THE GRADUATE COLLEGE OF THE

UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

Chelsea Marie Larabee

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE

GRADUATE COLLEGE
OKLAHOMA CENTER FOR NEUROSCIENCE

WEDNESDAY, MARCH 15, 2017
9:00 AM
BIOMEDICAL RESEARCH CENTER ROOM 109

OPTIC NEURITIS IN MOUSE MODELS OF MULTIPLE SCLEROSIS AND THE NEUROPROTECTIVE ROLE OF NRF2

COMMITTEE IN CHARGE: Scott M. Plafker, Ph.D., Chair; Kelly M, Standifer, Ph.D., Holly Van Remmen, Ph.D., Robert C. Axtell, Ph.D., Kenneth M. Humphries, Ph.D., Leonidas Tsiokas, Ph.D.

ABSTRACT: Inflammation of the optic nerve, called optic neuritis, is experienced by a majority of multiple sclerosis (MS) patients and is typically characterized by episodes of acute, monocular vision loss. These inflammatory episodes can lead to damage or degeneration of the retinal ganglion cells (RGCs) that comprise the optic nerve. Experimental autoimmune encephalomyelitis (EAE) is a well-established mouse model of MS that produces a neuro-autoimmunity and recapitulates cardinal hallmarks of the human disease, namely, demyelination, increased oxidative stress, and neurodegeneration. EAE mice exhibit spinal cord inflammation resulting in progressive ascending paralysis, which serves as a measure of clinical disability. Reliable treatment options for MS-associated optic neuritis are lacking due to major knowledge gaps in the mechanisms driving disease onset and progression. To bridge this gap, we rigorously characterized the functional and histological visual pathology in 3 variations of EAE. Visual acuity was measured daily using an optokinetic tracking (OKT) machine, and optic nerve inflammation and RGC degeneration were quantified using immunohistochemical techniques. All EAE variants exhibit monocular episodes of visual acuity impairment, the severity of which correlates to optic nerve inflammation and RGC degeneration. These striking similarities to human MS validate EAE as a legitimate model to study optic neuritis. It has been previously demonstrated that mice deficient for the master antioxidant transcription fact Nrf2 exhibit exacerbated motor deficits in EAE, but the role of this transcription factor in visual pathology was unknown. We established that, relative to wildtype controls, Nrf2-deficient mice exhibit more severe functional and histological visual pathology in EAE. An FDA-approved drug used for MS treatment called dimethyl fumarate (DMF) activates the Nrf2 pathway, but its efficacy for mitigating optic neuritis had not been investigated in animal models or humans. Our studies indicate that DMF is substantially more efficacious in preventing EAE motor disease compared to visual pathology and support the conclusion that additional therapeutics need to be developed to treat optic neuritis in MS patients.