

Interview with an expert 1 and 2

New studies focus on autoimmune bullous diseases

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In this article, I will show the results of very recent studies in autoimmune bullous skin diseases in which our department and institute have been involved.

In addition to the autoantibodies to desmogleins (Dsg), we have shown that autoantibodies to desmocollins (Dsc) are also frequently found in some pemphigus patients, particularly atypical pemphigus, pemphigus vegetans, pemphigus herpetiformis and paraneoplastic pemphigus (PNP). We also found autoantibodies to Dsc in classical pemphigus vulgaris. We have established ELISA for Dsc1-3 for large scale analysis.

We have collected a large number of patients with drug-induced pemphigus and shown that the major autoantigen is Dsg1. The identity for the 170 kDa PNP antigen was unknown for a long time. Using immunoprecipitation and proteomics techniques, a Swiss group and we have identified it as alpha-2-macroglobulin-like 1 (A2ML1), which is a unique secreted protein in the granular layer of the epidermis.

By the immunoprecipitation-immunoblotting method, we have also identified epiplakin, a unique new type of plakins family protein, as a new autoantigen for PNP.

We have analyzed bullous pemphigoid exclusively with anti-BP230 autoantibodies, and found a unique epitope profile for BP230 which may give us an insight into the epitope spreading mechanism. In addition to the C-terminal domain of BP180 and laminin 332, we

have also been investigating other cutaneous basement membrane zone proteins, and found that autoantibodies to integrin alpha-6 and beta-4 may play a role in some type of mucous membrane pemphigoid (MMP).

Dermatitis herpetiformis (DH) is very rare in Asia and Asian DH patients show different clinical and immunogenetic profiles than patients in Europe and the United States. We are now performing a large-scale study of HLA in Japanese DH and will compare it to European DH. In addition, we found that there are patients with a bullous disease clinically resembling DH, who show granular deposition of C3, but not of IgA, in the dermal-epidermal junction by direct immunofluorescence. We have collected nearly 30 such cases, and are characterizing them as a new disease entity. We are calling this disease tentatively as C3 DH or granular IgA dermatosis.

In 2009, we identified the autoantigen for anti-p200 pemphigoid as laminin-gamma-1 and renamed it anti-laminin-gamma-1 pemphigoid. There are still several autoimmune bullous diseases in which the responsible autoantigens are completely unknown, including the intraepidermal neutrophilic dermatosis type of IgA pemphigus and the sublamina densa type of linear IgA bullous dermatosis. The autoantigens in these diseases are difficult to identify because the techniques to detect antigens for IgA autoantibodies have not been well established. We are now establishing the techniques for IgA antibodies, and, using 2-dimensional gel electrophoresis and mass spectrometry (proteomic method), we have obtained candidate proteins for these diseases and are now performing confirmation

studies.

Furthermore, we are always searching for new autoantigens that may be involved in some type of autoimmune bullous diseases. These include a protein involving in endocytosis, which is now believed to play a role in the pathogenesis of pemphigus.

Nowadays, ELISA systems are most frequently used to detect autoantigens. We have been involved in establishing ELISA systems for various autoantigens, including Dsg1, Dsc3, BP180, BP230, type VII collagen, Dsc1-3, and LAD-1. We are now developing new ELISAs for laminin 332 and laminin-gamma-1.

In addition, ELISAs for epidermal transglutaminase (transglutaminase 3; TGM3), envoplakin, periplakin and A2ML1 have also been developed in other institutes.

We are now trying to use lower doses of oral steroids in both pemphigus and pemphigoid diseases. In bullous pemphigoid, the maximum dose should be prednisolone 30 mg daily. Even in severe cases of pemphigus vulgaris, we do not use prednisolone more than 40-50 mg daily. If the dose of prednisolone is not effective, other therapeutic options should be selected, instead of an increase of oral steroids.

As new treatments for autoimmune bullous diseases, we use routinely mizoribine, a new immunosuppressant, 150 mg once after breakfast, and have shown that this drug is effective in both pemphigus and pemphigoid groups. Mizoribine is successfully used for the treatments in other diseases, including cutaneous vasculitis, interstitial pneumonitis, autoimmune urticaria and atopic dermatitis.

The usefulness of IVIG in the treatment of pemphigus has been confirmed



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by a large-scale double blind study in Japan, and IVIG study for bullous pemphigoid is now underway. Topical oral application of cyclosporine (Neoral) solution was shown to be useful for the treatment of intractable oral mucosal lesions in pemphigus vulgaris.

As the treatments for bullous pemphigoid and related diseases, in addition to a combination therapy of minocycline (tetracycline) with niacinamide, roxithromycin 450 mg daily is useful for relatively mild cases. In nearly 20 intractable cases of bullous pemphigoid, we attempted to use interferon gamma injection therapy. This therapy was extremely effective and there was no adverse effects.

However, product of interferon gamma is now unavailable and this therapy should be re-evaluated by a large scale clinical trial. Rituximab may be the most potential option in the treatment of various types of bullous diseases, and a clinical trial is underway in our group.