CBR

The Centre for Blood Research Seminar Series

Wednesday, May 4, 2016
LSC 3 - Life Sciences Centre
2350 Health Sciences Mall
12-1pm

Dr. Lindsay Eltis

Professor,
Microbiology and Immunology, UBC
***Canada Research Chair** in Microbial Catabolism and Biocatalysis*

"Steroid use by a pathogen – a ring-side story"

Mycobacterium tuberculosis (Mtb) continues to be the leading cause world-wide of mortality from bacterial infections. With the prevalence of drug-resistant strains, novel therapeutics are urgently needed to decrease the length, and improve the efficacy, of treatment. Approximately 8 years ago, we discovered a cluster of ~80 cholesterol catabolic genes in Mtb. We and others have since established that cholesterol catabolism is essential for virulence. Nevertheless, many aspects of this catabolism remain unknown, particularly with respect to HIP, a metabolite that contains steroid rings C and D and represents the last half of the cholesterol molecule. Our research establishes that HIP catabolism is largely specified by the beta-oxidative enzymes encoded by the KstR2 regulon. Degradation is initiated by FadD3, a HIP-CoA synthetase, whose reaction product is the effector molecule of the KstR2 repressor. Metabolic profiling of gene deletion mutants has enabled us to identify a number of previously undescribed cholesterol-derived CoA thioesters. Based on this profiling and biochemical studies of enzymes encoded by the KstR2 regulon, we propose a model for HIP degradation in Mtb. Of the HIP catabolic enzymes, only IpdAB, a CoA transferase, appears to be essential for survival in infection models. An ΔipdAB mutant of Mtb was unable to grow on cholesterol or to grow on glycerol in the presence of cholesterol. Metabolic profiling provides insight into the basis of this toxicity. Finally, we have worked collaboratively to characterize inhibitors of Mtb growth in macrophages that target cholesterol catabolism. Metabolite profiling and enzymological studies are establishing the mode of action of these inhibitors, facilitating their development as novel therapeutics. This research was funded in part by a CIHR grant to LDE.

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