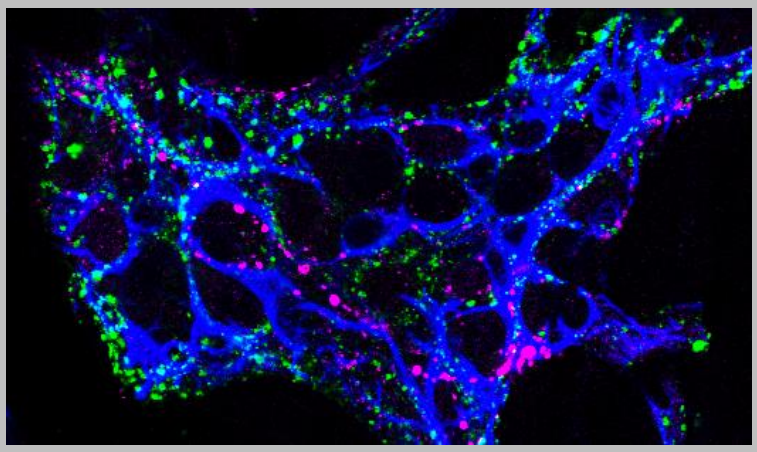
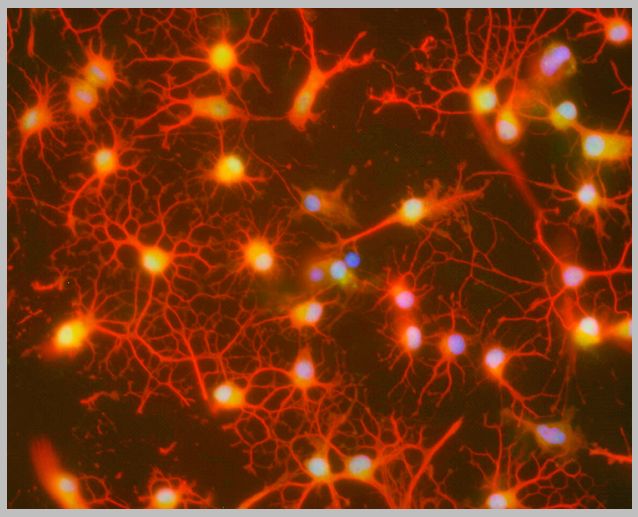
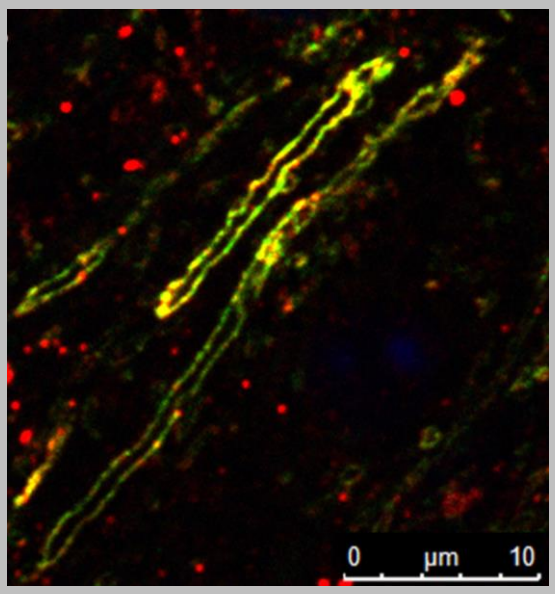
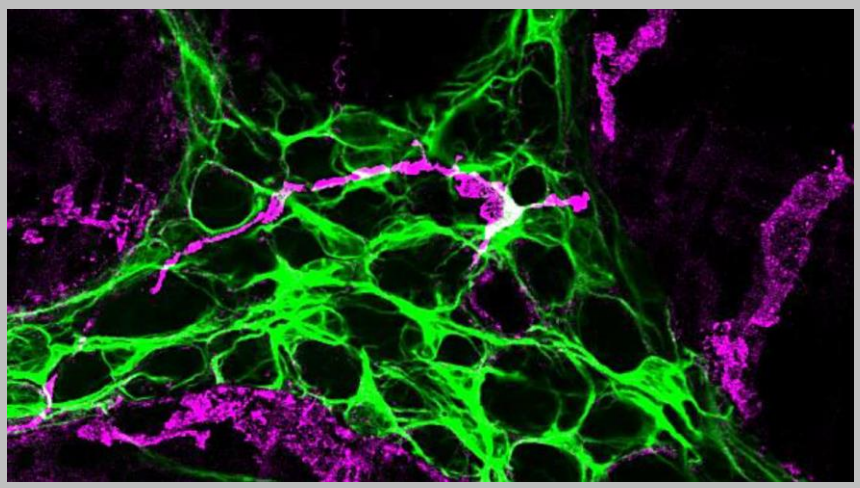
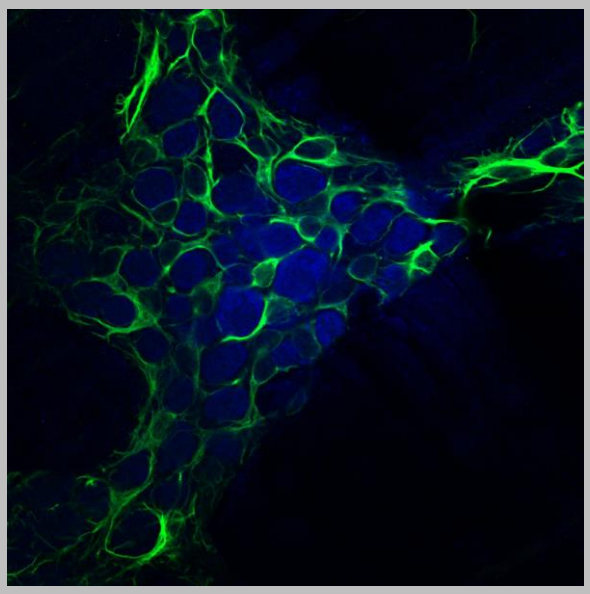
12th Great Lakes Glia Meeting











West Bay Beach Resort
Traverse City, MI

September 29th - October 1st, 2019

Great Lakes Glia 2019
West Bay Beach Resort, Traverse City, MI
https://greatlakesglia.org

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Cover Illustrations

Top Right: The image is a representative confocal image of enteric ganglia innervated by nerve fibers. The image represents enteric glia labeled in blue, Substance P positive nerve fibers in green, and TRPV1 positive nerve fibers in magenta. Wilmarie Morales Soto, Michigan State University, East Lansing MI.

Top Left: Primary rat OPCs immunostained with antibodies against a-tubulin (red) and Olig1 (green) and stained with DAPI (blue). Doug Feinstein Lab, University of Illinois at Chicago.

Bottom Left: Interactions between the enteric glia and resident immune cells
This is an overlay of the anti-GFAP and anti-CD45 immunofluorescence from the myenteric plexus of the mouse colon. Note the proximity of glial cells (green) and immunocytes (magenta) within the plexus. Image is a Z-projection 197 x 110 x 2 µm in X, Y, and Z dimensions.
Vladimir Grubišić, M.D., Ph.D. Postdoctoral research associate, Department of Physiology, Neuroscience Program Michigan State University, East Lansing, MI.

Middle Right: VPS11 (vacuolar associated protein) in red and MBP in green shows VPS11 is present in myelin sheath but not in axon. Our studies show VPS11 transports degraded myelin proteins (MBP and MAG) back to oligodendrocyte for degradation in lysosomes. (Skoff and Thummel lab, WSU).

Bottom Right: The following is a merged picture of GFAP (Glial fibrillary acidic protein) and Hu (neurons) taken from the myenteric plexus of a mouse colon. On green color, you can observe GFAP labeling enteric glial cells and on blue enteric neurons. Siomara Hernandez-Rivera, Ph.D. Research Associate Department of Physiology Michigan State University.

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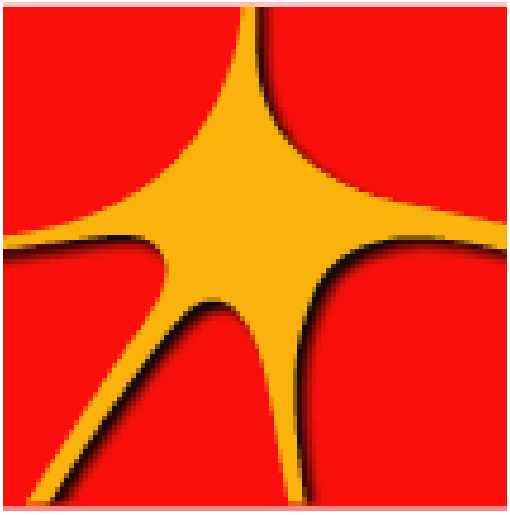

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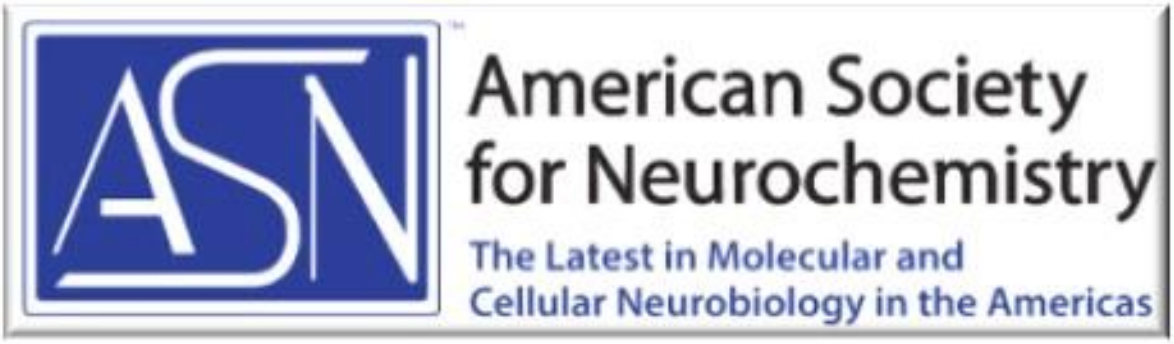

Editor in Chief
Douglas L. Feinstein
University of Illinois, Chicago

Great Lakes Glia 2019
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Schedule

Sunday, September 29th

4:30pm	**Opening Reception**	**View**
6:00pm	**Dinner**	**View**
7:45pm	**Session 1**	**Leelenau Conference Room**

Title: Neuroinflammation

Organizer: Shailendra Giri, Henry Ford Hospital

Ranjan Dutta, Cleveland Clinic Foundation
Pathogenesis of Multiple Sclerosis

Guang-Xian Zhang, Thomas Jefferson University
Ursolic Acid Promotes Neural Regeneration Through Both Immunomodulation and Direct Oligodendrocyte Maturation

Bonnie Dittel, Versiti Blood Research Institute
Leveraging Interactions Between Regulatory B Cells and Regulatory T Cells for the Treatment of CNS Autoimmunity

Kalipada Pahan, Rush Medical College
Selective Inhibition of TLR2 by TIDM Peptide Reduces Microglial Activation

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Monday, September 30th

8:00am	**Breakfast**	**View**
8:45am	**Session 2**	**Leelenau Conference Room**

Title: Glial and Neuronal Cell Signalling in Diseases

Organizer: Robert Miller, George Washington University

Wendy B. Macklin, University of Colorado
Signaling Regulating CNS Myelination

Gabriel Corfas, University of Michigan
Modulating Peripheral Myelin

Terri Wood, New Jersey Medical School
mTOR and Myelin Across the Ages

Fraser J. Sim, SUNY at Buffalo
Improving Myelin Repair by Modulation of Extracellular Heparin Sulfate Proteoglycan Sulfation

10:45am	**Break**	
11:00am	**Keynote Presentation**	**Leelenau Conference Room**

Peter Stys, University of Calgary

Axo-myelinic Neurotransmission: Role in Physiology and Diseases of Myelin

Noon	**Free time**	
3:30pm	**Poster Session**	**Torch Lake Room**
4:30pm	**Session 3**	**Leelenau Conference Room**

Title: Peripheral Glia

Organizer: Bruce Carter, Vanderbilt University

Jun Li, Wayne State University
Phosphoinositides and Myelination

Michael Granato, University of Pennsylvania
Molecular Mechanisms Directing Axon Glia Interactions During Peripheral Nerve Regeneration

Cody Smith, University Notre Dame
Peripheral Glia in Visceral Organs Beyond Schwann Cells

Bruce Carter, Vanderbilt University
Sensory Neuropathy Caused by Deficiencies in Schwann Cell Metabolism

7:00pm	**Dinner**	**View**
8:30pm	**Posters and Refreshments**	**Torch Lake Room**

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Tuesday, October 1st

7:30am **Breakfast** **View**

8:15am **Session 4** **Leelenau Conference Room**

Title: Astrocytes

Organizer: Doug Feinstein, University Illinois (Chicago)

Gordon Meares, West Virginia University
JAK1 drives ER Stress-Induced Gene Expression in Astrocytes

Doug Feinstein, University of Illinois (Chicago)
Disruption of Astrocyte Metabolism Exacerbates EAE

Robert McCullumsmith, University of Toledo
Alterations of Glutamate Transporter Expression in Severe Mental Illness

Grant Gordon, University of Calgary
Astrocyte Bioenergetics Control Cortical Plasticity During Stress

10:15am **Mini-break**

10:30am **Keynote Presentation** **Leelenau Conference Room**

W. Sue T. Griffin, University of Arkansas
Neuronal Stress, Neuroinflammation, Interleukin-1, and Self Repeating Consequences

11:30am **Lunch break out**

12:00am **Session 5** **Leelenau Conference Room**

Title: Microglia

Organizer: Jeff Dupree, Virginia Commonwealth University

Lauren Green, University of Notre Dame
Microglia in the CNS and PNS

Jeff Dupree, Virginia Commonwealth University
Microglial Regulation of Axon Initial Segment Structure and Function in Inflammatory Disease

Timothy Hammond, Harvard Medical School
Redefining Microglial States in Health and Disease

Marie-Ève Tremblay, Université Laval
Dark Microglia: Remodeling Neuronal Circuits in Health and Disease

2:00pm **End of Meeting**

Mechanism and Consequence of Abnormal Calcium Homeostasis in Rett Syndrome Astrocytes

Qiping Dong [1], Qing Liu [2], Ronghui Li [1], Anxin Wang [1], Qian Bu [1], Kuan-Hong Wang [2], and Qiang Chang [1, 3,*]

[1] *Waisman Center, University of Wisconsin-Madison, 1500 Highland Avenue, Madison, WI 53705*

[2] *Unit on Neural Circuits and Adaptive Behaviors, National Institute of Mental, Health, 35 Convent Drive, Bethesda, MD 20892,*

[3] *Departments of Medical Genetics and Neurology, University of Wisconsin-Madison*

**Correspondence should be addressed to Q.C. (qchang@waisman.wisc.edu).*

Astrocytes play an important role in Rett syndrome (RTT) disease progression. Although the non-cell-autonomous effect of RTT astrocytes on neurons was documented, cell-autonomous phenotypes and mechanisms within RTT astrocytes are not well understood. We found that spontaneous calcium activity is abnormal in RTT astrocytes *in vitro*, *in situ*, and *in vivo*. Such abnormal calcium activity is mediated by calcium overload in the endoplasmic reticulum caused by enhanced store operated calcium entry (SOCE), which is in part dependent on elevated expression of TRPC4. Furthermore, the abnormal calcium activity leads to excessive activation of extrasynaptic NR2B-containing NMDA receptors (eNMDARs) on neighboring neurons, increased network excitability, and susceptibility to epileptic activity in *Mecp2* knockout mice. Finally, both the abnormal astrocytic calcium activity and the excessive activation of eNMDARs are caused by *Mecp2* deletion in astrocytes in vivo. Our findings provide evidence that abnormal calcium homeostasis is a key cell-autonomous phenotype in RTT astrocytes, and reveal its mechanism and consequence.

Title: A Role for Macrophages in Peripheral Neuron activity

Authors: Jacob Brandt and Cody J. Smith

Affiliation: Department of Biological Sciences University of Notre Dame, Notre Dame, IN.

Abstract: The cellular response to neural activity is essential to build the nervous system. Emerging evidence shows that microglia and astrocytes serve a critical role in this aspect of neural development in the central nervous system. However, the cells necessary for similar events in the peripheral nervous system (PNS) are less understood. To fill this gap, we used time-lapse imaging in zebrafish to investigate the role of macrophages in PNS neural development. Using dorsal root ganglia (DRG) as a model, our data indicates spontaneous calcium transients in developing neurons and glia in the ganglia. We demonstrate macrophages arrive to the ganglia during this neurogenesis. Furthermore, spontaneous activity coincides with macrophage-DRG interactions. Together these data support the model that macrophages in the PNS may parallel the cellular response to neural activity of CNS cells like microglia or astrocytes.

Regional heterogeneity of cholecystokinin sensing by enteric glia

Seguella Luisa[1], Esposito Giuseppe[1], Gulbransen D Brian[2]
[1] Department of Physiology and Pharmacology "V. Erspamer", Sapienza University of Rome, Italy; [2] Department of Physiology, Michigan State University, East Lansing (MI), USA.

Abstract
Enteric glia are peripheral glia associated with the enteric nervous system (ENS) that function to orchestrate a variety of integrated ENS functions related to the autonomic control of gastrointestinal homeostasis. Enteric glia are also a key component of a complex gut-brain neuroepithelial circuit by which the brain quickly perceives gut sensory cues. Transcriptomics data show that enteric glia express low levels of mRNA encoding cholecystokinin (CCK) receptors A and B in the colon (35.16% and 19.36%, respectively vs *P2RY1* mRNA expression, a known glia-expressed gene) and suggest that enteric glia contribute to gut-brain signalling by sensing CCK. Here, we tested the hypothesis that enteric glia detect CCK and that glial responsiveness to CCK differs among gut regions. We assessed the effects of CCK on enteric glia by using *in situ* Ca^{2+} imaging in whole-mount preparations of myenteric plexus from *Sox10*CreER^{T2}::Polr2a$^{tm1[CAG-GCaMP5g,-tdTomato]Tvrd}$ mice that express the optogenetic probe GCaMP5g in enteric glial cells. A comparable percentage of glia responded to 100µM ADP in duodenum and colon (82.4% and 89.2%, respectively; *n*=120 glial cells in the duodenum and *n*=130 in the colon), but the percentage of glia responding to 100nM CCK was higher in the colon than in the duodenum (66.4% vs 38.3%, respectively). Interestingly, blocking neuronal activity with 300nM tetrodotoxin increased the percentage of glia responding to CCK in the duodenum, but not in the colon (57.1% in the colon vs 64.8% in the duodenum). Despite higher numbers of glia responding to CCK in the colon than duodenum, CCK resulted a greater peak Ca^{2+} response in the duodenum than in the colon when it is compared to ADP response peak (24.8% of ADP-induced response in the colon; 33.8% of ADP-induced response in the duodenum). Glial responses to CCK in the duodenum were potentiated by blocking neuronal activity with tetrodotoxin (30% of ADP-induced response in the colon; 93.3% of ADP-induced response in the duodenum). Together, these data show that enteric glia respond to CCK and that glial responses to CCK differ in duodenum and colon. Glial sensitivity to CCK involves signalling with neurons, suggesting a possible region-specific mechanism to locally modulate gut-brain.

Abstracts

Title: Vision and motor deficits due to loss of Vps11 function in a zebrafish model of genetic leukoencephalopathy

Authors: Shreya Banerjee[1], Lillian Ranspach[1], Xixia Luo[1], Joseph Fogerty[2], Brian Perkins[2] and Ryan Thummel[1]
Affliations: [1]Department of Ophthalmology, Visual and Anatomical Sciences, Wayne State University School of Medicine, Detroit, MI; [2]Cole Eye Institute, Cleveland Clinic Foundation, Cleveland, OH

Abstract Body: Genetic Leukoencephalopathies (gLEs) are white matter disorders affecting the central nervous system, causing progressive abnormalities in the visual and motor systems. A mutation in *VPS11* has been identified as a causative allele of gLE in Ashkenazi Jewish individuals, with a high carrier rate of 1:250. VPS11 forms membrane tethering complexes with three additional VPS proteins to control crucial cellular processes in the endolysosomal and autophagy pathways. Here, we are characterizing two zebrafish *vps11* mutants as potential models for gLE. Behavioral responses to visual and acoustic cues was performed at 5 and 7 days post-fertilization using the DanioVision tracking system. In addition, optokinetic response (OKR) analysis was performed at 5 dpf to test visual acuity. Behavioral analysis showed that *vps11* mutant fish could visualize changes in light and dark backgrounds, but OKR analysis indicated the animals were functionally blind and not able to make out an image. In regard to motor movement, no difference in response to alternating light-dark backgrounds was observed between the mutant and wild-type larvae at 5 dpf, but a significant reduction in movement and velocity of the mutants at 7 dpf. Mutants also showed significant reduction in movement to non-visual, acoustic stimuli. Together, these results suggest that loss of Vps11 function has a progressive adverse effect on visual sensory and motor systems in zebrafish larvae. Our findings support the use of zebrafish to further characterize the vision and motor defects associated with loss of Vps11 function.

Title: Elucidating the Role of Cardiac Nexus Glia

Authors: Nina Kikel, Mike O'Dea, Isabel Correia, & Cody J. Smith
Affiliation: Department of Biological Sciences University of Notre Dame, Notre Dame, IN.

Abstract: The Intracardiac Nervous System (ICNS) is essential to maintaining heart rate and rhythm by acting as an integration site between cardiomyocytes and ganglia outputs. However, there is limited research on its cellular composition. As diverse glial populations are integral to maintaining the nervous system, it is critical that we elucidate their role in the ICNS. To study the development and function of glia in the ICNS, we used confocal microscopy, time-lapse imaging, and CRISPR-induced mutagenesis in a zebrafish model. We have identified a robust population of neural crest derived GFAP+ glia in the heart that is conserved across species. Through a pilot genetic screen we have identified Meteorin signaling as a key determinant of these cells. Ablation of these glia leads to both tachycardia and arrhythmia, demonstrating their critical role on cardiovascular homeostasis.

Investigation of altered phosphoinositides in myelin-enriched fractions from the neurodegenerative disorder, Niemann-Pick Disease, type C1

Koralege C. Pathmasiri[1], Melissa R. Pergande[1], Fernando Tobias[1], Rima Rebiai, Ernesto R. Bongarzone[2] and Stephanie M. Cologna[1]
[1]Department of Chemistry, University of Illinois at Chicago, Chicago, IL
[2]Department of Anatomy and Cell Biology, University of Illinois at Chicago, Chicago, IL

Niemann-Pick Disease, type C1 (NPC1) is an autosomal recessive, neurodegenerative lipid storage disorder characterized by endo/lysosomal accumulation of unesterified cholesterol and glycosphingolipids. Severe demyelination and cerebral atrophy are major hallmarks in this disease. Phosphoinositides (PIs) are a family of critical signaling lipids responsible for cellular functions ranging from growth and differentiation to trafficking. In this study we utilized mass spectrometry imaging and liquid chromatography-mass spectrometry to evaluate phosphoinositide levels in control and NPC1 mutant mouse brain lysates. Our data indicates a decrease in multiple PIs in the cerebellar myelin of NPC1 mutant animals. Additionally, we found alterations in the 4-kinase responsible for phosphoinositide metabolism in NPC1 mouse cerebellum. Our future work is focused on studying functional correlation between phosphoinositide alteration and demyelination in NPC1.

Agonists of Sigma 1 and Melanocortin Receptors Protect Oligodendrocytes from Cytotoxic Products of B Cells from MS Patients

R. Lisak[a], L. Nedelkoska[a], H. Touil[b], A. Bar-Or[b], J. Benjamins[a]
Wayne State University[a]; University of Pennsylvania[b]

Objective: Determine if melanocortin receptor (MCR) and sigma-1 receptor (s-1R) agonists protect oligodendrocytes (OL) from cytotoxic factors released by MS B cells.
Background: No disease modifying therapy for relapsing MS directly protects OL. MCR agonist ACTH 1-39 and s-1R agonists dextromethorphan (DM) and Anavex®2- 73 protect OL *in vitro* from excitotoxicity, ROS, inflammation and apoptosis. B cells cultured from MS blood release factors/s that kill OL.
Methods: Supernatants (Sup) from B cells cultured without *in vitro* stimulation were added to rat glial cultures with/without ACTH, DM, or Anavex®2-73.
Results: Sup from MS B cells are toxic to OL, those from controls are not. ACTH, DM and Anavex®2-73 markedly inhibit OL death induced by MS B cell Sup. Antagonists of MCR or s-1R reverse the ability to block MS B cell Sup cytotoxicity. **Conclusions:** ACTH, DM and Anavex®2-73 inhibit B cell Sup mediated OL death. Agonists for MCR and s-1R are potential protective therapies to decrease the progression and degeneration that occurs in many treated MS patients.

Abstracts

The BHMT–betaine methylation pathway modulates oligodendrocyte energetics

S. Sternbach, N. Singhal, E. Freeman, J. McDonough
Department of Biological Sciences, School of Biomedical Sciences, Kent State University, Kent Ohio 44242

Multiple Sclerosis (MS) is characterized by neurological dysfunction and demyelination of the central nervous system. Further, oligodendrocytes are killed off and myelin production is halted, with progenitor cells (OPCs) unable to differentiate. We have previously shown that methionine metabolism is dysregulated in MS. Furthermore, activation of the betaine homocysteine methyltransferase (BHMT)–betaine pathway contributes to epigenetic changes on histone H3 and alleviates neurological deficits in the cuprizone and EAE models of MS. We have also found that BHMT regulates histone methyltransferase activity and gene expression in neurons. In the present study, we are investigating the role of BHMT in oligodendrocytes, hypothesizing that through betaine supplementation, the BHMT–betaine pathway locally contributes to SAM synthesis for methylation of DNA and histones in oligodendrocytes. We have found that BHMT is expressed in oligodendrocytes in both the cytoplasm and nucleus, and chromatin fractionation revealed that BHMT is bound to chromatin in oligodendrocytes. In addition, Seahorse respirometry was performed to determine the effect of betaine on mitochondrial function in oligodendrocytes following oxidative damage. Our data show that betaine modulates oligodendrocyte energetics by increasing glycolysis in mature oligodendrocytes. These data suggest that changes in methionine metabolism in MS may be linked to defects in oligodendroglial energetics. Thus, activation of the BHMT-betaine pathway may provide epigenetic control required for oligodendrocyte maintenance.

Title: Microglia dynamically exhibit selective transitions between stable states

Authors: Abigail Zellmer, Michelle Wang and Cody J. Smith
Department of Biological Sciences, Center for Stem Cells and Regenerative Medicine

Microglia survey the CNS and phagocytize apoptotic or impaired neurons to maintain proper nerve assembly driving behavior, learning, and survival. Literature shows that microglia exhibit morphological differences based on their activation status, however, little is known about the flexibility of microglia to alter between the different states. Using time-lapse imaging in zebrafish, we have shown that microglia dynamically populate in three distinct states: a resting state, surveying state, and a phagocytically active state. Strikingly, we only detect microglia that exhibit transitions between states in a unidirectional manner. These unidirectional transitions appear in microglia of the retina, brain and spinal cord opening the possibility that a single microglia may not be capable of returning to a deactivated state once it has undergone phagocytic activation. We are now investigating the mechanisms in place to maintain proper control of these phagocytic immune cells once activated, as unregulated activated microglia are increasingly shown to be hallmark for neurodegenerative diseases

Title: Hemin-induced activation of microglial phagocytosis and therapeutic targeting using the TLR4 antagonist TAK-242

Authors: Joseph R. Geraghty,[1,2] Milen Spegar,[1] Jeffrey A. Loeb[1], and Fernando D. Testai[1]

Affiliations: [1]Department of Neurology & Rehabilitation, [2]Medical Scientist Training Program (MSTP), University of Illinois at Chicago College of Medicine, Chicago, IL

Abstract:
Subarachnoid hemorrhage (SAH) is a devastating neurological injury resulting from the rupture of cerebral aneurysms. It accounts for 5% of strokes annually but 27% of all stroke-related years of potential life lost due to long-term disability and mortality. The first 24-72 hours after aneurysm rupture is a critical window during which the degree of early brain injury likely sets the stage for delayed and long-term outcomes. One principal mechanism of early brain injury involves a robust inflammatory response initially generated by microglia, the resident immune cells of the brain. We hypothesized that blood products such as hemin released from degrading erythrocytes trigger this inflammatory response by binding to Toll-like receptor-4 (TLR4). In this study, we developed an *in vitro* system to study the effects of hemin on primary microglia isolated from CX3CR1-GFP mice. Primary microglia were exposed to various concentrations of hemin with and without the presence of the TLR4 antagonist TAK-242 for a period up to 24 hours. We then ran a phagocytosis assay using 2 um fluorescent latex beads. We find that compared to neurons, microglia show minimal cell death in a lactate dehydrogenase assay. However, exposure to 40 uM hemin results in a significant increase in microglial phagocytic activity (32.2% increase in cells with beads compared to vehicle control, p=0.0286). Hemin-treated microglia also contain a higher number of beads per cell (6.5 compared to 1.1 in hemin-vehicle, p=0.0323). Co-treatment with TAK-242 appears to reduce microglial phagocytic activity in response to hemin, as determined by the average number of beads per cell, although this remains elevated compared to controls. Hemin and other blood products released into the subarachnoid space following SAH therefore can act as damage-associated molecular patterns to trigger inflammatory responses in the brain, and may influence outcome. Future studies will involve use of the endovascular perforation rat model of SAH and treatment with TAK242 to assess the effects of this therapeutic strategy in vivo. This work may offer new mechanistic insight and potential therapeutic strategies focusing on the role of microglial responses after SAH.

ER stress initiates Janus Kinase (JAK) 1-dependent gene expression in astrocytes.

Savannah G. Sims, Gordon P. Meares

West Virginia University, Department of Microbiology, Immunology, and Cell Biology, Morgantown, WV

Neurodegenerative diseases are associated with the accumulation of misfolded proteins in the endoplasmic reticulum (ER). ER stress occurs when the protein folding capacity of the ER is overwhelmed, resulting in the initiation of the unfolded protein response (UPR) to restore homeostasis. Unresolved UPR activation leads to cell death and inflammation. Evidence indicates ER stress and inflammation are linked, and we have described a canonical Janus Kinase (JAK) 1- Signal Transducer and Activator of Transcription (STAT) 3-dependent mechanism that promotes expression of inflammatory mediators like Interleukin-6 (IL-6) and chemokine C-C motif ligand 2 (CCL2). JAK1 is well-established to be initiated by cytokine receptor stimulation to promote inflammatory gene expression, and we have shown that ER stress also activates JAK1. Using siRNA knockdown and RNA-seq, we found that JAK1 regulates over 10% of ER stress-induced gene expression in astrocytes. This includes genes that have not been previously associated with JAK1 signaling, such as tribbles (TRIB) 3 and growth arrest and DNA damage inducible (GADD45) α. RNA-seq revealed that JAK1 drives a distinct gene expression program in response to ER stress compared to that induced by cytokines. Less than 10% of the ER stress-induced JAK1-dependent genes are also induced by cytokine stimulation, demonstrating that ER stress and cytokine stimulation induce distinct JAK1-dependent transcriptional profiles. GADD45α and TRIB3 are known ATF4 target genes, therefore we investigated activating transcription factor (ATF) 4. We found that TRIB3 and GADD45α were both JAK1 and ATF4 dependent in response to ER stress and pharmacologically inhibiting the kinase domain of JAK1 fails to abrogate ER stress-induced expression of these genes. We hypothesize that ATF4 can be utilized by JAK1 as an alternative transcription factor to mediate cell stress-induced inflammatory responses. Our data demonstrate that JAK1 elicits noncanonical signaling during ER stress that we hypothesize is independent of JAK1 kinase activity. These findings suggest JAK1 is a major driver of transcriptional adaptation in response to cellular stress, and JAK1 exhibits novel signaling mechanisms in response to cell stress to regulate gene expression.

Phosphorylation State of ZFP24 Controls Oligodendrocyte Differentiation

Benayahu Elbaz[1], Anna Kolarzyk[1], Zack Mielko[2], Ariel Afek[2], Raluca Gordân [2], and Brian Popko[1]
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Abstract

Myelin is a multilayer lipid membrane structure that ensheaths and insulates axons. In the central nervous system (CNS), myelin is formed by oligodendrocytes. During CNS development oligodendrocyte progenitor cells terminally differentiate into mature oligodendrocytes, produce myelin and wrap axons. The differentiation of oligodendrocytes and their expression of myelin protein genes are under tight transcriptional control. Zinc finger protein ZFP24, formerly known as ZFP191, is necessary for oligodendrocyte maturation and CNS myelination. We have demonstrated that ZFP24 binds to a consensus DNA sequence in proximity to genes important for oligodendrocyte differentiation and CNS myelination, and we have shown that this binding enhances target gene expression. We have also demonstrated that ZFP24 DNA binding is controlled by phosphorylation. Phosphorylated ZFP24, which does not bind DNA, is the predominant form in oligodendrocyte progenitor cells. As these cells mature into oligodendrocytes, the non-phosphorylated, DNA-binding form accumulates. In addition, we found that active, non-phosphorylated, ZFP24 is capable of inducing oligodendrocyte differentiation. We performed a large, unbiased screen and found that ZFP24 is phosphorylated by several isoforms of Protein Kinase C (PKC) and Calcium and Calmodulin dependent Kinase (CAMK). We also discovered that ZFP24 is dephosphorylated by the calcium and calmodulin dependent phosphatase Calcineurin. Using the Cuprizone model, we established that ZFP24 is important for CNS remyelination. Therefore, our studies provide potential therapeutic targets, the modulation of which might enhance the presence of the non-phosphorylated form of ZFP24 and promote oligodendrocyte maturation and CNS remyelination.

Glial activation alters development in murine models of oligodendritic connexin deficiency.

***S. Keil**, M. Freidin, C. K. Abrams;
[1]Neurol. and Rehabilitation, Univ. of Illinois Chicago, Chicago, IL

In the central nervous system (CNS), glia rely on the family of proteins called connexins (Cxs) to communicate the signals necessary for homeostatic maintenance. Cxs form low resistance transmembrane channels between cells or to the cells' external environment, creating conduits for the molecules and ions necessary throughout development, synchronization and immune regulation. Genetic mutations to these cell and tissue-specific proteins have been linked to a variety of debilitating diseases. In oligodendrocytes, Cx deficiency of Cx32 or Cx47 causes X-linked Charcot-Marie-Tooth disease (CMT1X) and Pelizaeus-Merzbacher-Like disease 1 (PMLD1) respectively. In vitro and in vivo analysis of Cx32 and Cx47 knockout mice found Cx loss dysregulates CNS glia. There are significantly fewer $O4^+$ cells, with a decrease in proliferation in both mature oligodendrocytes and $Pdgfr\alpha^+$ progenitor cells. There is a sig. increase in activation and presence of $Iba1^+$ cells, as well as a sig. activation and proliferation of in $GFAP^+$ cells.

Astrocytic PERK drives synergistic expression of neuroinflammatory genes in response to ER stress and cytokines.

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Misfolded protein accumulation in endoplasmic reticulum (ER) lumen leads to ER stress, which is causally associated with various neuropathological disorders. Cells in response to ER stress initiate the unfolded protein response (UPR) pathway, which is partly mediated by the activation of ER transmembrane protein PKR-like ER kinase (PERK). However, chronic UPR activation due to unresolved ER stress can lead to aberrant inflammation and cell death. We have previously established that ER stress induces PERK dependent proinflammatory gene expression in astrocytes. Furthermore, we have observed proinflammatory cytokines oncostatin M (OSM) and tumor necrosis factor-α (TNF-α) are increased concomitantly with ER stress in the neuroinflammatory model Experimental Autoimmune Encephalomyelitis (EAE). We therefore hypothesized that ER stress will exacerbate neuroinflammation produced by astrocytes in response to proinflammatory cytokines in a PERK dependent manner. We found that in primary murine astrocytes, the ER stress inducing drug thapsigargin (thaps) promoted gene expression of the proinflammatory cytokine IL-6 and the chemokine CCL20. Moreover, the IL6 and CCL20 gene expression was synergistically upregulated when astrocytes were treated with thaps and TNF-α or OSM. However, PERK knockout in astrocytes significantly abrogated this synergistic gene expression. Similarly, thaps and TNF-α treatment together induced synergistic expression of IL-6 protein in astrocytes, which is also PERK dependent. ISRIB, an eIF2B agonist significantly abrogated IL-6 and CCL20 transcriptional synergy in astrocytes. RNA sequencing of astrocytes treated with thaps and TNF-α revealed that ER stress alters the overall transcriptional program driven by TNF-α alone. To examine the mechanism of synergy, astrocytic IL-6 mRNA stability was measured which was unaffected by thaps and TNF-α or OSM treatment together. Additionally, thaps reduced suppressor of cytokine signaling 3 (SOCS3) gene expression and nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IκB-α) protein expression in astrocytes, which are established negative regulators of OSM and TNF-α induced gene expression, respectively. This indicates that suppression of negative feedback mechanisms contribute to augmented gene expression. Overall, our data suggests that in astrocytes, ER stress in conjunction with cytokines TNF-α and OSM can synergistically mediate PERK-dependent proinflammatory gene expression.

ENTERIC GLIA MODULATE NOCICEPTOR SIGNALING THROUGH CONNEXIN-43 UNDER PRO-INFLAMMATORY CONDITIONS

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Enteric glia regulate intestinal motility, secretions, and neuroinflammation through intercellular signaling mechanisms that involve connexin-43 (Cx43) hemichannels. Glial Cx43 signaling is active during the acute phase of colitis when the sensitization of nociceptors occurs and is implicated in the induction and maintenance of chronic pain. How enteric glia contribute to nociceptor sensitization is not well understood. We hypothesized that alterations to intercellular signaling between glia and nociceptors mediated by Cx43 contribute to the sensitization of nociceptors during gut inflammation. We used the dinitrobenzene sulfonic acid (DNBS) model of acute colitis to drive visceral hypersensitivity and tested the effects on enteric glia using immunohistochemistry, multiplex immunoassays, and ethidium bromide dye uptake to measure glial Cx43 channel activity. Specific interactions between glia and nociceptors were assessed by imaging intracellular Ca^{2+} responses in nociceptive nerve fibers in the myenteric plexus of TRPV1-GCaMP5g-tdT mice. DNBS colitis drove an increase in proinflammatory cytokines including IL6, TNFα, and IL17, and IL1β showed a 5-fold increase ($p<0.05$) at peak inflammation. Enteric glia contribute to IL1β production and immunolabeling data show a 40% increase in glial IL1β ($p<0.05$) that was confirmed by RNAseq data (2-fold, $p<0.05$). The pro-inflammatory mediators IL1β, IL6, IFNy, and TNFα increase glial dye uptake under basal conditions and IL1β and IL6 potentiated ADP-stimulated dye uptake by 24% and 53% respectively ($p<0.0001$) in a Cx43 dependent manner that was confirmed by both selective antagonists of Cx43 and in samples from animals where Cx43 was ablated in enteric glia ($Sox10Cre^{ERT2;}Cx43^{fl/fl}$). IL1β and glial activation were necessary to induce a significant increase in nerve fiber calcium responses to capsaicin ($p<0.05$) that were inhibited by Cx43 antagonists. Together, these data identify IL1β as a candidate glial mediator that has the capacity to affect nociceptors by influencing glial Cx43 hemichannels.

Title: **Connexin-43-dependent production of M-CSF by enteric glia modulates macrophage phenotype and visceral sensitivity following chronic inflammation**

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Background: Abdominal pain involves altered neuro-immune interactions in the gastrointestinal tract, but the signaling processes that link immune activation with visceral hypersensitivity are unresolved. We hypothesized that enteric glia link the neural and immune systems of the gut and that communication between enteric glia and immune cells modulates the development of visceral hypersensitivity. **Methods:** Cx43 was ablated in enteric glial cells using *Sox10::CreER*^{T2}/Cx43$^{f/f}$ mice. Acute colitis was induced by 2% dextran sodium sulfate (DSS) in drinking water for 1 week and chronic colitis was driven by intermittent exposure to DSS (1 week on/ 1 off) for 3 weeks. Body weight and macroscopic damage were used to assess inflammation, and immunohistochemistry was used to determine numbers of neurons, glia and immune cells. Visceral sensitivity was tested by visceromotor responses to colonic distensions and cytokine profiles were assayed by plate array. Fixed human colon samples and ELISA on supernatants from primary human enteric glial cells were used to confirm mouse mechanisms in humans. **Results:** DSS caused weight loss and macroscopic tissue damage without driving significant neurodegeneration in the myenteric plexus of *Sox10::CreER*^{T2}/Cx43$^{f/f}$ mice and littermate controls. Visceromotor responses to colonic distensions were increased to similar extent after acute colitis, but the ablation of glial Cx43 prevented development of chronic visceral hypersensitivity [P = 0.661 (acute DSS) and 0.025 (chronic DSS), two-way ANOVA for genotype]. DSS colitis induced a significant increase in macrophage colony stimulating factor (M-CSF) and CD68+ immune cells in control mice that was not observed in mice lacking enteric glial Cx43 [$P < 0.031$ (controls) and $P > 0.904$ (*Sox10::CreER*^{T2}/Cx43$^{f/f}$), 2-way ANOVA for treatment). The proinflammatory cytokine IL-1β stimulated M-CSF production from primary human enteric glia and the Cx43 hemichannel blocker 43Gap26 prevented the IL-1β-induced increase in CD68 staining in control colonic preparations (P = 0.007 and 0.039, 2-way ANOVA for treatment). Furthermore, M-CSF immunoreactivity was significantly increased in the colonic myenteric plexus in samples from individuals with Crohn's disease compared to tissues from patients without abdominal pain (P = 0.002, Student's t test). **Conclusions:** Our findings show that the protective effects of glial manipulation were mediated by disrupting the glial-mediated activation of macrophages through M-CSF. Collectively, our data identify enteric glia as a critical link between gastrointestinal neural and immune systems that could be harnessed by therapies to improve abdominal pain.

Title: Gastrointestinal neuroimmune disruption in a mouse Gulf War Illness model

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Gulf War Illness (GWI) is a chronic disorder characterized by a spectrum of six symptoms that include gastrointestinal disorders. Exposure to the anti-nerve gas drug pyridostigmine bromide (PB) is linked with the development of GWI, but the exact mechanisms remain unclear. We hypothesize that PB disrupts gut functions by creating persistent neuroinflammation within the enteric nervous system (ENS). We tested the effects of PB in vivo by exposing male and female mice to 9 µg/mL or 90 µg/mL PB for 7 and 30 days and subsequently assessing gut function using in vivo and ex vivo tests of colonic motility and barrier function. Neurochemistry of the ENS was assessed by immunohistochemistry and immune responses were studied using multiplex cytokine and chemokine arrays in the gut and brain. Acutely exposing whole mount preparations of myenteric plexus to PB drove calcium responses in enteric glia (181.0%, $p<0.001$) and neurons. In vivo, exposure to PB acutely increased fecal pellet output (44.3%, $p<0.05$) and increased fecal fluid content (13.2%, $p<0.05$) in male mice, but decreased fecal pellet output (62.5%, $p<0.05$) and reduced fecal fluid content (18.1%, $p<0.05$) in females. Regardless of sex, PB treatment altered neuromuscular control, slower colonic bead expulsion (male 504.4%, $p<0.001$; female 275.8%, $p<0.01$), and reduced colon length (male 9.4%, $p<0.05$; female 9.9%, $p<0.05$). PB also drove enteric neurodegeneration in male mice (15.5% neuronal loss, $p<0.05$) and increased the proportion of excitatory enteric neurons (by 67.7% in 90 µg/mL group, $p<0.05$) in females. Despite having no effect on colonic permeability, exposure to PB caused major shifts in the expression of pro-inflammatory cytokines and chemokines in the colon and brain that suggest immunosuppressive effects. Interestingly, immune disruption was still evident in the colon and brain of female animals at one month following exposure to PB. Our results show that the paradigm of PB exposure experienced by veterans of the Persian Gulf War contributes to long-lasting pathophysiology by driving enteric neuroinflammation, promoting immunosuppression, and altering functional anatomy of the colon in a sex-dependent manner.

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Her4 regulates Müller glia reprogramming in zebrafish retinal regeneration following intense light damage

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The zebrafish retina can undergo a robust regenerative response following a significant loss of retinal neurons. Damage signals from dying neurons initiate this response by inducing Müller glial cells to dedifferentiate, reenter the cell cycle, and undergo an asymmetric cell division to produce neuronal progenitor cells (NPCs). The NPCs then amplify before migrating to the region of damage where they differentiate into the appropriate retinal cell types. Currently, it remains unclear how zebrafish Müller glia are induced to act as stem cells, and consequently it is important to characterize the signaling pathways that allow Müller glia to exit the initial gliotic response and become proliferative. The Notch signaling pathway was identified as an important regulator of this response, however, the mechanisms through which the pathway acts are not well understood. The transcription factor Her4 is well-documented as a downstream effector of the Notch signaling pathway, and here we characterize the role of Her4 in zebrafish retinal regeneration following intense light damage. We targeted Her4 for knockdown with a morpholino that was injected and electroporated into the eyes of adult *albino*$^{b4/b4}$; Tg(*gfap:EGFP*)^{nt11} zebrafish prior to light damage, and found the number of Müller glia was reduced relative to a standard control. To determine the involvement of Her4 in Müller glia reprogramming, we used a reporter line for *sox2*, Tg(*sox2-2A-sfGFP*), a neuronal stem cell-associated transcription factor and known regulator of Müller glia reprogramming. Knockdown of Her4 in these fish resulted in reduced GFP expression as relative to control retinas. These results establish Her4 as necessary for Müller glia proliferation and as a regulator of reprogramming in the regenerating zebrafish retina.

An atypical microglial population responds to large-scale CNS injury

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Microglia perform critical roles in response to neural cell death; however, the dynamic microglial response to large-scale death needs more investigation. To study this, we performed radial glial ablation in embryonic zebrafish. At 4 days post-injury, immunohistochemistry and confocal microscopy revealed significantly more cells labeled with a microglia-specific marker in and around the spinal cords of ablated animals. Further data demonstrated the majority of these cells did not express the myeloid transcription factor, PU.1. Nuclear staining suggested these cells may contain multiple nuclei and significant accumulations of GFAP, presumably from ablated radial glia, exceeding the size of typical debris puncta. Time-lapse imaging of GFAP-containing surveying cells suggested fusion or homotypic engulfment of these cells in the spinal cord. Further, we observed these cells emigrating from the spinal cord, surveying outside the spinal cord, and re-entering the spinal cord. These findings support the hypothesis that a subset of microglia-like cells with atypical morphology respond to large-scale CNS injury.

Dynamic regulation of IL-10 and TGFβ receptors on astrocytes during experimental autoimmune encephalomyelitis

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A common feature among neurological diseases is aberrant inflammation. Although there are benefits of inflammation in the CNS, uncontrolled neuroinflammation can be detrimental. It is well known that glial cells contribute to onset and progression of neuroinflammation, and that resident brain cells can contribute to the disease state. Astrocytes and microglia have an important role in producing and responding to immunological factors such as cytokines and chemokines, and it has been shown that long term exposure to inflammatory cytokines can result in local tissue damage. We are interested in examining the location and capacity of astrocytes to respond to anti-inflammatory and pro-inflammatory cytokines, such as IL-10, TGFβ, IL-1β, and TNFα, which are elevated during experimental autoimmune encephalomyelitis (EAE). Using flow cytometry, we observed changes in cytokine receptors on astrocytes in naïve mice and during disease course in adoptive transfer EAE. Brain sections observed in naïve mice included the spinal cord, cerebellum, cortex, hippocampus, and striatum, while sections observed in EAE mice included the spinal cord and cerebellum. Mice were immunized with myelin oligodendrocyte glycoprotein (MOG), and splenocytes and lymphocytes were collected ten days after immunization. T cells were obtained and transferred to wild-type C57BL/6J female mice. Cytokine receptor changes were observed in astrocytes of naïve mice and in peak and chronic phases of EAE. Our data shows that the IL-10 and TGFβ receptors appear to be co-expressed by a distinct population of astrocytes, and there are differences in expression between the spinal cord and cerebellum. We hypothesize that IL-10 and TGFβ receptor-expressing astrocytes may constrain neuroinflammation.

Jedi-1 deficiency increases sensory neuron excitability through a non-cell autonomous mechanism

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The dorsal root ganglia (DRG) house the primary afferent neurons responsible for somatosensation, including pain. We previously identified Jedi-1 (PEAR1/MEGF12) as a phagocytic receptor expressed by satellite glia in the DRG involved in clearing apoptotic neurons during development. Here, we further investigated the function of this receptor *in vivo* using Jedi-1 null mice. In addition to satellite glia, we found Jedi-1 expression in perineurial glia and endothelial cells, but not in sensory neurons. We did not detect any morphological or functional changes in the glial cells or vasculature of Jedi-1 knockout mice. Surprisingly, we did observe changes in DRG neuron activity. In neurons from Jedi-1 knockout (KO) mice, there was an increase in the fraction of capsaicin-sensitive cells relative to wild type (WT) controls. Patch-clamp electrophysiology revealed an increase in excitability, with a shift from phasic to tonic action potential firing patterns in KO neurons. We also found alterations in the properties of voltage-gated sodium channel currents in Jedi-1 null neurons. These results provide new insight into the expression pattern of Jedi-1 in the peripheral nervous system and indicate that loss of Jedi-1 alters DRG neuron activity indirectly through an intercellular interaction between non-neuronal cells and the sensory neurons.

Higher *Firmicutes/Bacteroidetes* ratio in oral microbiome of identical twins with most severe multiple sclerosis

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Multiple sclerosis (MS) is still of unknown etiology and scant genetic risk factors, body fluid biomarkers, or imaging can predict prognostic severity in a context of highly heterogeneous disease. Recently, new generation sequencing technology started to map gut and oral microbiomes to pinpoint the role of diet as an environmental factor, and evaluate its direct role in inflammation on autoimmunity. In humans, two main phyla dominate in the gut: *Firmicutes* (carnivore diet) and *Bacteroidetes* (vegetarian and omnivore), with Western diet reportedly associated with a skewed ratio toward more *Firmicutes*. MS patients have gut dysbiosis when compared to healthy subjects, and high disease activity was reported to correlate with a higher *Firmicutes/Bacteroidetes* ratio. Some *Bacteroidetes* types have been shown to promote Treg number and function in MS and healthy subjects. Overall, a higher ratio of *Firmicutes* is associated with inflammation in gut in healthy subjects as well as in patients affected by neurodegenerative diseases, and MS-derived gut microbiota aggravates an MS-like autoimmune disease in a transgenic mouse model. With regards to the oral microbiome, few studies comparing gut and oral flora did not show a stringent overlap, but confirmed in the oral microbiome that *Firmicutes* and *Bacteroidetes* are the main phyla, along with *Proteobacteria* and *Actinobacteria*. Differences in oral biota were found in children with autism compared to normal children, prompting us to investigate the status of oral microbiome in identical twins discordant for MS severity, where one was still clinically isolated syndrome (CIS) after 10 years, and the other twin had confirmed diagnosis of relapsing-remitting MS fulfilling the 2010 McDonald criteria. At the time of oral DNA collection, the twins followed an identical low fat-vegetable rich diet, had no oral infection, and were off medication for 18 months. The goal was implemented by taxonomic and functional profiling of about 25 million per patient of unmapped reads from human whole genome sequencing We found in the relapsing-remitting twin a higher *Firmicutes/Bacteroidetes* ratio (=1.01) than in the CIS twin (ratio=0.86), along with a higher ratio of *Candidatus*, *Actinobacteria* and *Proteobacteria*. Functional Kegg analysis identified differences in pathways involved in immunity and environmental responses. MS clinical severity seems to correlate with higher ratio of higher *Firmicutes/Bacteroidetes*, similarly to that reported in gut. Studying identical twins removed the confounding factor of genetic inter-individual variability and revealed also that recent diet may not be the key of MS severity. This work was supported by a VA Merit Award to DLF.

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A novel leukoencephalopathy targets myelination defects due to loss of vacuolar protein sorting (Vps11) function

Genetic Leukoencephalopathies (gLE) are genetic disorders affecting the white matter of the central nervous system. Our collaborators recently identified a mutation in *VPS11* as a causative allele in the gLE phenotypes observed in individuals from Ashkenazi Jewish families. VPS11 functions in a complex of four C-VPS proteins, which are conserved from yeast to humans, and control critical cellular processes in the endolysosomal and autophagy pathways. Here, we characterize for the first time in mammals the cell type and distribution of Vps11. Vps11 is highly enriched in oligodendrocytes and is closely associated with myelin. At low magnification, Vps11 appears localized to the same compartment as myelin but at higher magnifications, Vps11 and MBP do not co-localize. Rather, Vps11 forms numerous bead-like structures throughout the myelin sheath, suggestive of its localization to Schmidt-Lanterman clefts. Vps11 and Mag are clearly in the inner tongue of myelin, generally separate but with moderate co-localization. Vps11 is not in the axon; however, in longitudinal and cross sections, NF proteins (low and high) co-localize with Vps11. Vps11 is tightly regulated by proteolipid protein as it is significantly increased in *Plp1* null mutants and significantly decreased in *Plp1* mutants with duplications. Our preliminary observations suggest Vps11 transports axonal and myelin proteins for degradation to oligodendrocyte endosomal and lysosomal structures. Vps11 thus appears to be the first identified protein to shuttle cargo from axonal-myelin compartments back to the cell body.

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