Type II Cytokines Direct Choices of Early Thymic Progenitor Lineage and Influence Negative Selection of Myelin-Reactive T Cells

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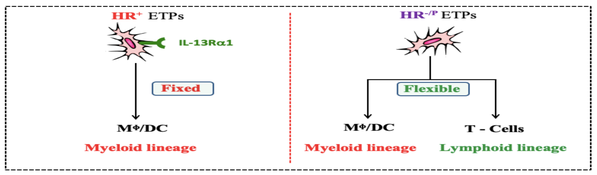
INTRODUCTION

Autoimmune diseases have been known for having a strong genetic component; however, there is growing indication that shows the environment also plays an important role. One way in which the environment plays a role is though influencing central tolerance via fine tuning of the thymic microenvironment. It has been shown that early thymic progenitors (ETPs) that express the heteroreceptor (HR), which are comprised of both IL-13Rα1 and IL-4Rα chain, are directed toward the myeloid lineage and serve as antigen presenting cells (APCs). Due to the role of APCs in T cell negative selection, this research looks to investigate whether type II cytokines can determine ETP lineage choice and subsequently alter negative T cell selection.

BACKGROUND

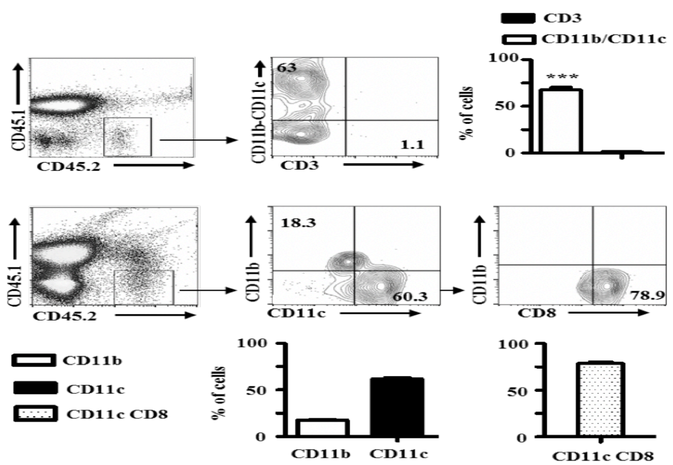
- Dendritic cells (DCs) are antigen-presenting cells in the immune system that function to process antigen material and present it on the cell surface to T cells
- Autoreactive cells function to produce an immune response
- In negative selection, DCs present antigen on MHC and remove autoreactive cells



Objective: To investigate whether type II cytokines can determine ETP lineage choice and therefore alter negative T cell selection

RESULTS

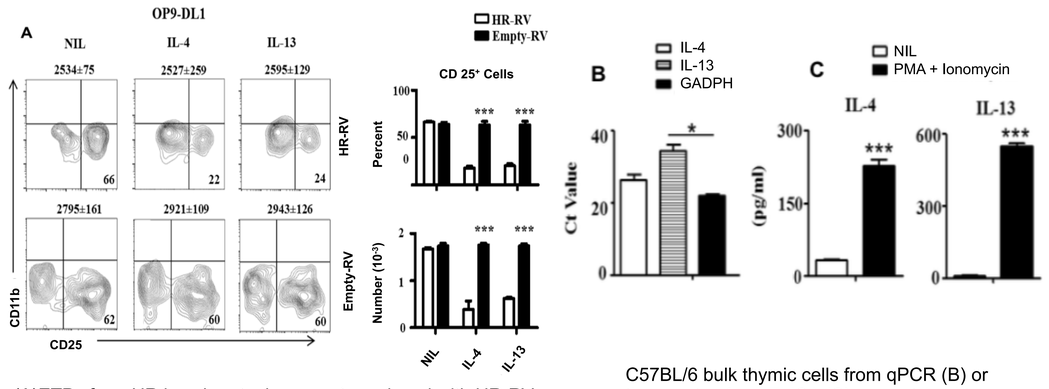
Figure 1: HR+ ETPs give rise to CD8α DCs in vivo



HR+ETPs were transferred in vivo to a congenic host and monitored for commitment to either (A) T cells or (B) dendritic cells.

RESULTS

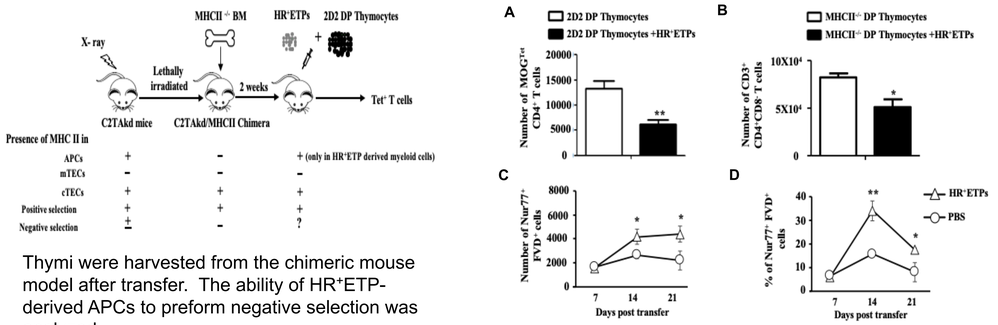
Figure 2: HR expression eliminates the potential of ETPs to commit to T cell lineage in a cytokine- dependent way



(A)ETPs from HR knock-out mice were transduced with HR-RV or empty-RV and tested for either IL-4 or IL-13 driven maturation *in vitro*

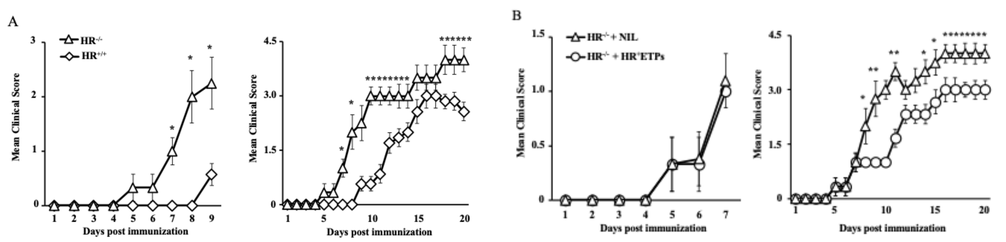
C57BL/6 bulk thymic cells from qPCR (B) or thymocytes from ELISA (C) were utilized to analyze IL-4 and IL-13 within the thymus, respectively.

Figure 3: Thymic negative T cell selection is supported by HR+ ETP-derived thymic APCs



Thymi were harvested from the chimeric mouse model after transfer. The ability of HR+ETP-derived APCs to preform negative selection was analyzed

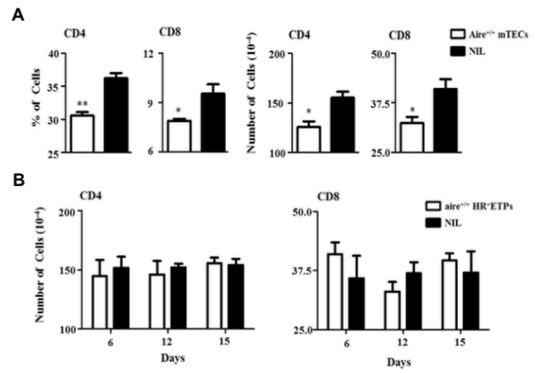
Figure 4: EAE susceptibility is reduced by supplementation by HR+ ETP-derived APCs



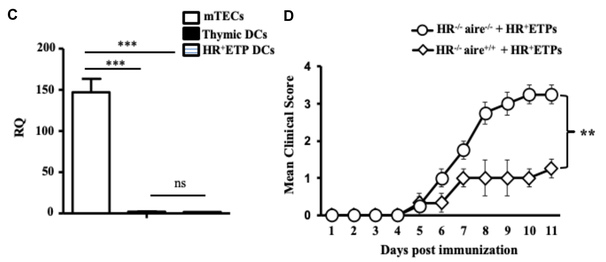
(A) Shows paralysis scores during induction and progression of EAE $HR^{+/+}$ or $HR^{-/-}$ mice

(B) $HR^{-/-}$ mice received HR^{+} ETPs or NIL, were stimulated for EAE, and monitored for induction and progression.

Figure 5: Aire is required for by HR+ ETP-derived APCs to induce protection against EAE



Aire-sufficient mTECs (A) or HR^{+} ETPs (B) were given to *Aire*$^{-/-}$ C57BL/6 hosts . Thymic T cells were analyzed at the indicated days



C) mTECs, thymic DCs, and HR^{+} ETP-derived APCs were tested for *aire* expression. D) $HR^{-/-}$ *Aire*$^{-/-}$ and $HR^{-/-}$ *Aire*$^{+/+}$ C57BL/6 mice were given HR^{+} ETPs and later induced for EAE

CONCLUSIONS

- HR^{+} ETPs yield cDC1 ($CD11c^{+}$ $CD8\alpha^{+}$) cells in vivo
- This lineage development is dependent on signaling through the HR
- In order for lineage restriction to happen, IL-4 or IL-13 must be present
- HR^{+} ETP-derived APCs contribute to thymic negative selection of both transgenic and polyclonal T cells
- HR^{+} ETP-derived APCs can provide protection from EAE in an *aire*-dependent manner

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