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Molecular organization of the basement membrane zone

Sana Hashmi, BS[a], M. Peter Marinkovich, MD[b,c,*]

[a]*Stanford University School of Medicine, Li Ka Shing Building, 291 Campus Drive, Stanford, CA 94305, USA*
[b]*Department of Dermatology, Stanford University School of Medicine, Center for Clinical Sciences Research, 269 Campus Drive #2145, Stanford, CA 94305, USA*
[c]*Division of Dermatology, VA Palo Alto Health Care System, 3801 Miranda Avenue, Palo Alto, CA 94304, USA*

Abstract The dermal-epidermal basement membrane is a complex assembly of proteins that provide adhesion and regulate many important processes such as development, wound healing, and cancer progression. This contribution focuses on the structure and function of individual components of the basement membrane, how they assemble together, and how they participate in human tissues and diseases, with an emphasis on skin involvement. Understanding the composition and structure of the basement membrane provides insight into the pathophysiology of inherited blistering disorders, such as epidermolysis bullosa, and acquired bullous diseases, such as the pemphigoid group of autoimmune diseases and epidermolysis bullosa acquisita.
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Introduction

The basement membrane zone (BMZ) is a highly dynamic and complex structure that is important in the regulation of cell adhesion, differentiation, and motility; in the transmission of extracellular signals and growth factors; and in the formation of permeability barriers. This contribution discusses the supramolecular assembly and function of various components of the BMZ, especially with regard to pathophysiology.

Although the PAS (periodic acid Schiff) stain is commonly used to locate the region of the BMZ, the stain extends far greater than the BMZ's boundaries. In fact, the BMZ is too small to be identified through light microscopy and can be visualized only by electron microscopy. The BMZ contains a 50-nm electron-dense zone called the lamina densa and a 40-nm electron-lucent zone referred to as the lamina lucida. Collectively, the lamina densa and lamina lucida form the basal lamina.[1,2] Although these structures comprise the BMZ in most tissues, tissue exposed to disruptive external forces, such as stratified squamous epithelium of the skin; oral-pharyngeal, portions of the gastrointestinal (GI), genitourinary (GU), and respiratory mucosa; cornea; and amnion, have evolved specialized BMZ structures that provide added cohesion. Ultrastructurally, these specialized structures can be seen in condensations of basal keratinocyte plasma membrane structures called hemidesmosomes. The inner layer of hemidesmosomes interfaces with intermediate filaments, and the outer layer interfaces with the plasma membrane. Immediately underlying hemidesmosomes are thin structures known as anchoring filaments, which span across the lamina lucida and insert on the lamina densa.[3]

Newer techniques using high-pressure freeze substitution electron microscopy have led to enhanced tissue preservation with more physiological tissue architecture.[4] Examination of

* Corresponding author. Tel.: +1 650 498 5425; fax: +1 650 723 8726.
E-mail address: mpm@stanford.edu (M.P. Marinkovich).

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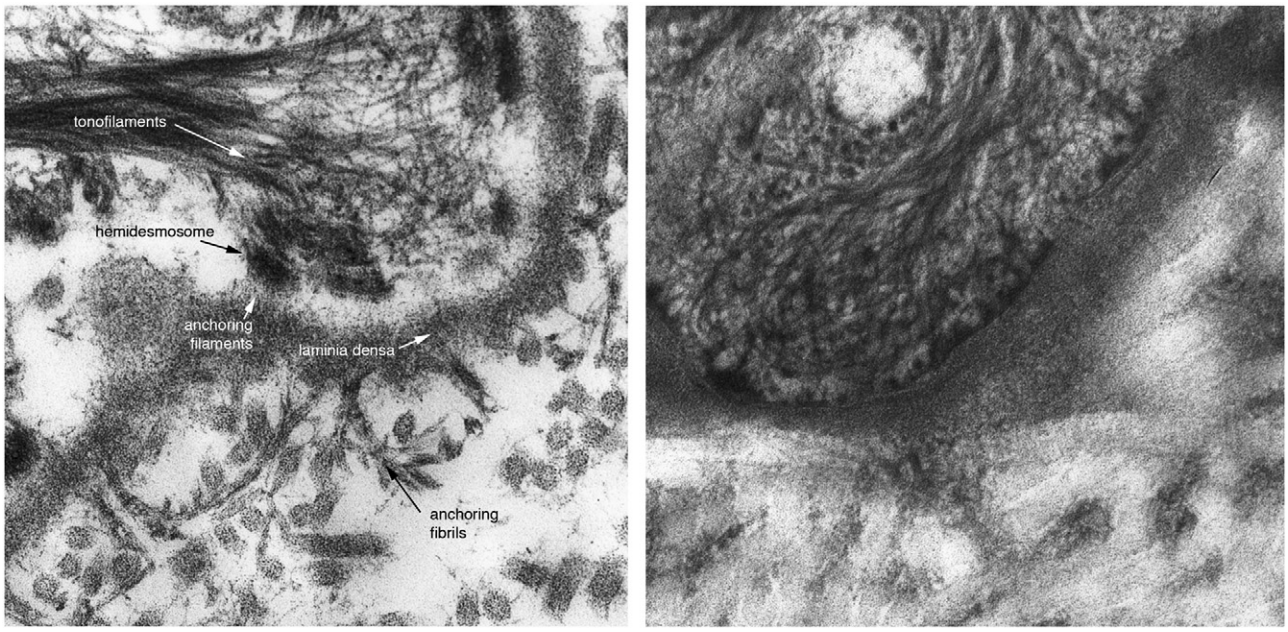

Fig. 1 Ultrastructure of the dermal-epidermal basement membrane. Dehydration artifact during normal electron microscopy fixation stretches the lamina densa away from the plasma membrane, suggesting that the lamina lucida is an artifactual space, and anchoring filaments may reside in the lamina densa instead of the lamina lucida. Left, conventional transmission electron microscopy showing the characteristic specialized ultrastructural entities (labeled). Right, transmission electron microscopy as performed by high-pressure freeze substitution, note absence of lamina lucida and anchoring filaments.

the BMZ using high-pressure freeze substitution, as shown in Figure 1, has revealed that the conventional dermal-epidermal division may be an artifact of tissue preparation and dehydration. The most significant finding is the absent lamina lucida, leading to the appearance of a continuous matrix from the basal plasma membrane to the dermis. The dehydration that occurs during electron microscopy fixations pulls the plasma membrane away, exposing the lamina lucida. Thus, it is likely that the lamina lucida is a dehydration artifact and that the anchoring filaments may actually be located in the lamina densa. Despite this, the ultrastructure in conventional electron microscopy is still helpful in understanding BMZ structure[3,4] and therefore conventional terms will continued to be used in this contribution.

As shown in Figure 2, the BMZ represents a complex and precise assembly of both intracellular and extracellular proteins that function in a collective manner to preserve tissue integrity. Certain proteins, such as nidogen, type IV collagen, perlecan, and large laminins like laminin-511, are found ubiquitously in the BMZ throughout the body. These molecules are important in building the basic scaffolding structure of the BMZ.[5] Nidogens can be thought of as one of the key organizers of basement membrane assembly, serving as linker proteins to connect laminins with type IV collagen and perlecan.[6]

With these ubiquitous proteins forming the basal lamina foundation, the additional structures of specialized BMZ contain an array of specialized proteins that work together to provide tighter cohesion that is needed to withstand external disruptive forces. The dermal-epidermal BMZ is one of the most well studied examples of this type of specialized structure. The most superior aspects of the dermal-epidermal BMZ contain the specialized intracellular keratin linker proteins plectin and BPAG1 (BP230). These in turn are connected to specialized transmembrane proteins, which include integrins $\alpha 6\beta 4$ and $\alpha 3\beta 1$ and type XVII collagen (BP180/BPAG2). Collectively, these intracellular and transmembrane proteins form the hemidesmosome. The integrins and type XVII collagen also connect to specialized extracellular proteins laminin-332 and laminin-311, together forming anchoring filaments. The interaction between these specialized extracellular proteins and ubiquitous proteins, which include laminin-511, type IV collagen, and nidogen, form the lamina densa. Finally, extending out of the lamina densa is another specialized extracellular structure known as the anchoring fibril. Anchoring fibrils are thick-banded structures, extending as perpendicular extensions from the lamina densa, looping through interstitial collagen fibrils in the dermis, and reinserting back onto the lamina densa. The primary constituent of anchoring fibrils is type VII collagen.

Ubiquitous BMZ components

Nidogen/Entactin

Nidogen, also known as entactin, is a glycoprotein containing an N-terminal G1 domain, G2, and C-terminal G3 domain, which are separated from each other by two