


C2H2-Type Zinc Finger Proteins: Evolutionarily Old and New Partners of the Nuclear Hormone Receptors

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Abstract

Nuclear hormone receptors (NRs) are evolutionarily conserved ligand-dependent transcription factors. They are essential for human life, mediating the actions of lipophilic molecules, such as steroid hormones and metabolites of fatty acid, cholesterol, and external toxic compounds. The C2H2-type zinc finger proteins (ZNFs) form the largest family of the transcription factors in humans and are characterized by multiple, tandemly arranged zinc fingers. Many of the C2H2-type ZNFs are conserved throughout evolution, suggesting their involvement in preserved biological activities, such as general transcriptional regulation and development/differentiation of organs/tissues observed in the early embryonic phase. However, some C2H2-type ZNFs, such as those with the Krüppel-associated box (KRAB) domain, appeared relatively late in evolution and have significantly increased family members in mammals including humans, possibly modulating their complicated transcriptional network and/or supporting the morphological development/functions specific to them. Such evolutionary characteristics of the C2H2-type ZNFs indicate that these molecules influence the NR functions conserved through evolution, whereas some also adjust them to meet with specific needs of higher organisms. We review the interaction between NRs and C2H2-type ZNFs by focusing on some of the latter molecules.

Keywords

Broad-Complex, Tramtrack, and Bric-a-brac (BTB)/poxvirus and zinc finger (POZ), coregulator, evolution, Krüppel-associated box (KRAB), noncoding RNA, SCAN

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Abbreviations

AF, activation function; APL, acute promyelocytic leukemia; AR, androgen receptor; Bcl2, B-cell lymphoma 2; BTB, Broad-Complex, Tramtrack, and Bric-a-brac; CAR, constitutive androstane receptor; CBP, CREB-binding protein; CHD8, chromodomain helicase DNA-binding protein 8; CLAMP, chromatin-linked adaptor for MSL protein; CNS, central nervous system; CoCoA, coiled-coil coactivator; COUP-TF, ovalbumin upstream promoter-transcription factor; CtBP, C-terminal tail-binding protein; CTCF, CCCTC-binding protein; DAX-1, dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1; DBD, DNA-binding domain; DRIP, VDR-interacting protein; EAR2, V-erbA-related protein 2; E2F1, E2F transcription factor 1; ER, estrogen receptor; FXR, farnesoid X receptor; Gas5, growth arrest-specific 5; GCNF, germ cell nuclear factor; GIOT-1, gonadotropin-inducible ovarian transcription factor-1; GR, glucocorticoid receptor; HAT, histone

acetyltransferase; HDAC, histone deacetylase; HNF4, hepatocyte nuclear factor 4; HP1, heterochromatin protein 1; HTLV-1, human T-cell leukemia virus type-1; HUB1, HTLV-1 U5RE-binding protein 1; KAP-1, KRAB-associated protein-1; KLF, Krüppel-like factor; KRAB, Krüppel-associated box; KRIP1, KRAB-A-interacting protein 1; LBD, ligand-binding domain; lincRNA, long intergenic ncRNA; lncRNA, long ncRNA; LXR, liver X receptor; miRNA, microRNA; MR, mineralocorticoid receptor; MSL, male-specific lethal; nc, protein noncoding; NCoA, nuclear receptor coactivator; NCoR, nuclear receptor corepressor; NOR1, neuron-derived

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orphan receptor 1; NRs, nuclear hormone receptors; NTD, N-terminal domain; NUR77, nerve growth factor 1B; NURR1, nuclear receptor related 1; Paris, parkin-interacting substrate; p/CAF, p300/CBP-associated factor; PCG-1 α , PPAR γ coactivator-1 α ; PCGEM1, prostate-specific transcript 1; PLZF, promyelocytic leukemia zinc finger protein; PNR, photo-specific nuclear receptor; POZ, poxvirus and zinc finger; PPAR, peroxisome proliferator-activated receptor; PR, progesterone receptor; PRC, polycomb-repressive complex; PRDM, PR domain zinc finger protein; PRNCR1, prostate cancer associated noncoding RNA 1p; PXR, pregnane X receptor; RAR, retinoic acid receptor; ROR, RAR-related orphan receptor; RXR, retinoid X receptor; SETDB1, histone H3K9 methyltransferase SET domain bifurcated 1; SF-1, steroidogenic factor-1; SHP, small heterodimer partner; SMRT, silencing mediator for retinoid and thyroid hormone receptors; SP, specificity protein; SR, steroid hormone receptor; SRA, steroid receptor RNA activator; STAT5, signal transducer and activator of transcription 5; TAD, topologically associated domain; TFIIA, transcription factor IIIA; TFIIC, transcription factor IIIC; TFIID, transcription factor IID; TIF1, transcription intermediary factor 1; TLX or TLL, timeless receptor; TR, thyroid hormone receptor; TRAP, TR-associated protein; TRIM, tripartite motif protein; TRE, TR response element; U5RE, U5 repressive element; VDR, vitamin D receptor; WT1, Wilms tumor 1; YY1, Yin-Yang 1; ZER6, zinc finger-estrogen receptor interaction, clone 6; ZF, zinc finger; ZNF, zinc finger protein.

Introduction

Gene transcription is essential for maintaining life of organisms through expression of the effector component proteins and influences every aspect of their activities. However, skewed gene expression leads to the development of various disorders in humans, such as metabolic abnormalities, infection, inflammation, and cancer. Thus, higher organisms have developed a sophisticated regulatory system of gene transcription to control the expression of encoding proteins in appropriate places (organs/tissues) at the right timing, to create their complex body components, and to maintain their appropriate functionality.¹ This is also evident by the fact that higher organisms have expanded their genome content, particularly the nonprotein-coding genome area, which harbors plenty of regulatory elements, such as promoters, enhancers, and insulators (98.5% of the entire genome in humans), in contrast to the area and the number of the protein-coding genes, which remained unchanged from lower to higher organisms (~20 000-30 000 genes).² Thus, expansion of the noncoding genomic area provides a more complex and sophisticated regulation on the expression of a limited number of coding genes. Interestingly, a substantial part of the nonprotein-coding genome area expresses numerous numbers and different forms of nonprotein-coding (nc) RNAs, which provides an additional layer of the regulatory mechanisms on gene transcription and protein function.^{3,4}

In addition to genome regulatory elements and abundant ncRNAs for organizing gene transcription, transcription factors are the major protein components that translate cellular internal/external changes to gene transcription.⁵ Indeed, small changes in their expression/activation can result in dramatic yet concordant alteration in the entire functional network in organisms.⁵ They usually contain the structural domain(s) for binding to DNA and the effector components attracting the transcriptional regulatory machinery.⁶ Transcription factors include 2 large families, nuclear hormone receptors (NRs) and C2H2-type zinc finger proteins (ZNFs).⁷ The former proteins are evolutionarily conserved and function as ligand-dependent transcription factors by mediating the biological actions of small lipophilic compounds.⁷ On the contrary, the latter molecules demonstrate characteristic expansion of their member proteins in higher organisms and act as transcription factors and/or transcriptional regulators/cofactors through their multiple zinc fingers (ZFs) and other distinct functional modules.⁸ Involved in diverse and important biological functions as well as exposed to the strong evolutionary pressure, NRs and C2H2-type ZNFs have developed mutual and multilayered interactions to coordinate each other's activities. In this review, we will discuss these 2 families and highlight their roles and mutual interaction from an evolutionary point of view.

Nuclear Hormone Receptors

NRs are transcription factors, the activity of which is dependent on their association with their cognate ligands.⁷ NRs are essential for organisms to support their numerous activities, including development, reproduction, energy metabolism, neural, musculoskeletal, gastrointestinal, and immune functions.^{7,9} Upon binding to ligand, NRs, either by translocating into the nucleus or by constitutively residing in this subcellular component, interact physically with their specific DNA sequences called response elements.¹⁰ DNA-bound NRs then change the transcription rates of their responsive genes by communicating with many co-regulatory molecules.¹¹

The NR family consists of more than 200 members in general and more than 40 in mammals (48 in humans) currently cloned and characterized across species.^{7,12} Their encoding genes are categorized into 7 major subfamilies from NR0 to NR6, depending on their phylogenetic proximity¹³ (Table 1). NRs have common structural features: the N-terminal domain (NTD), a middle DNA-binding domain (DBD), and the C-terminal ligand-binding domain (LBD)^{12,14} (Figure 1). There is a short sequence called hinge region (HR) between DBD and LBD. The NTD of NRs is the most variable domain, presumably mediating receptor-specific transcriptional activity through the transactivation domain(s) (activation function-1 [AF-1]) residing in this domain.¹⁵ In contrast, the DBD is highly conserved among NRs and consists of 2 C4-type ZFs through which it directly binds receptor-specific response elements.¹² These sequences are mostly present in tandem, as many of NRs

Table 1. NR Family Proteins.

Protein name	Gene name	Type ^a	Ligands	Biological actions	Reference
TR α	<i>NR1A1</i>	2	Thyroid hormones	Energy metabolism, CNS development and function	Cheng et al ¹⁹
TR β	<i>NR1A2</i>	2	Thyroid hormones	Energy metabolism, CNS development and function	Cheng et al ¹⁹
RAR α	<i>NR1B1</i>	2	All-trans retinoic acid, 9-cis retinoic acid	Brain and other organ development	Giguere ²⁰
RAR β	<i>NR1B2</i>	2	All-trans retinoic acid, 9-cis retinoic acid	Brain and other organ development	Giguere ²⁰
RAR γ	<i>NR1B3</i>	2	All-trans retinoic acid, 9-cis retinoic acid	Brain and other organ development	Giguere ²⁰
PPAR α	<i>NR1C1</i>	1	Fatty acids, leukotriene B4, fibrates	Lipid and energy metabolism	Berger and Moller ²¹
PPAR β/δ	<i>NR1C2</i>	1	Fatty acids	Lipid and energy metabolism	Berger and Moller ²¹
PPAR γ	<i>NR1C3</i>	1	Fatty acids, prostaglandin J2	Lipid and energy metabolism	Knouff and Auwerx ²²
Rev-erb α	<i>NR1D1</i>	3	Heme (structural)	Circadian rhythm	Yin et al ²³
Rev-erb β	<i>NR1D2</i>	3	Heme (structural)	Lipid and energy metabolism	Yin et al ²³
ROR α	<i>NR1F1</i>	1	Cholesterol, cholesteryl sulfate	Brain and immune development, lipid and bone metabolism	Zhang et al ²⁴
ROR β	<i>NR1F2</i>	1	Retinoic acid	Brain function?	Zhang et al ²⁴
ROR γ	<i>NR1F3</i>	1	Desmosterol, zymosterol	Immune response (T-helper 17)	Zhang et al ²⁴
LXR α	<i>NR1H3</i>	1	Oxysterol	Cholesterol and fatty acid metabolism	Jakobsson et al ²⁵
LXR β	<i>NR1H2</i>	1	Oxysterol	Cholesterol and fatty acid metabolism	Jakobsson et al ²⁵
FXR α	<i>NR1H4</i>	1	Bile acids	Bile acid synthesis and cholesterol metabolism	Chiang ²⁶
FXR β^b	<i>NR1H5</i>	1	Lanosterol	Cholesterol metabolism	Chiang ²⁶
VDR	<i>NR1I1</i>	2	1.25-dihydroxyvitamin D	Bone and calcium metabolism	Jurutka ²⁷
PXR	<i>NR1I2</i>	1	Xenobiotics	Xenobiotics	Kliwer ²⁸
CAR	<i>NR1I3</i>	1	Xenobiotics	Xenobiotics	Willson and Kliwer ²⁹
HNF4 α	<i>NR2A1</i>	3	Fatty acids (Linoleic acid?)	Glucose and lipid metabolism	Sladek and Giguere ³⁰
HNF4 γ	<i>NR2A2</i>	3	Fatty acids (Linoleic acid?)	Glucose and lipid metabolism	Sladek and Giguere ³⁰
RXR α	<i>NR2B1</i>	1	9cis-retinoic acid	Hetro-dimerize with other NRs	Giguere ³¹
RXR β	<i>NR2B2</i>	1	9cis-retinoic acid	Hetro-dimerize with other NRs	Giguere ³¹
RXR γ	<i>NR2B3</i>	1	9cis-retinoic acid	Hetro-dimerize with other NRs	Giguere ³¹
TR2	<i>NR2C1</i>	3		Regulation of sex steroid receptor and PPAR activity	Lee et al ³²
TR4	<i>NR2C2</i>	3		Cellular differentiation/homeostasis, oxidative stress	Lee et al ³²
TLX	<i>NR2E1</i>	3		Neural and retinal development, brain function	Benod et al, ³³ Wang et al ³⁴
PNR	<i>NR2E3</i>	3		Embryonic/retinal development	Kobayashi et al ³⁵
COUP-TFI	<i>NR2F1</i>	3		CNS development and function	Tsai and Tsai ³⁶
COUP-TFII	<i>NR2F2</i>	3		CNS development and function	Tsai and Tsai ³⁶
EAR2	<i>NR2F6</i>	3		Brain function and hematopoiesis	Zhu et al ³⁷
ER α	<i>NR3A1</i>	2	Estradiol	Reproduction and female body composition	Couse and Korach ³⁸
ER β	<i>NR3A2</i>	2	Estradiol	Reproduction and female body composition	Koehler et al ³⁹
ERR α	<i>NR3B1</i>	3		Regulation of estrogen actions	Horard and Vanacker ⁴⁰
ERR β	<i>NR3B2</i>	2	Diethylstilbestrol	Regulation of estrogen actions	Horard and Vanacker ⁴⁰
ERR γ	<i>NR3B3</i>	2	Diethylstilbestrol	Regulation of estrogen actions	Horard and Vanacker ⁴⁰
GR	<i>NR3C1</i>	2	Glucocorticoids	Stress response and immune regulation	Kino ¹²

(continued)

Table 1. (continued)

Protein name	Gene name	Type ^a	Ligands	Biological actions	Reference
MR	<i>NR3C2</i>	2	Mineralocorticoids	Water and electrolyte homeostasis	Funder ⁴¹
PR	<i>NR3C3</i>	2	Progestins	Reproduction and female body composition	Graham and Clarke ⁴²
AR	<i>NR3C4</i>	2	Androgens	Reproduction and male body composition	Heinlein and Chang, ⁴³ Quigley et al ⁴⁴
NUR77	<i>NR4A1</i>	3		Brain function, steroidogenesis, and immune activity	Bassett and White, ⁴⁵ Hsu et al, ⁴⁶ Ranhotra ⁴⁷
NURR1	<i>NR4A2</i>	3		Brain function (dopaminergic system) and immune activity	McMorrow and Murphy, ⁴⁸ Perlmann et al ⁴⁹
NOR1	<i>NR4A3</i>	3		Immune regulation and hematopoiesis	McMorrow and Murphy, ⁴⁸ Perlmann et al, ⁴⁹ Mullican et al ⁵⁰
SF-1	<i>NR5A1</i>	3	Phosphoinositol (structural)	Sexual development, reproduction, and steroidogenesis	Ozsisik et al ⁵¹
LRH-1	<i>NR5A2</i>	3		Cell proliferation and immune regulation	Stein and Schoonjans ⁵²
GCNF	<i>NR6A1</i>	3		Embryogenesis and germ cell differentiation	Zechel ⁵³
DAX-1	<i>NR0B1</i>	3		Development of steroid-producing/regulating organs	El-Khairi et al ⁵⁴
SHP	<i>NR0B2</i>	3		Inhibition of other NR activity, intermediary metabolism	Zhang et al ⁵⁵

Note. NR = nuclear hormone receptor; TR = thyroid hormone receptor; CNS = central nervous system; RAR = retinoic acid receptor; PPAR = peroxisome proliferator-activated receptor; ROR = RAR-related orphan receptor; LXR = liver X receptor; FXR = farnesoid X receptor; VDR = vitamin D receptor; PXR = pregnane X receptor; CAR = constitutive androstane receptor; HNF = hepatocyte nuclear factor; RXR = retinoid X receptor; TLX = Timeless receptor; PNR: photo-specific nuclear receptor; COUP-TF = chicken ovalbumin upstream promoter-transcription factors; EAR = V-erbA-related protein; GR = glucocorticoid receptor; MR = mineralocorticoid receptor; PR = progesterone receptor; NUR77 = nerve growth factor IB; NURR1 = Nuclear receptor related I; NOR1 = neuron-derived orphan receptor I; SF-1 = steroidogenic factor -1; GCNF = germ cell nuclear factor; DAX-1 = dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1; LRH-1 = liver receptor homolog-1; SHP = small heterodimer partner.

^a1: metabolic sensor (adopted orphan) receptor, 2: endocrine receptor, 3: orphan receptor.

^bFXR β is a pseudogene in humans but is a functional lanosterol receptor in mice.^{13,56}

bind these sequences as a homo- or a heterodimer.¹⁶ The LBD has a ligand-binding pocket and a transactivation domain (AF-2), which is created through ligand-dependent conformational changes inside this domain.¹⁷ This second transactivation domain interacts with the histone acetyltransferase (HAT) coactivators, including the CREB-binding protein (CBP)/p300 and the nuclear receptor coactivators (NCoAs), through the latter's LxxLL coactivator motifs, and stimulates NR's ligand-dependent transcriptional activity by cooperating with the first transactivation domain located in NTD. In addition to HAT coactivators, NRs interact with numerous cofactor molecules, including mediator/TR-associated protein (TRAP)/VDR-interacting protein (DRIP) and switch/ sucrose non-fermenting (SWI/SNF) protein complexes, and each of their component proteins appears to influence the transcriptional activity of a specific fraction of the NR-responsive genes.¹⁸

NRs are empirically and functionally categorized into 3 major groups: (1) metabolic sensor (or adopted orphan) receptors, (2) endocrine receptors, and (3) orphan receptors.⁷ NRs of the first group, including peroxisome proliferator-activated receptors (PPARs), liver X receptors (LXRs), pregnane X

receptor (PXR), and constitutive androstane receptor (CAR), act as sensors for lipid metabolites, such as fatty acids, prostanooids, oxysterols, bile acids, dietary lipids, and xenobiotics, by binding to these compounds as ligands with relatively low affinity.⁷ NRs in the second group (endocrine receptors), including steroid hormone receptors (SRs) (glucocorticoid receptor [GR], mineralocorticoid receptor [MR], androgen receptor [AR], progesterone receptor [PR] and estrogen receptors [ERs]), thyroid hormone receptors (TRs), retinoic acid receptors (RARs), and the vitamin D receptor (VDR), act as receptors for steroid hormones (glucocorticoids, mineralocorticoids, androgens, progestins, and estrogens), retinoid acids, thyroid hormones, and vitamin D, with high affinity interaction to these compounds.⁷ The last group, orphan receptors, including Nerve growth factor IB (NUR77), chicken ovalbumin upstream promoter-transcription factors (COUP-TFs), hepatocyte nuclear factor 4s (HNF4s), and dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1 (DAX-1), do not regularly have known ligands.⁷ However, some of these receptors (eg, HNF4s and steroidogenic factor-1 [SF-1]) can constitutively bind "structural" ligands, which function as components of their LBDs.⁵⁹⁻⁶¹

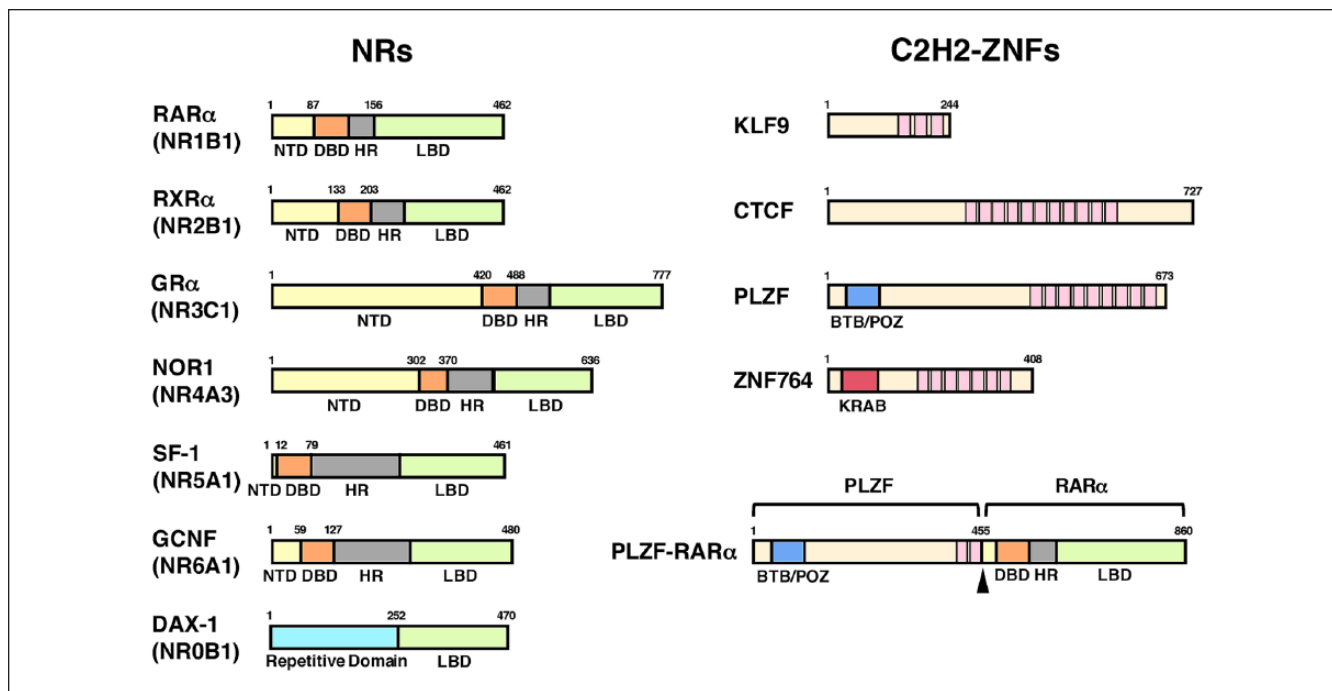


Figure 1. Linearized structure of the representative NRs and C2H2-type ZNFs, and their functional domains.

Note. Linearized molecules of the human NRs (RAR α , RXR α , GR α , NOR1, SF-1, GCNF, and DAX-1 with gene names in parentheses), C2H2-type ZNFs (poly-ZNFs: KLF9 and CTCF, BTB/POZ-ZNF: PLZF and KRAB-ZNF: ZNF764), and the PLZF-RAR α fusion protein are shown. Their functional domains are indicated with different colors. C2H2-type ZFs are shown in pink. DAX-1 does not have NTD and DBD, but is composed of a repetitive domain, which contains 3 LxxLL-like motifs used for interacting with selected NRs.⁵⁷ PLZF-RAR α is a fusion protein found in the acute promyelocytic leukemia with t(11;17)(q23;q21) translocation. This fusion protein consists of the N-terminal part of PLZF containing BTB-POZ domain and 2 ZFs, and the C-terminal part of RAR α harboring DBD and LBD.⁵⁸ Black triangle indicates the junction between PLZF and RAR α protein sequences. Distribution of functional domains is based on Ensembl (<http://asia.ensembl.org/index.html>). NRs = nuclear hormone receptors; ZNFs = zinc finger proteins; RAR = retinoic acid receptor; NTD = N-terminal domain; DBD = DNA-binding domain; HR = hinge region; LBD = ligand-binding domain; KLF = Krüppel-like factor; RXR = retinoid X receptor; CTCF = CCCTC-binding protein; GR = glucocorticoid receptor; PLZF = promyelocytic leukemia zinc finger protein; BTB/POZ = Broad-Complex, Tramtrack, and Bric-a-brac/poxvirus and zinc finger; NOR = neuron-derived orphan receptor; KRAB = Krüppel-associated box; SF-1 = steroidogenic factor -1; GCNF = germ cell nuclear factor; DAX-1 = dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1.

NRs, particularly SRs, are among the molecules most well examined phylogenetically.^{56,62} Some NRs are present even in simple metazoans with multiple cellular components, whereas substantial numbers of NRs have been reported for metazoans like *Caenorhabditis elegans*.⁵⁶ The ancestral SR first appeared in primitive vertebrate lamprey, and all SRs can be found in ray-finned fish.⁶² Therefore, NRs are observed from the early evolutionary period particularly before and around the time of vertebrate emergence and, thus, their functionality is relatively conserved.

NRs have a major impact on diverse regulatory activities in humans (Figure 2 and Table 1). For example, a substantial number of NRs (TR α and β , timeless receptor [TLX or TLL], COUP-TFs, RARs, RAR-related orphan receptor [RORs], V-erbA-related protein 2 [EAR2], NUR77, nuclear receptor related 1 [NURR1], neuron-derived orphan receptor 1 [NOR1], and germ cell nuclear factor [GCNF]) play critical roles in the embryonic development, especially in the development/differentiation of the central nervous system (CNS).⁶³⁻⁶⁷ Another biological actions of NRs (such as

by TRs, COUP-TFs, PPARs, Rev-erb β , ROR α , LXRs, farnesoid X receptor [FXR], VDR, HNF4s, GR, MR, and small heterodimer partner [SHP]) lie in the regulation of energy, intermediary and electrolyte metabolism, such as for glucose, cholesterol, fatty acids, sodium/potassium, and calcium, consistent with the fact that many of the NRs employ metabolites of these biological pathways as their ligands.⁶⁸⁻⁷⁰ Reproduction and development/maintenance of reproductive organs are also important biological activities regulated by NRs, such as ERs, estrogen-related receptors (ERRs), PR, AR, NUR77, SF-1, and DAX-1.^{71,72} Furthermore, most of the NRs, including PPARs, RORs, LXRs, VDR, ERs, GR, PR, NUR77, NURR, NOR1, and RORs, have immune regulatory activities, whereas some others play roles in hematopoiesis.^{73,74} Rev-erbs and RORs are important components of the circadian CLOCK system that synchronizes the body's activities to diurnal day-night changes caused by rotation of the earth.⁷⁵ PXR and CAR play a central role in the xenobiotic metabolism by binding toxic metabolites/exogenous compounds as their ligands and by regulating the expression of

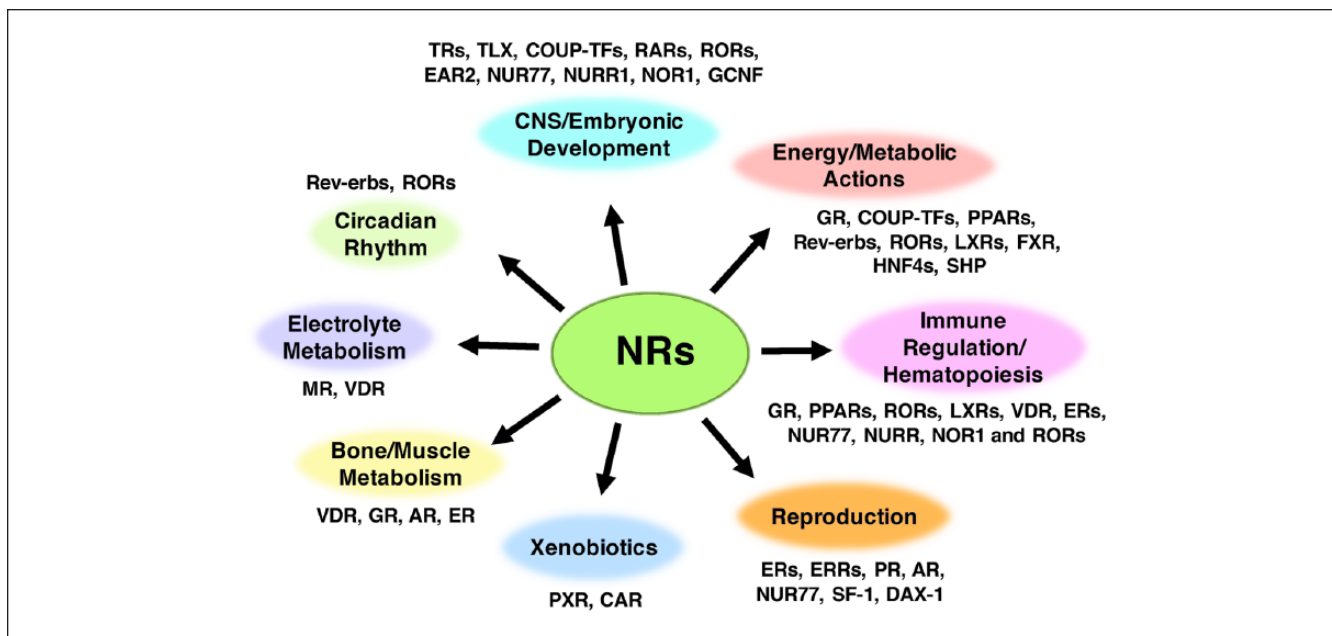


Figure 2. NRs have diverse regulatory actions on human activities.

Note. NRs virtually influence every aspect of human activities, including embryonic development, energy metabolism, immunity, reproduction, electrolyte/bone/skeletal muscle maintenance, circadian rhythm, and xenobiotics through their various members. Examples of the NRs that have regulatory roles in the indicated biological activities are shown. NRs = nuclear hormone receptors; TRs = thyroid hormone receptors; TLX = timeless receptor; COUP-TFs = ovalbumin upstream promoter-transcription factors; RARs = retinoic acid receptors; RORs = RAR-related orphan receptors; EAR2 = V-erbA-related protein 2; NURR1 = nuclear receptor related 1; NOR 1 = neuron-derived orphan receptor 1; GCNF = germ cell nuclear factor; CNS = central nervous system; GR = glucocorticoid receptor; PPAR = peroxisome proliferator-activated receptor; LXR = liver X receptor; FXR = farnesoid x receptor; HNF4 = hepatocyte nuclear factors 4; NUR77 = nerve growth factor 1B; SHP = small heterodimer partner; MR = mineralocorticoid receptor; VDR = vitamin D receptor; ER = estrogen receptor; ERR = estrogen-related receptors; AR = androgen receptor; PXR = pregnane X receptor; CAR = constitutive androstane receptor; PR = progesterone receptor; SF-1 = steroidogenic factor-1; DAX-1 = dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1.

their metabolizing enzymes including cytochrome P450-related reductases.²⁹

C2H2-Type ZNFs

C2H2-type ZNFs are another major group of transcription factors. Zinc fingers are small peptide domains with a secondary structure stabilized by a zinc ion bound to the cysteine and/or histidine residues of the finger.⁷⁶ Different combinations of these 2 residues lead to the development of different classes of ZFs, such as C2H2, C2HC, C2C2 (C4: eg, NRs), and C2C2C2C2 fingers. Among the combinations of ZFs, the C2H2-type ZF motif is known as the “classic ZF.”⁷⁶ In humans, more than 700 proteins have this motif, constituting the largest class of putative human transcription factors.⁷⁷ The C2H2-type ZF comprises up to 30 amino acids in the consensus sequence CX₂₋₄CX₁₂HX₂₋₈H (X refers to any amino acid), which forms 1 α -helix and 2 β -sheets, respectively, in the C- and N-terminal portion.⁷⁸⁻⁸⁰ These secondary structures of the peptide fold into a stable assembly through hydrophobic interactions and enclosure of a zinc ion by 2 conserved cysteine and 2 conserved histidine residues.^{81,82} Multiple ZFs are usually present in tandem and are connected by linkers with conserved amino acid sequences.⁸³ C2H2-type ZNFs function primarily as DNA-binding proteins by forming various

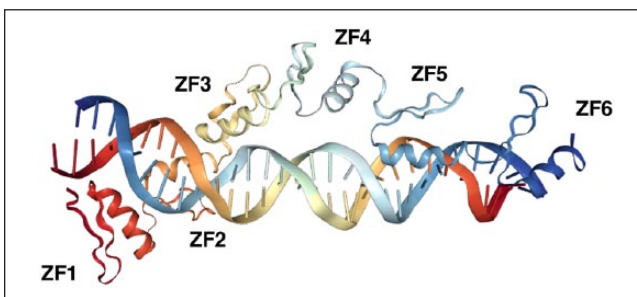


Figure 3. Binding of C2H2-type ZNF to DNA.

Note. Crystallographic structure of the xenopus transcription factor IIIA (TFIIIA) ZFs and the target DNA (5S ribosomal RNA gene internal control region) (PDB: 1SF6) is shown.⁸⁶ TFIIIA has 9 C2H2-type ZFs and its N-terminally located 6 ZFs (ZF1 to ZF6) are demonstrated. ZF1 to ZF3 are positioned relatively tightly to the major groove of DNA, whereas ZF4 to ZF6 face only one side of the DNA double helix and form a loose extended association to DNA in which only ZF5 makes a direct contact. Thus, ZFs of TFIIIA differentially contribute to the TFIIIA-DNA interaction by wrapping around its target sequences. ZNF = zinc finger protein; ZF = zinc finger.

modes of contacts to target DNA double helices with their ZFs, as shown in the interaction of the transcription factor IIIA (TFIIIA) with DNA (Figure 3). In addition to the primary role as DNA-binding factors, some C2H2-type ZNFs

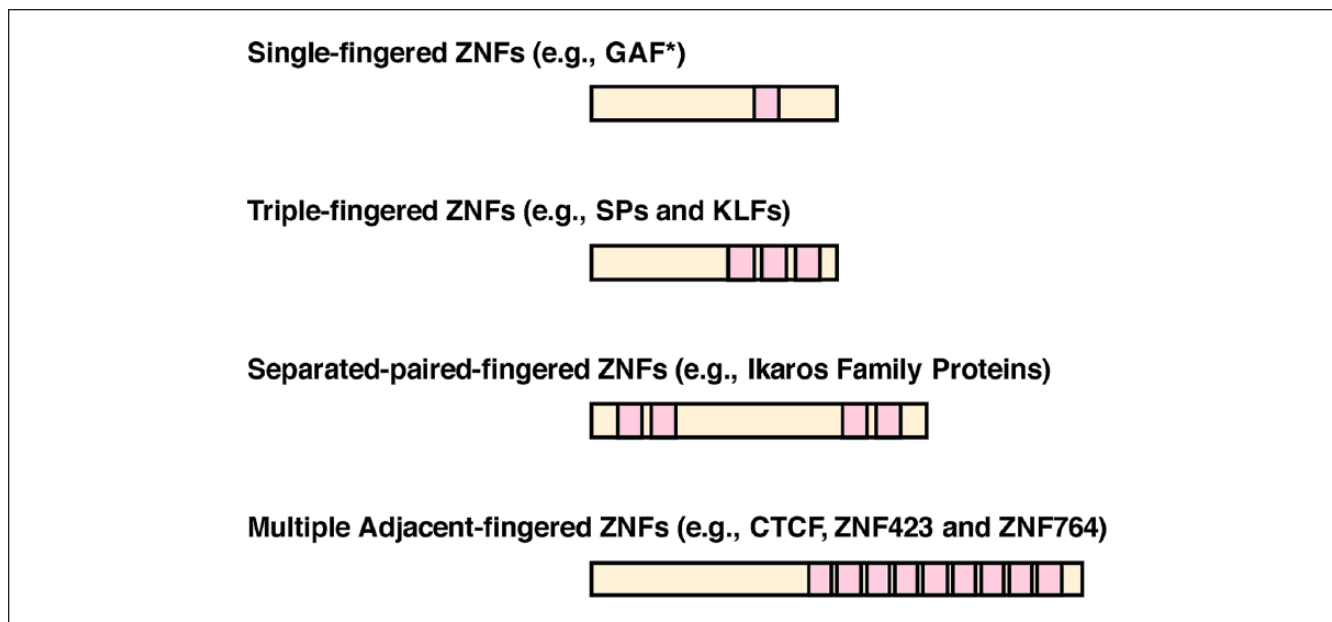


Figure 4. Subtypes of C2H2-type ZNFs based on the number and arrangement of their ZFs.

Note. C2H2-type ZNFs can be categorized into 4 subtypes (single-fingered, triple-fingered, separated-paired-fingered, and multiple adjacent-fingered ZNFs) based on the number and arrangement of their ZFs. Schematic protein organization of these C2H2-type ZNF subtypes are shown. C2H2-type ZFs are shown in pink. *: GAF (GAGA factor) is a drosophila protein.⁸⁹ ZNF = zinc finger protein; ZFs = zinc fingers; SPs = specificity proteins; KLFs = Krüppel-like factors; CTCF = CCCTC-binding protein.

use their ZFs for interacting with other proteins or double-stranded RNAs, which may be important for their communication with other proteins/RNAs also attracted to the multimolecule transcriptional complex formed on DNA.⁸³⁻⁸⁵

Based on the number, localization, and arrangement of ZFs within a molecule, C2H2-type ZNFs can be divided into 4 classes: (1) single-fingered, (2) triple-fingered, (3) separated-paired-fingered, and (4) multiple adjacent-fingered, and this classification may explain to some extent the functions of the proteins in the respective class⁸⁷ (Figure 4). C2H2-ZNFs that interact with NRs are found among triple-fingered or multiple adjacent-fingered ZNFs. Besides ZFs, C2H2-type ZNFs harbor additional structural modules, such as the Broad-Complex, Tramtrack, and Bric-a-brac (BTB)/poxvirus and zinc finger (POZ), Krüppel-associated box (KRAB), and SCAN domains.⁸ These domains are usually located in the N-terminal portion and function as platforms for protein-protein interactions, whereas ZFs are positioned in the C-terminal area^{8,88} (Figure 4). The BTB/POZ and KRAB domains have transcriptional regulatory activity (mostly repressive), while the SCAN domain does not.⁸ Among human C2H2-type ZNFs, about 7% have a BTB/POZ domain (BTB/POZ-ZNFs), 43% harbor a KRAB domain (KRAB-ZNFs), and 7% contain a SCAN domain (SCAN-ZNFs).⁷⁷ Sixty-seven percent of the human C2H2-type ZNFs have only ZFs without any of these domains (thus, they are “poly-ZNFs”).⁷⁷ Some C2H2-type ZNFs contain multiple of the same or of different domains, whereas the SCAN domain appears as a sole domain in one molecule.⁸⁸

Evolution of C2H2-Type ZNFs

The C2H2-type ZNFs are present throughout the organisms from yeasts to humans. They have expanded their member proteins following evolution, becoming the largest transcription factor family in humans, in contrast to the C4-type ZNFs (mostly NRs), the numbers of which are similar in vertebrates but show a characteristic increase in *Nematodes*^{77,90} (Table 2). The number of C2H2-type ZNFs particularly increases in vertebrates, eg, becoming almost double in humans compared with Takifugu fish or to Zebrafish⁷⁷ (Table 2). BTB/POZ-ZNFs are seen from yeasts to humans, while KRAB-ZNFs and SCAN-ZNFs appear in vertebrates and mammals, respectively.⁷⁷ The number of KRAB-ZNFs and SCAN-ZNFs increase significantly in higher organisms with the former demonstrating this tendency more obviously⁷⁷ (Table 3). Thus, the addition of these domains to C2H2-type ZNFs, particularly the KRAB domain, appears to be required for the functions specific to higher organisms, such as the complex transcriptional regulation of genes that enables development, differentiation, and/or function of their complicated organs and tissues. As poly-ZNFs and BTB/POZ-ZNFs are observed early in evolution, they may support more fundamental and/or conserved functions of the organisms, such as general transcriptional regulation and early embryonic development shared among different organisms. In contrast, KRAB-ZNFs and SCAN-ZNFs are likely to play roles in the activities specific to higher organisms. For example, the characteristic expression of the KRAB-ZNFs in human brain

Table 2. Number of the C2H2-Type and C4-Type Genes in the Genome of Various Species.

Organism	Total number of genes	Number of C2H2-type genes	Number of C4-type genes
Human	23 299	712 (3.0%)	48 (0.21%)
Mouse	24 948	573 (2.3%)	47 (0.19%)
Rat	21 278	466 (2.2%)	47 (0.22%)
Zebrafish	20 062	344 (1.7%)	53 (0.26%)
Drosophila	13 525	298 (2.2%)	21 (0.16%)
Anopheles	14 653	296 (2.0%)	20 (0.14%)
<i>Caenorhabditis elegans</i>	19 564	173 (0.9%)	270 (1.3%)
<i>Caenorhabditis briggsae</i>	11 884	115 (0.9%)	167 (1.4%)

Note. Modified from Klug and obtained permission for Table use from the Journal.

Table 3. Number of C2H2-Type ZNFs Through Evolution.

Species	C2H2-type ZNF	BTB/POZ-ZNF	KRAB-ZNF	SCAN-ZNF
Human	712	50	304	53
Mouse	583	44	219	38
Cow	482	41	106	28
Dog	329	41	61	17
Chicken	224	26	33	0
Xenopus	347	30	21	0
Zebrafish	405	46	0	0
Takifugu fish	364	41	0	0
Drosophila	251	11	0	0
Anopheles	263	9	0	0
Ciona	103	7	0	0
<i>Caenorhabditis elegans</i>	108	1	0	0

Note. Modified from Emerson and Thomas and obtained permission for Table use from the Journal. ZNF = zinc finger protein; BTB/POZ = Broad-Complex, Tramtrack, and Bric-a-brac/poxvirus and zinc finger; KRAB = Krüppel-associated box.

appears to be required for the transcriptional network that drives human-specific brain functions, such as enhanced cognitive activities and significantly larger brain size, compared with other primates like chimpanzees.⁹¹

Regulation of NR Activity by C2H2-Type ZNFs

NRs regulate and influence numerous critical activities of organisms as we explained above,⁹ and C2H2-type ZNFs are among their important partners. Based on the previous observation for other proteins,⁹² it appears that C2H2-type ZNFs appeared from lower organisms, such as poly-ZNFs and BTB/POZ-ZNFs, may regulate the actions of NRs, which are fundamental and/or commonly observed in many organisms. On the contrary, the C2H2-type ZNFs found only in higher organisms like KRAB-ZNFs seem to modulate the actions of NRs involved in complex regulatory mechanisms or in adjusting the NR actions for species-specific needs. Although overall actions of C2H2-type ZNFs on NRs are still largely unknown at this moment, the above-indicated tendency can be seen in some of these molecules^{91,93} (Figure 5). Below, we

review the functional interactions between C2H2-type ZNFs and NRs (listed in Table 4), focusing on their physiologic and pathologic importance. NRs functionally and/or physically interact with poly-ZNFs, BTB/POZ-ZNFs, and KRAB-ZNFs, but none of them have been found to cooperate with SCAN-ZNFs to date.

Poly-ZNFs

Poly-ZNFs that do not contain BTB/POZ, KRAB, or SCAN domain are the oldest members of the C2H2-type ZNF family.⁷⁷ Most of these proteins are evolutionarily conserved.^{98,132,133} Many of the triple-fingered and some of the multiple adjacent-fingered poly-ZNFs function as classic transcription factors, while others act as transcriptional modulators incorporated in the transcriptional regulatory complex formed on other DNA-binding factors. Representatives of the triple-fingered poly-ZNFs interacting with NRs are the specificity protein (SP)/Krüppel-like factor (KLF) family transcription factors, while those of the multiple adjacent-fingered poly-ZNFs also influencing the NR activities, include the Yin-Yang 1 (YY1) and Wilms tumor 1 (WT1) transcription

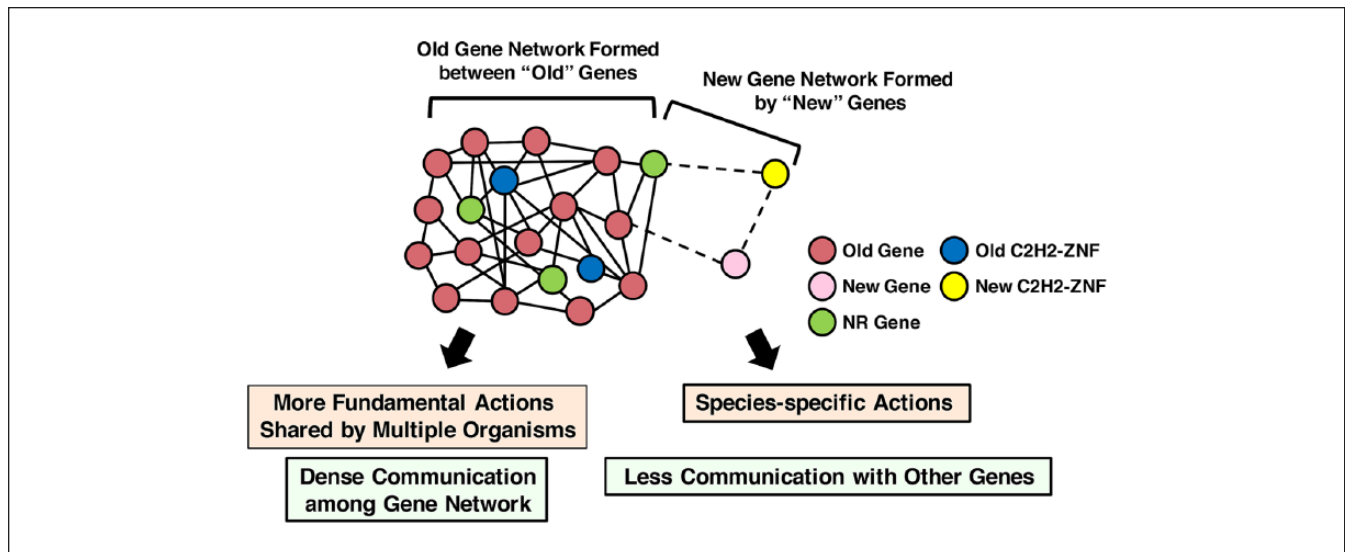


Figure 5. Gene network formed between NRs and evolutionarily old or new C2H2-type ZNFs.

Note. NR genes are considered as evolutionarily old genes, as most of the family genes appear before and around the time of vertebrate emergence.⁵⁶ Thus, NRs are well incorporated in the gene network formed between other old genes including those encoding C2H2-type ZNFs and support fundamental functions shared by several organisms.⁹⁴ On the contrary, newly appeared genes found only in higher organisms, such as KRAB-ZNFs, have less gene communication, but support the NR-related functions important and specific to respective species (eg, brain function in humans). Solid and dotted lines indicate well-established and newly developing gene networks, respectively. NRs = nuclear hormone receptors; ZNFs = zinc finger proteins.

Table 4. C2H2-Type ZNFs That Interact With NRs.

Name	Synonym	Zinc fingers		Interacting NRs	Domain		References
		Type	Number		BTB/POZ	KRAB	
SPI		Triple-fingered	3	GR, MR, AR, PPAR γ			Kolla and Litwack, ⁹⁵ Kolla et al, ⁹⁶ Suehiro et al ⁹⁷
KLFs		Triple-fingered	3	ER, PR, GR, SHP, PPAR γ			McConnell and Yang, ⁹⁸ Oishi et al, ⁹⁹ Simmen et al ¹⁰⁰
YY1		Multiple adjacent-fingered	4	PXR, VDR, GR			Bookout et al, ⁹ Deng et al, ¹⁰¹ Nem et al, ¹⁰² Raval-Pandya et al ¹⁰³
WT1		Multiple adjacent-fingered	4	SF-1, DAX-1, AR, RAR α , VDR, PPAR β			Goodyer et al, ¹⁰⁴ Kim et al, ¹⁰⁵ Nachtigal et al, ¹⁰⁶ Reizner et al, ¹⁰⁷ Zaia et al ¹⁰⁸
Zip67	ZNF653	Multiple adjacent-fingered	5	SF-1, LXR α , NUR77, GR, ER			Borud et al ¹⁰⁹
Zac1	LOT1, Zac	Multiple adjacent-fingered	7	TR β , AR, ER α , PPAR γ			Barz et al, ¹¹⁰ Huang and Stallcup ¹¹¹
ZNF217	ZABC1	Multiple adjacent-fingered	7	ER α			Frietze et al ⁸⁵
ZNF536		Multiple adjacent-fingered	9	RAR α			Qin et al ¹¹²
CTCF		Multiple adjacent-fingered	11	NRs, ER α , TR			Carroll et al, ¹¹³ Kim et al, ¹¹⁴ Ross-Innes et al, ¹¹⁵ Awad et al, ¹¹⁶ Lutz et al ¹¹⁷
ZNF366		Multiple adjacent-fingered	11	ER α			Lopez-Garcia ¹¹⁸
ZNF423	Roaz, OAZ, Zfp104	Multiple adjacent-fingered	30	RAR α , RXR α , PPAR γ			Gupta et al, ¹¹⁹ Huang et al, ¹²⁰ Ingle et al ¹²¹
Kaiso	ZNF348, ZBTB33	Triple-fingered	3	NRs associating with NCoR	+		Klose and Bird ¹²²
PLZF	ZBTB16	Multiple adjacent-fingered	9	RARs	+		Martin et al, ¹²³ Ward et al, ¹²⁴ Wasim et al ¹²⁵

(continued)

Table 4. (continued)

Name	Synonym	Zinc fingers		Interacting NRs	Domain		References
		Type	Number		BTB/POZ	KRAB	
ZNF746	PARIS	Multiple adjacent-fingered	4	PPARs, NRs associating with PCG-1 α	+		Shin et al ¹²⁶
ZNF282	HUB1	Multiple adjacent-fingered	5	ER α , GR, THR, AR	+		Wu et al, ¹⁸ Yu et al ¹²⁷
ZNF764		Multiple adjacent-fingered	7	AR, GR, MR, TRs	+		Kino et al ¹²⁸
ZNF398	ZER6	Multiple adjacent-fingered	9	ER α	+		Conroy et al ¹³⁰
ZNF461	GIOT-1	Multiple adjacent-fingered	12	SF-1, NUR77	+		Song et al ¹³¹

Note. ZNF = zinc finger protein; NR = nuclear hormone receptor; BTB/POZ = Broad-Complex, Tramtrack, and Bric-a-brac/poxvirus and zinc finger; KRAB = Krüppel-associated box; SP = specificity protein; GR = glucocorticoid receptor; MR = mineralocorticoid receptor; AR = androgen receptor; PPAR = peroxisome proliferator-activated receptor; KLF = Krüppel-like factor; ER = estrogen receptor; PR = progesterone receptor; SHP = small heterodimer partner; YY 1 = Yin-Yang 1; PXR = pregnane X receptor; VDR = vitamin D receptor; WT1 = Wilms tumor 1; SF-1 = steroidogenic factor -1; DAX-1 = dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1; LOT1 = lost on transformation 1; ZABC = zinc finger amplified in breast cancer; RAR = retinoic acid receptor; LXR = liver X receptor; TR = thyroid hormone receptor; CTCF = CCCTC-binding protein; ZBTB = zinc finger and BTB; NCoR = nuclear receptor corepressor; PLZF = promyelocytic leukemia zinc finger protein; PARIS = parkin-interacting substrate; PCG-1 α = PPAR γ coactivator-1 α ; HUB = HTLV-1 USRE-binding protein; ZER = zinc finger-estrogen receptor interaction; GIOT = gonadotropin-inducible ovarian transcription factor.

factors, and the CCCTC-binding protein (CTCF) transcriptional regulator.

SP/KLF Transcription Factors

This family consists of 2 subgroups, SP1- and KLF-related proteins.¹³³ The former group is composed of 9 members (SP1 to SP9) in humans, while the latter has 17 (KLF1 to KLF17).⁹⁸ Their orthologs are present across species from drosophila to humans.⁹⁸ These ZNFs have 3 C2H2-type ZFs in their C-terminal portion⁹⁸ (Figure 1). SP proteins contain the Bottomhead box (BTD) just N-terminally to their ZFs, whereas KLFs do not have this motif.^{133,134} Both SP- and KLF-related proteins bind the DNA sequences called GC and GR boxes (5'-GGGGCGGGG-3' and 5'-GGTGTGGGG-3', respectively) frequently found in CpG islands associated with the promoter of downstream coding sequences.¹³³ SP1, a representative of the SP family proteins, is essential for the transcription of TATA-less genes, facilitating the formation of the transcription initiation complex on their promoters through interaction with TFIID, which is a multiprotein complex including the TATA-binding protein and plays a central role in the RNA polymerase II-mediated transcription.¹³⁵ Due to its interaction with TFIID and binding to CpG islands, SP1 is required for the transcription of a substantial number of protein-coding genes, obviously functioning as a component of the general transcriptional complex. In contrast, KLF family proteins function as "regular" transcription factors, by binding to the response elements located in the promoter or enhancer regions and by stimulating the transcription of downstream protein-coding genes.⁹⁸ Knockout mice for the SP/KLF family member genes generally demonstrate early embryonic/perinatal death or severe functional defects in

various organs.⁹⁸ Thus, these poly-ZNFs play important roles in the general transcriptional regulation and/or in the organ development/differentiation observed in the early embryonic phase shared by many organisms. Characteristically, SP/KLF transcription factors have 3 major modes of action on NRs¹³⁶ (Figure 6). First, SPs/KLFs and NRs mutually influence each other's transcriptional activity through either direct or indirect interaction at their regulating genes. Second, SPs/KLFs modulate the expression of NRs, and augment/repress the transcriptional activity of NRs. Third, NRs alter the expression of certain SP/KLF family proteins, employing them as mediators of NR activities.

SP1 is the most well-studied member of the SP subfamily. SP1 can modulate the transcriptional activity of ER α / β , PR, AR, PPAR γ , COUP-TFs, and SF-1, through either direct or indirect interaction with these receptors.¹³⁷ For example, SP1 regulates estrogen-induced cell growth by influencing the transcriptional activity of ERs on the genes encoding c-fos, cyclin D1, B-cell lymphoma 2 (bcl2) and E2F transcription factor 1 (E2F1) and the hormonal activation of the mitogen-activated kinase pathway.¹³⁷ SP1 is required for AR to repress gonadotropin-stimulated luteinizing hormone receptor expression.¹³⁸ SP1 enhances AR-induced expression of the p21 cell cycle component protein.¹³⁹ Furthermore, SP1 is required for PPAR γ -mediated repression of the thromboxan gene possibly by tethering this receptor to the promoter site where SP1 binds.¹⁴⁰ Finally, SP1 facilitates SF-1-mediated expression of the steroidogenic acute regulatory protein (StAR), a key molecule for cholesterol trafficking in mitochondria and thus for steroidogenesis.¹⁴¹ SP1 and some of these NRs seem to interact physically through the former's C-terminal domain and latter's DBD. In addition, SP1 appears to influence the expression of a substantial number

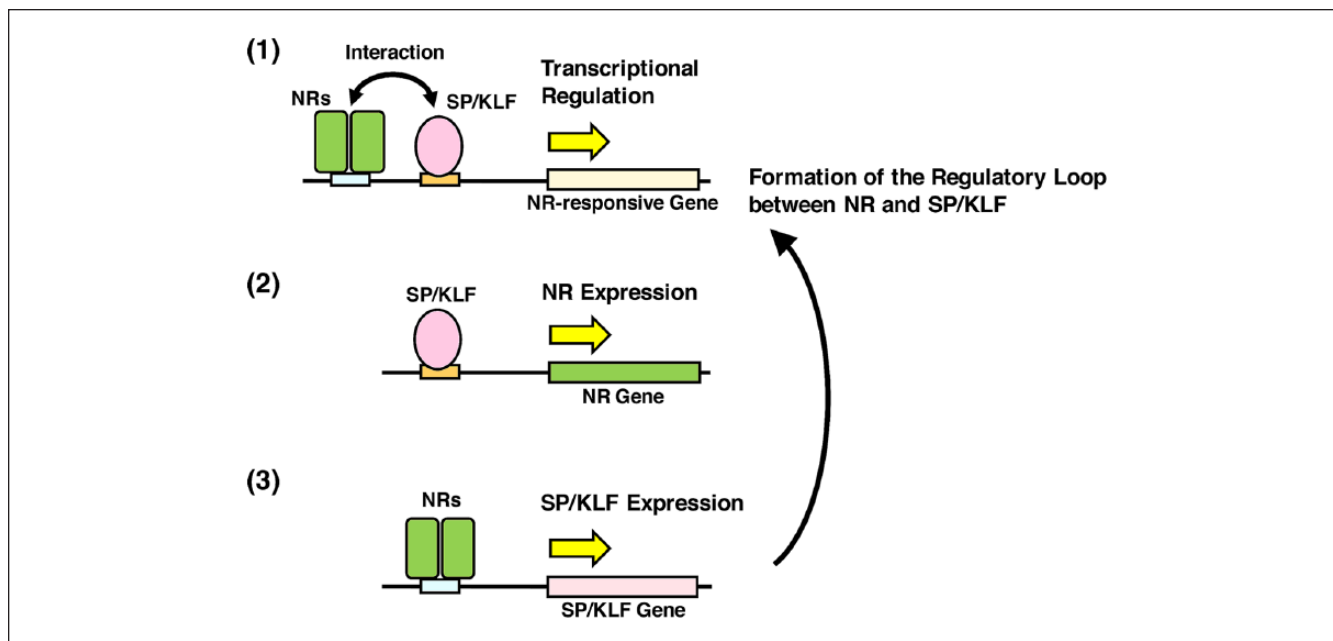


Figure 6. Regulatory mechanisms of the SP/KLF family transcription factors on NRs.

Note. SP/KLF transcription factors have 3 major modes of actions on NRs: (1) SPs/KLFs influence NR-induced transcriptional activity through either direct or indirect interaction on their responsive genes. SPs/KLFs and NRs may also bind DNA directly or indirectly. (2) SPs/KLFs alter the expression of NRs, and subsequently modulate their transcriptional activity. (3) NRs alter the expression of certain SP/KLF family proteins, employing as mediators of their activities. Some SP/KLFs, the expression of which is regulated by particular NRs, influence the transcriptional activity of such NRs through the mechanism (1), forming a feed-forward transcriptional regulatory loop between them. SP = specificity protein; KLF = Krüppel-like factor; NRs = nuclear hormone receptors.

of NRs through its ubiquitous DNA-binding sites found in the promoter region of the NR genes.⁹⁷ This indicates that SP1 regulates the activity of these NRs by changing their expression levels.

KLF family proteins are important transcription factors involved in cell proliferation, differentiation, and induction of apoptosis by regulating the expression of numerous effector molecules, including cyclin D1, cyclin B1, and c-Myc, and are essential for cardiac and vascular development and hematopoiesis in the embryonic phase.⁹⁸ They are also required for adipogenesis, lymphocyte and monocyte/macrophage differentiation, and maintenance of intestinal epithelial cells after birth.⁹⁸ KLF proteins influence the transcriptional activity of key NRs involved in these biological pathways, such as PPAR γ (KLF5, 2 and 7) for adipogenesis and ERs (KLF9) for breast tissue differentiation and breast cancer proliferation.^{98,99} KLF4, KLF9, KLF11, and KLF13 regulate hormone-dependent proliferation and differentiation of uterine endometrium and myometrium by influencing directly or indirectly the transcriptional activity of ERs and PR on the E2F transcription factors and the Wnt/ β -catenin signaling pathway.^{98,99} KLF9 and KLF13, respectively, modulate ER- and PR-mediated signaling pathway by stimulating the expression of these receptors.¹⁰⁰ KLF11 cooperates with GR for the expression of the monoamine oxidase-A gene, the protein product of which degrades monoamine-related neurotransmitters important for the actions of CNS.¹⁴² KLF4 also

cooperates with GR for the expression of genes involved in the formation of the skin barrier function in prenatal fetus.^{98,143} The orphan receptor SHP inhibits the transcriptional activity of KLF6 on the matrix metalloproteinase-9 gene to regulate endothelial cell motility.¹⁴⁴

In addition to acting as regulators of the NRs' transcriptional activity, KLFs function as their downstream mediators, being their encoding genes responsive to NRs. For example, the KLF9 gene promoter contains glucocorticoid response elements (GREs) and induction of KLF9 by GR is important for the survival of the newly differentiated hippocampal granule cells originating from adult neural stem cells (these neuronal cells play important roles in memory consolidation) as well as for the regulation of the inflammatory response in macrophages.^{136,145,146} Glucocorticoids/GR are known to have strong effects on these activities.^{147,148} Induction of KLF15 by glucocorticoids is important for the expression of enzymes that catalyze branched-chain amino acids and for the proteasomal degradation of cellular proteins, which ultimately contribute to the development of muscle wasting observed with chronic glucocorticoid excess.¹³⁶ In colon cancer, PPAR γ stimulates the expression of KLF10, which underlies the anti-cancer effect of this receptor.¹³⁶ As many of the above-indicated KLFs, the expression of which is regulated by NRs, also function as regulators for the transcriptional activity of corresponding NRs, they form a feed-forward transcriptional regulatory loop in the signaling pathways functional for NRs (Figure 6).

YY1 and WT1

YY1 is an ubiquitously expressed transcription factor containing 4 C2H2-type ZFs in its C-terminal portion.¹⁴⁹ As the name “Yin-Yang” indicates, YY1 regulates the transcription of its responsive genes positively or negatively.¹⁴⁹ YY1 influences cell proliferation and differentiation, and is essential for the embryonic development.¹⁴⁹ In addition, YY1 contributes to cancer biology. Its aberrant expression is found in various cancers, and it modulates the expression of genes involved in cancer development and progression.¹⁴⁹ YY1 physically interacts with AR and regulates the latter’s transcriptional activity on the prostate-specific antigen gene, which is an indicator of prostate cancer progression.¹⁰¹ YY1 cooperates with PXR for the regulation of the cytochrome P450 enzymes involved in xenobiotic metabolism, such as CYP3A4 and CYP3A5.¹⁰² YY1 represses the transcriptional activity of VDR on vitamin D-responsive genes in osteoblastic cells.¹⁴⁹ In renal cells, it represses VDR-mediated transcription of the 24(OH) gene whose encoding enzyme inactivates vitamin D (25-dihydroxyvitamin D₃).¹⁰³ YY1, GR and the signal transducer and activator of transcription 5 (STAT5) cooperate with each other in stimulating the transcription of the growth hormone gene by forming a transcription factor complex on its promoter.¹⁵¹

WT1 is also a transcription factor containing 4 C2H2-type ZFs in its C-terminal portion. WT1 regulates cell proliferation and differentiation, and is essential for controlling the transition between the mesenchymal and epithelial state of cells.¹⁵² It plays critical roles in the development of urogenital organs, including kidneys, gonadal organs, and external genitalia.¹⁵³ WT1 is also involved in hematopoiesis, blood vessel formation, and development of various benign/malignant tumors, including Wilms tumor, acute myeloid leukemia, uterine sarcoma, and breast cancer.^{153,154} WT1 facilitates SF-1-induced transcriptional activity on the genes associated with sexual differentiation, whereas DAX-1 opposes to this WT1/SF-1 cooperation.¹⁰⁶ Furthermore, WT1 contributes to the sexual differentiation by regulating the expression of DAX-1.¹⁰⁵ WT1 interacts with ER α and suppresses estrogen-stimulated expression of the insulin-like growth factor-1 receptor, antagonizing to the estrogen-dependent growth of breast cancer cells.¹⁰⁷ WT1 also represses the transcriptional activity of AR, functioning as a negative regulator for prostate cancer development and progression.¹⁰⁸ In renal cells, WT1 stimulates the expression of VDR and augments vitamin D-induced modulation of their cell fate.^{155,156} WT1 suppresses RAR α expression, while PPAR β inhibits WT1 expression and suppresses melanoma cell proliferation.^{104,157}

CCCTC-Binding Protein

CTCF consists of 11 C2H2-type ZFs (Figure 1) and acts as an architectural protein for maintaining/regulating 3-dimensional chromatin interaction by cooperating with the cohesin

protein complex and other accessory factors, including TFIIC, ZNF143, PR domain zinc finger protein 5 (PRDM5), and chromodomain helicase DNA-binding protein 8 (CHD8).⁹³ CTCF is evolutionarily conserved and widely present in bilaterian phyla, but absent in other eukaryotes.¹³² CTCF forms chromatin loops through which it organizes long-range DNA interactions between 2 and more genomic areas.⁹³ Although it is called as “CCCTC-binding” factor, it can bind sequences with extensive variations by using selected sets of its ZFs.⁹³ The human genome contains ~15 000 CTCF-binding sites and some of them are distributed in insulators or borders of the topologically associated domains (TADs), but substantial CTCF-binding sites are found inside TADs and intragenomic regions.^{93,158} This distribution pattern of the CTCF-binding sites indicates that CTCF acts not only as an organizer of TADs by blocking the action of the regulatory gene sequences/propagation of specific histone marks but also as a regulator of the enhancer/promoter switch (Figure 7). Thus, CTCF regulates the transcriptional activity of the associated protein-coding genes positively or negatively by changing their interaction to specific enhancers/promoters, ultimately contributing to the tissue/phase-specific expression of these genes. In addition to acting as an organizer for chromatin interactions, CTCF plays roles in the recombination of immunoglobulin genes and transcriptional pausing and alternative splicing.¹⁵⁹ As CTCF acts as a general architectural protein, it virtually influences the transcriptional activity of all NRs. The effect of CTCF was examined in details for the transcriptional regulation by ER α .^{113,114,160} In a genome-wide analysis, CTCF-binding sites are enriched in ER α -binding regions, suggesting that CTCF acts as a cofactor for ER α -mediated transcription by facilitating the association of DNA-bound ER α and the promoter regions of ER α -regulating genes in a 3-dimensional fashion.¹⁶¹ Furthermore, CTCF-binding sites are more likely to overlap with cell line-specific ER α -binding sites, indicating that CTCF determines tissue-specific actions of estrogens by organizing enhancer/promoter interaction of the ER α -regulating genes through formation of the chromatin loops.¹¹⁵ CTCF also cooperates with TR. Some enhancers/promoters responding to TR through their TR response elements (TREs) also have CTCF-binding sites.¹¹⁶ Indeed, about 18% of CTCF-binding sites harbor TREs.¹⁶² CTCF- and TR-binding sites sometimes form composite elements having their binding sites closely, and CTCF-mediated enhancer-blocking activity is dependent on the presence of the TR bound on these composite elements,¹⁶² indicating that TR modulates the genome regulatory activity of CTCF.

Other Poly-ZNFs

Zip67, Zac1, ZNF217, and ZNF536 are multiple adjacent-fingered poly-ZNFs. Their biological/physiological actions are not well elucidated, but they act as cofactors for the transcriptional activity of some NRs. Similar to other multiple

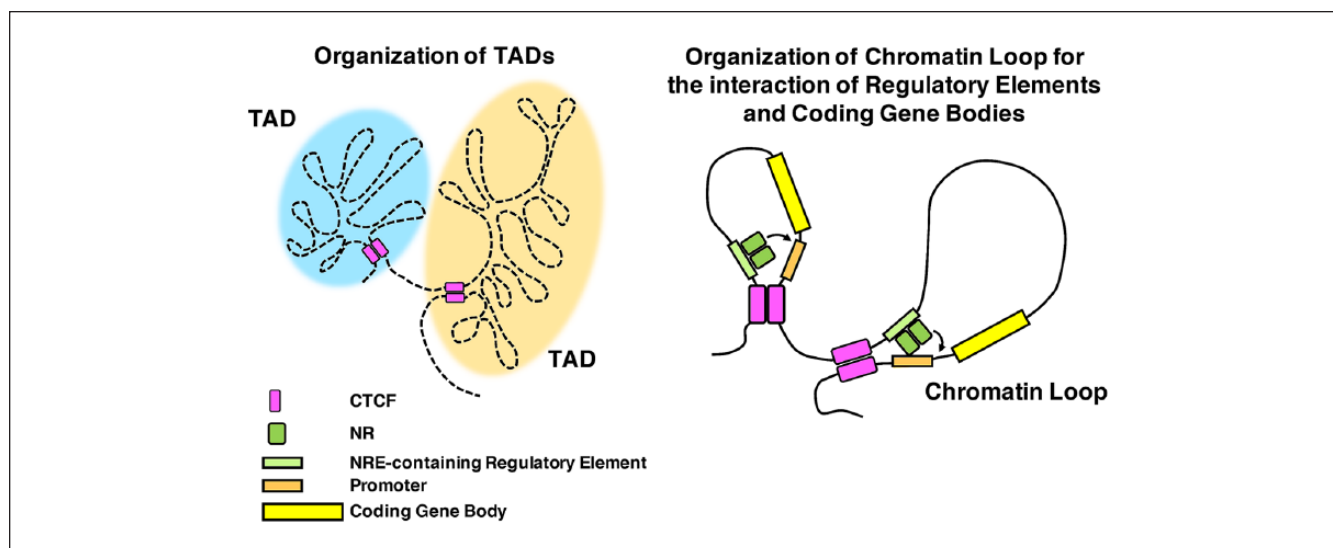


Figure 7. Organization of TADs and chromatin looping by CTCF for differential expression of NR-responsive genes.

Note. CTCF organizes 3-dimensional chromatin interaction for the formation of TADs and chromatin looping, in cooperating with the cohesin protein complex and other component proteins. Chromatin loop-forming activity of CTCF is essential for differential use of enhancers/promoters by NR-responsive genes, and underlies NR-associated organ/tissue-specific functions. TADs = topologically associated domains; CTCF = CCCTC-binding protein; NR = nuclear hormone receptor; NRE = NR-response element.

adjacent-fingered poly-ZNFs, such as ZNF592 and ZNF687, these ZNFs are likely to be incorporated in the transcriptional complex formed on NRs and modulate their transcriptional activity through communication with other regulatory molecules inside the complex.¹¹

Zip67 or ZNF653 contains 5 ZFs and was identified as a regulator of SF-1-induced transcriptional activity.¹⁰⁹ Zip67 directly interacts with SF-1 LBD and represses SF-1-induced transcriptional activity.¹⁰⁹ Zip67 also represses the transcriptional activity of LXR α , NUR77, GR, and ER, suggesting that Zip67 functions as a general cofactor for some NRs.¹⁰⁹

Zac1 or PLAG1 (PLAG-like zinc finger 1) has 7 ZFs and was first identified as a putative transcriptional activator involved in the regulation of apoptosis and cell cycle.^{163,164} Zac1 physically interacts with the HAT coactivators, p300 and p300/CBP-associated factor (p/CAF) through its ZFs, and regulates the latter's HAT activity.^{165,166} Zac1 can coactivate or corepress the hormone-dependent transcriptional activity of AR, ER α , and TR β 1.¹¹¹ Zac1 also stimulates PPAR γ expression by binding to the proximal portion of the *PPAR* γ promoter, suggesting that Zac1 exerts its anti-proliferative effects on various cancer cells through modulating the expression of this receptor.¹¹⁰

ZNF217 possesses 8 ZFs. ZNF217 acts as a coactivator of ER α -induced transcriptional activity in various cell lines.⁸⁵ In the chromatin immunoprecipitation (ChIP) followed by high throughput sequence analysis, ZNF217- and ER α -binding sites are clustered in the distal enhancer region, and ZNF217 interacts physically with ER α through the former's C-terminal portion harboring ZFs and the latter's hinge region.⁸⁵ Interestingly, expression of ZNF217 was correlated

with that of ER α in breast cancer tissues, and its higher expression is linked to worse prognosis of the patients with breast cancer, possibly by enhancing the proliferation-stimulating activity of ER α .⁸⁵ Indeed, ZNF217 is found to be overexpressed in more than 20% of the breast cancers, and its elevated expression is associated with aggressive tumor behavior.¹⁶⁷

ZNF536 was identified as a novel protein interacting with the C-terminal tail-binding protein (CtBP) in the yeast two-hybrid screening.¹¹² ZNF536 has 10 ZFs, is highly conserved in vertebrates, and is most abundantly expressed in the neural cells especially of developing brain.¹¹² ZNF536 regulates neuronal differentiation by repressing retinoic acid/RAR-induced transcriptional activity, presumably through competing with RAR α for binding to the latter's response elements, as ZNF536 can bind these elements similar to RAR α .¹¹²

ZNF366 is an 11 ZFs-containing protein identified as a molecule interacting with ER α in the yeast two-hybrid screening using an ER α mutant lacking LBD as bait.¹¹⁸ ZNF366 acts as a corepressor for ER α -induced transcriptional activity by interacting with receptor-interacting protein 140 (RIP140) and CtBP. ZNF366 represses estrogen-responsive genes in breast cancer cells,¹¹⁸ suggesting that it may function as a negative factor for estrogen-dependent proliferation of breast cancer cells.

ZNF423 or Roaz contains 30 ZFs and was first described as a binding partner of the EBF1/OLF1 transcription factor.^{168,169} ZNF423 is important for the differentiation of adipocytes and olfactory neurons and for the development of B-cell lymphoma.¹⁷⁰ ZNF423 is a critical factor required for the retinoic acid-induced differentiation of the neuroblastoma

cell lines, acting as a cofactor for RAR/RXR-induced transcriptional activity by binding directly to RAR α and RXR α .¹²⁰ High expression of ZNF423 in neuroblastoma tissues is associated with good prognosis of the patients harboring this tumor,¹²⁰ suggesting that ZNF423 is a promising clinical marker and/or a treatment target.¹⁷¹

BTB/POZ-ZNFs

BTB/POZ-ZNFs are also evolutionarily conserved proteins observed from *C. elegans* and insects in the evolutionary tree.^{8,77} The BTB/POZ domain spans ~120 amino acids and is also found in some actin-binding proteins containing a kelch motif.⁸ BTB/POZ domain has multiple activities, including oligomerization between family members and transcriptional repression through interaction with repressive cofactors.⁸ There are 2 BTB/POZ-ZNFs that interact with NRs, Kaiso, and the promyelocytic leukemia zinc finger protein (PLZF).

Kaiso

Kaiso, or ZNF348 or ZBTB33 (zinc finger and BTB-containing protein 33), is a triple-fingered ZNF having a BTB/POZ domain in its N-terminus and 3 ZFs in the C-terminus. Kaiso physically interacts with the p120-catenin signaling molecule and binds methylated CpG dinucleotides in the consensus sequence CGCG.¹²² In addition, Kaiso is physically associated with the nuclear receptor corepressor (NCoR) through its BTB/POZ domain and facilitates deacetylation of histone tails; thus, it acts as a methylation-dependent transcriptional repressor by binding to methylated CpG islands of the target gene promoters.¹²² As many NRs attract NCoR for their repression of responsive genes, Kaiso may be a key molecule for the interplay between gene silencing by DNA methylation and NR-mediated transcriptional repression through histone deacetylation. Kaiso represses GR expression by binding to the proximal promoter region of the *GR* gene in a methylation-dependent fashion, influencing the anti-apoptotic activity of this receptor in breast cancer cells.¹⁷² Kaiso also interacts with the unmethylated consensus sequence, CTGCNA, and represses expression of the molecules involved in the Wnt signaling pathway.¹²²

Promyelocytic Leukemia Zinc Finger Protein

PLZF or ZBTB16 (zinc finger and BTB-containing protein 16) is a BTB/POZ-ZNF with 9 ZFs (Figure 1). PLZF was first identified as the gene for chromosomal translocation t(11;17)(q23;q21) in acute promyelocytic leukemia (APL), which produces the PLZF-RAR α fusion protein¹⁷² (Figure 1). PLZF plays a role in the control of cell cycle progression and is involved in the forebrain organization, hindbrain segmentation and musculoskeletal/limb development, differentiation

of myeloid cells, and spermatogenesis.¹⁷⁴⁻¹⁷⁶ PLZF binds through its BTB/POZ domain some repressive cofactors, such as the silencing mediator for retinoid and thyroid hormone receptors (SMRT), NCoR, Sin3 and histone deacetylase 1 (HDAC1), and forms a transcription-repressive complex.¹⁷⁷ The PLZF-RAR α fusion protein disrupts normal transcriptional regulation organized by retinoic acids, leading to the development of APL by reciprocally attracting the polycomb-repressive complex 1 (PRC1) and PRC2 to RAR α -binding sites.¹⁷⁸ Progesterone and glucocorticoids strongly stimulate PLZF expression in human endometrial stromal cells and myometrial smooth muscle cells, suggesting that PLZF plays a role in the proliferation and/or differentiation of these cells during the menstrual cycle influenced by these steroid hormones.

KRAB-ZNFs

KRAB-ZNFs form the largest subfamily in C2H2-type ZNFs, comprising nearly half of these proteins in humans⁷⁷ (Table 3). KRAB-ZNFs appeared in the tetrapod vertebrates and they demonstrate a significant lineage-specific expansion in higher organisms.⁷⁷ This expansion is caused by segmental gene duplication, as evidenced by the fact that the genes encoding KRAB-ZNFs are found as clusters in particular portions of chromosomes, such as chromosome 19q13, 6p22, 16p13, and 16p11 in humans.¹⁷⁹ Rapid expansion of KRAB-ZNFs is particularly observed in the primate lineage, and substantial proportion of the human KRAB-ZNFs has no mouse orthologs.^{77,180} These pieces of evidence indicate rapid diversification of KRAB-ZNFs and their potential importance in the regulation of the biological functions specific to primates including humans. Indeed, they appear to be responsible for some of the major transcriptional differences found between humans and other primates.⁹¹ Furthermore, some human KRAB-ZNF genes (eg, *PRDM9*) demonstrate diversity in the number of their encoding ZFs among human populations, indicating that they may underlie the variability observed between different populations/individuals.¹⁸¹

KRAB-ZNFs are well known to act as transcriptional repressors, but some of them also function as transcriptional enhancers.^{8,88} KRAB-ZNFs have the KRAB domain in their N-terminal portion and multiple ZFs in the C-terminal area, which function respectively as a transcriptional regulatory unit and an anchoring component to DNA, RNA, and/or other protein molecules.⁸ Most of the KRAB-ZNFs have more than 4 ZFs and some contain more than 30 of these motifs (average number of ZFs: 7.5 and 8.5 in mouse and human, respectively), and they selectively use some of their multiple ZFs for interacting with specific DNA sequences and RNA/protein molecules, indicating a potential of having many different partner/target molecules/genes.^{8,77} The KRAB domain spans approximately 75 amino acids, and has one or

both of the KRAB-A and KRAB-B boxes.⁸ KRAB-A box consists of 45 amino acids and acts as a strong transcriptional repressor domain by recruiting several cofactor molecules including the KRAB-associated protein-1 (KAP-1),^{182,183} which is also known as the KRAB-A-interacting protein 1 (KRIP1), tripartite motif protein 28 (TRIM28), or transcription intermediary factor 1 β (TIF1 β).¹⁸⁴ In contrast, functions of KRAB-B box are not well known, but it enhances the activity of KRAB-A box.¹⁸⁵ KAP-1 binds KRAB domain as an oligomer and further recruits the heterochromatin protein 1 (HP1), HDACs, and the histone H3K9 methyltransferase SET domain bifurcated 1 (SETDB1) through which KRAB-ZNFs silence their associating genes by changing the chromatin status/structure.^{184,186} Importantly, KAP-1 acts as a coactivator for some NRs, similar to its homologous molecule TIF1 α (TRIM24).¹⁸⁷⁻¹⁸⁹ TIF1s physically interact with NRs and participate in their transcriptional regulation^{188,190}; thus, they are a link for the functional interaction between KRAB-ZNFs and NRs. Several KRAB-ZNFs, such as ZNF746 (Paris), ZNF282, ZNF764, ZNF398, and ZNF461, influence the transcriptional activity of NRs.

ZNF746

ZNF746 also known as the parkin-interacting substrate (Paris) is a KRAB-ZNF containing 4 ZFs. ZNF746 functions as a transcription repressor by binding to the TATTTT[T/G] consensus motif.¹²⁶ ZNF746 is a substrate of the ubiquitin E3 ligase Parkin and represses the transcription of the PPAR γ coactivator-1 α (*PGC-1 α*) gene in neurons.¹²⁶ Thus, the reduction of Parkin expression or the presence of its inactivating gene mutations results in increase of ZNF746 protein levels in these cells. Elevated ZNF746 in turn reduces PGC-1 α expression and contributes to the development of neurodegeneration observed in Parkinson disease through down-regulating the expression of PGC-1 α -dependent genes.¹²⁶ PGC-1 α is a coactivator for several NRs, including PPARs, ERs, RXR α , HNF4 α , and GR, by interacting physically with these receptors through its LxxLL coactivator motif, and regulates intermediary metabolism, adaptive thermogenesis, mitochondrial biogenesis, and adipocyte differentiation/function in part through these receptors.¹⁹¹ Thus, ZNF746 potentially influences the activity of these receptors indirectly by stimulating the expression of PGC-1 α .

ZNF282

ZNF282 is a KRAB-ZNF containing 5 ZFs and was originally identified as a protein that binds the U5 repressive element (U5RE) of the human T-cell leukemia virus type-I (HTLV-I) (thus, it is also called the HTLV-I U5RE-binding protein 1: HUB1).¹⁹² ZNF282 physically interacts and synergistically cooperates with the coiled-coil coactivator (CoCoA), a cofactor interacting with NCoA HAT coactivators

and contributing to NR-induced transcriptional activity.^{193,194} ZNF282 enhances ER α -mediated transcriptional activity in the presence of CoCoA and stimulates estrogen-dependent proliferation of breast cancer cells.¹²⁷ ZNF282 also enhances the transcriptional activity of GR, TR, and AR.¹²⁷ However, *in vivo* importance of such ZNF282-mediated regulation of NR activity is not known yet.

ZNF764

ZNF764 consists of 7 ZFs in its C-terminal portion and one KRAB-A domain in its N-terminal area (Figure 1). *ZNF764* was identified as a potential gene causing the multiple steroid hormone resistance observed in a patient with 16p11.2 microdeletion.¹²⁸ The 16p11.2 gene segment is highly susceptible to segmental duplications/deletions in the great ape lineage.¹⁹⁵ The gene rearrangement in the 16p11.2 segment is still ongoing in modern humans. For example, length of this segment has almost doubled in humans and chimpanzees compared with their ancestor orangutans.¹⁹⁵ This activity has also generated in the segment human-specific genes with beneficial effects, whereas it causes various congenital disorders by impacting appropriate copy numbers of residing genes, such as in the case of *ZNF764*.^{128,195} In human cells, ZNF764 enhances the transcriptional activity of GR, AR, MR, and TRs in cooperation with KAP-1.¹²⁸ In a genome-wide binding study using ChIP-sequencing in human HeLa cells, ZNF764- and GR-binding sites are found in close proximity, indicating that ZNF764 modulates GR transcriptional activity by incorporated in the transcriptional complex formed on DNA-bound GR.¹²⁹ The exact physiologic functions of ZNF764 in humans are not known, but it appears to regulate the GR activity involved in the stress response organized by the hypothalamic-pituitary-adrenal axis and the AR activity required for fetal development of male-type external genitalia.¹²⁸

ZNF398

ZNF398 also known as ZER6 (zinc finger-estrogen receptor interaction, clone 6) is a KRAB-ZNF containing 6 ZFs and was identified as an ER α -interacting protein in a yeast two-hybrid screening using full-length ER α as bait.¹³⁰ Alternative splicing generates 2 ZER6 isoforms, p52-ZER6 and p71-ZER6. ER α physically interacts with p52-ZER6 in a ligand-dependent fashion but not with p71-ZER6, due to the presence of the HUB1 domain in the latter isoform.¹³⁰ ER α strongly represses the transcriptional activity of ZER6 on the gene containing its response elements.¹³⁰ As ZER6 is specifically expressed in breast tissues, ZER6 may mediate some actions of estrogens in this organ.¹⁹⁶ ZER6 is also expressed in ER α -positive, but not ER α -negative breast cancers, suggesting its potential role in the regulation of estrogen-dependent proliferation in this malignancy.¹⁹⁶

ZNF461

ZNF461, also called as the gonadotropin-inducible ovarian transcription factor-1 (GIOT-1), was first identified as a molecule induced by the follicular stimulating hormone.¹⁹⁷ ZNF461 is predominantly expressed in steroidogenic tissues, including testicular Leydig cells, ovarian granulosa and theca cells and adrenocortical cells, indicating its primary role in the regulation of steroidogenesis in mammals.¹⁹⁸ ZNF461 contains one KRAB-A domain and 12 ZFs, and acts as a transcriptional repressor.¹⁹⁷ Expression of ZNF461 is regulated by SF-1 and NUR77, respectively, in ovarian granulosa cells and testicular K28 Leydig cells.¹⁹⁸ On the contrary, ZNF461 represses SF-1-mediated transcriptional activity by physically interacting with SF-1 and by attracting HDAC2, indicating a presence of auto-regulatory loop between ZNF461 and SF-1 in the steroid hormone production by gonads and adrenal glands.¹³¹

Conclusions and Future Perspectives

NRs are evolutionarily conserved ligand-dependent transcription factors that mediate the actions of lipophilic hormones and metabolites and/or intermediates of several important biological pathways.⁷ NRs are essential for human life, by affecting every aspect of human activities.^{7,9} On the contrary, C2H2-type ZNFs form an evolutionarily expanding family of transcription factors, characterized by multiple, tandemly arranged ZFs and distinct functional modules, such as BTB/POZ, KRAB, and SCAN domains.⁸ Among them, KRAB-ZNFs have expanded their members significantly in higher organisms, possibly organizing the species-specific biological actions through the transcriptional regulatory network that has also increased its complexity following evolution.^{2,77,90} Substantial numbers of C2H2-type ZNFs function as DNA-binding transcription factors, whereas others may act as transcriptional cofactors incorporated in the transcription complex formed on NRs. As both NRs and C2H2-type ZNFs have diverse regulatory actions on human biology, these 2 groups mutually interact with each other through their evolution/diversification, ultimately contributing not only to the functions conserved through evolution but also to the complex gene regulation and/or species-specific activities of higher organisms. Research on the former mainly mediated by the interaction between NRs and older C2H2-ZNFs has demonstrated major progress, as it plays roles in more fundamental biological systems shared by many organisms. In contrast, importance of the latter, eg, for the human-specific actions of KRAB-ZNFs, has just been recognized recently. Indeed, these younger genes tend to have less functional communication with other genes, in contrast to older genes that were well incorporated in the gene interaction network built through long evolutionary history⁹⁴ (Figure 5). Nevertheless,

the new genes including KRAB- or SCAN-ZNFs appear to be emerged to support the activities important for respective species, such as superb CNS functions observed in humans. Thus, revealing the actions of newly appeared C2H2-ZNFs is important to understand human-specific biological activities and is critical to elucidate causes and pathophysiology of human diseases (eg, depression and schizophrenia^{199,200}). Clarifying the regulatory actions of evolutionarily old and new C2H2-type ZNFs on NRs will ultimately improve our understanding on NR actions general to many organisms, but also those relevant and specific to humans.

Another important aspect of C2H2-type ZNFs is their interaction with abundant ncRNAs. Numbers of ncRNAs have been significantly increased in higher organisms following expansion of noncoding-gene area.² Many of the ncRNAs employ protein molecules as their functional targets and/or mediators of their effects.²⁰¹ For example, argonaute proteins are necessary for microRNAs (miRNAs) to interact with their target mRNAs, while many long ncRNAs (lncRNAs) interact with various proteins to exert their effects on chromatin/DNA.^{202,203} C2H2-type ZNFs are among such molecules that mediate the actions of ncRNAs. For example, roX, a drosophila lncRNA essential for dosage compensation of the sex chromosome by stimulating the transcription of single X chromosome in males, communicates with its target DNA sequences through the chromatin-linked adaptor for male-specific lethal (MSL) protein (CLAMP).²⁰⁴ CLAMP is a poly-ZNF with 7 ZFs and is a component of the MSL complex necessary for the dosage compensation by roX. CLAMP binds roX with its ZFs and guides this lncRNA to target DNA sequences.²⁰⁴ CTCF, a poly-ZNFs with 11 ZFs, exerts its insulator function by forming a complex with the DEAD-box RNA helicase p68 and the steroid receptor RNA activator (SRA) lncRNA.²⁰⁵ SRA participates in the transcriptional activity of SRs by interacting with their AF-1 transactivation domain and by forming a complex with p160-type NCoAs^{205,206}; thus, CTCF, SRA, and NRs cooperate with each other to regulate NR-induced transcriptional activity. Similar to SRA, the lncRNAs known to have regulatory actions on NRs, such as the growth arrest-specific 5 (Gas5), prostate cancer-associated noncoding RNA 1 (PRNCR1), and the prostate-specific transcript 1 (PCGEM1)^{207,208} might exert their effects through the interaction with C2H2-type ZNFs, as some C2H2-ZNFs are known to regulate the transcriptional activity of NRs for which these lncRNAs are also functional. Furthermore, lncRNAs and some C2H2-type ZNFs may play important regulatory roles in tissue-specific gene expression, indicating their functional overlap and potential cooperation in target biological activities. As increasing numbers of the ncRNAs with NR regulatory activities was observed during the last several years, elucidation of their interaction with C2H2-ZNFs may help revealing the regulatory actions of such ncRNAs on NRs.

Author Contributions

RM and TK wrote the article. AK created tables. RM, AKM, AF, and TK edited the article.

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