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AHR activation may regulate expression of pro-inflammatory factors in thymuses of AChR⁺ Myasthenia Gravis patients

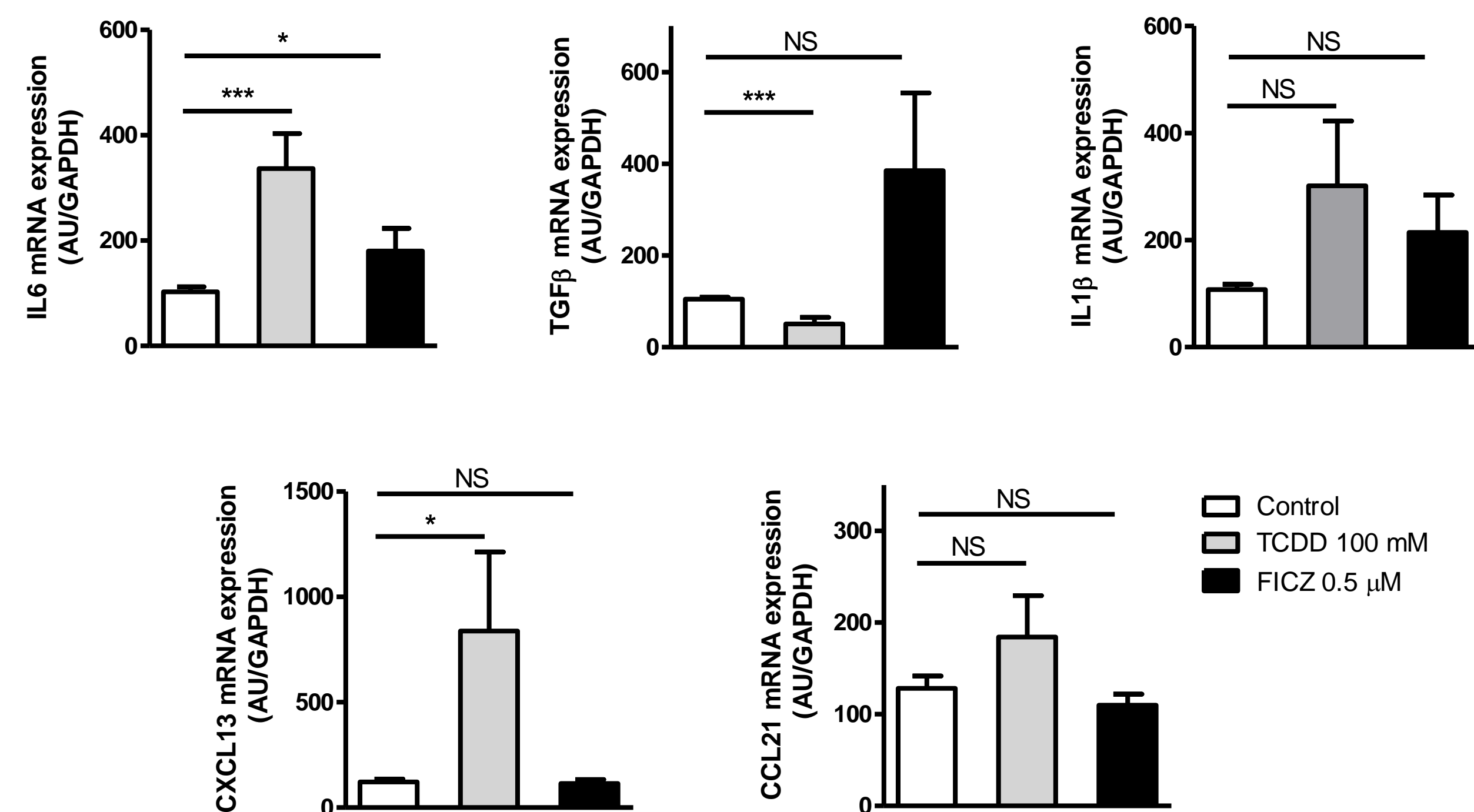
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Myasthenia gravis like most autoimmune diseases, is a multifactorial disease. Therefore, predisposition factors act in concert with unknown triggering factors (Anaya, 2012) (Moroni et al., 2012) (Kato and Fujita, 2014) (Berrih-Aknin and Le Panse, 2014). Hence, converging studies have demonstrated that environmental contaminants including dioxins and Poly-aromatic hydrocarbures (PAHs), through their transcription factor, the aryl hydrocarbon receptor (AHR), may contribute to the pathogenesis of many ADs (Busbee et al., 2013) (Quintero et al., 2012). Various studies have shown that AHR may contribute to a T-cell disequilibrium that could lead to autoimmunity (Hao & Whitelaw, 2013) (Zhu et al., 2014).

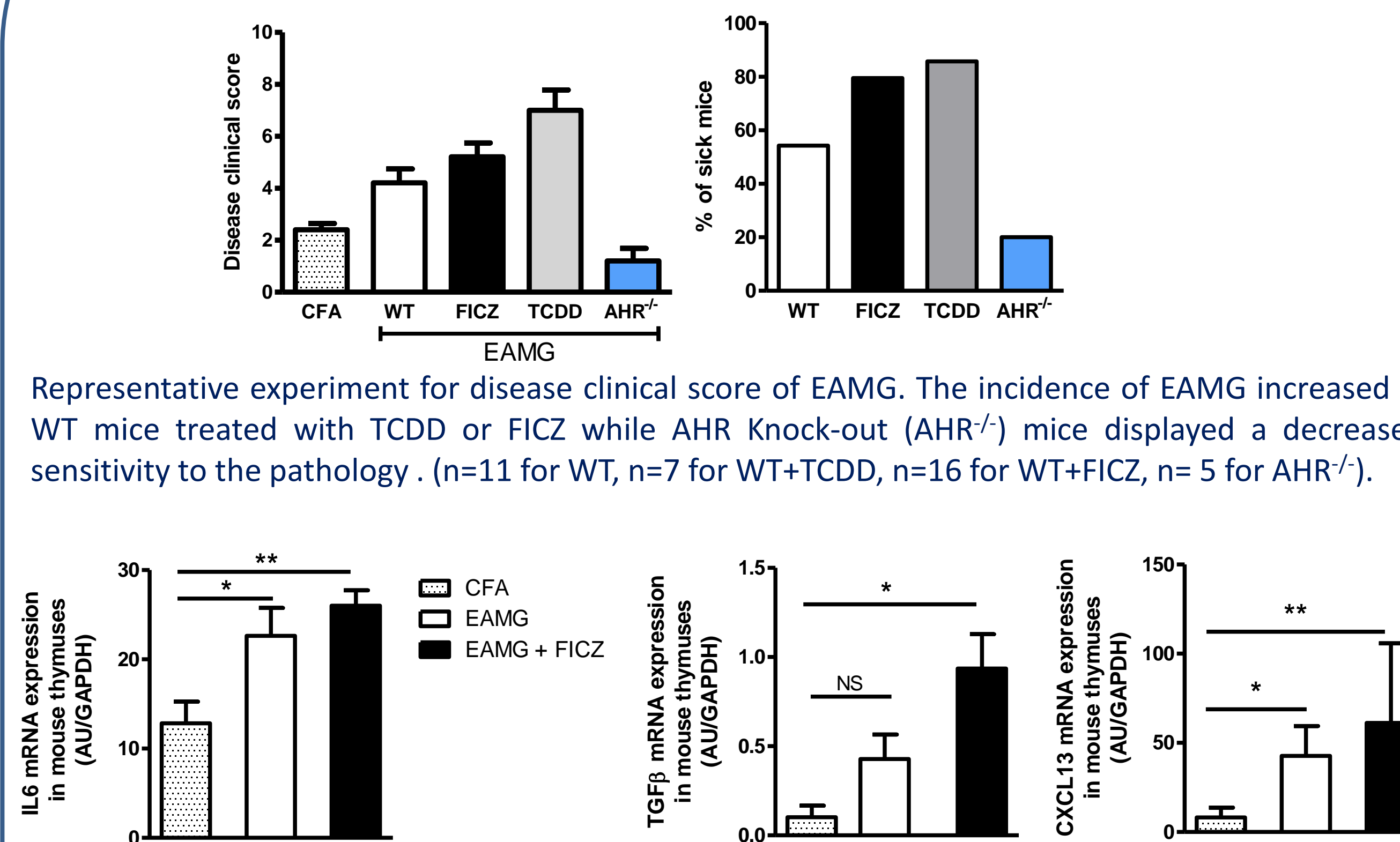
We then hypothesized that immune deregulation induced by AHR activation may trigger the development of MG. Here, we analyze AHR expression in AChR⁺ MG thymuses. We also examine the effect of AHR activation by either its exogenous ligand (2,3,7,8-Tetrachlorodibenzodioxin (TCDD)) or its endogenous ligand (6-Formylindolo (3,2-b)carbazole (FICZ)), *in vitro* on the physiopathological events occurring in thymic epithelial cells (TECs) and *in vivo* on the susceptibility to MG development in the experimental autoimmune model of MG (EAMG).

1 – AHR ligands deregulate cytokine and chemokine expression in primary human cultured TECs



AHR ligands stimulated, in TECs, the expression of cytokines involved in the regulation of TH17/ Treg cell balance. Only exogenous AHR ligand modified B cell chemokine attractant CXCL13 expression in primary human TECs (n>4). P values were obtained using the 1-way ANOVA test. *P < 0.05; ***P < 0.001.

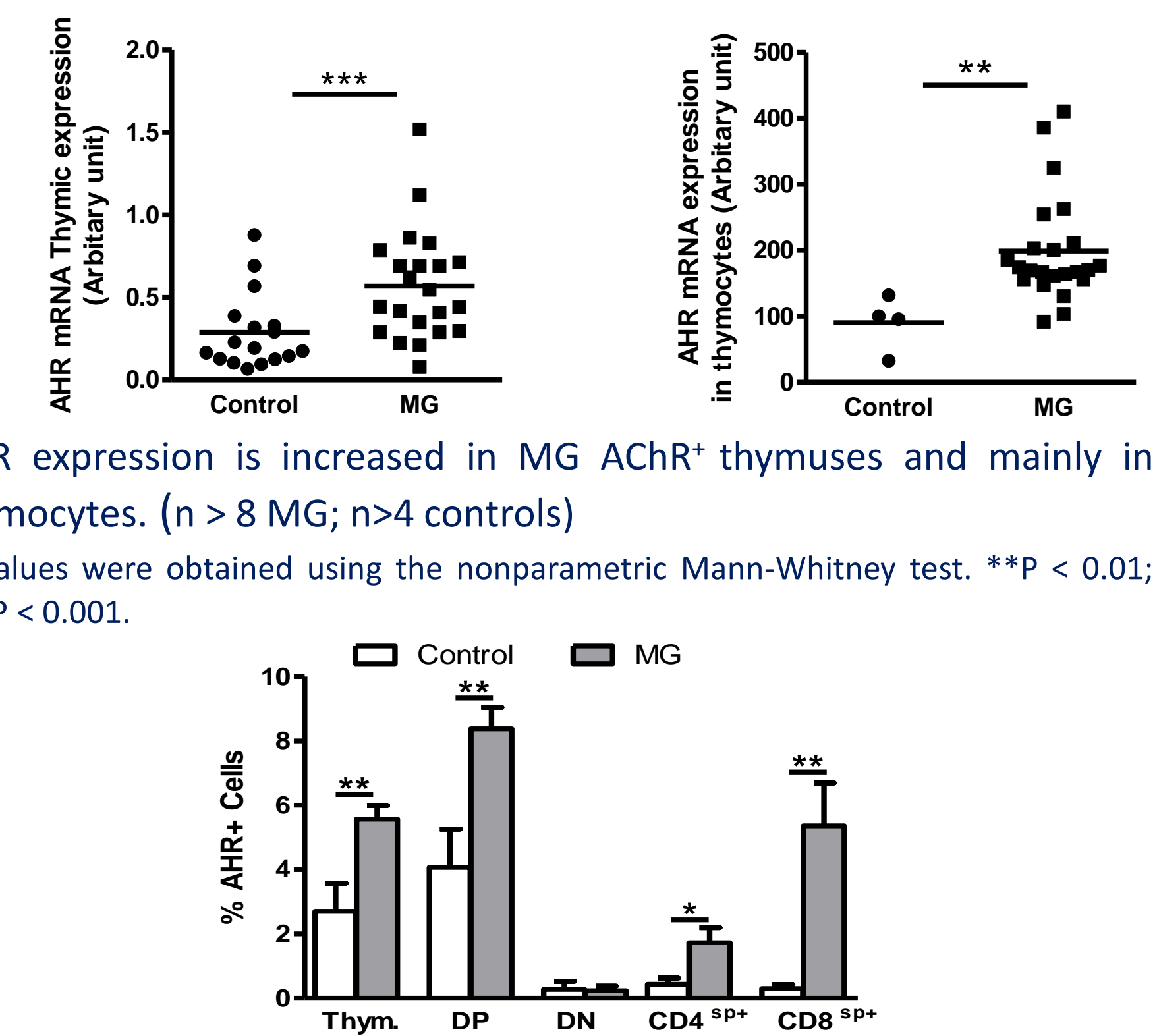
2 – AHR ligands increase EAMG incidence



Representative experiment for disease clinical score of EAMG. The incidence of EAMG increased in WT mice treated with TCDD or FICZ while AHR Knock-out (AHR^{-/-}) mice displayed a decreased sensitivity to the pathology. (n=11 for WT, n=7 for WT+TCDD, n=16 for WT+FICZ, n= 5 for AHR^{-/-}).

In vivo, AHR ligand FICZ exacerbated significantly the increased expression of cytokines and chemokines involved in physiopathologic events found in MG thymuses. P values were obtained using the nonparametric Mann-Whitney test. *P < 0.05; **P < 0.01.

3 – AHR is overexpressed in MG AChR⁺ thymuses



AHR expression is increased in MG AChR⁺ thymuses and mainly in thymocytes. (n > 8 MG; n>4 controls)

P values were obtained using the nonparametric Mann-Whitney test. **P < 0.01; ***P < 0.001.

We observed with flow cytometry analysis that AHR⁺ cells increased in most T-cell populations except in double negative ones. (n>8 MG; n>4 controls). P values were obtained using the nonparametric Mann-Whitney test. *P < 0.05; **P < 0.01.

We demonstrate that AHR activation induced the overexpression of IL-6, TGFβ, IL-1β, molecules increased in MG thymuses and involved in the regulation of Treg/Th17 cell balance. More, AHR activation also induced deregulation of CXCL13 expression, favoring a chemoattraction of B-cells in the thymus. *In vivo*, AHR ligands induced an increased mouse susceptibility to EAMG while the AHR KO were more resistant. Additionally, we observed that AHR was overexpressed in CD4/CD8 double positive T-cells, suggesting that AHR may be involved at an early stage of the immune development. We conclude that even though AHR ligands may probably not be the direct cause of the disease, they favor or sustain mechanisms that cause the development of autoimmune MG in predisposed subjects once a deregulation in immune system is set up.