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Development

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PTEN is a negative regulator of the conserved PI3K pathway. Mutations in this gene are strongly associated with neurodevelopmental disorders, epilepsy, and schizophrenia. Several reports suggest that an increase in the excitation/inhibition ratio in the brain is a hallmark of these disorders. However, it is not known whether PTEN activity can lead to this E/I imbalance. The C. elegans NM system, where both excitatory (ACh) and inhibitory (GABA) motor neurons regulate muscle activity, provides a suitable model for studying E/I balance. We found that daf-18 (C. elegans ortholog of PTEN) mutants phenotypes are typical of worms with GABAergic signaling deficits. We also found that daf-18 mutants exhibit a significantly high frequency of process defects, abnormal branching, and incomplete commissures in GABAergic neurons. These defects are observed in the earliest larval stage (L1), suggesting a neurodevelopment failure. In contrast, we did not find significant differences in the morphology of cholinergic neurons. Our genetic experiments demonstrated that the GABAergic deficit in daf-18 mutants is entirely dependent on the inactivation of the transcription factor DAF-16/FOXO3A. Interestingly, we found that all these defects are ameliorated when daf-18 mutants are exposed to the ketone body hydroxybutyrate, a FOXO3A inductor. These results may contribute to understanding PTEN-associated disorders and the mechanisms linking ketogenic diets with an improvement in these pathologies.