Increased misses/slips in the ladder rung walking task during the 3rd trial were found in both mutant strains when compared to WT, suggesting motor deficits.
- The percentage of buried marbles was increased in the mutant strains when compared to WT suggesting behavioral deficits like perseverative and repetitive behaviors.

ACKNOWLEDGEMENTS

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