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Review

Genome-wide interplay of nuclear receptors with the epigenome ☆

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ABSTRACT

The nuclear receptor superfamily consists of DNA binding transcription factors that are involved in regulating a wide variety of processes such as metabolism, development, reproduction, and immune responses. Upon binding, nuclear receptors modulate transcription through affecting the local chromatin environment via recruitment of various coregulatory proteins. The recent development of new high-throughput sequencing methods allowed for the first time the comprehensive examination of nuclear receptor action in the context of the epigenome. Here, we discuss how recent genome-wide analyses have provided important new insights on the interplay of nuclear receptors and the epigenome in health and disease. This article is part of a Special Issue entitled: Translating nuclear receptors from health to disease.

1. Epigenetics and nuclear receptors

DNA contains the genetic information that is used in the development and functioning of mammalian cells. However, to ensure a proper balance between induced and repressed states of transcription, DNA needs to be properly packed inside the nucleus. This packaging is accomplished through the dynamic regulation of a variety of chromatin modifications such as DNA methylation, nucleosome remodeling, and covalent modifications at histone amino acid residues such as acetylation, phosphorylation, and methylation [1–4]. Open chromatin configurations, characterized by "active" histone modifications, can be found at individual gene promoters or clusters of coordinately regulated genes that are actively transcribed. Transcriptional activity of these genes is often regulated through the exchange of these active histone modifications with repressive marks [5,6]. In contrast, DNA methylation has been tightly linked to transcriptional repression and has been suggested to prevent unwanted transcription. Moreover, it has an important role in structural maintenance and proper chromosome replication [7]. Taken together, the epigenetic regulatory mechanisms function to set up an epigenetic landscape that serves as a playground for the actions of other DNA interacting factors such as nuclear receptors. The nuclear receptor superfamily consists of DNA binding transcription factors that are involved in regulating a wide variety of processes such as metabolism, development, reproduction, and immune responses [8]. To regulate these physiological processes, many nuclear receptors respond to ligands such as fatty acids, vitamins, and various steroids including glucocorticoids, estrogens, androgens, and progesterone. Upon binding of these ligands to the nuclear receptor, a conformational change is induced that ultimately leads to activation of gene transcription [8]. Based on various studies, it is generally perceived that, upon binding, nuclear receptors modulate transcription through affecting the local chromatin environment via recruitment of various coregulatory proteins that are essential to recruit mediator components and RNA polymerase II to target gene promoters [9–13].

2. The nuclear receptor coregulator induced epigenetic state

Coregulators that are recruited by nuclear receptors typically possess diverse enzymatic activities that are important in modifying the chromatin state [9–12]. Based on their mode of action, coregulators, in the context of chromatin, can be broadly classified into three main categories. The first category consists of enzymes that covalently modify histones through, for example, acetylation, methylation, phosphorylation, and ubiquitylation activities. The second class is harbored by ATP dependent chromatin remodeling factors, which modulate chromatin accessibility, such as members of the SWI/SNF family. A third, but yet unexplored group, consists of proteins that are not known to possess inherent enzymatic activity but rather act as a platform for the recruitment of multiprotein complexes that possess enzymatic activities, such as thyroid hormone receptor interactor 6 (nTRIP6), which can mediate both transcriptional activation and repression, and the corepressors NCOR and SMRT.

Over the past decade, a multitude of studies have examined the local effects of nuclear receptor presence on chromatin modifications mediated via direct (e.g. through interaction with SRC1/p160 proteins) as well as indirect interaction (e.g. p300 and CREBBP

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though interaction with SRC1/p160 proteins) with chromatin modulators. One of the first studies identified a role of the p300 and CREBBP transcriptional coactivator in all-trans retinoic acid (ATRA) signaling. Here, the nuclear receptor heterodimer RAR:RXR was shown to interact with the proteins p300 and CREBBP [14], which, in the same year, were identified as proteins harboring histone acetyltransferase activity [15]. Taken together, these two studies suggested that recruitment of histone acetyltransferase (HAT) activity to RAR:RXR bound genomic regions was a key step in retinoic acid mediated transcriptional activation. Indeed, subsequent studies provided the first direct evidence for nuclear receptor recruitment of HAT activity mediated by the nuclear receptor coactivator 3 (NCOA3) and SRC1 [16,17]. In addition, it was shown that a specific amino acid motif, LXXLL, present in these coactivators was responsible for interaction with ligand bound nuclear receptors [18].

Contrary to the nuclear receptor mediated recruitment of coactivator proteins with HAT activity, a later study identified glucocorticoid receptor (GR) mediated recruitment of histone deacetylases to inflammatory gene promoters containing the acetyltransferase CREBBP and nuclear factor kappa B (NF-κB). Here, the inhibition of histone acetylation was proposed as a novel GR mediated mechanism to control inflammatory gene expression [19].

Apart from acetylation, many other histone modifications have since been shown to correlate with nuclear receptor binding and transcriptional regulation. For example, protein arginine methyltransferase 1 (PRMT1) was revealed to be recruited by the androgen receptor (AR) resulting in dimethylation of the third arginine of histone H4 [20]. Methylation of this arginine residue was subsequently shown to facilitate acetylation of histone H4 tails by p300, thereby facilitating transcriptional activation. One of the first reports that described a connection between nuclear receptor binding and H3K4 methylation, the hallmark modification associated with transcriptional activation, was the analysis of ecdysone signaling in Drosophila. Upon ecdysone binding, the nuclear receptor EcR was shown to heterodimerize with the retinoid X receptor homolog ultraspiracle. This heterodimer was subsequently shown to corecruit the H3K4me3 trimethylase TRR to ecdysone-inducible promoters [21].

In addition to recruitment of histone methyltransferases, the description of the first enzymes that could mediate histone demethylation [22,23] led to the investigation of the connection of these enzymatic activities with nuclear receptor signaling. This led to uncovering the roles of the H3K9me1 and H3K9me2 demethylating enzyme LSD1 and the H3K9me3 demethylating enzyme jumonji domain containing 2 C (JMJD2C) in androgen receptor (AR) signaling in prostate tissue [24,25]. Similarly, the H3K9-specific demethylase jumonji domain containing 1A (JMJD1A) was reported to bind to the peroxisome proliferator-activated receptor gamma (PPARγ) response element (PPRE) at the Ucp1 gene promoter, not only facilitating recruitment of PPARγ:RXRα and additional coregulators but also resulting in decreased levels of H3K9me2 [26].

Contrary to these enzymatic coregulatory proteins, the well characterized nuclear receptor corepressors NCOR and silencing mediator of retinoic acid and thyroid hormone (SMRT) do not possess any intrinsic enzymatic properties. Instead, NCOR and SMRT confer repressive characteristics by forming platforms for recruitment of repressive factors such as HDAC3 [12]. Similarly, a recent study on glucocorticoid receptor (GR) signaling identified a role of nTRIP6, a protein containing several protein interaction domains with no inherent enzymatic activity, as an orchestrator of multiprotein complexes [27].

Apart from these examples, many other studies on nuclear receptors have highlighted a pivotal role of coregulatory proteins in determining the epigenetic state of the chromatin in a cell type dependent manner. However, a major drawback of these studies was that they were based on analysis using a single or a small subset of genes. Therefore, the generality of the proposed mechanisms based on these studies was still obscure.

3. Genome-wide profiling approaches

With the development of new techniques that allowed investigation of larger genomic regions or even an entire mammalian genome, several studies in recent years have provided more global views on the interplay of nuclear receptor binding and epigenetic alterations. Initially, the techniques were based on combining chromatin immunoprecipitation (ChIP) with DNA hybridization to tiled oligonucleotide microarrays (ChIP-chip). Although this technique allowed global analysis of chromatin-associated proteins including transcription factors and modified histones, the spatial resolution and genomic coverage per microarray was relatively low. Moreover, as it required multiple arrays to cover a complete genome of higher eukaryotes, the technique was very costly in order to generate comprehensive views on nuclear receptor activity on chromatin. Despite these drawbacks, ChIP-chip has provided valuable insights into the general mechanisms underlying nuclear receptor action.

The first leap forward for genome-wide profiling in higher eukaryotes was the analysis of E2F binding on a 1500 promoter containing DNA microarray using human fibroblasts [28]. This study was later followed by many other ChIP-chip studies that examined in most cases only 1 or 2 proteins either on dedicated arrays, or, at later stages, array platforms with genome-wide coverage, such as the study of global TFIID binding in IMR90 cells [29]. As the ChIP-chip technique allowed for the first time the global binding analysis of factors interacting with DNA, it set the stage for the analysis of genome-wide nuclear receptor activity. One of the first large-scale studies involving nuclear receptors was the examination of estrogen receptor (ER) binding along the complete chromosome 22 [30]. This analysis was followed by many other ChIP-chip based studies (see also http://www.nursa.org), such as a genome-wide binding analysis of PPARγ in 3 T3-L1 cells [31], which was amongst the first comprehensive analyses to correlate nuclear receptor binding with the acetylation of histone H3.

However, during these analyses, several problems associated with ChIP-chip studies became apparent. These included not only the high costs of using multiple arrays to generate one profile but also the biases introduced in the ChIP-chip procedure that demanded extensive bioinformatic and statistical analysis. In addition, the large amounts of material needed to obtain genome-wide coverage restricted most studies to cell lines.

4. From ChIP-chip to ChIP-seq

More recently, techniques have been developed that couple ChIP with high-throughput sequencing (ChIP-seq). Here, massive sequencing of ChIP DNA generates libraries of relatively short DNA sequences that can be mapped to annotated genomes of interest, thereby determining localization of proteins or chromatin modifications of interest. This approach has been shown to be of significant importance as it offers for relatively low costs the possibility for genome-wide analysis at single base-pair resolution [32].

Indeed, the initial ChIP-seq studies were the first to describe globally several chromatin modifications in mouse and human cells, thereby creating the first comprehensive overviews of a complete epigenomic landscape [33,34]. These studies were setting the stage for many other genome-wide studies that examined a wide variety of chromatin modifications, from histone acetylation and lysine methylation to nucleosome occupancy, in a wide range of cellular systems such as mouse ES cells and human CD4 and CD133 cells [35–38]. Recently, these advances in sequencing resulted even in the description of the first DNA methylome at single base resolution [39].

The development of ChIP-seq allowed for the first time the extension of nuclear receptor studies towards different cell systems and variable experimental settings. Currently, genome-wide studies on nuclear receptors are stretched throughout all fields of molecular biology, from hematopoiesis to adipogenesis and from cancer to inflammation.

5. Nuclear receptors and the epigenome

The wealth of information on genome-wide nuclear receptor binding and its interplay with the epigenome has shed new lights on the actions of these proteins. Generally, two aspects were studied. First, many analysis were devoted to examining the epigenetic modifications that are induced upon nuclear receptor binding and identification of the responsible enzymes. A second theme was related to the key question on what determines nuclear receptor binding. Following the recent studies that examined genome-wide binding of nuclear receptors (reviewed in [8]), a main conclusion was that only a small fraction of consensus motifs are bound by receptors *in vivo* in a given cell line. Therefore, the specific binding of nuclear receptors to a subset of motifs in a given cell begged the question of how this selective binding was achieved. With the hypothesis that the epigenome is a main determinant to orchestrate nuclear receptor binding, a myriad of studies were devoted to unveil the interplay of nuclear receptors with the epigenome.

6. Nuclear receptors directing chromatin modifications

Classically, chromatin modifications at nuclear receptor binding sites have been proposed as dependent on the nuclear receptor itself. Small scale studies suggested that upon nuclear receptor binding, remodeling of chromatin leads to an open chromatin conformation and subsequent gene activation [40]. New technological developments have now for the first time allowed examining the generality of these mechanisms.

Indeed, global PPARγ:RXR binding during adipogenesis using an *in vitro* model in the 3 T3-L1 preadipocyte cell line [31,41] was described to correlate with increases in H3 acetylation, and these studies could be substantiated by PPARγ genome-wide localization in mouse macrophages [42]. Interestingly, a difference in factor colocalization was observed between the two cell types; while CCAAT/enhancer binding proteins (C/EBP) were found colocalizing with PPARγ in adipocytes, PU.1 was found colocalizing in macrophages. Despite these differences in factor colocalization, ChIP-qPCR experiments using sets of PPARγ binding regions in both cells highlighted the association of both PU.1/PPARγ and CEBP/PPARγ binding with increases in H3 acetylation and DNA accessibility. Interestingly, the presence of repressive marks H3K9me2 and H3K27me3 seemed to preclude binding of PPARγ, hinting at an important role of the epigenome in determining PPARγ binding. Recently, the PPARγ interactions with the epigenome were further extended towards a human model of adipogenesis [43], again revealing a correlation between adipocyte and preadipocyte-specific enhancers and regulation through histone acetylation.

The importance of H3 acetylation was further substantiated by showing that the acetyltransferase protein p300, along with GR, C/EBP, and MED1 laid down a transient H3 acetylation pattern at several genes, such as PPARγ2, that are involved in adipocyte differentiation [44].

ER cistromes have also been correlated with cell type specific epigenetic histone modifications. For example, estrogen was shown to induce H3R17me2 and mediate p300 and SRC1 recruitment, thereby acetylating H3K18, H3K27, and H4K12 in addition to increasing the DNA accessibility at subsets of estrogen receptor bound sites [45], while another ChIP-chip study also reported a strong correlation between ER binding at promoters of E2 stimulated genes, SRC recruitment, and acetylated histones [46]. In addition, the interplay of ER with H3 acetylation was observed in an alternative setting in which the cooperative interaction between retinoic acid receptor alpha (RARα) and ER in breast cancer was investigated [47]. Following the analysis of the genome-wide ER and RARα binding profiles that uncovered ER dependent recruitment of RARα to genomic regions, ChIP-qPCR was used to show a role for RARα in recruitment of the acetyltransferase protein p300 to ER bound genomic regions and subsequent increases in histone H3 acetylation.

7. Chromatin states and pioneering proteins define lineage specific nuclear receptor binding sites

It is increasingly evident that, apart from the DNA consensus motif, other factors have important roles in determining transcription factor interaction with chromatin [8]. Indeed, recent genome-wide studies of transcription factors point out that a large fraction of mapped binding sites are epigenetically pre-marked and that these chromatin modifications could be main determinants of cell-specific binding patterns of transcription factors. For example, inflammatory enhancers responsible for cell type specific NF-κB and AP-1 target gene regulation are found to be marked with specific histone modifications as well as with the coactivator p300 and the transcription factor PU.1 [48]. It is plausible to think that these cell type specific epigenetic hotspots confer important pioneering regions for cell type specific effects of nuclear receptors. Indeed, several studies have already highlighted an important role for histone modification patterns and pioneering proteins in determining nuclear receptor action. In these studies, a central role for a specific chromatin mark, histone H3 lysine 4 dimethylation, and FOXA1 binding was revealed [49–52].

In estrogen signaling, FOXA1 was shown to be a main determinant for directing ER recruitment to chromatin in MCF-7 cells. Similarly, in LNCap cells, FOXA1 was important for AR recruitment. Comparison of FOXA1 binding in these cell types uncovered cell type specific binding, suggesting that in a given cell type, the distribution of FOXA1 demarcates sites for nuclear receptor action. Subsequent epigenetic analysis revealed the underlying chromatin as the key determinant of cell type specific FOXA1 binding. While FOXA1 preferentially bound regions marked with H3K4me2, inactive enhancer regions were marked by H3K9me2 [49,50]. Both of these marks are expected to influence chromatin accessibility. Indeed, FOXA1 sites with increases in H3K9ac and H3K4me2 are high in accessibility as determined by FAIRE (formaldehyde-assisted isolation of regulatory elements) while H3K9me1 and H3K9me2 increases correlate with low accessibility regions [51].

The importance of the H3K4me2 marked chromatin regions was further exemplified by showing that the presence of this mark at 2 nucleosomes spaced around nuclear receptor consensus motifs directs FOXA1 binding and subsequent receptor recruitment [52]. These results show that histone marks, in conjunction with (pioneering) transcription factors, represent a mechanism for determining cell-specific binding of nuclear receptors to DNA and regulating chromatin accessibility during lineage commitment (Fig. 1).

The fact that cells undergo epigenomic programming during lineage commitment to encode cell-specific hormonal responses could be further substantiated by other studies. ChIP-chip analysis revealed that DNAseI hypersensitive sites (DHS) were found at a wide spectrum of regulatory regions such as promoters, enhancers, and locus control regions [53] and that these sites recruited glucocorticoid receptor (GR). Interestingly, binding of GR was observed both at constitutive as well as hormone induced accessible sites, which were enriched with the histone variant H2A.z. This study emphasized that the DHS profile is highly cell type specific and again implicated the chromatin landscape as a critical determinant of tissue-selective receptor function.

8. The cancer epigenome

The interplay of chromatin with nuclear receptors has important consequences in disease. Alterations at the chromatin level can influence nuclear receptor signaling while aberrant nuclear receptor regulation can severely impact the chromatin environment. This is illustrated by two recent studies on oncofusion proteins associated with specific types of cancer. The first one examined the genome-wide actions of an aberrantly regulated retinoic acid receptor in acute promyelocytic leukemia (APL). In this leukemia, a chromosomal translocation involving the PML gene on chromosome 15 and the retinoic acid receptor alpha (RARα) on chromosome 17 results in the expression of the PML-RARα oncofusion gene in hematopoietic myeloid cells [54–56]. Expression of PML-RARα was shown to distort normal all-trans retinoic acid (ATRA) signaling at multiple levels (Fig. 2); the fusion protein deregulated RARα:RXR target genes by occupying their binding sites and, in addition, it also bound the genes encoding RARα, β, and γ, thereby influencing expression of the genes that transduce the ATRA signal [57]. In addition to deregulation of RAR signaling, genome-wide epigenetic studies revealed that PML-RARα/RXR functioned as a local chromatin modulator, regulating levels of H3 acetylation, but not H3K27me3, H3K9me3, and DNA methylation, identifying the acetylome as a prime target for the oncofusion protein. Furthermore, this study also uncovered that many genes bound by PML-RARα encode epigenetic enzymes. Through modulation of their expression, PML-RARα could significantly impact many other epigenetic modifications at the global level.

In an alternative study, the genome-wide actions of the prostate cancer associated oncofusion protein TMPRSS2-ERG, which accounts for 40%–80% of prostate cancers [58,59], was analyzed. Although AR was found to activate genes involved in prostate differentiation, TMPRSS2-ERG was found to disrupt AR signaling via binding to AR itself as well as to many AR target genes (Fig. 2)[60]. Interestingly, TMPRSS2-ERG expression also activated the PcG protein and H3K27 histone methyltransferase EZH2. In conjunction with increased EZH2 expression, EZH2 target genes were repressed, thus supporting a role for TMPRSS2-ERG activation of EZH2-mediated epigenetic silencing in prostate cancer.

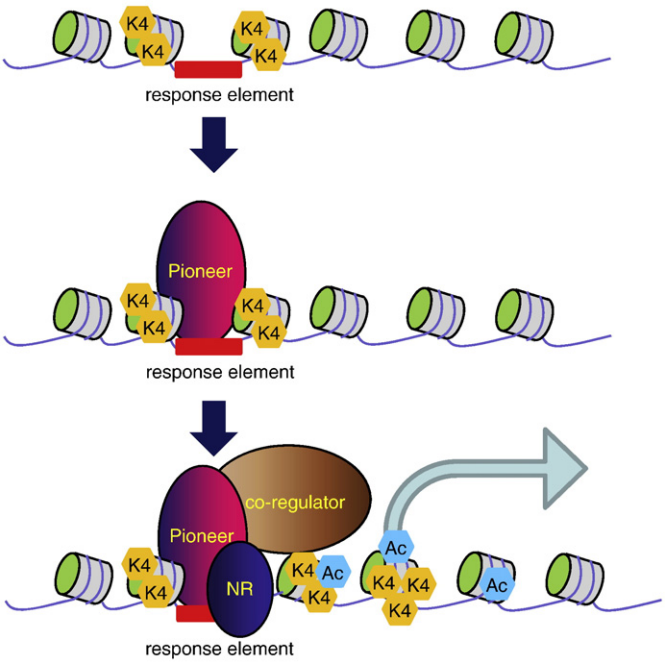

Fig. 1. The interplay of chromatin and nuclear receptors. Cell type specific marking of nucleosomes with H3K4me2 (top) identifies DNA response elements that can be bound by pioneering factors such as FOXA1 (middle). Subsequently, these pioneering factors direct the recruitment of nuclear receptors, resulting in alterations in chromatin state and transcriptional activity (bottom).

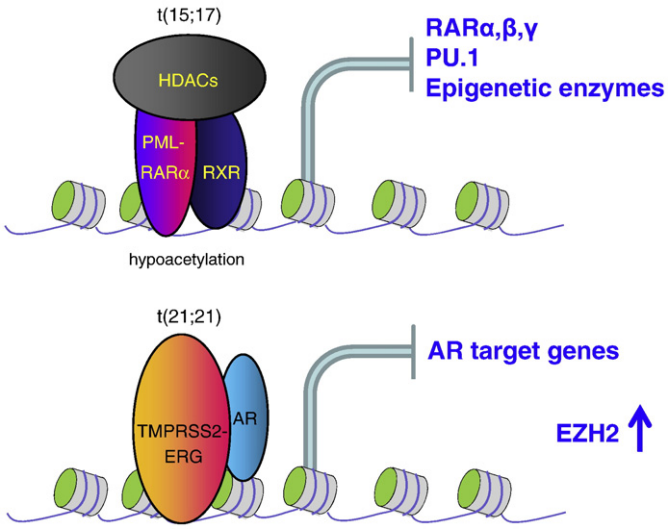

Fig. 2. Aberrant nuclear receptor activity. PML-RARα, in conjunction with RXR, binds specific DNA sequences and recruits repressor complexes resulting in histone hypoacetylation and transcriptional silencing of target genes such as RARα, β, and γ, the hematopoietic key regulator PU.1, and many genes that encode proteins that modulate chromatin structure (top). TMPRSS2-ERG disrupts AR signaling through binding of AR as well as to AR target genes (bottom). In the process, expression of the histone methyltransferase EZH2 is upregulated.

9. Concluding remarks

Although the role of the epigenome in nuclear receptor signaling has only been examined for a small number of nuclear receptors and has mostly been restricted to cell line models, the importance of the interplay between nuclear receptors, chromatin modifications, and accessibility has become a mainstay in understanding nuclear receptor signaling. It is becoming exceedingly clear that nuclear receptors are not the only responsible factors in altering the epigenetic environment but that also the epigenome itself is a main contributor in directing the nuclear receptor response. With the current technology rapidly progressing, the knowledge of genome-wide nuclear receptor action and its interplay with chromatin will undoubtedly increase further and will allow the extension of many of the important findings from cell lines into more relevant tissues and to many other nuclear receptors. These studies are expected to shed further light on the general mechanisms and genome-wide consequences that underlie nuclear receptor action, both in health and disease.

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