Strategy to unveil and overcome autoimmune diseases

Research purpose

Autoimmune diseases are intractable diseases whose pathogenesis remains unclear. It is important to further develop targeted therapies with fewer side effects. By clarifying the pathogenesis of pemphigus, an autoimmune disease that targets the skin and mucous membranes, we aim to elucidate the universal immune phenomena and develop more selective immunosuppressive therapies.

Research overview

1. cDNA cloning of the pemphigus vulgaris target antigen

The cDNA of pemphigus vulgaris antigen was isolated by immunoscreening an expression library generated from cultured human normal epidermal cells using pemphigus IgG autoantibodies as antibody probes. Sequence analysis of the isolated cDNA revealed that the pemphigus vulgaris antigen is a cadherin-type intercellular adhesion molecule, Dsg3.
Amagai M, et al. Cell 67: 869-877, 1991

2. Creation of recombinant protein of the pemphigus target antigen

Using a baculovirus expression system in insect cells, we generated recombinant proteins of the extracellular Dsg1 and Dsg3 domains as secreted proteins. The column packed with these recombinant proteins specifically adsorbed and removed autoantibodies present in patient sera. Following column treatment, the serum was confirmed to be free of its blister-forming ability. Furthermore, that the blister-forming ability of the Dsg-specific IgG adsorbed on the column was confirmed.
Amagai M, et al. J Clin Invest 94: 59-67, 1994. Amagai M, et al. J Invest Dermatol 104: 895-901, 1995

3. Development of ELISA using recombinant pemphigus target autoantigens as a diagnostic tool

An ELISA using recombinant Dsg1 and Dsg3 was developed and listed on the Japanese National Health Insurance database as a serological diagnostic agent for pemphigus in July 2003. In daily practice, pemphigus, a rare and intractable disease, can now be diagnosed more quickly and reliably, and disease activity can be objectively evaluated by monitoring the serum antibody titer using ELISA.
Ishii K, et al. J Immunol 159: 2010-2017, 1997. Amagai M, et al. Br J Dermatol 140: 351-357, 1999

4. Identification of pathological autoantibodies that induce blister formation in paraneoplastic pemphigus

Paraneoplastic pemphigus is mainly associated with lymphoproliferative diseases. The pathological autoantibodies that induce blisters in paraneoplastic pemphigus have been unknown since the concept of the disease has been proposed. Our study revealed that autoantibodies against Dsg3 and Dsg1 were responsible for blister formation. In paraneoplastic pemphigus, not only autoantibodies, but also epidermal and mucosal epithelial damage caused by cellular immunity are thought to be involved in its pathogenesis.
Amagai M, et al. J Clin Invest 102: 775-782, 1998

Strategy to unveil and overcome autoimmune diseases

5. A logical explanation for intraepidermal blister formation by the desmoglein compensation theory

We proposed the desmoglein compensation theory, which postulates that when Dsg3 and Dsg1 are both expressed in the same cell, they compensate for the intercellular adhesion function of the two molecules. This theory logically explains the difference in intraepithelial blister formation, which depends on pemphigus subtypes.
Mahoney MG, et al. J Clin Invest 103: 461-468, 1999. Amagai M J Dermatol Sci 20: 92-102, 1999

6. Elucidation of the mechanism of action of the exfoliative toxin produced by *Staphylococcus aureus*

The molecular mechanism by which the *Staphylococcus aureus* toxin (exfoliative toxin, ET) causes blistering in the upper epidermis in bullous impetigo and staphylococcal scalded skin syndrome (SSSS) has been unknown for 30 years since its identification. Based on the clinical and pathological similarities between pemphigus foliaceus and SSSS, ET was hypothesized to act on Dsg1. Three known isoforms of ET, ETA, ETB, and ETD, have been shown to be serine proteases that cleave the extracellular region of Dsg1 at one site.
Amagai M, et al. Nature Medicine 2000;6: 1275-1277

7. Development of a pemphigus mouse model

Taking advantage of the fact that autoantigen-knockout mice do not have immune tolerance to the missing autoantigens, we developed a new method to generate a mouse model of organ-specific autoimmune diseases by adoptive transfer of lymphocytes from autoantigen-knockout mice into autoantigen-expressing mice. When the splenocytes of Dsg3-/- mice were adoptively transferred into Rag2-/- immunodeficient mice, anti-Dsg3 IgG antibodies were persistently produced, and the mice developed a phenotype characteristic of pemphigus, including erosions on the mucosa. The mouse model of pemphigus provides a useful basic tool for various projects, including isolation of pathogenic anti-Dsg3 monoclonal antibodies, elucidation of immune tolerance mechanisms to peripheral autoantigens, and evaluation systems for immunosuppressive therapy.
Amagai M, et al. J Clin Invest 105: 625-631, 2000

8. Development of a Dsg3-specific autoimmune dermatitis model

Using the pemphigus mouse model, we established Dsg3-specific CD4+ T cell clones and created a Dsg3-specific T cell receptor transgenic mouse (Dsg3H1 mouse) using the Dsg3-specific T cell receptor genes isolated from one of the pathogenic clones. The Dsg3-specific T cells derived from Dsg3H1 mice not only induced pemphigus blisters by inducing anti-Dsg3 antibody production from B cells, but also induced autoimmune dermatitis by infiltrating the Dsg3-expressing epidermis and directly attacking keratinocytes. This is a very useful T cell-dependent dermatitis model targeting physiological epidermal autoantigens for immunological analysis and can be used as an evaluation system for new therapies.
Takahashi H, Kouno M, et al. J Clin Invest 121:3677-3688, 2011

9. Interdisciplinary research on immune function and cholesterol metabolism and its application in disease control

Cholesterol is not only an extremely important lipid present in cell membranes, but also has a wide range of other functions, including hormone synthesis. In the past, little attention has been paid to the function of cholesterol in the immune system, but with recent advances in analytical technology, the importance of its role in immune cells has gained increasing attention. We are also focusing on cholesterol metabolism in immune cells, including helper T cells, and are conducting research to clarify its role in immune functions. In particular, we aimed to clarify its functions in disease control and consider its future therapeutic potential.