BIOGRAPHICAL SKETCH

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NAME: Jakobs, Tatjana C.

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Assistant Professor of Ophthalmology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Wuerzburg, Germany	MD	1985-1992	Medicine
Medizinische Poliklinik, University of Wuerzburg	fellow	1992-1997	Molecular Medicine
University of Nagasaki, Japan	fellow	1997-1999	Genetics
Massachusetts General Hospital	fellow	2000-2007	Neurosurgery Research

A. Personal Statement

My lab has used various models of glaucomatous and traumatic injury to the optic nerve (DBA/2J mice, optic nerve crush, transient elevation of the intraocular pressure, microbead occlusion model, optic nerve crush) to identify morphological changes and underlying differential gene expression in the optic nerve and the retina. In the past, I have performed detailed anatomical studies of retinal ganglion cells and their synapses and the optic nerve head, including 3-dimensional reconstructions of individual astrocytes, the blood vessel plexus in the optic nerve, and the glial structures that support ganglion cell axons.

I started my research career with studying the regulation of hormone metabolism using genetic and molecular biological techniques. In 2000, I joined the laboratory of Richard Masland, then at Mass General Hospital to study cell-type specific gene expression in the retina. During the course of these studies, I developed an interest in neuronal imaging. Currently my lab is using a combined approach using immunohistochemistry, electron microscopy, transgenic animals, virus-mediated gene delivery, visual testing (ERG, optokinetic reflex), and molecular biology to understand the behavior of retinal ganglion cells, their axons, and the glial cells of the optic nerve in glaucoma and in traumatic optic neuropathy. We are using microarray screening of the retina and the optic nerve to identify candidate genes that are involved in signaling between neurons and astrocytes and in the process of astrocyte reactivity.

1. Sun D, Moore S, and Jakobs TC; Optic nerve astrocyte reactivity protects function in experimental glaucoma and other nerve injuries. (2017) *J Exp Med,* 214(5), 1411-1430

2. Qu J, and Jakobs TC; The time course of gene expression during reactive gliosis in the optic nerve. (2013) *PLoS ONE*, 8(6) e67094

3. Sun D, Lye-Barthel M, Masland RH, and Jakobs TC; Structural remodeling of fibrous astrocytes after optic nerve injury. (2010) *J Neurosci* 30, 14008-14019

4. Jakobs TC, Libby RT, Ben Y, John SWM, Masland RH; Retinal ganglion cell degeneration is topological but not cell type specific in DBA/2J mice. (2005) *J Cell Biol* 171(2), 313-325

B. Positions and Honors

Positions and Employment

2008-2009 Assistant Cell Biologist, Massachusetts General Hospital
2008-2010 Instructor in Ophthalmology, Harvard Medical School
Nov 2010- Assistant Professor of Ophthalmology, Harvard Medical School

Honors

1997 1st von-Basedow Research Prize of the German Endocrine Society
1997-1999 Full Scholarship from the Japan Society for the Promotion of Science (JSPS)
2012 Dolly Green Special Scholar Award, Research to Prevent Blindness

C. Contribution to Science

1. Distribution of excitatory synapses on retinal ganglion cells:
There are at least 15 different types of retinal ganglion cells, but for many cell types it is not currently known which feature they extract from the visual world to report to the brain. In Dr. Masland's lab at MGH, we studied the distribution of excitatory synaptic inputs to ganglion cells of different types to see whether they show obvious differences. For this purpose, we developed an ex-vivo tissue culture of rabbit retina and transfected the retina with a plasmid encoding a fusion protein from PSD95 (the major structural protein of excitatory synapses) and GFP. We found that synaptic inputs to all types of retinal ganglion cells follow a single generic plan and that synapses are evenly spaced about 3 µm apart. We have also studied the pattern of excitatory synapses of glaucomatous retinal ganglion cells.

Jakobs TC, Ben Y, and Masland RH; Expression of mRNA for Glutamate Receptor Subunits Distinguishes the Major Classes of Retinal Neurons, but is Less Specific for Individual Cell Types. (2007) *Molecular Vision* 13, 933-948

Jakobs TC, Koizumi A, and Masland RH; The spatial distribution of glutamatergic inputs to dendrites of retinal ganglion cells. (2008) *J Comp Neurol* 510, 221-236

Koizumi A, Jakobs TC, and Masland RH; A Mosaic of Synaptic Contacts among Three Retinal Neurons. (2011) *J Comp Neurol*, 519(2), 341-357

Berry RH, Qu J, John SWM, Howell GR, and Jakobs TC; Synapse loss and dendrite remodeling in a mouse model of glaucoma. (2015) *PLoS ONE* 10(12): e0144341

2. The topography of retinal ganglion cell loss in the DBA/2J mouse model of glaucoma:
In collaboration with the group of Dr. John (The Jackson Laboratory), we studied whether particular types of retinal ganglion cells are particularly vulnerable to glaucomatous degeneration. For this purpose, I used retrograde labeling and particle-mediated dye transfer to study ganglion cell morphology in detail. I found that the degeneration of ganglion cells was not dependent on the cell type as much as on the localization of the cell in the retina: there were sectors of degenerating cells adjacent to sectors that were quite well-preserved. The obvious interpretation of this finding is that the initial insult to the ganglion cells happens at the site of the optic nerve head where the ganglion cell axons run as bundles with a topographic relationship to the axons. I then collaborated on a follow-up study verifying this finding in transgenic mouse strains.

Jakobs TC, Libby RT, Ben Y, John SWM, and Masland RH; Retinal ganglion cell degeneration is topological but not cell type specific in DBA/2J mice. (2005) *J Cell Biol* 171(2), 313-325

Howell GR, Libby RT, Jakobs TC, Phalan FC, Barter JW, Barbay JM, Smith RS, Whitmore AV, Masland RH, and John SWM; Axons of retinal ganglion cells are insulted in the lamina early in an inherited mouse model of glaucoma. (2007) *J Cell Biol* 179(7), 1523-1537

3. The morphology and gene expression profile of reactive white-matter astrocytes:
At the outset of the work in my own lab at MEEI, much more was known about protoplasmic astrocytes than about white-matter (fibrous) astrocytes, such as those in the optic nerve. We are studying optic nerve head astrocytes because they form the direct cellular environment of the unmyelinated ganglion cell axons in this

segment of the nerve and may be directly involved in the pathogenesis of glaucoma. We identified a morphologically unique type of astrocyte in the glial lamina of the optic nerve and studied its changes in pathological conditions. We found that, unlike protoplasmic astrocytes, white-matter astrocytes react in a biphasic manner. In a first phase (days after injury), they retract their processes and reduce spatial coverage. In a second phase (>14 days), they extend new processes and assume a more normal morphology. This is accompanied by profound changes in gene expression that proceeds in three waves: an initial up-regulation of genes involved in inflammation and immunity, a second wave of cell proliferation, followed by a stage of debris clearance and tissue remodeling.

Sun D, Lye-Barthel M, Masland RH, and Jakobs TC; The morphology and spatial arrangement of astrocytes in the optic nerve head of the mouse. (2009) *J Comp Neurol* 516, 1-15

Sun D, Lye-Barthel M, Masland RH, and Jakobs TC; Structural remodeling of fibrous astrocytes after optic nerve injury. (2010) *J Neurosci*. 30(42), 14008-14019

Lye-Barthel M, Sun D, and Jakobs TC; Morphology of astrocytes in a glaucomatous optic nerve. (2013) *Invest Ophthalmol Vis Sci*, 54, 909-917

Wang R, Seifert P, and Jakobs TC; Astrocytes in the optic nerve head of glaucomatous mice display a characteristic reactive phenotype. (2017) *Invest Ophthalmol Vis Sci*, 58, 924-932

4. Establishing new models of optic nerve damage:
We were interested in establishing acute models of optic nerve damage that would allow us to investigate the earliest changes in glaucoma. In one of these approaches, we cannulate the anterior chamber and inflict a short, moderate increase of intraocular pressure to the eye (1-2 h, 30 mmHg). We found that this is sufficient to cause morphologically obvious signs of astrocyte reactivity in the optic nerve that are fully reversible within weeks after the injury and are not accompanied by damage to the ganglion cell axons. This indicates that astrocyte reactivity is not deleterious to axons per se, and may be even beneficial, at least in the early stages. We are currently testing this hypothesis by using transgenic mouse strains with impaired astrocyte function. Another injury model we have established is a “distal” lesion to the optic nerve. The background for this experiment is the consideration that most other injury models (such as optic nerve crush) also affect astrocytes directly. We are interested in signaling processes that may go on between injured axons and the astrocytes in their vicinity. We have therefore used a lesion to the intracranial portion of the optic nerve and are studying the effects of such an injury on the morphology and gene expression in the nerve head.

Sun D, Qu J, and Jakobs TC; Reversible reactivity by optic nerve astrocytes. (2013) *Glia*, 61(8), 1218-1235

Qu J and Jakobs TC; The time course of gene expression during reactive gliosis in the optic nerve. (2013) *PLoS ONE*, 8(6) e67094

Choi HJ, Sun D, and Jakobs TC; Isolation of intact astrocytes from the optic nerve head of adult mice. (2015) *Exp Eye Res*, 137,103-110

5. Studying the relationship between common genetic glaucoma susceptibility variants and their phenotype:
Genome-wide association studies have identified genetic variants in several loci that predispose to glaucoma, but it is not always clear what the mechanism may be. We are using transgenic mouse models to study the influence of these genes on retinal and optic nerve function.

Gao S, and Jakobs TC; Mice homozygous for a deletion in the glaucoma susceptibility locus *INK4* show increased vulnerability of retinal ganglion cells to elevated intraocular pressure. (2016) *Am J Pathol*, 186(4), 985-1005

URL to My Bibliography at NCBI:
https://www.ncbi.nlm.nih.gov/sites/myncbi/tatjana.jakobs.1/bibliography/40343803/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

2R01 EY019703 Jakobs (PI) 03/01/2016 – 02/28/2020
NIH/NEI
Cell Biology of Astrocytes in the Optic Nerve Head
The goal of this project is to identify transcription factors and signaling molecules that are involved in orchestrating astrocyte reactivity.
Role: PI

Pending

None

Completed Research Support (last 3 years)

Research to Prevent Blindness Jakobs (PI) 01/01/2016 – 12/31/2016
Retinal and optic nerve microglia in a mouse with a deletion in the glaucoma susceptibility locus Ink4
The goal of this project is to isolate retinal microglia from mutant mice for genetic analysis.
Role: PI

R01 EY22092 Masland (PI) 09/01/2013 – 07/31/2016
NIH/NEI
The induction of reactivity in optic nerve astrocytes
The goal of this project is to identify signaling events between retinal ganglion cells and optic nerve astrocytes after injury to the nerve.
Role: Co-investigator

Ellison Foundation Jakobs (PI) 1/1/2015 – 12/31/2015
Macrophages in the optic nerve head – a potential target for glaucoma therapy?
The goal of this application is to characterize a population of macrophages or atypical microglia in the optic nerve head.
Role: PI

R01 EY019703 Jakobs (PI) 09/30/2009 – 08/31/2015
NIH/NEI
Cell Biology of Astrocytes in the Optic Nerve Head
This project is concerned with optic nerve astrocytes; it focuses on the long-term consequences of elevated IOP in a murine model of glaucoma (DBA/2J), optic nerve crush, or laser-mediated transsection of axon bundles on the retinal surface.
Role: PI