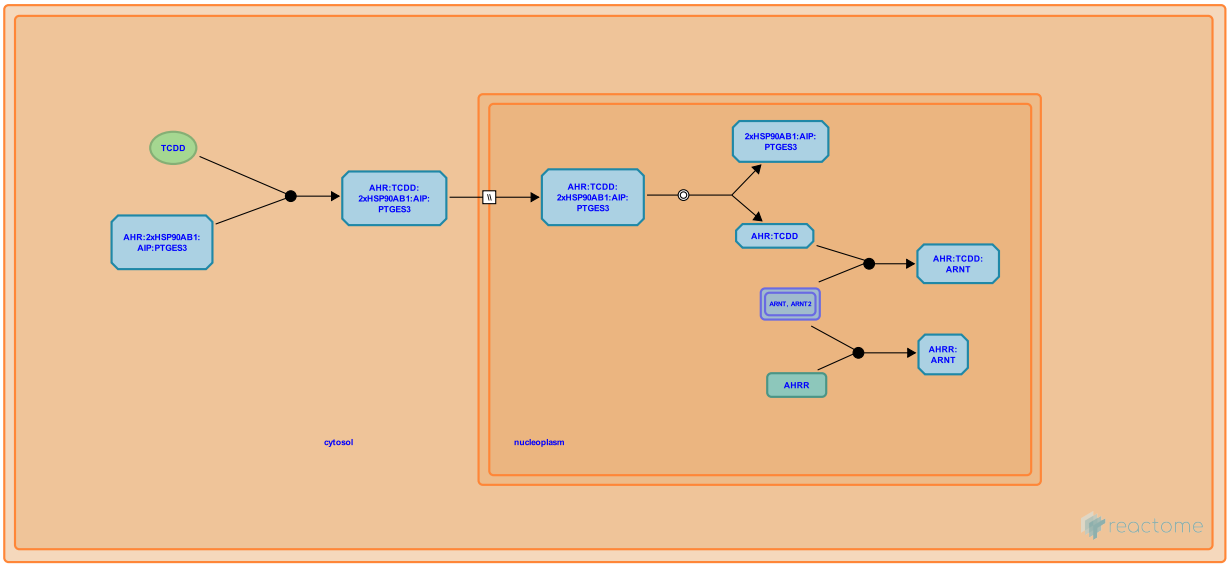
Aryl hydrocarbon receptor signalling



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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

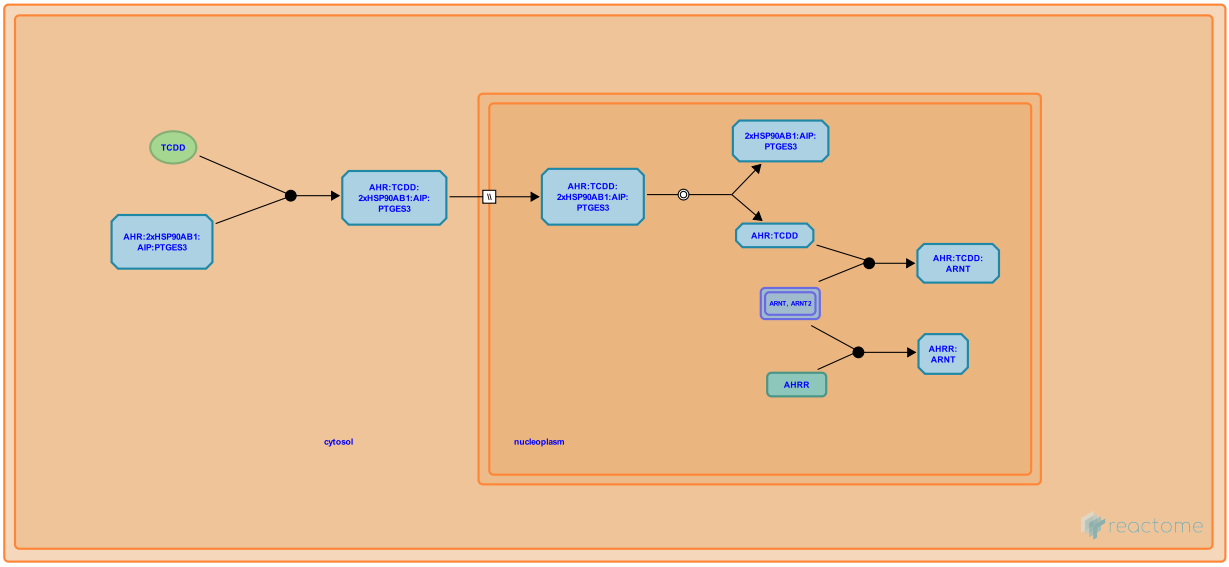
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Aryl hydrocarbon receptor signalling ↗

Stable identifier: R-HSA-8937144



The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor that belongs to the basic helix-loop-helix/PER-ARNT-SIM family of DNA binding proteins and controls the expression of a diverse set of genes. Two major types of environmental compounds can activate AHR signaling: halogenated aromatic hydrocarbons such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and polycyclic aromatic hydrocarbons (PAH) such as benzo(a)pyrene. Unliganded AHR forms a complex in the cytosol with two copies of 90kD heat shock protein (HSP90AB1), one X-associated protein (AIP), and one p23 molecular chaperone protein (PTGES3). After ligand binding and activation, the AHR complex translocates to the nucleus, disassociates from the chaperone subunits, dimerises with the aryl hydrocarbon receptor nuclear translocator (ARNT) and transactivates target genes via binding to xenobiotic response elements (XREs) in their promoter regions. AHR targets genes of Phase I and Phase II metabolism, such as cytochrome P450 1A1 (CYP1A1), cytochorme P450 1B1 (CYP1B1), NAD(P)H:quinone oxidoreductase I (NQO1) and aldehyde dehydrogenase 3 (ALHD3A1). This is thought to be an organism's response to foreign chemical exposure and normally, foreign chemicals are made less reactive by the induction and therefore increased activity of these enzymes (Beischlag et al. 2008).

AHR itself is regulated by the aryl hydrocarbon receptor repressor (AHRR, aka BHLHE77, KIAA1234), an evolutionarily conserved bHLH-PAS protein that inhibits both xenobiotic-induced and constitutively active AHR transcriptional activity in many species. AHRR resides predominantly in the nuclear compartment where it competes with AHR for binding to ARNT. As a result, there is competition between AHR:ARNT and AHRR:ARNT complexes for binding to XREs in target genes and AHRR can repress the transcription activity of AHR (Hahn et al. 2009, Haarmann-Stemmann & Abel 2006).

Literature references

Haarmann-Stemmann, T., Abel, J. (2006). The arylhydrocarbon receptor repressor (AhRR): structure, expression, and function. *Biol. Chem., 387*, 1195-9. ↗

Hahn, ME., Allan, LL., Sherr, DH. (2009). Regulation of constitutive and inducible AHR signaling: complex interactions involving the AHR repressor. *Biochem. Pharmacol., 77*, 485-97. ↗

Beischlag, TV., Luis Morales, J., Hollingshead, BD., Perdew, GH. (2008). The aryl hydrocarbon receptor complex and the control of gene expression. *Crit. Rev. Eukaryot. Gene Expr., 18*, 207-50. ↗

Editions

2016-08-30	Authored, Edited	Jassal, B.
2016-10-11	Reviewed	D'Eustachio, P.

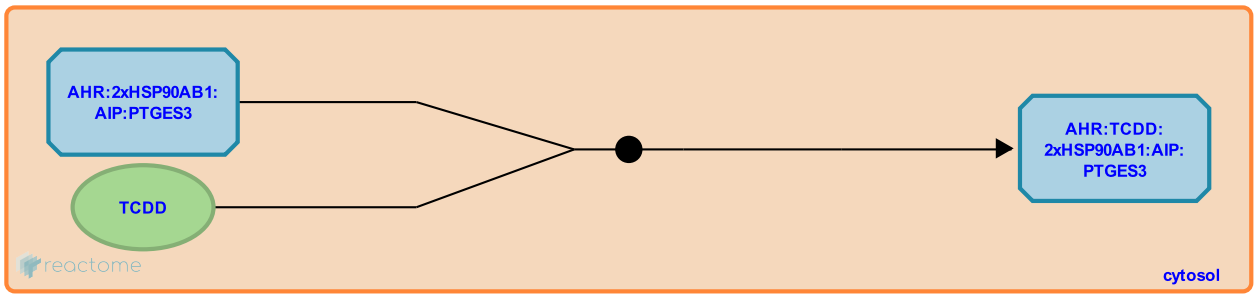
AHR:2xHSP90:AIP:PTGES3 binds TCDD ↗

Location: Aryl hydrocarbon receptor signalling

Stable identifier: R-HSA-8936849

Type: binding

Compartments: cytosol



The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor that can control the expression of a diverse set of genes. Two major types of environmental compounds can activate AHR signaling: halogenated aromatic hydrocarbons such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and polycyclic aromatic hydrocarbons (PAH) such as benzo(a)pyrene. Unliganded AHR forms a complex in the cytosol with two copies of 90kD heat shock protein (HSP90AB1) (Forsythe et al. 2001), one X-associated protein (AIP) (Meyer et al. 1998), and one p23 molecular chaperone protein (PTGES3) (Nguyen et al. 2012, Beischlag et al. 2008). Here, the binding of TCDD is shown.

Literature references

Nguyen, PM., Wang, D., Wang, Y., Li, Y., Uchizono, JA., Chan, WK. (2012). p23 co-chaperone protects the aryl hydrocarbon receptor from degradation in mouse and human cell lines. *Biochem. Pharmacol., 84*, 838-50. ↗

Forsythe, HL., Jarvis, JL., Turner, JW., Elmore, LW., Holt, SE. (2001). Stable association of hsp90 and p23, but Not hsp70, with active human telomerase. *J Biol Chem, 276*, 15571-4. ↗

Ema, M., Ohe, N., Suzuki, M., Mimura, J., Sogawa, K., Ikawa, S. et al. (1994). Dioxin binding activities of polymorphic forms of mouse and human arylhydrocarbon receptors. *J. Biol. Chem., 269*, 27337-43. ↗

Mimura, J., Fujii-Kuriyama, Y. (2003). Functional role of AhR in the expression of toxic effects by TCDD. *Biochim. Biophys. Acta, 1619*, 263-8. ↗

Beischlag, TV., Luis Morales, J., Hollingshead, BD., Perdew, GH. (2008). The aryl hydrocarbon receptor complex and the control of gene expression. *Crit. Rev. Eukaryot. Gene Expr., 18*, 207-50. ↗

Editions

2016-08-24	Authored, Edited	Jassal, B.
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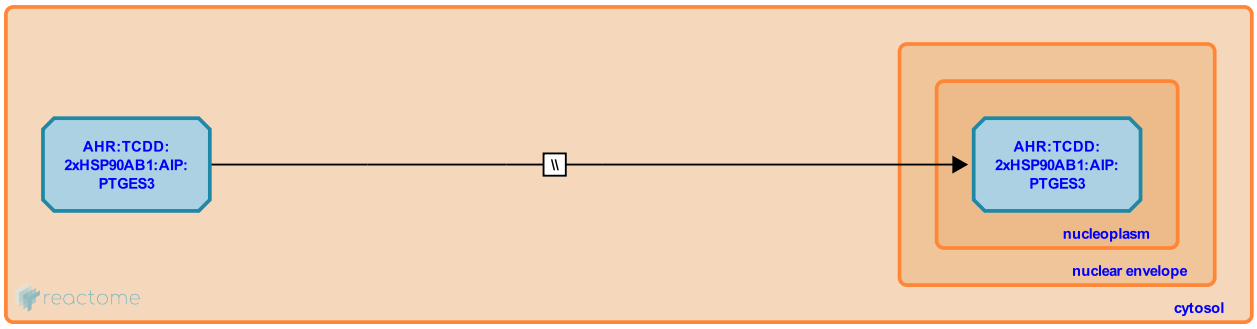
AHR:TCDD:2xHSP90AB1:AIP:PTGES3 translocates from cytosol to nucleoplasm ↗

Location: Aryl hydrocarbon receptor signalling

Stable identifier: R-HSA-8937169

Type: omitted

Compartments: cytosol, nucleoplasm



After ligand binding and activation, the AHR complex translocates to the nucleus by an unknown mechanism (Beischlag et al. 2008) but it has been hypothesised that ligand binding to AHR promoted p23-associated hsp90 complex-mediated interaction of AHR with the nuclear import receptor protein pendulin and subsequent nuclear translocation of the receptor (Kazlauskas et al. 2001).

Literature references

Beischlag, TV., Luis Morales, J., Hollingshead, BD., Perdew, GH. (2008). The aryl hydrocarbon receptor complex and the control of gene expression. *Crit. Rev. Eukaryot. Gene Expr., 18*, 207-50. ↗

Kazlauskas, A., Sundström, S., Poellinger, L., Pongratz, I. (2001). The hsp90 chaperone complex regulates intracellular localization of the dioxin receptor. *Mol. Cell. Biol., 21*, 2594-607. ↗

Editions

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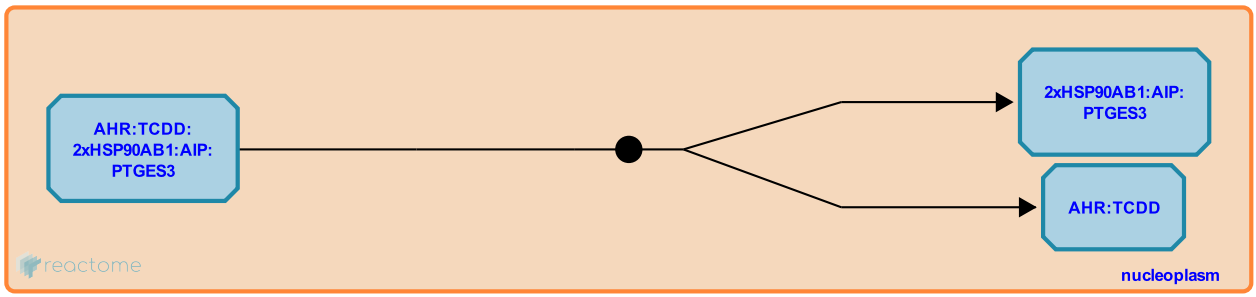
AHR:TCDD:2xHSP90AB1:AIP:PTGES3 dissociates ↗

Location: Aryl hydrocarbon receptor signalling

Stable identifier: R-HSA-8937191

Type: dissociation

Compartments: nucleoplasm



After ligand binding and activation, the AHR complex translocates to the nucleus where it disassociates from the chaperone subunits to then dimerise with the aryl hydrocarbon receptor nuclear translocator (ARNT) (Lees & Whitelaw 1999).

Literature references

Lees, MJ., Whitelaw, ML. (1999). Multiple roles of ligand in transforming the dioxin receptor to an active basic helix-loop-helix/PAS transcription factor complex with the nuclear protein Arnt. *Mol. Cell. Biol., 19*, 5811-22. ↗

Editions

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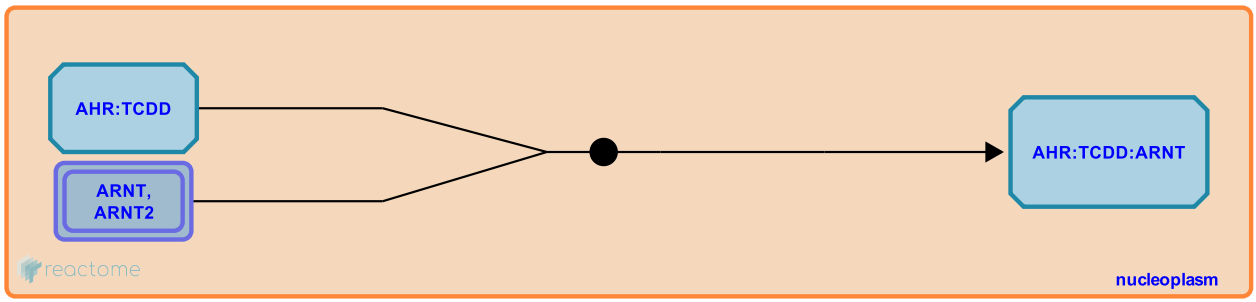
AHR:TCDD binds ARNT ↗

Location: Aryl hydrocarbon receptor signalling

Stable identifier: R-HSA-8937177

Type: binding

Compartments: nucleoplasm



Ligand-bound aryl hydrocarbon receptor (AHR:TCDD) disassociates from the chaperone subunits to then dimerise with the aryl hydrocarbon receptor nuclear translocator (ARNT) (Lees & Whitelaw 1999).

Literature references

Lees, MJ., Whitelaw, ML. (1999). Multiple roles of ligand in transforming the dioxin receptor to an active basic helix-loop-helix/PAS transcription factor complex with the nuclear protein Arnt. *Mol. Cell. Biol., 19*, 5811-22. ↗

Editions

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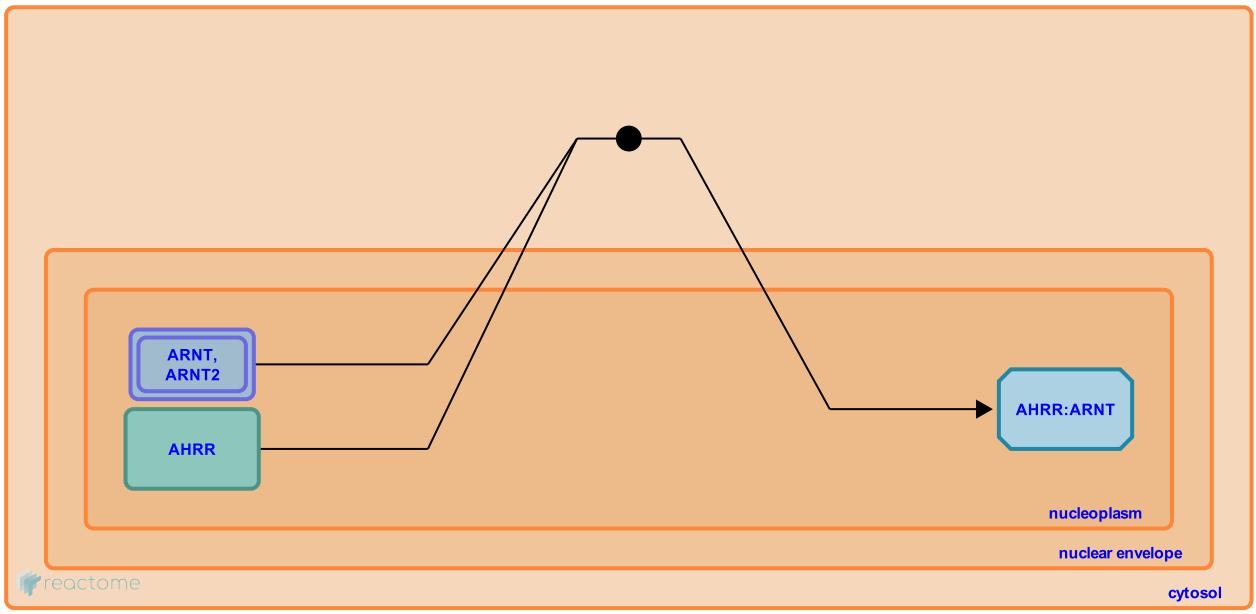
AHRR binds ARNT ↗

Location: Aryl hydrocarbon receptor signalling

Stable identifier: R-HSA-8936851

Type: binding

Compartments: cytosol



The aryl hydrocarbon receptor repressor (AHRR) is predominantly localised in the nucleus of cells (Kanno et al. 2007) and can bind AHR nuclear translocator (ARNT). The resultant AHRR:ARNT complex can compete with AHR:ARNT for binding to the xenobiotic response element (XRE) on target genes such CYP1A1 (Evans et al. 2008, Hahn et al. 2009).

Literature references

Kanno, Y., Miyama, Y., Takane, Y., Nakahama, T., Inouye, Y. (2007). Identification of intracellular localization signals and of mechanisms underlining the nucleocytoplasmic shuttling of human aryl hydrocarbon receptor repressor. *Biochem. Biophys. Res. Commun., 364*, 1026-31. ↗

Hahn, ME., Allan, LL., Sherr, DH. (2009). Regulation of constitutive and inducible AHR signaling: complex interactions involving the AHR repressor. *Biochem. Pharmacol., 77*, 485-97. ↗

Evans, BR., Karchner, SI., Allan, LL., Pollenz, RS., Tanguay, RL., Jenny, MJ. et al. (2008). Repression of aryl hydrocarbon receptor (AHR) signaling by AHR repressor: role of DNA binding and competition for AHR nuclear translocator. *Mol. Pharmacol., 73*, 387-98. ↗

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2016-08-24	Authored, Edited	Jassal, B.
2016-10-11	Reviewed	D'Eustachio, P.

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