Vincent Archambault is a principal investigator at the Institute for Research in Immunology and Cancer and an Assistant Professor in the Department of Biochemistry and Molecular Medicine of Université de Montréal. After completing in B.Sc. in this department in 1999, Dr. Archambault obtained his Ph.D. in 2004 at The Rockefeller University in New York City, under the supervision of Mike Rout and Fred Cross. He then conducted postdoctoral research as an EMBO and HFSP fellow in the lab of David Glover in the Department of Genetics of University of Cambridge, UK. Dr Archambault launched his group in 2009 to dissect the molecular mechanisms controlling the cell cycle using Drosophila as a model.

Abstract

Cell cycle control by the Greatwall-PP2A axis

The eukaryotic cell cycle is regulated by reversible phosphorylation. Cyclin B-Cdk1 triggers the events of mitotic entry by the phosphorylation of multiple substrates. At mitotic exit, several of these substrates are dephosphorylated to allow the cells to return to interphase. While the role of Cyclin B-Cdk1 and its regulation in this process have been appreciated for decades, the implication of phosphatases and their regulation have come into light more recently. In animals, the Protein Phosphatase 2A in complex with its regulatory subunit B55 (PP2A-B55) plays an important role in the dephosphorylation of Cyclin B-Cdk1 substrates at mitotic exit. A loss of PP2A-B55 activity leads to defects in chromosome segregation, nuclear reassembly and cytokinesis. Work by several groups including ours has uncovered how PP2A-B55 is regulated in the cell cycle. Greatwall (Gwl) has been discovered in Drosophila as a kinase required for mitosis and meiosis. Genetic studies in flies and biochemical work in frog egg extracts have determined that Gwl is required to antagonize PP2A-B55 at mitotic entry by phosphorylating endosulfine, which then becomes a potent and specific inhibitor of PP2A-B55. A failure in this mechanism leads to mitotic collapse after nuclear envelope breakdown. While Gwl is nuclear in interphase, PP2A-B55 is mostly cytoplasmic. We have shown that Gwl suddenly relocalizes from the nucleus to the cytoplasm during mitotic entry, just before nuclear envelope breakdown, and that this strict control of Gwl localization is required for its function. We are investigating the importance and the molecular mechanisms of the spatiotemporal regulation of the Gwl-PP2A module. We are also using genetic and proteomic approaches to identify the crucial substrates of PP2A-B55 that must be protected from its activity at mitotic entry and dephosphorylated by it at mitotic exit. Our work reveals fundamental molecular mechanisms regulating the cell division cycle. This knowledge serves as a basis to better understand aberrant cell division in cancer and envision new therapeutic avenues.