Review

The nature and biology of basement membranes

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Abstract

Basement membranes are delicate, nanoscale and pliable sheets of extracellular matrices that often act as linings or partitions in organisms. Previously considered as passive scaffolds segregating polarized cells, such as epithelial or endothelial cells, from the underlying mesenchyme, basement membranes have now reached the center stage of biology. They play a multitude of roles from blood filtration to muscle homeostasis, from storing growth factors and cytokines to controlling angiogenesis and tumor growth, from maintaining skin integrity and neuromuscular structure to affecting adipogenesis and fibrosis. Here, we will address developmental, structural and biochemical aspects of basement membranes and discuss some of the pathogenetic mechanisms causing diseases linked to abnormal basement membranes.

Introduction

Basement membranes (BMs) are cell-adherent extracellular matrices widely distributed in metazoan tissues. First identified in skeletal muscle 176 years ago [1], elucidation of BM constituents, structure, functions and genetics has required advances in multiple fields stretched over many years. The beginning of a molecular understanding of BMs dates to the 1970s and 1980s when Kefalides discovered collagen IV and Kuhn, Timpl, Martin, Bruckner, Robey, Rhode and others exploited the Engelbreth-Holm-Swarm tumor as a source for obtaining soluble BM components for analysis. Since then, a combination of biochemical, biophysical, cell biological, genetic, bioengineering and other approaches led to our current understanding of BMs. We are pleased to present a special edition of *Matrix Biology* entitled "Basement Membranes in Health and Disease" containing a collection of twenty-six articles from specialists in the field where the physiological and pathological functions of BM components are critically assessed.

How many proteins are incorporated into a typical basement membrane?

The core structural components of BMs are laminins, collagen IV, nidogens, and the heparan sulfate proteoglycans (HSPGs) perlecan and agrin (Fig. 1). We envision core components as those macromolecules for which there is an embryonic phenotype of failed or structurally-defective BM assembly upon knockout with the provision that compensation can sometimes mask a structure-forming role. These glycoproteins and proteoglycans, initially secreted in a soluble state, become organized into insoluble cell scaffoldings and constitute a complex meshwork of proteins present in multicellular organisms [2]. In addition, BMs contain "matricellular proteins" that provide

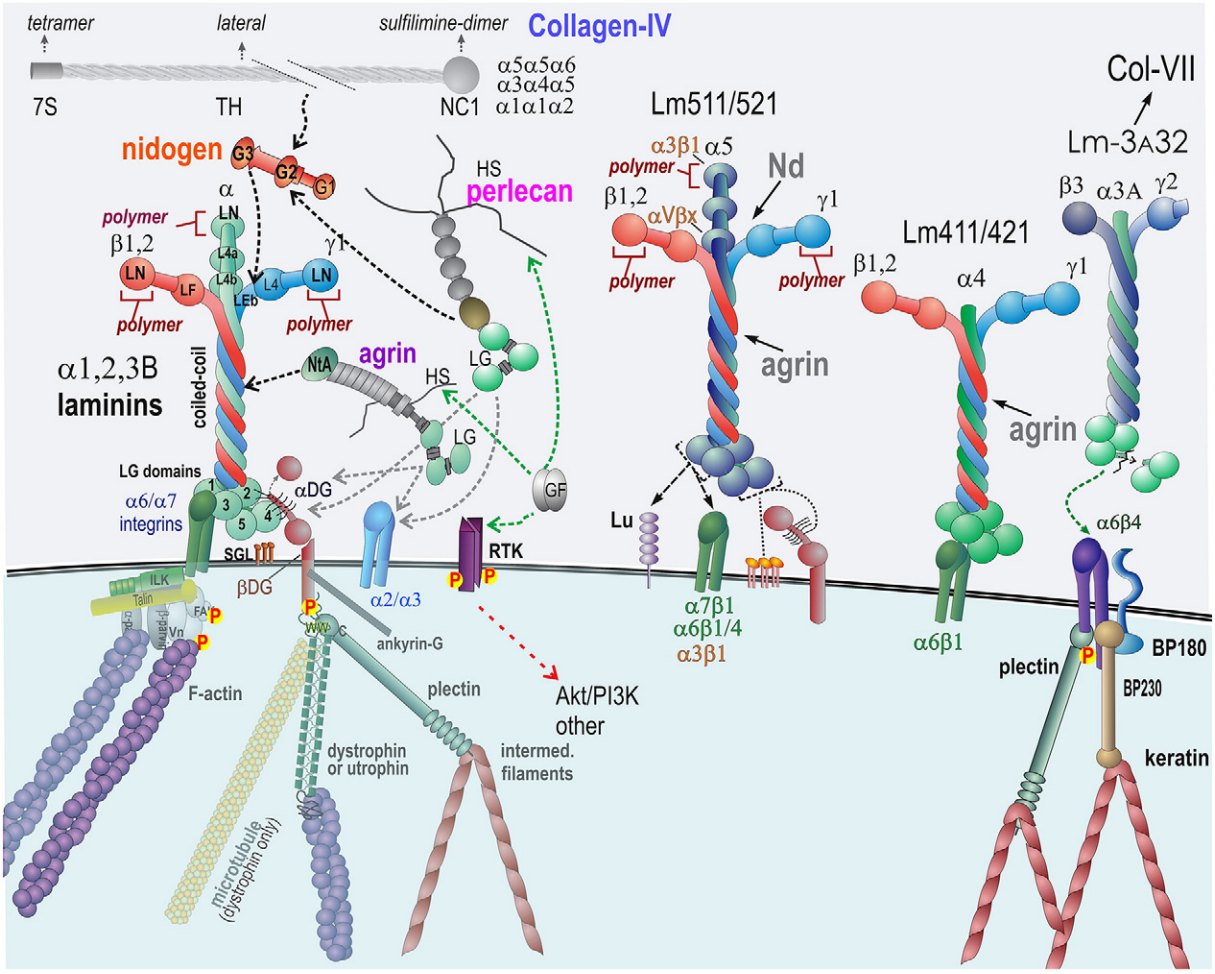

Fig. 1. Core basement membrane components and binding interactions. Laminins (Lms) are central organizers of BMs. Lm111, a prototypical laminin expressed in embryogenesis, binds to cell surface sulfated glycolipids (SGL), several integrins, α-dystroglycan (αDG), nidogens (Nd), agrin, and polymerizes via its LN domains. Collagen-IV (three isoforms) and perlecan bind to nidogen, completing the core basement membrane scaffold. Agrin and perlecan HS chains attach to growth factors, promoting their interactions with receptor tyrosine kinases (RTK). Integrin and αDG attach through adaptor proteins to the cytoskeleton. Lm411, an isoform that does not polymerize, exhibits weak integrin and αDG binding but strong binding to SGLs (gal sulfatide). Lm511/521, polymerizing laminins, binds to multiple integrins both in the LG domains and α5 short arm, to the Lutheran receptor (Lu), and moderately well to αDG. Lm3A32, a non-polymerizing laminin found in epithelia, binds strongly to α6β4 integrin of hemidesmosomes and links to collagen VII of the anchoring fibrils.

additional, often tissue-specific, functions but are not essential for BM assembly or architecture [3]. Examples are SPARC and nephronectin. Various growth factors/morphogens, many belonging to the TGFβ superfamily, are found tethered to BMs (in particular to proteoglycan HS chains) and act to provide specific signals to BM-adherent cells. Additionally, collagen XV and XVIII are found at the stromal interface. Finally, proteinases and their inhibitors, regulatory macromolecules and serum factors are found associated with BMs. Collectively, these components, organized into or associated with BMs, provide cell and tissue support and act as complex signaling platforms.

Evolution and embryogenesis of basement membranes

Laminin domains integrated within proteins such as cadherins exist in single-cell motile choanoflagellates representing primitive species that pre-date the evolutionary emergence of BMs [4]. These unicellular organisms can aggregate to form clusters, suggesting BM/cadherin precursors serve cell-cell adhesive functions. BMs are thought to have first emerged in metazoans as a requirement for organizing epithelial tissues. Laminin α-like, β-like and γ-like subunits, each with a laminin N-terminal (LN) and coiled-coil domains, and collagen IV-like