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Nuclear receptor modifications and endocrine cell proliferation☆

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Abstract

Heritable and reversible changes in gene expression can occur without alterations in DNA sequence largely dependent upon the position of a gene within an accessible (euchromatic) chromatin environment. This position effect variegation in *Drosophila* and *S. pombe*, and higher order chromatin structure regulation in yeast, is orchestrated by modifier genes of the *Su*(*var*) group (e.g. histone deacetylases (HDACs), protein phosphatases) and enhancer *E*(*var*) group (e.g. ATP-dependent nucleosome remodeling proteins). Higher order chromatin structure is regulated in part by covalent modification of the N-terminal histone tails of chromatin and histone tails in turn serve as platforms for recruitment of signaling modules that include non-histone proteins such as HP1 and NuRD. As the enzymes governing chromatin structure through covalent modifications of histones (acetylation, methylation, phosphorylation, ubiquitination) can also target non-histone substrates, a mechanism is in place by which epigenetic regulatory processes can affect the function of these alternate substrates. The nuclear receptor (NR) superfamily consists of conserved modular transcriptional regulators. Herein, we review the functional properties of nuclear receptors regulated by their direct acetylation including ligand-dependent activation, cellular growth and apoptosis.

Keywords: Chromatin; Transcriptional regulators; Histones

1. Introduction

Histone acetylases (HATs) modify histones, coactivators, nuclear transport proteins, structural proteins, cell cycle components and transcription factors including p53 and nuclear receptors (NRs). The estrogen and androgen receptor (AR) are members of the nuclear receptor superfamily. The overall functional domain structure common to the "classical" nuclear receptor subclass comprise an N-terminal region (activation function 1 (AF1)), a well-conserved central DNA-binding domain (DBD) with two zinc finger structures and a C-terminal region which includes the hinge (H) and ligand-binding domain (LBD). In the absence of ligand, the NR LBD consists of 12 α-helices projected away from the hormone-binding pocket. In the presence of ligand the most carboxyl-terminal helix folds over the ligand-binding hydrophobic pocket thereby creating structural surfaces that bind the basal transcriptional apparatus and recruit coactivators required for efficient transactivation. The estrogen receptor (ERα) and the androgen receptor (AR) are directly acetylated by HATs at a motif that is conserved between species and other NR.

2. Nuclear receptors superfamily

Steroid receptors, including the AR and ERα, are members of the nuclear receptor superfamily which generally function as ligand-dependent transcriptional regulators [1]. The AR is expressed in a variety of cell types and plays an important role in embryogenic development, male sexual differentiation, and prostate cellular proliferation. The functional domains of the AR and ERα (termed A–F) are conserved with other members of the classical receptor subclass. The C-terminal region of the AR, including the hinge region and ligand-binding domain, is responsible for ligand binding and dimerization. The well-conserved DNA-binding domain consists of 68 amino acids with two zinc finger structures. The N-terminal region contributes to transcriptional activation through its activation function 1 [2–4]. In contrast to several other hormone-regulated NRs, the AR lacks an intrinsic AF-2 function in the LBD. The LBD, which consists of 12 helices projecting away from the hormone-binding pocket in the absence of ligand, undergoes substantial conformational changes in the presence of ligand. The folding of the most carboxyl-terminal helix 12 over the ligand-binding

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pocket in turn creates new structural surfaces that bind coactivators required for efficient transactivation [5].

The two activation domains of ERα contribute synergistically to transcription of target genes. The AF-1 function is both constitutive and induced by mitogen-activated protein kinases (MAPKs), by growth factors or oncoproteins [6], by p300 [7] and p68 RNA helicase A [8]. The ligand-dependent transactivation function (AF-2) domain of ERα consists of a conserved carboxyl-terminal helix. The AF-2 domain contributes to ligand-induced activity through further recruitment of coactivator proteins including the p160 family (SRC1, TIF2/glucocorticoid receptor-interacting protein 1 (GRIP1), AIB1/ACTR), the cointegrators (CBP, p300), and p300/CBP-associated factor (P/CAF) [8–10].

3. Nuclear receptor cofactors

3.1. Nuclear receptor coactivators

The transcriptional activity of the steroid hormone receptors is mediated through a large number of coregulatory proteins including coactivators, corepressors and other cofactors. The NR coregulators are recruited to the promoter of target genes through protein–protein interaction with the receptor. Most coactivator proteins are components of a multi-protein complex, which constitutes multiple activation domains or different enzyme activities. Upon recruitment to the promoters by nuclear receptors, the coactivators affect transcription by directly or indirectly modifying the chromatin structure through histone acetyltransferase and associated histone methyltransferase activities [11–13]. The best-studied group of NR coactivators is the p160 family of steroid receptor coactivator (SRC) proteins including SRC1, SRC2 (TIF2/GRIP1), and SRC3 (AIB1/ACTR). The interaction of p160 coactivators with the NR is ligand-regulated and requires an intact AF2 domain. The nuclear receptor interacting domain of the p160s is located in the central region of the protein and contains three conserved α-helical motifs with a consensus amino acid sequence LXXLL (where L stands for leucine, and X stands for any amino acid) [14–23]. The SRC proteins enhance transcriptional activity through intrinsic histone acetyltransferase activity and binding of additional factors, including p300/CBP.

A number of AR coactivators have also been identified and include the p160 proteins, the p300/CREB-binding protein (CBP) family, Ubc9, ARA54, ARA55, ARA70, SNURF, protein inhibitor of activated STAT family (PIAS1), PGC-1, β-catenin, BRCA1 and TIP60 [2,24–34]. The ERα coactivators include p300/CBP, P/CAF, p68, BRG-1, ARA70, RAP46, SRC family, TIP60, RIP-140 (reviewed in [35]). The efficient recruitment of several coactivators to the AR involves an association between both the AR amino terminus and the LBD. The transcriptional activity of the AR is affected by coactivators that influence a number of functional properties of the AR, including ligand selectivity, receptor stability, nuclear translocation and DNA-binding capacity. At the promoter of target genes, coregulators participate in DNA and protein modification, either directly through modification of histones, transcriptional factors including nuclear receptors or indirectly by the recruitment of chromatin-modifying complexes, as well as functioning in the recruitment of the basal transcriptional machinery [8,29,36].

3.2. Nuclear receptor corepressors

Corepressors are proteins associated with unliganded nuclear receptors that mediate transcriptional repression, either through the formation of a non-productive interaction with general transcription factors or through recruitment of histone deacetylase complexes. The best characterized of these corepressors are nuclear receptor corepressor (NCoR) silencing mediator for retinoid and thyroid hormone receptors (SMRT), which bind to unliganded nuclear receptors [11,37–44]. NcoR/SMRT, do not interact with ERα, GR, or PR in the absence of ligand. However, both NCoR and SMRT interact with ERα when bound to the mixed agonist tamoxifen, an ERα ligand that acts as an agonist or antagonist in a tissue-specific manner, and overexpression of either corepressor abolishes tamoxifen agonist activity (see reviewed [29]). NCoR interacts directly with the AR and represses dihydrotestosterone-stimulated AR transcriptional activity. The NCoR C-terminus, containing the receptor interacting domains, was necessary for repression [45]. The AR interacts directly with SMRT. One interacting surface on the AR was mapped to the ligand-binding domain. The binding surface on SMRT was mapped to the carboxyl-terminal ID2 region. Overexpression of SMRT inhibits dihydrotestosterone-dependent transactivation by AR, and enhances suppression of the AR by the antiandrogen flutamide [46]. We and others demonstrated that the AR forms a complex with NCoR and HDAC1 [47,48], and that cyclin D1, a cell cycle regulator of G1 phase, can repress ligand-dependent activation of the AR in a CDK-independent manner [49–51].

4. Histone acetyltransferase and acetylation of the nuclear receptors

The cointegrator proteins CBP/p300 regulate gene expression through several distinct mechanisms. CBP, and the related functional homologue p300 (CBP/p300), convey a bridging function between the DNA-bound transcription factor and the basal apparatus and provide a scaffold to assemble high molecular-weight enhanceosomes (reviewed in [52]). The cointegrator proteins p300 and CBP also share the capacity to acetylate histones, which correlates, under certain circumstances, with their transcriptional coactivator function. Acetylation facilitates binding of transcription factors to specific target DNA sequences by destabilizing

nucleosomes bound to the promoter region of a target gene [53,54]. Furthermore, cointegrators may directly acetylate non-histone proteins, including transcription factors, to regulate their activity (reviewed in [55–57]). Acetylation of the tumor suppressor p53 [58], the transcription factor erythroid Kruppel-like factor [59], and the erythroid cell differentiation factor GATA-1 enhanced their transactivation functions [60,61]. We and others demonstrated that nuclear hormone receptors including ACTR [36,47,62], the AR [36,47] and ERα [8,63] were direct targets of histone acetyltransferase. Direct acetylation of the nuclear receptor coactivator ACTR or ERα contributed to ligand-dependent transcriptional attenuation whereas acetylation of the AR is essential for the ligand-dependent transactivation [8,36,47,62].

4.1. Acetylation motif in the nuclear receptors

Our studies suggested that there is an acetylation motif KLKK in the AR hinge region (Fig. 1). This motif shares sequence similarity with the acetylation site K373 of the human p53 (HLKSKKGQ). The KLKK motif of the AR is evolutionarily conserved between different species from xenopus to humans. A similar acetylation site (KR/HS/TKK) is also found in the ERα hinge region which is homologous to the acetylation site K381, K382 of p53 (TSRHKKLM). The ERα acetylation motif is also conserved between species. The NR acetylation site is conserved with members of the phylogenetically related NR (Figure 7 in [8]), suggesting that NR acetylation modification could be a general mechanism in regulating diverse hormone functions.

4.2. Nuclear receptor acetylation and cell proliferation

The role of direct transcription factor acetylation in hormone signaling to endogenous androgen-regulated target genes is largely unknown. Point mutation of the AR lysine residues to arginine abrogated acetylation of the full-length AR protein [36] and substantially reduced DHT-dependent activation of several androgen-responsive reporter genes, including the PSA promoter, the MMTV promoter, and a simple synthetic androgen response element. This mutation of the AR acetylation site reduced AR coactivation by several AR regulators (Ubc9, SRC1, TIP60) [47]. Activation of the AR by SRC1 requires AD1 of SRC1, the same region responsible for recruitment of p300/CBP. The failed SRC1 coactivation of the AR acetylation site mutants is consistent with defective p300 binding by these AR mutants. TIP60, a coactivator with intrinsic HAT activity, binds the AR through a region including the acetylation site. Using these same AR mutants, Gaughan et al. recently showed that TIP60 and histone deacetylase 1 regulate androgen receptor activity through the acetylated lysine residues [48]. It is known that besides histone acetylase activity, the TIP60 complex conveys ATPase, DNA helicase, and structural DNA-binding activities. Ectopic expression of a TIP60 mutant lacking histone acetylase activity results in cells with defective double-strand DNA break repair. Importantly, the resulting cells lose their apoptotic competence, suggesting a defect in the cells' ability to signal the existence of DNA damage to the apoptotic machinery [64]. It will be of interest to further evaluate the role of TIP60 in AR-mediated apoptosis.

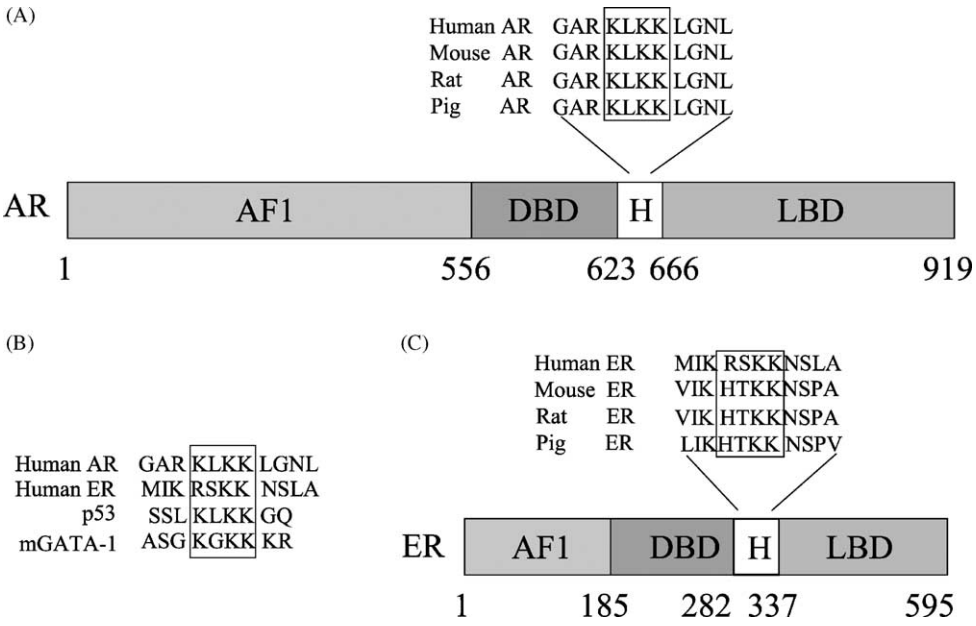

Fig. 1. The human AR and ERα are acetylated. (A) Schematic representation of the human AR indicating AF1 domain, the DNA-binding domain (DBD), the ligand-binding domain (LBD) and the hinge region (H). The KLKK acetylation motif conserved between several species is shown. (B) The ERα is acetylated in the hinge region. (C) Shown is the homology of the nuclear receptor acetylation motif with the conserved murine GATA-1 and human p53 proteins.

Transcriptional repression by NCoR involves a multiprotein complex that includes HDAC complexes, chromatin remodeling proteins, and a transducin β-like protein that interacts with histones [29]. In our studies, the acetylation mimic mutant of the AR (AR_{K630Q}), showed reduced NCoR binding in cultured prostate cancer cells and enhanced liganded activity ([47] and unpublished data). The finding that coactivator and corepressor surfaces of NR overlap substantially is compatible with a dynamic model in which enzymatic modifications of the NR coordinate the sequential disengagement of corepressors followed by coactivator binding. Enhanced coactivator binding of the AR acetylation mimic mutants and reduced corepressor binding suggests a role for the NR acetylation site in both the disengagement of corepressors and engagement of coactivators.

4.3. Steroid receptors and cellular proliferation

Sex steroid hormones, estrogen, progesterone and androgen, play pivotal roles in sexual differentiation and development, and in reproductive functions. Steroid receptors are required for the normal responsiveness of target tissues to the steroid hormones. The mutation or aberrant expression of sex steroid receptor or their coregulators disrupts normal development. Somatic mutations of the receptors in turn may also affect effect progression of hormone-responsive cancers [65].

Prostate cancer is dependent on androgen stimulation mediated by the AR. Several lines of evidence suggest the AR and its coactivators may play a role in prostate cancer. In primary prostate cancers, the AR was expressed however AR cofactor expression was altered with increased expression of PIAS1 and Ran/ARA24, decreased expression of ELE1/ARA70, with no change in TMF1/ARA160, ARA54, SRC1, or TRAP220 [66]. Expression of SRC1 and SRC2 were increased in clinical samples from androgen-independent prostate cancer [37,67] and SRC1 can augment AR transcriptional activity in the presence of therapeutic levels of the AR antagonist bicalutamide [11], implicating this coactivator in therapeutic resistance. The cytokine IL-6 regulates the growth of many tumor cells. The IL-6 receptor is expressed in most prostate carcinoma cell lines and overexpression of IL-6 has been implicated in the neoplastic transformation of prostate cells. IL-6 may also be involved in the androgen-independent progression of prostate cancer. p300 mediates androgen-independent transactivation of the AR by IL-6 and the HAT activity of p300 is necessary for this event [68]. Finally, somatic mutations of the AR are well described in prostate cancer, both in humans and in rodent models. Mechanistically, mutations at the carboxyl terminus may alter hormone responsiveness. A somatic mutation of the AR at the acetylation site, AR_{K630T}, is seen in prostate cancer [69]. This mutant, and another acetylation mimic mutation (AR_{K630Q}), rendered the AR resistant to the ligand antagonist flutamide, and promoted prostate cancer cellular growth with reduced apoptosis in vivo. The AR acetylation mimic altered the regulation of a selective subset of growth control target gene promoters increasing transcription of *cyclin D1* (M. Fu, R.G. Pestell, unpublished data). These findings suggest that AR acetylation might promote aberrant prostate cellular growth in vivo through regulation of coactivator/corepressor complex formation and altered regulation of the cell cycle control genes.

Breast cancer is the primary cause of cancer-related deaths in non-smoking women in the US. The ERα protein levels are elevated in many premalignant and malignant breast lesions. The ERα acetylation site mutation, $ER\alpha_{K303R}$, which showed enhanced ligand sensitivity [8] is a common mutation in the estrogen receptor (*ERα*) gene, found in 34% of atypical breast hyperplasias. The ERα mutation, which is located in the hinge region of the ERα, increased cellular proliferation at subphysiological levels of estrogen [70]. Together, these data raise the possibility that mutation at the ERα acetylation site may contribute to the development of human breast cancer [8,70].

5. Conclusions

Recent studies indicate that coactivators and corepressors modulate NR function, and that the NR serve as substrates for the histone acetyltransferase. NR and their coactivators serve as substrates for acetylation in vivo and in vitro through a common motif conserved between species. Residues within the acetylated motif of NR are mutated in cancer and these mutant receptors promote contact-independent growth. The finding that acetylation regulates growth control suggests that this post-translational modification may be amenable to direct therapeutic intervention. The physicochemical properties of NR that are altered upon acetylation, and the signaling pathways that are involved in regulating acetylation of the nuclear receptors remain to be explored.

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