206 Mechanisms of Axonal Damage in Optic Nerve Disease - Minisymposium

Monday, May 05, 2014 8:30 AM–10:15 AM
S 310A-D Minisymposium
Program #/Board # Range: 1247–1253
Organizing Section: Glaucoma

Program Number: 1247
Presentation Time: 8:30 AM–8:45 AM
Mechanisms of axonal degeneration
Gareth Howell. Jackson Laboratory, Bar Harbor, ME.

Presentation Description: Glaucoma is primarily an axonopathy but the processes that lead to RGC axon degeneration are not clear. Using a combination of genetic and genomic approaches in mice we have identified a number of processes in non-neuronal cells such as astrocytes and microglia/monocytes that appear to be precede obvious axon dysfunction including axon transport compromise. Targeting these processes has both beneficial and damaging effects in mice and so it will be important to understand these processes fully before developing human therapies.

Commercial Relationships: Gareth Howell, None
Support: NH Grant EY021525

Program Number: 1248
Presentation Time: 8:45 AM–9:00 AM
Stress-Induced Modulators of Axonopathy in Glaucoma
David J. Calkins. Vanderbilt Eye Institute and Vanderbilt Brain Institute, Vanderbilt University Medical Center, Nashville, TN.

Presentation Description: Glaucoma involves two broad degenerative programs that challenge the survival of retinal ganglion cells (RGCs). An early distal program affects RGC axons in the optic projection, progressing spatially in retinotopic sectors, while a proximal program targets dendrites, synapses and cell bodies in the retina. Two primary stressors influence progression: aging and sensitivity to intraocular pressure. A major area of emphasis includes how age and pressure combine to induce both distal degeneration and intrinsic neuronal and astrocytic repair responses in the optic projection that may slow axonopathy. The talk also will address the relationship between distal and proximal programs, recent experimental therapies that target molecular regulators of stress, and what new interventions teach us about the mechanisms of axonopathy.

Commercial Relationships: David J. Calkins, Alcon Research (F), Allergan (C), Harbor Therapeutics (F)
Support: NIH Grants EY017427 and P30EY008126; BrightFocus Foundation; Research to Prevent Blindness; Glaucoma Research Foundation

Program Number: 1249
Presentation Time: 9:00 AM–9:15 AM
Transcellular degradation of axonal mitochondria by optic nerve astrocytes
Nick Marsh-Armstrong. Neuroscience and Ophthalmology, Johns Hopkins University School of Medicine, Baltimore, MD.

Presentation Description: Previously we had described that astrocytes in the optic nerve head of wildtype mice phagocytose material derived from axons, and that several molecular markers associated with this phagocytic activity are elevated in animal models of glaucoma. Here, we demonstrate that a major axonal component being phagocytosed by the optic nerve astrocytes of wildtype mice are retinal ganglion cell mitochondria. By a combination of block-face scanning electron microscopy, a novel viral reporter for degrading mitochondria, and a second novel method to detect degrading mitochondria, we demonstrate that large numbers of retinal ganglion cell mitochondria are degraded by this heretofore unknown transcellular degradation process.

Commercial Relationships: Nick Marsh-Armstrong, None
Support: RO1 EY022680 and “Catalyst for a Cure” grant from the Glaucoma Research Foundation and the Melza M and Frank Theodore Barr Foundation

Program Number: 1250
Presentation Time: 9:15 AM–9:30 AM
Mitochondrial OXPHOS failure - a burden for long axons
Ian Trounce. Center for Eye Research Australia, University of Melbourne, Melbourne, VIC, Australia.

Presentation Description: A common theme in mitochondrial diseases is the preferential demise of neurons with extended axons, with the retinal ganglion cell being a model case. In addition to the classic mitochondrial optic neuropathies, RGCs and the optic nerve are often affected in syndromic mitochondrial diseases. The interplay between OXPHOS dysfunction, mitochondrial turnover, and axonal transport of the organelle will be discussed from the perspective of both in vitro and in vivo models, with an emphasis on implications for glaucoma pathogenesis.

Commercial Relationships: Ian Trounce, None
Support: NH&MRC, ORIA, AHAF

Program Number: 1251
Presentation Time: 9:30 AM–9:45 AM
Axonal damage, autophagy and neuronal survival
Patricia Boya. Cellular and Molecular Biology, CIB-CSIC, Madrid, Spain.

Presentation Description: Autophagy as the main process for intracellular recycling of macromolecules and organelle is essential to maintain cellular function in postmitotic cells, such as neurons. This protective function of autophagy in neurons is highly relevant from the developmental stage, since deleting Atg5 or Atg7 only in neural precursors has important consequences in adult life resulting on neurodegeneration and premature death. In addition autophagy is implicated in neurodegeneration either as a pro-survival or a pro-death mechanism. How autophagy exerts these dual effects is currently unknown. Recent evidence from our laboratory demonstrates that autophagy can protect the cell soma after axonal traumatic injury. Using a well-known model of RGC degeneration, optic nerve axotomy, we show that autophagy is strongly upregulated following the insult and before cell death. Genetic downregulation of autophagy using knockout mice for several autophagy regulators reduces cell survival after optic nerve axotomy, whereas pharmacological induction of autophagy in vivo increases the number of surviving cells. In this presentation I will explain the idea that autophagy has a cytoprotective role in RGCs after axonal damage and may provide a new therapeutic strategy to ameliorate retinal diseases.

Commercial Relationships: Patricia Boya, None
Support: SAF2009-08082

Program Number: 1252
Presentation Time: 9:45 AM–10:00 AM
Axon-oligodendrocyte interactions
Peter Van Wijngaarden. ‘Cambridge University, Cambridge, United Kingdom; ‘Centre for Eye Research Australia, East Melbourne, VIC, Australia.

Presentation Description: This presentation will provide an overview of recent advances in our understanding of oligodendrocyte biology, with a key focus on remyelination. Remyelination, the process in which resident oligodendrocyte progenitor cells (OPC)
differentiate into remyelinating oligodendrocytes, serves as an endogenous repair mechanism following episodes of demyelination. Unfortunately the efficiency of this repair process declines dramatically with age, largely as a result of the failure of OPC differentiation. Recent work utilizing the experimental paradigm of heterochronic parabiosis has demonstrated a central role of monocytes in the process and has highlighted that remyelination can be rejuvenated. Insights gleaned from this and other work examining axon-oligodendrocyte interactions will be presented in the context of ophthalmic disease.

**Commercial Relationships:** Peter Van Wijngaarden, None  
**Support:** NHMRC of Australia (Post-doctoral Research Fellowship); European Leukodystrophy Association; Research into Ageing; the UK Multiple Sclerosis Society and the National Multiple Sclerosis Society.

**Program Number:** 1253  
**Presentation Time:** 10:00 AM–10:15 AM  
**Imaging axonal transport and degeneration**  
*Brad Fortune.* Devers Eye Institute, Legacy Health, Portland, OR.

**Presentation Description:** This presentation will review techniques we have used for in vivo assessment of axonal transport and degeneration in experimental models of optic nerve injury including experimental glaucoma. Results will be presented in the context of their translational potential to clinical diagnostics, patient management and pathophysiological sequence of glaucoma.

**Commercial Relationships:** Brad Fortune, Carl Zeiss Meditec, Inc. (equipment support) (F), Heidelberg Engineering, GmbH (equipment support) (F)  
**Support:** NIH/NEI: R01-EY019327, R21-EY021311