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AhR activation in thymic epithelial cells can modify immune tolerance process

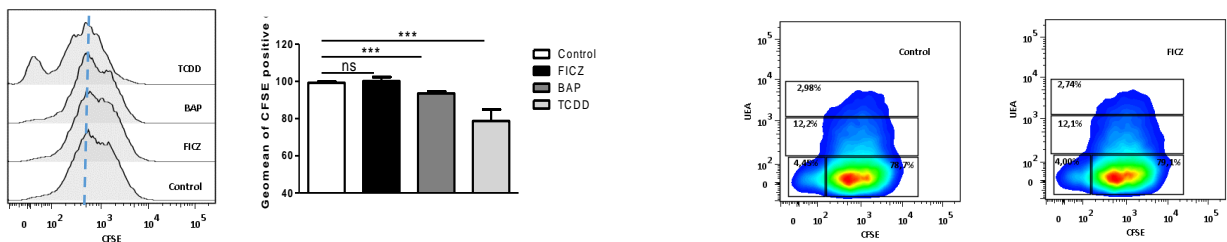
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Environmental contaminants (ECs) are associated with pathogenesis and etiology of numerous chronic diseases. The aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor is the intracellular mediator of the EC effects (Busbee et al., 2013). Various studies have shown that AhR activation induces T-cell disequilibrium that could lead to autoimmunity. We aimed to study the impact of AhR activation in medullary thymic epithelial cells that are essential for central tolerance mechanisms and T-cell differentiation.

Here, we analyze the effect of AhR activation by either its exogenous ligand (2,3,7,8-Tetrachlorodibenzodioxin (TCDD), and Benz[a]pyrene (BAP)) or its endogenous ligand (6-Formylindolo (3,2-b)carbazole (FICZ)), in vitro on the homeostasis and physiological function (expression of immune tolerance key factors, cytokines and chemokines) of primo-cultured human thymic epithelial cells (TECs). All the studies on human thymuses were approved by the local Ethics Committee (CCP, Ile de France-Paris 7, agreement N°C09-36). P values were obtained using the 1-way ANOVA test. *P < 0.05; **P < 0.001; ***P < 0.0001

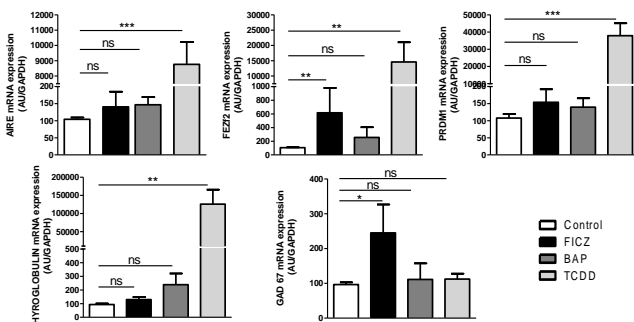
1 –AhR ligands modulate proliferation of primary human cultured TECs



The proliferation of primary human cultured TECs (CFSE staining) is modulated, in an AhR ligand-dependent manner. Exogenous AhR ligands (TCDD and BAP) tended to accelerate TECs proliferation while endogenous ligand (FICZ) had no significant effect.

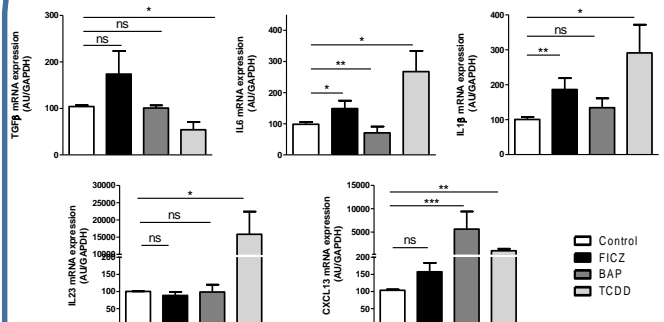
More, using UEA labelling (marker of mature mTECs), we observed that exogenous AhR ligands may also modulate the maturation of mTECs in vitro. (n>5). FICZ:0,5µM; BAP:1µM; TCDD:100nM

2 –Expression of factors involved in thymic central tolerance



Only the exogenous AhR ligand, TCDD, significantly modulates in primary human TECs the expression of the three main transcription factors (AIRE, FEZ2, PRDM1) involved in central tolerance processes. Endogenous AhR ligand, FICZ, modulates expression of FEZ2. In addition, expression of the tissue-specific antigen (TSA) regulated by AIRE (thyroglobulin) is modified by TCDD while the expression of the TSA non regulated by AIRE (GAD67) is modulated by FICZ. (n>7). FICZ:0,5µM; BAP:1µM; TCDD:100nM

3 –AhR ligands deregulate cytokine expression in primary human cultured TECs



AhR ligands (endogenous FICZ, and exogenous BAP and TCDD) modulate in TECs, the expression of cytokines involved in the regulation of T-cell differentiation and Th17/ Treg cell balance. By contrast, only exogenous AhR ligands (TCDD and BAP) modified B cell chemokine attractant CXCL13 expression in primary human TECs (n>7). FICZ:0,5µM; BAP:1µM; TCDD:100nM

These results suggest that AhR activation in mTECs affects cell proliferation, TSA expression and cytokine secretion. These effects could alter the negative selection process (permitting the escape of autoreactive T cells) and the balance of T cell subpopulations. More, AhR activation also induced upregulation of CXCL13 expression, favoring a chemoattraction of B-cells, an event occurring in the tissue, challenging cell infiltration in autoimmune diseases. Therefore, activation of the AhR pathway in TEC could favor the development of autoimmune disorders in predisposed subjects.