

Armand-Frappier Outstanding Student Award Recipient:

Dr. Ryan Gaudet, University of Toronto, Toronto, ON

Sponsored by Public Health Ontario



Ryan's research focuses on understanding how the mammalian innate immune system identifies and responds to microbial threats. Central to this response is the discrimination of self from non-self. Pattern recognition receptors expressed by mammalian cells detect conserved molecular signatures unique to microbes yet absent from the host. These molecules, termed pathogen-associated molecular patterns (PAMPs), are invariant structures broadly represented among microbial taxa and have essential roles in microbial physiology. Consequently, only an extremely select group of molecules have been found to function as PAMPs. Ryan's PhD research led to the discovery of a novel PAMP that signals the host to the presence of Gram-negative bacteria. He then uncovered an immunosurveillance pathway operating in the cytosol of mammalian cells that specifically detects this PAMP. His research sheds new light on how the innate immune system interprets bacterial threats, and offers potential in immune therapy and as a vaccine adjuvant. A native of Prince Edward Island, Ryan has recently completed his PhD training in Dr. Scott

Gray-Owen's lab at the University of Toronto. He has now joined the lab of Dr. John MacMicking at Yale University as a postdoctoral fellow, where he will continue his research on further defining the host-pathogen interface.

ARMAND-FRAPPIER
FOUNDATION
INRS
UNIVERSITY

Public
Health
Ontario
PARTNERS FOR HEALTH

Santé
publique
Ontario
PARTENAIRES POUR LA SANTÉ

Heptose sounds the alarm: Innate sensing of a bacterial sugar stimulates immunity

Ryan GAUDET, University of Toronto, S GRAY-OWEN¹, ¹University of Toronto

Host recognition of pathogen-associated molecular patterns (PAMPs) initiates an innate immune response that is critical for pathogen elimination and engagement of adaptive immunity. There are several well characterized PAMPs; however, recent work suggests that metazoans can detect other components of microbes, the combination of which provides the host with critical contextual information about the nature of the pathogen. Our work has identified one such molecule, the bacterial monosaccharide heptose 1,7-bisphosphate (HBP). A metabolic intermediate in lipopolysaccharide (LPS) biosynthesis, HBP is highly conserved in Gram-negative bacteria, yet absent from eukaryotes. Detection of HBP within the host cytosol activated the NF- κ B pathway *in vitro*, and induced innate and adaptive immune responses *in vivo*. HBP-induced signaling was independent of known pattern recognition receptor pathways. Therefore, we used a genome-wide RNAi screen to uncover a novel innate immune signaling axis, mediated by the TRAF interacting protein with forkhead-associated domain (TIFA). Contamination of the cytosol with HBP induced TIFA phosphorylation-dependent oligomerization and downstream activation of the ubiquitin ligase TRAF6. In the context of a pathogenic infection, we show TIFA is essential for the immune response to intracellular Gram-negative bacteria. Invasive *Shigella flexneri* released HBP during growth in the host cytosol, triggering a sustained wave of TIFA-driven inflammation that reflected the rate of bacterial replication. Our findings identify HBP as a novel PAMP, and as a corollary, TIFA as a new innate immune signaling effector that is the keystone of an immunosurveillance system that detects Gram-negative bacterial infection.