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Control of lymphocyte homeostasis and effector function by the aryl hydrocarbon receptor

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ABSTRACT

The adaptive immune system, composed of lymphocytes, recognizes diversified antigens and generates immunological memory. According to the canonical model, it is the innate immune system that captures pathogens and senses environment to activate adaptive lymphocytes through antigen presentation, costimulatory signals and cytokine milieu. Emerging evidence indicates that environmental cues can be directly conveyed to lymphocytes by the aryl hydrocarbon receptor (AhR). AhR is a ligand-activated transcription factor that widely expresses in many immune cell lineages and recognizes a broad range of ligands including endogenous and dietary metabolites, microbial derivatives and xenobiotics. This review will focus on the regulatory role of AhR in not only adaptive but also innate lymphocytes including recently discovered innate lymphoid cells.

1. Introduction

1.1. AhR is a bHLH-PAS transcription factor

The aryl hydrocarbon receptor (AhR) protein belongs to a transcription factor family whose members contain bHLH (basic helix–loop–helix) and PAS (period [per]-aryl hydrocarbon receptor nuclear translocator [ARNT]-single minded [SIM]) domains. Through relatively well-conserved bHLH and PAS domains, bHLH-PAS transcription factors heterodimerize to form a functional DNA binding complex to regulate transcription [1]. In AhR, The bHLH domain locates near the amino terminal and performs DNA binding function and dimerization. The PAS domains, composed of PAS-A and PAS-B, mediate vital interaction with ARNT to co-translocate into the nucleus. The ligand binding motif is identified mainly at PAS-B. The chaperone heat shock protein 90 (HSP90) binds to AhR through the region largely overlapping with the ligand binding motif. Such interaction with HSP90 silences AhR until activated by ligands. Transcriptional activation binding domain exists close to the carboxyl terminal, which contains a proline-rich (Q-rich) domain [2,3]. The schematic structure of AhR is depicted in Fig. 1A.

1.2. Ligand-induced activation of the AhR pathway

In the steady state, inactivated AhR exists within a complex with HSP90, AIP, p23 and actin filament in the cytoplasm. Upon ligand binding, the AhR complex changes the conformation and translocates into the nucleus where another bHLH-PAS transcription factor family member ARNT dimerizes with the dissociated AhR to form a functional DNA binding complex. The AhR/ARNT dimer recognizes genomic sequences containing AhR-responsive elements (AhRE, also called dioxin- or xenobiotic-responsive element, DRE or XRE, core sequence 5′-GCGTG-3′ Fig. 1B) to regulate gene transcription [4]. The putative AhR-binding sites are mapped across the whole genome [5]. Many studies have demonstrated that AhR can regulate a large number of gene expressions with diversified functions [6,7]. Notably, a well-characterised outcome of ligand-induced AhR activation is to initiate the negative feedback to limit the AhR signalling [8]. First, the activation of AhR induces the expression of key metabolizing enzymes, such as CYP1A1 (cytochrome P450, family 1, subfamily A, polypeptide 1), to biotransform or eliminate the AhR ligands. Second, the AhR-induced AhR repressor (AhRR) is also upregulated to compete with AhR by dimerizing with ARNT. Third, ligand-activated AhR is exported from the nucleus and degraded by the ubiquitin/proteasome pathway. A simplified model of ligand-induced AhR activation is shown in Fig. 1C.

The ligands of AhR constitute an expanding family with new members being continuously identified. We can categorize them into four major sources: endogenous metabolites, dietary metabolites, microbial derivatives and xenobiotics (Fig. 2) [2,9,10]. Such categorization is general rather than strict. Many AhR ligands are derived from tryptophan as a result of various biological and physiochemical processes. They are related to each other and may fall into more than one class. AhR ligands vary greatly in their chemical structures and binding affinities, with equilibrium dissociation constant (K_D) ranging from the pM range (strong ligands) to the μM range (weak ligands) [9]. The potency of ligands is also determined by the bioavailability and pharmacokinetics

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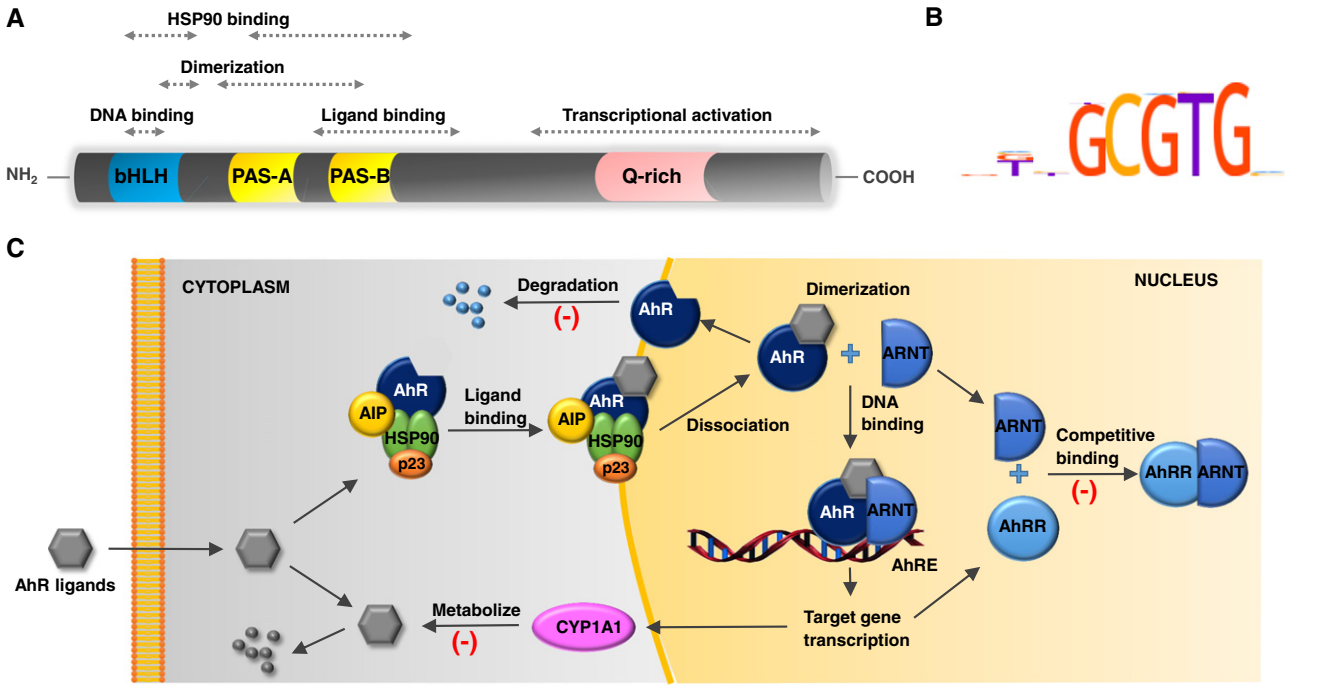

Fig. 1. The regulation of the AhR activation. A) Functional domains of the AhR protein. AhR includes three major functional domains: bHLH (basic helix–loop–helix), PAS (PER-ARNT-SER) and Q-rich (proline rich). The bHLH domain performs DNA binding and dimerization, while the two PAS domains participate in dimerization and ligand binding. Both the bHLH and PAS are required for HSP90 interaction. Q-rich domain contributes to transcriptional activation. B) The core motif of AhR response elements (AhRE). C) The model of the activation of AhR. Ligands penetrate cell membrane and bind to the cytoplasmic AhR complex which remains inactive by interacting with HSP90, p23 and AIP (AhR interacting protein). The activated AhR then translocates into the nucleus to dimerize with ARNT. The dimer recognizes AhRE to transactivate target genes such as *Cyp1a1* and *Ahrr*. CYP1A1 catalyses the metabolism of ligands. AhRR competes with AhR to dimerize with ARNT. Ligand-activated AhR is also imported to the plasma for degradation, mainly by proteosome. "Red minus" symbols indicate the negative feedback pathways to reduce the activation of AhR.

in vivo. For example, 2,3,7,8-tetrachlorodibenzodioxin (TCDD) is considered as one of the most toxic AhR ligands due to both high binding affinity (the pM range) and long half-life (~seven years in humans) [11]. To be noted, AhR ligands can be often classified as agonists or antagonists. In many occasions, antagonists are partial/weak agonists, which may have a similar affinity as full agonists but never elicit maximal/optimal response [10]. The AhR ligands are comprehensively reviewed by [9,10].

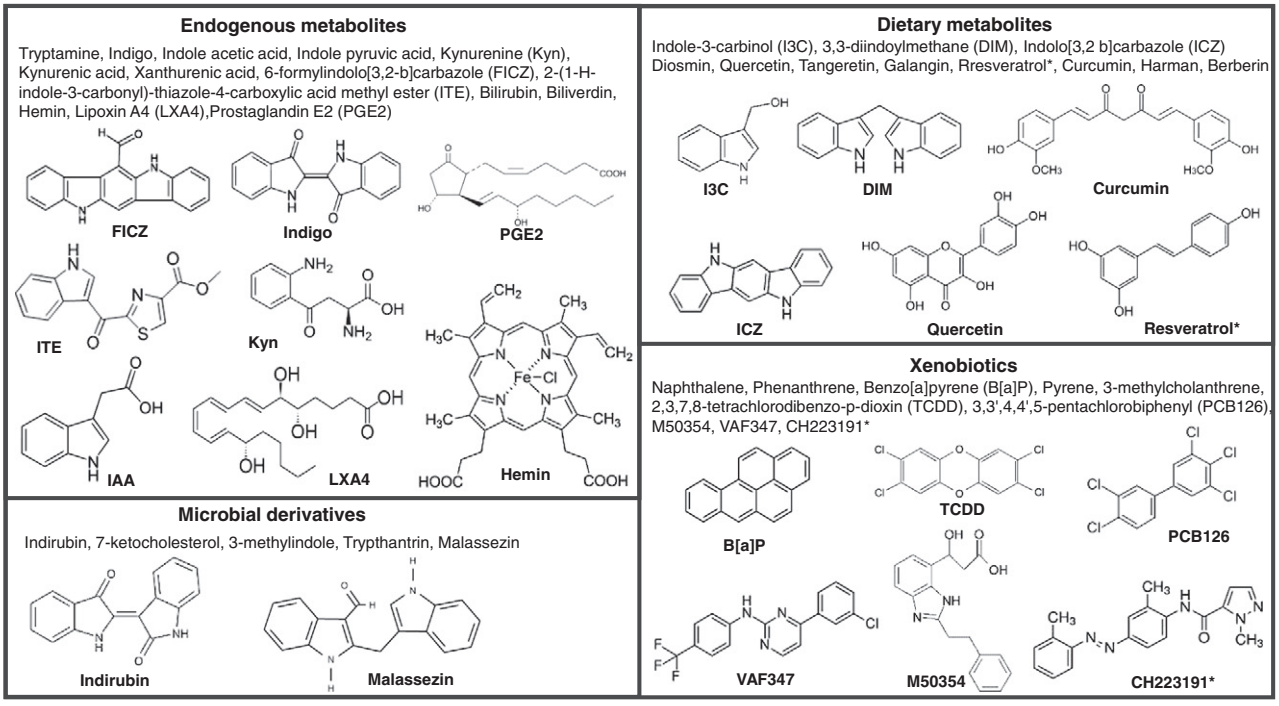

Fig. 2. Four major sources of AhR ligands. AhR ligands can be categorized into four major sources: endogenous metabolites, dietary metabolites, microbial derivatives and xenobiotics. Examples and chemical structures for each category are shown. Most ligands are classified as the AhR agonists and the antagonistic ligands are labelled with asterisks.