Basement Membrane Zone

Discovery of Basement Membrane Zone Ultrastructural Entities by Electron Microscopy

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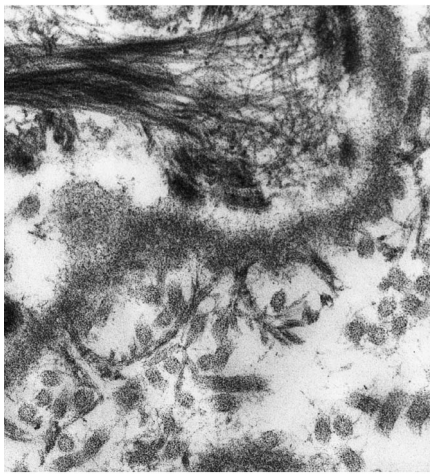
Early studies using transmission electron microscopy of the human skin, performed in the 1950s and 1960s, revealed some of the key landmarks of the basement membrane zone of the dermal–epidermal junction (DEJ). However, it was not until later, with higher resolution imaging, that the full structural complexity of the DEJ became much clearer and better understood. Briggaman and Wheeler (1975a, b) provided the first comprehensive review of the numerous ultrastructural components of the DEJ, accompanied by a terminology that is still in current use. We were then introduced to the concept of a structural, and as we now know, functional, interrelationship between hemidesmosomes, anchoring filaments and anchoring fibrils, which are now recognized as major constituents of the 'anchoring complex' linking basal keratinocytes to the basement membrane and superficial dermis.



Although electron microscopy studies of the DEJ have been valuable in defining key steps in processes such as normal development, ageing and carcinogenesis, a major application has been in the studies of blistering disorders, both hereditary and acquired. Pearson (1962) delineated the differences between the primary levels of skin separation in the three main types of hereditary epidermolysis bullosa, and others drew attention to disorders of anchoring fibrils in the dystrophic forms of the disease (Briggaman and Wheeter, 1975a, b; Anton-Lamprecht and Hashimoto, 1976; Tidman and Eady, 1985) when the association between anchoring fibrils and type VII collagen was still unknown. Yet these observations provided an important clue to the later discovery that mutations of type VII collagen, an anchoring fibril component, cause dystrophic epidermolysis bullosa. Other research underscored the importance of structural abnormalities of hemidesmosomes in both the Herlitz (Hashimoto *et al.*, 1976) and non-Herlitz (Tidman and Eady, 1986) forms of junctional epidermolysis bullosa.

Localizing antigens in the DEJ at the ultrastructural level has been of lasting interest, especially in studies of autoimmune or congenital bullous disorders. Preliminary research (for example, Schreiner and Wolff, 1970) used horseradish peroxidase to provide an insoluble marker to localize immunoglobulin deposition in lupus erythematosus. However, it was much later, when colloidal gold was introduced to immunoelectron microscopy, that precise molecular localization became possible. Thus, for the first time, we could see convincingly that type VII collagen localized to anchoring fibrils (Sakai *et al.*, 1986) and that kalinin (now known as laminin 5) (Rousselle *et al.*, 1991) was associated with anchoring filaments. The immunolocalization of intracellular proteins, such as bullous pemphigoid antigen 1, was more problematic, initially requiring permeabilization of the cell membrane to allow access of the labelling antibody (Westgate *et al.*, 1985). However, a new approach entailing freeze substitution and post-embedding (or on-section) labelling enabled both intracellular and extracellular antigen labelling with good membrane preservation (Shimizu *et al.*, 1989). Whereas one study (Keene *et al.*, 1987) elegantly demonstrated that anchoring fibrils form an extensive network beneath the lamina densa and link with small discrete 'anchoring plaques', another (Shimizu *et al.*, 1997) found that nearly all anchoring fibrils insert at both ends in the lamina densa. These contrasting findings have probably come about because of major differences in skin sample processing and the mode of gold labelling. The former used a pre-embedding en-bloc labelling method, and the latter a post-embedding technique, as described above.

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