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PERSPECTIVES IN BASIC SCIENCE

Nuclear receptors and their coregulators in kidney

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Nuclear receptors and their coregulators in kidney. Nuclear receptors are transcription factors that are essential in embryonic development, maintenance of differentiated cellular phenotypes, metabolism, and apoptosis. Dysfunction of nuclear receptor signaling leads to a wide spectra of proliferative, reproductive, and metabolic diseases, including cancers, infertility, obesity, and diabetes. In addition, many proteins have been identified as coregulators which can be recruited by DNA-binding nuclear receptors to affect transcriptional regulation. The cellular level of coregulators is crucial for nuclear receptor-mediated transcription and many coregulators have been shown to be targets for diverse intracellular signaling pathways and posttranslational modifications. This review provides a general overview of the roles and mechanism of action of nuclear receptors and their coregulators. Since progression of renal diseases is almost always associated with inflammatory processes and/or involve metabolic disorders of lipid and glucose, cell proliferation, hypertrophy, apoptosis, and hypertension, the importance of nuclear receptors and their coregulators in these contexts will be addressed.

Nuclear receptors comprise a family of transcription factors that regulate gene expression in a ligand-dependent manner. The nuclear receptor superfamily presently includes 49 distinct members for steroid hormones, such as estrogens and glucocorticoids, receptors for nonsteroidal ligands, such as thyroid hormones and retinoic acid, as well as receptors that bind diverse products of lipid metabolism, such as fatty acids and prostaglandins [1]. The nuclear receptor superfamily also includes a large number of orphan receptors for which regulatory ligands have not been identified [2]. Nuclear receptors exert diverse roles in the regulation of growth, development, and homeostasis. Members of the nuclear receptor superfamily directly activate or repress target genes by binding to hormone response elements (HREs) in promoter or enhancer regions which provide specificity to receptor homodimer/heterodimer binding, and by binding to other DNA sequence-specific activators. They also inhibit the transcriptional activities of other classes of transcription factors by transrepression [3].

Recent studies have also led to the identification of many associated proteins that interact with nuclear receptors in a ligand-dependent manner to mediate their transcriptional regulation. These factors with no specific DNA-binding affinity have been called nuclear receptor coregulators. Regulation of gene transcription by nuclear receptors requires the recruitment of coregulators, with ligand-dependent exchange of corepressors for coactivators serving as the basic mechanism for switching from gene repression to activation. In this review, we will discuss nuclear receptors, with particular emphasis on the roles of the coactivator/corepressor in gene transcriptional regulation, and its significance role in controlling inflammatory processes and metabolic disorders in kidney.

Key words: nuclear receptor, nuclear receptor coregulator, kidney disease.

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NUCLEAR RECEPTORS

Basic structure of nuclear receptors

The nuclear receptor superfamily consists of 49 nuclear receptors (Table 1). The structure for all members is very similar. It usually contains four major functional domains (Fig. 1): the N-terminal ligand-independent transactivation domain (A/B domain), the DNA binding domain (DBD or C domain), hinge region (D domain) and the C-terminal E/F domain, including ligand-binding domain, and the ligand-dependent transactivation domain. The N-terminal A/B domain contains a transactivation domain (AF-1) which is of variable length and sequence in the different family members and is recognized by coactivators and/or other transcription factors. The ligand-binding domain is connected to the DBD domain by a short flexible linker and mediates ligand-dependent transactivation functions. A short conserved helical sequence within the carboxyl terminus of the ligand-binding domain, referred to as activation function 2 (AF-2), is required for ligand-dependent activation [4, 5].

Table 1. Nuclear receptor family

Name	Abbreviation	Ligand
Thyroid hormone receptor[a,c]	TRα	Thyroid hormone
	TRβ	Thyroid hormone
Retinoic acid receptor[a]	RARα	Retinoic acid
	RARβ	Retinoic acid
	RARγ	Retinoic acid
Peroxisome proliferators activated receptor[a]	PPARα	Fatty acid, leukotriene B4, fibrate
	PPARβ	Fatty acids
	PPARγ	Fatty acids, prostaglandin J_2
Reverse erbA[b,c]	Rev-erb α	Orphan
	Rev-erb β	Orphan
RAR-related orphan receptor[b,c]	ROR α	Cholesterol, cholesteryl sulphate
	RORβ	Retinoic acid
	RORγ	Retinoic acid
Liver X receptor[a]	LXRα	Oxysterols, T0901317, GW3965
	LXRβ	Oxysterols, T0901317, GW3965
Farnesoid X receptor[a]	FXRα	Bile acids, fexaramine
	FXRβ	Lanosterol
Vitamin D receptor[a,b]	VDR	1,25 $(OH)_2$vitamin D_3, litocholic acid
Pregnane X receptor	PXR	Xenobiotics, PCN
Constitutive androstane receptor	CAR	Xenobiotics, phenobarbital
Human nuclear receptor 4[b]	HNF4α	Orphan
	HNFγ	Orphan
Retinoid X receptor	RXRα	Retinoic acid
	RXRβ	Retinoic acid
	RXRγ	Retinoic acid
Testis receptor	TR2	Orphan
	TR4	Orphan
Tailless	TLL	Orphan
Photoreceptor-specific receptor	PNR	Orphan
Chicken ovalbumin upstream-promoter transcription factor[b]	COUP-TFI	Orphan
	COUP-TFII	Orphan
ErbA2-related gene-2	EAR2	Orphan
Estrogen receptor[b]	ERα	Estradiol-17β, tamoxifen, raloxifene
	ERβ	Estradiol-17β,various synthetic compounds
Estrogen receptor-related receptor	ERRα	Orphan
	ERRβ	DES, 4-OH tamoxifen
	ERRγ	DES, 4-OH tamoxifen
Glucocorticoid receptor[b]	GR	Cortisol, dexamethasone
Mineralocorticoid receptor[b]	MR	Aldosterone, spirolactone
Progesterone receptor[b]	PR	Progesterone, medroxyprogesterone acetate, RU468
Androgen receptor[b]	AR	Testosterone, flutamide
NGF-induced factor B[c]	NGFIB	Orphan
Nur related factor 1	NURR1	Orphan
Neuron-derived orphan receptor1	NOR1	Orphan
Steroidogenic factor 1[c]	SF1	Orphan
Liver receptor homologous- protein 1	LRH1	Orphan
Germ cell nuclear factor	GCNF	Orphan
DSS-AHC critical region on the chromosome, gene1	DAX1	Orphan
Short heterodimeric partner	SHP	Orphan

[a]Heterodimers with retinoid X receptor; [b]Homodimers; [c]Monomers RXR.

Function of nuclear receptors

The nuclear receptors are essential in embryonic development, maintenance of differentiated cellular phenotypes, and metabolism. The activity of many nuclear receptors is controlled by the binding of small, lipophilic ligands that include hormones, metabolites such as fatty acids, bile acids, oxysterols, and xeno- and endobiotics. Many nuclear receptors control glucose, cholesterol, bile acid, and xenobiotic metabolism. The major function of these nuclear receptors is to act as sensors of the above molecules to bring about molecular control of important metabolic pathways. Once activated by a ligand, they control a variety of genes for several pathways of intermediary metabolism. In general, nuclear receptors have four functions, including ligand-dependent transactivation, ligand-dependent coactivation, active repression, and transrepression as shown in Figure 2.

Ligand-dependent transactivation and coactivation. The typical activity of nuclear receptors is ligand-dependent transactivation (Fig. 2A). In the presence of ligands, nuclear receptors can activate target genes by

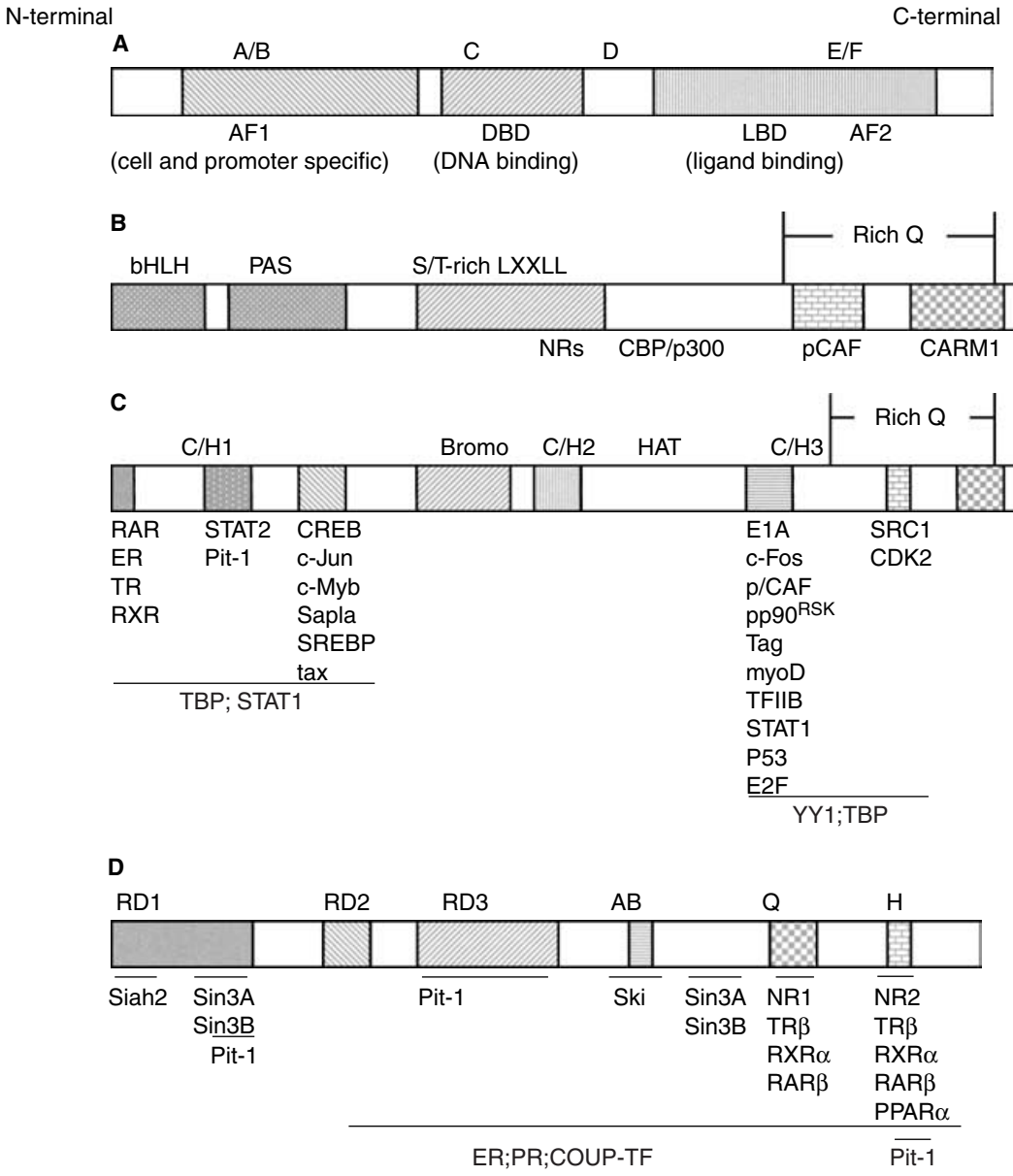

Fig. 1. Domains of nuclear receptors and co-activator proteins. (*A*) Nuclear receptor structure. Nuclear receptor contains four major functional domains: the N-terminal ligand-independent transactivation domain (A/B domain), the DNA binding domain (DBD or C domain), hinge region (D domain), and the C-terminal E/F domain, including ligand-binding domain (LBD) and the ligand-dependent transactivation domain. (*B*) The p160 coactivator structure, including the amino terminus (PAS and bHLH homology regions), a central region that interact with nuclear receptors [such as retinoic acid receptor (RAR), estrogen receptor (ER) and thyroid hormone receptor (TR)] and involved in nuclear receptor interaction and transaction, and a carboxy-terminal region mediate interactions with either CBP/p300 or protein-arginine methyltransferase CARM1. (*C*) CBP/p300 structure. Regions involved in interaction with STAT1 and STAT2, nuclear receptors [retinoic acid receptor (RAR), estrogen receptor (ER), and retinoid X receptor (RXR)], Jun, CREB, YY1, Fos, E1A, p/CAF, pp90^{RSK}, and SRC-1 are indicated. (*D*) The structure for nuclear receptor corepressor (NCoR). Regions involved in interaction with Siah2, Sin3A, Sin3B and nuclear receptors are indicated. Abbreviations are: bromo, bromodomain; bHLH, basic helix-loop-helix; PAS, period/ary hydrocarbon receptor/single minded; S/T-rich, serine/threonine-rich domain; CH, cysteine-rich; rich-Q, glutamine-rich domain; TBP, TATA-binding protein; RD, repression domain; AB, acidic basic; H, α helical.

binding directly to HREs as monomers [e.g., steroidogenic factor 1 (SF1)]; homo- (e.g., steroid receptor) or heterodimers with the promiscuous retinoid X receptor [e.g., retinoic acid receptor, peroxisome proliferator activated receptor γ (PPARγ), thyroid hormone receptor, vitamin D receptor, and several orphan nuclear receptors]. There is an allosteric interaction between heterodimeric nuclear receptors [6]. Some heterodimeric combinations, such PPAR-retinoid X receptor, can be activated in response to either PPAR ligands or 9-cis RA which is a retinoid X receptor ligand. In contrast, other heterodimeric combinations, including retinoid X receptor-retinoic acid receptor, and retinoid X receptor-thyroid hormone receptor heterodimers, exhibit transcriptional responses that are

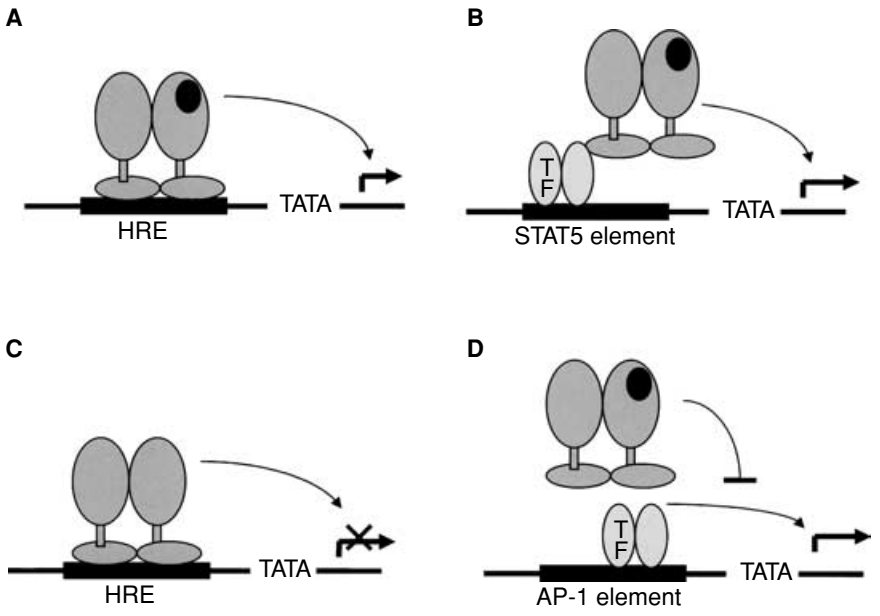

Fig. 2. Transcriptional activities of nuclear receptors. Members of the nuclear receptor family can both activate and inhibit gene expression. (*A*) Transactivation: the prototypic activity of nuclear receptors is ligand-dependent activation of transcription upon binding to specific hormone-response elements (HREs) in target genes. (*B*) Coactivation. Nuclear receptors have also been documented to contribute to gene activation by acting as coactivators for other transcription factors (TF), as demonstrated in the case of the glucocorticoid receptor for certain STAT-5-responsive genes. (*C*) Active repression. A subset of nuclear receptors that heterodimerize with the retinoid X receptor, including the thyroid hormone receptor, and retinoic acid receptor, are capable of actively repressing target genes upon binding to HREs in the absence of ligand. (*D*) Transrepression. In addition, several nuclear receptors, exemplified by the glucocorticoid receptors are capable of suppressing target genes by inhibiting the activities of other classes of transcription factors, such as AP-1, in a ligand-dependent manner. This effect does not require DNA binding by the nuclear receptor.

selective for retinoic acid and thyroid hormone receptor ligands, respectively. Selective responses have been demonstrated to result from allosteric interactions between retinoic acid receptor or thyroid hormone receptor and retinoid X receptor that prevent the binding of retinoid X receptor ligands. Thus, the transcriptional response of the retinoic acid receptor-retinoid X receptor heterodimer remains retinoic acid receptor–specific, but retinoid X receptor ligands can serve to potentiate this response [7].

Ligand-dependent transactivation by nuclear receptors has been found to depend on a highly conserved motif in ligand-binding domains, referred to as AF-2 [5]. In the unliganded retinoid X receptor structure, the AF-2 helix extends away from the ligand-binding domain [8], whereas in the agonist-bound retinoic acid receptor γ, thyroid hormone receptor α, estrogen receptor, and PPARγ ligand-binding domain structures, the AF-2 helix is tightly packed against the body of the ligand-binding domain and makes direct contacts with ligand [9]. These studies have suggested that ligand-dependent changes in the conformation of the AF-2 helix result in the formation of a surface (or surfaces) that facilitates activation of target genes.

In addition, nuclear receptors can activate target genes by acting as coactivators and binding other classes of DNA-bound transcription factors, as demonstrated in the case of the glucocorticoid receptor for certain signal transducer and activator of transcription (STAT)-5 responsive genes. This effect does not require DNA binding and is termed ligand-dependent coactivation (Fig. 2B).

Active repression and transrepression. Certain nuclear receptors, such as glucocorticoid receptor, needs to be complexed with ligand to translocate to the nucleus and bind DNA. Other receptors are capable of binding to DNA in the unliganded state and are associated with repressor complexes that actively repress transcription. For example, unliganded liver X receptor inhibits its target gene adenosine triphosphate (ATP)-binding cassette transporter A1 (ABCA1) expression [10]. Other subsets of nuclear receptors that heterodimerize with the retinoid X receptor, including the thyroid hormone receptor and retinoic acid receptor, are also capable of actively repressing target genes upon binding to HREs in the absence of ligand. This repression has been called as active repression of nuclear receptor (Fig. 2C).

Ligand-dependent activation of nuclear receptors could alter the expression of a component of a signal transduction pathway that exerts a negative effect, termed ligand-dependent transrepression (Fig. 2D). For example, glucocorticoid receptor has also been demonstrated to inhibit nuclear factor-kappaB (NF-κB) function in lymphocytes, in part, by up-regulating the expression of the inhibitory factor IκBβ [11]. Activation of the glucocorticoid receptor also blunts the response of an activating protein-1 (AP-1)–dependent promoter to phorbol ester or Ras stimulation [12]. Similar results have also been found in other nuclear receptors, such as retinoic acid receptor [13].

Multiplicity of nuclear receptors

Some nuclear receptors have many paralogues for a given ligands (Table 1). For example, three paralogues exist for retinoic acid receptor, PPAR, retinoid X receptor, retinoic acid receptor–related orphan receptor

(ROR), and two paralogues for thyroid hormone receptor, estrogen receptor, liver X receptor, and, farnesoid X receptor. The multiplicity of nuclear receptors is important for both signal diversification and specification. For example, estrogen signaling depends on a balancing act between estrogen receptor α and estrogen receptor β. Estrogen receptor α is often an activating factor, whereas estrogen receptor β suppresses the effects of estrogen receptor α though the ligands are the same [14]; glucocorticoid receptor α mediates the anti-inflammation effect of corticosteroids, but glucocorticoid receptor β acts as a dominant-negative form of glucocorticoid receptor [15]. Three PPAR, retinoic acid receptor isoforms also have distinct functions. The multiplicity of nuclear receptors also appears to have the facility that one isoform controls multigenes with opposite biologic effects. For example, liver X receptor activates both ABCA1 gene and sterol-responsive element-binding protein 1c (SREBP1c) gene expression. Induction of ABCA1 gene increases cholesterol efflux from peripheral tissue and reduces atherosclerosis, whereas activation of SREBP1c seems to increase fatty acids synthesis and plasma very low-density lipoprotein (VLDL) level [10]. The net effect depends on a fine balance between various factors relating the ratio of nuclear receptor isoforms, the specificity of the ligands, and recruitment of coregulators.

NUCLEAR RECEPTOR COREGULATORS IN TRANSCRIPTIONAL REGULATION

In the past several years, a large number of nuclear receptor coregulators have been identified (Table 2). These proteins, including coactivators and corepressors, are associated with nuclear receptors in a ligand-dependent manner. In general, ligand binding is believed to increase the affinity of nuclear receptors for coactivators [16]. Ligand-dependent recruitment of coregulators is dependent on a ligand-dependent conformational change in AF-2. On the other hand, an important aspect of antagonist action is to place the AF-2 helix in a configuration that prevents coactivator binding.

Nuclear receptor coactivators (NCoA)

A large number of potential NCoAs have been identified [6]. Although coactivator proteins show little or no DNA-binding ability of their own, they are capable of increasing or inducing transcriptional activity.

The p160 family. The P160 family has been identified as major proteins interacting with nuclear receptors. The family contains three homologues, termed (*1*) NCoA1/steroid receptor coactivator 1 (SRC1)/p160 (/is "also known as" or "alias") (Table 2), (*2*) NCoA2/transcriptional intermediary factor 2 (TIF2)/glucocorticoid receptor interacting protein 1 (GRIP1)/p160, and (*3*) NCoA3/p300 cyclic adenosine monophosphate (cAMP) response element binding protein (CREB)-binding protein (CBP)-cointegrator-associated protein (pCIP)/receptor-associated co-activator 3 (RAC3)/amplified in breast cancer 1 (AIB1)/activator of the thyroid and receptor activator (RA) (ACTR)/thyroid hormone receptor-activator molecule 1 (TRAM1)/p160 [6]. The p160 factors consisting of above three members exhibit a common domain structure (Fig. 1B). These proteins are most highly related in an amino-terminal region that contains a period/aryl hydrocarbon receptor/single minded (PAS)-A-basic helix-loop-helix (bHLH) homology domain. PAS domains have been shown to function as dimerization motifs. The central conserved domain mediates ligand-dependent interactions with nuclear receptor, ligand-binding domain, whereas the conserved C-terminal transcriptional activation domains mediate interactions with either CBP/p300 or protein-arginine methyltransferase, such as coactivator-associated arginine methyltransferase (CARM1) and protein arginine methyltransferase (PRMT1) [18, 19]. Analysis of the amino acid sequences of the nuclear receptor interaction domains (central domains) of p160 factors revealed the presence of leucine-rich motifs of the consensus sequence LXXLL, where L represents leucine and X any amino acid. The LXXLL sequence and a short stretch of amino- and carboxy-terminal amino acids are both necessary and sufficient for ligand-dependent interactions of p160 proteins with nuclear receptor ligand-binding domains [20]. Different LXXLL motifs are selectively required to support functions of different nuclear receptors. This functional specificity correlates with the difference in affinity between each LXXLL motif and different nuclear receptors. Mice lacking p160 factors, such as NCoA1/SRC1/p160 are viable and grossly normal, probably because of functional redundancy between the three class members. Nevertheless, deletion of NCoA1/SRC1/p160 results in steroid and thyroid hormone resistance [21]. Increased level of NCoA3/pCIP/RAC3/AIB1/ACTR/TRAM1/p160 has been found in breast cancers [22].

CBP/p300. CBP was originally isolated on the basis of its association with CREB in response to cyclic adenosine monophosphate (cAMP) signaling. Its close homologue, p300, was purified as a cellular binding protein of the adenoviral protein E1A. CBP and p300 have been identified as crucial components of nuclear receptor transactivation and have been shown to directly interact with numerous members of the nuclear receptor coregulators. For example, it has been shown that NCoA1/SRC1/p160 interacts with CBP through two helical domains that contain the core LXXLL consensus sequence [20]. NCoA6/activating signal cointegrator 2 (ASC2)/nuclear receptor-activating protein 250

Table 2. Nuclear receptor coregulators

Chromatin remodeling and acetylation	**Proliferation/apoptosis**	**Bromodomain proteins**
ADA2	ARA24/RAN/TC4	p120/SMAP
ADA3	Bcl3	**HMG proteins**
BRG1	BRCA1	HMG1
CBP	Cyclin D1	TRIP7/HMG17-like
GCN5	E1A	BZIP factors
MTA1	Nm23-1	p45/NF-E2
NcoA62	Nm23-2	**Cytoskeleton**
P300	p53	TRIP5/EG5
PCAF	Rbp2	TRIP11/TRIP230/CEV14
Prothymosinα	REA/BAP37/D-prohibition	**Miscellaneous**
RbAp48	RAP46/BAG-1	CRABPII
RIP140	TRIP10/CIP4	NIX
SSN6	TRIP13/HPV16	NRIF3/β3-endonexin
TIF1	Zac1/Lot1	PELP1/p160
Methyltransferases	**RNA/RNA interacting proteins**	PNRC2
CARM	CIA/KIAA1637	RBF1/ATP synthgase
PIMT	dUTPase	SUN-CoR/C1D
PRMT1	L7/SPA/L7a/TRUP	TRIP3/CG8204
NcoAs	MINT/SHARP/KIAA0929	TRIP4/ASC1
NcoA1/SRC1/p160	p72/p68	**Not in GeneBank**
NcoA2/TIF2/GRIP1/SRC2/p160	PGC1	ARA267α
NcoA3/pCIP/ACTR/AIB1/RAC3/TRAM1/SRC3/p160	PSF/NonO/p54^{nrb}	ERAP160/p160
	SRA	p3/BCATm
NcoA4/ARA70	TLS/p65	p48
NcoA6/ASC2/RAP250/NCR/PRIP/TRBP/AIB3	**Cytokine-associated proteins**	p80
	NF-κB/p65	p140
NCoRs	p50/Rel	PNRC
NcoR1/RIP13	PIASxα/ARIP3	TRAC
NcoR2/SMRT/TRAC1	PIASxβ/MIZ1	VIP(170)
Mediator-related proteins	PIAS1/GBP	**LIM domain proteins**
TRAPs (complex)	PIAS3	ARA55/Hic5
TRAP80/DRIP80/CRSP77	TRIP9/IκBβ	FHL2/DRAL/Slim3
TRAP95/DRIP92	TRIP14/p59	TRIP6/OIP1/ZRP1
TRAP100	**SIN-associated proteins**	**Basal transcription factors**
TRAP150	mSin3a	CAK
TRAP170/CRSP150/CXORF4	mSin3b	dTAFii110
TRAP230	SAP18	MBF1
TRAP240	SAP30	MMS19
PBP/TRIP2/TRAP220/DRIP205/RB18A	**EF-hand proteins**	TAF(ii)30
DRIPs (complex)	REC55/E6BP/RCN2/VAF1	TBP
PC2	**Forkhead proteins**	TFIIB
PC4	FKHR	TFIIF
Proteolysis	**Zinc finger proteins**	TFIIH
JAB1	FOG2	TMF/ARA160
TRIP1/Sug1	RIP110/RAP80	**SMADs**
TRIP12/E6-AP	TRIP8/Hairless/5qNCA	Smad3
TRIP15/Alien/COP9-S2	POU-domain proteins	Smad7
Ubc9	Oct1	**RING proteins**
		ARA54/RNF14/HFB30
		SNURF/RNF4

/means "also known as."

(RAP250)/nuclear receptor coregulator (NRC)/PPAR-interacting protein (PRIP)/thyroid hormone receptor-binding protein (TRBP)/AIB3 has been recently characterized to interact not only with nuclear receptors via an LXXLL motif in the N-terminal, but also with CBP/p300 in its C-terminus [23]. This interaction is in a ligand-dependent manner and relies on the conserved nuclear receptor functional domain AF-2. CBP can also associate with the CBP-associated factor (p/CAF) [24] and with RNA polymerase II holoenzyme [25]. Thus, CBP recruits a series of coactivators and other components of the transcriptional apparatus to form a large complex which appears to function in nuclear receptor–dependent gene expression (Fig. 1C). Deletion of CBP or p300 in mice results in early death in embryogenesis, suggesting precise levels of p300/CBP are important in development and transcription control [26–28].

Other coactivators. In addition to the p160 family and CBP/p300, a large number of coactivators have been identified using biochemical and expression cloning studies. These include NCoA4/androgen receptor activator 70 (ARA70), PPAR binding protein (PBP)/thyroid hormone receptor interacting protein 2 (TRIP2)/thyroid hormone receptor-associated protein 220 (TRAP220)/

vitamin D receptor interacting protein 205 (DRIP205)/ reinoblastomas suppressor protein 18A (RB18A), DRIP130/coactivator required for Sp1 activation 130 (CRSP130),TR associated protein (TRAP80, 93, 95,97,100,150,170,220, and 230), p140 factors [estrogen receptor-associated protein 140 (ERAP140) and RIP140, GRIP95, 120, 170, TRIP1, and TIF1 (Table 2)]. However the functions for these proteins are less informative.

Tissue and pathway specificity of coactivators. Many coregulators normally show tissue-specific distribution, and the levels of different coactivators, for example CBP, can vary dramatically among specific cell types [29]. Such differences in expression levels might indicate cell specificity of nuclear receptor–mediated transcriptional regulation, and might partially explain how the same gene can be regulated differentially in different cell types [30]. For example, PPARγ can activate transcription of the uncoupling protein 1 (*UCP-1*) gene in brown fat but not in fibroblasts [31]. The levels of cold-inducible coactivator PPARγ coactivator 1 (PGC1) are normally low in brown fat cells but can be dramatically increased by thermal stimulation and subsequently provide a cell- and tissue-specific mechanism for transcriptional regulation by PPARγ in brown fat [31]. p/CIP/SRC3 exerts effects on somatic growth, modulating cell-autonomous cell cycle events [32, 33]. Cell-specific coactivators may also play critical roles in gene-specific transcriptional activation. Comparing the p160 family and CBP/p300, some coactivators seem to be more tissue specific. For example, ARA70, which is expressed in prostate, has been identified an androgen receptor specific coactivator. GRIP95,120, and 170 and TRAP80 are also specific coactivators for glucocorticoid receptors and thyroid hormone receptors.

Different classes of signal-activated transcription factors require distinct coactivator components, including CBP, the p160 family members, and p/CAF. For example, the steroid-activated nuclear receptors require CBP, NCoA1/SRC1, p/CIP, and p/CAF [6], whereas cAMP-activated CREB requires CBP, p/CIP, and p/CAF but not NCoA1/SRC1 [34]. Interferon gamma (INF-γ)-activated STAT-1 requires the action of CBP and pCIP but neither p/CAF nor NCoA1/SRC1 [28]. These data suggest that nuclear receptors and their coactivators could be a key to determine tissue-specific transactivation.

Corepressors: Nuclear receptor corepressor (NCoR) and silencing mediator for retinoic acid and thyroid hormone receptors (SMRT)

Unliganded nuclear receptors that have the ability to bind DNA and steroid receptors on treatment with antagonists recruit corepressor proteins that inhibit transcription [35, 36]. A factor of ~270 kD that mediates repression effects by unliganded thyroid hormone receptors and retinoic acid receptors has been identified. This protein is termed NCoR [37, 38], a portion of which had been isolated previously in a yeast two-hybrid screen as RIP13 [39]. The highly related factor SMRT has also been identified [40].

NCoR and SMRT appear to be the major proteins associated with transcription repression for a number of nuclear receptors in the unliganded state (called active repression Fig. 2C). Deletion of the murine NCoR locus relieves nuclear receptor–mediated repression of specific genes [41]. The binding of either NCoR or SMRT to unliganded nuclear receptors, such as thyroid hormone receptors and retinoic acid receptors, is robust and is enhanced either by addition of receptor antagonists or the deletion of the AF-2 domain [37, 40]. Furthermore, unliganded steroid hormone receptors, such as glucocorticoid receptors and estrogen receptors, do not appear to interact with NCoR or SMRT, but strong interactions are observed in the presence of antagonists [42, 43]. The recruitment of NCoR or SMRT appears to be essential for the antagonist activity of nuclear receptors.

Both NCoR and SMRT contain a conserved bipartite nuclear receptor interaction domain (Fig. 1D) [44, 45] and interact with unliganded nuclear receptors in a fashion analogous to that utilized by coactivators with liganded receptors. Interaction of NCoR and SMRT with unliganded nuclerar receptors is mediated by a conserved extended helical motif, referred to as the CoRNR box, of consensus sequence LXXI/HIXXXI/L which utilizes overlapping surfaces with LXXLL motif in co-activators for interactions with nuclear receptors [46].

COACTIVATOR AND COREPRESSOR COMPLEXES

Both coactivators and corepressors recruit multifactors to form complexes. Binding of ligand results in a conformational change in the ligand-binding domain that reduces affinity for NCoR and SMRT complexes while simultaneously enhancing affinity for coactivators that contain a conserved LXXLL interaction motif [47], thereby converting the receptor from a transcriptional repressor to an activator (Fig. 3). This exchange could be a molecular switch for gene activation.

Coactivator complexes

As chromatinized transcription units are "repressed" compared with naked DNA, a critical aspect of gene activation involves nucleosomal remodeling [48]. It is believed that nuclear receptor–mediated transcription requires several different protein complexes that can act sequentially, combinatorially, or in parallel. One primary step is believed to be the recruitment of proteins that disrupt chromatin formation. Two general classes of chromatin remodeling factors have been identified that appear to play critical roles in transcriptional activation

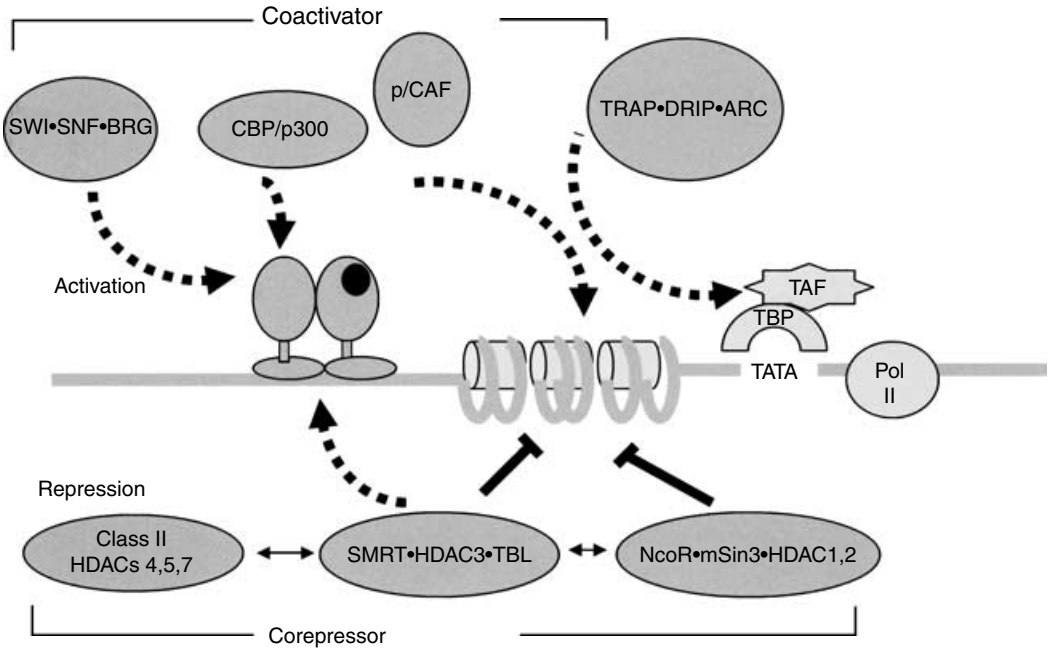

Fig. 3. "Yin-Yang" balance between coactivator and corepressor complexes in regulation of gene transcription. Different protein complexes can act either sequentially, combinatorially, or in parallel, to manipulate gene transcription. The SWI-SNF complex and the CBP·p/CAF possess adenosine triphosphate (ATP)-dependent chromatin remodeling and histone acetyltransferase activities, respectively. These complexes may act in concert to relieve chromatin-mediated repression, with the TRAP·DRIP·ARC complex functioning to recruit core transcription factors RNA polymerase II. Corepressor complexes include the NCoR·SIN3·HDAC, SMRT·HDAC3·TBL1 and HDACs 4.5,7 which possess histone deacetylase activity and functions are augmented by additional interactions. HDACs are thought to reverse the actions of histone acetyltransferase-containing complexes. Binding of hormone or ligand results in a conformational change in ligand-binding domain that reduces affinity for NCoR and SMRT complexes, while simultaneously enhancing affinity for coactivators complexes.

by nuclear receptors. These are ATP-dependent nucleosome remodeling complexes and factors that contain histone acetyltransferase (HAT) activity.

Switch (SWI)·Sucrose nonfermenting (SNF): ATP-dependent chromatin remodeling complexes. The yeast SWI-SNF complex facilitates the binding of sequence-specific transcription factors to nucleosomal DNA and can cause local changes in chromatin structure in an ATP-dependent manner [49]. SWI2/SNF2 protein is contained in a native multisubunit complex of ~2 MDa termed SWI/SNF and has sequence motifs closely related to those found in DNA-stimulated ATPases/DNA helicases [50]. Mammalian homologues of *Drosophila* SWI2/SNF2 such as Brg1 and Brm function as components of large multiprotein complexes that contain components related to subunits of yeast SWI/SNF [51, 52]. Both Brg1 and Brm have been shown to interact with the nuclear receptor in a ligand-dependent fashion [53]. Transfection of ATPase-defective alleles of either Brg1 or Brm into several mammalian cell lines leads to a significant decrease in the ability of several nuclear receptors to activate transcription, including retinoic acid receptors, estrogen receptos, and glucocorticoid receptors to activate transcription [54, 55]. These data suggest that these proteins may serve as the energy-transducing component of chromatin-remodeling machines.

CBP·SRC-1·p/CAF: The complex with HAT activity. A highly ordered chromatin structure presents a physical obstacle for gene transcription, presumably by limiting the access of transcription factors and RNA polymerase II core machinery to the target DNA. Histone acetylation results in decreased affinity between core histone subunits and DNA, and is correlated with transcriptional activation, whereas the opposite is true of hypoacetylated histones [56]. The rates of gene transcription roughly correlate with the degree of histone acetylation [57]. Thus, the specific recruitment of a complex with HAT activity to a promoter may play a critical role in overcoming repressive effects of chromatin structure on transcription [57].

It has been demonstrated that CBP/p300 [58, 59] and p/CAF contain HAT domains and have strong HAT activities. The carboxyl terminus of NCoA1/SRC1/p160 [60] and pCIP/ACTR/AIB1 [26] have been reported to possess HAT activity, though this activity is much weaker than the HAT activity of CBP/p300, and p/CAF. NCoA1/SRC1/p160 has been shown to interact with a conserved region in the carboxyl terminus of CBP and p300 and result in the cooperative formation of CBP·SRC1·p/CAF complex which brings HAT activity to nuclear receptor complex. Based on the presence of three regulatory domains, members of the p160 family

have been suggested to function as co-activators, at least in part, by serving as adapter molecules that recruit CBP and/or p300 complexes to promoter-bound nuclear receptors in a ligand-dependent manner [28, 61].

TRAP·DRIP·ARC: The complex for recruitment of RNA polymerase. In addition to coactivator complexes that harbor ATP-dependent nucleosome remodeling or HAT activities, other coactivator complexes without intrinsic HAT activity have been identified. The best characterized of these is the TRAP·DRIP·ARC complex that enhances the transcriptional activities of nuclear receptors. This complex is recruited to nuclear receptors in a ligand-dependent manner via a 220 kD component referred to as PBP/TRIP2/TRAP220/DRIP205, which contains two alternatively utilized LXXLL nuclear receptor interaction motifs [62]. The TRAP·DRIP·ARC complex consists of more than a dozen polypeptides, a subset of which appears to constitute modules that are components of other activator complexes, including CRSP, Suppressor of RNA polymerase B (SRB)/MED-containing cofactor complex (SMCC) and mouse mediator [63, 64]. These factors have no known enzymatic functions and may function to recruit RNA polymerase II holoenzyme to ligand-bound nuclear receptors.

Corepressor complexes

NCoR and SMRT contain multi-independent repressor domains that can interact with proteins that mediate transcriptional repression, including Sin3 deacetylase and histone deacetylase (HDACs). This interaction is dynamically regulated and exhibits promoter and cell-type specificity [65, 66]. Corepressors can disrupt activating interactions with the basal transcription apparatus, and/or recruit enzymes with HDAC activity that provides a critical step in active repression [67].

NcoR·mSin3·HDAC. NcoR·mSin3·HDAC complex is a basic repressor complex which has been proposed to be recruited via the NCoR or SMRT and required for repression mediated by unliganded nuclear receptors. The core mSin3 complex contains multiple components including retinoblastoma suppressor protein associated protein 46, 48 (RbAp46,48), HDAC1,2 and two small proteins, Sin-associated protein 30 and 18 (SAP30 and SAP18) which could serve as an adapter to bridge the connection between the core mSin3 complex and sequence-specific transcriptional repressors [68, 69]. This complex possesses HDAC activity and is thought to reverse actions of HAT-containing complexes.

SMRT·HDAC3·TBL1. Another corepressor complexes from HeLa cells termed SMRT·HDAC3·TBL1 complex has recently been identified, which potentiates active repression [47]. These repression functions may be augmented by additional interactions with the NcoR·mSin3·HDAC complex, as well as HDAC4, HDAC5, and HDAC7 [70, 71], implying a redundant or combinatorial deacetylase-dependent repression [47].

Molecular switch for gene transcription: Coactivators and corepressors in the integration of transcriptional response

Coactivators and corepressors seem to counteract the effects of one another in a "yin-yang" fashion, resulting in a homeostatically regulated and balanced control of transcription. Kinetically, transcription may be viewed as a multistep procedure: a derepression process followed by transcriptional initiation. The former refers to relief of the repression imposed by high order chromatin structure and the latter is assembly of the core RNA polymerase II machinery and the initiation of transcription. It is likely that different protein complexes can act either sequentially, combinatorially, or in parallel to manipulate gene transcription [36, 72]. Binding of hormone or ligand results in a conformational change in the ligand-binding domain that reduces affinity for NCoR or SMRT complexes while simultaneously enhancing affinity for coactivators that contain a conserved LXXLL interaction motif [3]. Initially, Brg-1·Brm-like complexes carry out chromatin remodeling while ligand-dependent recruitment of p160 factors bring required HAT activities, in concert with other factors such as CBP, p300, and p/CAF. Finally, recruitment of complexes such as the TRAP·DRIP·ARC complex may function to enhance RNA polymerase II recruitment to the promoter, thereby converting the receptor from a transcriptional repressor to an activator (Fig. 3).

MODIFICATIONS OF COREGULATOR ACTIVITY

The coregulator can be modified by acetylation, methylation, proteolysis, and phosphorylation. These modifications may change translocation or function of coregulators and provide a combinatorial code for tissue- and gene-specific gene transcription.

Acetylation and methylation

Many coregulators, including CBP, p300, pCAF, and GCN5 have acetyltransferase activities which result in histone acetylation and transcriptional activation after being recruited by nuclear receptor in ligand-dependent manner. In addition, acetylation of other coregulators is a critical regulatory event for transcriptional regulation. For example, the p160 coactivator, such as NCoA3/pCIP/ACTR/AIB1/RAC3/TRAM1/SRC3/p160 can be acetylated by CBP in a ligand-dependent manner. This event has a negative effect on the interaction of this coactivator with nuclear receptors, thus providing a putative negative feedback loop on ligand-induced transcription [73]. Protein methylation may also affect gene

transcription. It has been demonstrated that the nuclear receptor coactivator CARM1 is an arginine methyltransferase that is complexed with other coactivators, such as NCoA1/SRC1/p160 [18]. Additional protein methyltransferases, such as PRMT1, have recently been shown to interact with p160s and increase nuclear receptor transcriptional activity [19]. It has been shown that several RNA processing factors can be modulated by methylation which may modulate gene transcription [74].

Proteolysis

Another mechanism for modulating cellular coregulator levels is regulated proteolysis which links to cell cycle regulation [75]. Several proteins involved in proteolysis have been suggested as nuclear receptor coregulators, including TRIPs [76]. Recent studies have demonstrated that the corepressor NCoR, which binds to unliganded nuclear receptors and antagonist-bound steroid receptors, can be regulated proteolytically. Specifically, the seven-in-absentia-homologue-2 (Siah2) binds to the N-terminus of NCoR, and mediates proteasome-dependent proteolysis which decreases NcoR protein levels [77]. This is a good example of how regulated proteolysis can lead indirectly to an increase of transcriptional activity.

Phosphorylation

The functions of coactivator and corepressor complexes can be regulated by multisignal transduction pathways. Phosphorylation events may result in increased or decreased affinity between protein factors, leading to changes in components of the complexes. One example is the SWI-SNF complex, the components of which change at different stages of the cell cycle. In addition, its chromatin remodeling activity depends on the phosphorylation state of some of the subunits, such as Brg1 [78]. CBP/p300 can be phosphorylated in vivo [79]. The HAT activity of CBP/p300 can be regulated by signal-induced phosphorylation events and also by cyclin-dependent kinases, which presumably alter its coactivator activities during the cell cycle [80]. Activation of different intracellular signaling pathways and kinase cascades by membrane receptors modulates coactivator complexes, and seems to determine which acetyltransferases, such as CBP or pCAF, are recruited to a particular coactivator complex in a specific context [81]. In addition to CBP and p300, a large number of coactivators, including the p160 factors, have recently been reported to be substrates for different kinases. For example, the phosphorylation of p160 coactivators in response to different signaling events can cause redistribution of p/CIP from the cytoplasm to the nucleus.

Similarly, corepressors are apparent targets of signal transduction pathways. Activation of mitogen-activated protein (MAP) kinase cascades correlates with a redistribution of SMRT from a predominantly nuclear location to a predominantly perinuclear or cytoplasmic compartment [82]. It has been shown that the association of NCoR and SMRT with nuclear receptors is also modulated by cell signaling events. For example, phosphorylation of the estrogen receptor N-terminus by activation of MAP kinase decreased association of NCoR with estrogen receptor occurs in the presence of the antagonist tamoxifen [35]. The serine phosphorylation of thyroid hormone receptor β1 inhibits interactions between SMRT and nuclear receptors [83]. It has been also demonstrated that signal-dependent phosphorylation of c-Jun results in removal of NCoR/HDAC3/TBL1/TBLR1 complexes through recruitment of a specific ubiquitylation complex. This procedure allows binding of c-Jun/c-Fos heterodimers and transcriptional activation of AP-1. Therefore, phosporylation can contribute to increased coactivator and decreased corepressor activity.

Translocation

Certain nuclear receptor coregulators with no known DNA-binding capacity of their own might shuttle between intracellular compartments, including TRIP4/ASC1 [84] and NCoA3/pCIP/ACTR/AIB1/RAC3/TRAM1/SRC3/p160 [33]. These coactivators are located primarily in the cytoplasm of quiescent fibroblasts and in the nucleus of mitotic cells, thereby establishing a connection between subcellular localization and the mitotic state of the cell. It has been demonstrated that the translocation of coactivators is influenced by phosphorylation and CBP. For example, the translocation of NCoA3/pCIP/ACTR/AIB1/RAC3/TRAM1/SRC3/p160 is enhanced by phosphorylation [33]. In addition, TRIP4/ASC1/CG11710 translocates to the nucleus after cotransfection with CBP in quiescent rat-1 cells, suggesting acetyltransferase activity of CBP may be involved in the mechanism [84].

NCoR is localized both in the nucleus and the cytoplasm suggesting that corepressors also can translocate [85]. MAP kinase kinase (MEKK1 kinase) enhances the nuclear location of SMRT. However, very little is understood regarding the regulation of shuttling of coactivators and corepressors.

NUCLEAR RECEPTORS/COREGULATORS IN KIDNEY DISEASES

Since the progression of renal diseases is almost always associated with inflammatory processes, metabolic disorders, cell proliferation, hypertrophy and apoptosis, matrix expansion, and hypertension, the importance of nuclear receptors and their coregulators in these contexts will be addressed.

The role of nuclear receptors in regulation of inflammation

Inflammatory mediators are pathogenic in many renal diseases but inflammation affects renal function by different mechanisms. NF-κB is a cytokine-inducible transcription factor that plays a key role in the expression of a variety of genes involved in inflammatory responses and cell survival. In acute inflammation, NF-κB is activated and increases the expression of multiple proinflammatory genes. It has been demonstrated that NF-κB acts as coregulator for nuclear receptor–mediated transcriptional regulation and recruits a coactivator complex that has striking similarities to that recruited by nuclear receptors.

Like nuclear receptors-dependent gene expression, NFκB-dependent gene expression requires specific LXXLL motifs in one of the p160 family members. It has been shown that a member of the p160 family, NCoA1/SRC1/p160, potentiates the transcriptional activity of NF-κB by interacting with the p50 component of NF-κB [88]. Microinjection of anti-NCoA1/SRC1/p160 demonstrates that this coactivator is essential for p65-dependent transactivation in vivo. The second member of the p160 family NCoA2/TIF2/GRIP1/p160 also stimulates NF-κB–dependent gene expression.

The CBP-associated protein p/CAF is another important component of the NF-κB coactivator complex. The enhancement of NF-κB activity requires the HAT activity of p/CAF [61]. Microinjection of anti-p/CAF antibodies into living cells blocked p65 transactivation. The p65 component of NF-κB can also bind to the coactivator CBP and p300 [89]. Although NF-κB does not require CBP's HAT activity [90], CBP provides a platform for a variety of proteins that are important in NF-κB–dependent gene expression.

NF-κB–dependent activation requires the p160 family, CBP, and p/CAF. Interestingly, none of these coactivators can function alone, which suggests that they may form functional complexes in vivo. Additionally, overexpression of any of the coactivators leads to activation of transcription, suggesting that their amounts are limited in vivo [91]. These data suggest that nuclear receptor coregulators could be determinants for NF-κB activation and could be useful targets in preventing NF-κB–mediated inflammation in kidney disease.

On the other hand, although glucocorticoids, a ligand for glucocorticoid receptor, are the most powerful anti-inflammation drugs **t**he detailed mechanisms of glucocorticoid action in idiopathic nephrotic syndrome and progressive glomerulonephritides have not been clearly elucidated. It has been shown that all subsets of human glomerular cells definitely express the glucocorticoid receptor protein [92]. Glucocorticoid receptor α inhibits the expression of the cytokines, including interleukin (IL)-1β, tumor necrosis factor-α (TNF-α), granulocyte monocyte-colony-stimulating factor (GM-CSF), IL-4, IL-5, and IL-8. In addition, many other nuclear receptorss, such as PPARs and retinoic acid receptors, have also been shown to have powerful anti-inflammation features. Ligands of PPARs significantly inhibit proinflammatory cytokines, such as vascular cell adhesion molecule-1 (VCAM-1) and IL-6 expression in various cell types [93, 94]. It has been demonstrated that all three PPAR isoforms are differentially expressed in the kidney [95]. Recently, we have demonstrated that both eicosapentaenoic acid (EPA) and docosahexcenoic acid (DHA) which are ω-3 polyunsaturated fatty acids and thought to be ligands for PPARs down-regulate lipopolysaccharide (LPS)-induced activation of NF-κB via a PPARγ-dependent pathway in human kidney-2 (HK-2) cells [96].

PPARs and glucocorticoid receptor α inhibit the expression of proinflammatory genes by antagonizing the effects of other classes of transcription factors such as NF-κB, AP-1, and STAT [97, 98]. Their anti-inflammatory actions can be exerted through different mechanisms. First, they can alter signaling pathways leading to transcription factor activation. For example, glucocorticoid receptor α can inhibit Jun kinase activity leading to the abolition of c-Jun phosphorylation and subsequent AP-1 activation. PPARs repress NF-κB transcriptional activity in a ligand-dependent manner by either inhibiting IκB kinase and consequently preventing IκB degradation, or increasing IκB expression in cytokine-stimulated mesangial cells [99]. The inhibitory effect of glucocorticoid receptor α and PPARs on AP-1, NF-κB, and STAT-dependent genes might also be due to competition for the recruitment of their coactivator CBP/p300, the concentration of which is functionally limiting, and which is a common coactivator of these transcription factors. Thus activation of one factor could result in an inhibitory effect in others because of limited CBP/p300 [100]. Glucocorticoid receptor α and PPARs can also inhibit gene transcription by directly interacting with AP-1, NF-κB, and STAT [101]. An additional mechanism whereby glucocorticoid receptor and PPARs can alter gene expression is by modifying the acetylation of histones. Glucocorticoids repress histone acetylation by directly inhibiting CBP-associated HAT activity and by recruiting histone deacetylases [102]. As noted above, the deacetylation of histones reduces access of the transcription factors, such as AP-1 and NF-κB, to their response elements on DNA. Finally, PPARs and glucocorticoid receptor α can bind NCoR, a corepressor molecule, to exert anti-inflammatory activity.

Lipid-mediated renal and vascular injury: Role of nuclear receptor and its coregulators in cholesterol homeostasis

Cardiovascular disease is the most important cause of death at all stages of progression of renal disease, accounting for approximately 50% of the mortality among

patients on long-term dialysis and after renal transplantation [103]. In addition, lipid-mediated injury plays an important role in the pathogenesis of many renal diseases, including diabetic nephropathy [104, 105]. Diabetic kidneys specifically express several genes normally found in adipocytes, including adipocyte differentiation-regulated protein (ADRP) or adipophilin in humans, suggesting a switch of kidney phenotype in favor of lipid accumulation in diabetes. Many nuclear receptors (termed as metabolic nuclear receptors) and their coregulators play an important role in controlling cellular and whole-body sterol homeostasis, including (*1*) fatty acid, triglyceride, and lipoprotein metabolism via PPARα, β/δ, and γ, (*2*) reverse cholesterol transport and cholesterol absorption through the liver X receptors and liver receptor homologue-1 (LRH-1), and (*3*) bile acid metabolism through the farnesol X receptor, liver X receptors, and LRH-1 [107].

PPARs are important in controlling the homeostasis of fatty acid and triglyceride, which are increased in the patients with chronic renal failure. Binding to PPARα by fatty acid, eicosanoid, and fibrate drug ligands leads to activation of numerous genes involved in the uptake and β oxidative catabolism of fatty acids in heart, kidney, and muscle. Increased diversion of fatty acids into β oxidation decreases the availability of fatty-acyl conenzymeA (CoA) substrates for triglyceride synthesis and, therefore, decreases VLDL secretion by the liver [108]. PPAR agonists may also decrease triglyceride levels by increasing the expression of lipoprotein lipase (LPL) in the liver (PPARα) and in adipocytes, skeletal muscle (PPARγ), and macrophages (PPARα and γ) [109, 110].

Liver X receptors regulate the expression of genes involved in cholesterol and fatty acid homeostasis, including the genes for ABCA1 and SREBP1. Liver X receptors are thought to be a cholesterol sensor in peripheral tissue, including kidney, blood vessel, and monocyte-macrophages. We and others have previously shown that liver X receptor α is expressed in renal glomeruli and functionally present in mesangial cells where its activation mediates cholesterol efflux via ABCA1 [111, 112]. Liver X receptors are regulated by oxidized derivatives of cholesterol termed oxysterols and heterodimerize with retinoid X receptors [113]. Direct regulation of liver X receptor by oxysterols, liver X receptor autoregulation, indirect regulation of liver X receptor via PPARα and PPARγ, and possibly liver X receptor–independent regulation by PPARβ/δ induces ABCA1 expression in peripheral tissue [1]. ABCA1 transporter pumps cholesterol out of cells and processes it into high-density lipoprotein (HDL), which the liver removes from the blood stream. Defective ABCA1 in patients with Tangier disease results in very low HDL and cholesterol-stuffed macrophages that form foam cells, which can cause atherogenesis. Although activation of liver X receptor leads to ABCA1-mediated cholesterol efflux from kidney cells, the possible adverse effect is that an enhanced SREBP1c induced by liver X receptor may increase fatty acids synthesis and plasma triglyceride levels. It has been demonstrated that unliganded liver X receptor inhibits its target gene ABCA1 expression and that loss of liver X receptor in liver X receptor$^{-/-}$ mice leads to derepression of the ABCA1 gene in macrophages and the intestine, while the SREBP1c gene remains transcriptionally silent [10]. It is important to develop synthetic ligands for liver X receptors which remove active suppression induced by unliganded liver X receptor, without activating its target gene SREBP1c.

In liver, farnesoid X receptor which senses bile acids also dimerizes with retinoid X receptor. When activated, it shuts off bile production by stimulating transcription of the small heterodimer partner (SHP), which is an orphan receptor and strong inhibitor of CYP7A1, a target gene of liver X receptor-retinoid X receptor [1]. The inhibition of CY7A1, the rate-limiting enzyme in bile acid production, lowers bile availability in the intestine, hindering the emulsification and absorption of cholesterol and other fats. Therefore, liver X receptor and farnesoid X receptor act as sensors in different tissues to keep cholesterol absorption and transport in balance.

We have previously demonstrated that inflammation can disrupt this fine balance and promote intracellular lipid accumulation in human mesangial cells (HMCs) by inhibiting cholesterol efflux through inhibition of the PPAR-liver X receptor-ABCA1 pathway [111], presumably, it also increases bile acid synthesis and cholesterol absorption which may contribute dyslipidemia in the patients with chronic renal diseases. Both PPARα and PPARγ ligands prevent lipid accumulation in HMCs [111]. These results suggest potential mechanisms whereby inflammation may exacerbate lipid-mediated cellular injury in the glomerulus and in other tissues, and indicate that PPAR agonists may have a protective effect.

Glucose-mediated renal and vascular injury: Role of nuclear receptor and its coregulators in glucose homeostasis

Microvascular injury and mesangial dysfunction contribute to the pathogenesis of diabetic glomerulosclerosis. All three PPAR isoforms seem to play important roles in the development of diabetic nephropathy in type 2 diabetes. PPARγ mRNA is reduced by 77% in glomeruli of diabetic mice [114]. PPARγ agonists, such as thiazolidinediones, have been used as insulin-sensitizing agents for treating diabetes and metabolic syndrome [115] and also provides superior renal protection in a rat model of type 2 diabetes with obesity by reducing the proteinuria

and glomerular and tubular kidney damage [116]. On the other hand, both mRNA and protein of PPARα are elevated in glomeruli, cortical tubules, and renal arterial vessels of db/db mice [106]. Interestingly, there is some evidence to suggest either activating or inhibiting a nuclear receptor may have a similar biologic effect. For example, both PPARγ agonist and antagonist improve insulin resistance in type 2 diabetic subjects and have clinical potential for the treatment of diabetes type 2 and obesity [117]. Glucose metabolism is tightly controlled by a variety of hormones, including insulin, epinephrine, glucagon, and glucocorticoids acting on various cell types, including kidney. It has been demonstrated that dexamethasone induction of hypertension and diabetes is PPARα-dependent in LDL receptor-null mice, suggesting that activation of PPARα may involve in glucocorticoid-induced insulin resistance and hypertension [119].

HNF4α protein, an orphan receptor, was detected in glomerulus, and distal and collecting tubular epithelial cells of kidney. A loss-of-function mutation in human HNF4α causes a form of diabetes mellitus called maturity-onset diabetes of the young type 1 (MODY1) which is characterized in part by a diminished insulin secretory response to glucose [120]. Vitamin D receptor is decreased in both intestine and kidney of genetically diabetic db/db mice which may link to hyperplasia of kidney [121].

Cell proliferation, differentiation, and apoptosis

It has been shown that many nuclear receptors and their coregulators are involved in the regulation of cell proliferation, differentiation, and apoptosis. Cytokine-driven proliferation plays important roles in the development of glomerulosclerosis. All three isoforms of PPARs have been suggested to play a role in regulating the cell cycle and in carcinogenesis. It has also demonstrated that PPARγ ligands rosiglitazone and troglitazone inhibit platelet-derived growth factor–induced DNA synthesis in rat mesangial cells [122]. PPARγ activation may inhibit mesangial growth directly by affecting MAP kinase and cell cycle regulatory proteins [123]. PPARγ activation also significant inhibits HK-2 proliferation induced by high glucose. In vivo, PPARγ agonist troglitazone protects against nondiabetic glomerulosclerosis in rats independent of insulin/glucose effects and is thought to be associated with regulation of glomerular cell proliferation and hypertrophy [125].

Another nuclear receptor involving in mesangial cell proliferation is vitamin D receptor [126]. 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) has a major inhibitory effect on the G_1/S checkpoint of the cell cycle by up-regulating the cyclin-dependent kinase inhibitors p27 and p21, and by inhibiting cyclin D1 [127]. We have demonstrated that $1,25(OH)_2D_3$ inhibits mesangial cell proliferation via vitamin D receptor (Ruan, unpublished data). Vitamin D receptor function is impaired by several factors including hypocalcemia, hyperphosphatemia, accumulation of uremic toxins, and reduction in cellular levels of the vitamin D receptor partner, retinoid X receptor [128], which may result in mesangial cell proliferation. In addition, retinoids play a fundamental role in regulating normal cell proliferation and differentiation in either a retinoic acid receptor–dependent or independent manner [129]. Retinoids also limit glomerular proliferation, glomerular lesions, and albuminuria in an established model of renal damage.

Activation of retinoic acid receptors by ligands prevents puromycin aminonucleoside nephrosis (PAN) and oxidative stress–induced apoptosis in podocytes and mesangial cells [131]. On the other hand, $1,25(OH)_2D_3$ via vitamin D receptor may induce apoptosis either indirectly through effects on the insulin-like growth receptor and TNF-α or more directly via the Bcl-2 family system, the ceramide pathway, the death receptors (e.g., Fas) and the stress-activated protein kinase pathways (Jun N terminal kinase and p38) [127]. In addition, nerve growth factor (NGF)-induced factor B (NGFIB) is an inducible orphan nuclear receptor that initiates apoptosis [132]. p300 seems also to be involved in apoptosis control in mesangial cells [133].

Matrix expansion and renal fibrosis

Diabetic glomerulosclerosis is characterized by the accumulation of extracellular matrix in the mesangium. Estrogens seem to retard whereas estrogen deficiency seems to accelerate progressive glomerulosclerosis. Estrogen action is mediated via estrogen receptor subtypes α and β. Both estrogen receptor subtypes were expressed in human and mouse mesangial cells. It has been demonstrated that estrogens suppress transforming growth factor-β (TGF-β)–induced gene expression, such as type IV collagen in kidney mesangial cells. Estrogen also increased matrix metalloproteinase 9 (MMP-9) activity which results in extracellular matrix turnover and protects against progression of diabetic glomerulosclerosis [135]. Estrogen receptor modulator LY-117018 suppressed mesangial cell type IV and type I collagen gene expression in a dose-dependent manner. Genistein, which selectively binds to estrogen receptor β suppressed type I and type IV collagen synthesis, suggesting that estrogen receptor β mediates the effects of estrogen on collagen synthesis. In addition, estrogens also exert potent antioxidant effects that may contribute to the protective effect of female gender on the course of renal disease [137]. These observations suggest that sex hormones per se may be important determinants of the greater susceptibility of the male kidney to progressive renal injury.

It has been shown that PPARα ligands inhibit H_2O_2-mediated activation of TGF-β1 in HMCs. Troglitazone, a PPARγ agonist, suppresses the secretion of type I collagen by mesangial cells in vitro and also prevents mesangial expansion and glomerulosclerosis in diabetic rats [139]. Pioglitazone inhibits TGF-β–induced fibronectin expression by inhibiting AP-1 activation dependent on PPARβ, while 15d-prostaglandin J_2 (PGJ_2) acts through a dual mechanism independent of and dependent on PPARγ activation in mouse mesangial cells [140].

It has been reported that coactivator SRC-1 mRNA level is down-regulated by dexamethasone treatment in rat renal mesangial cells in vitro, and p300 is important molecule in TGF-β/Smad-pathway-mediated α2(I) collagen expression in mouse mesangial cells [141].

Hypertension

High blood pressure is a common finding in severe nephritic patients. The renin-angiotensin-aldosterone system (RAAS) plays an important role in its pathogenesis. Aldosterone acting through Mineralocorticoid receptor is thought to play a role in the development of hypertension. Aldosterone receptor antagonists have been shown to antagonize all these effects in experimental models [142]. Glucocorticoid receptor activation by glucocorticoids enhances blood pressure by inducing water retention and increasing plasma angiotensinogen concentration through increased hepatic synthesis [143]. On the other hand, activation of retinoic acid receptor by retinoids can intervene in the above systems and reduce systemic blood pressure and RAS activity [144]. The antihypertensive effect of the PPARγ agonist rosiglitazone has been reported in patients with diabetes or obesity [145]. Cytochrome P450–dependent arachidonic acid metabolites may act as mediators in the regulation of vascular tone and renal function. It has been shown that both PPARα and cytochrome P4504A are expressed in renal proximal tubules. Treatment with clofibrate, the PPARα agonist, increased cytochrome P4504A protein levels and production of 20-hydroxyarachidonic acid (20-HETE) which may ameliorate hypertension by restoring P450-dependent arachidonic acid hydroxylase activities [147]. Recently, liver X receptor has been identified as cAMP-responsive nuclear modulator of renin and c-myc expression; liver X receptor α activated renin gene expression may play an important role in blood pressure control [148].

Others

Nuclear receptors also play very important role in renal development, calcium/phosphorus metabolism, and elimination of harmful endogenous and exogenous c¨ompounds. For example, Deficiency of retinoic acid receptor causes abnormalities in fetal kidneys and reduced nephron number, which might be responsible for adult diseases such as hypertension and nephritis [149]. Vitamin D receptor forms vitamin D receptor · retinoid X receptor·coregulator complex which binds to vitamin D response elements in the promoter region of target genes to regulate the homeostasis of calcium and phosphorus, and also controls the expression of parathyroid hormone (PTH). It has been shown that impaired production of $1,25(OH)_2D_3$ and reduced parathyroid vitamin D receptor content in chronic kidney disease are major contributors to the generation and maintenance of parathyroid hyperplasia and increased synthesis/secretion of PTH [128]. There are many patients (>40% in some series) with chronic renal failure in whom administration of $1,25(OH)_2D_3$ does not decrease serum PTH levels [150]. This may be related to a number of factors, such as decreased parathyroid levels of the vitamin D receptor and the calcium-sensing receptor, monoclonality of the parathyroid hyperplasia, and hyperphosphatemia [151]. In addition, increased calreticulin induced by hypocalcemia prevents the binding of vitamin D receptor · retinoid X receptor to vitamin D response response element and results in the transcriptional effect of $1,25(OH)_2D_3$ on the PTH gene [151]. Detoxification is mainly through hepatic cytochrome P450 enzymes which are pregsnane X receptor target gene, and both pregsnane X receptor and cytochrome P4503A express in kidney, one of the sites of drug-metabolism [152]. Dysregulation of pregsnane X receptor may be involved in drug, or endo-, and xenobiotic-mediated renal injury.

CONCLUSION

Nuclear receptors can serve as activators or repressors dependent on the exchange or binding of coregulator complexes. These processes are regulated by various signal transduction pathways. The role of coregulators in controlling gene transcription in kidney cells remains less explored and further investigation will be required. It is clear that many nuclear receptors and coregulators are key factors in regulating inflammatory processes, metabolic disorders, cell proliferation, apoptosis, hypertrophy, and hypertension. These nuclear receptors and their coregulators may be useful targets for medication. It is possible to develop ligands with a large spectrum of full, partial, or inverse agonist or antagonist activity as well as compounds called selective nuclear receptor modulators that activate only a subset of the function induced by cognate ligand or that act in a cell type–selective manner. Such studies will lead to novel prevention and treatment strategies for many chronic renal diseases and its complications, such as atherosclerosis. The analysis of nuclear receptor functions in health and disease, as

reviewed, underscores a critical role for these receptors and their cognate ligands in the fine-tuned adaptive responses to fluctuating metabolic demands and inflammatory stresses.

ABBREVIATIONS

ABCA1 ATP binding cassette A1
ACTR Activator of the thyroid and RA receptor
AIB1 Amplified in breast cancer 1
ARA Androgen receptor activator
ARC Activator-recruited cofactor
ARIP Androgen receptor-interacting protein
ASC Activating signal co-integrator
BRG Brahma-related gene
CARM Coactivator-associated arginine methyltransferase
CBP CREB-binding protein
CREB cAMP-response element-binding protein
CRSP Coactivator required for Sp1 activation
DAX1 DSS-AHC critical region on the chromosome gene 1
DRIP Vitamin D receptor-interacting protein
ETO Eight-twenty-one translocation
GCN General control of amino acid synthesis
GBP RNA helicase Gu binding protein
GCNF Germ cell nuclear factor
GRIP Glucocorticoid receptor interacting protein
HAT Histone acetyltransferase
HDAC Histone deacetylase
MAP Mitogen-activated protein
MEKK MAP kinase kinase kinase
NCoA Nuclear receptor coactivator
NCoR Nuclear receptor corepressor
NF-κB Nuclear factor-κB
NGFIB NGF-induced factor B
NRC Nuclear receptor coregulator
pCAF p300/CBP-associated factor
pCIP p300/CBP cointegrator-associated protein
PBP PPAR binding protein
PIAS Protein inhibitor of activated STAT
PGC PPAR γ coactivator
PKA cAMP-dependent protein kinase
PRIP PPAR-interacting protein
PRMT Protein arginine methyltransferase
RAC Receptor-associated coactivator
RAP Nuclear receptor-activating protein
RB Retinoblastoma suppressor protein
RIP Receptor-interacting protein
SAP mSin3 associated protein
SMAD Similar to mad
SMCC SRB/MED-containing cofactor complex
SMRT Silencing mediator of retinoic acid and thyroid hormone receptor
SNF Sucrose nonfermenting
SRA Steroid receptor RNA activator
SRB Suppressor of RNA polymerase B
SRC Steroid receptor coactivator
SREBP Sterol-responsive element-binding protein
STAT Signal transducer and activator of transcription
SWI Switch
TAF TBP-associated factor
TBP TATA-binding protein
TBL Transducin-like protein 1
TBLR TBL1-related protein
TIF Transcriptional intermediary factor
TRAC Thyroid hormone receptor associated cofactor
TRAM Thyroid hormone receptor activator molecule
TRAP Thyroid hormone receptor associated protein
TRBP Thyroid hormone receptor binding protein
TRIP Thyroid hormone receptor interacting protein
UCP-1 Uncoupling protein 1

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