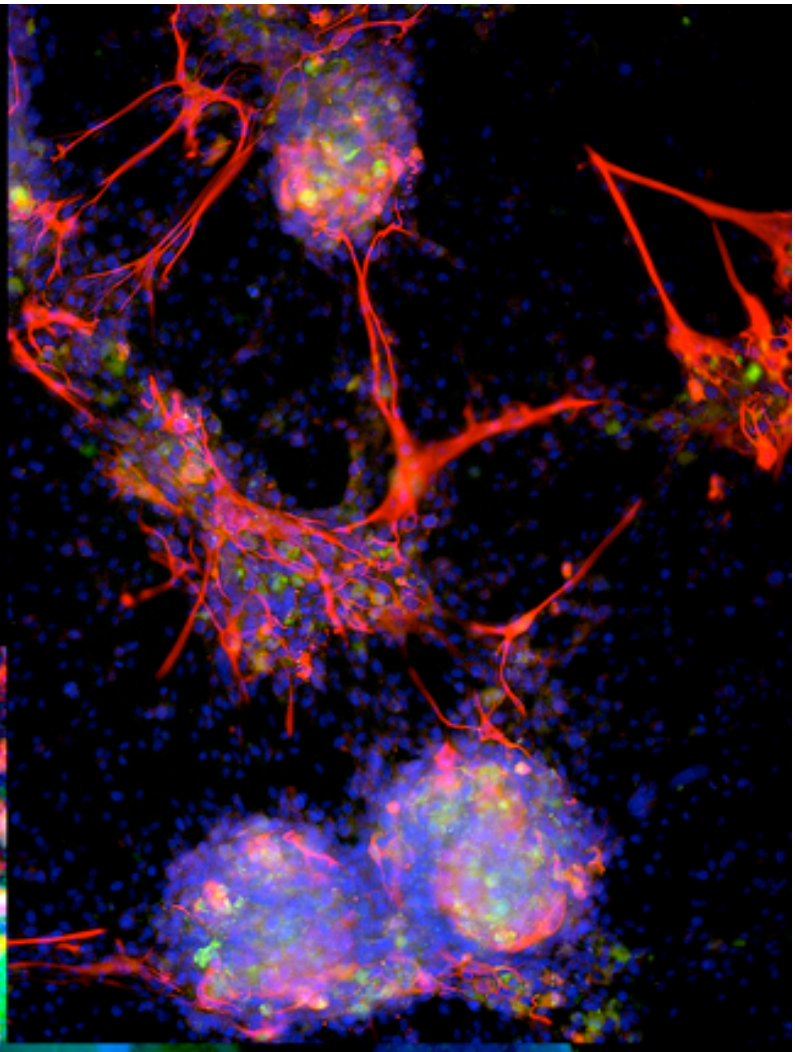
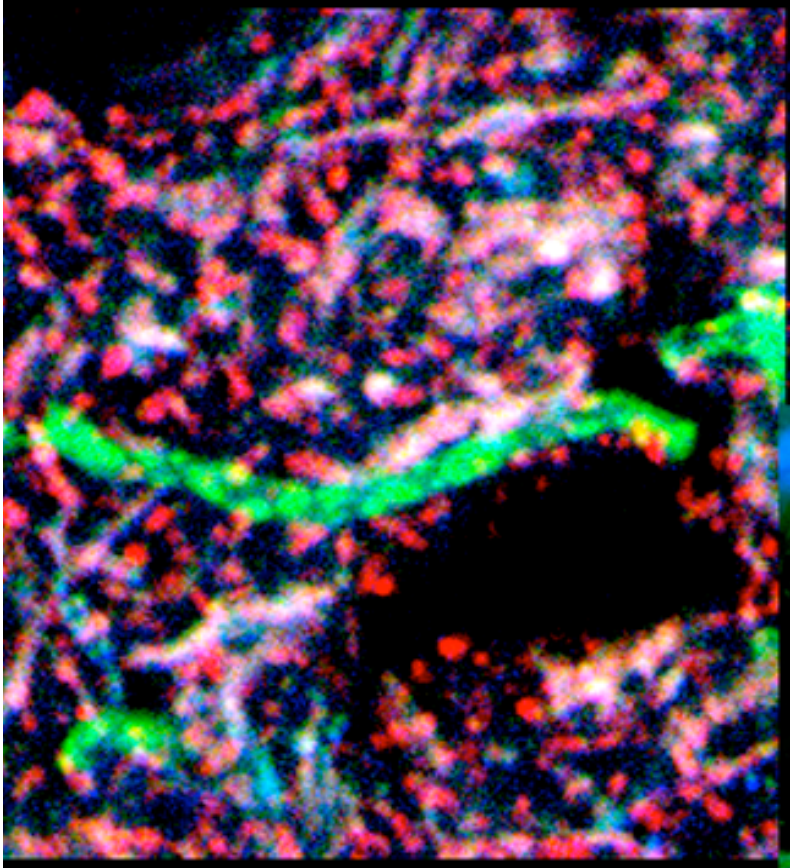
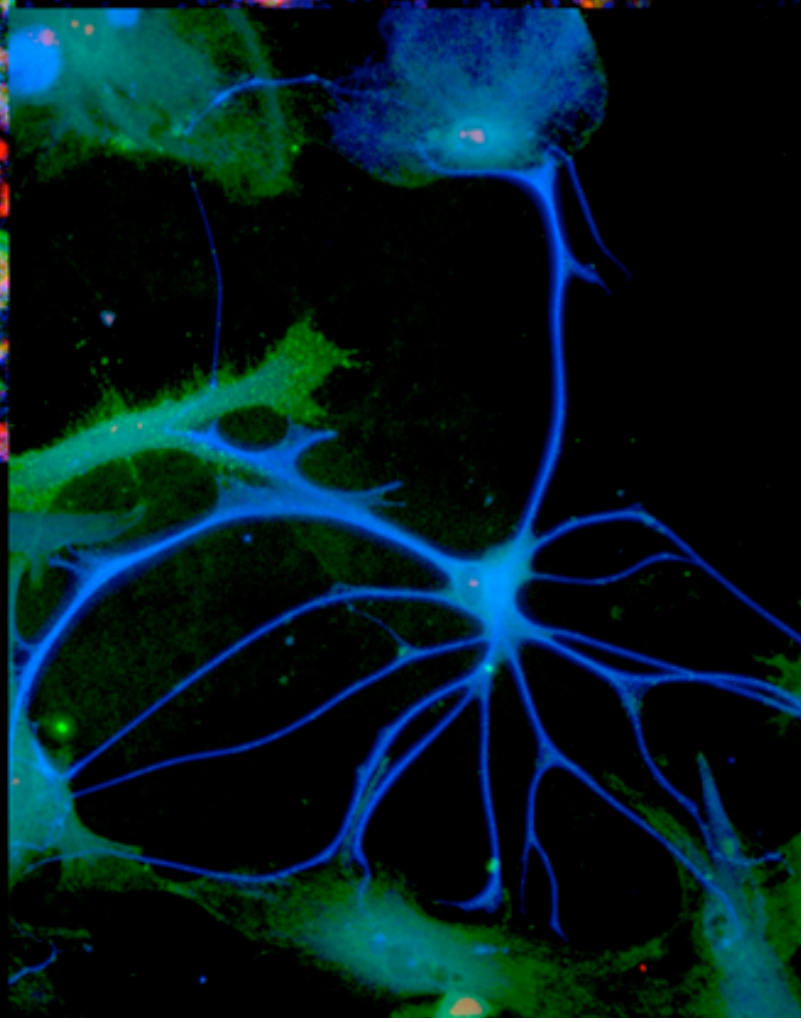
10th Great Lakes Glia Meeting







Park Place Hotel
Traverse City, MI

September 27-29, 2015

Great Lakes Glia 2015
http://www.grad.uiowa.edu/GLG
The Park Place Hotel, Traverse City, MI

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The Park Place Hotel, Traverse City, MI
September 27th – 29th
http://www.grad.uiowa.edu/GLG

Committees

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Cover illustrations

Center left: confocal microscopy from a mouse brain with extra copies of the *Plp1* gene stained for myelin with proteolipid protein ab (green), COX1 in mitochondria (blue), Mia40 a mitochondrial import and folding protein (red), showing co-localization of all 3 markers in white. SKOFF lab at Wayne State University.

Upper right: Cultured astrocytes derived from LKB1 (liver kinase B1) floxed mice. GFAP is in red, AAV-Cre-GFP (green) shows LKB1 knocked out with GFAP and GFP in yellow showing overlap. FEINSTEIN lab at University of Illinois Chicago.

Bottom right: Cultured type 1 and type 2 cortical astrocytes after a cytotoxicity assay. Type 1 astrocytes are stained only with GFAP (blue), Type 2 astrocytes are stained with GFAP (blue) and A2B5 (green), and dead astrocytic nucleus are stained with ethidium homodimer (red). JAIMAN-CRUZ lab at Michigan State University.

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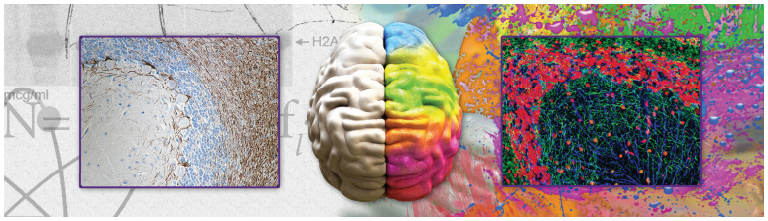

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Great Lakes Glia 2015
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Sunday, September 27th

4:30 PM **Opening Reception** **Top of the Park**

5:30 PM **Dinner** **Top of the Park**

7:00 PM **Session 1 – Microglia** **Lakes Room**

Organizers: Douglas Feinstein, University of Illinois, Chicago
Jyoti Watters, University of Wisconsin, Madison

Jyoti Watters, University of Wisconsin, Madison
Regulation of microglial plasticity by epigenetic mechanisms

Richard Kraig, University of Chicago
Microglia, migraine & multiple sclerosis

Diana Norden, The Ohio State University, Columbus
Microglia of the aged brain: primed to be activated and resistant to regulation

Great Lakes Glia 2015
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Monday September 28th

8:00 AM **Breakfast** **Ballroom Dome**

8:45 AM **Keynote Presentation** **Lakes Room**

Wendy Macklin, University of Colorado at Denver
What signals regulate CNS myelination and are they important?

9:45 AM **Break**

10:00 AM **Session 2 – Stem Cells and iPSCS** **Lakes Room**
Organizer: Margot Mayer Proschel, University of Rochester

John Kessler, Northwestern University, Chicago
Regulation of gliosis after spinal cord injury
Chris Proschel, University of Rochester
Heterogeneity of pluripotent stem cell derived astrocytes: impact on regeneration
Mark Noble, University of Rochester
Melding metabolism and stem cell biology to develop new treatments for gliomas and for lysosomal storage disorders
David Braun, University of Illinois, Chicago
LKB1 depletion from astrocytes induces a stem cell phenotype
Biplab Dasgupta, University of Cincinnati
AMP-ing up our understanding of AMPK function in cancer

Noon **Free time**

3:30 PM **Poster Session** **Courtyard**

4:30 PM **Session 3 – Astrocytes** **Lakes Room**
Organizer: Sandra Hewett, Syracuse University

Marion Buckwalter, Stanford University, Palo Alto
Astrocytic TGF-beta signaling regulates brain inflammation in toxoplasmic encephalitis
M. Kerry O'Banion, University of Rochester
New roles for neuroinflammation in Alzheimer's disease
Sandra Hewett, Syracuse University
Astrocyte system xc- at the cross-roads of injury and protection
John Bethea, Drexel University, Philadelphia
Astroglial-NFkB and TNF signaling in CNS injury and repair

7:00 PM **Dinner** **Top of the Park**

8:30 PM **Posters and Refreshments** **Courtyard**

Great Lakes Glia 2015
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Tuesday September 29th

7:30 AM **Breakfast** **Top of the Park**

8:15 AM **Keynote Presentation** **Lakes Room**

Larry Wrabetz, University of Buffalo
Endoplasmic stress and proteostasis in the pathogenesis and treatment of demyelination

9:30 AM **Session 4 – Peripheral Neuropathies** **Lakes Room**
Organizer: Jun Li, Vanderbilt University, Nashville

Bruce Carter, Vanderbilt University, Nashville
Role of NFkB signaling in the demyelination of CMT1A
Riqiang Yan, Cleveland Clinic Foundation, Cleveland
BACE1 in axons and Schwann cells for remyelination
Michael Shy, University of Iowa, Iowa City
Myelin protein zero and UPR
Kelly Monk, Washington University, St. Louis
Molecular and genetic mechanisms of Schwann cell development
Jun Li, Vanderbilt University, Nashville
Tuning p21-activated kinase to rescue abnormal myelin permeability in HNPP

11:30 PM **Distribution of box lunches**

11:45 AM **Session 5 – Glial Cells in Aging** **Lakes Room**
Organizer: Anne Boullerne, University of Illinois at Chicago

Patrizia Casaccia-Bonnefil, Mount Sinai School of Medicine, New York
Epigenetic changes in aging glia
Carmela Abraham, Boston University School of Medicine
The role of the anti-aging protein Klotho in OPC differentiation and remyelination of the CNS
Wolfgang Streit, University of Florida, Gainesville
Microglial senescence during normal and pathological aging
Laura Kubik, Duke University, Durham
Astrocyte mitochondria: region-specific susceptibility in aging
Farida Sohrabji, Texas A&M HSC, Bryan-College Station
Astrocytes during aging

1:45 PM **End of meeting**

Abstracts

The role of the anti-aging protein Klotho in OPC differentiation and remyelination of the CNS

Carmela R. Abraham
Departments of Biochemistry and Pharmacology & Experimental Therapeutics, Boston University School of Medicine, Boston, MA 02118

Normal aging of the brain presents as significant changes in the white matter, while the gray matter is largely spared. In a comprehensive cross sectional study which included behavior, MRI, electron microscopy, immunohistochemistry and biochemistry in young, middle age and old rhesus monkeys, our group reported an age-related cognitive decline in 50% of the animals, a steady decline in white matter volume, ultrastructural abnormalities of the myelin sheath, breakdown of the myelin at the biochemical level and activation of microglia and astrocytes in the white, but not the gray matter. To understand potential mechanisms leading to white matter deterioration and associated cognitive decline, we conducted a microarray analysis of RNA isolated from young and old monkey brains. One of the genes significantly downregulated in the aged brain was Klotho. Klotho is an anti-aging gene discovered in a Klotho deficient mouse that exhibited many signs of aging and premature death. Klotho is expressed mainly in kidney and brain, and while in the kidney, Klotho controls the levels of phosphate, calcium and Vitamin D via its interaction with the FGF receptor and FGF23, its brain function was unknown. We showed that Klotho knockout mice suffer from severe hypomyelination. Furthermore, the addition of Klotho to oligodendrocyte progenitor cells induces their maturation to myelin producing oligodendrocytes. Most interestingly, Klotho overexpressing mice have better cognition on a number of behavioral tasks. Finally, when demyelination was induced by cuprizone in wild type and Klotho overexpressing mice, the number of remyelinated axons was twice as high in the Klotho overexpressing mice compared to their control littermates. In summary, Klotho is an important factor for the integrity of myelin and increasing its levels in the brain using small molecule compounds can improve myelin integrity and cognition in normal aging and demyelinating diseases.

Genetic- and Chemical-based Corrections for Myelin Disorders

Matt Elitt[1], Mayur Madhaven[1], Elizabeth Shick[1], Paul Tesar[1]
[1]Case Western Reserve University, Department of Genetics and Gen. Sci.

Leukodystrophies afflict 1 in 7,500 newborns in the United States, and are characterized by oligodendrocyte loss, severe hypomyelination, and pronounced neurological deficits. These diseases can be interrogated by a number of animal models including the well-characterized *jimpy* mouse. This mouse harbors a dominant-negative point mutation in its *proteolipid protein 1* (*PLP1)* gene on the X chromosome, and recapitulates many of the pathological hallmarks of Pelizaeus-Merzbacher Disease (PMD)---a severe human leukodystrophy. We have recently reprogramed *jimpy* mouse fibroblasts to generate multiple induced pluripotent stem cell lines. This cellular platform provides a scalable source of material to characterize key developmental events by molecular, phentotypic, and functional means *in vitro*. This resource also facilitates the development of CRISPR-based therapies and the screening of small molecules in a high-throughput format to identify novel therapeutics, both for the purpose of ameliorating the underlying pathology seen in the *jimpy* mouse. Furthermore these two treatment paradigms may be directly translatable to human PMD patients.

Abstracts

ACTH1-39 Protects Oligodendroglia by Both Direct and Indirect Mechanisms Robert P. Lisak, Liljana Nedelkoska and Joyce A. Benjamins
Dept. of Neurology, Wayne State University School of Medicine, Detroit MI

ACTH acts on melanocortin receptors to directly protect purified OL from death induced by staurosporine, glutamate, NMDA, AMPA or kainate, quinolinic acid (QA) or ROS, but not NO or kynurenic acid (KA). To investigate if ACTH can also protect OL indirectly via effects on astroglia (AS) or microglia (MG), we treated purified AS or MG with ACTH for 24 hours, removed ACTH, then cultured for 24 hours to produce conditioned medium (CM ACTH**).** Rat OL were cultured with ACTH, AS CM ACTH, MG CM ACTH or control medium with or without the toxic molecules; OL death was assessed by trypan blue uptake. AS CM ACTH protected from glutamate, NMDA, AMPA, QA or ROS but not kainate, stauro-sporine, NO or KA. MG CM ACTH did not protect from any of these molecules, nor did CM from AS or MG not treated with ACTH. Conclusions**:** Protection of OL by ACTH from several toxic molecules involves direct effects on OL. ACTH induces AS to produce soluble mediators that protect against some of these molecules but not others. ACTH does not stimulate MG to provide protection under these conditions. Thus the protective effects of ACTH for OL are complex, varying with the toxic molecules. *Investigator Initiated Research Award (RPL) from Mallinckrodt Pharm., Autoimmune & Rare Diseases (formerly Questcor Pharm.) and Parker Webber Chair in Neurology (DMC Foundation/WSU)(RPL).*

Cyclic AMP Inhibits IFN-γ Induction of MHC II and ICAM-1 in Schwann Cells Robert P. Lisak, Beverly Bealmear, Joyce A. Benjamins
Dept. of Neurology, Wayne State University Sch. Med., Detroit, MI

Incubation of SC with IFN-γ upregulates MHC class II and ICAM-1. In nerves of EAN animals and patients with PNS diseases, MHC II is expressed on inflammatory cells, rarely on SC. We hypothesized that the state of SC maturation, in part regulated by axolemma, influences SC expression of MHC II and ICAM-1. We reported that incubation of SC *in vitro* with 8-bromo cAMP mimics some *in vivo* axolemma effects and inhibits IFN-γ increases in MHC II and ICAM-1. To determine if IFN-γ effects were *reversed* by cAMP and if IFN-γ upregulated MHC II and ICAM-1 by SC already treated with Br cAMP, we incubated SC from neonatal rat sciatic nerve with various combinations of IFN-γ and Br cAMP. IFN-γ induced MHC II on 50% of SC; control SC and SC with Br cAMP alone did not express MHC II. IFN-γ upregulated ICAM-1 above a low basal level. Br cAMP and IFN-γ together inhibited MHC II and ICAM-1. Adding Br cAMP after IFN-γ inhibited ongoing expression of MHC II and ICAM-1. Adding IFN-γ to SC already exposed to Br cAMP also reduced expression of both MHC II and ICAM-1. Variability in expression of MHC II and ICAM-1 by SC *in vivo* in the presence of inflammatory cytokines may represent variability in axolemmal signals to SC. *Supported by GBS/CIDP Foundation Int.(RPL) and the Parker Webber Chair Endowment (DMC Foundation/WSU)(RPL).*

Abstracts

ONE OR TWO BANDS? QUESTION FOR IGM OLIGOCLONAL BANDS IN CONFIRMED MULTIPLE SCLEROSIS

Anne Boullerne1, Charlotte Hvaring2, Noor Alawad1, Snezana Vujicic1, Harald Hovdal2,3, Linda White2,3
1 University of Chicago at Illinois, Department of Anesthesiology, Medical Sciences Building, Chicago, USA. 2 Norwegian University of Science and Technology, Department of Neuroscience, Trondheim, Norway
3 Norwegian University of Science and Technology St. Olavs Hospital, Department of Neurology, Trondheim, Norway

Background We previously reported specific IgM against *S*-nitrosylated proteins (anti-SNOcys) in the cerebrospinal fluid (CSF) of relapsing–remitting multiple sclerosis (RRMS) patients. By contrast, anti-SNOcys IgM were not detected in the CSF of patients with mild neurological conditions and normal IgM levels, whereas RRMS patient CSF had moderately elevated IgM levels. We formerly showed that CSF anti-SNOcys IgM inversely correlate with relapse onset, suggesting this specific IgM antibody is a potential biomarker from intrathecal synthesis. We aimed to (1) verify intrathecal synthesis by occurrence of IgM oligoclonal bands in CSF; (2) compare these bands with established mathematical formulae including IgM index and Reibergram; and finally (3) explore how well the presence of anti-SNOcys IgM in CSF measures to these factors, particularly IgM oligoclonal bands, for MS diagnosis accuracy.
Methods CSF from 18 patients with RRMS and 14 patients with mild neurological symptoms were analysed for IgM levels, oligoclonal bands, 5 mathematical formulae of intrathecal synthesis and anti-SNOcys IgM. Sensitivity, specificity, and receiver operating characteristic curves were generated to examine the ability of these parameters to accurately distinguish RRMS patients from controls.
Results The presence of only one extra IgM oligoclonal band in CSF gave the best accuracy for MS diagnosis. If the conventional cut-off of two bands was applied, several false negatives arose, though no false positives. The IgM index was found the most accurate of all mathematical formulae followed by anti-SNOcys IgM.
Conclusions We conclude that the IgM index appears to be an old robust formula which can be more easily applied if the delicate detection of IgM oligoclonal bands is not feasible. The current standard of two extra IgM oligoclonal bands may be too stringent for a diagnosis of MS. The demonstration of at least one extra IgM oligoclonal band in CSF supports a prominent role of IgM in RRMS, and confirms anti-SNOcys IgM as potential biomarker. This work is supported by a grant from the Norwegian University of Science and Technology (NTNU) Faculty of Medicine.

Abstracts

David Braun, Paul Polak, and Douglas L. Feinstein
University of Illinois at Chicago

Our lab recently identified a single nucleotide polymorphism in the STK11 gene as a novel risk factor for multiple sclerosis in women. STK11 encodes the liver kinase b1 (LKB1) protein, a serine/threonine kinase involved in many vital signaling pathways including those controlling cell meta-bolism, growth, and polarity. It is also a known tumor suppressor, and mutations in STK11 are found in numerous forms of cancer in peripheral tissues. To study the role of LKB1 in the central nervous system, we acquired a strain of mice with STK11 flanked by loxP sites. Using an adenoassociated virus driving Cre recombinase expression, we knocked out LKB1 from primary cortical astrocytes cultured from post-natal day 1 mouse pups. Subsequently, the LKB1 knockout astrocytes (ALKO cells) began to proliferate rapidly and demonstrate characteristics of transformed cells: loss of contact inhibition, anchorage independent proliferation, enhanced migratory capability, and immortalization. Interestingly, the ALKO cells also began to express the stem cell markers Sox2, Oct4, and Nanog. In preliminary experiments we have also successfully driven the expression of oligodendrocyte and neuron specific markers in these cells. These findings have two major implications. The first is that decline in LKB1 expression or activity may play a role in glioma pathology, and that this cell line may be useful as a glioma model. The second is that inhibition of LKB1 activity may represent a novel way of reprogramming astrocytes back into multi- or pluripotent cells. Further studies to explore the relevance of LKB1 dysfunction in human gliomas, map the multi- or pluripotent potential of these cells, and validate their use as a model system are underway. Additionally, we are currently attempting to replicate the results using siRNA knockdown of LKB1 expression.

Activation of Enteric Glia Contributes to Enteric Neuron Death in Inflammation

Brown I[1], McClain J[1], Patel B[2] and Gulbransen B[1]
[1]Michigan State University and [2]University of Brighton

Enteric glia (EG) surround enteric neurons and aid in the upkeep of enteric circuits and normal gut function. Astroglial activation in the CNS drives neuron death during inflammation thus, we hypothesized that EG activation promotes neuronal loss in the ENS. We activated EG in situ with P2Y1 receptor agonists and measured glial ATP release and neuronal survival. Glial activity was monitored using Ca2+ imaging and glial ATP release pathways were modulated by altering nitric oxide (NO) and connexin-43. P2Y1R agonists activated EG, drove ATP release through Cx43 channels and reduced neuron density. Inhibition or ablation of glial Cx43 prevented P2X7R-driven neuron death *in situ* and *in vivo*. Cx43-dependent glial ATP release was potentiated by NO and Cx43 inhibition protected against NO-mediated neuron death. Our data demonstrates a novel pathogenic role of enteric glia where direct glial activation is sufficient to cause enteric neuron loss in a Cx43 and NO dependent manner.

Abstracts

Chronic Stimulation of GFAP::hM3Dq Receptors on Glia Induces Functional but not Morphological Changes in the ENS

Delvalle-Dorta NM, Fried DE, McClain JL, Gulbransen BD
Michigan State University, East Lansing MI 48824

The Enteric Nervous System (ENS) is the major neural regulator of gastrointestinal (GI) function exerting control over GI reflexes including peristalsis. Enteric circuits require precise interactions between neurons and glia and breakdown of these circuits leads to GI dysfunction. During inflammation, these circuits are altered and enteric glia undergo reactive gliosis that can alter their function. Using novel GFAP::hM3Dq transgenic mice, this study aims to study the role of enteric gliosis in the development of motility dysfunction. Glia were selectively activated *in vivo* and morphological and functional changes were measured by immunohistochemistry, pellet production assay and colonic migrating motor complex recordings. Although stimulation did not induce morphological changes in glia, functional changes were observed in GI motility suggesting other mechanisms of activation may be involved in inducing enteric gliosis.

A two-pronged approach to study myelination

Mitch D'Rozario, Sarah Petersen, Amit Mogha, Breanne Harty, Sarah Ackerman, Amy Herbert, Zachary Spence, Charleen Johnson, Kelly R. Monk
Department of Developmental Biology, Washington University School of Medicine, St. Louis, MO

Schwann cells (SC) are specialized glial cells that form myelin around axons in the peripheral nervous system. During development, immature SCs array around many axons, radially segregate axon segments into a 1:1 relationship, and repeatedly wrap their membranes around their associated axon to create the myelin sheath. The importance of myelin is best underscored in diseases in which loss or damage of myelin have devastating symptoms. To date, no effective therapeutic strategies exist. Despite the importance of myelin, the genetic and molecular mechanisms that govern glial cell development and myelination are still not completely understood. Here we show reverse and forward genetic approaches to study SC biology. We have established the role of the adhesion G protein-coupled receptor (aGPCR), Gpr126, during SC development and myelination in zebrafish and mouse. We have demonstrated that Gpr126 drives radial sorting and elevates cAMP in SC to promote myelination. In addition to the role of Gpr126, we sought to uncover novel myelin regulators and have completed a large-scale forward genetic screen in zebrafish for mutants with defects in myelination. We are now further characterizing these mutants and mapping their respective lesions through whole-genome sequencing.

Abstracts

Molecular control of Schwann cell development by Fbxw7

Breanne L. Harty[1], Melanie Holmgren[1], Sarah D. Ackerman[1], Amy L. Herbert[1], Charleen L. Johnson[1], Kelly R. Monk[1,2]
[1] Washington University School of Medicine
[2] Hope Center for Neurological Disorders

Myelin is a multilamellar sheath generated by specialized glial cells that iteratively spiral their plasma membranes around axon segments. Myelinating glia provide trophic support that is essential for neuronal survival and myelination is critical for the rapid propagation of action potentials. In the peripheral nervous system (PNS), myelin is made by Schwann cells (SCs). Disruptions in SC development and myelination lead to devastating symptoms in many neurological disorders. To develop effective therapies for these patients, we must first understand the mechanisms that govern SC development, myelination, and myelin maintenance.

In a forward genetic screen in zebrafish to define new regulators of myelinating glial cell development, we recovered *stl64* mutants, which display increased expression of myelin-related genes and hypermyelination in both the CNS and PNS. Using whole genome sequencing, we determined that *stl64* disrupts *fbxw7,* which encodes the substrate recognition component of E3 ubiquitin ligase complexes. Notable Fbxw7 targets are master regulators of transcription and cell cycle including: mTOR, Notch, and cyclin E. Thus, Fbxw7 is required for critical cellular processes such as proliferation and differentiation.

Fbxw7 can be regulated in part by differential expression of three splice isoforms – α, β, γ – which dictate subcellular localization. Our preliminary data suggests that SCs only express the *fbxw7α* isoform, and our work to define isoform-specific Fbxw7 functions in SCs will be discussed. Furthermore, ultrastructural analyses of *stl64* mutants revealed an increase in Schwann cell number as well as significantly thicker myelin in the PNS. Given that mTOR levels must be tightly regulated to achieve proper myelin thickness, current work to test if loss of Fbxw7 regulation of mTOR is the primary cause of the SC defects observed in *stl64* mutants will also be discussed. Additionally, we will discuss progress made towards parsing out the mechanisms behind the increase in Schwann cell numbers as well as dissecting the cellular autonomy of these phenotypes. *Importantly, our preliminary analyses of fbxw7^{stl64} zebrafish mutants provide the first evidence that Fbxw7 is an important modulator of Schwann cell development and myelination.*

Delivering proteins to glial cells with Quantum Dots.

Walters, R.O., Medintz, I., Dawson, P., and Dawson, G.
UChicago, US Naval Res. Labs, Scripps Res and UChicago.

The extracellular matrix of glial cells in rich in negatively charged proteoglycans such as chondroitin sulfates and sialoglycoconjugates which can regulate the delivery of proteins (for example therapeutic lysosomal hydrolases) to glia. Quantum Dots (QDs) with a CdSe core, a ZnS shell, a negatively charged compact molecular ligand coating (CL4), and a cell-membrane penetrating lipopeptide (WG(Palmitoyl)VKIKKP$_9$G$_2$H$_6$), which binds to Zn on the surface of the QDs, selectively target peptides and proteins to neurons rather than glia in rat hippocampal slices. In order to target to glia we decreased the negative charge of the compact ligand coat and synthesized a positively charged (NH_2) polyethylene glycol (PEG) coat. This greatly increased uptake by glia. By pre-digesting neonatal rat hippocampal slices with chondroitinase ABC to reduce the negative charge we also increased uptake of QDs by oligodendrocytes. Protein delivery was demonstrated by uptake of histidine6-tagged green fluorescent protein (3XeGFP).His_6).

Abstracts

Lanthionine Ketimine-Ethyl Ester Shifts Microglia Toward an M2 Phenotype Characterized By Notable Induction of Arginase-1

Kenneth Hensley*, Ashleigh LaFountaine, Kalina Venkova, Alexandar Hristov,

*Associate Professor, Department of Pathology and Department of Neuroscience, University of Toledo Medical Center, Toledo OH USA 43614. Email Kenneth.hensley@utoledo.edu

Department of Pathology, University of Toledo Health Science Campus, Toledo OH 43614

Microglia perform protective functions in the adult CNS, helping to regulate the neuronal environment; repair and resolve damaged tissue; and mount host defense responses. Expression of the proper microglial phenotype can be beneficial to sick or injured tissue, but expression of a suboptimal phenotype can be damaging. Under conditions of inflammatory cytokine activation, microglia tend to adopt a host-defense or M1 phenotype characterized by upregulation of cytokine genes, inducible nitric oxide synthase (iNOS) and activation of reactive oxygen species (ROS)-producing NADPH oxidase. Contrastingly, microglia can adopt a more neurotrophic or M2 phenotype characterized by markers such as arginase-1 (Arg-1). Arg-1 acts as an antagonist of nitric oxide producing pathways by consuming arginine which otherwise would act as an iNOS substrate. Previously we have demonstrated that derivatives of the natural brain sulfur amino acid metabolite lanthionine ketimine (LK) suppress pro-inflammatory M1 microglial activation after exposure of microglia to inflammatory cytokines. In this study we focus on the M2-activating qualities of LK derivatives and show that a brain-penetrating synthetic LK ester (LKE) upregulates Arg-1 even in the absence of exogenous cytokine stimulation. In murine EOC-20 microglia, LKE dose-dependently increased Arg-1 from 1-100 μM over a 24h period, with greater than 3-fold increased Arg-1 protein at pharmacological LKE concentrations. The results suggest that LK derivatives have potential to treat neuroinflammatory pathologies by fundamentally altering microglial behavior.

*Disclosure: Dr. Hensley is inventor of lanthionine ketimine-ethyl ester and co-founder of XoNovo Therapeutics which is developing the compound for commercial purposes.

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Abstracts

TITLE: COMPARATIVE EFFECTS OF MEHG ON GLUTAMATE LEVELS OF CEREBELLAR AND CORTICAL ASTROCYTES

AUTHORS: Jaiman, Rosa J.[1]; Atchison, William D.[1, 2]
INSTITUTIONS 1. Neuroscience Program, Michigan State University, East Lansing, MI, United States. 2. Pharmacology & Toxicology, Michigan State University, East Lansing, MI, United States.

Methylmercury (MeHg) is an environmental neurotoxicant that preferentially targets granule cells in the cerebellum. Studies have demonstrated that MeHg increases the internal calcium concentration in granule cells, which induces an increase in glutamate release and eventually cytotoxicity. Astrocytes can buffer glutamate from the extracellular environment and prevent excitotoxic cell damage. Despite the fact that MeHg primarily affects granule cells, astrocytes are also targets of this metal. MeHg-induced neurotoxicity in astrocytes has been studied extensively in the cortical layer. However, effects on cerebellar astrocytes are less studied, and regional differences can occur in astrocytes between the two areas. The goal of this study was to compare levels of glutamate in the media of cerebellar and cortical astrocytes after an acute MeHg exposure. Determining the levels of glutamate in the media would allow us to know if MeHg induces release or decrease in absorption of glutamate in astrocytes. Primary astrocyte cultures from the cerebellum and cortical forebrain layer were obtained from 7 to 8 day old C57BL/6 mice. At 13-15 DIV, cells were exposed for 3h to 0µM, 1µM, 2µM, or 5µM MeHg. Levels of glutamate in the media were measured 24h later, using a colorimetric assay. The glutamate release and absorption from astrocytes culture were calculated by subtracting the amount of glutamate obtained in the cell culture with the amount of glutamate obtained in a parallel dish that contained only media. There was a significant decrease in glutamate absorption at 5µM MeHg in cortical astrocytes. However, there was a significant decrease in glutamate absorption at 1µM and 2µM MeHg and an absolute glutamate release at 5µM MeHg in cerebellar astrocytes. The noticeable effects of MeHg exposure in glutamate levels observed on cerebellar astrocytes might contribute to the preferential sensitivity of the granule cells to MeHg. Supported by NIH grants R01ES03299, R25NS54467 and T32GM092715.

Title: Development of a fluorine-18 labeled PET tracer for multiple sclerosis based on 4-aminopyridine

Authors: Pedro Brugarolas[1], J. Sanchez-Rodriguez[2], A. V. Caprariello[5], Shih Hsun Cheng[3], J. Lacroix[2], Dhanabalan Murali[4], T. E. Banhart[4], Richard Freifelder[3], Chin-Tu Chen[3], Onofre DeJesus[4], Robert Miller[5], Francisco Bezanilla[2], Brian Popko[1]
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Abstract: 4-aminopyridine (4AP) is a clinically approved drug to improve walking in people with multiple sclerosis. This effect is most likely caused by the enhancement of conduction velocity of demyelinated axons through the blockage of potassium channels that have become exposed during demyelination. Based on this, we hypothesized that a radioactively labeled form of 4AP could be used to visualize demyelination using positron emission tomography (PET). In this project, we developed a fluorine-containing derivative of 4AP (compatible with PET) and evaluated its uptake in several mouse models of demyelination. We found greater uptake of this tracer in demyelinated *vs*. control areas indicating that this compound is a promising tracer for monitoring changes in myelination non-invasively.

Abstracts

Title: Peripheral viral challenge elevates tonic glutamate in the hippocampus leading to hyperexcitability

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Abstract:
Peripheral infections increase the propensity and severity of seizures in susceptible populations. However, the underlying mechanisms have not been defined. In a quest to elucidate these mechanisms, we have developed a preclinical model in which intraperitoneal injection of a viral mimic, polyinosinic-polycytidylic acid (PIC), elicits a protracted hypersusceptibility of mice to kainic acid (KA)-induced seizures. The present study was undertaken to characterize the underlying mechanisms. Briefly, eight-week old female C57BL/6 mice were intraperitoneally injected with PIC and after 24 hours, glutamate homeostasis in the hippocampus, the ictal region of KA-induced seizures, was monitored using the enzyme-based microelectrode arrays. The study revealed a several-fold increase of resting (tonic) extracellular glutamate level in PIC-challenged vs. control mice. K+-evoked presynaptic glutamate release was not affected by PIC challenge. However, glutamate uptake was profoundly impaired while non-vesicular glutamate release was robustly increased. Electrophysiological examination of hippocampal slices showed a several fold increase in postsynaptic transmission with no significant effect on presynaptic activity in PIC-challenged vs. control mice. Altogether, these results implicate a dysregulation of astrocytic glutamate metabolism as the underlying mechanism for seizure hypersusceptibility induced by peripheral PIC challenge.

The consequence of dysfunctional myelin on neural processing

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In the current study, we have generated mutant mice that lack Claudin 11 (Cldn11) tight junctions in CNS myelin sheaths. In myelin sheaths, Cldn11 forms tight junctions located along the outer and inner edges of the membrane spiral, preventing ions and small molecules from entering the intramyelinic space. The function of Cldn11 tight junctions is to increase membrane resistance and reduce capacitance, thereby improving the speed of saltatory conduction. In its absence, conduction velocity is slowed most dramatically in small diameter myelinated fibers. Notably, the absence of Cldn11 is without degenerative myelin pathology, enabling direct study on the impact of dysfunctional myelin on neural processing.

Herein, this work explores the impact of dysfunctional myelin on neural processing in the conserved integration circuit of the auditory brainstem. We find that dysfunctional myelin alters neural processing, generating an inability to lateralize sound sources on the azimuth plane. Extrapolating this information to higher order circuitry within the cortex, we find that dysfunctional myelin generates a disconnection between brain regions.

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Abstracts

Myelin Proteolipid Protein: Shocking Findings about Its Role in Mitochondrial Function and Inflammation

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Mutations in the proteolipid protein gene (*PLP1*/*Plp1*) are referred to as Pelizaeus-Merzbacher disease (PMD). Behavioral deficits and shortened lifespan in PMD patients have been attributed to PLP's localization in CNS myelin. Downstream of 1° abnormalities are a host of 2° abnormalities that include a reactive microglial response, pro-inflammatory cytokine/chemokine up-regulation and neuronal death. The mechanisms that lead to these 2° events are unclear. We show that PLP is inserted into mitochondria via the Mia40/Tom40-Erv1 pathway when the gene is duplicated and in diseased states. This insertion can be blocked by drugs known to block this pathway and by mutations to PLP. Mitochondrial function and inflammation are interdependent and may occur under various stress conditions, including hypoxia. We show HI induced PLP in blastocyst cells and in hypoxic neonatal mouse brains with PLP expression increasing in both conditions. If low O_2 levels are prolonged, cells activate adapting mechanisms dependent on various transcription factors that are strictly bound to mitochondrial function. We show that PLP contains several oxygen responsive elements (ORE's) and an HIF-1 element. These ORE's in the sequence of the *PLP1* gene could partially explain the secondary inflammation events that occur during over-expression of PLP and create a link between PLP's insertion into mitochondria and the role it plays there, which is currently unknown.

Fear and Learning in Mutant Myelin Mouse Models

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Myelin is critical to the normal function of the vertebrate nervous system. Myelin diseases affecting humans, for example Pelizaeus-Merzbacher disease, result from primary myelin etiology, and myelin dysfunction has been implicated in a number of disorders including multiple sclerosis, schizophrenia, anxiety, and depression. Our lab uses animal models to probe the consequences of dysfunctional myelin. This study uses Pavlovian fear extinction to elucidate the consequences of myelin dysfunction on learning and memory in two colonies of transgenic mice. The *OBiden* mouse is an adult-onset degenerative model where we metabolically stress oligodendrocytes repeatedly and chronically causing subsets of oligos to die, select remyelination and repeated stress throughout the animals' life. The other model, the *Claudin11* (*Cldn11*) knockout mouse, is a non-degenerative model. Claudin11 forms tight junctions between layers of myelin sheaths, increasing electrical resistance of the myelin membrane and improving conduction velocity along axons. Both mouse models have exhibited previous behavioral deficiencies, and this study aimed to see if the well-defined learning and memory pathway was affected in either of our mice.

Abstracts

The Function of Gpr126 in Peripheral Myelin Maintenance and Remyelination

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Adhesion G protein-coupled receptors (aGPCRs) are a unique class of GPCRs defined by a large extracellular region containing various domains that may be involved in cell-cell or cell-matrix adhesion as well as the classical 7-transmembrane (7TM) region that may be involved in cell signaling. Being a rather understudied class of GPCRs, in general, it is unclear if aGPCRs function as adhesion molecules by virtue of the long N-terminus, as traditional GPCRs that signal through heterotrimeric G proteins by virtue of the 7TM, or if the same molecule can perform both functions. We previously showed that the aGPCR Gpr126 is essential for Schwann cell development and myelination in the zebrafish and mouse PNS. More recently, we showed that Gpr126 performs these functions by directly regulating cAMP concentrations via coupling to heterotrimeric G-proteins in Schwann cells. Interestingly, the expression of Gpr126 is maintained in adult Schwann cells, suggestive of a function in the adult PNS. We have therefore begun to analyze the role of Gpr126 in myelin maintenance and remyelination after injury by studying a Schwann cell-specific tamoxifen-inducible knockout *PLPCre-ERT2;Gpr126*$^{fl/fl}$ mouse model. Here, we show that deletion of *Gpr126* in mature Schwann cells does not affect myelin maintenance, but remyelination is severely delayed after nerve crush injury. Moreover, we observe several non-cell autonomous defects in injured nerved with reduced Gpr126 in Schwann cells. This work demonstrates that Gpr126 is dispensable for myelin maintenance but essential for proper nerve repair.

iPSC-derived oligodendrocytes reveal patient-specific PLP1 defects

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Pelizaeus-Merzbacher Disease (PMD [MIM 312080]) is a pediatric leukodystrophy affecting central nervous system myelin that results in severe motor impairment, intellectual delay, and premature death. PMD is a single-gene disorder, but presents as a spectrum of clinical severity attributed to hundreds of different mutations in the myelin gene *PLP1* (MIM 300401). Protein misfolding and endoplasmic reticulum stress have been implicated in the pathogenesis of PLP1 overexpression, but this may not hold true for the many known *PLP1* point mutations and deletions. Investigation of PLP1's normal function and the etiology of PMD are also complicated by a lack of access to primary human oligodendrocytes (OLs). To address this need, we have generated a panel of patient-derived iPSCs from children with duplications, triplications, deletions, and point mutations in *PLP1* that encompass the genotypic variation in patients. From these, we have derived pure populations of OLs in order to dissect individual patient phenotypes at a cellular level. This unique resource has allowed us to identify patient-specific molecular, morphological, and pathway defects that inform the pursuit of new patient-specific therapies.

Abstracts

Microglia of the Aged Brain: Primed to be Activated and Resistant to Regulation

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Innate immunity within the central nervous system (CNS) is primarily provided by resident microglia. Microglia are pivotal in immune surveillance and also facilitate the coordinated responses between the immune system and the brain. Transient microglial activation helps mount the appropriate physiological and behavioral response following peripheral infection. With normal aging, however, microglia develop a more inflammatory phenotype. For instance, in several models of aging there are increased pro-inflammatory cytokines in the brain and increased expression of inflammatory receptors on microglia. This increased inflammatory status of microglia with aging is referred to as primed, reactive, or sensitized. A modest increase in the inflammatory profile of the CNS and altered microglial function in aging has behavioral and cognitive consequences. Nonetheless, there are major differences in microglial biology between young and old age when the immune system is challenged and microglia are activated. In this context, microglial activation is amplified and prolonged in the aged brain compared to adults. Microglial hyper-activation following immune challenge leads to exaggerated neuroinflammation, sickness behavior, depressive-like behavior and cognitive deficits. The cause of this amplified microglial activation may be related to impairments in several key regulatory systems with age that make it more difficult to resolve microglial activation. Here we show evidence of a novel mechanism that prolonged neuroinflammation following a peripheral inflammatory challenge in the aged is caused by impaired astrocyte-dependent inhibition of microglial activation. Although a dynamic relationship clearly exists between microglia and astrocytes in neuroinflammatory responses, this relationship is understudied. Several lines of data indicate that impaired responsiveness of aged astrocytes to anti-inflammatory feedback provided by IL-10 is a critical component to prolonged microglial activation in the aged brain. Our studies extend previous aging work and identify astrocytes as pivotal cells in the failure to resolve microglial activation in the aged brain following immune challenge.

Abstracts

Microglial Phenotype in Interleukin-1 Dependent Amyloid Plaque Clearance

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Abstract: Objective We previously found that sustained expression of interleukin (IL)-1β in mouse brain led to reduction in plaque pathology associated with increased evidence of glial activation, a finding that has been reproduced by others using proinflammatory stimuli. The present study explored the role of microglia and their activation status on amyloid-β (Aβ) plaque clearance in a proinflammatory setting. **Methods** APPswe/PS-1dE9 mice were intrahippocampally injected with AAV2-hIL-1 or control virus and assayed 4 weeks later for plaque pathology, microglial phenotypes, and association of Ab with specific microglia. In separate experiments some mice were also infused with a neutralizing antibody to IL-4ra or control antibody to explore the role of IL-4 receptor activation in microglial phenotype changes. **Results** (1) IL-1 overexpression led to increased numbers of argninase-1+ microglia that were preferentially associated with Aβ. (2) IL-4 was elevated following sustained IL-1 expression and IL-4 injection led to increased numbers of argninase-1+ cells and plaque reduction. (3) Blocking IL-4 signaling reduced numbers of arginase-1+ microglia, and this reduction coincided with less plaque clearance in the Alzheimer's model mice. **Conclusion** Sustained IL-1β expression leads to an IL-4 dependent alternative activation of microglia that play a major role in clearing Aβ.
This work was funded by NIH grant RO1 AG030149.

Depletion of astrocyte LKB1: Implications for glioma and stem cell research

Neurodegenerative Consequences of Episodic Oligodendrocyte Stress
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Multiple Sclerosis (MS) is characterized as an autoimmune disease, but evidence from new animal models and clinical trials has indicated other potential etiologies. To test a potential oligodendrocyte contribution to disease, our lab has developed the *OBiden* (*OBi*) mouse model. *OBi* mice develop normally until 2 months of age, and then metabolic stress is induced in mature oligodendrocytes once per week. We investigate the secondary neurodegenerative affects of our primary oligodendrocyte stress starting with *in vivo* MRI identifying significant 3rd ventricle enlargement in the *OBi* mice. Longitudinal behavioral tests find the mice exhibit significant increases in a depression-like endophenotype that is a common symptom in MS patients. In addition, we find deficits in short-term memory of our mice using a T-Maze test, similar to MS cognitive deficits. We are also analyzing the molecular characteristics of gray and white matter in the *OBi* mice to define consistently affected pathways or common gene expression in the degenerating CNS. Using western blot and immunocytochemistry, we find disrupted neurofilaments in normal appearing gray matter (NAGM) indicating an early stage of degenerative pathology. Finally, experiments are on going to determine changes at the RNA level to identify genes and pathways affected in NAGM.

Abstracts

FTY720 (Gilenya) Stimulates Oligodendroglial BDNF and NGF Expression by Increasing Histone Acetylation

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Multiple system atrophy (MSA) is a rare incurable neurodegenerative disorder that shows toxic α-synuclein (aSyn) protein accumulation in oligodendroglia cells (OLGs). MSA patients and models have reduced BDNF and GDNF expression, while their supplementation reduces MSA-like dysfunction. NGF, another trophic factor, also protects OLGs and neurons in part by reducing neuroinflammation. Thus, drugs that stimulate neurotrophins expression may help reverse MSA pathology. The FDA-approved drug FTY720 (Gilenya) stimulates BDNF and GDNF expression and reduces neuroinflammation. Histone deacetylase (HDAC) inhibitors, including FTY720, increase levels of acetylated histone 3 (AcH3) and histone 4 (AcH4); a mechanism that up-regulates neurotrophins expression in neurons and glia but has never been studied in OLGs. To do so we treated an OLG cell line, OLN-93, with FTY720 and measured AcH3/AcH4 levels by immunoblotting, as well as neurotrophins expression by qPCR. FTY720 significantly increased AcH3/AcH4 levels, as well as NGF and BDNF expression in OLN-93. This suggests that a novel protective property for MSA could occur by stimulating NGF and BDNF expression in OLGs using FTY720.

Microglial senescence during normal and pathological aging.

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The primary function of microglia in the normal CNS is to provide neuronal protection and immune surveillance. With ageing, human microglia undergo a number of characteristic morphological changes that result in the presentation of a dystrophic phenotype likely reflecting the development of cell senescence. We believe that microglial senescence involves a diminution of microglial neuroprotective functions and accordingly have hypothesized that Alzheimer-type neurofibrillary degeneration (tau pathology) occurs as a consequence of an ageing-related decline in microglial ability to support neurons. To this end, we have studied microglial phenotypes specifically in those areas of the human cerebral cortex known to undergo primary neurofibrillary degeneration, i.e. the mesial temporal lobe. Our findings show that the appearance of tau-positive structures (neurofibrillary tangles, neuropil threads, senile plaques) in the entorhinal cortex and surrounding temporal gyri is accompanied and preceded by the development of widespread microglial dystrophy. The extent of microglial senescent degeneration correlates positively with the development of neurodegeneration in both Alzheimer and Down syndrome brain, and we therefore take these findings to support our hypothesis of microglial dysfunction. At the same time, our findings which failed to show the presence of activated microglia in the human temporal cortex provide evidence against the longstanding idea that neuronal degeneration is a result of overly activated, out-of-control microglia believed to produce a variety of detrimental neurotoxins. Thus, we believe that the brain's innate immune system (similar to the systemic immune system) is subject to an ageing-related decline in function due to the senescent deterioration of microglia. The implications for potential therapeutic approaches are profound: instead of trying to suppress microglia with anti-inflammatory drugs to prevent neurodegeneration, it may be more effective to develop agents that can stimulate microglial cell activity.

Abstracts

Oligodendrocyte death results in late-onset immune-mediated CNS demyelination in the *DTA* mouse model

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Multiple sclerosis (MS) is the most common neurological disease characterized by CNS inflammation and demyelination induced by myelin-specific T lymphocytes. Although MS is considered an inflammatory neurodegenerative disease, its primary etiology remains unknown. Here we used the *DTA* mouse model (Traka et al., Brain 2010 Oct;133(10):3017-29) to investigate whether oligodendrocyte death could cause autoreactivity against myelin antigens and, secondarily, lead to inflammation and demyelination in the CNS i.e. the 'inside-out' hypothesis. Upon activation with tamoxifen, *DTA* mice develop widespread CNS demyelination, resulting from pervasive oligodendrocyte loss, that peaks at 5 weeks and resolves by 10 weeks: approximately 30 weeks later, *DTA* mice develop a severe, secondary demyelinating disease characterized by focal inflammatory demyelinating lesions that progress to extensive myelin and axonal loss at later disease stages. Contrary to the acute demyelinating disease, the late-onset disease is associated with increased numbers of activated CD4+ T cells in the CNS and myelin oligodendrocyte glycoprotein (MOG)-specific T cells in peripheral lymphoid organs. To evaluate the encephalitogenic potential of MOG-specific T cells in tamoxifen-treated *DTA* mice during the late-onset disease, we transferred these cells to naïve *Rag1*-deficient mice that produce no mature T cells and B cells. This approach resulted in neurological defects that correlated with CNS white matter inflammation. Furthermore, immune tolerization against MOG significantly ameliorated the late-onset disease symptoms in the *DTA* mice. Overall, these data indicate that primary oligodendrocyte death is sufficient to trigger an adaptive autoimmune response against myelin, suggesting that a similar process can occur in the pathogenesis of MS, consistent with the 'inside-out' hypothesis.

Abstracts

The Lyme disease spirochete *Borrelia burgdorferi* induces expression of multiple neuroinflammatory factors in human microglial cells *in vitro*.

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The spirochete *Borrelia burgdorferi* (*Bb*) causes multiple neurological complications, collectively termed *neuroborreliosis*. However, the contributions of microglial cells to the pathogenesis of *neuroborreliosis* have not yet been elucidated. To begin characterization of this response, highly pure cultures of primary human microglia were incubated with live or antibiotic-killed virulent *Bb* to elucidate the cell specific responses to the bacterium. Cultures were analyzed by ELISA, immuno-cytochemistry, and real time PCR array. Our results demonstrate a robust increase in numerous inflammatory chemokines, cytokines and related genes in all treatment conditions. Most prominent was an increase in the neutrophil chemoattractants IL-8, CXCL1 and CXCL10. These data suggest that the microglial response to *Bb* may promote infiltration of potentially neurotoxic systemic immune cells as additional contributors to the onset of *neuroborreliosis*.

HIV-1 Tat inhibits autotaxin lysophospholipase D activity and modulates oligodendrocytes differentiation

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White matter injury has been frequently reported in HIV^+ patients. Previous studies showed that HIV viral protein Tat (transactivator of transcription), a viral protein that is produced and secreted by HIV-infected cells, is a toxic factor to oligodendrocytes (OLGs). Adding Tat to the culture medium reduced the viability of immature OLGs, and the survived OLGs exhibited a reduction in process networks, indicating defective differentiation/maturation. Oligodendroglial lineage cells produce and secrete autotaxin, an ecto-enzyme containing a lysophospholipase D (lysoPLD) domain that converts lysophosphatidylcholine (LPC) to lysophosphatidic acid (LPA). It has been recently reported that the lysoPLD activity of autotaxin modulates HDAC 1/2 activity and OLG gene expression, and affects the differentiation of OLG progenitors to early differentiating OLGs. Thus, we hypothesized that Tat affects OLG development by interfering with the autotaxin-LPA-HDAC signaling. Our data shows that 18 hr Tat treatment leads to decreased expression of OLG differentiation genes, *Ugt8* and *Cnp*, which can be rescued by the addition of LPA. Tat-treated OLGs do not alter LPA receptor gene expression. However, supernatant collected from Tat-treated OLGs show significantly reduced lysoPLD activity. In addition, adding Tat to supernatant collected from vehicle-treated OLGs also resulted in significantly decreased Atx lysoPLD activity, suggesting Tat interferes with LPA production, possibly via blocking autotaxin lysoPLD activity. Together, Tat has been shown to influence the affect of Atx lysoPLD activity on OLG gene differentiation through a potential physical interaction.

Abstracts

Endoplasmic stress and proteostasis in the pathogenesis and treatment of demyelination

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Endoplasmic Reticulum (ER) Stress has been implicated in the pathogenesis of both acquired and hereditary neuropathies. For example, mutant proteins associated with several Charcot-Marie-Tooth (CMT) neuropathies provoke ER stress and an unfolded protein response (UPR), and limiting the UPR reduces the severity of neuropathy. P0 glycoprotein is abundantly synthesized in myelinating Schwann cells. The mutant P0S63del causes CMT1B neuropathy in humans, and a very similar demyelinating neuropathy in S63del transgenic mice. P0S63del elicits an UPR associated with translational attenuation. We have shown that ablation of CHOP, a UPR mediator downstream of the PERK kinase sensor of unfolded proteins, ameliorates demyelination in S63del nerves. In addition, Gadd34 is a detrimental effector of CHOP that reactivates translation too aggressively in myelinating Schwann cells. Limiting Gadd34 function improves myelination in S63del nerves, and reduces accumulation of P0S63del in the ER by prolonging translational attenuation. Surprisingly, ablation of PERK in Schwann cells, which activates translation and therefore should worsen demyelination, actually improves myelination and neuropathy. PERK may have additional promyelinating targets outside of the UPR. Limiting Gadd34 in order to reset translational homeostasis may provide a therapeutic strategy in tissues challenged by misfolded proteins.

Astrocyte system x_c^- at the cross-roads of injury and protection

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Interleukin-1 (IL-1) is a cytokine released by many cell types that acts in autocrine and/or paracrine fashion, thereby stimulating a variety of signaling pathways. Evidence supports the involvement of IL-1β in the pathogenesis of both acute and chronic neurological disorders/disease although the precise cellular and molecular targets responsible for injury have not been fully elucidated. Toward this end, our laboratory demonstrated that astrocyte-mediated alterations in system x_c^- (cystine/glutamate antiporter) activity contributes to the development and progression of inflammatory (IL-1β-enhanced) hypoxic neuronal injury ─an *in vitro* model of the ischemic penumbra. Interestingly, this same transporter has a well-characterized role in the synthesis and maintenance of the antioxidant molecule glutathione (GSH) raising the intriguing possibility that under certain circumstances, IL-1β could upregulate processes that protect against oxidative stress. Indeed, we find that IL-1β can enhance astrocyte GSH production and release. Further, following IL-1β treatment, astrocyte susceptibility to oxidant-induced injury is significantly attenuated. Hence, under the appropriate conditions, IL-1β may be an important stimulus for increasing total antioxidant capacity in brain. Specifically, our evidence suggests that the increase in IL-1β expression that occurs after insult/injury may be part of a protective response that under ultimately goes awry. Supported by 2R01NS051445 – 06

Abstracts

Title: Rescue of Apoptosis and Metabolic Stress in Oligodendrocytes from 4ebp Transgenic rumpshaker Mice

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Abstract:
Coding region mutations in the PROTEOLIPID PROTEIN 1 (PLP1) gene, which encodes the major transmembrane protein of central nervous system myelin, impairs the trafficking of this protein through the secretory pathway of oligodendrocytes, and activates the unfolded protein response (UPR). This disruption of cellular metabolism causes degenerative pathology in patients with Pelizaeus-Merzbacher disease (PMD) as well as an animal model of this disease, the rumpshaker mouse. Activation of the endoplasmic reticulum-resident UPR sensor protein, PERK, inhibits ribosome assembly by directly phosphorylating eIF2α, and indirectly inhibits cap-dependent translation by enabling expression of the eIF4E binding protein, 4E-BP. To counterbalance this suppression of translation initiation, the PI3K-AKT pathway can antagonize the inhibitory effects of the PERK pathway by phosphorylating 4E-BP on four sites, which liberates eIF4E to promote cap-dependent translation.

To characterize the role of 4E-BP in the UPR we generated transgenic mice expressing, in oligodendrocytes, a constitutively active form of hemagglutinin (HA)-tagged 4E-BP. The four major serine and threonine phosphorylation sites are mutated to alanine in this protein. Expression of the transgene is under regulatory control of the mouse myelin basic protein promoter/enhancer; thus, only myelinating oligodendrocytes express 4E-BP-HA. We have used an immunocytochemical / morphometric analysis to show that the transgene is expressed in all CC1+ oligodendrocytes in 5 brain regions from 3 independent lines of mice. In addition, we have bred these animals with rumpshaker mice to study the effect of active 4E-BP on the PERK pathway and determine if the transgene rescues or exacerbates the rumpshaker phenotype

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