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Epigenetics and PCBs

Commentary to "Androgen receptor activation by polychlorinated biphenyls: Epigenetic effects mediated by the histone demethylase Jarid1b"

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Epigenetic links genetics and environment in shaping several physiological mechanisms including endocrine functions. Growing evidences suggest an interplay among endocrine system, environment, and epigenetics in the etiology of many complex diseases, including some neuropsychiatric disorders. We have demonstrated that a prenatal exposure to polychlorinated biphenyls (PCBs) is able to modulate some epigenetic marks related to the steroid receptors, which (in particular androgen receptor, AR) are cofactors of histone remodeling enzymes; in our recent paper we focused on the interaction between PCBs–AR and the demethylase Jarid1b. Our studies indicate that PCBs induce AR transactivation in a dose-dependent way. Jarid1b potentiates transcriptional activity independently of ligand and of cell phenotype; in particular, Jarid1b increase the AR transactivation in the isoforms with a short polyQ expansion, which are normally present in the population. Since an inverse relationship appears to exist between the AR transcriptional activity and the polyQ repeat length, it is possible to hypothesize that Jarid1b–AR interaction strength depends on the polyQ lenght. PCBs auto-downregulate AR expression and this negative feedback is potentiated by Jarid1b and depends on AR promoter length. These results open new perspectives in the PCBs/AR/Jarid1b interplay possibly occurring in the pathogenesis of some neurological diseases like autism.

Keywords: epigenetics, PCBs, Jarid1b, histone modification, androgen receptor, endocrine disruptors, environment

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Epigenetics represents the programming of the genome to express the appropriate set of genes in specific cells at specific time points during life. Epigenetic patterns are generated during cellular differentiation by a highly programmed and organized process. Nevertheless, they are dynamic and responsive to the environment especially during the critical periods of gestation and early life. The epigenome is constituted by a set of chromatin regulators, such as DNA methylation, histone modifications, nucleoside remodeling and miRNA expression that dynamically interact to define a correct transcriptomic profile[1]; epigenetics represents the link between genetics and environment in shaping the physiological functions.[2,3] The NIH Roadmap Initiative on epigenetics has widened the term "Epigenetics" to include "Both heritable changes in gene activity and expression but also stable, long-term alterations in the transcriptional potential of a cell that are not necessarily heritable" (for more information go to http://nihroadmap.nih.gov/epigenomics). These changes might be produced in particular by the environment present in early life and might affect the health influencing the susceptibility to develop several diseases, from cancer to mental disorder during the entire life span.[4] The most studied environmental influences acting on epigenome are diet, infections, wasting, smoking and environmental pollutants, in particular endocrine disruptor compounds (EDCs). The exposure to compounds with endocrine interfering activity[5] plays a key role on the epigenome

shaping multiple aspects of the endocrine function. Several enzymes involved in epigenetic key processes, such as histone modifying enzymes, are affected and modulate the endocrine system. It is also known that nuclear steroid receptors interact with histone-modifying enzymes to regulate gene transcription and chromatin remodeling.[6] Interestingly, histone demethylases, the enzymes that catalyze the removal of the methyl groups from histones, complexes with steroid receptors, in particular with the androgen receptor (AR), facilitating the transcription of their target genes.[7]

One of the EDCs most studied as an epigenome modifier is the phytoestrogen genistein, which is able to modulate the activity of DNA methyltransferases. Moreover, alterations of the DNA methylation pattern in animals exposed to the synthetic estrogen diethylstilbestrol (DES) have also been found. Likewise, bisphenol A (a plasticizer) is able to disrupt the DNA methylation pattern of agouti mice exposed to this pollutant. Finally, vinclozolin, a fungicide with antiandrogenic activity, transgenerationally affects DNA methylation patterns in epydidimal sperm of the first generation of animals after parental exposure. These data, as well as further evidence present in the literature, indicate that some EDCs can act transgenerationally disrupting the epigenome, in particular when the exposure to these compounds occurs during the prenatal and earliest period of life (see[8] for references).

Polychlorinated biphenyls (PCBs) belong to EDCs and they are widely present in the environment. They were extensively used as dielectric and coolant fluids, for example in transformers, capacitors, and electric motors. Due to their environmental toxicity and classification as a persistent organic pollutant, PCB production was banned by the United States Congress in 1979 and by the Stockholm Convention on Persistent Organic Pollutants in 2001.[9] PCBs are a group of 209 congeners with a broad spectrum of biological and toxic effects.[10] Because of their different biochemical characteristics, some PCBs are classified as dioxin like (DL-PCBs), and non-dioxin compounds (NDL-PCBs). Many, but not all, effects of DL-PCBs are mediated by the activation of the arylhydrocarbon receptor (AhR) a transcription factor present in several cell types of different animal species, including man. The differential effects of these two classes of pollutants are not distinguishable in vivo, because animals and humans are exposed at the same time to both classes and the global effect is cumulative.[11] Although production of PCBs was discontinued many years ago, due to their high resistance to degradation, they are still present in the environment; chronic low-level exposure to PCBs remains a significant public health concern. PCBs might have direct toxic effects altering gene expression, particularly during development.[12] Many and diverse endocrine, metabolic and behavioral effects have been described after PCBs exposure in animals and humans.[13]

Few data are available on the epigenetic effects induced by PCBs. It seems that an exposure to a mixture containing 14 mono- and di-ortho PCB congeners, from the first day of gestation to the weaning, reduces the expression and the activity of DNA methyltransferases in the rat offspring liver.[14]

In our previous experiments we found that an in utero exposure to a reconstituted mixture of PCBs (PCB 126, 138, 153 and 180) is able to induce gene and protein expression of H3K4me demethylase (Jarid1b) and of SIRT1 (HDAC, Histone deacetylase) in the liver of exposed offspring. Consequently, we found an alteration of the H3K4me3 and H4K16ac contents in the liver of the exposed offspring. Moreover, we observed also a reduction of AR expression in the same animals.

Since, as mentioned before, steroid receptors are cofactors of histone remodeling enzymes, in our recent paper[15] we focused the attention on PCBs-AR-Jarid1b interaction. Two different levels of PCBs/AR/Jarid1b interaction were evaluated. On one side we investigated how PCBs could affect the AR/Jarid1b interaction in AR target gene transcription, on the other side we analyzed how PCBs could affect AR/Jarid1b interaction in modulating the AR negative control of its own transcription. In particular we have analyzed: (i) the AR transcriptional activity induced by PCBs; (ii) the role of PCBs and Jarid1b in the transactivation of different AR poly Q variants (isoforms with different transcriptional activities) and (iii) the role of Jarid1b in the AR activation and interaction with the AR promoter.[15]

PCBs treatment is able to induce AR transcriptional activity in a dose-dependent manner, even if the effect is much lower than that induced by the natural ligand, DHT (dihydrotestosterone), which is the active 5-α reduced testosterone metabolite, possessing a much higher affinity for AR than the native hormone, testosterone. Ligand binding studies have shown a direct and specific binding of several PCBs congeners to the ligand–binding domain of the AR protein.[16] Jarid1b might modulate the effects of AR ligand interaction. The interaction between Jarid1b and AR on AR transcriptional activity is described in the literature, especially in prostate cancer[17] and has been documented in our previous "*in vivo*" studies,[9] in which PCBs exposure stimulated the expression of the Jarid1b in the rat liver and concomitantly reduced AR expression.[11]

In the studies described in the our recent paper[15] the overexpression of Jarid1b cotransfected with AR increases transcriptional activity induced by DHT or by PCBs in three different cell types: HEK293, and two neuronal cell lines, NSC34 and GN11. The effect of Jarid1b overexpression is cell-phenotype and ligand independent.

The mechanism by which Jarid1b potentiates the AR transcriptional activity or AR nuclear translocation is still unclear. It is known that the enhancement of the AR transcriptional activity needs the preservation of the enzymatic activity, because deletion of the JmjC domain, the catalytic center of the demethylase, abolishes the stimulation.[17,18]

The interaction between PCBs and AR is also affected by differences in the structure of the AR gene present among individuals. It is known that AR transcriptional activity depends at least in part on the polyglutamine tract (polyQ, coded by a CAG repeat) length located in the trans-activating region of the AR. In the AR gene the CAG repeat number vary both within and between human

populations between 8 and 30 units[19,20] and thus the coded polyQ also is polymorphic in length. An inverse relationship exists between the AR transcriptional activity and the poly Q repeat length (AR CAGn[21-23]). Two recent reports by Bjork and coworkers[24,25] indicate that PCBs have a CAG/PolyQ length dependent effect on AR *"in vitro"*[25] and in some human prostatic cells.[24] In particular, PCB 153, one component of the mixture utilized in our studies, has a more pronounced effect on the *"in vitro"* AR transcriptional activity of the short poly Q isoforms. It is possible to hypothesize that Jarid1b-AR interaction affects the differential transcriptional activity of the AR isoforms as a function of the interaction strength which is lower for the longer isoform which possess a polyQ expansion. Indeed, Suzuki and colleagues have shown that the aberrant polyQ expansion potentiates the association between Rbp (Retinoblastoma Protein) and AR: this association appears to attenuate the recruitment of HDAC1 (an histone deacetylase class 1), a potent transcription cofactor.[32] It is conceivable that a similar mechanism could lead to the attenuated interaction shown in our studies for the longest isoform ARQ46. Conversely, the higher activation of the short AR seems mediated by a better interaction of this receptor with Jarid1b. This hypothesis is illustrated in **Figure 1**. On the left panel is represented the interaction Jarid1 b with the short isoform of AR (ARQ12) which potentiates AR transcriptional activity, following the binding of PCBs to AhR-AR complex. On the right panel the transactivation effect disappears since the longer AR isoform (ARQ46) is not able to produce a strong interaction with Jarid1b. The AR/Jarid1b binding on DNA of target gene is allowed by the presence of ARE (androgen responsive element) and by the presence of a binding site for Jarid1b (PLU1). The involvement of AhR in the AR transcription mechanism produced by PCBs is considered below.

These observations might be important in explaining the pathogenesis of Autism Spectrum Disorder (ASD) in which the genetic as well as important environmental effects might be involved. Indeed, ASD onset is possibly related to an excessive androgen prenatal exposure

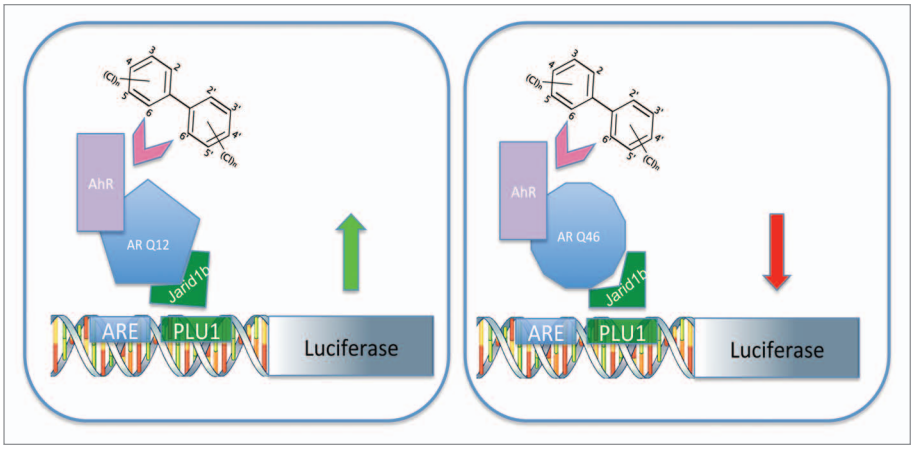

Figure 1. Left panel: the interaction between Jarid1b (green shape) and ARQ12 (blue shape) potentiates AR transcriptional activity (green arrow), after the binding of PCBs to AhR (purple shape)-AR complex. On the right panel the transactivation effect disappears (red arrow) since ARQ46 (blue shape) is not able to produce a strong interaction with Jarid1b (green shape). The AR/AhR/Jarid1b binding on DNA of target gene is allowed by the presence of ARE (androgen responsive element, blue box) and by the presence of a binding site for Jarid1b (PLU1, green box).

both in animals[26] and in humans.[27] The hyperandrogenization of the brain might be caused by a higher fetal androgen exposure, increased activity of testosterone (T) activating enzymes or enhanced AR activity, as might occur in presence of the short polyQ variant of AR and/or by the interaction of environmental induced epigenetic changes. A hyper-activation of AR induced by PCBs in presence of Jarid1b in some susceptible individuals, could be an important etiological mechanism in this complex disease.

Indeed, a higher prevalence of short CAG alleles in ASD female subjects has been reported,[28] and mutations within the genes encoding the H3K4-specific histone demethylase, JARID1C/SMCX, have been linked to autism.[29] The AR CAG repeat genotype might be one of many genetic component interacting with environment through epigenome contributing to ASD susceptibility. All these data suggest that an early-life exposure to PCBs might be involved in modulating AR effects through the mechanisms described above and/or by the activation of AhR.[11,30]

Since in previous in vivo studies we found that PCBs exposure reduces AR expression,[11,31,32] the second level of investigation of our recent paper focused on how PCBs could affect AR/Jarid1b interaction in the modulation of AR negative control of its own transcription. Analyzing the DNA sequence of the AR promoter, we observed the presence of binding sites for Jarid1b (PLU1) and AhR (XRE), along with some androgen responsive elements (ARE); this could be indicative of the possible direct effect of the demethylase in modulating the AR transactivation induced either by DHT or by PCBs also in AR negative feedback.[33] To study this aspect we have cotransfected HEK293 cells with plasmids coding for Jarid1b and AR promoters with a different length (long, intermediate and short) and a luciferase reporter gene. The results have shown that the effect of PCBs, but not of DHT, needs the presence of Jarid1b and of at least 2 PLU1 binding sites. Since the responsive element XRE, ARE and PLU1 are concomitantly present on the AR promoter, it is possible that the recruitment of Jarid1b is responsible of the complex AhR-AR interactions occurring after PCBs exposure, in particular in presence of coplanar congeners. The association between AR and AhR is complex and not fully understood.[34-36] To our knowledge, there is no data about a direct interaction between AhR and Jarid 1b, even if in mouse hepatoma cells (HEPA-1) the activation of the arylhydrocarbon receptor (AhR) produces epigenetic changes affecting the acetylation of lysine 16 of histone H4 and in the trimethylation of lysine 4 of histone H3.[37]

It is possible to conclude that PCBs induced AR modulation involves AR-Jarid1b interactions occurring in neuronal cell lines. This mechanism might

be involved in the etiology of a complex disorder like autism spectrum disorder. Further studies are needed to substantiate this hypothesis which involves a fine interplay between epigenome, environment and endocrine system in a complex disorder, such as ASD.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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