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Regulation of Schwann Cell Function by the Extracellular Matrix

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ABSTRACT
Laminins and collagens are extracellular matrix proteins that play essential roles in peripheral nervous system development. Laminin signals regulate Schwann cell proliferation and survival as well as actin cytoskeleton dynamics, which are essential steps for radial sorting and myelination of peripheral axons by Schwann cells. Collagen and their receptors promote Schwann cell adhesion, spreading, and myelination as well as neurite outgrowth. In this article, we will review the recent advances in the studies of laminin and collagen function in Schwann cell development.

INTRODUCTION

Extracellular matrix (ECM) proteins provide the substrate on which many types of cells reside. In addition to having a structural importance, these proteins also influence cell behavior through receptor interactions. They trigger many different intracellular signals to control cellular features such as proliferation, survival, differentiation, polarization, and morphogenesis (Aszodi et al., 2006). One such example is Schwann cell development. Several studies have demonstrated that Schwann cell interaction with ECM molecules is required for proper ensheathment and myelination of axons (reviewed in Yu et al., 2007). Typical protein components of the ECM include collagens, laminin heterotrimers, nidogen or entactin, and proteoglycans (Aszodi et al., 2006). This review addresses the role of laminin and collagens in development and function of the peripheral nervous system (PNS).

REGULATION OF SCHWANN CELL FUNCTION BY LAMININS AND LAMININ RECEPTORS

Laminins in the Peripheral Nervous System (PNS)

Laminins are heterotrimeric proteins that are critical components of the ECM. At present, five α chains, four β chains, and three γ chains have been identified, and 15 isoforms have been observed (Colognato and Yurchenco, 2000; Grimpe et al., 2002; Yin et al., 2003). Laminins play three overlapping roles in mammals (Miner and Yurchenco, 2004): (1) they give structure to the basement membrane (Tabernero et al., 1998; Timpl, 1996; Yurchenco et al., 2004); (2) provide attachment sites for cells via cell surface proteins [e.g., dystroglycan (DG)] (Henry and Campbell, 1996); and (3) act as ligands for receptors on cells (e.g., integrins), initiating signals that influence cell behavior and survival (Schwartz, 2001). Laminins are present in many neural tissues including the central nervous system (Grimpe et al., 2002; Hagg et al., 1989; Indyk et al., 2003), the neuromuscular junction (Noakes et al., 1995; Patton et al., 1997, 1998, 2001; Sanes and Lichtman, 2001), and peripheral nerves (Doyu et al., 1993).

Laminin 2 (α2,β1,γ1), laminin 8 (α4,β1,γ1), and laminin 10 (α5,β1,γ1) are expressed in the PNS (Feltri and Wrabetz, 2005) and play critical roles in the myelination of axons by Schwann cells [reviewed in (Yu et al., 2007)]. Studies using Schwann cell/neuronal co-cultures showed that laminin deposition is required for myelination *in vitro* (Fernandez-Valle et al., 1993, 1994; Podratz et al., 2001). *In vivo* evidence of this requirement was obtained when a mutation in the *laminin* α2 gene was found to cause a peripheral neuropathy in both humans (Helbling-Leclerc et al., 1995) and mice (Shorer et al., 1995; Sunada et al., 1995; Xu et al., 1994). Laminin α2 mutant mice, also known as dystrophic (dy and dy2J) mice, have hypomyelinated axons in which the naked axon bundles lack ensheathment and myelination, most obviously at the proximal region of the peripheral nerve (Bradley and Jenkison, 1973; Stirling, 1975). The endoneurium basal lamina is disrupted, and nerve conduction velocity also is reduced in the nerves of these mutant mice (Rasminsky et al., 1978). In the peripheral nerves of the laminin α2 mutant mice, both laminins α4 and α1 are upregulated in the endoneurium, and the phenotype is mild (Patton et al., 1997; Previtali et al., 2003).

Mouse Schwann cells lacking the laminin γ1 subunit lose all laminin expression, and mice carrying this

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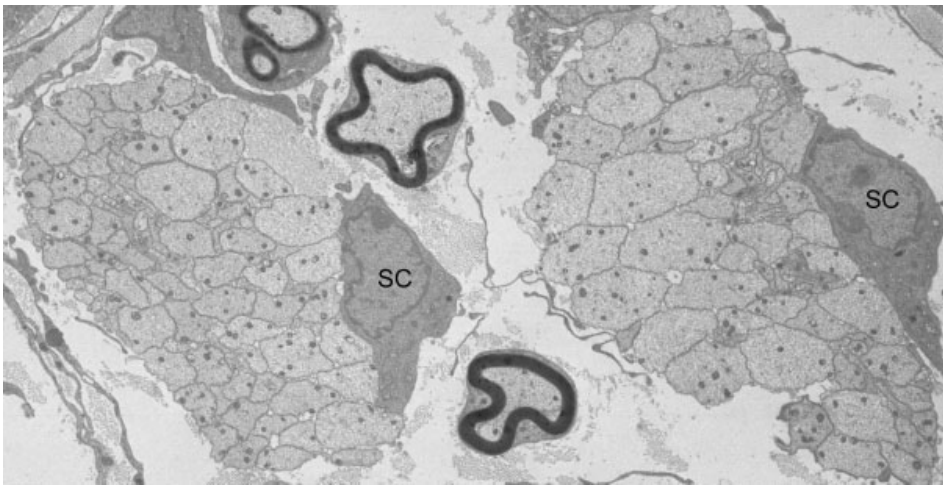

Fig. 1. Peripheral nerves lacking laminin γ1 have impaired radial sorting of axons. An electron micrograph of P28 sciatic nerves lacking laminin γ1 shows that mutant Schwann cells (SC) are unable to extend cytoplasmic processes to interdigitalize axons and leave axons unsorted in axonal bundles.

mutation show a severe phenotype (Yu et al., 2005, 2007). These mice exhibit tremor, muscle weakness, and hind limb paralysis, preventing most of them from reaching adulthood. The peripheral nerves of these mutants are much smaller than controls, and nerve conduction velocity is dramatically decreased. Under light or electron microscope, the nerve fibers are severely hypomyelinated, and most axons are naked and tightly compacted. Their Schwann cells do not extend processes between axons, and they lack a continuous basal lamina (Chen and Strickland, 2003; Yu et al., 2005). Proliferation of these mutant Schwann cells is also severely impaired, resulting in a dramatic decrease in Schwann cell number (Yu et al., 2005).

During development of peripheral nerves, neural crest precursor cells differentiate to become immature Schwann cells. When immature Schwann cells enter the myelinating lineage, they proliferate vigorously and begin differentiating into promyelinating cells. Individual cells then extend their cytoplasmic processes into bundles of axons, progressively separate them into even smaller bundles, and finally establish a 1:1 relationship with each larger diameter axon. This process is known as radial sorting (Martin and Webster, 1973; Webster et al., 1973). Therefore, the laminin mutant mice can be classified as having severe impairment of axonal radial sorting (see Fig. 1). Schwann cells from these laminin γ1 mutant mice also fail to downregulate Oct-6 and upregulate Krox-20, two transcription factors critical for Schwann cell differentiation and are arrested at the premyelinating stage. Postnatally, laminin γ1-null Schwann cells exhibit increased apoptosis (Yu et al., 2005).

Laminin α4 mutant mice show a similar hypomyelination phenotype in their peripheral nerves (Yang et al., 2005). However, in contrast to α2 mutants, which show more severe hypomyelination in the root compared with the distal part of peripheral nerve, the root is fairly normal and is less affected than the distal nerve. Additionally, the α4 laminin mutant nerve contains multiple unsorted axons that are wrapped by a myelin sheath and form polyaxonal myelinated bundles, a phenomenon rarely observed in laminin α2 or γ1 mutant mice (Yang et al., 2005). These differences may be due to compensation from different laminin isoforms, as both root and distal nerves are equally hypomyelinated in α2/α4 double mutant mice (Yang et al., 2005), which are similar to laminin γ1 mutant mice (Yu et al., 2005). These observations suggest that different laminin isoforms may play distinct roles in different parts of the PNS during development.

Laminin Receptors in the PNS

Schwann cells express several potential laminin receptors, including α6β1 and α6β4 integrins as well as DG (Previtali et al., 2003). The signaling effects of laminins are thought to be mediated primarily through β1 integrin. Cell culture and *in vivo* studies have shown that interfering with the function of β1 integrin leads to inhibition of myelination (Fernandez-Valle et al., 1994; Feltri et al., 2002; Podratz et al., 2001; Relvas et al., 2001). *In vitro* work demonstrated that β1 integrin forms a multimolecular complex with focal adhesion kinase (FAK), paxillin (an adaptor protein), and merlin/schwannomin when Schwann cells begin to form the basal lamina and differentiate (Chen et al., 2000; Fernandez-Valle et al., 2002; Obremski et al., 1998). Schwann cell-specific disruption of β1 integrin also causes a dysmyelinating peripheral neuropathy with impaired radial sorting of axons similar to the laminin mutant mice described earlier (Feltri et al., 2002), indicating that laminin function in axonal radial sorting is primarily mediated through β1 integrin. However, although disruption of laminins in Schwann cells causes decreased proliferation and increased cell death, disruption of β1 integrin causes variable effects on proliferation and survival depending on the mouse strain background (Feltri et al., 2002; Berti et al., manuscript in preparation). This suggests that laminins can employ other receptors to regulate Schwann cell number.

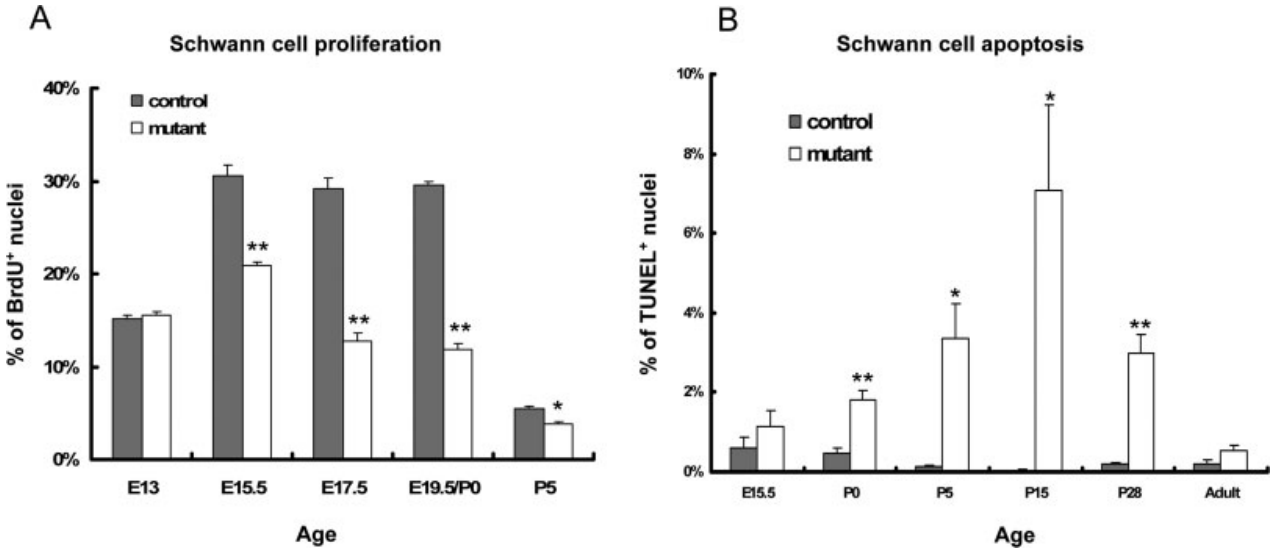

Fig. 2. Schwann cells lacking laminin γ1 show reduced proliferation and increased apoptosis. (**A**) Plot of the percentage of BrdU-positive nuclei at various developmental stages. The ratio of BrdU-incorporated nuclei are significantly reduced in mutant nerves at E15.5, E17.5, and E19.5/P0 ($n = 6$ per genotype per day, $^*P < 0.05$, $^{**}P < 0.001$). (**B**) Plot of the percentage of TUNEL-positive nuclei at various developmental stages. The ratio of TUNEL-positive nuclei are significantly higher in mutant than in controls at P0, P5, P15, and P28 ($n = 6$ per genotype per day, $^*P < 0.05$, $^{**}P < 0.001$).

DG also functions as a laminin receptor (Previtali et al., 2001, 2003). In contrast to β1 integrin-deficient Schwann cells, Schwann cell-specific ablation of DG does not severely affect radial sorting of axons. However, the myelin sheaths of DG-null Schwann cells are abnormally folded, and sodium channels are severely reduced at the nodes of Ranvier (Saito et al., 2003). These data suggest that DG functions at a later stage of myelination in the maintenance of the myelin sheath and plays a special role in the formation of the nodes of Ranvier.

Laminin Signaling in Schwann Cell Proliferation

During late embryonic to perinatal stages (E15 to P0 in mice), immature Schwann cells proliferate vigorously to rearrange, sort, and ensheath axons (Stewart et al., 1993) In laminin γ1 mutant and dy2J/α4 double mutant mice, Schwann cell proliferation is dramatically decreased during this developmental stage (Yang et al., 2005; Yu et al., 2005) (Fig. 2A). In contrast to laminin mutants, proliferation is less affected in β1 integrin-null Schwann cells (Berti et al., manuscript in preparation). Impaired radial sorting of axons in β1 integrin-null Schwann cells may be caused by a mechanism other than reduced Schwann cell proliferation. Radial sorting of axons requires Schwann cell proliferation and process extension, which are regulated through two distinct pathways: proliferation is mediated through β1 neregulin (NRG1)/ErbB receptor, and process extension is dependent on β1 integrin signaling (Benninger et al., 2007; Nodari et al., 2007). Exposure of cultured Schwann cells to NRG1 induces a strong activation of Cdc42 (Benninger et al., 2007). NRG1 also induces the association of FAK with the ErbB2/ErbB3 receptor (Vartanian et al., 2000). Loss of Cdc42 or FAK in Schwann cells results in decreased Schwann cell proliferation but does not affect process extension (Grove et al., 2007), indicating that these two molecules act downstream of NRG1/ErbB to control Schwann cell proliferation.

Laminins may influence Schwann cell proliferation through regulation of the NRG1/ErbB pathway. Axons are a major source of Schwann cell mitogens (Morrissey et al., 1995; Wood and Bunge, 1975). Neuregulin is a major axon-derived Schwann cell mitogen that can interact with and stimulate the phosphorylation of receptor tyrosine kinases ErbB2 and ErbB3 on Schwann cells (Morrissey et al., 1995). In laminin γ1 mutant nerves, the levels of total ErbB2 and ErbB3 are similar to that of the control nerves, but the phosphorylation of these two receptors is dramatically decreased (Yu et al., 2005). Impaired radial sorting of axons in laminin γ1-deficient Schwann cells can interfere with the interactions between Schwann cells and axons and prevent Schwann cell exposure to axon-derived mitogens, which all leads to reduced Schwann cell proliferation. Additionally, laminins in Schwann cell basal lamina could act as a scaffold to attract and bind growth factors and influence Schwann cell proliferation. The lack of laminin expression in Schwann cells may also directly contribute to decreased proliferation because laminins have been observed as mild Schwann cell mitogens *in vitro* (Baron-Van Evercooren et al., 1986; Macica et al., 2006; McGarvey et al., 1984; Yang et al., 2005).

Laminin Signaling in Schwann Cell Survival

At E12-13 in mice, the survival of Schwann cell precursors depends on axon-derived NRG1/Erb B pathway

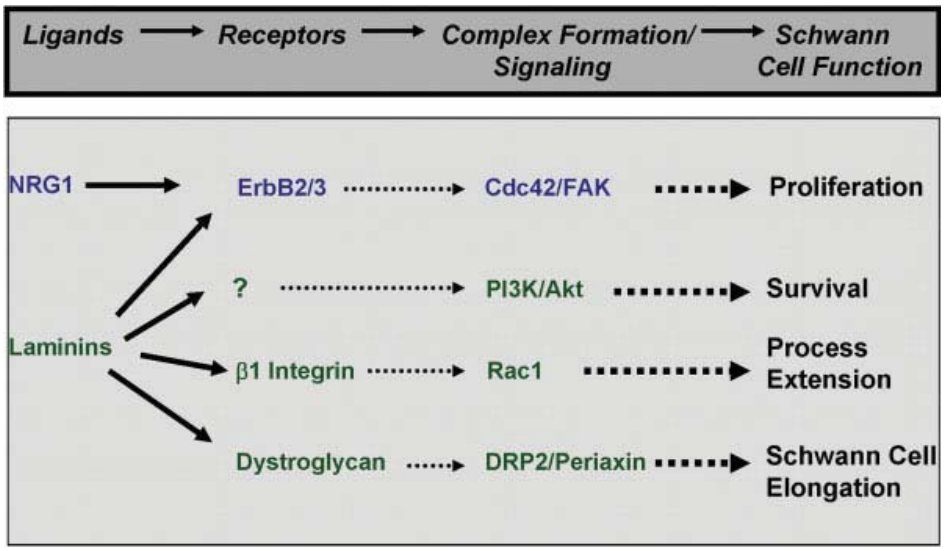

Fig. 3. Model for the role of laminins in Schwann cell development.

(Dong et al., 1995; Riethmacher et al., 1997). After this stage, Schwann cells may establish an autocrine survival loop (Jessen, 2005). In laminin γ1 mutant mice, disruption of laminins in Schwann cells occurs between E13.5 and E14.5, yet there is no significant cell death at this time. Increased Schwann cell apoptosis in these mice occurs only during postnatal stages (from P0 to P28) (Fig. 2B). Apoptosis in early postnatal stage (prior to P6) may be partly attributable to a lack of proper Schwann cell/axon relationship in laminin γ1 mutant nerves, as axon-derived survival signals are important in early developmental stages (Grinspan et al., 1996). However, apoptosis in the later postnatal period (P15–28) indicates that laminin may be required for long-term survival of Schwann cells as this was also suggested by Meier et al. (1999).

PI3-kinase/Akt and transforming growth factor β (TGFβ) pathways are important in regulating Schwann cell apoptosis (Maurel and Salzer, 2000; Parkinson et al., 2001). PI3-kinase activation in laminin-deficient Schwann cells is severely reduced (Yu et al., 2005), which may be a consequence of the impaired differentiation (Taveggia et al., 2005). However, disruption of laminins may also contribute to the reduction of this survival pathway, which results in apoptosis based on the following observations. At P0/P1, both control and laminin-deficient Schwann cells are at similar differentiating stages (premyelinating stage), but the mutant Schwann cells have reduced PI3-kinase activity and increased apoptosis (Yu et al., 2005). Additionally, mutant Schwann cells infused with laminin peptides show partial restoration of PI3-kinase activity and reduced apoptosis (Yu et al., 2005).

Laminin-deficient Schwann cells have reduced Krox-20 expression (Yu et al., 2005). As Krox-20 can suppress c-Jun-mediated TGFβ-induced Schwann cell apoptosis (Parkinson et al., 2004), increased Schwann cell apoptosis may result from the failure of Krox-20 to inhibit c-Jun activation. However, phosphorylation of c-Jun at postnatal stages between control and laminin mutant nerves was similar (WM Yu, ZL Chen, S Strickland, unpublished), suggesting that the TGFβ pathway does not play a major role in increased apoptosis of laminin-deficient Schwann cells.

Laminin Signaling in Schwann Cell Morphogenesis

Schwann cells lacking laminins do not extend processes that interdigitate between axonal bundles, a phenotype similar to Schwann cells lacking β1 integrin (Feltri et al., 2002; Yu et al., 2005). In β1 integrin-deficient Schwann cells, Rac1 activity is decreased (Nodari et al., 2007). Ablating Rac1 in Schwann cells impairs axonal sorting as well as myelination. Additionally, expressing constitutively active Rac1 in β1 integrin-null nerves partially rescues the sorting phenotype. These observations indicate that laminins regulate Schwann cell process extension through activation of β1 integrin/Rac1.

During PNS development, L-periaxin-deficient mice show focal thickenings, infoldings of internodal myelin, and late-onset demyelination, which is similar to DG-null mice (Gillespie et al., 2000). L-periaxin is required for the formation of the DG-dystrophin-related protein-2 (DG-DRP2) complex and is involved in the link between the ECM and the Schwann cell cytoskeleton (Sherman et al., 2001). Schwann cells lacking L-periaxin exhibit disruption of the Cajal bands, a cellular structure with a nutritive function, resulting in reduced Schwann cell length during nerve growth (Court et al., 2004). It is known that dystrophic mice also have reduced internodal length (Jaros and Jenkison, 1983). These results indicate that laminin may coordinate Schwann cell elongation at later stages of myelination through interaction with the DG-DRP2-periaxin complex. The interactions discussed earlier are summarized in Figure 3.

PERIPHERAL NERVE COLLAGENS

Collagens are another essential component of the Schwann cell ECM. Schwann cells express three general classes of collagen molecules: fibril forming collagens (Types I, III, and V), basement membrane collagens (Type IV), and hybrid molecules with collagen domains that have restricted localizations and specific functions (e.g. gliomedin). Collagens are structural proteins that are required for normal ECM assembly and organization (Chernousov et al., 1998). Schwann cells also express several integrin and nonintegrin collagen receptors (Jaakkola et al., 1993; Milner et al., 1997; Stewart et al., 1997) and adhere to and migrate on collagen substrates (Chernousov et al., 2001; Erdman et al., 2002). Thus, collagens also have the capacity to regulate Schwann cell function through regulation of intracellular signaling and may be required for myelination.

Structure of Peripheral Nerve Collagens

The distinguishing feature of collagen molecules is a rod-like helical domain formed by association of three polypeptides that contain repeating proline-rich sequences in which every third residue is glycine (Prockop and Kivirikko, 1995). Many collagen molecules undergo ascorbic acid-dependent posttranslational hydroxylation of proline and lysine side chains that stabilize the collagen trimer structure or produce covalent crosslinks among collagen trimers.

Fibril forming collagens

Endoneurial collagen fibrils first appear at around E15 in the mouse sciatic nerve (Osawa and Ide, 1986). The major fibril forming collagens are Type I and Type III collagens. As there are no fibroblasts in the endoneurium at this time, these collagen fibrils appear to be synthesized by the immature Schwann cells that are associated with the embryonic axons. This is consistent with studies of cultured cells, which show that immature Schwann cells are active producers of collagens (Bunge et al., 1980; Chernousov et al., 1998, 2000). The collagen fibrils in the endoneurium, with a diameter of ~250 Å, are thinner than collagen fibrils in the epineurium and are closely associated with the external surfaces of basement membrane matrix sheets that surround individual Schwann cells and their associated axons (Osawa and Ide, 1986).

Fibril-forming collagen polypeptides (Types I, III, and V) contain a large central collagen domain of ~1,000 amino acids flanked by noncollagen N-terminal and C-terminal domains. Most collagen molecules are heterotrimers consisting of two or three different α chains (e.g. $\alpha1(I)_2/\alpha2(I)_1$ for Type-I collagen and $\alpha1(V)/\alpha2(V)/\alpha3(V)$ for Schwann cell Type-V collagen). The C-terminal noncollagen domains initiate and guide assembly of the collagen triple helix from the three collagen polypeptides by noncovalent association mediated by a specific recognition domain in each C-terminal domain (Khoshnoodi et al., 2006). After trimer assembly is completed the C-terminal and N-terminal noncollagen domains are removed from Type-I and Type-III collagen trimers by specific endoproteases and are not part of the mature collagen molecules. In contrast, the noncollagen N-terminal domains of Type-V collagen chains are retained in the mature trimer and, as described below, have specific functions with respect to Schwann cells. Another difference between Types I/III and Type-V collagen is their localization in peripheral nerve tissue. The former are present exclusively in small diameter collagen fibrils associated with the external face of the Schwann cell basal laminae (Osawa and Ide, 1986). Type-V collagen colocalizes with Types I/III collagen in these fibrils and is also present in basal laminae surrounding myelinating Schwann cells (Chernousov et al., 2006).

Basement membrane collagens

Type-IV collagen is a member of the group of network-forming collagens and is an ubiquitous component of basement membranes, sheets of matrix that underlie epithelial cells and that surround Schwann cells and their associated axons. There are six Type-IV collagen genes, which show tissue-specific patterns of expression and specific patterns of heterotrimer assembly. The most abundant Type-IV collagen molecules in peripheral nerves are heterotrimers with the composition $\alpha1(IV)_2/\alpha2(IV)_1$ (Miner and Sanes, 1994). As the case for fibril-forming collagens, trimer assembly is directed by the noncollagen C-terminal domains but, in contrast to fibril forming collagens, the noncollagen C-terminal domains of the Type-IV collagen molecules are not removed after trimer assembly (Khoshnoodi et al., 2006). Type-IV collagen molecules form extended, flexible networks produced by tail-to-tail association of the noncollagen C-terminal domains and oligomerization of noncollagen N-terminal domains (NTD). The collagen domain of Type-IV collagen is interrupted by ~20 short noncollagen sequences. These loosen the triple helical structure and contribute to the flexibility of the collagen Type-IV network.

Collagen Function in the PNS

ECM assembly

Collagen trimers are essential for assembly of the Schwann cell ECM. This has been most clearly demonstrated using primary cultures of Schwann cells or Schwann cells co-cultured with DRG neurons. Cultures incubated in medium lacking ascorbic acid, an essential co-factor for collagen posttranslational modification, fail to secrete native collagen trimers and do not assemble fibrillar or basal lamina ECM (Chernousov et al., 1998; Moya et al., 1980), despite the fact that noncollagen ECM proteins including laminin and fibronectin are synthesized and secreted by the Schwann cells. Addition of

ascorbic acid results within a few hours in the deposition of ECM on the Schwann cell plasma membrane. This dependence of Schwann cell ECM assembly on ascorbic acid has been a useful tool to demonstrate the essential role of ECM contact on Schwann cell differentiation and myelin assembly (Carey and Todd, 1987; Carey et al., 1986; Eldridge et al., 1987, 1989).

Fibril forming collagens

The function of fibril forming collagens in peripheral nerves has not been studied in detail. In skin and tendon, they are known to be important contributors to the mechanical strength and flexibility of these tissues. Given the mechanical forces peripheral nerves must withstand, for example during cycles of muscle contraction and extension, fibril forming collagens are likely to carry out similar functions in nerves. This idea is supported by reports of peripheral neuropathies associated with the Ehlers-Danlos group of inherited connective tissue diseases (Galan and Kousseff, 1995; Muellbacher et al., 1992), although the molecular etiology of the neuropathies has not been investigated.

Type-V collagen

Type-V collagen is perhaps the most intensely studied Schwann cell collagen. Type-V collagen is often considered a "minor" fibril-forming collagen, although it is relatively abundant in peripheral nerve tissue, where it is expressed by Schwann cells. In tissues such as skin and tendon Type-V collagen molecules associate with Type-I collagen molecules and regulate the diameter of the collagen fibrils (Wenstrup et al., 2004). Thus, the abundance of Type-V collagen in peripheral nerve might explain the relatively small diameter of endoneurial collagen fibrils.

The α3(V) collagen chain was isolated initially from rat Schwann cell conditioned medium as a 200 kDa polypeptide, called p200, that binds with high affinity to heparan sulfate chains on the membrane-anchored proteoglycan syndecan-3 (Chernousov et al., 1999). When immobilized on culture dishes the purified α3(V) chain promotes Schwann cell adhesion and spreading as well as outgrowth of neurites from DRG neurons (Chernousov et al., 1996, 2001). Subsequent biochemical and molecular studies showed p200 to be a new member of the collagen Type-V gene family (Chernousov et al., 2000). The rat gene product was initially called α4 Type-V collagen based on apparent differences between the full length rat sequence and partial peptide sequence data from the human α3(V) chain. The same gene product was also cloned from mouse and human, however, and now appears to be α3(V) (Imamura et al., 2000).

Type-V collagen molecules synthesized by Schwann cells are trimers of α1(V)/α2(V)/α3(V) chains (Chernousov et al., 2000). In peripheral nerve tissue Type-V collagen is present in basal laminae of myelinated Schwann cell-axon units and in the surrounding ECM (Chernousov et al., 2006). In mature myelinated Schwann cell-axon units Type-V collagen localization is concentrated in the perinodal ECM (Melendez-Vasquez et al., 2005).

Membrane heparan sulfate proteoglycans as collagen receptors

Schwann cell adhesion activity of Type-V collagen is located primarily in the noncollagenous NTD of the α3(V) collagen chain (Erdman et al., 2002). Schwann cell adhesion to the α3(V)-NTD is mediated by binding to heparin sulfate (HS) molecules on the Schwann cell surface. The main HS-binding site in the NTD is a highly basic sequence that contains four nearly tandem repeats of the consensus heparin binding sequence BBXB (B = Arg or Lys). Model peptide studies have shown that multiple repeats of this consensus sequence substantially increases heparin-binding affinity (Verrecchio et al., 2000), which appears to explain the very tight binding of the α3(V)-NTD to HS.

These findings strongly suggest that the main Type-V collagen receptors on Schwann cells are membrane-anchored HS-proteoglycans, which consist of a core protein to which HS chains, long, unbranched highly sulfated carbohydrate polymers are covalently attached (Carey, 1997). Schwann cells express two main cell surface HS-proteoglycans: syndecan-3 (Carey et al., 1992) and glypican-1 (Carey et al., 1993), with transmembrane and glycosylphosphatidylinositol (GPI)-anchored core proteins, respectively.

Several lines of evidence point to glypican-1 as the main Schwann receptor for α3(V) collagen. Mutagenesis of the heparin-binding consensus sequence in the α3(V)-NTD abrogates Schwann cell adhesion to NTD or binding of soluble NTD to the Schwann cell plasma membrane (Erdman et al., 2002). siRNA-mediated suppression of Schwann cell glypican-1 expression, but not syndecan-3 expression, essentially abolishes Schwann cell adhesion to α3(V) or NTD binding to Schwann cells (Chernousov et al., 2006). α3(V)-NTD bound to Schwann cells co-localizes with cell surface glypican-1 molecules and induces clustering of glypican-1 molecules on the plasma membrane (Rothblum et al., 2004). siRNA-mediated suppression glypican-1 expression inhibits incorporation of Type-V collagen into the Schwann cell ECM. It is interesting to note that although Schwann cells express functional collagen-binding integrins α1β1 and α2β1, these receptors are not capable of mediating Schwann cell adhesion to Type-V collagen (Chernousov et al., 2001).

Schwann cell adhesion to Type-V collagen mediates Schwann cell spreading and actin cytoskeleton assembly and can promote Schwann cell adhesion (Erdman et al., 2002). An important question, therefore, is how does engagement of glypican-1, a GPI-anchored protein with no direct physical link to the cytosol, regulate these downstream cellular processes. A plausible mechanism

is that glypican-1 interacts with and regulates key signaling proteins by mutual association with lipid rafts, cholesterol, and glycolipid rich membrane subdomains. Glypican-1 is associated with lipid rafts in Schwann cell membranes and binding of α3(V)-NTD causes redistribution of cell surface glypican-1 molcules (R. Stahl, M. Chernousov, D. Carey, unpublished). Depletion of cholesterol, which prevents lipid raft assembly, inhibits Schwann cell adhesion to α3(V) collagen. The specific mechanisms by which glypican-1 engagement activate downstream signaling pathways linked to actin cytoskeleton organization have not been identified, although regulation of Rho family GTPases appears to be critical.

Type-V collagen and myelination

The high level of Type-V collagen in peripheral nerve, specific expression of the α3(V) chain by Schwann cells, localization to basal laminae surrounding myelin forming Schwann cells, and unusual mechanism for mediating Schwann cell adhesion, suggest that Type-V collagen carries out unique functions in Schwann cells. Consistent with this idea, siRNA mediated suppression of Type-V collagen synthesis (Chernousov et al., 2006) or dominant-negative inhibition of Type-V collagen assembly (K. Rothblum, M. Chernousov, D. Carey, unpublished) in Schwann cell-DRG neuron co-cultures significantly inhibits myelin assembly.

However, these findings have not been extended to *in vivo* models. Mice with homozygous null mutations in α3(V) collagen are viable and healthy, with no major peripheral nerve phenotype (D. Greenspan and D. Carey, unpublished). In contrast to what is observed in Schwann cell-DRG neuron co-cultures, however, where absence of the α3(V) collagen causes a substantial loss of all Type-V collagen molecules (Chernousov et al., 2006), Type-V collagen levels in peripheral nerves of α3(V) null mice are normal. In contrast, homozygous null mutations in the α1(V) collagen gene produce early embryonic lethality (Wenstrup et al., 2006). These findings are consistent with biochemical and other genetic data suggesting that the α1(V) and α2(V) chains are ubiquitously expressed and essential for Type-V collagen assembly, whereas the α3(V) chain is a tissue-specific subunit and is not essential for Type-V collagen trimer assembly. The α1(V)-NTD binds Schwann cell HS-proteoglycans and mediates Schwann cell adhesion, but more weakly than the α3(V)-NTD (Erdman et al., 2002), and so might compensate for genetic loss of α3(V) in peripheral nerve function. Analysis of mice with compound α1(V) and α3(V) mutations or Schwann cell-specific ablation of α1(V) collagen could be informative of the role of Type-V collagen in peripheral nerve function, but has not been reported.

Type-IV collagen

In addition to being an essential structural component of basement membranes Type-IV collagen molecules have important biological properties. Schwann cells can attach and spread on collagen Type-IV molecules by a mechanism that is mediated by α1β1 and α2β1 integrins on the Schwann cell surface (Chernousov et al., 2001). It is likely that these are part of the repertoire of molecular interactions between Schwann cells and the basement membrane that are critical to establishing and maintaining the Schwann cell differentiation. Type-IV collagen also promotes axonal growth of peripheral neurons through α1β1 integrin binding to the C-terminal noncollagen domain (Lein et al., 1991). Such an interaction could influence axonal growth during embryonic development or during regeneration following nerve injury.

α1(IV) and α2(IV) Type-IV collagen subunits are present in all basement membranes and may be essential for Type-IV collagen assembly. Null mutations in these genes are embryonic lethal in mammals and no human mutations in these genes have been described. Schwann cell-specific ablation of Type-IV collagen genes has not been reported. Interpreting the phenotypes of these animals could be challenging, however, as it would be difficult to distinguish essential structural roles of Type-IV collagen molecules from critical signaling functions.

Specialized Collagen Proteins

Gliomedin

Gliomedin is a transmembrane cell adhesion protein expressed by Schwann cells that binds to neurofascin and NrCAM on axonal membranes (Eshed et al., 2005). Gliomedin induces clustering of sodium channels at nodes of Ranvier. The gliomedin extracellular domain is released by proteolytic cleavage and associates with the ECM in the vicinity of nodes by a HS-dependent mechanism (Eshed et al., 2007; Maertens et al., 2007). Gliomedin contains collagen domains that mediate protein oligomerization and are required for ECM localization. Thus, gliomedin along with Type-V collagen, are collagens that show specific localization to nodes of Ranvier. They have in common high affinity binding to HS chains. Syndecan-3 is also localized to nodes of Ranvier (Melendez-Vasquez et al., 2005). These findings reveal the existence of a node-specific ECM that appears to have specific functions with respect to node organization, although the details on the structure, assembly, and function of this node-specific ECM remain to be elucidated.

CONCLUSIONS

Schwann cell contact with ECM is essential for differentiation and function. The peripheral nerve ECM is biochemically and structurally complex, and Schwann cells express an array of ECM receptors. Significant progress has been made in elucidating the functions of some key ECM components. Recent studies using mouse genetics have revealed the importance of laminin signaling.

Laminin signals modulate Schwann cell proliferation, survival, differentiation, and morphogenesis. However, several important questions remain to be addressed. Are there signaling functions initiated by collagens that are distinct from their essential structural roles in the ECM? How do Schwann cells integrate signals from multiple matrix proteins and receptors to generate appropriate functional responses? Further understanding of ECM signaling pathways in Schwann cell differentiation and myelination will help elucidate the pathophysiological mechanisms of merosin-deficient congenital muscular dystrophy, Charcot-Marie-Tooth disease, and other congenital peripheral neuropathies as well as suggest new therapeutics for these debilitating diseases.

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