Identifying Protocadherin Gamma-Dependent Signaling Pathways that Regulate Interneuron Survival in the Retina

Julia Qiao, Julie Lefebvre

Program for Neurosciences and Mental Health, The Hospital for Sick Children, Department of Molecular Genetics, The University of Toronto, Toronto, ON, Canada

Introduction

The clustered protocadherins (Pcdhs) encode a large family of transmembrane proteins. The 58 Pcdh genes are tandemly-arrayed in three clusters: Pcdh-alpha, Pcdh-beta, and Pcdh-gamma. In particular, the gamma Pcdhs (Pcdhγ) are especially important for promoting neuronal survival.

1. Neuronal survival during postnatal programmed cell death
2. PhosphoAKT expression

Goal

To determine if Pcdhγ promotes GABAergic interneuron survival through the PI3K-AKT pathway in the mouse retina

Objectives

1. Determine the function of PTEN in post-mitotic GABAergic interneuron survival in the retina.
2. Test for genetic interactions between PTEN and Pcdhγ

Methods

Conditional deletion alleles

Target GABAergic amacrine cells with Cre driver

Inactivates the 22 Pcdh genes

Gad-Cre: Early post-mitotic targeting of GABAergic neurons

Inactivates PTEN gene

Future Work

1. Are protein levels of Pcdhγ affected in PTEN mutants vs. WT?
2. Does PTEN regulate the cell surface expression of Pcdhγ?
3. Does Pcdhγ phosphorylation level change in PTEN mutants vs. WT?

Conclusions

1. PTEN regulates retinal GABAergic interneuron survival and in a cell-type autonomous manner.
2. Pcdhγ and PTEN converge in a similar pathway to regulate GABAergic interneuron survival.
3. Pcdhγ may function downstream of PTEN in the PI3K-AKT pro-survival pathway.

Results

1. Conditional deletion of PTEN is not sufficient to rescue GABAergic interneuron survival in Pcdhγ mutants

2. Conditional deletion of PTEN does not reduce apoptosis in Pcdhγ mutants during developmental programmed cell death

3. Conditional deletion of PTEN elevates phosphoAKT expression in Pcdhγ mutants despite increased programmed cell death