Signaling network map of the aryl hydrocarbon receptor

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Abbreviations

AHR	Aryl Hydrocarbon Receptor
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
PPI	Protein-protein interaction
PTM	Post-translational modification
HPRD	Human Protein Reference Database
SBML	Systems Biology Markup Language
PSI-MI	Proteomics Standards Initiative for Molecular Interaction
BioPAX	Biological Pathway Exchange

Introduction

The aryl hydrocarbon receptor (AHR) is a multi-domain cytosolic protein that belongs to the [basic helix-loop-helix/Per-Amt-Sim \(bHLH/PAS\)](#) family of transcription factors. Ligand

binding induces a conformational change in AHR and promotes nuclear translocation of the receptor (Kewley et al. 2004). AHR can either bind to exogenous (polycyclic aromatic hydrocarbons, dioxins, cigarette smoke) or endogenous ligands (arachidonic acid and leukotrienes, heme metabolites, UV photoproducts of tryptophan) within the cytoplasm. Exogenous ligands such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and 3-methylcholanthrene are known to activate AHR and mediate cellular toxic response. AHR is also activated by dietary compounds including indole-3-carbinol and flavonoids that mediate various physiological activities in the body (Nguyen and Bradfield 2008; Marconett et al. 2010). AHR ligands are classified as agonists and antagonists depending on the ability of ligands to activate or inhibit AHR induced activity. Previous reports indicate that ligands such as kaempferol, resveratrol, galangin, chrysin and quercetin act either as agonists or antagonists based on the ligand

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concentration and type of cells induced (Zhang et al. 2003). Thus, diversity of ligands makes AHR signaling a very dynamic and complex.

AHR in its inactive state is located in the cytoplasm and forms a complex with molecular chaperones, such as heat shock protein 90 (HSP90) and co-chaperons such as p23 and AHR-interacting protein (AIP) (Trivellin and Korbonits 2011). In presence of ligand, AHR undergoes nuclear translocation where it interacts with AHR nuclear transporter (ARNT) or AHR repressor (AHRR) through the PAS domain. It has been reported that nucleocytoplasmic transport mechanism of AHR varies between humans and mice. In humans, AHR both in stimulated or unstimulated state can undergo nuclear translocation complexed with AIP. In contrast, association of AIP prevents nucleocytoplasmic shuttling of AHR in mice in both stimulated and unstimulated states (Ramadoss et al. 2004). Once AHR is translocated to the nucleus it forms a heterodimer complex with ARNT and binds to xenobiotic response elements located in the promoter region of the target genes. This complex induces coordinated transcription of detoxifying enzymes for efficient absorption, distribution and elimination of xenobiotics from the body (Abel and Haarmann-Stemann 2010). Apart from this, AHR is known to exhibit endogenous functions such as cell proliferation, cell differentiation and apoptosis. It also acts as an endogenous regulator in several developmental and physiological processes including neurogenesis, hematopoietic stem cell regulation,

cellular stress response, immunoregulation and reproductive health (Lindsey and Papoutsakis 2012; Kadow et al. 2011; Hansen et al. 2014).

AHR is associated with various pathological and physiological disorders in the body including autoimmune diseases (Veldhoen et al. 2008), inflammation (Podechard et al. 2008; Ovrevik et al. 2014), cardiovascular diseases (Kerley-Hamilton et al. 2012; Savouret et al. 2003) and cancer. Activation of AHR in presence of cigarette smoke has been well documented in lung cancer (Martey et al. 2005; Tsay et al. 2013). Cigarette smoke induced AHR is also known to mediate immune signaling mechanism in chronic obstructive pulmonary disease (COPD) (Chen et al. 2011). Apart from playing an essential role in COPD and lung cancer, AHR expression has been reported in other cancers and adenomas. AHR is reported to be downregulated in growth hormone secreting pituitary adenomas (Jaffrain-Rea et al. 2009), while, increased expression levels of AHR are associated with tumorigenesis in medulloblastoma (Dever and Opanashuk 2012). The enhancement of AHR levels under ligand stimulation induced cell cycle arrest has been reported in pancreatic and gastric cancer (Koliopanos et al. 2002; Peng et al. 2009). Depending upon the type of ligand stimulation, AHR is either known to promote or inhibit tumor progression. Stimulation of AHR with TCDD, 2,3,7,8-tetrachlorodibenzofuran and 3,3'-diindolylmethane inhibits invasiveness and cell growth in breast cancer (Hall et al. 2010). In contrast, stimulation of AHR with n-butyl benzyl phthalate and dibutyl phthalate ligands enhances tumorigenic properties in breast cancer cells (Hsieh et al. 2012). Therefore, AHR could serve as a potential therapeutic target in several cancers (Murray et al. 2014) and hence it is important to develop AHR signaling pathway to understand the mechanism of AHR mediated tumor progression and regression. Although, the diverse role of AHR is documented in literature however a detailed network of AHR signaling is lacking. In this study, we have curated literature information pertaining to AHR induced signaling and developed a pathway map to facilitate better understanding of this receptor.

Materials and methods

Literature searches were carried out in PubMed with key terms including 'aryl hydrocarbon receptor' and 'AHR signaling'. Information pertaining to protein-protein interactions (PPIs), post-translational modifications (PTMs), activation/inhibition reactions, protein transport and gene expression events were curated from papers, which described those experiments as described earlier (Radhakrishnan et al. 2012; Nanjappa et al. 2011). These reactions were included under AHR stimulation by exogenous and/or endogenous ligands. We followed NetPath annotation criteria as described

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previously (Kandasamy et al. 2010) to capture AHR signaling reactions. The entries were added into ‘PathBuilder’, an annotation tool developed in-house for the manual annotation of signaling events (Kandasamy et al. 2009). Gene expression data was curated from experiments, which used only human cells in both normal and diseased conditions. The data was uploaded to NetPath after a series of manual curation and review processes. We also incorporated the suggestions provided by an expert in the field (pathway authority) in order to enhance confidence of the documented signaling events. The reactions were then used to generate AHR signaling pathway map using ‘PathVisio’ (<http://www.PathVisio.org>) (van Iersel et al. 2008).

Data formats and availability

We have made the pathway information for AHR signaling available in NetPath. The signaling pathway information is compatible with various international data exchange formats. This includes Proteomics Standards Initiative for Molecular Interaction (PSI-MI) (Hermjakob et al. 2004), Biological

Pathway eXchange (BioPAX level 3) (Demir et al. 2010) and Systems Biology Markup Language (SBML 3) (Hucka et al. 2003). These formats ensure interoperability with pathway analysis software tools such as Cytoscape and Ingenuity pathway analysis. The data for AHR signaling pathway can be downloaded in the above mentioned formats from NetPath (<http://www.netpath.org>).

Results and discussion

Over 3000 articles were screened from PubMed that are related to AHR signaling in response to exogenous or endogenous ligands. A total of 88 proteins were curated that are experimentally proven to be involved in AHR signaling cascade. These 88 proteins were found to participate in 49 PPIs, 37 PTMs, 21 translocation events, 4 activation/inhibition reactions. In addition, 17 site-specific PTMs were catalogued of which, sites and residues were mapped to RefSeq accessions for 13 proteins. Further, 311 differential gene expressions were documented in response to AHR-ligand stimulation. We have submitted the AHR pathway data to NetPath at http://www.netpath.org/pathways?path_

Fig. 1 A schematic representation of AHR signaling pathway. The pathway map represents reactions of AHR signaling pathway that are documented in NetPath. Different types of reactions and molecules are distinguished with different colors and arrows as provided in the legend

id=NetPath_164. The web page for AHR pathway in NetPath provides a brief description of AHR signaling pathway, molecule and reaction statistics of the pathway and different downloadable formats. Every molecule documented in NetPath is linked to a molecular page. To facilitate additional information on the curated data and provide it in a user friendly manner, molecular pages have been linked to external protein resources including NCBI RefSeq, Human Protein Reference Database (HPRD) (Prasad et al. 2009), Entrez gene (Maglott et al. 2011), Swiss-Prot (Boeckmann et al. 2003) and OMIM databases (Hamosh et al. 2005). A pictorial representation of AHR signaling map is shown in Fig. 1. Data presented in NetPath pertaining to this pathway will be periodically updated.

AHR along with chaperones remains in the cytoplasm in a dormant state. The signaling cascade initiating from ligand binding to transcription of target genes involves various co-activators and chaperones. HSP90, AIP and p23 are some of the molecules that are known to interact with AHR in the cytoplasm. AIP interacts with both AHR and HSP90 through its tetratricopeptide repeat (TPR) domains. Mutations in AIP affect the structural integrity of TPR domain and disrupt the binding of AHR to AIP, causing AHR destabilization and degradation (Morgan et al. 2012; Lees et al. 2003). Previous reports have also shown that AIP mutation leads to growth hormone secreting pituitary adenomas with increased IGF1 levels and reduced ARNT levels leading to pituitary tumorigenesis (Raitila et al. 2010; Heliovaara et al. 2009). AIP remains bound to AHR even under ligand induced state without hampering shuttling across nuclear membrane and represses its associated transcriptional activity (Ramadoss et al. 2004). In addition to AIP, HSP90 is also known to translocate from cytosol to nucleus complexed with AHR under ligand stimulated condition (Tsuji et al. 2014). Within the nucleus, ARNT facilitates the displacement of HSP90 from the complex resulting in the formation of AHR-ARNT heterodimer. AHR-ARNT dimer binds to the DNA sequences and mediates the recruitment of multiple co-activators, which helps in the transcriptional regulation of a number of genes. These include a cascade of detoxifying enzymes such as phase I enzymes, the phase II enzymes, the phase III transporters and solute carrier family proteins (Xu et al. 2005). Phase I enzymes are monooxygenases, which includes xenobiotic-metabolizing cytochrome P450 group of proteins while phase II enzymes include NAD(P)H:quinone oxidoreductase (NQO1) and glutathione S-transferase (GST). Increased gene expression of phase I and phase II enzymes are known to be involved in the detoxification mechanism of xenobiotics and endogenous substances leading to cellular homeostasis (Noda et al. 2003). Ligand bound AHR/ARNT plays a key role in sex hormone signaling especially in estrogen dependent transactivation of estrogen receptor alpha (Matthews et al. 2005). Beyond the direct transcriptional regulation of genes by AHR/ARNT complex, AHR also interacts with other

proteins that act as co-activators for target gene expression. Interaction of AHR with nuclear factor, erythroid 2 like 2 (NFE2L2) augments NAD(P)H dehydrogenase, quinone 1 (NQO1) gene expression, which in turn protects the cells from oxidative stress caused by cigarette smoke and other toxic ligands (Wang et al. 2013; Cheng et al. 2012). Activated AHR also associates with E2F transcription factor 1 (E2F1) that plays a crucial role in cell cycle transition. (Watabe et al. 2010). Consequently, the diverse role of AHR depends on the cell type and the stimuli that regulate the transcription of genes.

Conclusions

AHR signaling network is essential for understanding various biological processes mediated by AHR-regulated transcription of several genes. AHR is an emergent molecule that is involved in many diseases including cancer. Documentation of reactions pertaining to AHR signaling and development of pathway map based on the published literature will facilitate further research in AHR associated human diseases. The pathway data has been uploaded to NetPath database with the feasibility to download in various standard formats.

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Compliance with ethical standards

Conflict of interest No potential conflicts of interest were declared.

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