1. Anatomy and Physiology of the Optic Nerve

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Optic Nerve and Anterior Visual Pathways

- Anatomy
- Physiology
RETINA

- 9 Layers
- Anatomical layout (horizontal raphe)
- 3 “functional layers”
  - Photoreceptors (rods and cones)
  - Bipolar cells and “integrators”
  - Retinal ganglion cells
Original Ramon Y Cajal from Golgi stain
Why Visual Fields respect Horizontal Raphe: Cogan, trypsin digest
Lesions of the optic disc/nerve

- Visual field defect = arcuate/central
- Less than 50% loss no effect on:
  - VF
  - VA
  - Contrast
  - Color
  - Disc appearance
OK, Stranger...
What's the circumference of the Earth?.. Who wrote "The Odyssey" and "The Iliad"... What's the average rainfall of the Amazon Basin?

Bart, you fool! You can't shoot first and ask questions later!
1B. Neuro-retina
(Neuroprotection and Apoptosis)

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Why Visual Fields respect Horizontal Raphe: Cogan, trypsin digest
If Neuroprotection = good for neurons then:

- Wearing a bicycle helmet is neuroprotection
DEATH
Poor Signaling: Black sail sent Ageus leaping to his death
RGCs = Neurons

Die from a variety of processes

- **Necrosis**
  - Chromotolysis (cellular breakdown)
  - Membrane disruption
  - Swelling of peripheral cytosol
  - Noxious to adjacent cells
  - Release of glutamate
  - Inflammatory changes

- **Apoptosis**
APOPTOSIS

- “Cell suicide”
- Programmed cell death
- Energy dependent
- Orchestrated series of intra-cellular events
- Involution of cell/quiet death
- Sparing of collateral damage
APOPTOSIS

What’s so good about it?

- Ontogeny
- Tumor control
- Neuronal specificity
Mitochondria again

- Once free living bacteria
- Lynn Margulis model of synergy
- Incorporation of ATP factories
- Also a built in TIME BOMB
How do retinal ganglion cells die?

“Notice all the computations, theoretical scribblings, and lab equipment, Norm. ... Yes, curiosity killed these cats.”
Extra cellular Signaling
  – FAS-Ligand
  – TNF

Death domain
Mitochondrial

Key lynch-pin

Membrane pot.

affected by

- ROS
- BAX

Stabilized by

- BCL-2
Open pores
Cytochrome C released

Nuclear gene control
- P-53 promotes
- P-35 blocks
Release
Mechanisms of RGC death

- Ischemia
- Cytotoxic (NMDA)
- Inflammatory
- Pro-inflammatory
- Energy depletion
- ROS
- Axonal compromise
  - Axoplasmic flow
  - Retrograde degeneration
AIDS OPTIC NERVE

- Macrophage
- migrating from
- small vessel in
- septal tissue
- Note deg. axons
AIDS OPTIC NERVE

- Degenerated axons
- Long standing
- Myelination of debris
AIDS OPTIC NERVE

Axonal deg.

Various stages
AIDS OPTIC NERVE

Macrophage

Toxic expression?
That can induce apoptosis
- TNF
- IL-1
- IL-2b
- IL-6
- IFN-g

That may mitigate apoptosis
- IL-10
- NGF
TNF BINDING TO TNF R1

- Liberation of G proteins
- Causing release of phospholipases
- Stimulating the release of arachidonic acid
- Elaboration of protein kinases
- Secondarily activating xanthine oxidase
- And reactive oxygen species (ROS)
How does glaucoma kill RGCs?

- Pressure
- Ischemia
- Neurotrophic factors
Mitochondrial Apoptotic Index

Disease

\{ L H O N \}

Mn SOD

ROS

\text{ROS} / \text{mtT}_{\text{area}} = \text{MAI}

Compensation (patient and tissue specific)

\{ \text{mtDNA}_{c} \rightarrow \text{protein} \}

\text{mtDNA}_{c}

\text{mtT}_{\text{area}}

\Delta \psi

\text{MPTP}

\text{Cyt C}

Apoptosis

determines patient penetrance and tissue specificity

\text{1a} \rightarrow \text{1c} \rightarrow \text{2a} \rightarrow \text{2b}
WHERE IS THE BEST PLACE TO BLOCK APOPTOSIS?

1) 0-1 hr: blocking TNF or FAS receptors
2) 1-3 hrs: blocking mitochondrial pores
3) 3-6 hrs: blocking secondary caspases
4) 6-8 hrs: DNA fragmentation

But processes not serial