Donnelly Centre
for Cellular + Biomolecular Research
UNIVERSITY OF TORONTO

UNIVERSITY OF TORONTO

Donnelly Seminar Series

"SAMHD1 acts on stalled replication forks to prevent the induction of type I IFNs"

Philippe Pasero, PhD
Professor
Principal Investigator
Institute of Human Genetics (IGH)
Montpellier, France

Abstract:

SAMHD1 is a dNTPase that restricts HIV-1 infection in non-cycling cells. Mutations in SAMHD1 cause Aicardi-Goutières syndrome (AGS), a severe inflammatory disease, and have also been implicated in chronic lymphocytic leukemia (CLL). However, the molecular mechanisms by which SAMHD1 prevents inflammation and cancer development remain unknown. We have characterized a novel function of SAMHD1 in DNA replication that is independent of its dNTPase activity. We have found that SAMHD1 promotes the degradation of newly-synthesized DNA at arrested replication forks. This activity is required for checkpoint activation and for the recovery of stalled forks, indicating that SAMHD1 is a novel key player of the replication stress response. Remarkably, we also found that newly-replicated DNA diffuses out of the nucleus and accumulates in the cytosol in the absence of SAMHD1, leading to the activation of a type I interferon response. Together, these data indicate that SAHMD1 promotes fork restart and prevents inflammation by degrading ssDNA fragments produced by fork repair processes.

Thursday, April 06, 2017 | 11:00 am
James D. Friesen | Cecil C. Yip Red Seminar Room
Host: Grant W. Brown, PhD