0022-202X/82/7801-0001$02.00/0
THE JOURNAL OF INVESTIGATIVE DERMATOLOGY, 78:1-6, 1982
Copyright © 1982 by The Williams & Wilkins Co.
Vol. 78, No. 1
Printed in U.S.A.

Reprinted from

REVIEW ARTICLE

Progress in Dermatology

a bulletin published by the DERMATOLOGY FOUNDATION

Co-Editors:

Robert A. Briggaman, M.D.
North Carolina Memorial Hospital
Chapel Hill, North Carolina 27515

Lowell A. Goldsmith, M.D.
Box 3030, Duke Medical Center
Durham, North Carolina 27710

Biochemical Composition of the Epidermal-dermal Junction and Other Basement Membrane

ROBERT A. BRIGGAMAN, M.D.

Professor of Dermatology, University of North Carolina, School of Medicine, Department of Dermatology, Chapel Hill, North Carolina, U.S.A.

During the last several years, our knowledge of the biochemical composition of the epidermal-dermal junction and the ultrastructural location of the pathologic reaction in numerous skin diseases that affect this area has increased greatly. In this paper, our purpose is to review current information in these areas. The epidermal-dermal junction has been reviewed previously and the reader is referred to these sources for a more general and comprehensive review of the subject [1–5].

First, a brief review of the ultrastructural morphology of the epidermal-dermal junction is necessary to relate the subsequent studies. The epidermal-dermal junction is more complex and more highly organized ultrastructurally than the simple linear "basement membrane zone" between epidermis and dermis noted by light microscopy. Three different epidermal cell types, basal keratinocyte, melanocyte, and Merkel cell, comprise a portion of the epidermal-dermal junction with each cell type presenting a somewhat different appearance at the junction. Basal keratinocytes form the vast majority of the junction zone and will be the only cell considered here. The epidermal-dermal junction between basal keratinocytes and dermis can be divided, for convenience, into 4 areas proceeding from epidermis toward the dermis (Figure). These are: The basal cell plasma membrane with its special attachment structures, hemidesmosomes; lamina lucida; the basal lamina; and a sub-basal lamina fibrous zone.

The plasma membrane of basal keratinocytes is a trilaminar structure measuring approximately 7–9 nanometers (nm) in thickness. Electron dense thickenings stud the plasma membrane at frequent intervals. These structures are termed hemidesmosomes and are diagramatically presented in the Figure. The hemidesmosome is composed of an electron dense area, the attachment plaque, that is present on the cytoplasmic side of the internal leaflet of the plasma membrane. Tonofilaments course toward the attachment plaque but actually terminate in a relatively electron dense zone separated from the plaque by a narrow electron lucent zone.

The lamina lucida (intermembraneous space, lamina rara) is an electron lucent area located between the plasma membrane of the basal keratinocyte and the underlying basal lamina. Lamina lucida is approximately 20–40 nm in thickness and is amorphous in most areas. In the lamina lucida subjacent to hemidesmosomes a special structure termed the sub-basal dense plaque appears as an electron dense line beneath the hemidesmosome. In this area, fine filaments traverse the lamina lucida perpendicularly and mesh with the basal lamina. These filaments have been called anchoring filaments.

The basal lamina (lamina densa) is a continuous electron dense layer which runs parallel to the plasma membrane, separated from it by the lamina lucida. The basal lamina has an amorphous fine granular appearance and, although somewhat variable in thickness and density, measures approximately 30–50 nm. Reduplication of the basal lamina is relatively common even in normal skin and may result from remodeling of the epidermal-dermal junction as a function of cell detachment, migration, and re-attachment in this area. Reduplication of the basal lamina and other junctional structures may be markedly exaggerated in a variety of pathologic processes that affect the junctional zone. Marked reduplication of basal lamina is the ultrastructural counterpart of the basement membrane thickening, for example, as noted in cutaneous lupus erythematosus.

The subbasal lamina fibrous area is situated immediately beneath the basal lamina and is composed of three different types of fibrous structures: anchoring fibrils, dermal microfibril bundles, and collagen fibers. Anchoring fibrils have a unique structure which consist of a central, asymmetrically cross-banded region with fan-like arrays of smaller fibrillar components extending from both ends. The epidermal end of the anchoring fibril meshes with the basal lamina while the dermal end extends into the dermis. Frequently, the dermal portions of adjacent anchoring fibrils fuse forming an interlocking mesh-

This work was supported by Research Grant 2 R01 AM10546, National Institutes of Health.

Reprint requests to: Dr. Robert A. Briggaman, Department of Dermatology, The University of North Carolina, School of Medicine, Chapel Hill, NC 27514.

work in the dermis below the basal lamina. Collagen fibers are sometimes caught up in this mesh-work or surrounded by loops of connecting anchoring fibrils but are never directly connected to the anchoring fibril. The dermal microfibril bundle is a distinctive component in the sub-basal lamina area. These consist of bundles of parallel fibrils which pass deep into the dermis essentially perpendicularly from the epidermal-dermal junction. The epidermal ends of these bundles insert directly into the basal lamina. Individual fibrils are morphologically identical with the microfibrils that are a component of true elastic fibers [6,7]. Indeed, some dermal microfibril bundles have been traced to connections with morphologically distinct elastic fibers thus documenting a direct connection between the basal lamina and elastic fibers in the dermis via these structures [8]. Typical collagen fibers are the third fibrous component in the sub-basal lamina area. These are randomly oriented and are most commonly found as single fibers or occasionally in groups of several fibers. Collagen fibers do not attach directly to the basal lamina or to other junctional structures as yet identified.

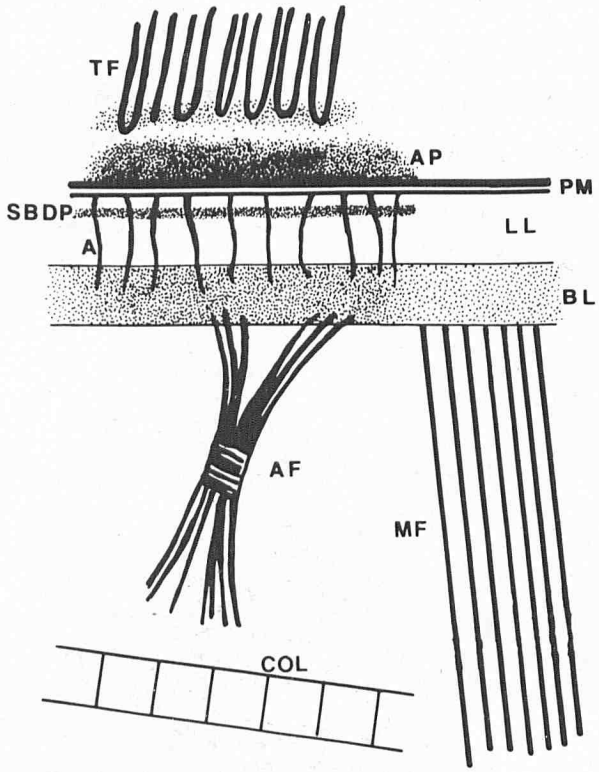

FIG Epidermal-dermal junction in region of a hemidesmosome. Tonofilaments (*TF*). Attachment plaque (*AP*). Plasma membrane (*PM*). Subbasal dense plaque (*SBDP*). Anchoring filaments (*A*). Lamina lucida (*LL*). Basal lamina (*BL*). Anchoring fibril (*AF*). Collagen fiber (*COL*). Dermal microfibril bundle (*MF*).

BIOCHEMICAL COMPOSITION OF BASEMENT MEMBRANE WITH PARTICULAR REFERENCE TO THE EPIDERMAL-DERMAL JUNCTION

Before concentrating on the epidermal-dermal junction, we will first review current knowledge of biochemical composition of basement membranes in general [9,10]. Basement membranes are composed of collagenous and noncollagenous components which are tabulated below (Table).

Basement Membrane Collagens

Current evidence indicates that the basement membrane collagens are distinct from the interstitial collagens and can be subdivided into 3 groups, designated type IV, type V (AB collagen), and 7S collagen.

Type IV collagens

Type IV collagen is composed of 3 polypeptide chains that form a macromolecule with triple helical domains similar to other collagens. However, the constituent polypeptide chains of type IV collagen are larger than other collagens and are disulfide-linked. In addition, nonhelical sequences constitute a larger

TABLE I. *Composition of basement membrane*

Basement membrane components (BM)	Mol. Wt. (K)	Source	Basement membrane distribution	Cutaneous localization	
				Presence	Ultrastructural
Collagenous					
Type IV collagens	>400				
α 1 (IV)	160	Mouse EHS sarcoma	Ubiquitous	+	Basal lamina
α 2 (IV)	140	Kidney and ocular BM			
Pro α 1 (IV)	185				
Pro α 2 (IV)	170	Fetal membranes			
Type V collagens	300				
α A	100	Fetal membranes	Vascular,	+	?
α B	100	muscle, skin,	muscle BM	−	
α C	—	bone, lung			
7S collagen	360	Mouse EHS sarcoma kidney, ocular BM fetal membranes	Ubiquitous	+	?
Noncollagenous					
Bullous pemphigoid antigens					
Epidermal	20, 9.2	Skin	Skin, other	+	Lamina lucida
Urinary	19	Urine	sq. epithelial		
High mol. wt.	220	Epidermal cell culture			
Laminins					
Soluble laminin	800–1000	EHS sarcoma	Ubiquitous	+	Lamina lucida
Subunits	220				
	440				
Insoluble laminin	—	EHS sarcoma	?	?	?
Heparan sulfate proteoglycan	750	EHS sarcoma	Ubiquitous	+	?
Fibronectin	440	Plasma,	Ubiquitous	+	Lamina lucida plus dermis
Subunits	220	Fibroblastic cells			
Amyloid P-component	—	Kidney	Kidney	?	?

portion of type IV collagen than other collagens as indicated by the glycine content which is less than the 1/3 dictated by the Gly-X-Y helix sequence. Distinctive differences are also evident in the content of other amino acids and in the posttranslational hydroxylation and glycosylation of type IV collagen. The ratios of 3- to 4-hydroxyproline, of total hydroxyproline to proline and hydroxylysine to lysine are greater in type IV collagen and serve as distinguishing features. Type IV collagen also has a high carbohydrate content, most of which is present as disaccharides containing glucose and galactose bound to hydroxylysine.

Considerable controversy and confusion has arisen from attempts to extract and isolate type IV collagen and its constituent alpha chains and polypeptides from basement membrane-containing tissues. These studies have been fraught with many technical problems including the very small amount of basement membrane components in most tissues and their relative inexcessibility. A particularly difficult problem has been the very limited solubility of basement membrane collagens such that harsh procedures are required for their solubilization. These procedures have complicated the interpretation of the studies.

Initial studies utilizing pepsin solubilization of kidney and ocular basement membranes indicated that the major collagenous component was an alpha chain (100 K), 3 of which were assembled into a single triple helix and designated α $(IV)_3$ [11–13].

Subsequently, others have found greater heterogeneity in the collagenous components of basement membrane. The degree of heterogeneity has varied among the studies with some studies reporting extreme heterogeneity of collagenous components that varied in molecular weight from 25,000 to 205,000 daltons [14,15]. Recently, considerable evidence has established the occurrence in basement membranes of at least 2 distinct alpha chain-like components that represent different gene products [16–22]. Much of the apparent heterogenity of type IV collagen can be accounted for by the presence of pepsin sensitive sites within the polypeptide chains [16,22].

An important recent contribution to this field was the discovery of a transplantable murine tumor, EHS sarcoma, that produces an extra-cellular matrix resembling basement membrane [23]. A special advantage of the tumor is that basement membrane collagens can be isolated without harsh solubilization treatments required in most other basement membrane isolation procedures. Dilute acetic acid extraction of the tumor matrix has lead to the isolation of two collagenous polypeptide chains with molecular weights of 160,000 and 140,000 daltons. These polypeptides have helical as well as nonhelical domains and exist in the matrix as a trimer with molecular weight over 400,000 daltons. The chains are cross-linked by disulfide bonds and have an amino acid composition similar to basement membrane collagen purified from authentic basement membranes [21–24]. Antibodies prepared against mouse tumor basement membrane collagen localized to the tumor matrix and to a variety of basement membranes in tissues, including skin, thus confirming the basement membrane distribution of these proteins [21,25].

In biosynthetic studies, cultured cells from various sources, including EHS tumor, produce and release into the media collagenous basement membrane polypeptides [26–28]. Two major polypeptides (approximately 180–185 K and 160–170 K) were isolated without harsh solibulization procedures. The 2 polypeptides differ significantly from each other in the peptide patterns produced by cleavage with cyanogen bromide or pepsin and are believed to represent distinct gene products. In the case of EHS tumor cells [26], evidence indicates that the larger (185 K and 170 K) polypeptides are precursors of the smaller tissue forms (160 K and 140 K) as a result of *in vivo* processing. Evidence supporting this is that antibodies prepared to 160 K or 140 K chains precipitated the respective larger peptides. In addition, similar polypeptide fragments were found after cleavage with cyanogen bromide and pepsin. The larger peptides have been designated pro-α 1 (IV) and pro-α2 (IV) to indicate their precursor relationship to the smaller tissue forms that are now termed α 1 (IV) and α 2 (IV) [26–28]. It is believed that these represent the major alpha chain-like components of type IV collagen although other minor components have been identified but not yet characterized [28].

Type V (AB) collagens

Concomitantly, 2 groups of investigators [29,30] discovered 2 new collagen chains, termed α A and α B (or A and B chains) from various tissues including human placenta, skin, muscle, lungs, bone and cartilate using limited pepsin protelysis followed by salt fractionation to isolate the collagenous fractions. These collagens have been termed type V collagen (AB collagen). Type V collagen share features with both interstitial collagens (Types I–III) and the basement membrane collagens. The molecular weights of the chains (approximately 100,000 daltons) and their resistance to pepsin digestion are similar to the interstitial collagens. However, their amino acid content is similar to peptides derived from isolated basement membranes. They contain relatively large amounts of 3-hydroxyproline and hydroxylysine and relatively small amounts of alanine. A and B chains differ significantly and are thought to be separate proteins. The molecular organization of A and B chains into AB collagen remains controversial. Some workers have found a constant 1:2 A:B ratio in extracted tissues indicating a structure of α A (α B_2) [29,32]. However, others have not found this constant relationship in different tissues [30,33] and have actually found the absence of one of the chains in some tissues, indicating that each are distinct collagens composed of 3 identical A or B chains (α A_3 and α B_3) rather than being heteropolymers. Because of the wide tissue distribution of type V collagens and since they are not isolated specifically from basement membrane, some have questioned their basement membrane association [10]. Indeed, it seems likely that type V collagens are not exclusively basement membrane components. However, immunohistologic studies have documented their basement membrane localization [34–36]. Antibodies to A chain, B chain and type V collagen have demonstrated their presence in a variety of basement membrane including lung and kidney. In the kidney, types IV and AB collagens are co-distributed in the basement membrane of tubules, glomeruli and Bowman's capsule as well as in the mesangial stock [36].

7-S collagen

7-S collagen was first found in the insoluble residue after extraction of mouse EHS tumor matrix [37] and later isolated from other sources including placenta, lens capsule, and kidney [38]. This collagen is separated from other basement membrane collagens by its relative resistance to bacterial collagenase. Its amino acid composition is similar to other basement membrane collagens except for elevated levels of cysteine and tyrosine. 7-S collagen occurs as a very stable triple helical molecule with a large number of disulfide bonds connecting component chains. It has a rod-like configuration on electron microscopy and occurs in 2 forms: large form with molecular weight of approximately 360,000 daltons and a sedimentation co-efficient of 7.2 S and a short form with molecular weight of approximately 225,000 daltons. 7S collagen is composed of subunit polypeptides with molecular weights of 25,000–27,000 daltons. 7-S collagen is immunologically distinct from interstitial and other basement membrane collagens. Immunofluorescent microscopy with a specific anti-7-S collagen antibody confirms that it is an abundant component of most basement membranes [38].

Noncollagenous glycoproteins: Noncollagenous glycoproteins and proteoglycans are significant components of basement membranes.

Bullous pemphigoid antigen: Bullous pemphigoid antigens (BP-Ag) are noncollagenous basement membrane glycoproteins that are identified by their reactivity with bullous pemphigoid antibodies derived from patients with that disease. Surprisingly,

a variety of materials have been recognized that react with bullous pemphigoid antibodies. Epidermal pemphigoid antigen isolated from skin consists of two components: one has a molecular weight of 20,000 daltons and the other a molecular weight of 9,200 daltons [39]. Pemphigoid antigen has also been isolated from the urine [40]. Urinary pemphigoid antigen occurs predominately as a monomeric form (18,000 daltons), but polymeric forms have also been noted. As might be expected, immunologic identity of pemphigoid antigens derived from epidermis, esophagus, saliva and urine was demonstrated using rabbit anti-epidermal pemphigoid antigen serum. Recently, a high molecular weight bullous pemphigoid antigen (approximately 220,000 daltons) was isolated from cultured epidermal cells [41]. The relationship of these antigens particularly the high and the low molecular weight materials is presently unknown. Bullous pemphigoid antigen is a product of epidermal cells and forms a lamellar layer of BP antigen under basal cells even in the absence of basal lamina [42,43].

Laminin: Laminin is a major noncollagenous basement membrane glycoprotein isolated originally by neutral buffer extraction (soluble laminin) of mouse basement membrane producing tumor matrix (EHS sarcoma) [44]. Soluble laminin is a large (800–1,000 K) asymmetrical molecule consisting of several subunits (220 K and 440 K) that are connected to each other by disulfide bonds. The disulfide bonds are largely localized to 2 domains that can be separated by pepsin cleavage (P1 and P2) and contain 85% and 10% of the bonds respectively. An insoluble form of laminin has also been identified [46]. Some evidence also suggests that other proteins related to laminin may be present in basement membranes [45,46]. Highly specific antibodies produced to soluble laminin have shown that laminin is immunologically distinct from all other basement membrane antigens. Immunofluorescence studies using these antibodies have demonstrated that laminin or closely related antigens are widely distributed in basement membranes in virtually all tissues and species tested [47–49]. Both epithelial and endothelial cells in culture produce laminin subunits (220 K and 440 K) but mesenchymal cells do not [49].

Heparan sulfate-containing proteoglycan: Heparan sulfate-containing proteoglycan is a large proteoglycan with a molecular weight of approximately 750,000 daltons [50]. This material was also first isolated from EHS sarcoma. Heparan sulfate-containing proteoglycan contains approximately equal amounts of protein and covalently linked heparan sulfate. Purified antibody to heparan sulfate proteoglycan was used to locate this material in a variety of tissues where it was found to be a ubiquitous component of basement membranes.

Amyloid P-component: Amyloid P-component is a glycoprotein found in all forms of amyloid and presumably is derived from serum amyloid P-component, a normal plasma constituent. The presence of amyloid P-component in normal, nonamyloid containing tissue was first detected by Schneider and Loos [51] who observed that anti-amyloid-P component antibody stained vascular and perivascular structures and suggested a basement membrane localization. This was confirmed by isolation of an antigen from glomerular and other vascular basement membranes and demonstration that it was immunochemically indistinguishable from serum amyloid P [52]. It has not as yet been proven that this antigen is biochemically identical with amyloid P component. No immunochemical cross-reactivity was detected between this material and other collagenous or non-collagenous basement membrane components. These studies suggest that amyloid-P component may be a normal matrix glycoprotein of some basement membranes.

Fibronectin: Fibronectins are a family of high molecular weight glycoproteins that are widely distributed in most tissues, particularly on the surface of cells and in connective tissue matrices. Fibronectins are also found in the plasma and as a component of basement membranes. The fibronectins are known by a variety of other names owing largely to their varied sources and interesting biologic activities [53]. Two closely related forms are now recognized. Plasma fibronectin is a soluble component of blood (cold-insoluble globulin) while cellular (cell surface) fibronectin is insoluble and distributed in fibrillar arrays or aggregates loosely bound to cell surfaces and connective tissue matrices. Both forms are similar although not identical in composition and consist of dimers of 2 subunit polypeptides (200–250 K each) connected near one end by disulfide bonds. Unusual oligosacchrides chains, approximately 4–6 per polypeptide, consist of a N-acetylglucosamine and mannose core linked to asparagine residues in the polypeptide subunit. These oligosacchride side chains account for a significant portion of the biologic activity of these molecules. Cell surface fibronectin may also exist in larger multimeric forms. Although fibronectin cannot be considered a unique basement membrane glycoprotein, it is nevertheless a component in a variety of basement membranes including skin. Many interesting biologic activities have been found for fibronectins *in vitro*. These include cell-cell aggregation, cell-substratrum adhesiveness and specific binding to macromolecule including collagen, particularly type III collagen. The role of fibronectins *in vivo* remains to be clarified. Recently, a possible function in wound healing has been suggested.

Composition of the epidermal-dermal junction: Until recently, virtually nothing was known of the biochemical composition of the structural components of the epidermal-dermal junction. Attempts to isolate junction components has proven difficult owing to the limited accessibility of the epidermal-dermal junction and the relatively small content and anticipated low yield of these materials. Several recent studies [54–56] have reported limited success in this direction but have not yet lead to biochemical characterization of the components.

Using an indirect approach considerable success has been achieved in which highly purified antibodies to basement membrane components derived from other sources are used as probes to analyze the composition of the epidermal-dermal junction. By this approach, it is possible to localize the isolated basement membrane collagenous and noncollagenous components to the epidermal-dermal junction utilizing immunofluorescence and ultrastructural immunoelectron microscopic procedures. A summary of these results is shown in the Table. Antibodies to type IV collagen (derived from murine tumor) localized type IV collagen to the basement membrane zone of human skin by immunofluorescence [57]. Staining was noted around skin appendages and vessels as well. By immunoelectron microscopy, antibodies to type IV collagen localize to the basal lamina only [57,58]. The lamina lucida and anchoring fibrils, dermal microfibril bundles and collagen fibers in the sub-basal lamina fibrous area were nonreactive.

Confusion exists regarding the presence of type V (AB) collagen at the epidermal-dermal junction. Stenn, Madri, and Roll [59] reported the localization of antibodies to AB_2 collagen in mouse epidermal-dermal junction. However, Gay et al [60] could not demonstrate A and B chains or type V collagen in human epidermal-dermal junction utilizing antibodies specific for these components. An explanation for these discrepancies is not presently available.

Antibodies specific for 7S collagen have demonstrated the presence of 7S collagen in epidermal-dermal junction by immunofluorescence [38]. Immunoelectron microscopy has not been reported as yet to localize 7S collagen to a specific junctional structure.

Several noncollagenous glycoproteins have also been shown to be present in skin. Antibodies specific for laminin derived from murine tumor localized to the lamina lucida on immunoelectron microscopic studies in human skin. Bullous pemphigoid antigen has also been located in the lamina lucida [57]. Some studies have found bullous pemphigoid antigen predominately on the basal cell surface [61]. Bullous pemphigoid antigen can also be found on dissociated basal cells after trypsin separation as a fluorescent area at one pole of the cell indicating its previous basal localization. Heparin sulfate-containing pro-

teoglycan has been localized to the basement membrane zone of skin using an antibody specific for this material [50]. Immunoelectron microscopy has not as yet been carried out to determine its ultrastructural localization. Its distribution in other tissues, however, suggests localization in the lamina lucida. Fibronectin has been demonstrated at the basement membrane zone of skin by immunofluorescent techniques [62–64]. It is also present in other areas of skin including the papillary and reticular dermis. By immunoelectron microscopy, fibronectin is localized ultrastructurally to the lamina lucida, particularly near the basal surface, and in the area below the basal lamina but not specifically associated with sub-basal fibrous structures [63]. Basal lamina showed no reaction indicating that fibronectin is not a component of basal lamina.

In summary, these data indicate a heterogeneous composition of the epidermal-dermal junction composed of both collagenous (type IV, 7S and perhaps type V collagens) and noncollagenous glycoproteins and proteoglycans (laminin, bullous pemphigoid antigen, heparin sulfate containing glycoprotein and fibronectin).

Functional aspects of basement membrane components

Major efforts to date have concentrated on the definition of the components of basement membranes. It seems that the major basement membrane components are now identified, although other minor basement membrane constituents will possibly be discovered with further study. However, little is known regarding the quantitative composition of different basement membranes and how the basement membrane components are organized and intergrated into functional basement membranes. Some investigations have begun to explore the functional aspects of these components. Four main functions have been postulated for basement membranes. These include the following: (1) support or scaffolding function, (2) attachment of cells, usually of different origin (eg. epithelial or endothelial), to connective tissue, (3) regulation of permeability across the membrane, (4) a role in development and morphogenesis.

It is likely that the scaffolding function of basement membrane is provided by the basement membrane collagens, including type IV, 7S and probably type V collagens. In their native state, their insolubility and stability make these collagens ideal structural proteins. The documented presence of type IV collagen in the cutaneous basal lamina places it at the center of the junctional area.

Fibronectin, bullous pemphigoid antigen, and laminin are all candidates for attachment functions. Fibroblast attachment to artificial or collagenous substrates requires fibronectin which may be synthesized by the fibroblasts themselves or provided by serum supplementation [53,65]. With few exceptions [66], the attachment of epithelial cells is not facilitated by fibronectin [67–69], so that other attachment factors have been sought. There is some evidence that bullous pemphigoid antigen may be an attachment factor for epidermal cells to substrate. Bullous pemphigoid antigen is present on trypsin associated epidermal basal cells where it is situated on the cell surface at one pole of the cell [61]. Only basal cells, presumably with BP-AG, attach and grow when dissociated cells are cultured [70]. The presence of bullous pemphigoid antibody inhibits epidermal cell attachment *in vitro* [61], suggesting that bullous pemphigoid antigen may be involved.

Considerable support has developed for laminin as a specific attachment protein for epithelial cells. Several types of epithelial cells, including freshly isolated epidermal cells, show preferential binding to a type IV collagen substrate in preference to other collagen types [67,71]. However, binding is relatively slow, increasing over a 24-hr time course [67]. Moreover, attachment is blocked by antilaminin antibody [68] suggesting that laminin produced by the cells facilitates attachment. Laminin has been shown to bind specifically to type IV collagen [68]. In addition, laminin promoted the attachment of an epithelial cell line (PAM 212) in low concentrations. The ultrastructural localization of laminin as well as bullous pemphigoid antigen and fibronectin places these materials in a strategic localization between basal lamina (type IV collagen) and epidermal cell to serve this attachment function.

Heparan sulfate proteoglycan and possibly other protein associated glycosaminoglycans may function in regulating the permeability of the basement membrane. In kidney, the removal of heparan sulfate with heparinase significantly alters permeability characteristics of membrane [72].

Laminin and type IV collagen may also play an important role in morphogenesis. Laminin is known to be present from very early stages in developing tissues [73]. In several tissues it has been suggested that the selective deposition of laminin and/or type IV collagen may be a facilitating mechanism in morphogenesis [74].

REFERENCES

1. Briggaman R, Wheeler CE Jr.: The epidermal-dermal junction. J Invest Dermatol 65:71, 1975
2. Daroczy J, Feldman J, Kiraly K: Human epidermal basal lamina: Its structure, connections and functions. Front Matrix Biol 7:208, 1979
3. Briggaman R: Basement membrane formation and origin with special reference to skin. Front Matrix Biol 9:142, 1981
4. Foidart J, Yaar M: Type IV collagen, laminin and fibronectin at the dermo-epidermal junction. Front Matrix Biol 9:175, 1981
5. Daroczy J, Feldmann J: Microfilaments of the human epidermal-dermal junction. Front Matrix Biol 9:155, 1981
6. Cotta-Pereira G, Rodrigo F, Bittencourt-Sampaio S: Oxytalan, elaunin and elastic fibers in the human skin. J Invest Dermatol 66:143–148, 1976
7. Cotta-Pereira G, Kattenbach W, Guerra-Rodrigo F: Elastic-related fibers in basement membrane. Front Matrix Biol 7:90–100, 1979
8. Kobayasi T: Anchoring of basal lamina to elastic fibers by elastic fibrils. J Invest Dermatol 68:389, 1977
9. Kefalides N: Biology and Chemistry of Basement Membranes. New York, Academic Press, 1978
10. Kefalides N, Alper R, Clark C: Biochemistry and metabolism of basement membranes. Int Rev Cytol 61:167, 1979
11. Kefalides N: Isolation of a collagen from basement membranes containing three identical alpha chains. Biochem Biophys Res Comm 45:226, 1971
12. Kefalides N: Structure and biosynthesis of basement membranes. Int Rev Connect Tissue Res 6:63, 1973
13. Dehm P, Kefalides N: The collagenous component of lens basement membrane. J Biol Chem 253:6680, 1978
14. Hudson B, Spiro R: Studies of native and reduced alkylated renal glomerular basement membrane. J Biol Chem 247:4229, 1972
15. Sato T, Spiro R: Studies on the subunit composition of the renal glomerular basement membrane. J Biol Chem 251:4062, 1976
16. Sage H, Woodbury R, Bornstein P: Structural studies on human type IV collagen. J Biol Chem 254:9893, 1979
17. Kresina T, Miller E: Isolation and characterization of basement membrane collagen from human placental tissue. Biochemistry 18:3089, 1979
18. Glanville R, Rauter A, Fietzek P: Isolation and characterization of a native placental basement membrane collagen and its component alpha chains. Eur J Biochem 95:383, 1979
19. Dixit S: Isolation and characterization of two alpha chains size collagenous polypeptide chains C and D from glomerular basement membrane. FEBS Letters 106:379, 1979
20. Dixit S, Kang A: Anterior lens capsule collagens. Cyanogen bromide peptides of the C chain. Biochemistry 18:5686, 1979
21. Timpl R, Martin G, Bruckner P, Wick G, Wiedemann H: Nature of the collagenous protein in a tumor basement membrane. Eur J Biochem 84:43, 1978
22. Timpl R, Bruckner P, Fietzel P: Characterization of pepsin fragments of basement membrane collagen obtained from a mouse tumor. Eur J Biochem 95:255, 1979
23. Orkin R, Gehron P, McGoodwin E, Martin G, Valentine T, Swarm R: A murine tumor producing a matrix of basement membrane. J Exp Med 145:204, 1977
24. Schuppan D, Timpl R, Granville R: Discontinuities in the triple helical sequences Gly-X-Y of basement membrane (type IV) collagen. FEBS Lett 115:297, 1980
25. Timpl R, Granville R, Wick G, Martin G: Immunochemical study on basement membrane (type IV) collagen. Immunology 38:109, 1979
26. Tryggvason K, Gehron P, Robey P, Martin G: Biosynthesis of type IV procollagens. Biochemistry 19:1284, 1980
27. Alitalo K, Vaheri A, Kreig T, Timpl R: Biosynthesis of two subunits of type IV procollagen and of other basement membrane proteins by a human tumor cell line. Eur J Biochem 109:247, 1980

28. Crouch E, Sage H, Bornstein P: Structural basis for apparent heterogeneity of collagens in human basement membranes: Type IV procollagen contains two distinct chains. Proc Natl Acad Sci. USA 77:745, 1980
29. Burgeson R, Adli F, Kaitila I, Hollister D: Fetal membrane collagens: Identification of 2 new collagen alpha chains. Proc Natl Acad Sci 73:2579, 1976
30. Chung E, Rhodes K, Miller E: Isolation of three collagenous components of probable basement membrane origin from several tissues. Biochem Biophys Res Commun 71:1167, 1976
31. Rhodes R, Miller E: Physiochemical characterization and molecular organization of collagen A and B chains. Biochemistry 17:3442, 1978
32. Bentz H, Bachinger H, Granville R, Kuhn K: Physical evidence for the assembly of A and B chains of human placental collagen in a single triple helix. Eur J Biochem 92:563, 1978
33. Sage H, Bornstein P: Characterization of a novel collagen chain in human placenta and its relation to AB collagen. Biochemistry 18:3815, 1979
34. Madri J, Furthmayr H: Isolation and tissue localization of type AB_2 collagen from normal lung parenchyma. Am J Pathol 94:323, 1979
35. Bailey A, Duance V, Sims T, Beard H: Immunofluorescence localization of basement membrane in skeletal muscle and placenta and preliminary characterization of basement membrane in some other tissues. Front Matrix Biol 7:49, 1979
36. Roll F, Madri J, Albert J, Furthmayr H: Codistribution of collagen types IV and AB_2 in basement membranes and mesangium of the kidney. J Cell Biol 85:597, 1980
37. Timpl R, Risteli J, Bachinger H: Identification of a new basement membrane collagen by the aid of a large fragment resistant to bacterial collagenase. FEBS Lett 101:265, 1979
38. Risteli J, Bachinger H, Engel J, Furthmayr H, Timpl R: 7-S collagen: Characterization of an unusual basement membrane structure. Eur J Biochem 108:239, 1980
39. Diaz L, Calvanico N, Tomasi T, Jordon R: Bullous pemphigoid antigen: Isolation from normal human skin. J Immunol 118:455, 1977
40. Diaz L, Patel H, Calvanico N: Bullous pemphigoid antigen: Isolation from the urine of a patient. J Immunol 122:605, 1979
41. Stanley J, Hawley-Nelson P, Yuspa S, Shevach E, Katz S: Characterization of bullous pemphigoid antigen—A unique basement membrane protein of stratified squamous epithelia. Cell, in press
42. Diaz L, Marcello C: Pemphigoid and pemphigus antigens in cultured epidermal cells. Br J Dermatol 98:631, 1978
43. Woodley D, Didierjean L, Regnier M, Saurat J, Prunieras M: Bullous pemphigoid antigen synthesized in vitro by human epidermal cells. J Invest Dermatol 75:148, 1980
44. Timpl R, Rhode H, Robey P, Rennard S, Foidart J, Martin G: Laminin-a glycoprotein from basement membranes. J Biol Chem 254:9933, 1979
45. Chung A, Jaffe R, Freeman I, Vergnes J, Braginski J, Carlin B: Properties of a basement membrane related glycoprotein synthesized in culture by a mouse embryonal carcinoma derived cell line. Cell 16:277, 1979
46. Rohde H, Bachinger H, Timpl R: Characterization of pepsin fragments of laminin in a tumor basement membrane. Evidence for the existence of related proteins. Hoppe-Seyler's Z Physiol Chem 361:1651, 1980
47. Rohde H, Wick G, Timpl R: Immunochemical characterization of the basement membrane glycoprotein laminin. Eur J Biochem 102:195, 1979
48. Madri J, Roll F, Furthmayr H, Foidart J: Ultrastructural localization of fibronectin and laminin in the basement membranes of the murine kidney. J Cell Biol 86:682, 1980
49. Foidart J, Bere E, Yaar M, Rennard S, Guillino M, Martin G, Katz S: Distribution and immunoelectron microscopic localization of laminin, a non-collagenous basement membrane glycoprotein. Lab Invest 42:336, 1980
50. Hassell J, Gehron Robey P, Barrach H, Wilczek J, Rennard S, Martin G: Isolation of a heparan sulfate-containing proteoglycan from basement membrane. Proc Natl Acad Sci USA 77:4494, 1980
51. Schneider H, Loos M: Amyloid P-component-a special type of collagen? Virchows Arch B Cell Pathol 29:225, 1978
52. Dyck R, Lockwood C, Kershaw M, McHugh N, Duance V, Baltz M, Pepys M: Amyloid P-component is a constituent of normal human glomerular basement membrane. J Exp Med 152:1162, 1980
53. Yamada K, Olden K: Fibronectins-adhesive glycoproteins of cell surface and blood. Nature 275:179, 1978
54. Heaphy M, Winkelmann RK: The human cutaneous basement membrane-anchoring fibril complex. J Invest Dermatol 68:177, 1977
55. Heaphy M, Jordon R: Immunohistochemical studies of the human cutaneous basement membrane-anchoring fibril complex. J Invest Dermatol 69:513, 1977
56. Scaletta L, Occhino J, MacCallum D, Lillie J: Isolation and immunologic identification of basement membrane zone antigens from human skin. Lab Invest 39:1, 1978
57. Yaiota H, Foidart J, Katz S: Localization of the collagenous component in skin basement membrane. J Invest Dermatol 70:191, 1978
58. Foidart J, Bere E, Gullino M, Brown K, Martin G, Yaar M, Katz S: Nature localization and function of type IV collagen and laminin in basement membranes. Clinical Res 27:241A, 1978
59. Stenn K, Madri J, Roll F: Migrating epidermis produces AB_2 collagen and requires continual collagen synthesis for movement. Nature 277:229, 1979
60. Gay S, Kresina T, Gay R, Miller E, Montes L: Immunohistochemical demonstration of basement membrane collagen in normal skin and in psoriasis. J Cutan Pathol 6:91, 1979
61. Grekin P, Levy G, King A, Diaz L: Some biochemical properties of pemphigoid antigen bound to the surface of dissociated epidermal basal cells. J Invest Dermatol 76:190, 1981
62. Stenman S, Vaheri A: Distribution of a major connective tissue protein, fibronectin in normal tissue. J Exp Med 147:1054, 1978
63. Couchman J, Gibson W, Thom D, Weaver A, Dees D, Parish W: Fibronectin distribution in epithelial and associated tissues in the rat. Arch Dermatol Res 266:296, 1979
64. Fyrand O: Studies on fibronectin in the skin. Br J Dermatol 101: 263, 1979
65. Pearlstein E, Gold L, Garcia-Pardo A: Fibronectin: A review of its structure and biological activity. Mol Cell Biochem 29:103, 1980
66. Gold L, Pearlstein E: Fibronectin collagen binding and requirements during cellular adhesion. Biochem J 186:551, 1980
67. Murray J, Stingl G, Kleinman H, Martin G, Katz S: Epidermal cells adhere preferentially to type IV (basement membrane) collagen. J Cell Biol 80:197, 1979
68. Terranova V, Rohrbach D, Martin G: Role of laminin in the attachment of PAM 212 (Epithelial) cells to basement membrane collagen. Cell 22:719, 1980
69. Federgreen W, Stenn K: Fibronectin (LETS) does not support epithelial cell spreading. J Invest Dermatol 75:261, 1980
70. Stanley J, Foidart J, Murray J, Martin G, Katz S: The epidermal cell which selectively adheres to a collagen substrate is the basal cell. J Invest Dermatol 74:54, 1980
71. Wicha M, Liotta L, Garbisa S, Kidwell W: Basement membrane collagen requirements for attachment and growth of mammary epithelium. Exp Cell Res 124:181, 1979
72. Kanwar Y, Linker A, Farquhar M: Increased permeability of the glomerular basement membrane to ferritin after removal of glycosamino-glycans by enzyme digestion. J Cell Biol 86:688, 1980
73. Leivo I, Vaheri A, Timpl R, Wartiovarra J: Appearance and distribution of collagens and laminin in the early mouse embryo. Dev Biol 79:100, 1980
74. Ekblom P, Alitalo K, Vaheri A, Timpl R, Saxen L: Induction of a basement membrane glycoprotein in embryonic kidney: Possible role of laminin morphogenesis. Proc Natl Acad Sci 77:485, 1980