Review Article

Extracellular Matrix Components Regulate Cellular Polarity and Tissue Structure in the Developing and Mature Retina

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Abstract

While genetic networks and other intrinsic mechanisms regulate much of retinal development, interactions with the extracellular environment shape these networks and modify their output. The present review has focused on the role of one family of extracellular matrix molecules and their signaling pathways in retinal development. In addition to their effects on the developing retina, laminins play a role in maintaining Müller cell polarity and compartmentalization, thereby contributing to retinal homeostasis. This article which is intended for the clinical audience, reviews the fundamentals of retinal development, extracellular matrix organization and the role of laminins in retinal development. The role of laminin in cortical development is also briefly discussed.

Keywords: Dystroglycanopathy; Laminin; Müller Cell; Retinal Progenitor Cell

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INTRODUCTION

Mammalian vision begins with transmission of light through the cornea and lens to the retina. The highly specialized retina converts energy from absorbed photons into neural activity such that the brain can interpret the pattern of the detected photons.[1]

Light energy is transduced into changes in membrane potential in the photoreceptor outer segments, and then into changes in synaptic transmitter output to second order neurons. The retinal network, with complex connectivity among the retinal interneurons, leads to multiple paths of temporally and spatially encoded information about the visual world, including color, motion, size and orientation. This information is transmitted out of the retina by retinal ganglion cells to numerous sites in the brain.

The encoding of light energy into neuronal signaling is produced in the meticulously polarized retina with a defined laminar architecture which underlies its function [Figure 1]. The polarized organization of retinal structure is dependent on appropriate positioning and spacing of cells, as well as proper development of neuronal connections which are required for the generation of functional circuitry. Moreover, retinal homeostasis is dependent on the polarized morphology of Müller cells.[2]

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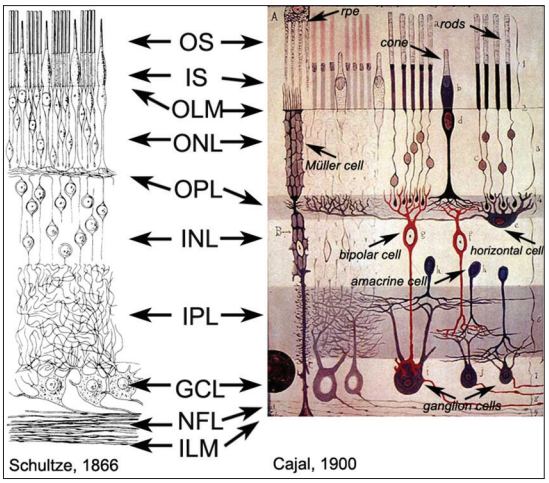

Figure 1. Cross sectional diagrams of the mammalian retina. All vertebrate retinas are composed of three layers of nerve cell bodies and two layers of synapses. The light transducers, photoreceptors (rods and cones), are positioned outermost in the retina, against the retinal pigment epithelium (rpe) and choroid (not shown). Light is transduced in the outer segments (OS) of rods and cones. The outer nuclear layer (ONL) contains cell bodies of the rods and cones; the inner nuclear layer (INL) contains cell bodies of the bipolar, horizontal and amacrine cells. The output neurons of the retina, ganglion cells, lie in the ganglion cell layer (GCL). Ganglion cell axons course through the nerve fiber layer (NFL) abutting the inner limiting membrane (ILM). In between these cell layers are two synaptic, or plexiform, layers. Synaptic connections between photoreceptors, and bipolar cells and horizontal cells are contained in the outer plexiform layer (OPL) while synapses among bipolar cells, amacrine cells and ganglion cells are found in the inner plexiform layer (IPL). The resident glial cell of the retina, the Müller cell spans nearly the entire thickness of the neural retina. Its end feet adhere to the ILM at the basal surface and it forms adherens junctions with photoreceptors at the apical surface, forming the outer limiting membrane (OLM). Modified with additions from original drawings of Schultze;[103] Ramon y Cajal[104].

The unifying theme in all these processes is establishment and maintenance of cell and tissue polarity.

The seven different types of retinal cells, of which six are neurons and one is a glial cell, the Müller cell (MC), are precisely positioned [Figure 1].[3,4] The input neurons (rod and cone photoreceptors) have nuclei in the outer nuclear layer (ONL); the retinal interneurons (horizontal, bipolar and amacrine cells) have nuclei in the inner nuclear layer (INL). A single class of projection neurons, the retinal ganglion cells, is in the eponymous layer, named the retinal ganglion cell layer (GCL). Between these three nuclei and cytoplasm-rich layers, there are nuclei-poor layers in which retinal neurons make synapses, called the outer and inner plexiform layers. The outer plexiform layer (OPL) separates the ONL from the INL and the inner plexiform layer (IPL) separates the INL from the GCL [Figure 1]. A specialized basement membrane, the inner limiting membrane, separates the GCL from the vitreous body and serves as an attachment surface for a variety of retinal cells.

THE EXTRACELLULAR MATRIX AND RETINAL BASEMENT MEMBRANES

In all metazoans, components of the extracellular matrix (ECM) are organized into thin specialized sheets of basement membranes.[5] The functions of basement membranes are to act as platforms for cell adhesion, to provide structural support to a tissue, to divide tissues into compartments, and to regulate cell behavior including polarity. Polarized cellular functions are regulated by the ECM in a variety of cell types including epithelial cells,[6] neurons,[6-8] immune cells[9] and glial cells such as astrocytes, oligodendrocytes and Schwann cells.[10]

Interactions of cells with basement membranes are mediated by transmembrane cell surface receptors which connect the cell's cytoskeleton with the extracellular environment, leading to the formation of site-specific focal adhesions.[11,12] The extracellular cues established by binding of cells to the ECM are propagated to the nucleus from the cell surface by cytoskeletal molecules such as actin and tubulin, resulting in outside-to-inside signaling.[13,14] Disruptions along this pathway have been reported in both developmental deformities and pathologies in kidney, muscle, skin, central nervous system (CNS), brain and retina.[13,15-18]

The mature, polarized retina is structurally and functionally supported by two basement membranes i.e., Bruch's membrane, at the interface of the retinal pigmented epithelium with the choroid, and the inner limiting membrane (ILM) at the interface of the neural retina with the vitreous body [Figure 1]. Several retinal pathologies result from changes in the organization or composition of these basement membranes. These pathologies include diabetic retinopathy, retinopathy of prematurity, age related macular degeneration and proliferative vitreoretinopathy.[19,20]

In the present article, retinal basement membranes will be discussed, including one important class of basement membrane components, the laminins; the interaction of retinal basement membranes with neighboring cells will also be addressed. We will then focus on the role of retinal basement membranes, especially the ILM, in establishing and maintaining cellular polarity within the retina. This polarity is required for the development and function of various retinal cells including retinal progenitor cells, retinal ganglion cells and Müller glial cells. First, the general process of retinal development will be reviewed in this context.

RETINAL DEVELOPMENT FROM A COMMON PROGENITOR CELL

The retina arises from an out-pocketing of the

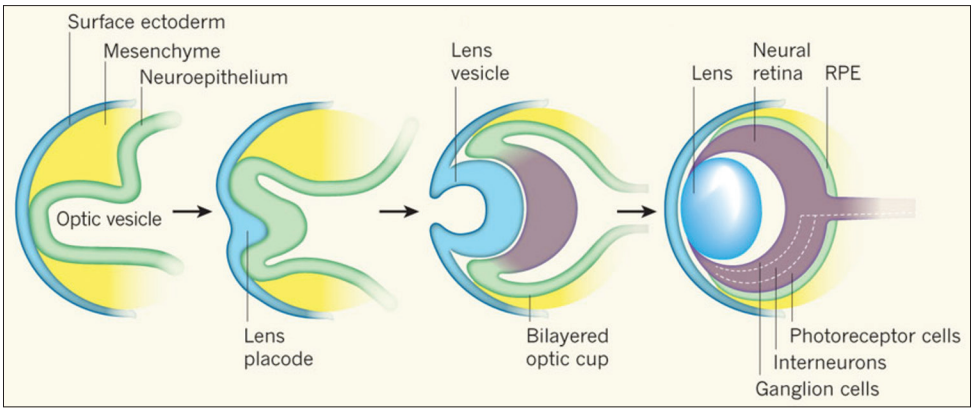

Figure 2. Illustration of eye development from the neural plate. The neural plate folds and bulges to give rise to two optic vesicles, each of which will become an eye. The development of one eye from one of the optic vesicles is depicted here. (a) The neuroepithelium of the optic vesicle merges with the invaginating surface ectoderm, leading to induction of the lens placode. (b) The optic vesicle invaginates and the inner layer becomes the bilayered optic cup. The lens placode begins to form the lens vesicle. (c) The optic cup gives rise to the neural retina and the outer layer gives rise to the retinal pigmented epithelium (RPE). The mature eye structure with photoreceptors, interneurons, and ganglion cells is depicted. From Ali and Sowden;[105] copyright license obtained.

diencephalon that projects toward and contacts the surface ectoderm. As the result of interactions between the eye vesicle and the overlying ectoderm (lens placode), the optic vesicle involutes, forming a double-walled eyecup. Each layer of this dual layered eyecup undergoes its own morphological change: The inner layer becomes the neural retina and expands dramatically into a multi-layered structure, while the outer layer, the retinal pigmented epithelium, remains a single cell layer [Figure 2].

The early embryonic retina is a single sheet of pseudostratified neuroepithelial cells and its single class of progenitor cells gives rise to all of the retinal neurons and Müller glial cells.[21] In contrast, the mature neural retina is comprised of six major classes of neuronal cell [Figure 3], each of which has stereotyped organization and connectivity.

The cells of the mature neural retina arise in a temporal sequence which is ordered in two overlapping waves, largely conserved among vertebrates [Figure 3]. The first wave generates ganglion cells, amacrine cells and horizontal cells, along with cone photoreceptor cells. The second wave produces rod photoreceptor cells and bipolar cells, along with Müller glial cells.[22,23] Although this sequence of events is largely conserved among vertebrates, the precise timing of neurogenesis and its component waves varies from species to species; in mice, the first wave begins at approximately embryonic day 11 and the second wave is complete by postnatal day 10.[24]

The orderly exit from mitosis and subsequent differentiation in the retina is crucial for the production of properly layered retina. The regulation of cell cycle length and the mode of cytokinesis both determine whether any given cell division is symmetric or asymmetric and thereby contributes to the regulation of cell neurogenesis.

Symmetric divisions generate two daughters of the same fate: Both remain progenitors, or both become neurons. In contrast, asymmetric divisions produce daughters taking on different fates: One remains a progenitor and the other takes a neuronal fate.[25,26] The plane of cytokinesis is critical in determining if the division is symmetric or asymmetric: Those cell divisions whose plane of cytokinesis is perpendicular to the surface are symmetric, whereas those being parallel to the neuroepithelial surface are asymmetric.[21]

During early retinal development, the typical cell division is symmetric, resulting in two identical progenitor cells and leading to an increase in the pool of proliferating cells. The duration and number of these symmetric divisions is critical for regulating retinal size and sustaining genesis of later cell types. As development proceeds, the number of asymmetric divisions increases, leading to the generation of one progenitor cell and one neuron. Finally, during late retinal development, a fundamental change takes place: At this stage, symmetric divisions result in the generation of two neurons of the same type, whereas asymmetric divisions lead to the genesis of two neurons of different types.

Tight control between the number of retinal progenitor cells (RPCs) remaining proliferative and those exiting the cell cycle to take on a neuronal fate is critical in assuring a steady supply of progenitors for subsequent divisions and for regulating the size of any given pool of neurons.[27] During the early phase of neurogenesis (during the embryonic period in mice), excessive divisions which result in neurons will deplete the pool of progenitors at the expense of late born cell types, whereas a paucity of divisions that result in neurons will increase the progenitor pool present for later-generated neurons, thereby shifting the proportion of neurons in the mature retina to normally later born types. Among the factors

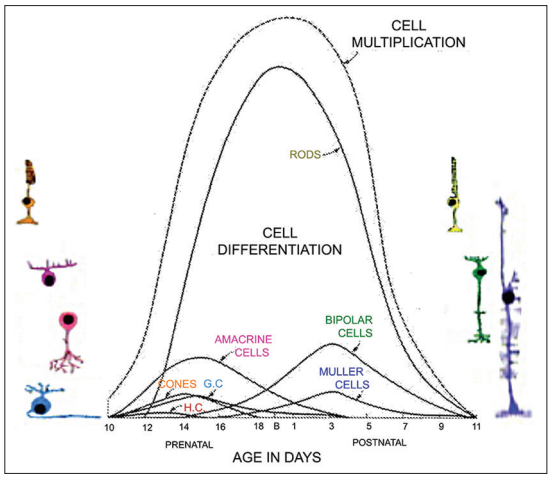

Figure 3. Chronological order of retinal cell genesis. Retinal neurogenesis (multiplication and differentiation) begins before embryonic day 10 and persists until postnatal day 11 in the mouse. Retinal cells differentiate largely in two overlapping waves: In the first wave, cone photoreceptors (cones), horizontal cells (H.C.), retinal ganglion cells (G.C.), and amacrine cells are produced; in the second wave, bipolar cells and Müller (glial) cells are produced. Rod photoreceptors (rods) are produced throughout these waves. Note there is considerable overlap during the production of various retinal cell types. The size of each wave represents the approximate proportion of each cell type in the mature retina. Modified from Young[28] and Marquardt and Gruss,[106] copyright licenses obtained.

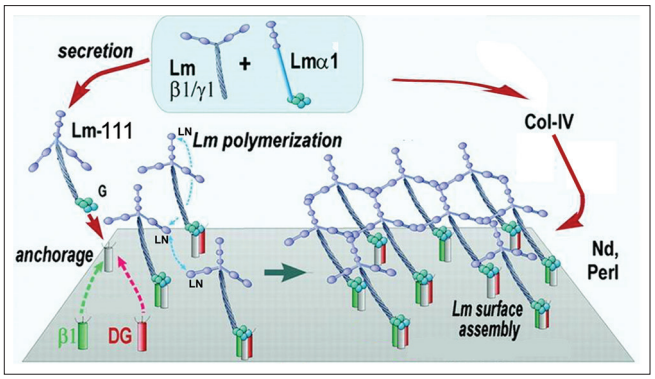

Figure 4. Laminin assembly in basement membranes. Laminins self-polymerize in the extracellular space through their LN domains and create a "nascent" scaffold. A self-assembled collagen polymer joins this scaffold, which is further linked by nidogen (Nd), perlecan (Perl) and agrin (not shown), resulting in increased stability and complexity of the basement membrane (grey surface). Laminins in the basement membrane (e.g., here, Lm-111) interact via their G domain with cell receptors including integrins (here, integrin β1 subunit shown) and dystroglycan (DG) for anchorage. Col IV, Type IV Collagen; Nd, nidogen; Perl, perlecan; Modified from Li et al,[32] noncommercial reuse permitted by Rockefeller University Press.

controlling these processes there are components of basement membranes.

BASEMENT MEMBRANES: AN OVERVIEW

Basement membranes are cell surface associated extracellular matrices (ECMs) containing a fundamental basic "tool kit"[5] which includes laminins, type IV collagens, nidogens and members of the heparan sulfate proteoglycan family (perlecan and agrin). Beyond providing support to cells, basement membranes establish and maintain cell polarity and associated tissues required for proper development, maturation and function of tissues.

The central scaffold of the basement membrane [Figure 4] is composed of independently assembled polymers of laminins and type IV collagen that are cross-coupled to form a network for cell attachment.[28-30] Nidogen (also known as entactin) acts as a connecting link between two polymers of laminins and type IV collagen.[31,32] The first step of assembly of basement membranes is the stabilization of laminins by sulfated glycolipids at the cell surface, leading to the nucleation of the polymerization of laminins, followed by further stabilization of laminin polymers by their binding to transmembrane receptors. Recruitment and binding of other secreted proteoglycans to the growing basement membrane results in increased stability and complexity of the basement membrane.[12,33]

Basement membranes are heterogeneous, not only among different tissues, but also within a given tissue and during development. The spatial and temporal regulation of deposition of basement membrane components results from complex developmental mechanisms. Diversification in the architecture of basement membrane in different tissues and during development is due in part to variations in the composition of the basic tool kit. For example, in humans, there are 16 different isoforms of laminin and six different isoforms of collagen type IV, in addition to complex modifications of glycoproteins such as heparan sulfate and chondroitin sulfate proteoglycans.[34] Additionally, even greater heterogeneity is brought about by growth factors that are differentially sequestered in basement membranes.[29-31,35]

Animal models with deletion or mutations in the genes encoding basement membrane molecules provide strong evidence supporting the role of basement membrane-mediated regulation in myriad cellular processes including adhesion, survival, proliferation, differentiation and migration.[36,37] Basement membranes regulate essential processes in cellular behavior, in part, due to their ability to sequester growth factors and connect to the cell via cell surface receptors that modulate intracellular pathways. One family of basement membrane molecules consistently shown to be involved in providing cues for cell proliferation, polarity and survival is the laminins.

ROLES OF LAMININS AND THEIR RECEPTORS IN THE CNS

The ectodermal lineage of the retina (and the entire CNS) implies that the basement membrane organization provides crucial guidance during retinal development. Ectodermal formation and epithelial development is critically dependent on the laminin-rich basement membrane, which confers polarity cues, regulates proliferation and provides a substrate for migration.

The central nervous system (CNS) including the brain, spinal cord and retina arises from an invagination of the primitive ectoderm, ultimately forming from a tube composed of pseudostratified neuroepithelial cells. In primates, the cranial end of this tube is massively expanded into the neocortex, a complex structure that is divided into over 50 cytoarchitectonic regions. Although the processes of CNS development have been the subjects of study for well over a hundred years, only recently have the molecular mechanisms underlying these processes become coherent.

Despite the broad array of behavior among species, the fundamentals of CNS development and connectivity are shared across many species. In general, the process of CNS development proceeds through several stereotyped phases: (1) Proliferation i.e., neurogenesis and gliogenesis during which cell populations expand from progenitors to the full complement of cells in the adult CNS and after which cells, in general, become post-mitotic; (2) neuronal migration and maturation, after terminal mitosis, during which neurons migrate from the site of genesis to their adult position and begin to take on their adult characteristics and shape; (3) neuronal axon outgrowth and target selection, through which neurons send processes varying in length from microns to meters to reach out and contact another neurons; (4) neuronal synaptogenesis, during which neurons make functional connections with each other.

All four of these developmental processes are regulated, to varying degrees, by laminins. A dramatic example is that for laminins in the cortex. Laminins are expressed in the ventricular zone of the developing neocortex,[38,39] and defects in laminins or their downstream signaling partners lead to lamination defects in the neocortex.[40-42]

In order to understand the role of laminins in developmental processes in the CNS, simplified model systems are advantageous. Historically, one portion of the CNS, the vertebrate retina, has proven to be an excellent and very approachable model for general CNS development. The retina is easily removable; it has a relatively small number of cell types and a characteristic architecture which is generally preserved across most vertebrates. Comparable with the rest of the CNS, retinal development is a highly coordinated process that is tightly regulated by both intrinsic (genetic, cell autonomous) as well as extrinsic (epigenetic, cell non-autonomous) factors. Thus, retinal development encapsulates development of the CNS, but in a simpler manner than in other regions of the nervous system including the cortex. In order to assess the roles of laminins in development, it is necessary to analyze their expression and function.

LAMININS: DIVERSE EXPRESSION AND FUNCTION

Laminins are large heterotrimeric glycoproteins that contain an alpha chain, a beta chain and a gamma chain joined together in a coiled-coiled structure [Figure 5]. The α, β and γ chains are found in five, three and three genetic variants, respectively. Although most trimeric combinations are possible, the γ2 chain and β3 chains have been isolated only in association with each other and with the α3 chain, thereby restricting the feasible combination of the *in vivo* laminin heterotrimers to twenty-one of these possible trimers. Sixteen trimers have been identified *in vivo*, and are differentially expressed both temporally and spatially in various tissues.[35,43-46]

The highly regulated developmental expression of laminins leads to distinctive biological defects upon disruption or deletion of different laminin chains. Generally, deletion of those laminin subunits which are expressed early during embryogenesis leads to lethality, whereas deletions of laminin chains expressed later in development leads to tissue-specific defects.

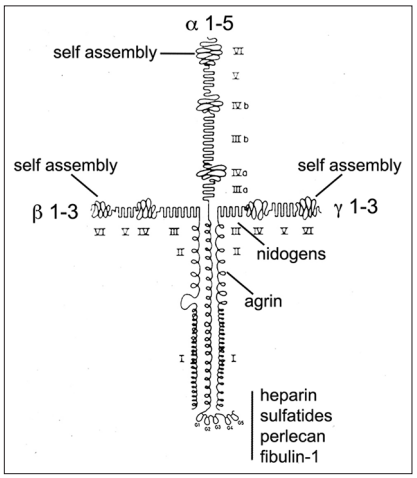

Figure 5. Simplified illustration of a laminin heterotrimer. Schematic of a prototypical laminin heterotrimer. Each chain is comprised of six domains (I-VI). The α-helical coiled-coil regions in domains I and II of the "long arm" regions of all three chains are covalently linked to one another by disulfide bonds.[107,108] The self-assembly domain of each chain is responsible for self-polymerization required for basement membrane assembly. The terminal globular domain of the α chain interacts with cell surface receptors, and is responsible for communication between cells and the basement membrane. The sites for interaction of laminins with other basement membrane molecules such as nidogens (in domain III of the γ1 chain)[109] and agrin (in the laminin "long arm" consisting of α, β and γ chains)[110] are shown.

For example, the laminin γ1 subunit is the most ubiquitously expressed laminin chain, found in most of the known heterotrimers and expressed both embryonically and extra-embryonically.[47,48] Consequently, targeted deletion of the laminin γ1 chain in mice results in embryonic lethality due to an arrest in blastocyst differentiation.[47,48] On the other hand, deletion or mutation of the laminin α2 chain, which is expressed in skeletal and cardiac muscle, peripheral nerve, capillaries, placenta and the brain, results in postnatal lethal muscular dystrophy and peripheral nerve defects in mice and humans. Additionally, CNS defects are present in humans with mutations in the α2 chain.[30,49,50] Similarly, genetic disruptions of the laminin α5 chain lead only to disruptions in the muscle, kidney and various epithelial glands.[51-53] These data indicate that laminins may share many functional properties, however, the contribution of individual chains is specific and frequently non-redundant.

LAMININ RECEPTORS: LINKING THE EXTRACELLULAR MATRIX TO THE CELL

The interaction of receptors for ECM molecules with the ECM is crucial for the maintenance of cellular phenotype and tissue integrity. Perturbations of the interaction between receptors for ECM and the ECM in mice and humans lead to pathologies such as muscular dystrophies, brain and ocular dystrophies, and blistering diseases of the skin such as epidermolysis bullosa.[54-57]

The major receptors for laminins can be broadly classified as integrins and non-integrins. Integrins [Figure 6] are a large family of αβ heterodimers that combine to form 24 different αβ heterodimeric receptors, each with their own ligand. The αβ heterodimer which is engaged by the cell to interact with the matrix depends both on the composition of the ECM and the cell type itself. For instance, integrin α7β1 binds to laminins-211 and 221 (via the laminin α2 chain); integrins α3β1, α6β1 and α6β4 bind to laminin-332 (via the laminin α3 chain) and integrin α6β4 binds to laminins-511, 521 (via the laminin α5 chain).[58,59] Furthermore, the specific integrin αβ heterodimers bridging the ECM and the cell are also tasked with specification of the downstream signaling effectors.[59]

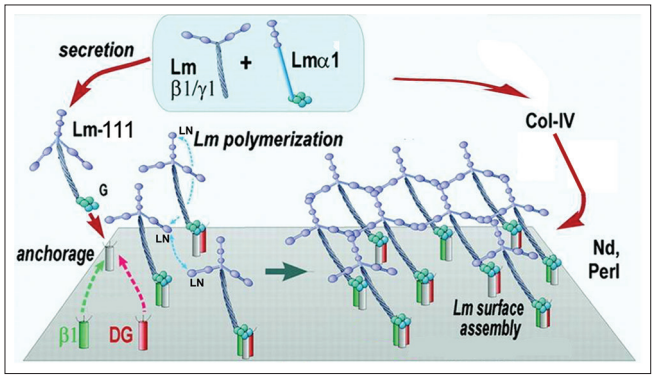

Figure 6. Integrins influence multiple functions by anchoring cells to the extracellular matrix (ECM). Integrins and dystroglycan in the extracellular space act as a bridge between the laminin-containing ECM and the cytoskeleton of the cell in the cytosol including dystrophin, resulting in changes in cell polarity, shape and migration. Integrins, after binding to the ECM, also act as signaling platforms by recruiting adaptors and signaling enzymes that control differentiation, shape and migration.

The second class of laminin receptors, non-integrin receptors such as dystroglycan, plays a critical function in muscle, the central and peripheral nervous systems, the blood-brain barrier and kidney.[60-62] Dystroglycan forms a part of the dystrophin-glycoprotein complex which interacts with other cytoskeleton molecules [Figure 6].

After translation, the dystroglycan gene product is cleaved, resulting in the production of α-dystroglycan (a peripheral membrane protein at the external surface of the membrane) and β-dystroglycan (a transmembrane protein) [Figure 6]. α-dystroglycan interacts with the ECM via high affinity interactions with the laminin α1 and α2 LG 4-5 domains. β-dystroglycan interacts with the cytoskeleton via molecules including dystrophin [Figure 6]. Although these interactions have been most extensively studied in skeletal muscle, the dystroglycan-laminin interaction is of high significance for maintenance of adhesion in multiple tissues.

There are additional non-integrin laminin receptors. These include collagen XVII (formerly known as BP180 or BPAG2), a transmembrane protein and a critical component of hemi-desmosomes associated with keratinocyte adhesion.[63] Collagen XVII is also expressed in the CNS and the retina, where it may be important in synapse formation.[64] A fragment of another collagen, collagen XXV, is associated with amyloid plaques in Alzheimer's disease.[65] Other receptors associated with laminins include four types of cell-surface syndecans[66,67] and the Lutheran blood group glycoprotein, BCAM (a transmembrane protein found on erythrocyte, muscle and epithelial cells), which in addition to other functions, acts as a receptor for the α5 subunit of laminin.[68,69]

The multidomain structure of laminins, as well as the presence of different isoforms of laminin in each tissue, leads to variability in the affinity of expressed laminins towards different receptors, thereby contributing to the diverse array of laminin-mediated regulation which affects cellular functions [Figure 6]. Two retinal cell types regulated by laminins are retinal ganglion cells and Müller glial cells.

RETINAL GANGLION CELLS: THE OUTPUT NEURONS OF THE RETINA

As the final common pathway from the retina to the brain, retinal ganglion cells (RGCs) are critical conduits

for normal vision. Two aspects of RGC organization are of particular importance: First is the spatial distribution of RGCs over the surface of the retina; second is the lamination pattern of RGC dendrites in the inner plexiform layer. Various RGC subtypes exist, each with precise non-random distributions over the surface of the retina and unique connectivity in the brain. This arrangement assures that the entire visual world is sampled by diverse yet overlapping subclasses of RGC.

The physiological output of RGCs is produced upon synapsing with a particular array of retinal interneurons. This is accomplished by the production of a stereotyped pattern of dendritic development and synaptic refinement in the IPL. For example, different types of RGCs have defined patterns of dendritic arborization in the IPL in three dimensions. The first is relative to the branching from the cell body; the second is relative to the surface topography of the retina (dendritic area) and the third is relative to the depth of the IPL (dendritic lamination). Together, these spatial properties of the dendritic arbors of RGCs define the physiologic properties of the RGC that contribute to visual processing.

Thus, a thorough understanding of retinal development requires understanding how RGCs are generated; how RGC numbers are regulated; and the mechanisms of RGC dendritic development. Both intrinsic and extrinsic factors regulate this process. The number of RGCs is governed by intrinsic factors including transcriptional factors,[70,71] as well as extrinsic factors including molecules that regulate cell death[72] and neurotrophic molecules.[73] In addition, adhesion[74] and ECM molecules[75,76] contribute to the development of GCs by acting as survival factors and promoting dendritic development.

MÜLLER CELLS: THE PRINCIPAL GLIAL CELLS OF THE RETINA

Two glial cells are present in the retina: Müller cells (MCs) and astrocytes. MCs are intrinsic to the retina and share a common progenitor with neural cells of the retina, whereas astrocytes are extrinsic to the retina and migrate into the retina via the optic nerve. During their final differentiation, retinal progenitor cells express specialized glial genes and take on glial homeostatic functions.[77] This has led to the hypothesis that, MCs are late progenitor cells. Indeed, in non-mammalian retina MCs can be induced to regenerate neurons of the retina under experimental conditions.[78]

MCs span the entire thickness of the neural retina and contact and ensheathe all neuronal cell bodies and processes [Figure 7]. Their structure not only provides stability to the retina, but their morphological proximity to neurons also promotes neuronal survival. In addition,

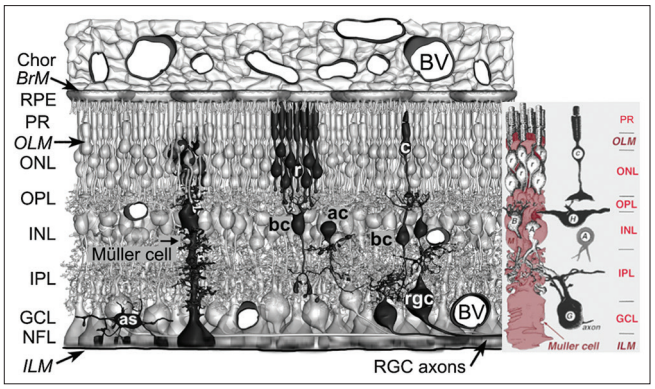

Figure 7. Müller cells are closely associated with, and interact with, all retinal neurons. The interactions among Müller cells and retinal neurons are vital to retinal homeostasis. Müller cells span nearly the entire thickness of the retina, from ILM at NFL to OLM at the junction of the inner and outer segments of PR. Neuronal somata and processes are ensheathed by the processes of Müller cells (one Müller cell is shaded pink at right). Chor, choroid; BrM, Bruch's membrane; RPE, retinal pigmented epithelium; PR, photoreceptor outer segments; OLM, outer limiting membrane; ONL, outer nuclear layer; OPL, outer plexiform layer; INL, inner nuclear layer; IPL, inner plexiform layer; GCL, ganglion cell layer; NFL, nerve fiber layer; ILM, inner limiting membrane; BV, blood vessel; r, R, rod photoreceptor cell; c, cone photoreceptor cell; H, horizontal cell; bc, B, bipolar cell; ac, A, amacrine cell; rgc, G, retinal ganglion cell; M, Müller cell; as, astrocyte. Left: Modified from Bringmann et al.[111] Subject to creative commons attribution license. Right: Modified from Reichenbach et al;[79] Reichenbach et al[80] copyright license obtained.

this proximity to neurons may contribute to retinal information processing.[79-82]

MCs are capable of performing multiple functions in part due to their highly polarized morphology. Among their homeostatic functions, MCs contribute to extracellular ion homeostasis[83] and neurotransmitter recycling.[84] In addition, MCs promote neuronal survival by the release of neurotrophic substances.[2] In addition, at their basal end-foot MCs make contact with the ILM using a variety of cell-matrix receptors[85] and at their apical surface, MCs make adhesion complexes with each other and photoreceptors forming a band of tight junctions at the outer limiting membrane.[86] Despite its name, the outer limiting membrane is not a membrane, but rather contains components of both adherens and tight junctions.[87]

In retinal injuries and diseases such as retinal detachment, MCs undergo reactive gliosis and manifest changes in morphology, cytoskeletal structure and the subcellular compartmentalization of ion or water channels.[88,89] Reactive gliosis is characterized by alterations in biochemical and physiological functions, in addition to hypertrophy and proliferation of MCs. These changes are similar

to those seen in proliferative vitreoretinopathy[90] and transient ischemia.[91]

ATTACHMENT TO RETINAL BASEMENT MEMBRANES IS IMPORTANT FOR RETINAL ARCHITECTURE AND HOMEOSTASIS

The retina is delimited by two basement membranes: Bruch's membrane at the sclerad (outer, distal) side, and the inner limiting membrane (ILM) at the vitread (inner, proximal) side. These two membranes act as boundaries for the neural retina.

Bruch's membrane is a five-layered extracellular matrix structure located at the interface of the metabolically active retinal pigmented epithelium (RPE) and the source of nutrition for the RPE, the choriocapillaris. Bruch's membrane not only provides physical support for the RPE, it also regulates RPE differentiation and acts as a barrier that prevents choroidal neovascularization, a process in which choroidal vascular cells inappropriately invade the retina.[92,93] Alterations in the composition or organization of Bruch's membrane severely compromises the normal function of RPE cells, and this disruption results in retinal pathologies including age-related macular degeneration, pseudoxanthoma elasticum and Sorsby's fundus dystrophy.[94]

The inner limiting membrane (ILM) lies on the vitread side of the retina which is the opposite side of the retina from Bruch's membrane [Figure 7]. The ILM is not only the structural interface between the retina and the vitreous, it also provides support for the neural retina, and is responsible for organizing and maintaining the laminated structure of the retina and guiding astrocyte migration during vascular development.[95] Disruptions or changes in the ILM are associated with retinal dysplasia as well as retinal pathologies such as diabetic retinopathy, proliferative vitreoretinopathy and retinopathy of prematurity.[19,20]

In the developing retina, RPCs adhere to the ILM via interactions between RPC basal end-feet and the ILM. Laminins are important constituents of the ILM that are likely involved in this adhesion: Major laminin subunit constituents of the ILM are α1, α5, β2, and γ1, whereas minor laminin subunit constituents of the ILM are α3, β1, γ2, and γ3.[96]

In addition to adhesion, laminins and laminin-mediated signaling contribute to dendrite-axonal specification and neuronal development *in vitro* and *in vivo*,[97-99] suggesting that laminins play an important role in retinal development and organization. During retinal development, RPCs undergo tightly regulated proliferation and differentiation; these processes are regulated by, *inter alia*, symmetrical versus asymmetrical division. Further, organization of the complex retinal structure depends on both appropriate positioning and spacing of the cells in the retina, and proper dendritic-axonal development required for the generation of functional circuitry in the retina. All of these developmental processes are influenced by laminins.

Loss of laminin-mediated signaling in the retina results in retinal dysplasia and may lead to visual impairment.[100-102] Upon the loss of laminins, these pathologies result from disturbing the apical-basal polarity of MCs as well as the subcellular compartmentalization in MC.[91,102] In addition to the contribution of laminins to MC polarity, we hypothesize that β2 and γ3 laminin chains establish apical-basal polarity in RPCs much as they do in MCs.

Adhesion to the ILM is likely important for establishing apical-basal polarity in the RPCs and required for maintaining correct timing between proliferation and neurogenesis. The ILM is also critical for MCs, the terminal progeny of RPCs, for subcellular compartmentalization of transporters, ion channels, and perhaps signaling cascade mechanisms. Finally, laminins likely provide cues to regulate RGC spacing, dendritic arborization and axonal guidance.

SUMMARY

Adhesion to the ILM is critical in establishing the apical-basal polarity of RPCs (required for maintaining the correct timing between proliferation and neurogenesis in the retina), proper differentiation of MCs (required for compartmentalization of signaling domains to different regions of the cell) and providing cues that regulate RGC development (spacing, dendritic arborization and axonal guidance). Continued elucidation of these interactions will further advance our knowledge of retinal development and the organization of the retina's complex laminar architecture. Furthermore, this knowledge will likely have applications for regenerative studies on retinal tissue.

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Conflicts of Interest

There are no conflicts of interest.

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