REVIEW

Androgen receptor enhancer usage and the chromatin regulatory landscape in human prostate cancers

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Abstract

The androgen receptor (AR) is commonly known as a key transcription factor in prostate cancer development, progression and therapy resistance. Genome-wide chromatin association studies revealed that transcriptional regulation by AR mainly depends on binding to distal regulatory enhancer elements that control gene expression through chromatin looping to gene promoters. Changes in the chromatin epigenetic landscape and DNA sequence can locally alter AR-DNA-binding capacity and consequently impact transcriptional output and disease outcome. The vast majority of reports describing AR chromatin interactions have been limited to cell lines, identifying numerous other factors and interacting transcription factors that impact AR chromatin interactions. Do these factors also impact AR cistromics – the genome-wide chromatin-binding landscape of AR – *in vivo*? Recent technological advances now enable researchers to identify AR chromatin-binding sites and their target genes in human specimens. In this review, we provide an overview of the different factors that influence AR chromatin binding in prostate cancer specimens, which is complemented with knowledge from cell line studies. Finally, we discuss novel perspectives on studying AR cistromics in clinical samples.

Key Words

- ▶ androgen receptor
- ▶ prostate cancer
- ▶ ChIP-seq
- ▶ cistrome
- ▶ subtypes

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Transcription factor binding

By 2003, the DNA sequence of the entire human genome was annotated by The Human Genome Project ([International Human Genome Sequencing Consortium 2004](https://erc.bioscientifica.com)). However, as informative the primary DNA sequence information is on the protein-coding genome (~2% of the total human DNA), interpretation of the remaining ~98% of the human genome appears more challenging. One of the major challenges in functionally interpreting the non-protein-coding human genome is that the primary

sequence itself does not explain how the DNA is packaged into chromatin and where transcription factors (TFs) bind. Some TFs bind indirectly to the DNA via protein–protein interactions by means of tethering, while other TFs recognize specific DNA sequences, often referred to as TF motifs, footprints or grammar ([Fig. 1A](#)). Many computational methods have been developed to scan for these TF motifs across the entire genome to predict the capacity of a particular TF to bind specific regions, such as

Figure 1

Transcription factor binding and transcription. (A) Transcription factors (TFs) interact with DNA to regulate gene expression. TFs can bind the DNA directly via recognition of sequence-specific elements or indirectly through other TFs. (B) Sequence logo depicting the androgen response element (ARE, MC00468). The logo is a graphical representation of a position weight matrix (PWM), which describes the nucleotide preference at each nucleotide position within the motif. (C) Graphical representation of AR-bound enhancer–promoter interaction. Accessible chromatin regions are flanked by active histone marks, such as H3K27ac at enhancers and H3K4me3 at promoters. Ligand-bound AR dimers bind to androgen-response elements (AREs) mostly at distal intergenic or intronic regions – enhancers. These enhancers are often distally located from genes with varying distances of ~20–300 kb. Some enhancers are bi-directionally transcribed to produce eRNAs.

the SeqPos motif tool (Liu *et al.* 2011) and HOMER (Heinz *et al.* 2010). In addition, other algorithms (e.g. MEME Suite; Bailey *et al.* 2015) can be applied to discover DNA sequence patterns in given regions. However, the presence of a TF motif does not imply that the TF is actually capable to bind this region. For example, the AR – the main driver in prostate cancer development and progression –

recognizes a palindromic dihexameric androgen-responsive element (ARE), 5'-AGAACAnnnTGTTCT-3' (Fig. 1B), which occurs a few million times throughout the human genome. However, only hundreds to tens of thousands AREs appear to be functionally active in a given context and occupied by AR in prostate cell lines (Yu *et al.* 2010, Massie *et al.* 2011, Toropainen *et al.* 2016,

Table 1 List of AR and H3K27ac ChIP-seq datasets on human specimens.

Study	Accession number	Factor	Normal cells	Primary tumor	CRPC	Stroma
Yu <i>et al.</i> (2010)	GSE14097	AR			1	
Sharma <i>et al.</i> (2013)	GSE28219	AR	2	5	5	–
Chen <i>et al.</i> (2015)	GSE43791	AR	2	4	–	–
Pomerantz <i>et al.</i> (2015)	GSE56288	AR	7	13	–	–
Stelloo <i>et al.</i> (2015)	GSE65478	AR	–	4	3	–
Chen <i>et al.</i> (2018)	GSE99378	AR V7/HOXB13	–	–	3	–
Stelloo <i>et al.</i> (2018b)	GSE120738	AR	–	88	–	–
		H3K27ac		92		
Kron <i>et al.</i> (2017)	GSE96652	H3K27ac	–	19	–	–
Takeda <i>et al.</i> (2018)	GSE114385	H3K27ac	–	6	4	–
Cioni <i>et al.</i> (2018)	GSE126852	AR	–	–	–	2
		H3K27ac				

McNair *et al.* 2017, Stelloo *et al.* 2018a) and tissue samples (Sharma *et al.* 2013, Chen *et al.* 2015, Pomerantz *et al.* 2015, Stelloo *et al.* 2015, 2018b). In addition, all cells in the human body carry an identical genome; yet, TFs regulate gene expression patterns to dictate organ development and identity. Key questions to further understand AR action on a genome-wide scale are the following: Where does AR bind the genome in different contexts, and what are the biological consequences thereof? While full discussion on the biological significance of AR in prostate cancer is beyond the scope of this review, this subject has been covered elsewhere (Culig & Santer 2014, Copeland *et al.* 2018, Isaacs 2018, Ken-ichi 2018). Another question is how AR chromatin binding is regulated and to what degree is this context dependent? Furthermore, with more reports describing AR cistromics in clinical samples

(Table 1), what did we learn from this, and how could we use this information in the clinical setting? In particular, we focus on the technological developments (Table 2) that have made the transition from cell line models toward the study of clinical specimens. This review will address these points systematically and will highlight the potential future research directions aimed to enhance our understanding of genome regulation in prostate cancer.

AR cistromics

Where does AR bind the chromatin in cell lines?

Prior to the era of genome-wide mapping of TF binding, AR binding was predominantly studied at the *Kallikrein-3* (*KLK3*) gene locus, encoding the commonly used serum

Table 2 List of methods.

Method	Full method name	Approach for	References
ChIP-on-chip	Chromatin immunoprecipitation followed by genomic tiling microarray hybridization	Genome-wide analysis of transcription factor binding and histone modifications	Outdated technology AR (Takayama <i>et al.</i> 2007, Wang <i>et al.</i> 2007, 2009) Barski <i>et al.</i> (2007)
ChIP-seq	Chromatin immunoprecipitation followed by sequencing	Genome-wide analysis of transcription factor binding and histone modifications	
ChIP-re-ChIP	Sequential chromatin immunoprecipitations	Genome-wide analysis of co-occupancy of proteins at genomic loci	AR (Wang <i>et al.</i> 2007, Cao <i>et al.</i> 2014)
FFPE ChIP	ChIP-seq analysis on formalin-fixed paraffin-embedded tissue samples	Genome-wide analysis of histone modifications using FFPE material	Fanelli <i>et al.</i> (2010), Cejas <i>et al.</i> (2016)
ChiA-PET	Chromatin interaction analysis by paired-end tag	Protein-centered view of genome architecture	Fullwood <i>et al.</i> (2009)
3C	Chromosome conformation capture	Exploring the interaction between two genomic loci (one locus to one locus)	AR (Zhang <i>et al.</i> 2019) (Dekker <i>et al.</i> 2002)
4C	Circular chromosome conformation capture on chip	Exploring all possible interactions with a single genomic locus (one locus to all loci)	Simonis <i>et al.</i> (2006), Zhao <i>et al.</i> (2006)
MC-4C	Multicontact-4C	Studying multiway chromatin interaction between many genomic loci at single allele resolution	Allahyar <i>et al.</i> (2018)
Hi-C	Genome-wide chromatin conformation capture	Exploring all chromatin interactions within the genome (all loci to all loci)	Lieberman-Aiden <i>et al.</i> (2009)
p-CHI-C	Promoter capture-Hi-C	Hi-C coupled with RNA bait capture probes targeting all promoters (promoters to all loci)	Schoenfelder <i>et al.</i> (2018)
ATAC-seq	Assay for transposase-accessible chromatin using sequencing	Genome-wide analysis of accessible chromatin	Buenrostro <i>et al.</i> (2013)
RNA-seq	Ribonucleic acid sequencing	Measuring steady-state mRNA levels	Mortazavi <i>et al.</i> (2008)
GRO-seq	Global run-on sequencing	Measuring nascent RNA transcripts	Core <i>et al.</i> (2008)
RIME	Rapid immunoprecipitation mass spectrometry of endogenous protein	Studying endogenous protein complexes	Mohammed <i>et al.</i> (2013)
qPLEX-RIME	Quantitative multiplexed method – rapid immunoprecipitation mass spectrometry of endogenous protein	Studying the dynamics of endogenous protein-protein interaction	Papachristou <i>et al.</i> (2018)
WGS	Whole genome sequencing	Providing the nucleotide sequence of the entire genome	
CRISP-seq	Combining single-cell RNA-seq and CRISPR-based perturbations	Linking phenotypes at the level of the transcriptome with gene functions	Jaitin <i>et al.</i> (2016)
Perturb-seq	Combining single-cell RNA-seq and CRISPR-based perturbations	Same as CRISP-seq	Dixit <i>et al.</i> (2016)

biomarker prostate-specific antigen (PSA). PSA expression was shown to be upregulated upon androgen stimulation in LNCaP cells, implicating this gene as a bona fide AR target (Young *et al.* 1991, Henttu *et al.* 1992). In response to androgens, AR along with its coregulators (Shang *et al.* 2002) is recruited to *cis* elements upstream at the promoter (ARE I and ARE II) (Pang *et al.* 1995, Cleutjens *et al.* 1996) and enhancer (ARE III) (Cleutjens *et al.* 1997) regions of the *KLK3* gene.

After extensive studies using chromatin immunoprecipitation assays (ChIP) to study AR chromatin binding at specific loci, technological advances enabled for ChIP assays followed by genomic tiling microarray hybridization (ChIP-on-chip) and later on massive parallel sequencing (ChIP-seq). These technological developments truly revolutionized the field, allowing for unbiased discovery of TF-binding sites on a genome-wide scale. The pioneering studies of AR ChIP-on-chip assays capturing 30Mb human genomic DNA (Takayama *et al.* 2007), two chromosomes (Wang *et al.* 2007) or the entire human genome (Wang *et al.* 2009) reported hormone-induced AR-DNA binding mostly located in non-promoter proximal regions far from transcription start sites (20–50kb). Later, AR ChIP-seq in LNCaP and VCaP cell lines confirmed that ~90% of the AR-binding sites can be found at distal *cis*-regulatory elements (Fig. 1C) (Yu *et al.* 2010, Massie *et al.* 2011). These AR-binding events, the AR cistrome, define the transcriptional response associated with AR activation.

How to identify AR target genes?

We and others defined direct AR target genes as those genes with an AR-binding site within 20–50kb of the genes (Wang *et al.* 2009, Sharma *et al.* 2013, Stelloo *et al.* 2015). This approach is a simple solution, but not well suited as AR-bound enhancer–target gene interaction can go far beyond a linear distance of 20–50kb as recently shown for the enhancer of the *AR* gene (650kb) (Takeda *et al.* 2018). In addition, promoter capture Hi-C in primary hematopoietic cell types revealed a median linear distance of 331kb between promoters and distal regulatory elements (Javierre *et al.* 2016). Furthermore, capture Hi-C and chromatin interaction analysis by paired-end tag sequencing (ChIA-PET) revealed that one single promoter can interact with multiple enhancers, but also revealed the regulation of multiple genes by the same enhancer (Fullwood *et al.* 2009, Javierre *et al.* 2016, Zhang *et al.* 2019). Recently, novel methods have been developed such as multicontact 4C and single-cell Hi-C

to rule out whether interactions co-occur simultaneously in individual cells or independently in different cells (Ramani *et al.* 2017, Allahyar *et al.* 2018). Moreover, to uncover combinatorial relationships between enhancers, several laboratories applied CRISPR genome editing or CRISPR interference (CRISPRi) to silence individual or multiple enhancer regions. These data on other steroid hormone receptors, such as the estrogen receptor alpha (ER α) and the glucocorticoid receptor (GR), provided evidence for cooperative interaction between several hormone receptor-bound enhancers (Carleton *et al.* 2017, Thormann *et al.* 2018). It is likely that AR functions in a comparable manner, given the close homology between AR, GR and ER, but conclusive AR-centered studies on chromatin looping are yet to be reported.

Enhancer–gene interactions can also be predicted in clinical specimens with assays, such as Hi-C and ATAC-seq (Schmitt *et al.* 2016, Beagrie *et al.* 2017, Corces *et al.* 2017, Diaz *et al.* 2018). ATAC-seq data from prostate cancer samples has become recently available (Corces *et al.* 2018), while Hi-C in clinical specimens remains to be performed. ATAC-seq is a technique to assess genome-wide chromatin accessibility, and not genetic interactions per se, but enhancer–gene interactions can be studied by correlating ATAC-seq accessibility and gene expression data (Corces *et al.* 2018). However, Hi-C is specifically developed to measure long-range interaction on a genome-wide scale. Hi-C datasets on prostate cell lines have been generated (Rickman *et al.* 2012, Taberlay *et al.* 2016, Luo *et al.* 2017), albeit without hormone stimulation. Furthermore, these datasets suffer from limited resolution, which prevents functional linkage between distal regulatory elements and their target genes. Based on data from chromosome conformation capture (3C) experiments, hormone stimulation is known to enhance AR-bound enhancer looping to its target gene promoters (Wang *et al.* 2005, 2007, Chen *et al.* 2011). This is supported by genome-wide chromatin interaction studies, showing that long-range chromatin interactions exist in the absence of hormones and that the frequency of pre-existing interactions increases upon hormone (e.g. glucocorticoids) stimulation (Kuznetsova *et al.* 2015, D'Ippolito *et al.* 2018, Le Dily & Beato 2018). It would be therefore of interest to perform for example promoter capture Hi-C, both in hormone-deprived as well as hormone-stimulated prostate cancer cell lines to characterize the AR enhancer–target gene interactome along with the potential dynamics thereof. Very recently, AR-centered chromatin interactions in VCaP cells were mapped with ChIA-PET (Zhang *et al.* 2019).

However, AR ChIA-PET data in the absence of hormones would not be informative, as unliganded AR resides in the cytoplasm. Due to this limitation, AR ChIA-PET data cannot be used to assess whether these long-range interactions are *de novo* established upon hormone stimulations or pre-exist in the absence of hormones.

A further elucidation of direct AR target genes has been performed by combining AR chromatin-binding profiles with gene expression profiling. Upon androgen stimulation, hundreds to thousands of genes are being either up- or downregulated, dependent on hormone stimulation times and bioinformatics cut-offs used (DePrimo *et al.* 2002, Nelson *et al.* 2002, Hendriksen *et al.* 2006, Wang *et al.* 2007, Massie *et al.* 2011, Toropainen *et al.* 2016). Apart from protein-coding genes, non-coding transcripts are also under direct control of AR (Wang *et al.* 2011, Toropainen *et al.* 2016). Transcripts from active enhancer regions, termed enhancer RNAs (eRNAs), have been measured using Global Run-On sequencing (GRO-seq) (Fig. 1C) (Core *et al.* 2008). Traditional transcriptomic profiling methods (e.g. RNA-seq) cannot successfully capture these transcripts because they are very unstable. Many studies reported that eRNA levels correlated with enhancer-related chromatin features, such as H3K27ac and H3K4me1 histone modifications, and expression level of the corresponding gene (Li *et al.* 2016). There are enhancer-dense regions, often referred to as super-enhancers, which have exceptionally high levels of H3K27ac as well as presence of bromodomain-containing protein 4 (BRD4), the mediator complex subunit 1 (MED1) and eRNAs (Zuber *et al.* 2017). Of note, the number of genome-wide AR-binding sites is considerably higher than the number of differentially expressed genes upon androgen stimulation. Moreover, merely 30% of the AR-bound enhancers show eRNA production (Toropainen *et al.* 2016). This suggests that only a fraction of AR-bound enhancers are functional or that these enhancers can function without eRNA transcription. However, eRNA detection might be hindered due to their instability and/or short half-life and it remains to be determined what the functional and biological contributions are for the vast majority of eRNAs.

Multiple studies reported diverse molecular mechanisms by which eRNAs impact gene expression. eRNA binding in the histone acetyltransferase (HAT) domain of CBP/p300 has been reported to induce their acetyltransferase activity, increasing H3K27ac level and gene expression (Bose *et al.* 2017). Furthermore, others showed eRNA (e.g. KLK3 eRNA) binding to cyclin T1,

a member of the positive transcription elongation factor (P-TEFb) complex, leading to increased phosphorylation of RNA polymerase II to facilitate transcription (Zhao *et al.* 2016). Knockdown of KLK3 eRNA resulted in reduced enhancer–promoter interactions and decreased KLK3 gene transcription (Hsieh *et al.* 2014, Zhao *et al.* 2016). Cumulatively, these studies suggest that eRNAs are not merely by-products of enhancer activity, but have a functional role in hormone-regulated gene expression. Further studies of eRNAs are necessary to uncover which individual eRNAs carry what distinct biological functions.

Factors affecting AR chromatin binding

AR cistromic regulation is a tightly-orchestrated process, impacting AR-responsive genes that are selectively controlled in a cell type-specific manner to fulfill distinct biological functions in various cell types and tissues. In the case of prostate cancer, the AR cistrome is altered at different stages of disease, impacting expression of a selective repertoire of responsive genes in a context- and stage-specific manner. In normal prostate epithelial cells, AR regulates expression of genes involved in differentiation and growth suppression (Isaacs 2018). In contrast, AR signaling in prostate cancer stimulates proliferation and survival of tumor cells (Isaacs 2018). Consistent with the altered AR transcriptional program in tumorigenesis, recent ChIP-seq analysis in prostate tissue has revealed a unique AR cistrome in normal prostate tissue versus primary prostate cancers (Pomerantz *et al.* 2015). These AR cistromes are in part reprogrammed through the action of the TFs forkhead box protein A (FOXA1) and homeobox B13 (HOXB13). Overexpression of both FOXA1 and HOXB13 in normal prostate epithelial cells with exogenously introduced AR (LHSAR) resulted in redistribution of AR to genomic regions containing forkhead and homeodomain motifs, resembling an AR chromatin-binding profile as observed in human tumor specimens (Fig. 2A and B) (Pomerantz *et al.* 2015, Stelloo *et al.* 2018a). This finding is corroborated in tissue samples, where higher expression of FOXA1 and HOXB13 was observed in tumors as compared to normal tissue (Stelloo *et al.* 2018a). While the biological impact of FOXA1 and HOXB13 in directing AR function is slowly becoming apparent, it remains unclear how increased expression of FOXA1 and HOXB13 in prostate cancer development is regulated.

Figure 2

AR cistrome during disease development and progression. (A) In normal prostate epithelial cells, AR mainly occupies genomic regions containing canonical AR-binding motifs. These genomic regions are not enriched for forkhead and homeobox motifs. (B) In primary prostate cancer cells, altered expression of other transcription factors and chromatin modifiers can change the behavior of AR chromatin binding, being redistributed to genomic regions containing forkhead and homeobox motifs. (C) One potential mechanism of AR reactivation in castration-resistant prostate cancer (CRPC) cells is the expression of C-terminally truncated, constitutively active AR variants lacking the ligand-binding domain, such as AR-V7. AR-V7 can dimerize with AR full-length and also homodimerize. AR-V7 interacts with HOXB13, which regulates AR-V7 chromatin binding. (D) AR activation in prostatic fibroblasts results in recruitment of AR to the DNA by tethering to AP1 complexes. (E) Alterations in regulatory elements by deletions, amplification or mutation can impact AR-DNA binding.

FOXA1

FOXA1 is both sufficient and essential for a prostate cancer cell to adopt a 'tumor-like AR cistrome', as loss of FOXA1 expression also alters the AR cistrome repertoire in prostate cancer cell lines, as reported by three groups (Sahu *et al.* 2011, Wang *et al.* 2011, Jin *et al.* 2014). FOXA1 is frequently mutated in primary and metastatic castration-resistant prostate cancer (Barbieri *et al.* 2012, Grasso *et al.* 2012, Cancer Genome Atlas Research Network 2015, Robinson *et al.* 2015, Armenia *et al.* 2018), but to date, it remains elusive which effects such mutations have on the AR cistrome. The mutations in the FOXA1 gene were identified around the forkhead DNA-binding (FK) domain or in the C-terminal transactivation domain with a frequency of 3–12% in both primary prostate cancers and metastases (Barbieri *et al.* 2012, Grasso *et al.* 2012, Cancer Genome Atlas Research Network 2015, Armenia *et al.* 2018). The FK domain is necessary for stable FOXA1 binding to nucleosomal DNA and the C-terminal domain of the protein interacts with core histones H3 and H4 to mediate chromatin accessibility (Cirillo *et al.* 2002). In the TCGA cohort, primary tumors with FOXA1 mutation have

been classified into one of the seven molecular subtypes, hallmarked by elevated AR target gene expression and a distinct DNA methylation profile (Cancer Genome Atlas Research Network 2015). In addition, profiling of AR, H3K27ac, H3K4me3 and H3K27me3 in primary prostate tumors identified subtype-specific chromatin landscapes, with one distinct subgroup capturing all samples bearing FOXA1 mutations (Fig. 3) (Stelloo *et al.* 2018b). Cumulatively, these reports demonstrated that FOXA1 mutations influence AR chromatin binding and alter its downstream transcriptional profile. Further characterization of individual FOXA1 mutations is required to elucidate whether distinct mutations would differentially impact FOXA1 function and alter the AR cistrome in different ways, and whether this would impact tumorigenesis and response to hormonal therapy. In a cohort of 28 patients receiving neoadjuvant docetaxel and androgen deprivation therapy (ADT), a pathological complete response was achieved in three patients, two of which carried a FOXA1 mutation (Beltran *et al.* 2017). Clinical studies with information on FOXA1 mutation status are however largely underpowered, and it remains to be determined whether FOXA1 mutations would impact hormone therapy response.

The widespread chromatin and transcriptional alterations as seen in ERG fusion-positive prostate cancers render ERG and its downstream targets highly interesting targets for therapy (Kron *et al.* 2017, Wang *et al.* 2017).

CHD1

One other frequent alteration reported in primary prostate cancer is loss of *chromodomain helicase DNA-binding protein 1* (*CHD1*), which is mostly observed in ERG fusion-negative tumors and not ERG fusion-positive tumors. The mutual exclusivity of *CHD1* loss with *ERG* rearrangements might be explained by the fact that loss of *CHD1* acts synthetically lethal with loss of *phosphatase and tensin homolog* (*PTEN*) in human prostate cancer cell lines (Zhao *et al.* 2017), and *PTEN* loss frequently co-occurs with *ERG* gene fusion (Taylor *et al.* 2010). However, this result was not observed in murine prostates, where loss of *CHD1* and *PTEN* led to the development of invasive carcinoma, while *CHD1* loss alone was insufficient to drive tumorigenesis (Augello *et al.* 2019). The cause of this discrepancy is unknown, although speculative it may arise from mouse/human species differences.

Knockdown of *CHD1* prevents androgen-induced chromosomal rearrangement resulting in the absence of *TMPRSS2-ERG* fusion transcripts (Burkhardt *et al.* 2013, Metzger *et al.* 2016). This finding might be explained by the role of *CHD1* in DNA repair. Both non-homologous end joining (NHEJ) and homologs recombination (HR) DNA repair processes are involved in transcription-associated DNA damage, but which repair pathway is affected by *CHD1* is still under debate (Hedayati *et al.* 2016, Kari *et al.* 2016, Shenoy *et al.* 2017). In addition to its role in DNA repair, *CHD1* maintains chromatin in an accessible state for AR and other TF to bind. Knockdown of *CHD1* impairs AR recruitment to promoters of AR-responsive genes (*KLK3*, *TMPRSS2*, *FKBP5*, *ELK4* and *KLK2*) (Burkhardt *et al.* 2013). The genome-wide experiments further demonstrated overlapping *CHD1*- and AR chromatin-binding sites (Metzger *et al.* 2016, Augello *et al.* 2019). In addition, a large proportion of the *CHD1* chromatin-associated protein complex represents members of the AR interactome, suggesting a role of *CHD1* in AR signaling. Indeed, loss of *CHD1* was recently reported to rewire AR signaling by redistributing AR binding to *HOXB13*-enriched sites (Augello *et al.* 2019). This was confirmed with AR ChIP-seq on tissue samples deficient for *CHD1* (Fig. 3) (Augello *et al.* 2019).

Previous work demonstrated that a substantial number of AR-binding sites are accessible prior to

hormone stimulation, while other sites become accessible after hormone stimulation (He *et al.* 2012, Tewari *et al.* 2012), providing a plausible explanation why not all AR sites are affected by *CHD1* loss. However, whether tumors with loss of *CHD1* have distinct nucleosome remodeling patterns needs to be determined.

Others

Genetic alterations in other epigenetic regulators, including *Lysine (K)-specific methyltransferase 2C* (*KMT2C*) and *zinc finger MYM-type containing 3* (*ZMYM3*), are less frequent in primary prostate cancer (Barbieri *et al.* 2012, Cancer Genome Atlas Research Network 2015). Nonetheless, the interplay between AR and epigenetic pathways as well as studies on other hormone receptors hint toward a role of these proteins in AR biology. For example, knockdown of *KMT2C* in breast cancer cells has been shown to suppress estrogen-dependent gene expression via loss of H3K4me1 and H3K27ac selectively at ER α enhancers (Jozwik *et al.* 2016, Gala *et al.* 2018). However, *KMT2C* knockdown did not result in a major loss of ER α chromatin binding but likely impairs recruitment of cofactors to the ER α complex (Gala *et al.* 2018). Indeed, the recruitment of cofactors to AR-bound enhancers is crucial for AR-mediated transcriptional activation or repression. New technologies such as rapid immunoprecipitation mass spectrometry of endogenous protein (RIME) (Mohammed *et al.* 2013) led to increased knowledge of the AR-enhanceosome – the protein complex at AR-bound enhancers. We and others have identified novel AR protein interactions in prostate cancer cell lines (Paltoglou *et al.* 2017, Stelloo *et al.* 2018a); however, the functional impact of all newly identified AR interaction partners still needs to be unraveled. A recently developed technique, quantitative multiplexed method (qPLEX-RIME) (Papachristou *et al.* 2018), may shed light on the composition of these AR multiprotein complexes in human tissue samples.

Factors affecting AR chromatin binding in castration-resistant prostate cancer

Castration-resistant prostate cancer (CRPC) refers to the disease stage in which the tumor progresses despite reduced serum testosterone levels due to ADT. As a consequence of selection pressure from ADT or anti-androgens on AR signaling axis, AR-dependent resistance mechanisms emerge including AR amplification, overexpression, somatic point mutations and constitutively active splice

variants (Claessens *et al.* 2014). Moreover, genome-wide selectivity of AR-binding patterns has been reported in CRPC (Sharma *et al.* 2013, Stelloo *et al.* 2015), suggesting CRPC-specific factors to configure AR reprogramming.

AR amplifications

AR amplifications are significantly enriched in metastatic CRPC as compared to primary prostate cancer. These AR amplifications involve copy number gain of the AR enhancer (Fig. 2E), the AR gene or both resulting in increased AR expression (Takeda *et al.* 2018, Viswanathan *et al.* 2018). *In vitro*, overexpression of AR allows the cells to activate AR signaling in low androgen environment resulting in increased AR chromatin-binding sites and downstream regulated genes (Urbanucci *et al.* 2012). Whether this effect is also observed in clinical samples remains to be determined.

AR splice variants

Besides AR amplification, treatment selection pressure by ADT induces aberrant AR mRNA splicing. Over 20 AR variants are described to date, including the most intensively studied variant AR-V7. AR-V7 is hardly expressed in primary prostate cancer samples and associated with increased total AR expression (Sharp *et al.* 2018, He *et al.* 2018). As overall AR is often overexpressed in CRPC, AR-V7 is consequently more frequently observed in CRPC samples as well. Most models studied thus far either express full-length AR or a variant, which does not represent the clinical situation where different types of AR-Vs are often simultaneously coexpressed with full-length AR. With the development of AR-V specific antibodies, it is now possible to perform ChIP-seq with AR-V-specific antibodies and C-terminal antibodies to distinguish the variant from the full length in more physiologically relevant model systems as well as in human specimens (Chen *et al.* 2018).

As AR-V7 lacks the ligand-binding domain, the receptor is constitutively active, with nuclear localization and chromatin binding in the absence of ligand. AR-V7 mostly binds regions with canonical AREs, as a homodimer (Fig. 2C) (Chan *et al.* 2015, He *et al.* 2018). In addition, AR-V7 and full-length AR have been reported to heterodimerize, as determined with ChIP-re-ChIP experiments (Cao *et al.* 2014) and co-immunoprecipitations (He *et al.* 2018). AR-V7 chromatin binding appeared to be less dependent on FOXA1, but rather selectively dependent on HOXB13 for its chromatin interactions instead (He *et al.* 2018).

In line with this, silencing of HOXB13 significantly decreases AR-V7 chromatin binding (Chen *et al.* 2018). Whether this is unique to AR-V7 could not be addressed, as full-length AR protein levels were significantly decreased in HOXB13-silenced LNCaP cells causing examination of full-length AR cistrome non-informative (Pomerantz *et al.* 2015).

Multiple reports have shown AR-V7 preferential chromatin-binding sites and differential gene expression as compared to full-length AR (Hu *et al.* 2012, Cao *et al.* 2014, Krause *et al.* 2014, Lu *et al.* 2015, He *et al.* 2018), but this was contradicted by one other study (Chan *et al.* 2015). These AR-V7 gene signatures as well as the expression of AR-V7 itself are associated with disease progression (Lu *et al.* 2015, Sharp *et al.* 2018). However, it remains unclear whether AR-V7 contributes to resistance. Although AR-V7 is a predictive biomarker for conventional AR-targeted therapies, most likely because cells expressing AR full length are sensitive to castration and antiandrogen treatment, whereas AR-V7-expressing cells are indifferent to therapy (Guo *et al.* 2009, Chan *et al.* 2015). Therefore, the next challenge is discovering and testing AR-V7-targeted therapies, such as alternative druggable regions on AR or by targeting its cofactors. Dalal *et al.* recently published compounds that block the AR-DNA-binding domain (DBD) dimerization interface, inhibiting both AR and AR variant transcriptional activity (Dalal *et al.* 2018). Targeting other functional domains such as the transactivation domain are promising as well, for example, the EPI compounds of which EPI-506 is currently evaluated in a phase I dose escalation clinical trial (NCT02606123) (Andersen *et al.* 2010). Besides small molecules, an alternative approach can be the expression of decoy peptides representing the AR N-terminal domain. These decoys have been shown to inhibit both androgen-dependent prostate cancer and CRPC growth, most likely by competitive binding to AR-interacting proteins required for AR transcriptional activity (Quayle *et al.* 2007, Myung *et al.* 2017). In fact, many more inhibitors targeting the AR have been reported and are reviewed by others (Centenera *et al.* 2018).

Single nucleotide variants in enhancers

Another level of AR cistrome deregulation is reflected in single nucleotide variants (SNVs), including SNPs and somatic point mutations at *cis*-regulatory elements (Fig. 2E). With the growing number of genome-wide association studies (GWAS) and whole genome

sequencing (WGS) efforts, millions of SNVs have been identified, most with unknown significance and >90% found in non-protein regions (1000 Genomes Project Consortium *et al.* 2012, Baca *et al.* 2013, Espiritu *et al.* 2018, Quigley *et al.* 2018, Schumacher *et al.* 2018). Interestingly, prostate cancer risk SNPs are found enriched at enhancer elements including those bound by AR (Lu *et al.* 2012, Bu *et al.* 2016, Whittington *et al.* 2016, Dadaev *et al.* 2018). Causal regulatory SNPs altering AR binding has been demonstrated in the enhancer of *sex determining region Y box 9* (SOX9) gene (Zhang *et al.* 2012), an intron of the *melanophilin* (MLPH) gene (Bu *et al.* 2016) and the promoter of *KLK3* (Lai *et al.* 2007). Moreover, an increased mutational load proximal to AR-binding sites and other transcriptional regulators such as HOXB13 and FOXA1 has been reported (Mazrooei *et al.* 2018, Morova *et al.* 2017). However, only ~20% of the somatic SNVs which lie within regulatory elements marked with H3K27ac and binding of AR, FOXA1, HOXB13 are predicted to impact binding of these TFs (Mazrooei *et al.* 2018). Knowing whether a regulatory SNV potentially disrupts or creates new binding sites would aid to elucidate their target genes and their potential functional impact on prostate cancer. In addition, *in vitro* validation of these variants would be crucial to distinguish driver events from non-pathogenic passenger variants. As it is difficult to study the consequence of variants on TF binding in clinical samples, a functional impact of variants is generally studied by computational approaches and/or *in vitro* experimental methodologies. Given the growing number of genomic datasets (e.g. ATAC-seq, WGS, ChIP-seq) on clinical samples, it may become possible in the future to functionally connect variants with TF binding in human tumor samples, although larger sample sizes with matched genomic datasets would be required. Using computational approaches, TF-DNA-binding specificity can be estimated based on deviations of the position weight matrices (PWM) (Fig. 1B), which is a matrix of scores which correspond to the frequencies of the nucleotides at each position in the TF motif (Deplancke *et al.* 2016). Other methods rely on integration of multidimensional data including accessible chromatin regions, chromatin marks and TF-binding profiles (Deplancke *et al.* 2016). Furthermore, to functionally validate the significance of SNVs on TF binding *in vitro*, typically assays such as electrophoretic mobility shift assays (EMSA) are used, aimed to study DNA–protein interactions as well as luciferase reporter assays. Recently, the development of a massively parallel reporter assay made it possible to test different SNVs simultaneously, as

shown for red blood cell trait-associated variants (Ulirsch *et al.* 2016). Additionally, the advent of CRISPR technology enables the study of variants in a native genomic context either by editing one single locus or by performing enhancer screens. Using the latter strategy, Korkmaz *et al.* identified ER α -binding sites that are required for breast cancer proliferation (Korkmaz *et al.* 2016). Given the work on ER α , the very same approach can be applied to analyze AR-binding sites and thereby infer causal SNVs. Alternatively, one can envision a genetic screen targeting AR-bound enhancers with transcriptional profiles as readout to infer enhancer-target gene pairs with methods such as Perturb-seq (Dixit *et al.* 2016) or CRISP-seq (Jaitin *et al.* 2016) which combine CRISPR-based perturbations with single-cell RNA-seq. This framework has recently been shown to be successful in detecting enhancer-gene pairs (Xie *et al.* 2017, Gasperini *et al.* 2019). Such efforts for AR-binding sites will characterize downstream biological consequences of genetic variants.

Larger cistromic datasets

In this review, several factors have been described that influence AR-binding patterns in prostate cancer. While original reports were largely focused on cell lines, gradually an increasing body of evidence is being generated that study AR chromatin binding in clinical specimens. This transition to tumor material is of added value for multiple reasons. First, cell lines are (albeit powerful and extremely useful) just a model that would always require further validation in a physiologically more-relevant setting. Secondly, in order to draw conclusions in cell lines for eventual translation of such concepts to clinical implementation, validation of such basic biology observations in tissue specimens is a crucial intermediate step. Lastly, as prostate cancer is considered a heterogeneous disease with multiple genomic (Cancer Genome Atlas Research Network 2015) and epigenetic (Stelloo *et al.* 2018b) subtypes, and the biological complexity of the disease is not fully covered by the limited set of available cell line models.

Large-scale ChIP-seq datasets on patient cohorts can help to better understand prostate cancer subtype-specific chromatin landscapes in a tissue context. Many AR-binding sites are patient specific (inter-individual heterogeneity), but defining common features of chromatin landscapes shared among tumors is helpful for defining subtypes. Determining subtype-specific chromatin landscapes requires differential binding algorithms such as DiffBind

(Ross-Innes *et al.* 2012), a ranking normalization strategy (Patten *et al.* 2018), ChromHMM followed by MCA (multiple correspondence analysis) factorial analysis (Lomberk *et al.* 2018) or matrix factorization algorithms (Stelloo *et al.* 2018b). New bioinformatic tools and pipelines continue to emerge, aimed to ingrate both epigenetic and genomics data to better understand specific phenotypes. Analysis of 100 primary prostate cancers revealed a relationship between chromatin landscapes and their regulation of gene expression associated with three subtypes (Fig. 3) (Stelloo *et al.* 2018b). In addition, two main prostate cancer subtypes related to *ERG* gene fusions were identified. These results are consistent with previous prostate cancer profiling studies (see above; *ERG*), but the results also provided unique insights, such as the discovery of a third subtype. Tumors classified in this subtype have a low AR pathway activity as reflected by the low number of AR-binding sites and low AR activity score. This opens new avenues for therapeutic decisions as tumors with low AR activity score are more prone to develop resistance to hormone therapy (Spratt *et al.* 2018).

Whereas the studies so far focused on inter-individual chromatin landscape variability, studying one tumor/single foci of one patient, the intra-tumor heterogeneity remains to be explored. This is of special interest as the majority of primary prostate cancers harbor multiple tumor foci (Andreoiu & Cheng 2010). These foci revealed differences on the level of gene expression, DNA methylation, copy number and mutation status (Boutros *et al.* 2015, Mundbjerg *et al.* 2017, Espiritu *et al.* 2018), suggesting that the observed variation might also be reflected in the chromatin landscape. Improvement of ChIP efficiency on limited quantities of tissues (Dahl & Gilfillan 2018, Singh *et al.* 2019) holds great promise to study multiple clones and also infer relationship between primary tumor foci and metastatic lesions with respect to the chromatin landscape. Another undoubted advancement is the usage of formalin-fixed paraffin-embedded (FFPE) specimens for ChIP (Fanelli *et al.* 2010, Cejas *et al.* 2016), which has been successfully applied to study histone marks but not yet TFs.

AR cistrome-based classifiers for patient stratification

Even though AR chromatin binding in primary prostate cancer specimens is a determinant of the genomic landscape of prostate cancer subtypes, these binding sites did not appear to be associated with patient outcome

(Stelloo *et al.* 2018b). However, a subset of AR-binding sites, identified through differential binding analysis in benign versus primary prostate cancer or primary prostate cancer versus progressive disease bear prognostic potential (Sharma *et al.* 2013, Chen *et al.* 2015, Pomerantz *et al.* 2015, Stelloo *et al.* 2015). To be more specific, actually the genes proximal to these AR-binding sites were tested and validated for their prognostic potential. Even though promising, as for example, our 9-gene expression signature was able to identify patients with an ultra-high risk to develop biochemical recurrence after radical prostatectomy (Stelloo *et al.* 2015); none of these classifiers are used in daily clinical practice yet. Application of classifiers based on differentially bound regions rather than genes would be costly and laborious, limiting the application of ChIP-based classifiers in clinical practice. The establishment of an automated workflow for both ChIP and library preparation would render the approach more cost-effective and robust. For example, a method such as ChIP-string, which is a modified NanoString's nCounter Analysis System platform to measure enriched genomic DNA of loci of interest from ChIP experiments (Ram *et al.* 2011), would be more suitable for clinical application.

Clinically useful interpretation of cistrome-based classifiers requires appropriate pathology review, as bulk tumor and normal tissue samples will have varying degrees of epithelial content and stromal contamination. Fibroblasts, the most abundant cell type in stroma, express AR albeit at lower levels as compared to prostate epithelial cells (Leach *et al.* 2017, Cioni *et al.* 2018, Nash *et al.* 2018). In fibroblasts, it was shown that AR chromatin binding is disparate from epithelial AR cistrome, with preferential AR binding at sites enriched for motifs of FOS and JUN family members (Leach *et al.* 2017, Cioni *et al.* 2018). Knockdown of Jun reduced AR binding at three loci (Leach *et al.* 2017), but whether this affects global AR binding remains to be addressed. However, the data suggest that AR binding in prostate fibroblasts is dependent on the AP1 complex, a complex consisting of homo/heterodimer combinations of FOS and JUN members, rather than classical pioneer factors such as FOXA1 (Fig. 2D). This phenomenon of enrichment of other motifs than AREs, forkhead and homeodomain motifs, is also seen in AR ChIP-seq on human caput epididymis (Yang *et al.* 2018) and mouse kidney and epididymis (Pihlajamaa *et al.* 2014). These observed tissue-specific AR cistromes achieved by collaborating factors further supports a rationale to study AR cistromes in other cells of the tumor microenvironment.

Future perspectives

Although ChIP-seq studies using human specimens have provided a more detailed understanding of AR chromatin binding in prostate cancer, a lot remains to be explored (Fig. 4). Comparative studies of AR cistromes can be expanded to metastatic lesions and larger cohorts to provide clues on AR functioning and its target genes during prostate cancer progression. Collecting the primary tumor(s) as well as the metastases during disease progression and at time of death is of great interest, enabling the identification of AR cistrome characteristics of the primary tumor lesion that ultimately gave rise to the lethal metastatic lesion. Despite limited to one case, Haffner *et al.* defined the origin of metastatic lesions by performing WGS on primary prostate foci and metastasis (Haffner *et al.* 2013). In addition, evaluation of AR cistromes from samples collected before, on and after treatment (NCT03297385), as well after acquisition of treatment resistance will provide valuable information to better understand how AR signaling is associated with disease progression. We can learn from research on ER α chromatin binding in breast specimens before and after neoadjuvant tamoxifen treatment (Severson *et al.* 2016), where drug-induced changes in ER α chromatin binding were observed.

Another interesting approach, applicable for patients with large burden of ctDNA, could be identification of nucleosome footprints in ctDNA. Analysis of two plasma samples taken 12 months apart, during which the prostate

adenocarcinoma transdifferentiated to a treatment-emergent small-cell neuroendocrine prostate carcinoma (t-SCNC, AR-independent disease state), showed no longer accessibility of AR-binding sites during the disease course (Ulz *et al.* 2018). Given the paucity of serial sample collections at different points during the disease course, alternative models such as patient-derived xenografts (PDX), *ex vivo* cultures and/or cell lines are required to monitor therapy effect on transcription factor dynamics.

The analysis of 100 primary prostate cancers is the largest AR cistromic dataset on prostate cancer (Stelloo *et al.* 2018b) and no such large cistromic data sets of ER α in breast cancer exist yet. Future research of ideally larger sample sizes for breast cancer may be considered to study cistrome differences underlying clinical and genetic features of breast cancer subtypes.

In the era of single-cell genomics, advanced approaches enable complete characterization of the genome, transcriptome and epigenome at the single-cell level. This will enable us to assess cellular heterogeneity, cells in the tumor microenvironment and clinical specimens with too low tumor cell percentage for bulk sequencing. Also, a single-cell ChIP-seq (scChIP-seq) protocol has been published (Rotem *et al.* 2015), but is yet to be validated. With improvement in throughput, quantitation and sensitivity, scChIP-seq might become more valuable to analyze cell-to-cell variability in chromatin landscapes across a population. Ultimately, combining different single-cell methods to investigate for example epigenetic and transcriptome correlation

Figure 4

Future directions. Schematic illustration of models for addressing AR genomics in prostate cancer development and progression. The cellular model systems (patient-derived xenograft (PDX), organoids and cell lines) offer an unprecedented opportunity to assess the effect of various drugs, different stimuli and other perturbations (e.g. CRISPR experiments) on the genomic landscape. The use of human specimens will allow us to relate genomic results to clinical outcome at various stages of the disease. Complementing genomics with advances in single-cell approaches can provide insights into the genomic landscape of heterogeneous tumors and cells of the tumor microenvironment.

and how these are associated with cellular phenotypes will lead towards a comprehensive understanding of the behavior of individual cells in prostate cancer.

Conclusions

To date, the vast majority of functional genomic studies on AR have used a limited panel of cell line models. Due to improved technological advances, a comprehensive understanding of AR together with a detailed picture of the epigenomic landscapes in prostate cancer specimens is beginning to emerge. Research has highlighted the involvement of numerous features beyond sequence motifs alone to be involved in AR cistrome reprogramming, such as ERG fusions and TF overexpression (e.g. FOXA1 and HOXB13). Further characterization of mechanisms underlying AR reprogramming during prostate tumorigenesis and progression – from normal to prostatic intraepithelial neoplasia, metastatic and therapy-resistant disease – will enable identification of affected target genes. Identification of those genes may enhance the translational potential of ChIP-seq data. This will stimulate the discovery of promising targets for therapeutic intervention and new biomarkers of early detection and resistance.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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