Basement Membrane Zone

Discovery of Specialized Basement Membrane Zone Proteins and their Alterations in Epidermolysis Bullosa

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Based on electron microscopic observations, in the 1970s it was assumed that the hemidesmosome–anchoring filaments–anchoring fibrils complex mediated the stable adhesion of the epithelium to the basement membrane, and that the external surface of the hemidesmosome carried a receptor for unidentified matrix component(s) responsible for hemidesmosome adhesion. However, the chemical nature of the hemidesmosome and that of the anchoring devices was unknown. A crucial milestone was the identification of collagen VII and laminin 5 as the specialized basement membrane zone proteins that compose the anchoring fibrils and anchoring filaments, respectively. In 1986, Sakai *et al.* (1986) reported the development of a monoclonal antibody specific for collagen VII that was immunoreactive with all the tissues known to synthesize anchoring fibrils. Furthermore, ultrastructural immunolocalization of the monoclonal antibody disclosed the exclusive presence of collagen VII within the anchoring fibrils, and visualization of the antibody–collagen VII complex after rotary shadowing revealed the dimeric nature of the collagen VII molecules. The authors also provided evidence that anchoring fibrils are unstaggered parallel arrays of dimeric collagen VII, which is mainly synthesized by the epithelium. The assumption that collagen VII is the major component of anchoring fibrils was confirmed 3 years later by Bruckner-Tuderman *et al.* (1989). Using immunoelectron microscopy and immunochemistry approaches, these authors clearly demonstrated that the absence of anchoring fibrils in patients with dystrophic epidermolysis bullosa, a severe inherited skin-blistering disease characterized by an extreme fragility of upper papillary dermis, correlated with an impaired expression of collagen VII. This study unveiled the pivotal role of collagen VII in the stability of dermal–epidermal junction and for the first time designated a gene encoding a basement membrane protein, collagen VII, as a candidate in a skin condition characterized by disadhesion of the epithelial cell/basement membrane from the underlying mesenchyme.

In 1991, an elegant study by Rousselle *et al.* (1991) reported the identification of kalinin, a basement membrane protein synthesized by the keratinocytes that predominantly colocalizes with anchoring filaments. Kalinin was characterized using a combination of techniques (immunoelectron microscopy, biochemistry and cell biology) that disclosed the functional complexity of this adhesion ligand, which strongly modulates the motility of epithelial cells. Interestingly, the tissue distribution and the electrophoretic pattern of kalinin resembled that of BM600 (later renamed nicein), a heterotrimeric protein of the dermal–epidermal junction described by Verrando *et al.* (1991). BM600–nicein was detected in all the epithelial basement membranes that harbor hemidesmosomes, but its expression was found to be strongly reduced in patients with junctional epidermolysis bullosa. This inherited skin disease is characterized by blister formation correlated with the perturbation of hemidesmosomal integrity and cleavage within the lamina lucida of the dermal–epidermal junction, which is where the anchoring filaments are localized. In 1993, a timely work by Marinkovich *et al.* (1993) provided extensive biochemical and immunologic evidence that kalinin and nicein are identical. This breakthrough clarified the overall picture drawn from the increasing information on the diverse roles of kalinin–nicein (later renamed laminin 5) in cell adhesion, proliferation and differentiation.

The papers highlighted above underscore the transition from the 'classic' approaches of cutaneous biology, which was essentially based on morphologic analyses, to studies relying on tools and methods allowing exploration at the molecular and genetic levels for the function(s) of the specific components of the cutaneous basement membrane involved in the different forms of epidermolysis bullosa.

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