

CHROMATIN ARCHITECTURE ABERRATIONS IN PROSTATE CANCER AND LEUKEMIA

by

James Hawley

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Graduate Department of Medical Biophysics
University of Toronto

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Chapter 1

Introduction

1.1 Dissertation structure

I begin with ?? by exploring the *cis*-regulatory landscape of prostate cancer (PCa) and delineating the *cis*-regulatory elements (CREs) of the prostate oncogene *FOXA1*. I demonstrate the essentiality of *FOXA1* for prostate tumours, identify putative CREs based on integration of multi-omic datasets in PCa cell lines, and assess the functional impact of recurrent PCa single nucleotide variantss (SNVs) on *FOXA1* expression and transcription factor (TF) binding.

With the *cis*-regulatory network of *FOXA1* established in PCa, I attempt to construct the *cis*-regulatory landscape genome-wide in PCa with chromatin conformation capture (3C) mapping in ??. Using Hi-C, I characterize the three-dimensional chromatin organization of PCa and investigate the relationship between chromatin organization, structural variants (SVs), and the hijacking of *cis*-regulatory networks more generally.

In assessing the impact of SVs on chromatin organization, I uncovered a statistical problem stemming from the lack of recurrent SVs across PCa patients, leading to unbalanced experimental comparisons. To address this problem, I developed a statistical method for reducing error in gene expression fold-change estimates from unbalanced experimental designs in ?? and characterize the method.

Given the shared importance of mutations to TFs and epigenetic enzymes in prostate cancer and leukemias, in ?? I explore the epigenetic landscape of B-cell acute lymphoblastic leukemia (B-ALL) and its relapse after treatment. I characterize molecular changes to B-ALL tumours over the course of disease relapse and identify important changes to DNA methylation (DNAm) that indicate the

reversion to a stem-like phenotype, often present in a subpopulation of cells at diagnosis.