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PBCs environmental pollution and epigenome: a new role for androgen receptor-dependent modulation?

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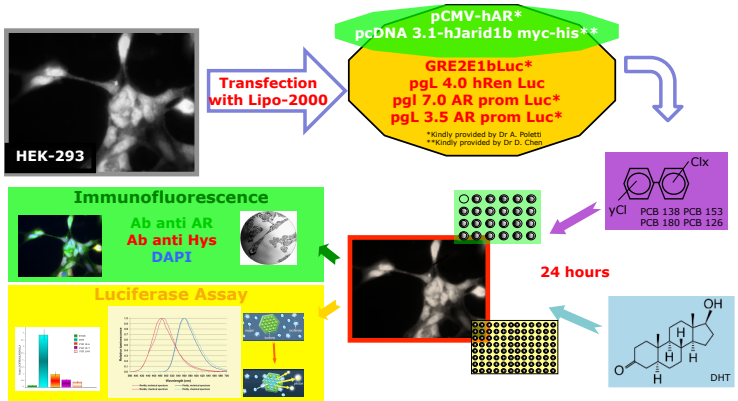
Epigenetic represents the programming of the genome to express the appropriate set of genes in specific cells at specific time points in life. The two main epigenetic controls are the methylation of cytosines in CpG islands and the post-translational modification of histone tails. Epigenome is an important target of environmental effects, especially during gestation and childhood, modulating disease susceptibility during the whole life. Disruption of epigenetics may be responsible of an alteration of trascription during critical periods of development, resulting in stable modifications in adulthood [1].

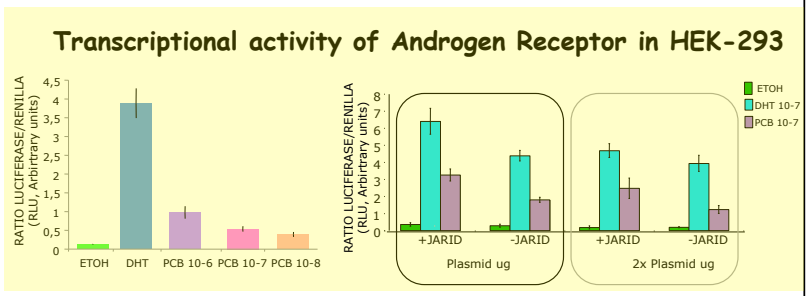
In our previous studies we have demonstrated that prenatal exposure to polychlorinated biphenyls (PCBs), an important class of endocrine disruptors, alters in liver some histone post-translational modifications (H3K4me3/H4K16Ac) and the expression of the corresponding modulating enzymes (Jarid1b/SirtT1) and reduces the androgen receptor (AR) levels [2]. Furthermore, it is known that steroid receptors could act also as co-regulator of histone modification enzymes. It is also remarkable that AR and Jarid1b (demethylating enzyme) interact each other and that Jarid1b is able to potentiate the transcriptional activity of AR [3]. The AR down-regulation, shown by our data, is not directly related to the reduction of H3K4me3 levels in the AR promoter, as our ChIP experiments have indicated [2]. The observed AR reduction might be related to the down-regulation of AR induced by its own activation [4].

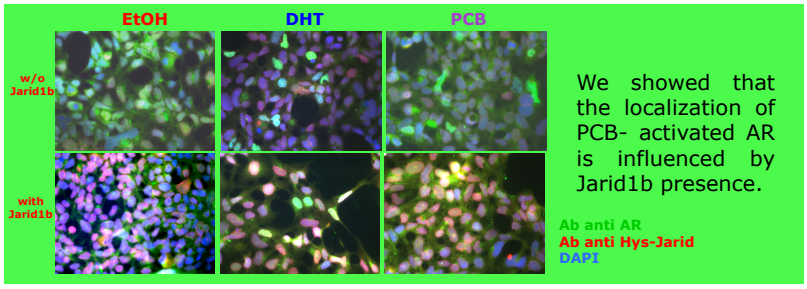
Aim of this work was to characterize the complex scenario of AR involvement in regulating histone modifications after an exposure to a mixture of PCBs.



Results:

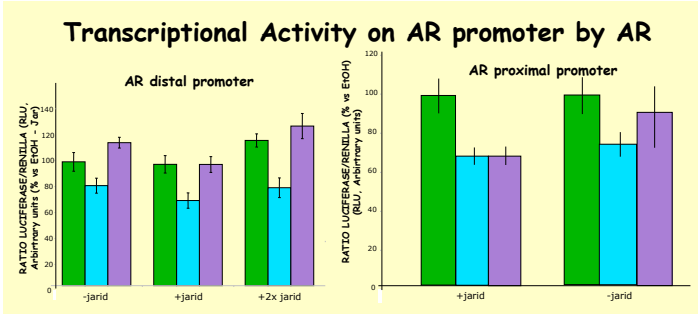
First of all, we investigated if a reconstituted mixture of PCBs is able to modulate AR transcriptional activity; we observed that PCBs are able to induce AR mediated transcription in a dose dependent way and that Jarid1b presence potentiates the PCB effect on AR transcriptional activity.





We showed that the localization of PCB- activated AR is influenced by Jarid1b presence.

Finally, using AR promoter fused with a reporter gene, we found that PCBs are able to auto-downregulate AR, especially at the presence of Jarid1b.



In conclusion it is possible to hypothesize that AR modulation exerted by PCB pass through chromatin structure remodelling. It remains to clarify if AR is involved in mediating PCB induced disruption of Jarid1b.

1. Foley D.L., Craig J.M., Morley R., Olsson C.J., Dwyer T., Smith K., Saffery R. Prospects for epigenetic epidemiology. AM J EPID 169(4):389-400 (2009)
2. Casati L. Sendra R., Colciago A., Negri Cesi P., Esteller M., Celotti F. PBCs environmental pollution affects the histone modification pattern in early development of rats: a role for androgen receptor-dependent modulation. Submitted for publication.
3. Xiang Y, Zhu Z, Han G, Ye X, Xu B, Peng Z, Ma Y, Yu Y, Lin H, Chen AP, Chen CD. JARID1B is a histone H3 lysine 4 demethylase up-regulated in prostate cancer. Proc Natl Acad Sci. 2007
4. Vismara G, Simonini F, Onesto E, Bignamini M, Miceli V, Martini L, Poletti A. Androgens inhibit androgen receptor promoter activation in motor neurons. Neurobiol Dis. 2009