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PXR- and CAR-mediated herbal effect on human diseases☆

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ABSTRACT

The pregnane X receptor (PXR) and constitutive androstane receptor (CAR) are two members of the nuclear receptor superfamily that regulate a broad range of genes involved in drug metabolism and transport. A variety of naturally occurring compounds present in herbal medicines were identified as ligands of PXR and CAR. Recently, accumulative evidences have revealed the PXR- and CAR-mediated herbal effect against multiple human diseases, including inflammatory bowel disease (IBD), cholestatic liver disease, and jaundice. The current review summarized the recent progress in identifying the expanding libraries of herbal medicine as ligands for PXR and CAR. Moreover, the potential for herbal medicines as promising therapeutic agents which were mainly regulated through PXR/CAR signaling pathways was also discussed. The discovery of herbal medicines as modulators of PXR and CAR, and their PXR- and CAR-mediated effect on human diseases will provide a basis for rational drug design, and eventually be explored as a novel therapeutic approach against human diseases. This article is part of a Special Issue entitled: Xenobiotic nuclear receptors: New Tricks for An Old Dog, edited by Dr. Wen Xie.

1. Introduction

1.1. Nuclear receptor

Nuclear receptors (NRs) comprise a large superfamily of ligand-dependent transcription factors that are involved in diverse developmental and physiological events of fundamental importance [1]. NRs can be regulated by small lipophilic substances, such as endogenous hormones, vitamins A and D, fatty acid, and xenobiotics including drugs and environmental toxicants. Structural analysis of NRs reveals that they share certain amount of structural homology, which is characterized by an N-terminal zinc-finger type DNA-binding domain (DBD) and a C-terminal ligand-binding domain (LBD). In contrast to the highly conserved structure of DBD and LBD, other regions of the proteins are usually poorly conserved and their structure is largely unknown [2]. Forty-eight functional NR genes have been identified in the human genome, which are divided into seven subfamilies (Nuclear Receptors Nomenclature Committee, 1999) [3]. For the past two decades, considerable studies have revealed the important role of NRs in regulating the signaling pathways under physiological and pathological conditions. NRs have been identified as the therapeutic targets for development of novel drugs for various diseases, including type 2 diabetes, cardiovascular disease, inflammatory bowel disease, cancer, etc [4–6].

1.2. PXR and CAR

The pregnane X receptor (PXR, NR1I2) and constitutive androstane receptor (CAR, NR1I3) are two closely related members of NRs, both of which function as ligand-activated transcription factors by interacting with the retinoid X receptor alpha (RXRα, NR2B1) on response elements located in the control regions of their target genes. PXR was first identified in 1998 as a member of the NR superfamily. In mammals, PXR is highly expressed in the major organs that are important in xenobiotic biotransformation including the liver and the intestine [7]. Moreover, the PXR mRNA has also been detected in both normal and neoplastic breast tissues, as well as in peripheral blood mononuclear cells (PBMCs) in humans [8,9]. PXR has been well

Abbreviations: ABC, ATP-binding cassette; AD, Alzheimer's disease; AhR, aryl hydrocarbon receptor; CAR, constitutive androstane receptor; CARKO, CAR-knockout; CGD, cholesterol gallstone disease; CPT1, carnitine palmitoyltransferase 1; CYP, cytochrome P450; DBD, DNA-binding domain; DIM, diindolylmethane; ECI, enoyl-CoA isomerase; EEPA, ethanol extract of *Phyllanthus amarus*; GBE, *Ginkgo biloba* extract; G6Pase, glucose-6-phosphatase; GST, glutathione S-transferase; IBD, inflammatory bowel disease; LBD, ligand-binding domain; LCA, lithocholic acid; MCD, methionine- and choline-deficient; MDR1, multidrug resistance 1; MRP2, multidrug resistance proteins 2; NASH, non-alcoholic steatohepatitis; NCoR, nuclear receptor co-repressor; NR, nuclear receptor; OA, oleanolic acid; OATP, organic anion transporting polypeptide; ob/ob mouse, leptin-deficient mouse; PBMCs, peripheral blood mononuclear cells; PBREM, phenobarbital-response element; PEPCK, phosphoenoylpyuvate caroxykinase; P-gp, P-glycoprotein; PXR, pregnane X receptor; R1, Notoginsenoside R1; Rb1, ginsenoside Rb1; RES, resveratrol; RXRα, retinoid X receptor alpha; SLCO, solute carrier organic anion; SRC, steroid receptor co-activators; TCMs, traditional Chinese medicines; TCPOBOP, 1,4-bis[2-(3,5-dichloropyridyloxy)]benzene; UGT, UDP-glucuronosyltransferase; WT, wild type; WZ, Wuzhi tablet; XREM, xenobiotic response element.

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established to function as a master-regulator of xenobiotic- and drug-inducible expression and activity of CYP3A, CYP2B, and CYP2C subfamily of the cytochrome P450 (CYP) drug-metabolizing enzymes in humans and rodents [10,11]. PXR target genes also encode enzymes that are involved in the metabolism of xenobiotic compounds, including glutathione S-transferase (GST), sulfotransferase, UDP-glucuronosyltransferase (UGT), and carboxylesterase in liver enzymes [12–14]. Moreover, PXR also regulates several important drug transporter proteins, such as organic anion transporting polypeptide 2 (OATP2), which is newly classified within the OATP/ solute carrier organic anion (SLCO) superfamily, and members in ATP-binding cassette (ABC) superfamily, including multidrug resistance 1 (MDR1)/ P-glycoprotein (P-gp), and multidrug resistance proteins 2, 3, 4, and 5 (MRP2/3/4/5) [15–17]. Experimental evidence has provided an understanding of the general steps involved in the activation of PXR. In the absence of ligands, PXR is localized in the cytoplasm forming a complex with co-repressor proteins such as nuclear receptor co-repressor (NCoR) that inhibits the transcriptional activity. However, ligand-binding of PXR results in dissociation from the co-repressor and recruitment of co-activator proteins such as steroid receptor co-activators (SRC1 and SRC2). The resultant ligand-bound PXR translocates to the nucleus, where it heterodimerizes with RXRα and binds to the responsive element in the promoter of the target genes [18].

Similar to PXR, CAR is also recognized as a xenobiotic-sensing NR mainly expressed in hepatic tissue and small intestine. It was originally demonstrated to regulate the phenobarbital-inducible expression of several genes encoding important members of the CYP2B subfamily of enzymes [19]. CAR has since been shown to regulate the expression and activity of a number of phase-I and phase-II metabolic enzymes, as well as important membrane transporter proteins involved in the biotransformation and transport of endogenous substances, naturally occurring compounds, drugs, and other xenobiotics [20]. In addition, CAR was also shown to regulate the repression of gluconeogenic enzymes, such as phosphoenoylpyuvate caroxykinase 1 (PEPCK1), carnitine palmitoyltransferase 1 (CPT1), and enoyl-CoA isomerase (ECI) [21,22]. Similar to the PXR-mediated gene activation, CAR translocates to the nucleus from the cytoplasm upon ligand binding, and forms a heterodimer with RXRα. Coactivators such as SRC1 are recruited to CAR following dissociation of corepressors such as NCoR. The complex of CAR-RXRα-coactivator then binds to the responsive element in the promoter of the target genes, resulting in increased gene transcription. As CAR is constitutively active, activation of CAR may also occur without direct binding of the ligand to CAR [18].

It has been well demonstrated that PXR and CAR share distinct but overlapping sets of target genes involved in drug and xenobiotic metabolism, often through shared NR-response elements. For instance, PXR regulates CYP2B genes through binding to the phenobarbital-response element (PBREM) in the promoter region, whereas CAR is also found to activate gene expression through the xenobiotic response element (XREM) in the upstream promoter of the CYP3A4 gene in humans [12,23,24]. Because PXR and CAR are activated by a myriad of xenobiotic compounds and regulate the expression and activity of multiple genes involved in drug and xenobiotic metabolism and transport, the activation of these two receptors may lead to profound up regulation of uptake, transport, metabolism, and elimination of potentially toxic compounds from the body and serve as a principal mechanism defending the body from toxic insult. However, PXR- and CAR-mediated gene activation may also represent the molecular basis for an important class of drug–drug, herb-drug, or food-drug interactions in the clinical practice. For example, drug-drug interactions (DDIs) have been implicated as an important clinical issue which may eventually lead to potentially fatal adverse drug reactions. The majority of DDIs are due to alterations in PXR and CAR-mediated gene activation of multiple drug metabolizing enzymes and transporters. If one drug activates or antagonizes PXR/CAR, it can be predicted that administration of this drug will alter the metabolism and elimination of other co-administrated drugs that are substrates of PXR/CAR-target gene encoded proteins. Therefore, the efficacy of these drug therapies will be changed in patients on combination therapy.

1.3. Herbal medicine

Herbal medicine has played a significant role in maintaining human health and improving the quality of life for centuries. The term herb refers not only to the leaf, but also the root, bark, flower, fruit, and seed of the plant. Herbal medicine has been used for multiple medicinal purposes, including relieving pain, improving digestion, and treating hypertension, inflammation, diabetes, etc. As indicated by the World Health Organization, approximately three quarters of the world's population rely on traditional medicine, the treatment of which involves the use of plant extracts or their active components [25]. In the United States, about one third of the population takes supplements derived from herbs [26]. In contrast to the substantial information on the structure and biological activity of chemical drugs, the mechanism of action of most herbal medicines has not been fully elucidated.

Accumulative evidences have revealed that PXR and CAR serve as biological targets of a number of herbal extract or active compounds contained in herbal medicine [27]. For example, St. John's wort was the first herbal medicine shown to possess the ability to activate PXR [28,29]. Since then, a variety of other herbal medicines have also been identified as ligands of PXR and CAR. Moreover, there is an emerging role for PXR and CAR as therapeutic targets in human diseases, such as inflammatory bowel disease, cholestasis, and jaundice. Therefore, we aim to review here this expanding literature by focusing on the information regarding the PXR- and CAR-mediated herbal effect on human diseases.

2. Modulators of PXR/CAR identified from herbs and plants

Plants provide us with an abundant source of biologically active substances that have played a critical role in developing novel pharmaceutics. Based on the knowledge of the traditional therapeutic applications of herbs, many of these herbal-derived products have demonstrated beneficial medicinal value in clinical practice. In the past two decades, numerous herbal-derived ligands of PXR and CAR have been identified. This section updates the current data on herb-derived PXR and CAR modulators (Tables 1–3).

2.1. Herb-derived dual modulators of PXR and CAR

As PXR and CAR share distinct but overlapping sets of target genes involved in drug and xenobiotic metabolism, herbal-derived compounds that regulate both PXR and CAR were discovered. Qianhu, the dried roots of *Peucedanum praeruptorum*, is a widely used traditional Chinese medicinal herb listed in the Chinese Pharmacopoeia. It has long been used for the treatment of certain respiratory diseases such as asthma, chronic bronchitis, and pulmonary hypertension [30]. Recent studies have also revealed a wide variety of pharmacological activities of Qianhu, including relaxing the smooth muscle of tracheas and pulmonary arteries, opening the ATP sensitive potassium channels, and inducing the mitochondria-mediated apoptosis [31–33]. The major active constituents isolated from Qianhu comprise praeruptorin A, C, D, and E. We previously demonstrated that praeruptorin A, C, and D significantly induced CYP3A4 luciferase activity, the mRNA and protein expression of CYP3A4, and the enzyme activity through the CAR-mediated pathway in LS174T cells [34]. Similar results were also obtained for MRP2, in which the expression of MRP2 was significantly upregulated by praeruptorin A and praeruptorin C via the CAR-mediated pathway in vitro [35]. Moreover, praeruptorin A and C induced PXR-mediated CYP3A4 luciferase activity, the mRNA and protein expression of CYP3A4, and the catalytic activity of CYP3A4 in a