Chromatin architecture aberrations in prostate cancer and leukemia

by

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Contents

Chapter 1

Introduction

Cancer is one of the largest causes of death worldwide, ranking in the top ten most frequent causes in over 150 countries and most frequent in over 40 [1]. Disease treatment is complicated by the fact that cancers are a myriad of diseases with unique origins, symptoms, and treatment options, often related to the cell of origin [2]. However, numerous hallmarks of cancers have emerged over the last 50 years to provide understanding about what biological aberrations cause tumours to initiate, how they develop over time, and how they respond to therapeutic interventions [3–6] (Figure 1.1).

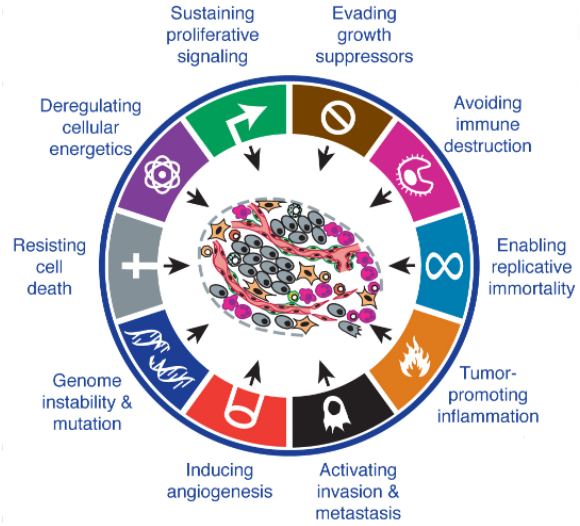

Figure 1.1: **The hallmarks of cancer.** Adapted from [REF 4].

Many of these hallmarks of cancer can be achieved through aberrations to the genome and the molecular machinery that enables cells to function normally [7]. For example, genome instability can be achieved by inhibiting deoxyribonucleic acid (DNA) repair machinery, as is observed with

abnormalities in *MLH1* and *MSH2* repair genes in colorectal cancers [8] or mutations to *BRCA1*, *BRCA2*, and *ATM* genes in prostate cancer (PCa) [9]. Similarly, replicative immortality can be achieved through telomere elongation by over-expression of the *TERT* gene [10]. Mutations to the *TERT* promoter, resulting in its over-expression, were first identified in melanomas [11, 12], but have since been further identified in bladder, thyroid, and brain cancers [10, 13, 14]. But while cancer has long been viewed as a disease of the genome [3, 7], there are many avenues cells can take to arrive these hallmarks resulting from aberrations of how genes are expressed inside the cell nucleus.

1.1 Normal chromatin architecture in mammalian cells

Genes, encoded as DNA, are expressed by being transcribed into ribonucleic acid (RNA) and subsequently translated into proteins in the process known as the Central Dogma of molecular biology [15] (Figure 1.2a). The transcription of genes into messenger RNA (mRNA) requires RNA polymerase to bind at transcription start sites (TSSs) within DNA elements found at the beginning of genes, termed promoters [16]. Promoters are one example of a class of DNA elements, termed *cis*-regulatory elements (CREs) because of their roles in regulating the expression of genes on the same strand of DNA. The recruitment of RNA polymerase is aided by a special class of proteins, termed transcription factors (TFs), that can bind at DNA sequences either close to a gene's promoter, or far from it at other CREs such as enhancers and insulators [17–22] (Figure 1.2b). Together, the binding of TFs to the DNA at specific CREs is fundamental for to initiating transcription and expressing genes.

1.1.1 DNA elements and features regulating transcription

The ability of TFs to bind at specific CREs is dependent on multiple features of the DNA. Many TFs bind to DNA at specific sequences, termed motifs [18, 23]. Finding the locations of a given motif in the genome is often the first step in determining the cistrome of a TF, the set of all sites and CREs a TF binds to *in vivo* [**lupienCistromicsHormoneDependentCancer2009**, 24]. The structural protein CCCTC-binding factor (CTCF) has a well-defined motif and binds to this sequence at thousands of locations across the human genome [25, 26]. Mutations to the sequence motif can alter CTCF's binding affinity for DNA, as is the case with many TFs [27–29]. Relying on more than just the genetic sequence, CTCF is also an example of a TF that is sensitive epigenetic features such as DNA methylation (DNAme), the addition of a methyl group to DNA nucleotides

[30–34], as are DNA methyltransferases DNMT1, DNMT3A, and DNMT3B [35, 36]. TF binding to DNA can also be affected by the presence of other proteins at binding sites. TFs can bind in a combinatorial manner at the same location [18, 19, 23] or be blocked from binding altogether by the presence of nucleosomes, protein complexes that DNA winds around to make it compact in three-dimensional space [37, 38]. The collection of DNA, nucleosomes, DNA-bound transcription factors, and chemical modifications is defined as the chromatin, and the presence and density of nucleosomes, as well as DNA coiling, make certain segments of the chromatin more or less accessible for TF binding (euchromatin and heterochromatin, respectively). This can affect normal cellular behaviour such as cell-type-specific gene expression [39, 40] and DNA damage repair in inaccessible regions [41]. Thus, both genetic and epigenetic chromatin features affect how TFs can bind and regulate transcription.

In addition to TF binding, transcription regulation depends on the ability of CREs to localize together in three-dimensional space across large genomic distances [42–44] (Figure 1.2c). Localization of CREs tens to thousands of basepairs (bps) apart form focal interactions is aided by the formation of topologically associated domains (TADs), domains of chromatin whose boundaries are linked by structural proteins, including CTCF and cohesin [22, 45–47]. In addition to TADs which can range in size from $10^4 - 10^6$ bp, chromatin is also organized into active or inactive compartments (A and B compartments, respectively) that range in size from $10^5 - 10^6$ bp [22, 48–50]. These two modes of chromatin organization facilitate the proper localization of CREs and TFs at the right time. While TADs and compartments are largely conserved across cell types [26, 51, 52], focal chromatin interactions can differ up to 45 % between cell types, providing a further mechanism to change chromatin state [49]. Different chromatin states enable cells with the same DNA sequence to express genes differently [17, 19, 45, 53–55], and thus identifying the repertoire of CREs, chromatin interactions, TADs, and compartments are vital in determining the regulation of genes in various cell types.

1.1.2 Methods for identifying DNA elements and chromatin interactions

High throughput sequencing protocols have enabled the characterization of functional elements from across the genome and rely on a similar concept to do so. This concept is to take a molecular feature of interest, be it an RNA transcript or nucleosome position, associate it with a short fragment of DNA, sequence these DNA fragments, and map it to the reference genome to identify where the original molecules came from (Figure 1.3). RNA sequencing (RNA-seq) methods reverse transcribed RNA into DNA that map back to individual genes, with the abundance of fragments indicating how

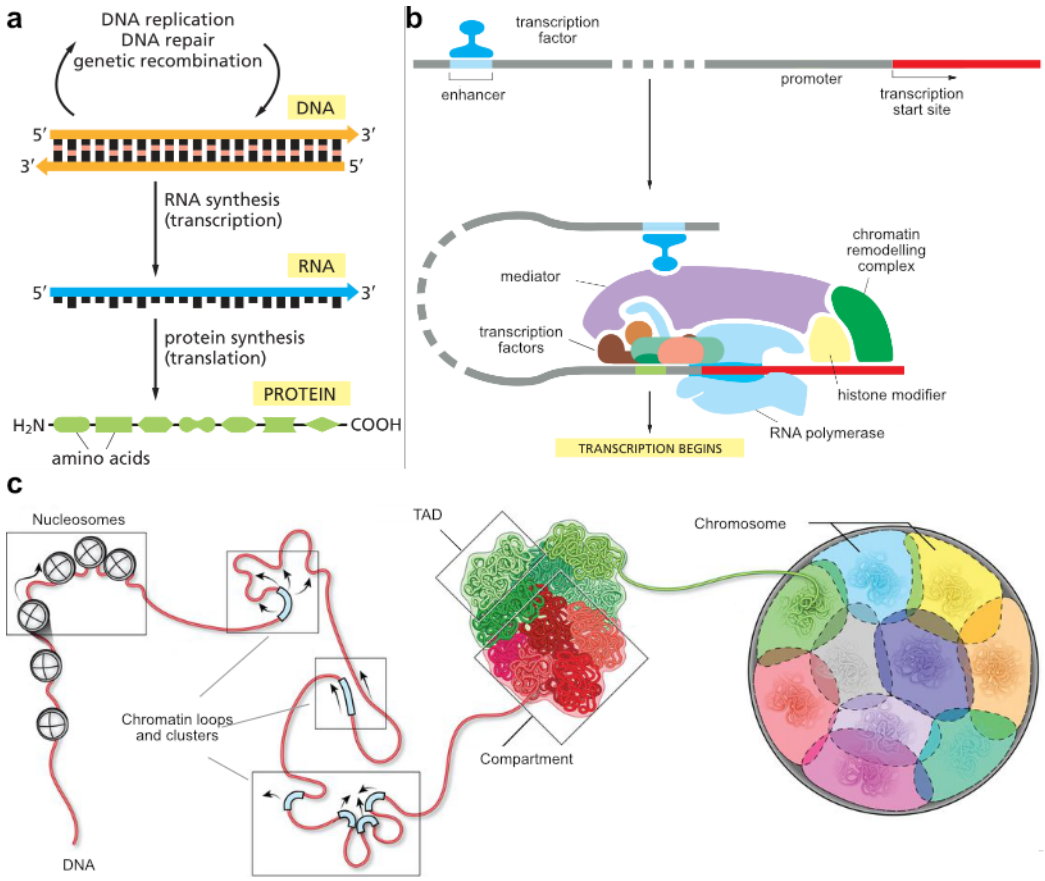

Figure 1.2: **The basics of gene expression inside the nucleus. a.** The central dogma of molecular biology. Adapted from [REF 15]. **b.** Schematic of the transcription machinery to initiate transcription. Adapted from [REF 15]. **c.** The scale of chromatin interactions across length scales. Adapted from [REF 47].

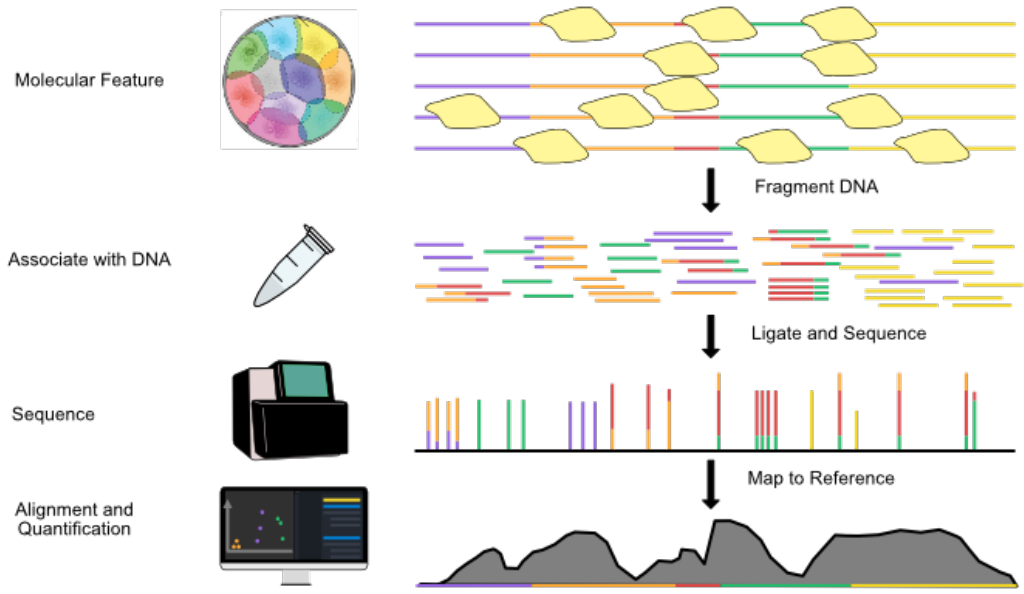

Figure 1.3: **Characterizing functional DNA elements with high throughput sequencing.**

much the gene is expressed [56]. Protein binding sites and histone post-translational modifications can be identified by fragmenting DNA around antibodies that bind to these proteins with techniques like chromatin immunoprecipitation sequencing (ChIP-seq) and cleavage under targets and release using nuclease (CUT&RUN) [57–59]. Accessible and inaccessible chromatin can be assessed by the chromatin's propensity to be cut by enzymes like DNase I, Tn5 transposase, and micrococcal nuclease in DNase I hypersensitive sequencing (DNase-seq), assay for transposase-accessible chromatin sequencing (ATAC-seq), and micrococcal nuclease sequencing (MNase-seq) protocols, respectively [60–64]. DNAme can be measured with bisulfite-sequencing assays [65], and distal chromatin interactions can be identified with chromatin conformation capture (3C) and 3C-based methods such as Hi-C [26, 48, 49, 66, 67]. Yet while these measurements help in identifying candidate CREs and important regions of the genome, determining their function and which target genes they regulate is a further complicating problem.

Varying chromatin states across cell types means that multiple measurements across multiple cell types are necessary to understand the breadth of functions a single CRE may have. In 2007, the ENCODE Project aimed to catalogue all biochemically functional elements in the human genome to better understand all the ways genes are expressed and how they are regulated in different cell types [68, 69]. Using these genome-wide sequencing techniques across a variety of human cell lines and tissues, the ENCODE Project has since catalogued nearly 10^6 candidate CREs, comprising nearly 8 % of the human genome [69]. Interpreting this data requires computational methods to correlate

and interpret measurements across samples. Genome segmentation methods such as ChromHMM [70] and Segway [71, 72] classify genomic regions according to their predicted function which can be validated with *in vitro* or *in vivo* experiments. Many techniques for experimental validation, including clustered regularly interspaced short palindromic repeat (CRISPR)-Cas9, small interfering RNA (siRNA), and small hairpin RNA (shRNA), can interfere with candidate CREs by deleting them from the genome, preventing TFs from binding to the chromatin, or preventing translation of mRNA transcripts into proteins [73, 74]. These same techniques can also be used to screen for candidate CREs themselves, through massively-parallel reporter assays (MRPAs) and CRISPR screens [74], necessitating their own suite of statistical and software tools for analyzing observations. Altogether, a collection of experimental and computational techniques enable the cataloguing and interpretation of thousands of CREs and chromatin interactions across many cell types. These catalogues facilitate understanding how genes are expressed within the complex chromatin architecture in normal cells and, importantly, how aberrations to this architecture can result in disease.

1.2 Aberrations to chromatin architecture in cancer

1.2.1 Genetic aberrations in cancer

Discovery of genetic mutations of oncogenes in tumours nearly 50 years ago spurred the widespread characterization of genetic aberrations in cancers [75–78]. These mutations occur within genic regions that code for proteins, but more than 98 % of somatic mutations acquired in tumours are found in non-coding regions [79]. Single nucleotide variants (SNVs), copy number variants (CNVs), and structural variants (SVs) are found throughout the genome, and interpreting the impact of these mutations on cancer is an active area of research [69, 78, 80, 81]. Analysis of recurrent somatic mutations in tumours led to the identification of *TP53* as a tumour suppressor gene [82], the frequently mutated *SPOP* gene to help define a molecular subtype of prostate tumours [83], and the interpretation of recurrent rearrangements of the proto-oncogene *MYC* in multiple cancers [84]. The impact of a mutation can also be predicted by identify overlapping regulatory elements or TF binding sites [28, 85, 86]. Grouping CREs by their putative target genes led to the identification of the *ESR1* gene as having its gene regulatory network recurrently mutated in ~10 % breast cancers, resulting in its over-expression, despite the gene itself being mutated in ~1 % of breast cancers [87]. Similarly, the binding sites of the *FOXA1*, *HOXB13*, *AR*, and *SOX9* TFs are enriched with mutations affecting their binding affinities [88] and recurrent amplifications of enhancers near the *AR* and *FOXA1*

genes are associated with increased rates of metastasis [89, 90]. Furthermore, mutations that do not directly target gene bodies or CREs can lead to oncogene over-expression. Multiple non-coding SVs in pediatric medulloblastoma patients were found to bring the *GFI1* and *GFI1B* oncogenes proximal to enhancer clusters, causing the oncogenes to become aberrantly regulated by this enhancer cluster [91]. This mechanism of enhancer hijacking has also been observed in developmental diseases [92, 93]. While this is not an exhaustive list, it is clear that genetic aberrations are abundant in cancers and that integrating genetic information with other components of the chromatin architecture can help identify driver events that promote oncogenesis or aggressive disease.

Mutations to DNA methyltransferases and chromatin remodelling proteins are common in cancers, and the impact of these mutations can be observed in their chromatin state. The isocitrate dehydrogenase (*IDH*) enzymes *IDH1*, *IDH2*, and the ten-eleven translocation (*TET*) enzymes *TET1* and *TET2* are frequently mutated in cancers, most often in leukemias and gliomas [94–98]. These mutations often affect the DNAme profiles of tumours and differentiation programs [94], such as loss of enhancer hydroxymethylation and germinal centre hyperplasia in diffuse large B-cell lymphoma (DLBCL) [99]. Similarly, mutations to the *EZH2* gene in leukemias can affect the ability of the EZH2 protein to write the H3K27me3 histone mark [100–103] and *EZH2* over-expression is associated with poor survival in PCa [104–107]. Together, these findings show that genetic aberrations to genes regulating other aspects of the chromatin architecture are abundant in multiple cancers and can drive specific programs in tumours. These programs can, in turn, affect progression of the disease and treatment strategies for patients. Importantly, the impact of these mutations is dependent on the function of the affected protein or CRE, which varies between different cancers. Thus, understanding how non-genetic aberrations affect tumours can be a vital step in understanding the impact of genetic aberrations.

1.2.2 Non-genetic aberrations in cancer

Non-genetic aberrations to chromatin have long been recognized as important factors in cancer development and progression [108, 109]. Methylation of gene promoters is associated with reduced gene expression and loss of DNAme (hypomethylation) across the genome and focal increases of DNAme (hypermethylation) have been found across numerous cancers [109, 110]. Importantly, these changes in DNAme can be found in the absence of mutations targeting DNA methyltransferases. Analysis of ~200 metastatic PCa patients with matching whole genome sequencing (WGS), RNA-seq, and whole genome bisulfite sequencing (WGBS) identified a subtype of tumours with a distinct

DNAme profile [111]. Ependymomas have also been found to display distinct DNAme profiles in the absence of recurrent mutations across patients [112] along with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), glioblastoma, and colorectal, liver, pancreatic, and ovarian cancers [113]. Notably, treatment of cancer cells with demethylating agents such as 5-aza-cytidine and 5-aza-2'-deoxycytidine for use in patients with AML and myelodisplastic syndrome (MDS) have shown to significantly increase survival times, demonstrating the clinical relevance of epigenetic marks in treatment strategies [114–116]. Though many causal mechanisms relating DNAme to cancer phenotype are lacking, the impact of DNAme on TF binding has been well-demonstrated. Variable CTCF binding across human cell lines has been shown to vary with DNAme levels, which can affect genome organization [30, 31]. In gastrointestinal cancer, CTCF binding sites are hypermethylated *SDH*-deficient tumours, resulting in widespread loss of CTCF and increased contact between the *FGF3* and *FGF4* oncogenes and a nearby enhancer cluster [117]. Moreover, aberrant contact of *FGF3* and *FGF4* is concomitant with increased H3K27ac modifications, further demonstrating the increased regulation and expression of the oncogenes. Disruptions of CTCF binding sites at TADs boundaries, resulting in aberrant regulation has also been found in T-cell ALL, leading to over-expression of the *TAL1* and *LMO2* oncogenes [118]. Both of these cases mimic the enhancer hijacking mechanism without the need for nearby genetic mutations. Together, these results show the importance of DNAme on three-dimensional genome organization and TF binding, and genetic and non-genetic aberrations can be observed in chromatin contacts and histone modifications.

The affect of chromatin variants on on gene regulation extends beyond DNAme. Cell type differences in nucleosome occupancy can lead to increased rates of mutation across the genome [119]. Similarly,TF binding can affect the ability of DNA damage repair complexes to perform local nucleotide excision repair [120, 121]. Thus, cell type differences in chromatin state can influence the frequency and location of DNA damage, which may describe some differences in recurrent mutations across cancer types. Many computational techniques have been developed in an attempt to prioritize the roles of different components of the chromatin architecture. One method, called similarity network fusion (SNF), integrates multiple chromatin measurements together to construct a mathematical graph whereby multiple samples cluster together if they share properties across multiple components [122]. Many similar methods exist that use machine learning-oriented and biology-oriented techniques to integrate multiple data types together to provide a comprehensive view of the chromatin architecture [123]. Taken together, these papers demonstrate the effect of differences in normal cell chromatin architecture on cancer and the multiple computational and experimental methods required to unravel these relationships.

Overall, these non-genetic aberrations of chromatin can be found across multiple cancer types. But we will continue to focus on two seemingly different cancer types that both display complex relationships between different components of the chromatin architecture: PCa and B-cell acute lymphoblastic leukemia (B-ALL).

1.3 Chromatin architecture of prostate cancer and B-cell acute lymphoblastic leukemia

1.3.1 Prostate cancer

Diagnosis, treatment, and risk factors

PCa is the second most commonly diagnosed cancer in men globally, with an estimated 23 300 men being diagnosed with the disease in Canada in 2020 [1, 124]. Diagnosis typically begins with the detection of prostate-specific antigen (PSA) in the blood, followed by a digital rectal exam for an enlarged prostate and a core needle biopsy to rule out benign prostate hyperplasia []. Once diagnosed, patients are typically grouped into one of several risk categories based on factors including PSA levels, histopathological assessment (i.e. Gleason or International Society of Urological Pathology (ISUP) scores), and medical imaging to detect for distal metastases (tumour node metastasis (TNM) staging)[]. PCa patients assessed to have a low mortality risk often undergo active surveillance to monitor for changes in the disease that pose a risk to the patient. Patients with high mortality risks often undergo one of multiple treatment regimens, including surgery, androgen deprivation therapy, chemotherapy, and radiotherapy []. While ~93 % of men with localized PCa survive, ~70 % of patients with metastatic disease will die [], accounting for ~10 % of all cancer deaths in men [124]. This highlights the need for accurate risk assessment at diagnosis and knowledge of what aberrations lead to aggressive, metastatic disease.

Risk of developing PCa is associated with age and the median age at diagnosis is 66 years old []. While developing PCa at a young age is rare (diagnosis at age < 40 accounts for !!!x!!! % of all PCa diagnoses), younger men who are diagnosed typically have a more aggressive disease and relatively poorer survival rates []. In addition to age, genetic ancestry is a risk factors for developing the disease. Men of African ancestry are ~1.6 times more likely to be diagnosed with PCa than men of western European ancestry, who in turn are ~2 times more likely than men of Asian ancestry []. Men of different ancestries also tend to accumulate different sets of mutations

in their tumours. For example, ~50 % of men of western European ancestry harbour a fusion of an *ETS* gene family member [125], whereas only ~10 % of men of Asian ancestry harboured a similar mutation [126]. Inherited germline mutations are also a risk factor for PCa, as men with *BRCA1* and *BRCA2* mutations are ~2 times more likely to develop PCa than those without. Men with germline mutations to *ATM* and *HOXB13* are also at a higher risk of developing the disease []. Studies identifying these risks demonstrate that familial history, in addition to age and genetic ancestry, are important factors for developing PCa.

Chromatin aberrations in prostate cancer

Large cohort studies of prostate tumours have identified numerous driver mutations for the disease. These driver mutations include, but are not limited to, coding mutations to the *BRCA1*, *BRCA2*, *CHD1*, *IDH1*, *MYC*, *NKX3-1*, *PTEN*, *RB1*, *SPOP*, and *TP53* genes, as well as *ETS*, *FOX*, *HOX*, *KLK*, and *KMT* factors [9, 125, 127]. *ETS* factor mutations, such as the *TMPRSS2-ERG* (T2E) fusion, can lead to a globally *cis*-regulatory landscape, affecting TF binding genome-wide and *NOTCH* signalling [128]. Metastatic tumours are enriched for amplifications to the *FOXA1* and androgen receptor (*AR*) genes compared to primary tumours, as well as mutations targeting epigenetic regulators, such as histone lysine methyltransferases (KMTs) [89, 129, 130]. Over-expression of *AR* is associated with castration resistance, reducing the effectiveness of androgen deprivation therapies []. Importantly, *FOXA1* is a pioneer TF that regulates *AR*, and over-expression of *FOXA1* is also more frequently found in metastatic than primary tumours [131]. Together, these two genes, their CREs, and their cistromes constitute important regions of chromatin that impact the progression of low-risk, localized PCa into high-risk metastatic PCa.

1.3.2 B-cell acute lymphoblastic leukemia

Diagnosis, treatment, and risk factors

Leukemia is the 15th most commonly diagnosed cancer globally, with an estimated 6 900 individuals being diagnosed with the disease in Canada in 2020 [1, 124]. Leukemias, generally, result from an overgrowth of undifferentiated blast cells that do not exhibit the same behaviours as fully differentiated cells in the hematopoietic hierarchy []. B-ALL is an acute clonal expansion of primitive cells restricted to the lymphoid hematopoietic lineage of B-cells and primarily occurs in children [132]. Currently, overall survival of pediatric B-ALL is ~90 % [132], yet disease relapse after treatment still occurs in 10 - 15 % of patients [133, 134]. Diagnosis of B-ALL typically begins with the detec-

tion of over-abundant lymphoblasts by microscopy and immunophenotypic assessment of cell surface markers indicating lineage commitment and developmental stage [133]. After diagnosis, mortality risk is assessed based on factors including age and white blood cell counts. Patients under 2 or over 10 years of age have worse prognoses than patients of other ages, as do patients with $\geq 50 \times 10^3$ cells / mL [132, 133]. Newly diagnosed patients typically undergo remission-induction therapy, intensification/consolidation therapy, and continuation/maintenance therapy over the span of 2 years [133]. Risk factors for developing the disease include sex, genetic ancestry, and chromosomal rearrangements, with men, African or Hispanic ancestry, and Down's syndrome all associated with an increased risk [132, 133]. Risk factors for disease relapse remain elusive; however, karyotpying and high throughput sequencing technologies are helping to identify new biomarkers.

Chromatin aberrations in B-cell acute lymphoblastic leukemia

B-ALL is commonly classified according to the presence of recurrent mutations. Hyperploidy and the presence of the fusion of the *ETV6* and *RUNX1* genes are associated with favourable outcomes, whereas hypoploidy with < 44 chromosomes, fusion of the *BCR* and *ABL1* genes, and mutations affecting the *PAX5*, *EBF1*, *MLL/KMT2A*, *CRLF2*, and *IKZF1* genes are all associated with poorer outcomes [132, 133]. Many of these affected genes regulate B-cell development, such as *PAX5* [135–137], *IKZF1* [137], and *EBF1* []. Similarly, *KMT2A* and *CREBBP* are histone writers, depositing methyl groups to the histone H3 lysine 4 residue and acetyl groups to the histone H3 lysine 56 residue, respectively [138–143]. Mutations in these genes are enriched in relapse [132, 144], suggesting that not only do epigenetic regulators play a key role in oncogenesis, but that they also promote relapse.

Aberrant changes to DNAme may also play a role in B-ALL relapse. DNAme has been shown to change across B-cell differentiation, with differentially methylated regions (DMRs) found in the cistromes of TFs that regulate differentiation, including *EBF1* and *PAX5* [145]. Additionally, the DNAme profile of B-ALL cells differ at thousands of loci across the genome, compared to normal B-cells, primarily in bivalent CREs and promoter regions [146, 147]. These findings suggest that aberrant DNAme pattern in B-ALL may be affecting B-cell differentiation through TF binding. Moreover, hypomethylation of the *IL2RA* gene is associated with a worse prognosis, as is aberrant DNAme in the presence of *E2A-PBX1* or *KMT2A* fusions [148]. This suggests that specific DNAme changes may cooperate with mutated epigenetic regulators to promote aggressive disease that is more likely to relapse after treatment. Overall, numerous genetic and epigenetic alterations in primary B-ALL and relapsed B-ALL suggest that multiple chromatin aberrations impact the development

and progression of this disease.

While cellular phenotypes and treatment strategies for PCa and B-ALL do not resemble each other, PCa oncogenesis, PCa metastases, and B-ALL relapse all harbour aberrations to different components of the chromatin architecture that interact with each other. Thus, to mitigate, or even prevent, these processes from occurring, this thesis investigates mutations targeting CREs of important TFs, the relationship between three-dimensional genome organization and SVs, and the effect of DNAme changes over the course of relapse.

1.4 Thesis structure

I begin with **??** by exploring the *cis*-regulatory landscape of PCa and delineating the CREs of the prostate oncogene *FOXA1*. I demonstrate the essentiality of *FOXA1* for prostate tumours, identify putative CREs based on integration of multiomic datasets in PCa cell lines, and assess the functional impact of recurrent PCa SNVs on *FOXA1* expression and 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 3C mapping in **??**. Using Hi-C, I characterize the three-dimensional chromatin organization of PCa and investigate changes to this structure over oncogenesis, and explore the relationship between chromatin organization, SVs, and CRE hijacking.

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

Together, this thesis investigates the multiple layers of the chromatin architecture that contribute to oncogenesis and cancer progression. I demonstrate that aberrations to the genome, epigenome, and three-dimensional organization of chromatin play important roles individually, and together, in the orchestration of the disease.

Glossary

3C chromatin conformation capture

ALL acute lymphoblastic leukemia

AML acute myeloid leukemia

ANOVA Analysis of Variance

AR androgen receptor

ATAC-seq assay for transposase-accessible chromatin sequencing

B-ALL B-cell acute lymphoblastic leukemia

bp basepair

cDNA complementary DNA

ChIP-seq chromatin immunoprecipitation sequencing

CLL chronic lymphocytic leukemia

CML chronic myeloid leukemia

CMP common myeloid progenitor

CNV copy number variant

CPC-GENE Canadian Prostate Cancer Genome Network

CpG CG dinucleotide

crRNA CRISPR RNA

CRE *cis*-regulatory element

CRISPR clustered regularly interspaced short palindromic repeat

CTCF CCCTC-binding factor

CUT&RUN cleavage under targets and release using nuclease

DEPMAP Cancer Dependency Map

DHS DNase I hypersensitive sites

DLBCL diffuse large B-cell lymphoma

DMR differentially methylated region

DNA deoxyribonucleic acid

DNAme DNA methylation

DNase-seq DNase I hypersensitive sequencing

dRI disease relapse-initiating

Dx diagnosis

EarlyProB early progenitor B cell

FDR false discovery rate

FN false negative

FP false positive

FOX forkhead box

GLM generalized linear model

GMP granulocyte-macrophage progenitor

GO gene ontology

gRNA guide RNA

HSC hematopoietic stem cell

HSPC hematopoietic stem and progenitor cell

IDH isocitrate dehydrogenase

IID independent and identically distributed

ISUP International Society of Urological Pathology

JS James-Stein

KMT histone lysine methyltransferase

KO knockout

LDA limiting dilution assay

LMPP lymphoid-primed multi-potent progenitor

MeCapSeq DNA methylation capture sequencing

MEP megakaryocyte-erythrocyte progenitor

MNase-seq microccocal nuclease sequencing

MSE mean square error

mCRPC metastatic castration-resistant prostate cancer

MDS myelodisplastic syndrome

MLP monocyte-lymphoid progenitor

MPP multi-potent progenitor

MRPA massively-parallel reporter assay

NSG NOD scid gamma

OLS ordinary least squares

mRNA messenger RNA

PCa prostate cancer

PDX patient-derived xenograft

PreProB pre-progenitor B cell

ProB progenitor B cell

PSA prostate-specific antigen

Rel relapse

RNA ribonucleic acid

RNAi RNA interference

RNA-seq RNA sequencing

shRNA small hairpin RNA

siRNA small interfering RNA

SNV single nucleotide variant

SRA Seqeuence Read Archive

SNF similarity network fusion

SV structural variant

T2E *TMPRSS2-ERG*

TAD topologically associated domain

TCGA The Cancer Genome Atlas

TET ten-eleven translocation

TSS transcription start site

TN true negative

TNM tumour node metastasis

TP true positive

TF transcription factor

tracrRNA trans-activating CPRISR RNA

UTR untranslated region

WES whole exome sequencing

WGBS whole genome bisulfite sequencing

WGS whole genome sequencing

WT wild-type

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