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Molecular biology of the aromatic hydrocarbon (dioxin) receptor

Allan B. Okey, David S. Riddick and Patricia A. Harper

The aromatic hydrocarbon (AH) (dioxin) receptor was discovered almost 20 years ago and achieved notoriety as the front-line site of action of highly toxic environmental chemicals such as halogenated dioxins and polychlorinated biphenyls. Increasing evidence suggests that the AH receptor plays a key role in proliferation and differentiation of cells exposed to dioxins and, perhaps, to endogenous ligands. Recent cloning of the AH receptor and its indispensable partner, the AH-receptor-nuclear-translocator protein, has opened new opportunities to determine how the AH receptor functions, how it evolved and what its multiple roles might be in normal physiology as well as in toxicology. This review by **Allan Okey, David Riddick and Patricia Harper** aims to provide a brief history of AH receptor research and gives a timely summary of what is known and what is not known about the structure and function of this fascinating protein.

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Would nature evolve a receptor that binds toxic foreign chemicals (Fig. 1) but has no endogenous ligand? This is a perennially vexatious question, and with regard to the aromatic hydrocarbon (AH) (dioxin) receptor there still is no satisfactory answer. Research papers specifically devoted to the AH receptor now number more than 70 per year and there is a broad spectrum of hundreds of papers in pharmacology and toxicology that have the AH receptor mechanism as their foundation.

Signal transduction by a ligand-activated transcription factor

Biochemical and toxic effects of halogenated aromatic hydrocarbons such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) are mediated by the AH receptor, which functions as a ligand-activated transcription factor via a mechanism that is superficially similar to that of members of the superfamily of steroid–thyroid–retinoic acid receptors[1–3]. However, recent cloning of cDNAs for the AH receptor and its partner, the AH-receptor-nuclear-translocator (ARNT) protein, reveal that they are basic helix–loop–helix DNA-binding proteins, unlike the steroid receptors, which are 'zinc-finger' proteins[4–6].

Events triggered by ligand binding

Prior to occupancy by a ligand, the inactive AH receptor resides in the cytoplasm of target cells in a soluble complex with the heat shock protein Hsp90 (Fig. 2) and possibly other proteins[7–9]. It appears that Hsp90 chaperones the AH receptor, maintains it in a ligand-binding conformation, and represses its intrinsic DNA-binding activity[10].

Binding of a ligand such as TCDD triggers translocation of the ligand–receptor complex into the nucleus (Fig. 2) in a temperature-dependent process[11]. The nuclear form of AH receptor binds with high affinity to specific DNA enhancer sequences known as AH-responsive elements [AHREs; also known as dioxin-responsive elements

(DREs) or xenobiotic-responsive elements (XREs)] (Refs 12,13) located in the 5'-flanking region of responsive genes. The core consensus AHRE sequence required for the binding of liganded AH receptor has been defined in recent years, as have the roles played by additional nucleotides flanking the core sequence[6,13]. Certain 'chromatin receptor-binding factors' also may play a role in interaction of the AH receptor with specific DNA sequences[14]. By nondenaturing hydrodynamic analyses, the nuclear form of AH receptor in mouse hepatoma cells has been demonstrated to have a molecular mass of ~175k Da whereas the cytosolic receptor complex (with Hsp90) has a molecular mass of ~270k Da (Ref. 15). Photoaffinity labelling or western blot analyses[16] under denaturing conditions have shown that the mass of the AH receptor protein that binds ligand varies from ~95 to 130k Da (depending upon the animal species and strain) and that the ligand-binding subunits of cytosolic and nuclear AH receptor have the same molecular mass (~95k Da for mouse AH receptor)[17]. Thus, the nuclear DNA-binding complex (~175k Da) is not the monomeric AH receptor alone but is a heterodimer[8,18]. The dimerization partner of the AH receptor was identified through cloning of the human ARNT protein[19]. Several recent lines of evidence confirm that the form of AH receptor that binds to AHREs consists of at least two proteins, the AH receptor and ARNT (Refs 20–23), and there is evidence to indicate that two distinct heteromeric DNA-binding forms of the AH receptor exist, possibly resulting from interaction of the AH receptor with different ARNT-like partner proteins containing compatible dimerization domains[24,25].

The process by which ligand binding transforms the cytosolic AH receptor to its functional DNA-binding state is complicated and still poorly understood. Phosphorylation of both AH receptor and ARNT appears to be important for generation of the functional DNA-binding complex[26–30]. Protein kinase C (PKC) is a reasonable candidate to catalyse the phosphorylation events[27,29,30], but recent data suggest that PKC activity is not required for TCDD-dependent AH receptor transformation nor for DNA binding as assessed *in vitro*[31]. In addition, other protein factors may play important roles in regulating AH receptor function:

(1) Constitutive (non-inducible) proteins have been shown to bind to AHREs and such proteins may act to inhibit binding of the transformed AH receptor to its response element[32,33].

(2) A labile repressor protein appears to associate with the AH receptor and prevent its interaction with AHREs (Refs 34,35).

(3) The AH receptor appears to be required for binding of an unknown protein factor to a G-rich element located immediately adjacent to one of the AHREs (Ref. 36).

Additional complexity is added by the fact that AH receptor-regulated genes such as *CYP1A1* [the gene responsible for the production of cytochrome P4501A1 (CYP1A1)] are also under the control of other regulatory

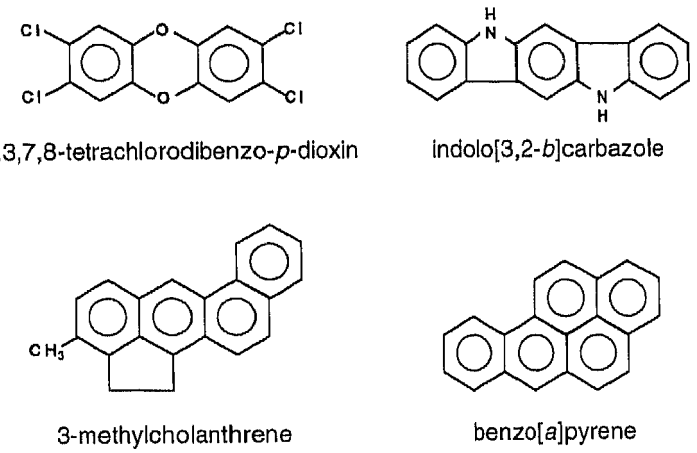

Fig. 1. Structures of aromatic hydrocarbon (AH) receptor ligands. Examples of toxic halogenated aromatic hydrocarbons (2,3,7,8-tetrachlorodibenzo-*p*-dioxin), carcinogenic nonhalogenated polycyclic aromatic hydrocarbons (3-methylcholanthrene and benzo[*a*]pyrene) and dietary constituents (indolo[3,2-*b*]carbazole) are shown.

elements including a basic transcriptional element (BTE) (Ref. 37) and a negative regulatory element (NRE) (Ref. 38). The various permutations of the several proteins involved greatly increase the potential flexibility and subtlety of response.

Transcriptional stimulation

CYP1A1 is by far the most extensively studied TCDD-responsive gene. In uninduced cells, the *CYP1A1* promoter region assumes a nucleosomal configuration and is inaccessible to its cognate binding proteins. Interaction of the AH receptor complex with an upstream AHRE induces a change in chromatin structure involving nucleosome disruption and leading to increased promoter accessibility[6,39]. After it enhances transcription, the fate of the nuclear AH receptor complex is not clear. However, within six hours after exposure of hepatoma cells in culture to TCDD, the total cellular content of AH receptor protein is reduced to only about 20% of the pre-TCDD levels, an apparent ligand-induced 'downregulation' of the receptor[40,41]. However, very low levels of nuclear AH receptor may be sufficient to maintain transcription of receptor-regulated genes for long time periods and there is evidence that *in vivo* exposure of rodents to TCDD may upregulate AH receptor levels in liver over several days[42].

Unanswered questions about the AH receptor and its partner proteins

(1) Are there structural components of the cytosolic AH receptor complex in addition to the AH receptor itself and Hsp90? If so, what are their identities and functions?

(2) Can the AH receptor dimerize with partner proteins other than ARNT? If so, what are the implications for the diversity of signal transduction pathways?

(3) What controls the level of expression of the AH receptor and ARNT? Are they autoregulated by AH receptor ligands?

(4) What is the subcellular localization of ARNT before and after ligand exposure?

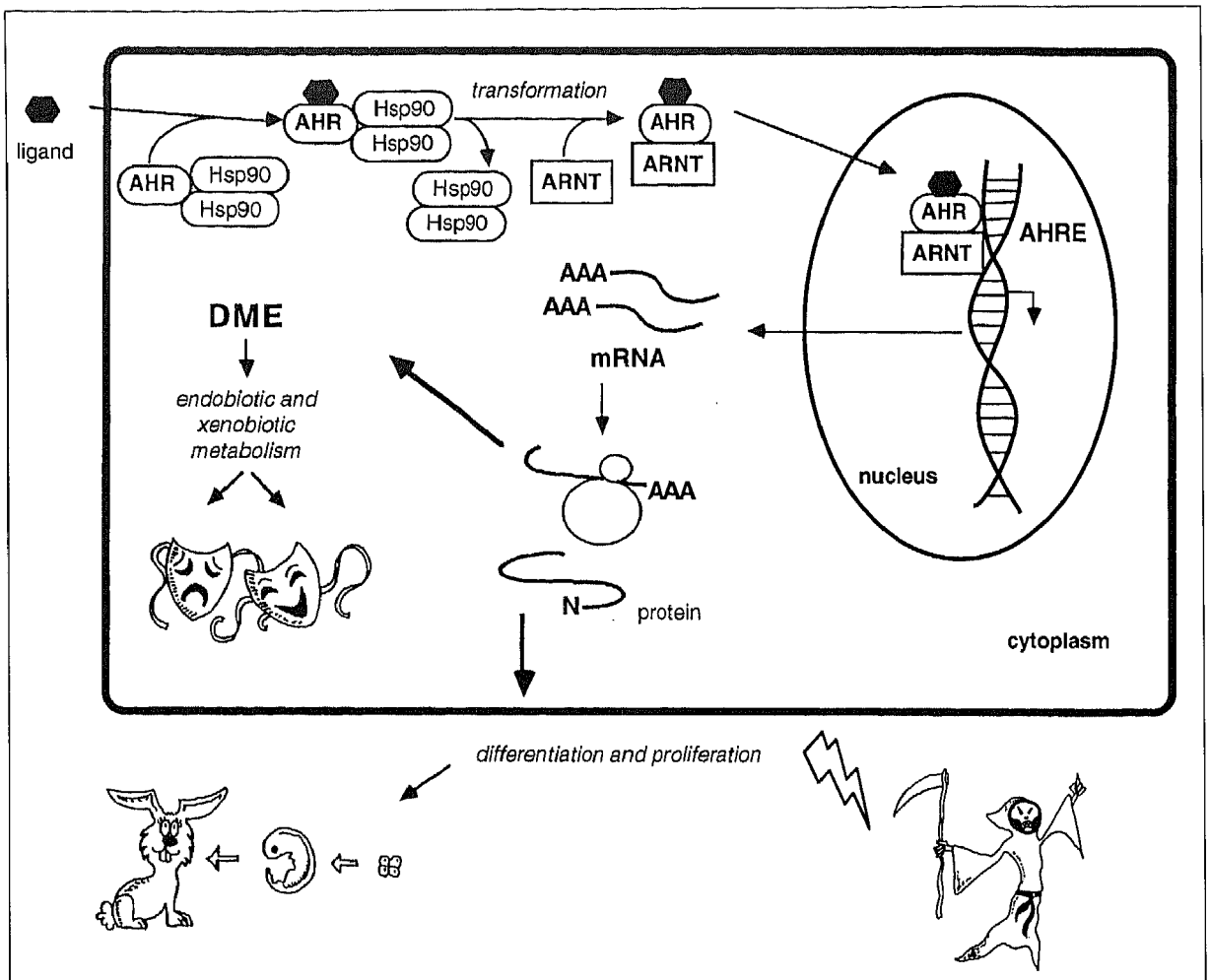

Fig. 2. Outline of the function of the aromatic hydrocarbon receptor (AHR) as a ligand-activated transcription factor. Genes that are under control of the AHR are depicted as belonging to two major functional groups: (1) Induction of several drug-metabolizing enzymes (DME) can alter the biotransformation capacity for endogenous and exogenous substances, potentially leading to both beneficial and detrimental outcomes. (2) Gene products that regulate cell differentiation and proliferation presumably play fundamental roles in normal development; their aberrant regulation may underlie the toxic manifestations of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and related aromatic hydrocarbons. AHRE, AH-responsive-element; ARNT, AH-receptor-nuclear-translocator; Hsp90, heat shock protein 90.

(5) What is the contribution of other signal transduction pathways and other transcription factors to the regulation in AH receptor-responsive systems?

Responses regulated by the AH receptor

Halogenated aromatic hydrocarbons produce a toxic syndrome in experimental animals that is characterized by wasting, lymphoid involution, hepatotoxicity, chloracne and epidermal changes, gastric lesions, urinary tract hyperplasia, endocrine dysfunction, embryotoxicity and carcinogenicity[43]. It is evident that many of the manifestations of toxicity involve alterations of cell growth and differentiation.

AH receptor and TCDD toxicity

The critical cellular targets for toxic effects of TCDD-like compounds are not known. However, considerable evidence implicates the AH receptor as the primary mediator of toxicity produced by this class of chemicals:

(1) Structure–activity relationships demonstrate that within a particular series of halogenated aromatics (for example, polychlorinated dioxins and polychlorinated biphenyls), the toxicity of individual congeners is correlated with the affinity with which the congeners bind to the AH receptor[1,2,43]. However, such relationships may not apply when comparing ligands from different structural classes[44].

(2) Susceptibility to a wide range of toxic effects of TCDD in mice segregates with the $Ah^{b\text{-}1}$ allele that encodes a 'high-affinity' form of the AH receptor in 'responsive' mouse strains such as C57BL/6 (Refs 1,2,5,43,45). The AH receptor from so-called 'nonresponsive' strains of mice (such as DBA/2) binds TCDD with an affinity that is about tenfold lower than in C57BL/6 mice[46], and this difference in affinity parallels the difference between the strains in their sensitivity to the biochemical and toxic effects of TCDD.

(3) Several AH receptor partial antagonists inhibit or reduce the toxic and biochemical effects of TCDD (Ref. 47).

There is considerable interest in identifying all AH

receptor-regulated genes and determining which of these genes and gene products are responsible for the manifestations of TCDD toxicity. To date, at least 26 genes have been shown to be either directly controlled by the AH receptor or to be responsive to AH receptor agonists[48]. Generally, products of these genes fall into one of two broad categories: growth-regulatory proteins or drug-metabolizing enzymes.

AH receptor-regulated genes in cell growth and differentiation

Several genes that encode growth-regulatory proteins appear to be responsive to AH receptor agonists. This group includes genes for the epidermal growth factor receptor, the oestrogen receptor, plasminogen activator inhibitor 2, interleukin 1β, and transforming growth factors α and β_2. In addition, TCDD induces expression of c-*fos* and c-*jun* proto-oncogenes and an increase in the transcription factor activity of activator protein 1 (AP-1) (by a mechanism that apparently does not involve a functional AH receptor or ARNT) (Refs 7,48). All these genes play roles in cell growth and differentiation. There has been no direct demonstration to indicate that derangements in expression of any of these particular genes is responsible for the toxic effects of TCDD-like compounds, but recent work suggests that TCDD-mediated down-regulation of the hepatic epidermal growth factor receptor may be a critical event in the carcinogenic action of TCDD (Ref. 49).

Drug-metabolizing enzymes regulated by the AH receptor

As described earlier, the best-understood role of the AH receptor is induction of CYP1A1 (Refs 6,45). Other drug-metabolizing enzymes regulated (at least in part) by the AH receptor include CYP1A2 (Ref. 50) and a new P450, CYP1B1 (Refs 51,52). Non-P450 enzymes regulated by the AH receptor include: glutathione-S-transferase Ya, the TCDD-inducible UDP-glucuronosyltransferase UGT1*06, NAD(P)H:quinone oxidoreductase NQO_1, and aldehyde dehydrogenase ALDH3c. Changes in these metabolic enzymes do not appear to mediate directly the toxic effects of TCDD. However, it is apparent that drug-metabolizing enzymes regulated by the AH receptor play their own life-or-death roles, in some cases bioactivating 'pretoxicants' to their ultimate cytotoxic, mutagenic, carcinogenic or teratogenic forms and in other cases 'detoxifying' potentially dangerous xenobiotics (Fig. 2). It is vital that the balance be tipped strongly in favour of 'detoxication', usually by efficiently conjugating the reactive metabolites generated by highly inducible P450s (Refs 45,53). In addition to biotransforming foreign chemicals, enzymes regulated by the AH receptor play a role in the metabolism of endogenous substances involved in the control of cell growth and differentiation, thereby potentially tying together the two main arms of AH receptor-mediated responses[45,54].

Unanswered questions concerning AH receptor function

(1) Is there an endogenous ligand for the AH receptor? (This is still the key question in the field. The nearest thing to a 'physiological' class of ligands are plant products such as indole carbinols[3,55]. It is possible that the AH receptor evolved as a mechanism of response to xenobiotic chemicals of plant origin, or even as a mechanism to cope with aromatic hydrocarbons that were present in abundance on the primitive earth. It is conceivable that there is no truly 'endogenous' ligand for the AH receptor, i.e. a ligand generated within the responsive organism itself.)

(2) Does the AH receptor play a role in normal developmental processes?

(3) What is the pattern of tissue expression and developmental expression of the AH receptor and receptor-mediated responses?

(4) Which AH receptor-regulated genes have primary roles in the toxic effects of halogenated aromatic hydrocarbons?

Molecular organization of the AH receptor

Primary structures of the AH receptor and ARNT

Purification and determination of a partial amino acid sequence for the N-terminal region of the C57BL/6 mouse AH receptor resulted in the cloning of cDNAs for murine AH receptors[56,57] and subsequently human AH receptors[58,59]. The deduced amino acid sequence of the C57BL/6 mouse AH receptor reveals a protein of about 90 kDa, in good agreement with the mass determined by denaturing gel electrophoresis[16]. A cDNA for ARNT, the dimerization partner of the AH receptor, also has been cloned[19] and encodes a protein of about 86 kDa. Comparison of the deduced amino acid sequences of AH receptor and ARNT with that of the steroid hormone receptors clearly shows that the AH receptor and ARNT do not have any characteristics of the steroid receptor family of zinc-finger proteins; rather the AH receptor and ARNT interact with DNA via basic helix–loop–helix domains, motifs found in many transcription factors that interact with DNA as homodimers or heterodimers. The presence of this motif in ARNT and the AH receptor (Fig. 3) suggests that these proteins heterodimerize. This is further supported by the observation from *in vitro* expression experiments where both ARNT and the AH receptor must be expressed to enable the AH receptor to interact with DNA; neither AH receptor nor ARNT interact with DNA when expressed alone[20,22,60].

The AH receptor and ARNT proteins are structurally similar to each other and also to two additional proteins: the *Drosophila* neurogenic protein Sim, and the *Drosophila* circadian rhythm protein Per. Together these four proteins constitute a (currently) small family of proteins that is characterized by a region of homology of approximately 250 amino acids referred to as the PAS domain (Per, AH receptor–ARNT, and Sim). The PAS sequence has not yet been identified in any other protein[5]. It is not

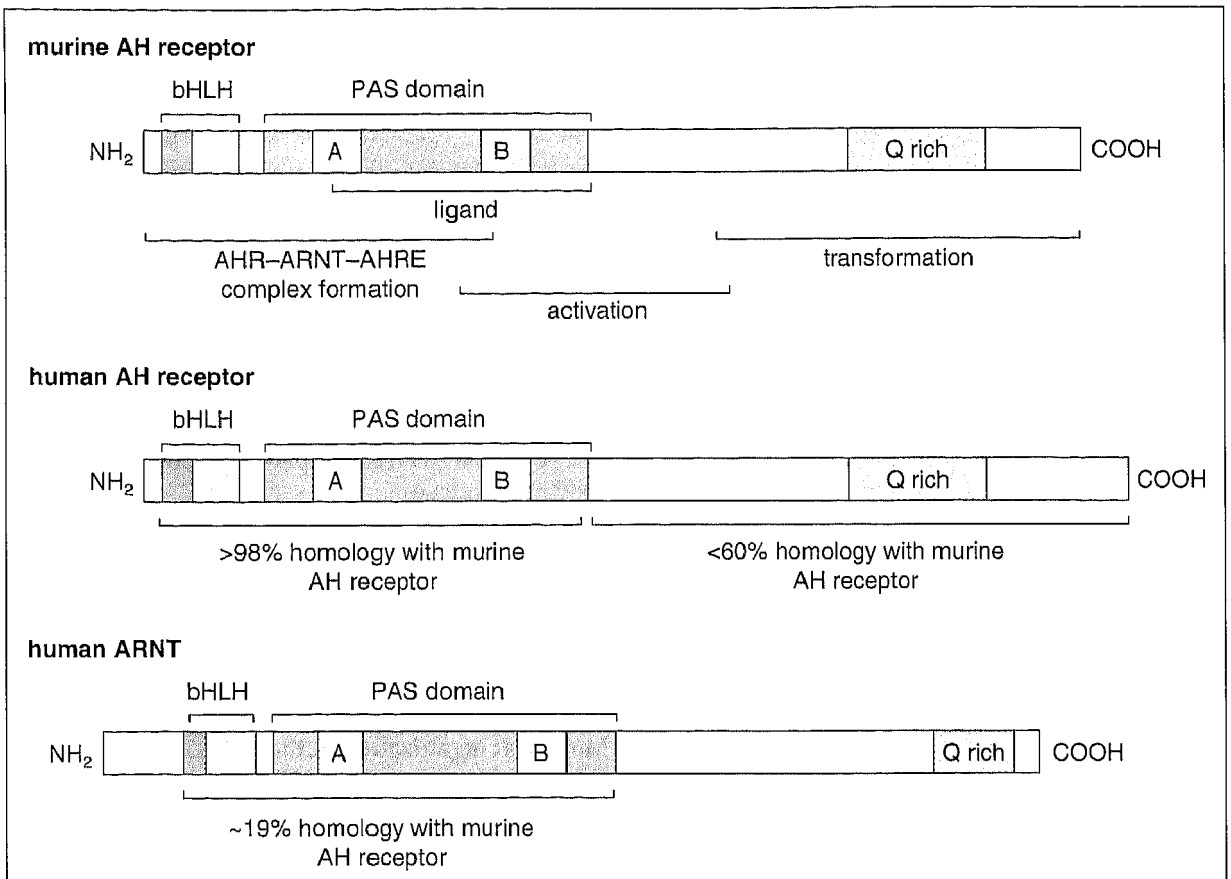

Fig. 3. Domains within the aromatic hydrocarbon (AH) receptor (AHR). The basic helix–loop–helix (bHLH) region contains the structural motifs for association with DNA and dimerization through the HLH region of the molecule. The PAS domain contains two 21 amino acid repeats termed A and B. A glutamine (Q)-rich region is in the C-terminal region of the molecule. These regions have been identified by sequence comparison in the human AH receptor and AH-receptor-nuclear-translocator (ARNT) proteins. Several other regions within the murine AH receptor molecule have been identified by deletion analysis: 'AHR–ARNT–AHRE' is necessary for binding to the AH-responsive-element (AHRE) in gel shift assays. 'Ligand' corresponds to the region necessary for ligand-binding and stable association with heat shock protein 90. The 'transformation' region is necessary for efficient transformation to the AHRE-binding form of the receptor. The 'activation' domain contains a region that represses constitutive DNA-binding. Data from Refs 60 and 61.

known if there is any functional relationship between the AH receptor–ARNT pair and Per or Sim.

Primary structure in relation to function

Functional domains within the murine AH receptor have been defined[60,61] (Fig. 3), and where analysed, the human AH receptor has demonstrated similar features[59]. There are three major domains within the molecule:

(1) The extreme N-terminus of the protein that encompasses the basic helix-loop-helix motif and probably is responsible for specific binding to DNA (basic region) as well as dimerization (helix-loop-helix region).

(2) The most characteristic region, the PAS domain, which in the AH receptor plays a role both in ligand binding and in dimerization with ARNT.

(3) A region near the C-terminus of the molecule that influences ligand-dependent transformation of the AH receptor to a form capable of generating a ligand–AH receptor–ARNT complex with the AHRE.

The C-terminus also contains several glutamine-rich motifs, a common feature of proteins involved in transcriptional activation[5]. In general, the greatest variability in the receptor sequence, both within species and across species, occurs in the C-terminal region that can be termed a hypervariable domain[62]. Although it is possible to conceptually divide the AH receptor protein into several unique functional domains, it is probable that features throughout the entire molecule influence, to some extent, each specific function.

Recombinant inbred mouse lines have been used to define and map the *Ah* locus. Four allelic variants have been identified in mouse and these encode AH receptor proteins of different molecular masses. Of these alleles, three have been studied in some detail at the cDNA level. The $Ah^{b\text{-}1}$ allele encodes a protein of about 95 kDa whereas the $Ah^{b\text{-}2}$ allele encodes a protein of about 104 kDa (Ref. 63). Comparison of the cDNA sequences of $Ah^{b\text{-}1}$ and $Ah^{b\text{-}2}$ reveal that these alleles are highly conserved and have only 37 nucleotide differences in about 5000 bases of the cDNA sequence. However, one difference occurs at nucleotide 2416 of $Ah^{b\text{-}2}$ that converts a stop (TGA) codon to an arginine (CGA) thereby replacing the termination codon found in the $Ah^{b\text{-}1}$ cDNA (Ref. 62). This results in a longer transcript and hence a larger protein, consistent

with the greater molecular mass observed for the AH^{b-2} protein.

The most extensively studied murine AH receptors are the Ah^{b-1} allele in C57BL/6 mice, which encodes a receptor with high affinity for TCDD, and the Ah^{d} allele in the DBA/2 strain, which encodes a protein with an approximately tenfold lower affinity for TCDD than the product of the Ah^{b-1} allele[46]. Comparison of the cDNA nucleotide sequences for these proteins revealed ten nucleotide differences between the Ah^{b-1} allele and Ah^{d} allele, five of which are silent and one that alters the stop codon (described above in the Ah^{b-1} allele) to arginine in the Ah^{d} allele. One of the remaining differences results in a leucine residue in the AH^{b-1} protein being replaced by a proline residue in the AH^{d} protein, an alteration that may disturb the secondary structure of the AH receptor and be responsible for the lowered affinity for TCDD observed for the AH^{d} protein[64]. The functional importance of the remaining changes is unknown at this time.

At a genomic level, molecular analysis indicates that the Ah^{b-2} gene is composed of 11 exons spanning more than 30 kb of DNA. The 5'-untranslated region and sequences upstream (−1 to −500) of the transcriptional start site are GC-rich. The *Ah* gene promoter does not contain either a TATA or CCAAT box, but sequence analysis indicates the presence of several potential binding sites for *trans*-acting factors[62]. Most interesting is the presence of DNA motifs that previously have been shown to confer placenta-specific expression. Although liver has been used as the major source of AH receptor in rodents, placental tissue is the richest known source of AH receptor in humans[65]. The structure and function of the human AH receptor continue to be characterized at biochemical, pharmacological, and molecular levels[66,67].

Additional molecular questions

(1) What are the roles of the AH receptor and ARNT in normal development? This question now can be addressed by creating transgenic mice with reporter constructs that localize functional AH receptor in different cells and tissues of developing embyros, and by 'knock-out' experiments in which the AH receptor gene has been inactivated to determine the impact of its loss on survival and development.

(2) Is the AH receptor directly involved in the process of carcinogenesis by TCDD? If so, what specific AH receptor-mediated biochemical and cellular pathways are responsible for neoplastic growth?

(3) Are there polymorphisms in the genes for the human AH receptor or ARNT? If so, what are the functional consequences of such polymorphisms in regard to normal development or responses to toxic TCDD-like xenobiotics?

(4) What is the evolutionary history of the AH receptor and ARNT? What is the phylogenetic distribution of AH receptor-like genes in present-day organisms? Are there additional proteins closely related to AH receptor and ARNT that remain to be discovered in the PAS family? If so, what are their functions?

Concluding remarks

The AH receptor was originally discovered in rodent liver and its role was perceived to be mainly as a regulator of P450 induction. Ensuing experiments have detected the receptor or its mRNA in cells and tissues as diverse as peripheral blood lymphocytes, brain, myocardium, skeletal muscle, urinary bladder and breast tumour cells[7]. The AH receptor is likely to have a ubiquitous occurrence in cells and tissues of humans and other mammals and the receptor has also been detected in poikilothermic vertebrates[68–70]. This very broad distribution in vertebrate tissues and cells implies an essential and fundamental role for the AH receptor in homeostasis. The AH receptor field has all the elements of a good gothic drama. Powerful forces are at work and we, in the audience, cannot quite understand them yet. A central character in the drama (the elusive endogenous ligand) lurks just offstage. That character may be real or it may be a phantom – but even if it remains an offstage apparition, its influence is certainly always felt. In science, there rarely is a conclusive denouement that wraps up all the loose ends. Resolving one mystery often leads to more puzzles within. The next few years of the AH receptor drama should continue to be very exciting indeed.

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