Functions of Nutrient-Sensing Nuclear Receptors in Health

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Summary

Nutrients play important roles in the regulation of physiological and pathophysiological events in higher animals. Nuclear receptors (NRs) share a common modular functional structure and constitute a transcription factor superfamily consisting of 48 members in humans. Some NRs are activated by the binding of small lipophilic molecules such as food components including fat-soluble vitamins (vitamins A, K, and D) or lipids (phosphatidylcholine, oleoylthanolamide, or fatty acids). NRs contribute to cell growth, differentiation, or metabolic regulation. Generally, NRs bound to their ligands function as a transcription factors targeting specific DNA sequences in genes. Additionally, ligand-bound NRs mediate the activation of specific intracellular signal transduction pathways. On the other hand, some NRs are functional without binding a ligand. Information on the roles and functions of nutrient-sensing NRs in physiological or pathophysiological events not only leads to an understanding of the need for nutrients, but also contributes to the prevention and amelioration of nutrition-related diseases.

Key Words retinoic acid receptor, steroid and xenobiotic receptor, vitamin D receptor, peroxisome proliferator-activated receptor α, farnesoid X receptor

Sequence analyses of the human genome revealed the existence of 48 members of nuclear receptor (NR) family (1). The NRs share a common modular structure composed of three typical functional domains: an N-terminal domain, a central DNA-binding domain (DBD), and a C-terminal ligand-binding domain (LBD). The DBD comprises two zinc-fingers allowing NRs to interact with specific response elements in target genes. There are various modes of DNA-binding for NRs, including binding as a monomer, homodimer, and heterodimer formed with a common partner, the retinoid X receptor (RXR). The binding of ligands to the LBD causes dramatic conformational change of the LBD and the recruitment of coregulators to modulate the transcriptional activity of target genes. Thus, ligands usually act as a trigger for NRs, and ligand-bound NRs play important roles in the transcriptional regulation of physiological (e.g., development, metabolism, reproduction, cell cycle, growth, and differentiation) and pathophysiological (e.g., osteoporosis, diabetes, cardiovascular disease, and cancer) processes. Ligands for NRs are hydrophobic endogenous and exogenous compounds. Some NRs bind nutrients such as fat-soluble vitamins, fatty acids, phospholipids, and bile acids.

Retinoic Acid Receptor (RAR)

Retinoids (e.g., retinol, retinal, and retinoic acid) are natural and synthetic compounds related to vitamin A. Vitamin A and its metabolites, particularly all-trans retinoic acid (ATRA) and 9-cis-retinoic acid, play important roles in many cellular processes such as cell differentiation, proliferation and apoptosis. These retinoids are potent transcriptional regulators modulating the expression levels of more than 500 genes. ATRA and 9-cis-retinoic acid are ligands of three RAR isotypes (RARα, RARβ, and RARγ), and three RXR isotypes (RXRα, RXRβ, and RXRγ), respectively. RARs and RXRs form heterodimers on the retinoic acid response element of ATRA-responsive genes and act as transcription factors regulating the expression of these genes. RARs are widely expressed during development. RARα1-knockout (KO) mice appear healthy and phenotypically normal, whereas an early postnatal lethality and testis degeneration are observed in KO mice expressing none of the RARα isotypes (2). In addition, RAR2-KO mice appear normal, but mice KO for all RARγ isotypes exhibit growth deficiency, early lethality, and male sterility (3). Thus, RAR subtypes likely have redundant functions.

Several studies have used transgenic mice expressing a dominant-negative RAR (RARdn), which inhibits RAR signaling, to understand ATRA and RAR signaling. Tissue-specific overexpression of RARdn results in tissue-specific ablation of RAR signaling. Overexpressing RARdn in pancreatic β-cells induces an age-dependent decrease in plasma insulin in response to feeding conditions and glucose challenges in mice (4). Additionally, β-cell mass and insulin per β-cell are reduced. Thus, RAR-mediated ATRA signaling is required in the adult pancreas to maintain β-cell function and mass. On the other hand, body weight and subcutaneous adipose tissue are increased in transgenic mice expressing RARdn in adipocytes compared with those of wild-type mice (5). Thus, transgenic mice have a large amount of subcutaneous fat. They have impaired glucose tolerance and higher concentrations of plasma free fatty acids.

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and liver triglycerides compared with those of control mice. Since retinoid deficiency affects many tissues simultaneously, ablation of tissue-specific AR/RA signaling should provide important information about the need for retinoids in each tissue.

**Steroid and Xenobiotic Receptor (SRX) for Vitamin K**

Vitamin K is a critical nutrient required for the activation of blood coagulation factors (e.g., prothrombin) and bone matrix proteins (e.g., osteocalcin). These proteins are activated by the vitamin K-dependent enzyme γ-glutamylcarboxylase, which carboxylates the γ-position of specific glutamate residues in these proteins, resulting in γ-carboxyglutamic acid residues (Gla). Vitamin K functions as a cofactor for this enzyme. Accumulating evidence for a novel function of vitamin K has shown that vitamin K suppresses osteoclastogenesis and stimulates osteoblastogenesis.

Interestingly, vitamin K is a ligand of the steroid and xenobiotic receptor (SRX in humans, pregnane X receptor (PXR) in mice) in the nucleus (6). SRX is activated by various biological and xenobiotic substances and functions as a transcription factor. SRX is expressed in the liver and small intestine, where drug-metabolizing enzymes are expressed, and in osteosarcoma cell lines. SRX forms a heterodimer with RXR and binds to SRX-response element to regulate the expression of target genes. SRX modulates the expression of extracellular matrix-related genes, which are involved in collagen assembly, in a vitamin K-dependent manner and contributes to bone homeostasis (7). Thus, vitamin K acts as a cofactor for Gla formation in osteocalcin. Moreover, it regulates the expression of factors involved in bone formation through SRX. SRX is expressed in humans, whereas the SRX ortholog PXR is expressed in mice. Loss-of-function approaches demonstrated that SRX/PXR promotes bone formation, represses bone resorption, and prevents age-dependent wearing of articular cartilage (8, 9). Therefore, identifying target genes regulated by SRX/PXR might contribute to the prevention and treatment of osteoporosis. Moreover, investigating the nuclear receptor SRX/PXR will likely bring insight into novel functions of vitamin K.

**Vitamin D Receptor**

Vitamin D is essential for maintaining bone mineral homeostasis by promoting the transport of calcium and phosphate. Vitamin D deficiency induces diseases such as rickets and osteoporosis. Vitamin D3 provided by the diet or vitamin D3 synthesized in the skin is metabolized to 25-hydroxyvitamin D3 (25(OH)D3) by CYP2R1 or CYP27A1 in the liver. The resulting 25(OH)D3 is hydroxylated by CYP27B1 in the kidney to produce 1α,25(OH)2D3. Active vitamin D3 binds to the vitamin D receptor (VDR), and ligand-bound VDR forms a heterodimer with RXR to regulate the expression of vitamin D-responsive genes involved in calcium and phosphate homeostasis. The active form of vitamin D3 for VDR is 1α,25(OH)2D3. The major form of vitamin D3 in the circulation is 25(OH)D3, and the serum concentration of 25(OH)D3 is an indicator of vitamin D sufficiency. Several studies suggested that 25(OH)D3 is a ligand of VDR, but details remain unclear (10).

Genetically modified mice have been used to understand the mechanism of action of vitamin D. CYP27B1-KO mice display typical rickets symptoms (11). When CYP27B1-KO mice are fed a diet containing normal calcium and vitamin D levels, the plasma concentration of 1α,25(OH)2D3 is below the detection limit. Administration of 25(OH)D3 to CYP27B1-KO mice ameliorates the symptoms of rickets, and surprisingly, results in plasma concentrations of 1α,25(OH)2D3 in the normal range. These results suggest that enzymes other than Cyp27B1 synthesize 1α,25(OH)2D3. Recently, the following three genetically modified rats have been generated: (i) CYP27B1-KO rats, (ii) VDR-KO rats, (iii) type II rickets model rats expressing a mutant VDR(R270L), which recognizes 1α,25(OH)2D3 with an affinity equivalent to that for 25(OH)D3 (12). These three rat models present symptoms of rickets, but their phenotypes are different. Lower plasma calcium concentrations are detected in CYP27B1-KO rats than in wild-type rats and the other two rat models. VDR-KO rats also show skin abnormalities and hair loss phenotypes. Administration of 25(OH)D3 to VDR(R270L) mutant rats abolishes the symptoms of rickets. These data indicate that 25(OH)D3 also has a physiological effect and suggest that administration of 25(OH)D3 might be beneficial for patients with type II rickets induced by VDR(R270L) mutation. Research using these genetically modified animals is expected to lead to the development of therapeutic agents against not only rickets but also diseases related to vitamin D deficiency such as osteoporosis.

**Peroxisome Proliferator-activated Receptor α (PPARα) and Farnesoid X Receptor (FXR)**

PPARs are composed of three isoforms (α, β/δ, and γ). PPARs form heterodimers with RXR and bind to a specific DNA sequence, called a direct repeat 1 response element separated by one nucleotide (DR1, 5′-AGGTCA N AGGTCA-3′; N, any single nucleotide) of target genes. PPARs are activated by plant-derived natural products, phosphatidylincholine, oleoylethanolamide, or fatty acids (e.g., linolenic acid, linoleic acid, petroselenic acid, and arachidonic acid for PPARα and PPARγ) and eicosanoids (e.g., 8(S)-hydroxyeicosatetraenoic acid for PPARα and 15-deoxy-D12,14-prostaglandin J2 for PPARγ). PPARα is abundantly expressed in the liver. PPARα-KO mice fed a high-fat diet accumulate more lipids in the liver than wild-type mice (13). PPARα-KO mice fasted for 24 h develop severe hypoglycemia and hypoketonemia and increase plasma fatty acid levels. Thus, PPARα play a role in lipid metabolism in the liver and feeding behaviors in the gut.

FXR acts as a sensor for bile acids (e.g., chenodeoxycholic acid and cholic acid) and is abundantly expressed in the liver, which is exposed to bile acids. FXR forms a heterodimer with RXR and binds to the DNA sequence of target genes to activate their transcription. FXR regulates target gene expression by binding to two func-
Disclosure of state of COI

No conflicts of interest to be declared.

REFERENCES