Pten regulates the timing of photoreceptor differentiation by altering glycolysis and pH

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Introduction

• Visual impairment is devastating, affecting 2 billion individuals worldwide.
• A notable cause of vision loss in several blinding eye diseases, such as age-related macular degeneration, is the death or dysfunction of photoreceptors.
• Designing novel therapies requires a deep understanding of the factors affecting photoreceptor differentiation.

Herein, we investigated the role of Pten in photoreceptor development by conditional deletion in retinal progenitor cells (RPCs), using a Cre: driver and Pten allele to generate Pten cKO mice.

Fewer rods are present in Pten RPC-cKOs from P7

Transcriptomic differences in P0 Pten RPC-cKOs

Rod photoreceptor gene expression higher in P0 Pten RPC-cKOs

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Increased P3K signaling in Pten RPC-cKOs

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Gene networks that commit RPCs to differentiation expressed at lower levels in P0 Pten RPC-cKOs

Increased lactate production in Pten RPC-cKOs

Increased lactate production in Pten RPC-cKOs

Upregulation of glycolysis genes

Upregulation of glycolysis genes

Increased lactate production in Pten RPC-cKOs

Conclusions

• Pten RPC-cKO mice showed early rod photoreceptor differentiation followed by a decline at postnatal stages.
• Overall Rod photoreceptor numbers were significantly reduced at P7.
• Rod and cone differentiation genes and generic neural differentiation genes are down in P0 Pten RPC-cKOs.
• Glycolytic pathway genes are up in P0 Pten RPC-cKOs, which results in increased lactate production and reduce pH.

Reducing pH elevates rod photoreceptor differentiation in retinal explants.

References


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