

Regulatory T cell is essential for deletion of autoreactive CD4⁺ T cells to desmoglein 3 in peripheral tolerance



Hisato Iriki¹, Hayato Takahashi¹, Naoko Wada¹, Masayuki Amagai^{1,2}
 1. Department of Dermatology, Keio University School of Medicine
 2. Laboratory for Skin Homeostasis, IMS, RIKEN

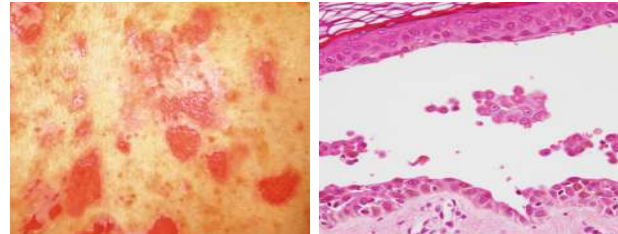
Introduction

Research on peripheral tolerance

- Analysis of peripheral tolerance is important for understanding the reason why autoimmune disease occurs and developing of the treatment.
- Research on peripheral tolerance has faced difficulties, because the method to control antigen expression only in thymus has not been established yet.

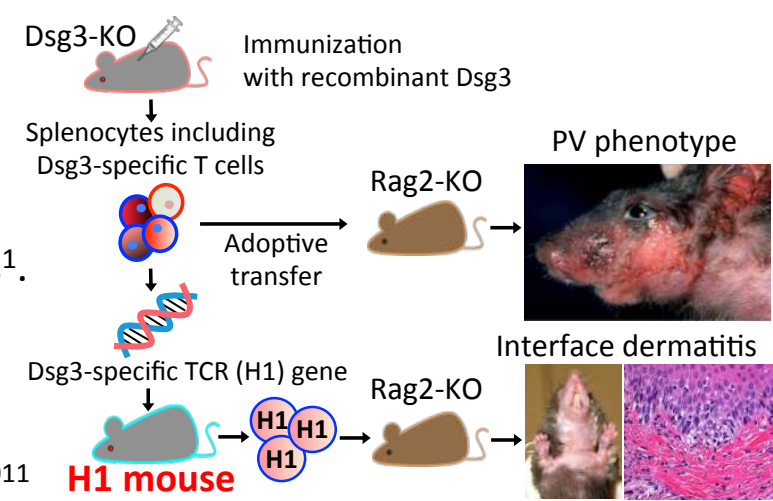
Pemphigus vulgaris (PV)

- PV is an autoimmune blistering disease caused by anti-Desmoglein3 (Dsg3) IgG.
- Dsg3-specific T cells are also important for efficient anti-Dsg3 IgG production.



Dsg3-specific TCR (H1) tg mouse

- H1 mouse was generated by TCR genes isolated from a pathogenic Dsg3-specific T cell clone, which induced PV phenotype with B cells¹.
- H1 CD4⁺ T cells directly attack Dsg3-bearing tissue².



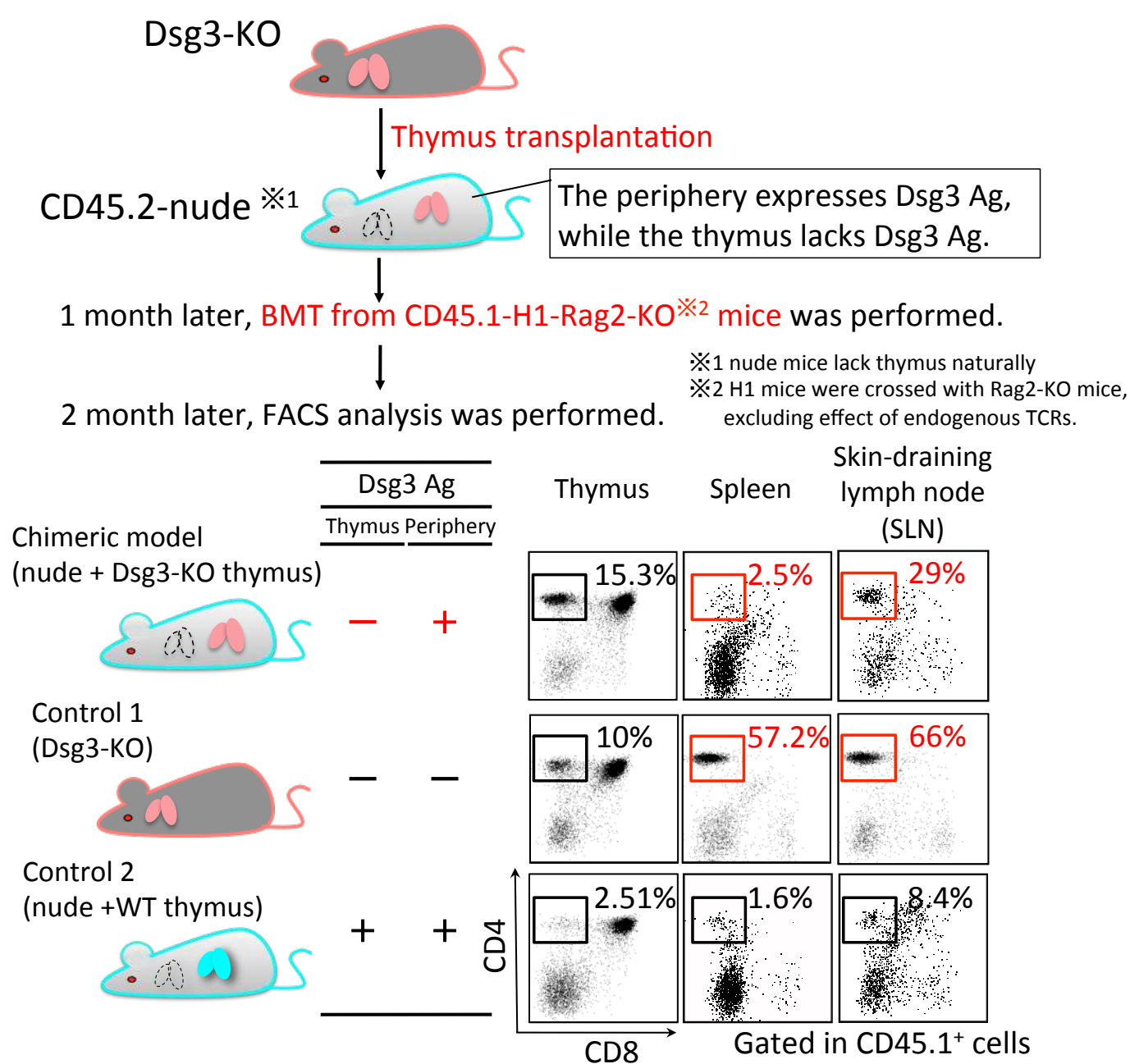
References

1) M Amagai et al. JCI 2000 2) H Takahashi et al. JCI 2011

Purpose

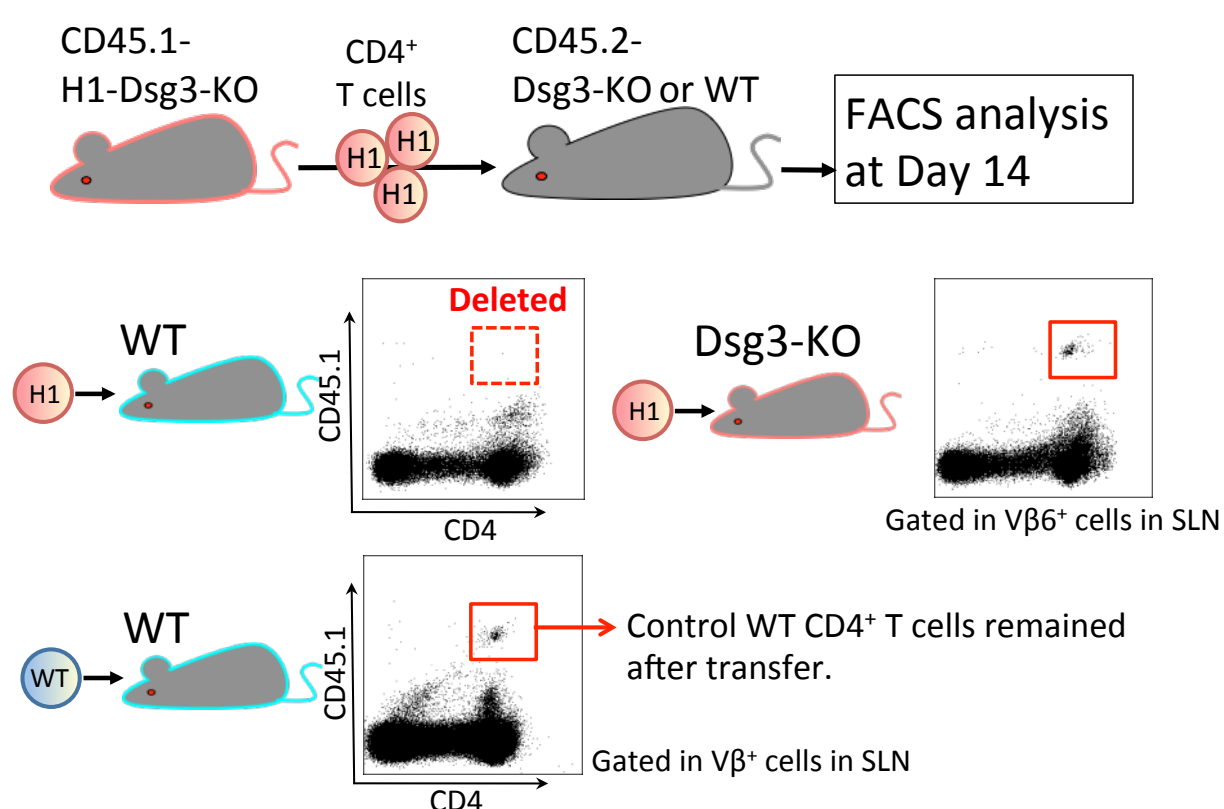
To clarify the mechanisms of peripheral tolerance to Dsg3-specific T cells.

1. Thymus-transplanted chimeric model confirmed the existence of peripheral tolerance against Dsg3



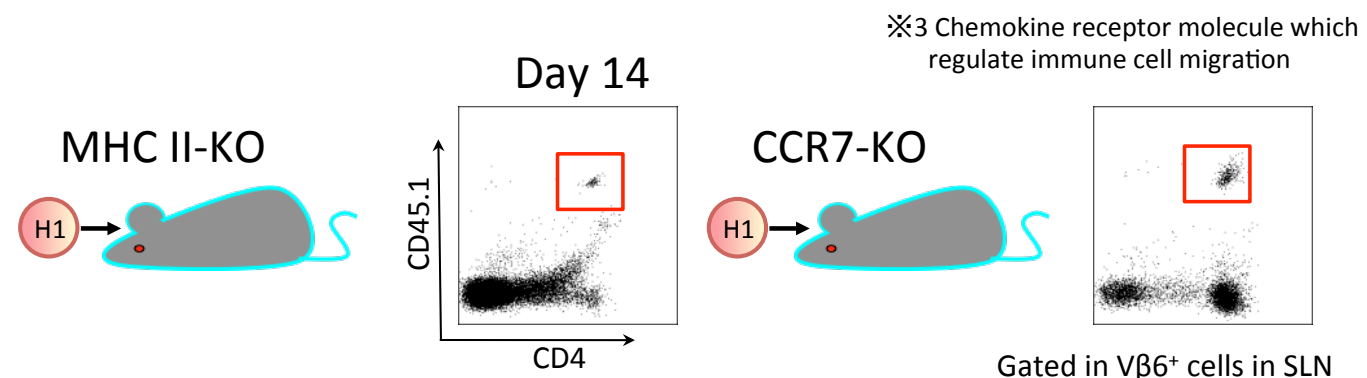
Dsg3-specific T cells developed in Dsg3 deficient thymus, and then, they decreased in proportion in Dsg3 expressing periphery.

2. Adoptive transfer model revealed deletional tolerance against H1 T cells in periphery



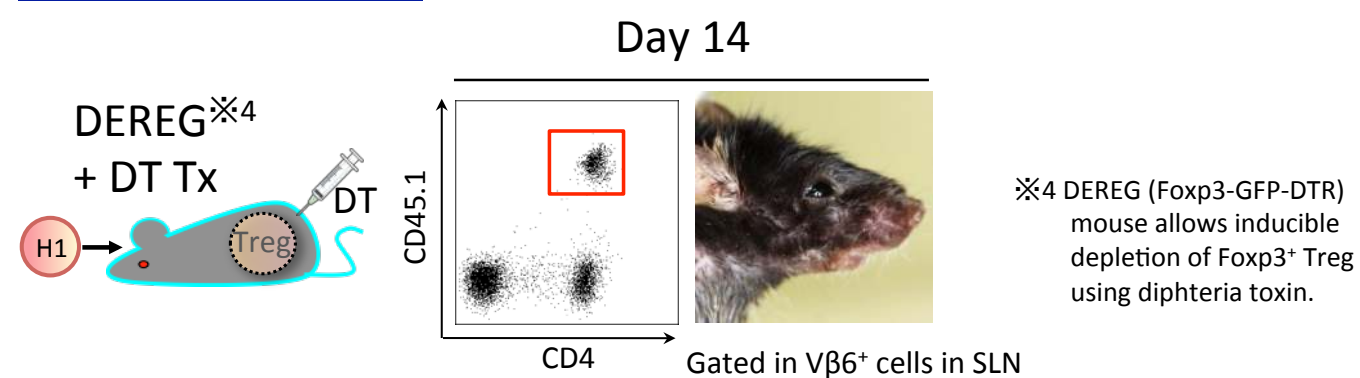
H1 T cells were deleted in Dsg3 expressing periphery in 14 days.

3. Peripheral tolerance against H1 T cells needed MHC II-restricted antigen presentation and depended on CCR7³



Deletion of H1 T cell were disturbed in the absence of MHC II-restricted antigen presentation and in dysfunction of immune cell migration depending on CCR7.

4. Tregs were indispensable for the peripheral tolerance against H1 T cells



In the absence of Tregs, H1 T cells remained and evoked dermatitis.

Conclusion

- Thymus-transplanted chimeric model was established for precise observation of peripheral tolerance.
- Dsg3-specific CD4⁺ T cells were deleted in Dsg3-expressing periphery.
- MHC II-restricted antigen presentation and CCR7 molecule were important for the deletional peripheral tolerance.
- Tregs played a key role in the tolerance.

