

## 【Grant-in-Aid for Scientific Research(S)】

### Biological Sciences (Medicine, dentistry, and pharmacy II)



**Title of Project : Clarification of the molecular and cellular mechanisms of central and peripheral tolerance to pemphigus autoantigen**

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Research Area : Medicine, dentistry, and pharmacy

Keyword : Cutaneous Immunology

#### 【Purpose and Background of the Research】

Autoimmune diseases are refractory diseases in which precise pathophysiological mechanisms are still largely unknown. In this study, we attempt to clarify the immunological mechanisms of central and peripheral tolerance to desmoglein 3 (Dsg3), which is the autoantigen of a life-threatening autoimmune blistering disease, pemphigus vulgaris. We also investigate roles for dendritic cells in autoimmune processes in establishment and maintenance of immunological tolerance to Dsg3 and explore a possibility of skin as an alternative extra-thymic immune regulatory organ. Our experimental models provide a unique system that allows us to analyze fates of Dsg3-reactive T cells in the presence and absence of Dsg3 in a physiological condition.

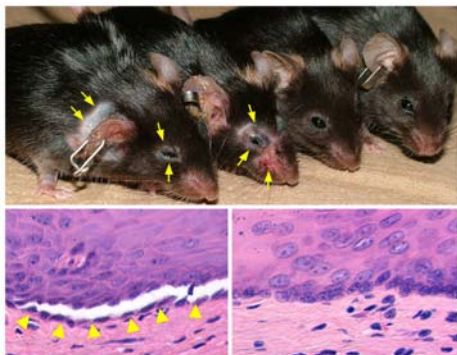
#### 【Research Methods】

##### 1) Immunological tolerance to Dsg3-reactive T cells

We will generate three sets of Dsg3-specific T cell receptor (TCR) transgenic mice from Dsg3-reactive T cell clones whose pathogenicity was characterized in pemphigus model mice. Two of them recognized the same peptide (Dsg3<sub>301-315</sub>) with different affinity levels. We will analyze the fates of Dsg3-reactive T cells in Dsg3-TCR Tg mice in the presence (wt) or absence (Dsg3<sup>-/-</sup>) of Dsg3.

##### 2) Induction of inflammatory T cells and paraneoplastic pemphigus

When lymphocytes from Dsg3<sup>-/-</sup> mice that received Dsg3<sup>+</sup> skin graft



Generation of pemphigus model mice with a single Dsg3-specific T cell clone

are transferred to Rag2<sup>-/-</sup> mice, the recipient mice not only produce anti-Dsg3 IgG, but also demonstrate skin infiltration of CD4<sup>+</sup> and CD8<sup>+</sup> T cells with apoptotic keratinocytes. This phenotype has similarities with that of paraneoplastic pemphigus, a subtype of pemphigus that occurs with lymphoproliferative disorders. We will analyze pathophysiological mechanisms of T cell-mediated skin diseases using this model.

##### 3) Clarification of roles of dendritic cells in antibody production and tolerance

We will first establish a murine system to eliminate subsets of skin dendritic cells with Cre-LoxP and DTR system. These mice will then be used as recipients in the pemphigus model, and the contribution of each dendritic cell subsets will be determined.

##### 4) Skin as an immune regulatory organ in adult

Combining the mice established in this study, we will create a condition in which skin, but not thymus, expresses Dsg3 and determine the fate of Dsg3-specific T cells.

#### 【Expected Research Achievements and Scientific Significance】

This study will help to understand how immunological tolerance is established under normal conditions, and also the processes leading to its disruption, and to develop a novel therapeutic strategy in which immunity is modulated in an antigen-specific manner.

#### 【Publications Relevant to the Project】

Takahashi H, et al: Novel system evaluating in vivo pathogenicity of desmoglein 3-reactive T cell clones using murine pemphigus vulgaris. *J Immunol* 181: 1526-1535, 2008.

Takahashi H, et al: A single helper T-cell clone is sufficient to commit polyclonal naïve B-cells to produce pathogenic IgG in experimental pemphigus vulgaris. *J Immunol* 182: 1740-1745, 2009..

【Term of Project】 FY2009-2013

【Budget Allocation】 161, 800 Thousand Yen

【Homepage Address and Other Contact Information】

<http://web.sc.itc.keio.ac.jp/derma/index.html>