Doctoral Dissertation Announcement

Carlie Aurubin

“Viruses and Burgers: The role of lipoproteins and lipoprotein receptors in gammaherpesvirus infection”

Candidate for Doctor of Philosophy in Microbiology & Immunology
Graduate School of Biomedical Sciences
Medical College of Wisconsin

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Live Public Viewing:
https://mcw-edu.zoom.us/j/94692181118?pwd=aWFzeENLRE0zSFoySGdWQTYzMVJZZz09
Passcode: ub2Ew9CQ

Committee Members:
Vera Tarakanova, PhD (advisor)
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Graduate Studies
Cellular & Microbiology Immunology
Classical & Molecular Genetics
Ethics and Integrity in Science
Research Ethics Discussion Series
Reading and Research
Doctoral Dissertation
Abstract
Gammaherpesviruses infect 95% of the human population. Infection lasts for the entire lifetime of the host and can be associated with several cancers. Despite the high prevalence, there is minimal understanding of how these viruses drive tumorigenesis. Recently, it has come to light that gammaherpesviruses interact with lipid synthesis to facilitate infection. We showed that endogenous cholesterol synthesis supports gammaherpesvirus replication. However, the role of exogenous cholesterol exchange and signaling during infection has not been addressed and remains a significant knowledge gap considering a high prevalence of both gammaherpesvirus infection and hypercholesterolemia.

The two human gammaherpesviruses are Epstein-Barr Virus (EBV) and Kaposi’s Sarcoma Associated herpesvirus (KSHV). These viruses are highly species-specific, which significantly limits the scope of EBV and KSHV studies. To overcome this limitation, murine gammaherpesvirus 68 (MHV68) is utilized in our studies. MHV68 is genetically and biologically related to KSHV and EBV and is a tractable experimental model for the study of gammaherpesvirus pathogenesis.

The exogenous cholesterol pathway utilizes lipoproteins, high-density lipoproteins (HDL), and low-density lipoproteins (LDL) to transport cholesterol in circulation due to cholesterol’s insolubility in serum. A protein component, called apolipoprotein, is embedded in lipoproteins and functions as ligands for lipoprotein receptors. LDL particles engage the LDL receptor (LDL-R) to facilitates internalization, providing cholesterol to fuel cellular function. Scavenger Receptor B Type I (SR-BI) binds HDL particles, enabling the removal of excess cellular cholesterol for hepatobiliary clearance or recycling. Apolipoprotein E (ApoE) functions as an exchangeable surface ligand for several lipoproteins, including HDL.

We found that LDL-R expression attenuates gammaherpesvirus replication during the early stages of the replication cycle, as evident by increased viral titers and viral gene expression in LDL-R\(^{-}\) primary macrophages. This exaggerated viral replication stems from LDL-R-dependent alterations in the endogenous cholesterol synthesis. Specifically, LDL-R suppresses endogenous cholesterol synthesis, limiting MHV68 access to this pro-viral pathway. Deletion of LDL-R did not alter gammaherpesvirus latency or reactivation in mice. Yet, BL6 and LDL-R\(^{-}\) mice placement on a hypercholesterolemia western diet attenuates MHV68 splenic reactivation. Intriguingly, neither diet nor genetic-induced hypercholesterolemia alters the adaptive immune response to MHV68.

We found that SR-BI supports MHV68 replication and suppresses Type I IFN response in primary macrophages. Ironically, HDL, the ligand for SR-BI, had differing effects, instead attenuating MHV68 gene expression. Yet, the anti-viral effect of HDL on MHV68 viral gene expression did not correlate with HDL effects on MHV68 replication. HDL supports MHV68 replication in a time-dependent manner. In vivo, SR-BI supports MHV68 reactivation but not latency in spleens of chronically infected mice. Like LDL-R, SR-BI does not alter MHV68-driven immune response.

MHV68 infection induces ApoE mRNA expression in primary macrophages in a type I interferon-dependent manner. Yet, ApoE is dispensable in MHV68 replication. In vivo, ApoE supports MHV68 latency and reactivation in chronically infected mice.
Overall, our study demonstrates that lipoproteins, their receptors, and components exert differential effects on infection through a complex network of interactions between metabolic and immune pathways of the host, revealing an insight into the regulation of gammaherpesvirus infection by the cholesterol metabolism. Defining this interplay is likely to offer a unique perspective on gammaherpesvirus infection and lymphomagenesis.
Curriculum Vitae

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EDUCATION

Doctor of Philosophy, Microbiology & Immunology (in progress) 2015 – present
Medical College of Wisconsin, Milwaukee, WI

Doctor of Medicine, (in progress) 2015 – present
Medical College of Wisconsin, Milwaukee, WI

Bachelor of Science, Biology 2010 – 2014
Magnum Cum Laude
Oakwood University, Huntsville, AL

RESEARCH EXPERIENCES

Graduate Student 2017 – present
Advisor: Vera Tarakanova, PhD
Microbiology & Immunology
Medical College of Wisconsin, Milwaukee, WI
Understanding the role of lipoproteins and lipoprotein receptors in gammaherpesvirus infection

Research Intern 2013
Advisor: Biswarup Mukhopadhyay, PhD
Microbiology in the Post Genome Era program
Virginia Tech, Blacksburg, VA
Determining the role of Dissimilatory Sulfite Reductase-like proteins in methanogenic archaea

Research Intern 2012
Advisor: Edward Collins, PhD
Summer of Learning and Research program
University of North Carolina, Chapel Hill, Chapel Hill, NC
Constructing antibody fragments to be used as a non-invasive imaging agent for pancreatic β-cells
PUBLICATIONS


Jondle CN, Johnson KE, Xin G, Aurubin CA, Sylvester P, Xin G, Cui W, Huppler AR, Tarakanova VL. Gammaherpesvirus usurps host IL-17 signaling to support chronic infection. mBio (in press)

CONFERENCE ABSTRACTS


Aurubin, C., Knaack, D., Sahoo, D. and and Tarakanova, V. The Tale of Two Receptors: Determining the role of lipoprotein receptors, SR-BI and LDL-R, in gammaherpesvirus infection. Immunology Retreat. (Milwaukee, WI 2018). Poster


Aurubin, C., Lange, P., Suazo, K., Distefano, M., and Tarakanova, V. Protein prenylation in the context of gammaherpesvirus infection. Graduate Student Poster Session. (Milwaukee, WI 2018). Poster

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GRANTS AND FELLOWSHIPS

Ruth L. Kirschstein Pre-Doctoral National Research Service Award 2019 – 2022
National Cancer Institute F30CA247000
The Tale of two receptors: Determining the role of lipoprotein Receptors, SR-BI and LDL-R, in gammaherpesvirus infection

EXTRAMURAL EXPERIENCE, POSITIONS AND SERVICE

WSTEM Program, Student Mentor 2020
Greater Milwaukee Free Clinic, Volunteer 2015 – 2019
Clinic Schedule Coordinator 2019
MSTP Class Representative 2018
American Society for Virology
Student Member