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Original Article

PXR as a mediator of herb–drug interaction

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ABSTRACT

Medicinal herbs have been a part of human medicine for thousands of years. The herb–drug interaction is an extension of drug–drug interaction, in which the consumptions of herbs cause alterations in the metabolism of drugs the patients happen to take at the same time. The pregnane X receptor (PXR) has been established as one of the most important transcriptional factors that regulate the expression of phase I enzymes, phase II enzymes, and drug transporters in the xenobiotic responses. Since its initial discovery, PXR has been implicated in multiple herb–drug interactions that can lead to alterations of the drug's pharmacokinetic properties and cause fluctuating therapeutic efficacies, possibly leading to complications. Regions of the world that heavily incorporate herbalism into their primary health care and people turning to alternative medicines as a personal choice could be at risk for adverse reactions or unintended results from these interactions. This article is intended to highlight our understanding of the PXR-mediated herb–drug interactions.

1. Discovery and early characterization of PXR as a xenobiotic receptor

Humans and other mammals are exposed to numerous xenobiotics every day either intentionally or unintentionally through food, water, air, or any other type of environmental exposure. Within the natural products realm of xenobiotics, there exists a seemingly limitless array of chemical entities that could hold the potential for pushing our understanding of currently puzzling diseases to the edge of the scientific frontier. These chemical entities from natural products, or phytochemicals, can become incorporated in the already vast and complex biochemical nature of the human body, and can lead to either intended benefit or unintended harm. The body's innate ability to sense, react to, and act upon these foreign substances is a remarkable feat that ensures efficient metabolism/detoxification and the restoration of homeostasis.

The cascade of transcription and expression of drug metabolizing enzymes and transporters upon exposure to xenobiotics has been traced to the nuclear receptor pregnane X receptor (PXR). In 1995, Phil Guzelian's laboratory discovered the existence a novel element in the CYP3A gene promoter

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that links the glucocorticoid signaling and subsequent CYP3A1 gene activation, which disproved the idea that direct binding of glucocorticoids such as dexamethasone (DEX) to the glucocorticoid receptor (GR) was the mechanism of CYP3A1 gene activation [1]. Two areas of conserved rodent DNA sequence, referred to as "footprints", within the CYP3A gene promoter lacked the typical glucocorticoid response element (GRE), which further supported the existence of a novel element that is bound by a yet to be defined cellular factor. One year later, Phil Guzelian's laboratory further proposed that the presence of unique "cellular factors" in each species, instead of allelic heterogeneity in the CYP3A gene itself, accounts for the well-known species specific induction of CYP3A enzymes by the same xenobiotics, such as rifampicin (RIF) and pregnenolone-16α-carbonitrile (PCN) [2]. Two years later, in 1998, PXR was first cloned in the laboratories of Steve Kliewer and Ron Evans utilizing cDNA libraries. PXR was demonstrated to be a novel nuclear receptor activated by endogenous and synthetic steroids and be present in highly metabolic tissues such as the liver and intestines [3,4]. The Kliewer group termed the nuclear receptor PXR since it was activated by the 21-carbon pregnanes, while the Evan's group termed it steroid and xenobiotic receptor (SXR) due to its activation by natural and synthetic steroid compounds and xenobiotics [3,4]. These findings ultimately set the stage for the discovery of the *in vivo* functionality of this nuclear receptor that sits at the heart of the xenobiotic response of enzymes and transporters. The DNA "footprints" in the promoter region of CYP3A that were discovered by the Guzelian group contain a PXR response element, which was bound to by the "cellular factor" PXR. This correlation therefore classifies CYP3A as a direct target gene of PXR [5]. This formed speculation of a connection between PXR and drug metabolizing enzyme induction involved in the drug response *in vivo*. In 2000, the Evans first reported the creation and characterization of the PXR knockout mice, in which the induction of CYP3A by PCN and DEX was completely abolished [6], and these results were independently verified in another strain of PXR knockout mice created in the Kliewer lab [7].

There is a considerable homology in the DNA binding-domain (DBD) of PXR between the human and mouse PXR. This conserved portion of the DBD allows PXR to share promoter binding sites in the CYP3A gene promoters of either the human or rodent origin. In a murine model, disruption of the N-terminal zinc finger portion of the DBD resulted in a truncated and inactive protein, unable to bind to DNA [7]. Homology in the C-terminal ligand binding-domain (LBD) was found to be much less between humans and mice, which postulates the idea of specificity of ligand recognition by PXR in different species [5]. Crystal structure studies of the LBD revealed a more in-depth reasoning for the diverse, yet distinct, ligand binding to PXR [8]. The large and rather unique LBD binding pocket is what allows PXR to bind to a diverse array of ligands, while other traditional nuclear receptors tend to have a more rigid specificity for their ligands [8]. The pocket itself is spherical, hydrophobic, and flexible, which are all characteristics that would be expected for a promiscuous receptor [8]. Within the large hydrophobic portions of the pocket, there exist a small number of polar head residues [8]. Changes within these polar residues can lead to variations in responsiveness to different xenobiotics. This ligand pocket variability supports the idea of species specific forms of PXR and consequently, different xenobiotic responses [8]. Cell transfection and mouse transgenic studies have functionally demonstrated that the species origin of PXR, rather than the structure of the promoter regions, dictates the response to xenobiotics [6]. As a direct result of this finding, "humanized" mice have been created by genetically replacing the mouse PXR (mPXR) with the human PXR (hPXR) [5]. The humanized mice were able to display a more human representative drug response profile rather than a mouse representative drug response profile [5]. The creation of "humanized" PXR mice is a significant step forward in creating a standard model that can be used to test drug–drug interactions, toxicity, and herb–drug interactions in order to create overall safer drugs [5]. This new model also gives us the opportunity to be able to observe potentially harmful interactions between herbal medicines and prescription medicines before they can occur in human patients.

Previous beliefs that PXR was solely in charge of the regulation of phase 1 cytochrome P450 enzymes have been debunked, because emerging evidence has shown that PXR also plays an essential role in the regulation of phase II drug metabolizing enzymes and drug transporters [5]. As of 2009, PXR target genes include phase I cytochrome P450's (*CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A1, CYP3A4, CYP3A5, CYP3A7, CYP4F12, CYP24, and CYP27A1*), phase II uridine diphosphate (UDP)-glucuronosyltransferases (*UGT1A1, UGT1A3, UGT1A4, UGT1A6, and UGT1A9*), sulfotransferases (*Sult2a1*), glutathione S-transferases (*Gsta2, GSTA4*), and carboxylesterases (8, 9, 16), and phase III P-glycoprotein (*MDR1/ABCB1*), multidrug resistance-associated protein 1 (Abcc1), multidrug resistance-associated protein 2 (*Abcc2*), multidrug resistance-associated protein 3 (*Abcc3*), and organic anion transporting polypeptide 2 (*OATP2*) [9,10]. As a result, PXR has since been defined as a master regulator of the xenobiotic response [5].

2. Herb–drug interactions

Medicinal herbs have been a part of human medicine for the last 5000 years and continue to be increasingly involved in modern medicine of the 21st century [11]. An herb is defined as being any type of plant or plant product from the tip of the plant down to the roots in the earth, including and leaves, flowers, and seeds [11]. Herbs contain various phytochemicals, but the proportions of these chemicals can vary substantially from plant to plant. This natural inconsistency lends into the great complexity of studying safety and efficacy of these natural products. In 2007, is has been reported that 40% of adults in America used some form of complementary and alternative medicine, 17.7% of which were natural products [12]. A third of Americans who consume an herbal product concomitantly consume other oral products [13]. On a larger scale, the WHO has reported 70% of the world's population uses some form of alternative medicine [14]. This becomes especially concerning when it comes to drugs such as chemotherapeutics and immunosuppressive agents because they have a narrow therapeutic index and fluctuations in

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