Proliferative reactive gliosis

Inducible p27 inactivation in adult retina recapitulates proliferative reactive gliosis

Loss of p27 binding to cyclin/CDKs increases Müller glial migration and GFAP upregulation

Forced p27 expression decreases OLM breakdown after retinal detachment

Pharmacological CDK inhibitors decrease Müller glial cell-cycle entry & nuclear migration in the p27 CKO

Genetic dissection of p27-mediated reactive gliosis

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Retinal trauma can activate Müller glia to enlarge, migrate, proliferate, and form scars

Virtually any challenge to adult mammalian CNS activates glia to undergo widespread molecular and cellular transformations, including hypertrophy, proliferation, migration and cytokine release. “Reactive gliosis” contributes to tissue repair but also to dysfunction, scar formation, aberrant neural rewiring, and vascular remodeling.

Inducible p27 inactivation in adult retina recapitulates proliferative reactive gliosis

A good candidate to target is the cell cycle inhibitor p27KIP1 (encoded by Cdkn1b). p27 downregulation correlates with early stages of glial reactivity and germline p27-deficiency results in a constitutive form of reactive gliosis. We have found out that conditional inactivation of p27 in adult mice results in upregulation of the intermediate filament GFAP (A-C), nuclear migration (D, E), and cell cycle entry (D-F) [Vázquez-Chona, submitted].

Pharmacological CDK inhibitors decrease Müller glial cell-cycle entry & nuclear migration in the p27 CKO

Pharmacological CDK inhibitors were injected into the eyes of p27 CKO mice. Our results are consistent with published data suggesting that CDK inhibitors decrease glial reactivity as well as enhance neuroprotection.

Model: p27 mediates negative regulation Müller glial reactivity by regulating cyclin-CDK complexes

Our genetic models suggest that p27 is a negative regulator of Müller glial reactivity. Conditional inactivation and forced expression of p27 as well as the loss of p27 binding to cyclins/CDKs suggest that p27 activity is most closely associated with glial migratory behavior and cell-cycle entry; whereas, gli hypertrophy appears to be a secondary event. We are currently optimizing the delivery and therapeutic window of pharmacological CDK inhibitors to rescue the down-regulation of p27 during trauma.