The Case for Neuroprotection in Glaucoma

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There is no RGC regeneration after optic nerve injury

Electrical Stimulation Protocol Mimics Retinal Activity in Developing RGCs

Electrical Activity Potentiates Survival in Response to BDNF
Electrical Stimulation Enters Clinical Trials

Bicarbonate stimulates RGC survival and axon growth

Ciliary Neurotrophic Factor (CNTF) Promotes Optic Nerve Regeneration

- Further enhanced by novel small molecule, F05 (NIH U01 grant)

Stem Cells Enhance RGC Axon Survival in Rat Glaucoma

Usher et al, J Neurosci 2009

Johnson et al. IOVS 2010

Usher et al, J Neurosci 2009
The Promise of Retinal Cell Transplant

Force Application Using Magnetic Microparticles

Do Neurons Lose the Ability to Regenerate Their Axons With Age?

Purification of Rat RGCs by Immunopanning

Embryonic and Postnatal RGCs Regenerate Axons in Vitro

Goldberg et al, Science 2002

1995
Embryonic RGCs Exhibit a Higher Intrinsic Axon Growth Rate

Axon Growth Ability Decreases Sharply Around Birth

What Changes in RGCs Underlie RGCs’ Developmental Loss of Intrinsic Axon Growth Ability?

Changing Gene Expression of Purified RGCs During Development

Cluster 1 - Decrease Perinatally

Cluster 2 - Increase Perinatally

Cluster 3 - Spike Perinatally

Changing Gene Expression of Purified RGCs During Development

Cluster 3 - Spike Perinatally
Few RGC Genes Change During Development and with Amacrine Cells

Change through development E17-P21

~75 of which change at P0-P1

Krüppel-like factor-4 (KLF4)
Overexpression Suppresses Neurite Growth

Total neurite length (% of control)

Optic Nerve Injury

DAYS 0 13 14

Optic nerve crush Anterograde label Collect nerves and retinas

RGCs Regenerate Further After Nerve Crush in KLF4 KO

KLF4 Is One of 17 KLF Family Members

Moore, Blackmore et al
Science, 2009
KLFs Differentially Affect Neurite Growth

KLFs’ Effects Sort By Sub-Family

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Summary II

• The KLF4 transcription factor is developmentally regulated in RGCs
• KLF4 overexpression decreases axon growth in RGCs in vitro (and in cortical neurons and hippocampal neurons)
• KLF4 KO during development enhances RGC regeneration in the optic nerve in the adult in vivo

Conclusions

• RGCs undergo a developmental decrease in intrinsic capacity for rapid axon growth
• Transcriptional control of axon growth ability through KLF family members may play a role in limiting axon regeneration in vivo

Future Directions

• Does modulating expression of multiple KLF family members enhance regeneration further?

Axon Loss 1st, RGC death 2nd

1. IOP raised early
2. Axon transport fails
3. Axon damaged
4. RGCs die late

Translation!!

• Neuroprotection
• Neuregeneration
• Neuroenhancement

• For us, science is slow…
• For patients, even slower…

Take Home

• Developing RGCs lose regenerative ability
• RGCs fail to survive after optic nerve injury
• Basic science approaches are yielding many candidates that deserve translation –
  – Electrical activity
  – Soluble adenylate cyclase, cAMP elevation
  – KLFs: more basic science left (NEI)
  – F05: moving to clinical predevelopment (NIH)
  – CNTF: in clinical trials for optic neuropathy now