University of Victoria | Graduate Studies

Notice of the Final Oral Examination
for the Degree of Doctor of Philosophy

of

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BSc (Portland State University, 2012)

"Insights into the Comparative Biological Roles of *S. cerevisiae* nucleoplasmin-like FKBPs Fpr3 and Fpr4"

Department of Biochemistry and Microbiology

Thursday, December 19, 2019
10:00 A.M.
Engineering / Computer Science Building
Room 130

Supervisory Committee:
Dr. Chris Nelson, Department of Biochemistry and Microbiology, University of Victoria (Supervisor)
Dr. Caren Helbing, Department of Biochemistry and Microbiology, UVic (Member)
Dr. Juan Ausio, Department of Biochemistry and Microbiology, UVic (Member)
Dr. Peter Constabel, Department of Biology, UVic (Outside Member)

External Examiner:
Dr. Michael Kobor, Department of Medical Genetics, University of British Columbia

Chair of Oral Examination:
Dr. Louise Page, Department of Biology, UVic

Dr. David Capson, Dean, Faculty of Graduate Studies

Abstract

The nucleoplasmin (NPM) family of acidic histone chaperones and the FK506-binding (FKBP) peptidyl proline isomerases are both linked to chromatin regulation. In vertebrates, NPM and FKBP domains are found on separate proteins. In lower eukaryotes, including fungi, NPMlike and FKBP domains are expressed as a single polypeptide in nucleoplasmin-like FKBP (NPLFKBP) histone chaperones. *Saccharomyces cerevisiae* has two NPL-FKBPs: Fpr3 and Fpr4. These paralogs are 72% similar and are clearly derived from a common ancestral gene. This suggests that they may have redundant functions. Their retention over millions of years of evolution also implies that each must contribute non-redundantly to organism fitness. The separate and redundant biological functions of these chromatin regulators have not been studied. In this dissertation I take a systems biology approach to fill this knowledge gap.

First, I refine the powerful synthetic genetic array (SGA) method of annotating gene-gene interactions, making it amenable for the analyses of paralogous genes. These 'paralog-SGA' screens define distinct genetic interactions unique to either Fpr3 or Fpr4, shared genetic interactions common to both paralogs, and masked genetic interactions which are direct evidence for processes where these enzymes are functionally redundant. I provide transcriptomic evidence that Fpr3 and Fpr4 co-operate to regulate genes involved in polyphosphate metabolism and ribosome biogenesis. I identify an important role for Fpr4 at the 5' ends of protein coding genes and the non-transcribed spacers of ribosomal DNA. Finally, I show that yeast lacking Fpr4 exhibit a genome instability phenotype at rDNA, implying that this histone chaperone regulates chromatin structure and DNA access at this locus. Collectively, these data demonstrate that Fpr3 and Fpr4 operate separately, co-operatively and redundantly to regulate a variety of chromatin environments. This work is the first comprehensive and comparative study of NPL-FKBP chaperones and as such represents a significant contribution to our understanding of their biological functions.