

Thymic epithelial cell-specific smad4 deficiency leads to lymphopenia and an increased suppressive capacity of CD103⁺CD25⁺CD4⁺ T cells

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Background and Introduction:

The thymus constitutes the primary lymphoid organ for the development of T cells of the $\alpha\beta$ TCR lineage. Regular thymic development depends on lympho-stromal crosstalk. Thymic epithelial cells (TECs) constitute the most abundant component of the stroma and express molecules critical for T cell development. In turn, thymocytes deliver signals that control TEC differentiation. However, the molecular mechanisms involved in TEC development allowing the formation of a fully functional thymus are at present poorly understood.

Defective thymic stroma leads to serious immunodeficiencies and autoimmune diseases in mice and humans (Nude phenotype, Bare lymphocyte syndrome and Autoimmune Polyendocrinopathy Ectodermal Dystrophy Syndrome).

Rational:

Smad4 takes a central position in the signaling cascade of members of the TGF- β family which are involved in many developmental processes. We hypothesized that smad4 is involved in the development of thymic epithelial cells. Since smad4^{-/-} mice are embryonic lethal, we have generated mice that exclusively lack smad4 in TECs but not in other components of the thymus.

Methods:

To achieve tissue-restricted smad4 deficiency we took advantage of the cre/loxP system using the FoxN1 promoter that is exclusively expressed in thymic and skin epithelium to drive cre expression.

Results:

1) Mice devoid of smad4 mediated signaling in their TECs display a thymic cellularity which is decreased by up to 80% when compared to control littermates. Surprisingly, the overall architecture of the thymus remains intact revealing a proper distinction between cortex and medulla.

Relative numbers of thymocyte subpopulations are normal.

2) Smad4 TEC deficient mice have a CD4 and CD8 T cell lymphopenia with an increased relative frequency of an activated/memory phenotype as well as an increased proportion of CD103⁺CD25⁺CD4⁺ cells. These regulatory T cells are on a per cell basis more potent to suppress T cell proliferation of naive CD4⁺ T cells than T Reg cells from control mice.

3) The increased regulatory capacity of CD103⁺CD25⁺CD4⁺ cells is unrelated to FoxP3 expression.

Discussion and Conclusion:

Taken together, our results indicate that smad4 is essential beyond embryonic day 12.5 for regular function of TECs and demonstrate that genetic changes of the thymic stroma persistently impact on the behavior of peripheral T cells despite the absence of inherent defects in the T cells themselves.

Finally, we demonstrate a suppression potential by regulatory T cells which is unrelated to FoxP3 expression.

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