芳香烃受体介导环境化学物毒作用的研究进展

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摘要：

芳香烃受体（AhR）是重要的环境化学物感受器。以往认为AhR可被二噁英等大分子化学物激活，作为转录因子调控包括多种代谢酶的靶基因表达。然而，近年来研究表明AhR可由不同类型的配体激活，调控多种靶基因表达。环境化学物可能通过AhR作用于多种信号通路，打破细胞稳态，导致病变。本文主要对AhR介导的环境化学物心脏发育毒性、神经毒性、致癌作用及免疫毒性及作用机制的最新进展进行综述。对AhR激活机制及其毒作用机制的深入了解将有助于预防和治疗环境化学物所导致的人类健康危害。

关键词：芳香烃受体；环境化学物；转录因子；细胞稳态

Advances on toxic effects of environmental chemicals mediated by aryl hydrocarbon receptors

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Abstract:

Aryl hydrocarbon receptor (AhR) is an important environmental chemical sensor. Traditionally, AhR is defined as a transcription factor activated by macromolecular chemicals such as dioxins, and regulating the expression of a variety of genes including metabolizing enzymes. However, recent studies show that AhR can be activated by different types of ligands and regulate a wide range of target genes. Environmental chemicals may affect multiple signaling pathways via AhR, and disrupt cellular homeostasis, resulting in pathologic changes. In this paper, we reviewed the recent progress and mechanisms of AhR-mediated cardiac developmental toxicity, neurotoxicity, carcinogenesis, immunotoxicity, and other toxicities of environmental chemicals. A comprehensive understanding of AhR activation and its toxicity mechanisms may conduce to the prevention and treatment of human diseases caused by environmental chemicals.

Keywords: aryl hydrocarbon receptor; environmental chemical; transcription factor; cellular homeostasis

芳香烃受体（aryl hydrocarbon receptor，AhR）是一种bHLH/PAS超家族转录因子，介导环境化学物的生物转化和致癌致畸等毒作用。早在20世纪70年代中期，AhR已被鉴定为能与四氯二苯并-*p*-二噁英（tetrachlorodibenzo-*p*-dioxin，TCDD）结合的具有极高亲和力的细胞质受体[1]，随后又发现AhR能与多环芳烃（polycyclic aromatic hydrocarbons，PAHs）等多种大分子外源化学物结合。细胞质中的AhR结合热休克蛋白90（heat shock proteins 90，Hsp 90）等分子维持非激活状态，受外源化学物等配体激活后转移到细胞核中，与芳香烃受体核转位因子（AhR nuclear translocator，ARNT）结合形成异二聚体，并结合到靶基因启动子或增强子区的外源化学物响应元件（xenobiotic responsive element，XRE），调控其转录[2]。AhR的下游靶基因包括细胞色素P450酶系家族1（cytochrome P450 1，CYP1）等Ⅰ相及Ⅱ相代谢酶类以及多种影响细胞功能的重要基因[3]。目前由AhR介导的毒性反应已被广泛报道，除了人们熟知的致癌、致畸外，还有心脏毒性、神经毒性、免疫毒性等[4-5]，几乎影响脊椎动物的每个器官和细胞类型。

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除作为受体直接介导外源化学物毒性外，越来越多的证据还表明AhR参与多种生理功能，在细胞周期、细胞迁移、细胞黏附和胚胎干细胞功能中发挥作用[6]。AhR的这些内在功能主要是对宿主细胞、微生物群或饮食中的内源性配体做出反应，因此AhR又被认为是一种能将外部环境信号连接到细胞的环境化学物感受器[7]。本文将对环境化学物激活AhR后所导致的毒作用及其分子机制进行综述，重点介绍近年来的研究进展。

1 AhR介导的外源环境化学物毒性

1.1 心脏发育毒性

心脏是胚胎发育最早的器官之一，对外界环境非常敏感。先天性心脏病位居新生儿致畸和致死率首位。多项研究表明二噁英类化学物等AhR激活剂影响心血管稳态并导致心脏发育异常[8]。流行病学研究表明，母体二噁英暴露增加新生儿先天性心脏病风险[9]。斑马鱼胚胎、小鼠研究结果表明，TCDD诱导的心脏发育毒性由AhR介导[10-11]。大气$PM_{2.5}$有机提取物中含多种PAHs类物质，包括苯并芘等AhR激活剂。本课题组利用斑马鱼胚胎和小鼠畸胎瘤细胞模型，通过AhR小分子抑制剂和基因敲减等手段，证实AhR介导了$PM_{2.5}$的心脏发育毒性[12-13]。此外，还发现AhR介导小分子污染物三氯乙烯所致斑马鱼胚胎的心脏发育异常[14]。

1.2 神经毒性

研究表明AhR缺失会导致小鼠海马神经发生异常，过度刺激AhR会抑制海马区神经元迁移并诱导神经元细胞凋亡[15]。Kimura等[16]发现小鼠大脑发育早期，AhR在海马、大脑皮层、小脑、嗅球和喙侧迁移流中均有表达。体外实验在小鼠海马神经祖细胞中同样检测到*AhR*的mRNA表达[17]。最新研究表明TCDD暴露能够增加神经退行性疾病的风险，其作用取决于AhR和丝裂原活化蛋白激酶（mitogen-activated protein kinase，MAPK）的激活，并且这两个信号通路之间有相互作用[18]。另有研究表明，二氯二苯基二氯乙烯通过AhR介导自噬相关的神经毒性[19]。

1.3 致癌作用

AhR激活剂TCDD能够诱导多种癌症发生，在乳腺癌、非小细胞肺癌、结肠癌和卵巢癌等肿瘤中已证实AhR表达异常升高[20]。在胶质母细胞瘤的研究中发现，AhR的促癌活性与转化生长因子-β（transforming growth factor-β，TGF-β）信号通路有关[21]。AhR异常表达还与多种神经系统癌症包括髓母细胞瘤和垂体腺瘤相关[22]。对肺癌的研究表明，PAHs能通过AhR促进细胞生长，促进肺癌细胞增殖[23]。对胃癌细胞的体内外实验研究表明，AhR激活可促进细胞生长、迁移和存活[24]。AhR在肝癌中的研究结果存在一定的矛盾，有研究表明AhR的激活与肝脏病变的进展无关[25]，也有研究认为TCDD可能通过AhR抑制肝癌细胞增殖[26]。对泌尿生殖系统肿瘤的研究表明，激活AhR在前列腺癌细胞中具有抗雄激素作用，并且AhR本身具有生长抑制作用[27]。

1.4 免疫毒性

AhR激活能直接促进多种促免疫因子的表达，还可以通过核因子-kB（nuclear factor-kB，NF-kB）通路的交互作用干扰炎症反应[28]。多数免疫细胞表达AhR，小鼠原代T细胞和B淋巴细胞暴露于TCDD可导致AhR激活[29]。AhR激活或过表达可引起细胞免疫屏障失调，导致多种疾病发生[30]。近年来研究发现，AhR激活能影响Th17和Treg细胞的分化。如TCDD能够激活Treg细胞，从而限制自身免疫反应[31]。6-甲酰基吲哚并[3，2-b]咔唑（6-formylindolo[3，2-b]carbazole，FICZ）作为内源性AhR激活剂可增强Th17细胞极化和促炎细胞因子的产生。*AhR*敲除小鼠进一步证实了AhR在免疫调节中的作用[32]。Di Meglio等[33]发现，AhR在角质形成细胞中通过控制与中性粒细胞吸引有关的趋化因子配体和抗菌肽的表达，预防皮肤过度炎症。此外，TCDD可直接损害B细胞，抑制IgM，并且对B细胞活化具有抑制作用[34]。

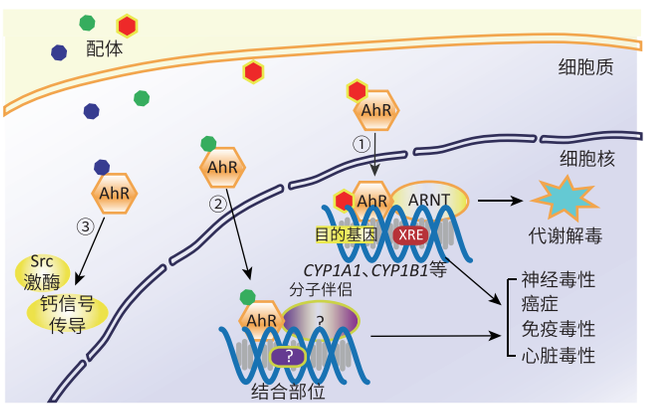
1.5 其他毒性

除了以上几种研究较多的毒作用外，AhR被环境化学物激活后还能引起广泛的胚胎发育毒性及多种疾病。TCDD、苯并芘等激活AhR能导致斑马鱼胚胎早期发育迟缓、脊柱扭曲等畸形及死亡率升高[35]。$PM_{2.5}$中的PAHs能引起多种非恶性呼吸疾病[36]。此外，环境化学物干扰色氨酸代谢等可影响内源性AhR配体，所导致的AhR异常激活与多种胃肠疾病及代谢疾病相关[37]。

2 AhR激活及毒作用的分子机制

AhR是一种高度保守的细胞内转录因子，其配体结合域可与多种类型的环境化学物相作用。典型的AhR配体一般为大分子，具有多环结构。近年来研究

表明，AhR还能结合多种非典型结构配体，与kruppel样因子6等ARNT之外的因子结合，识别不同于XRE的顺式反应元件，调控多种基因表达[38]。除入核作为转录因子外，一些配体还可能通过AhR引发更快速的非基因组反应，可在细胞质中激活Src激酶，并调控Ca^{2+}信号传导[39]。AhR非基因组功能是调节TCDD中毒相关促炎作用的关键机制[40]。研究发现，芘拮抗经典基因组AhR/ARNT/CYP1途径，选择性激活AhR非基因组信号传导，触发细胞内Ca^{2+}的快速和大量释放，导致细胞膜组织改变[41-42]。AhR基因组和非基因组信号传导可以独立触发，并且AhR非基因组信号传导的激活可能不限于经典的AhR激动剂[41]。见图1。



[注] ①经典基因组途径；②非经典基因组途径；③不依赖基因组途径。
[Note] ① Canonical genomic pathway; ② Non-canonical genomic pathway; ③ Non-genomic pathway.

图1 外源性化合物激活AhR示意图

Figure 1 Schematic diagram of AhR activation by xenobiotics

AhR是细胞中多个信号级联反应的汇合点，这可能部分解释了为何TCDD能引起多种疾病[7]。在胚胎干细胞分化过程中，TCDD诱导AhR持续激活能干扰Activin、BMP和Wnt等关键信号通路，从而导致心肌细胞丧失收缩性[43]。本课题组之前的研究发现，AhR通过氧化应激及抑制Wnt/β-catenin信号通路介导$PM_{2.5}$引起的斑马鱼胚胎心脏发育畸形[12-13, 35, 44]，还发现小鼠P19畸胎瘤细胞中，$PM_{2.5}$通过AhR引起细胞周期异常，抑制心肌细胞分化[13]。此外，癌症发生过程中，AhR对整联蛋白的调控受活化T细胞核因子和TGF-β信号通路介导，有助于癌细胞的迁移和侵袭[45]。AhR还可通过上皮-间充质转化增强癌细胞的迁移和侵袭能力[46]。$PM_{2.5}$引起的活性氧及其成分中的离子和PAHs等物质也可诱导上皮-间质转化介质。AhR激活后可与TGF-β/SMADs、NF-κB、ERK、PI3K/Akt、Wnt/β-catenin及Notch等信号通路相互作用，直接和间接地转导调节上皮细胞中上皮-间充质转化相关基因表达，诱导上皮形态和功能的特征性改变[47]。

AhR激活具有引起氧化应激、导致DNA损伤、凋亡及促进细胞外基质代谢等多种重要作用。本课题组发现斑马鱼胚胎心脏中$PM_{2.5}$有机提取物通过激活AHR引起活性氧升高、DNA损伤及细胞凋亡[35]。与此一致，焦炉工人PAHs暴露与其外周血细胞中DNA氧化损伤有线性剂量反应关系，同时母体PAHs暴露与脐血淋巴细胞DNA端粒长度也呈负相关[48-49]。AhR还能参与细胞外基质稳态的调节，激活AhR可导致细胞外基质失调，促进其代谢[50]。

3 结论与展望

除了调控外源化学物代谢，AhR所介导的心脏发育毒性、神经毒性、致癌和免疫毒性等也逐渐被了解。特别是AhR可被内源性配体激活，维持细胞稳态并参与多种生理功能。外源化学物可以通过AhR打破细胞稳态，干扰多条信号通路，导致病理变化。在典型结构配体之外，最近还发现多种非典型结构的外源化学物可以激活AhR，对细胞增殖/凋亡、线粒体损伤、自噬、氧化应激等产生影响。AhR的物种特异性也是重要的关注对象[51]。今后将需要更多的研究来阐明外源化学物通过AhR对生命活动的影响，并通过人胚胎干细胞等研究模型评估其对人类的健康危害。

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