

## Non-physiological cleavage of collagen XVII in aged skin

**Wataru Nishie**

*Department of Dermatology, Hokkaido University Hospital*

Bullous pemphigoid (BP) is the most common autoimmune blistering disorder, which affects elderly. IgG autoantibodies from BP patients target the transmembrane collagen XVII (COL17), a major component of hemidesmosomes in basal keratinocytes. Hemidesmosomes play a vital role for keeping stable adhesion between the dermis and the epidermis, thus, autoimmunity to COL17 results in blistering phenotype. However, the pathogenesis for breaking the tolerance to COL17 is still uncertain. The major epitopes for IgG autoantibodies from BP patients are clustering within the juxtamembranous non-collagenous (NC) 16A domain, and interestingly, extracellular domain of COL17 is physiologically cleaved within the NC16A domain. In addition, certain autoantibodies from BP patients preferentially react with the shed ectodomain but not with the full-length form. Furthermore, cleavage of COL17 can induce neoepitopes around the cleavage-sites on the NC16A domain. These findings suggest the ectodomain shedding of COL17 is closely related with the development of autoimmunity to COL17, and non-physiological ectopic cleavage of the molecule due to aging may be related with the autoimmunity development. To address these issues, we tried to identify non-physiological cleavage sites within the NC16A domain and to produce a novel cleavage site-specific antibody which can detect the non-pathological cleavage site. We first identified Ser<sup>508</sup> to be N-terminal cleavage site of COL17 ectodomain which is cleaved by plasmin, a potential serine protease expressing in lesional skin as well as blister fluid of BP. Second, we generated rabbit antibodies which specifically target pathological N-terminal cleavage site of cleaved COL17 ectodomain by immunizing short peptides corresponding to the identified cleavage site. The antibody demonstrated that COL17 is cleaved at Ser<sup>508</sup> in lesional skin of some BP patients, however, the cleavage was not observed physiological setting even aged skin.