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Epigenetic regulation of nuclear steroid receptors

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Abbreviations:
NR, nuclear receptor
AR, androgen receptor
ERα, estrogen receptor
PPARγ, peroxisome proliferator-activated receptor γ
HAT, histone acetyltransferase
HDAC, histone deacetylase
SRC, steroid receptor coactivator
N-CoR, nuclear receptor corepresssor
SMRT, silencing mediator of retinoid and thyroid hormone receptor
TSA, trichostatin A
SIRT1, Sirtuin 1
CBP, CREB binding protein
p/CAF, p300/CBP-associated factor
DNMT, DNA methyltransferase

ABSTRACT

Histone modifier proteins have come to the forefront in the study of gene regulation. It is now known that histone methyltransferases, acetytransferases, kinases, ubiquitinases, deacetylases and demethylases orchestrate expression of target genes by modifying both histone and non-histone proteins. The nuclear receptor (NR) superfamily govern such diverse biological processes as development, physiology and disease, including human cancer. The involvement of NR in complexes with coactivators and corepressors is necessary for regulation of target genes. This review focuses on the newly recognized interactions between the NR and histone modifying enzymes. In addition to regulating histones, the histone modifying proteins directly modify and thereby regulate NR activity. In the same manner that signaling platforms exist within the histone tails that are post-translationally processed by histone modifying proteins, cascades of post-translational modification have been identified within the NR that coordinate their activity. This review focuses on the regulation of the NR estrogen receptor (ERα), androgen receptor (AR) and peroxisome proliferator activated receptor-gamma (PPARγ), given their role in tumor onset and progression.

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ChIP, chromatin immunoprecipitation
LSD1, lysine specific demethylase

1. Introduction

Nuclear receptors (NR) are part of multi-protein complexes that include transcription factors and coactivator proteins that modify chromatin. The BRG/BRM proteins, for example, bind NR and regulate chromatin structure in an ATPase-dependent manner. NR associate with histone modifying proteins that convey transcriptional repression or activation. These histone modifying proteins, including histone acetyltransferases, kinases, ubiquitinases, deacetylases, histone methyltransferases and demethylases, can regulate the activity and/or the expression of NR. Several NR are directly modified by kinases and histone acetylases including the estrogen receptor α (ERα), androgen receptor (AR) and peroxisome proliferator receptor γ (PPARγ). The acetylation of NR occurs at a conserved motif. This motif is observed in most NR and is conserved between species. Acetylation of NR is regulated by physiological stimuli. This review focuses on the regulation of NR by histone modifying proteins and the effects of NR acetylation on their biological function.

2. Epigenomic modification

Epigenomic modifications can be defined as heritable, yet reversible, chromatin alterations that govern the expression of genes. This area has been examined for many years, beginning in 1983 with the discovery of methyltransferases that alter DNA [1]. While examining colorectal cells Feinberg and Vogelstein were the first to note an altered DNA methylation pattern in tumors. It was not until the identification of histone acetyltransferases, or HATs, in 1995 [2], that histone modification involved in cellular differentiation was more thoroughly examined. Since then several main chemical alterations of histones that regulate gene expression have been determined and well-studied. In addition to histone acetylation and DNA methylation, these alterations include histone phosphorylation, ubiquitination and methylation, all of which can either silence or activate gene expression.

In 1999 Holliday and Beck, Olek and Walter [3,4] commented on epigenomic modifications, hinting at the idea of ''deciphering an epigenetic code''. Strahl and Allis [5] proposed an inherited order to post-translational histone modifications; which became known as the 'histone code hypothesis'. Histone acetyltransferases (HATs) (CBP, p300, etc.), deacetylases (HDACs), kinases (Aurora) and methyltransferases (HMTs) have already been shown to play significant roles in cancer. As the epigenetic phenotype may be reversible, enzymes regulating these epigenomic changes may be ideal targets for cancer drug development. In fact, several different histone deacetylase inhibitors are currently in phase I or II clinical trials.

3. Nuclear receptors (NR)

NR, or steroid receptors, share structurally conserved domains and are regulated through steroids, thyroid hormone, retinoic acid, vitamins or other proteins. They function as transcription factors, often in complex with other coregulators, that govern transcription of target genes involved in such varied processes as homeostasis, reproduction, development and metabolism [6]. All NR contain four main conserved domains, the activation function domain (AF), the DNA binding domain (DBD), the hinge region and the ligand-binding domain (LBD). Protein–protein interactions are typically found through an N-terminal domain and the LBD. The DBD binds specific target DNA sequences, while the LBD additionally binds hormones.

Coregulator proteins that bind to NR help to modify target gene expression through protein complex formation. These interactions aid in either corepression or coactivation of gene expression. Coactivators work by recruiting protein complexes to function as a link between the NR and the transcriptional apparatus. They also can use their histone modifying abilities to alter the local chromatin structure. The coactivators that bind NR include steroid receptor coactivator-1 (SRC-1), amplified in breast cancer 1/thyroid and RA receptor/steroid receptor coactivator-2 (AIB1/ACTR/SRC-2), glucocorticoid receptor interacting protein 1/transcriptional intermediary factor 2/steroid receptor coactivator-3 (GRIP1/TIF-2/SRC-2), p300/CBP and p/CAF (p300/CBP-associated factor) [7–9]. NR corepressors typically interact with unliganded NR and recruit histone modifying proteins, like HDACs, to silence target gene expression. Several NR corepressors have been identified and include nuclear receptor corepressor (N-CoR), silencing mediator of retinoid and thyroid hormone receptor (SMRT), Sin3, HDACs, thyroid hormone receptor uncoupling protein (TRUP), BRCA1, NuRD, Suv39h1, DNMT1, pRb2/p130, and E2F4/5.

3.1. *Histone methylation*

Histone methylation is dynamically regulated by HMTs and demethylases, such as Lysine Specific demethylase 1 (LSD1), JHDM1, JHDM2A and JMJD2. Histone methylation regulates chromatin structure, transcription and the epigenetic state of the cell. Methylation occurs at lysine and arginine residues. Lysine residues can be mono-, di- or tri-methylated. Euchromatic histone methylation contributes to both transcriptional repression and activation. Methylation at H3-K4 and H3-K36 is typically linked to transcriptional activation, while H3 Lys 9 is typically a repressive mark.

All of the histone lysine methylases, except Dot, share a SET (Su(var), Enhancer of zeste, Trithorax) domain that is responsible for the addition of the S-adenosyl-L-methionine cofactor. HMTs add methyl groups to the ε-amino group of