ABSTRACT

Tick-borne flaviviruses (TBFVs), including Powassan virus and tick-borne encephalitis virus cause encephalitis or hemorrhagic fevers in humans with case-fatality rates ranging from 1-30%. Despite severe disease in human hosts, TBFV infection of natural rodent hosts has little noticeable effect. Currently, the basis for this resistance to disease is not known. We hypothesize that the coevolution of flaviviruses with their respective hosts has shaped the evolution of potent antiviral factors that suppress virus replication and protect the host from lethal infection. In the current study, we compared virus infection between reservoir host cells and related susceptible species. Infection of primary fibroblasts from the white-footed mouse (*Peromyscus leucopus*, a representative host) with multiple TBFVs showed up to a 10,000-fold reduction in virus titer compared to control *Mus musculus* cells. However, replication of the unrelated vesicular stomatitis virus was equivalent in *P. leucopus* and *M. musculus* cells suggesting that restriction was virus-specific. Stepwise comparison of the virus infection cycle revealed a significant block to viral RNA replication, but not virus entry, in *P. leucopus* cells. To understand the role of the type I interferon (IFN) response in virus restriction, we depleted signal transducer and activator of transcription 1 (STAT1) or the type I IFN receptor (IFNAR1) by RNA interference. Loss of IFNAR1 or STAT1 significantly relieved the block in virus replication in *P. leucopus* cells. The major IFN antagonist encoded by TBFV, nonstructural protein 5, was functional in *P. leucopus* cells, thus ruling out ineffective viral antagonism of the host IFN response and increased virus susceptibility to intrinsic cellular responses. Collectively, this work demonstrates that the IFN response of *P. leucopus* imparts a strong and virus-specific barrier to flavivirus replication. Future identification of the IFN-stimulated genes responsible for virus restriction specifically in *P. leucopus* will yield mechanistic insight into efficient control of virus replication and may inform the development of antiviral therapeutics.

DISSERTATION COMMITTEE

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The University of Toledo College of Medicine

Medical Microbiology & Immunology (MMI) Track

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THE UNIVERSITY OF TOLEDO
1872

DISSERTATION PRESENTATION

Adaeze Izuogu

May 17, 2017

Restriction of Tick-Borne Flaviviruses in the White-Footed Mouse

Ph.D. in Biomedical Sciences

PUBLICATIONS

Adaeze O. Izuogu, Kristin L. McNally, Stephen E. Harris, John B. Presloid, Brian H. Youseff, Christopher Burlak, Jason Munshi-South, Sonja M. Best, and R. Travis Taylor. Interferon signaling in *Peromyscus leucopus* confers a potent and specific restriction to vector-borne flaviviruses. *Revised manuscript in review*

Adaeze Izuogu, How the white-footed mouse can help humans fight diseases Toledo Blade. June 6, 2016

Adaeze O. Izuogu*, Brian H. Youseff* and R. Travis Taylor Innate weapons of host restriction against flaviviruses and viral countermeasures. *Manuscript in preparation*

Adaeze O. Izuogu, Brian H. Youseff and R. Travis Taylor. Construction of clonal over-expressing and knock-down cell lines using plasmid/lentiviruses. *Manuscript in preparation*

Brian H. Youseff, Thomas G. Brewer, Kristin L. McNally, **Adaeze O. Izuogu**, Kirk J. Lubick, John B. Presloid, Sonja M. Best, Xiche Hu, and R. Travis Taylor. TRAF6 Positively Regulates Tick-Borne Flavivirus Infection through Interaction with the NS3 Protease Domain. *Manuscript in preparation*

LEADERSHIP ROLES

2017 Certificate of graduation from the UT College of Business and Innovation Advanced Leadership academy

2015-2016 Representative of the UT College of Medicine and Life Sciences on the Graduate Student Association

2015-2016 Treasurer for the UT Council Of Biomedical Graduate Students

2014-2015 Representative of the IIT track on the Council of Biomedical Graduate students, UT College of Medicine and Life Sciences

ABSTRACTS & PRESENTATIONS

2017 Oral presentation titled 'Investigating the antiviral response to tick-borne flaviviruses in the white-footed mouse' at the University of Toledo Biomedical Science Graduate Research Forum

2016 Oral presentation titled 'Investigating the antiviral response to tick-borne flaviviruses in the white-footed mouse' at the IIT/MMI Annual Research Forum

2016 Oral presentation titled 'Investigating the antiviral response to tick-borne flaviviruses in the white-footed mouse' at the annual Midwest Graduate Research Symposium (MGRS)

2016 Poster presentation titled 'Investigating the antiviral response to tick-borne flaviviruses in the white-footed mouse' at the 35th annual meeting of the American Society for Virology

2016 Poster presentation titled 'Restriction of tick-borne flaviviruses by the white-footed mouse' at the Keystone Symposium on positive strand RNA viruses, Austin Texas

2015 Oral presentation titled 'Restriction of tick-borne flaviviruses by the white-footed mouse' at the University of Toledo Biomedical Science Graduate Research Forum

2015 Oral presentation titled 'Restriction of tick-borne flaviviruses by the white-footed mouse' at the IIT/MMI Annual Research Forum

2014 Oral presentation titled 'Restriction of tick-borne flaviviruses by the white-footed mouse' at the IIT/MMI Annual Research Forum

2014 Oral presentation titled 'Restriction of tick-borne flaviviruses by the white-footed mouse' at the 33rd annual meeting of the American Society for Virology, Fort Collins, Colorado

2014 Oral presentation titled 'Restriction of tick-borne flaviviruses by the white-footed mouse' at the Midwest Graduate Research Symposium

2014 Research poster presentation titled 'Restriction of tick-borne flaviviruses by the white-footed mouse' at the Biomedical Science Graduate Research Forum

AWARDS

2016 Robert R. Buell Memorial Achievement Award for Academic Excellence awarded by the University of Toledo College Of Graduate Studies to one graduate student annually

2016 American Society for Virology Travel Award to attend the 35th Annual meeting at Virginia Tech University

2016 Lyme Disease Association (LDA) Travel Award to attend the 2016 Annual Meeting in St. Paul, Minnesota

2016 University of Toledo Graduate Student Association research award to support research progress

2015 Lyme Disease Association (LDA) Travel Award to attend the 2015 Annual Meeting in Providence, Rhode Island

2015 Oral Presentation Award at the University of Toledo Annual Biomedical Science Graduate Research Forum (2nd place winner)

2014 American Society for Virology (ASV) Travel Award for the 33rd Annual Meeting at Colorado State University