Early life exposure to estradiol in neonate rats impairs mucosal and systemic immune response by modulating Th17/Treg cell balance : a study model for mecanistic pathways in early life supporting long lasting immunotoxic effects of bisphenols

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Background

Xenoestrogen (e.g. BPA, BPS…) = multiple absorption pathways as food contaminants and/or through dermal contact (transcutaneous absorption)

Perinatal exposure to BPA provokes long-term imprint on immune system in female offspring (**inflammation, immune defenses, oral tolerance**)

Braniste *et al.* PNAS 2010; Ménard *et al.* FASEB J / Plos One 2014

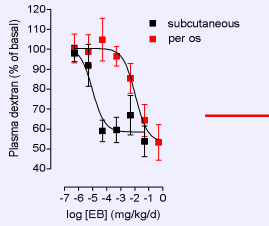
Aim of this study

To investigate *and* to compare the impact of estradiol (EB) **in early life *via* subcutaneous** and **oral routes on immune system maturation and responses in the intestine and at systemic level**

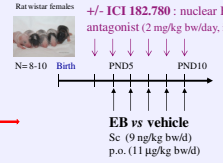
Methods

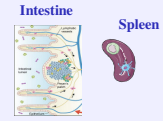
Dose-response to EB

Determination of ED50 for EB on intestinal permeability (i.e. a common target for estradiol) as physiological doses for immunotoxicity testing in neonate rats



Neonatal treatment with EB
subcutaneous *versus* per os



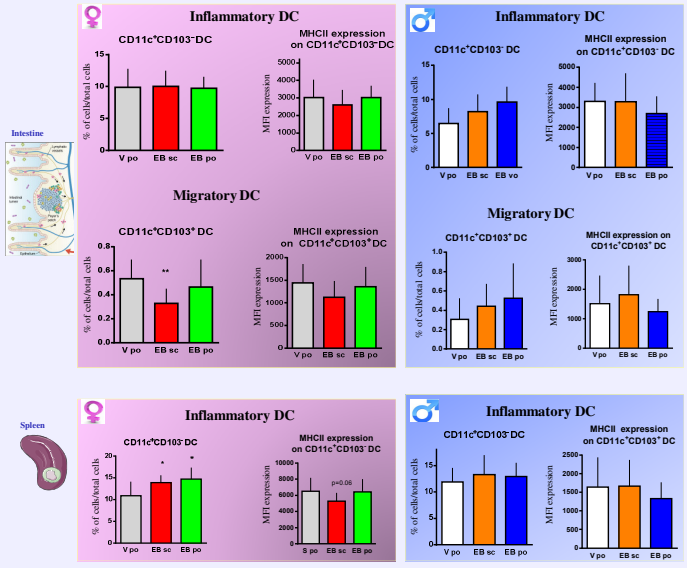


Systemic and intestinal immune response analysis

* : $p < 0.05$; ** : $p < 0.01$ and *** : $p < 0.001$

Results

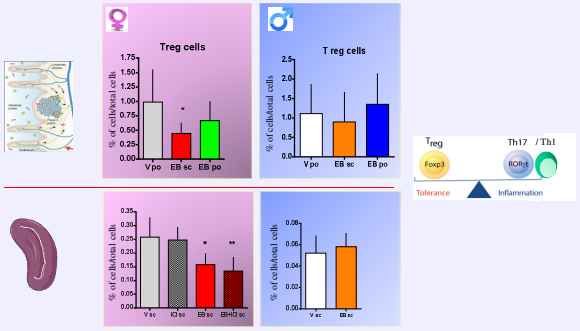
Dendritic cells (DC) frequency and maturation



➡ **Sex-dependent effect of EB on dendritic cells subpopulations,** whatever the route of exposure **:**

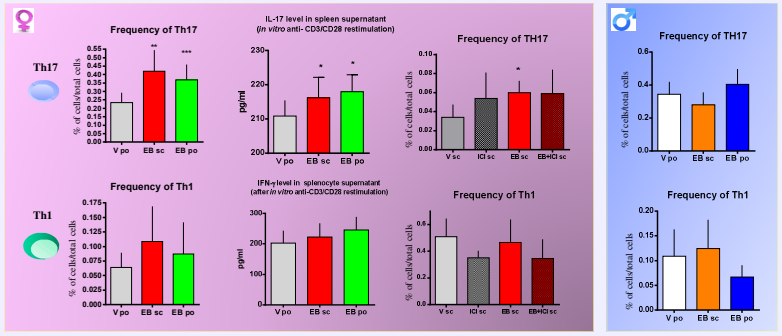
- A decrease of migratory DC frequency in gut *lamina propria* in female pups only
- An increase of inflammatory DC at systemic level in the spleen

T regulatory (Treg) cells frequency in spleen and intestine



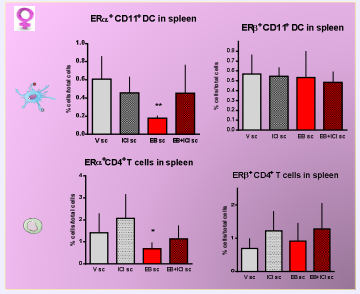
➡ Subcutaneous exposure to EB evokes a **decrease of Treg frequency** in spleen and *lamina propria*, in female pups only. No involvement of **nuclear ER pathway**

Th1/Th17 frequency and inflammatory immune responses in spleen



➡ In female pups only, both **s.c. and p.o. exposure to EB induced an increase of Th17 frequency** in spleen and *lamina propria*.
This EB effect led to an increase of **IL-17 cytokine** production by splenic T cells.

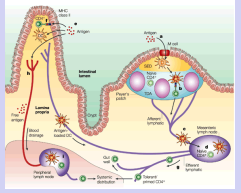
ERα and ERβ-positive DC and T cell subsets in spleen



➡ A decrease of **ERα+ DC** and of **ERα+ T cell populations** in spleen of female pups after EB s.c. injection only.

This EB effect was **mediated by nuclear ERs** (i.e. ICI-sensitive)

Conclusion



➢ **Oral *or* subcutaneous exposure to EB** at physiological doses **affects immune cell populations and function in the spleen and the intestine of rat neonates**

➢ **Sex-dependent impairment of mucosal and/or tolerogenic functions**, *and* **promotion of Th17 inflammatory systemic immune response in females**