RETRACTED ARTICLE: Transcriptional Controls by Nuclear Fat-Soluble Vitamin Receptors through Chromatin Reorganization

The following article has been retracted from publication in Bioscience, Biotechnology, and Biochemistry.


The Editorial Board of Bioscience, Biotechnology, and Biochemistry has recently confirmed that the Award Review article above written by Shigeaki KATO and Ryoji FUJIKI, contains a number of references to previous publications by the same authors, several of which contain some problematic images, which have resulted in the conclusions of those papers to be brought into question and those papers retracted. These images include fabrication and falsification of images through inappropriate processing and duplicate use of identical image data for different publications. These instances of misconduct have been confirmed by the University of Tokyo Scientific Research Code of Conduct Committee which raised questions over the validity of the Award Review article, published in Bioscience, Biotechnology, and Biochemistry. Following COPE guidelines and in consultation with the author, the Japan Society for Bioscience, Biotechnology, and Agrochemistry has decided to rescind the award given to the authors. After discussion with the authors, the Editorial Board and the authors have jointly decided to retract this Award Review article from Bioscience, Biotechnology, and Biochemistry.

As Editor-in-Chief, I regret the time that peer reviewers and others spent on reviewing this paper.

Yoshihito Suzuki
Editor-in-Chief,
Bioscience, Biotechnology, and Biochemistry

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Fat-soluble ligands like vitamin A/D and steroid hormones activate their cognate nuclear receptors for ligand-dependent transcriptional regulation. Nuclear receptors constitute a gene superfamily with 48 members in higher mammals, and act as ligand-dependent transcription factors to bind stably to specific DNA elements in ligand/NR target gene promoters. Hence, most of biological actions of fat-soluble ligands are generally thought to mediate NR-mediated gene regulation. Starting in early 1990, transcriptional co-regulators supporting ligand-dependent transcriptional controls by NRs have been characterized. Initially, the transcriptional co-regulators were believed to couple with histone acetylation/deacetylation, and thereby histone deacetylases (HDACs) and histone acetyltransferases (HATs) were characterized as NR co-activators and co-repressor, respectively. However, recent progress in chromatin biology and epigenome have revealed that other histone modifying enzymes and chromatin remodelers are potential co-regulators for NRs. In this review, these cutting-edge aspects are discussed together with our recent findings on NR co-regulators.

Key words: fat-soluble ligand; nuclear receptor; transcriptional co-regulator; histone modification; ATP-dependent chromatin remodeling

Fat-soluble ligands like vitamin A/D and steroid hormones show a wide variety of biological actions by binding to nuclear receptors (NRs) (Fig. 1). NR members (48 members in human) form a gene superfamily and act as ligand-dependent transcription factors. NRs bind directly to specific DNA elements in target gene promoters, and positively and negatively control transcription in ligand-dependent manners.1,2 For ligand-dependent transcriptional controls by NRs, a number of transcriptional co-regulators are required, besides of a set of basic transcription factors.3,4 Recent molecular dissection of such transcriptional co-regulators have revealed that these factors serve as regulators of chromatin reorganization by chromatin remodeling and histone modification.5,6 Since chromatin reorganization is a fundamental process in constituting the epigenomic platform, transcriptional co-regulators are now considered to act as regulators for epigenomic platform formation. In this review, the functions of NR transcriptional co-regulators are discussed.

I. Chromatin Reorganization Is Prerequisite for Transcriptional Control

Since physical interaction between chromosomal DNA and histone octamers hinders local DNA sequences from associating with DNA-binding transcription factors including NRs, nucleosomal units are in general inhibitory of transcriptional events.7 Hence transcriptional events directed by NRs require chromatin reorganization to enable the factors to recognize specifically and bind stably to specific DNA sequences by two processes. The first is histone octamer transfer, most evident when daughter DNA strands assume their proper nucleosomal structure immediately after DNA replication.8 Such histone octamer transfer and eviction also occur at gene promoters, where nucleosomal rearrangement is required to facilitate transcriptional activation or inactivation. The second process is histone octamer sliding (Fig. 2). Histone octamers slide while chromosomal DNA winds continuously.9 These two processes probably proceed by means of ATP-dependent chromatin remodeling complexes and histone chaperones. Chromatin remodeling complexes are classified into four groups, based on the major catalytic subunits, the ATPases.

II. Histone Modification and the Histone Code

The N-tails of histones extend outside DNA-histone octamers and serve as substrates for a variety of histone-modifying enzymes. Post-translational modifications (PTMs) of histone tails include eight chemical modifications, including acetylation, methylation, and ubiquitination (Fig. 3). These histone modifications due to chemical moieties of small molecular weights are reversible.5 Certain combinations of histone modifications constitute a non-DNA genetic code (the histone code).10 In transcriptionally active euchromatin, histones at gene promoters are methylated at the histone H3 lysine 4 (H3K4 Me) and 36 (H3K36 Me) residues in addition to histone H3 hyperacetylation. On the other hand, in inactive heterochromatin, methylation at H3K9...
and K27 (H3K9 Me and H3K27 Me) and H3 hypo-acetylation is common.\(^{11}\) In addition, histone mono-ubiquitination probably facilitates the elongation process in transcription.\(^{12}\) Histone modifications appear to cross-talk and to be altered in response to intracellular and extracellular conditions.\(^{13}\)

In transcriptional events, H3K4, K9, K27, and K36 residue methylation is probably the most significant hallmark. The regulation process of methylations at these residues appears highly complicated, since up to three methyl moieties can be transferred at each histone lysine residue.\(^{11}\) Moreover, multiple histone methyl-

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**Fig. 1.** The Molecular Mechanism of Nuclear Receptor Action.

After binding of fat-soluble ligand, activated NRs translocate into the nucleus and directly bind to their cognate hormone response elements (HREs). Co-regulator complexes rendezvous with the NRs and reconfigure (open/close) the chromatin structure surrounding the core promoter. Thus, NRs alter the rate of target gene transcription by controlling pre-initiation complex formation and RNA polymerase II recruitment.

**Fig. 2.** Composition of the Four Different Chromatin Remodeler Complexes and Reversible Organization of Nucleosomal Arrays.

SWI/SNF, CHD, ISWI, and INO80-type chromatin remodelers share similar ATPase components as catalytic subunit, but differ in the complex composition of the associating subunits, shown in the upper panel. The reversible organization of nucleosomal arrays is mediated by these chromatin remodeler complexes through several processes, including (1) histone octamer sliding and (2) histone octamer transfer (histone eviction and histone displacement), as shown in the lower panel.
transferases are reportedly active at the same lysine residue. Similarly, multiple demethylases drive demethylation at the same lysine residue. Though the physiological impact of the various histone methyltransferases and demethylases remains to be defined in living animals, it is evident from their cell- and tissue-specific expression patterns that the various enzymes have unique roles in physiological and pathological processes.

III. Histone-Modifying Enzymes That Serve as Transcriptional Co-Regulators

Histone-modifying enzymes are regulators of chromatin organization and indirectly support transcriptional control by NRs as transcriptional co-regulators (Fig. 4). Likewise, the overt function of ATP-dependent chromatin remodelers and histone chaperones is transcriptional co-regulation. It is not surprising that there are numerous transcriptional co-regulators. The environments of gene promoters appear highly diverse and controlling the proper spatio-temporal expression of a given gene requires specific co-regulators.

IV. NR Co-Regulators Form Complexes

Chromatin remodelers and histone modifiers often form multisubunit complexes. The assembly of multitudes complexes is believed to be advantageous in comparison to a single subunit in terms of supplying more interfaces for complex associations of multiple interactants. In this respect, complex formation of histone modifiers and chromatin remodelers (Fig. 4) accounts for their functions as common co-regulators for many classes of DNA binding-transcription factors, besides of NRs.

The compositions of co-regulator complexes appear not to be uniform among cell types. Prime components like catalytic subunits are commonly shared with subclass complexes, but regulatory (auxiliary) subunits are cell type-specific, presumably owing to their spatio-temporal expression. One of the best characterized NR co-activators, PGC-1, can be categorized as a shared regulatory subunit in multiple complexes, since PGC-1 coregulates NRs by docking HATs or other NR co-regulators.

V. Functional Regulation of Complex Components by Post-Translational Protein Modification (PTM)

The transcriptional activities of NRs are modulated by other cellular signaling pathways. A cross-talk mechanism between NR- and cell membrane receptor-mediated signals has been found at many cellular levels. However, based on recent observations, it appears likely that the cross-talk of NR signals with other signals appears to occur also at NR co-regulator complex subunit levels. The complex subunits look substrates for numerous modifying enzymes, and indeed we found that a histone demethylase (PHF2) is enzymatically activated by its phosphorylation by protein kinase A (PKA). Likewise, we reported recently that O-monoglycosylation (GlcNAcylation) of subunits evokes HKMT activity of MLL5 through assembly of the complex. Protein O-GlcNAcylation is reversible and under the control of extracellular glucose levels and the cellular energy state. Thus this PTM is assumed to participate in cross-talk between glucose/energy-related signals and NR signals.

VI. Concluding Remarks

NR co-regulators, based on our interpretation of available data, are illustrated in Fig. 4. Until about 2000, the major interest in NR co-regulator functions was related to histone acetylation and physical mediators bridging NRs with basal transcriptional machinery. The discovered function of the two oppositely acting enzymes, HATs and HDACs (in NCoR/SMAT complexes), suggests that ligand-dependency in NR-mediated transcription control mediates the ligand binding-induced switching of direct interaction of co-repressors into co-activators. Currently, the mechanism underlying chromatin organization, the HAT/HDAC-type NR co-regulators, appears unlikely to be
capable of supporting more dynamic promoter activation and repression that mediating chromatin reorganization. Dynamically regulated promoters clearly require methylation-related enzymes and histone remodelers.

The quickly expanding field of chromatin/epigenome biology is providing new clues as to how previously underestimated NR co-regulators assist NR function. Dynamic reorganization of chromatin is triggered by activated NRs, and most likely requires chromatin reorganization-related factors, since dynamic promoter activation and repression are associated with significant chromatin reorganization, which constitutes the epigenomic platform. Thus, chromatin remodelers, histone modifiers, and histone chaperons are potential NR co-regulators.

References