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INTEGRINS IN THE DEVELOPMENT, FUNCTION AND DYSFUNCTION OF THE NERVOUS SYSTEM

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1. ABSTRACT

Integrin receptors mediate cell-cell and cell-extracellular matrix (ECM) interactions in many different cell types, including neuronal cells. Earlier studies have shown a clear role for integrins in axon extension and cell adhesion/migration in CNS inflammation. Here we summarize more recent work that shows integrin functions in many phases of neural development, from neuroblast migration to synapse formation. Integrins of the beta-1 and alpha-v family are widely expressed on neurons at many stages of development, and their activity is regulated. Integrins are also important in the adult nervous system, since they have been implicated in synaptic plasticity involved in memory and learning. In addition, several diseases of the nervous system appear to involve beta-1, beta-2, and alpha-v integrins on leukocytes and glial cells. Research challenges for the future include understanding functions of specific integrin heterodimers and identifying the relevant integrin ligands that function in the nervous system.

2. INTRODUCTION

Neuronal cells have unique requirements for their proper development and function. First, they must get to the right place. This requires a sometimes long migrational journey by neuroblasts involving contact with many cells and substrates. Following migration, neurons differentiate and generate dendrites and axons, often with elaborate branches and patterns. Another unique requirement is to make specialized synaptic contacts with other cells. Synapses are assembled with as many as 1000 partners, and they are maintained as plastic structures that can be modified by experience. In light of these requirements, it is no surprise that neurons express an extensive array of cell adhesion molecules (CAMs), including immunoglobulin family receptors, cadherins, and integrins. In this review, we will summarize recent studies of the integrin family of receptors in the nervous system. Since their discovery in 1986, over 21,000 papers have been published on integrins, and over 2000 of these are reviews! However, few of these focus on the roles fulfilled by integrins in the development and function of the nervous system.

Integrins are a family of (alpha-beta) heterodimeric receptors that mediate both cell-cell and cell-matrix interactions in a wide variety of cell types (1-3). Recent analyses of whole genomes have provided insights into the phylogenetic distribution of integrins (4-6). Proteins distantly related to integrins have been detected in yeast (7), and more convincing integrin homologues have been identified in sponges (8). Thus, integrins in their current form appear to have arisen coincidentally with a metazoan lifestyle. Caenorhabditis elegans has 4 alpha subunit genes and 2 beta subunit genes, and Drosophila

melanogaster has 7 integrin alpha genes and 2 beta genes (5). It is estimated that the fly has 500 or so genes implicated in cell adhesion events (including receptors and ligands), which accounts for 4% of the genome (4). The sequencing of the human genome uncovered 24 alpha and 9 beta subunit genes, whereas previous studies had identified 18 alpha and 8 beta subunits (5). It will be interesting to see if the integrins predicted can be verified and further characterized.

Table 1 shows the integrin heterodimers that have been identified and characterized to date, with known ligands. Although all combinations of alpha and beta are not possible, and only 24 integrin heterodimers have been characterized thus far, the complexity is greater than this because some alpha and beta subunits have splice variants with different distributions and different signaling properties (9, 10). For example, the beta-1 subunit has 5 cytoplasmic splice variants, and one can act as a dominant negative to another (11). A single integrin heterodimer can often bind more than one ligand, and a single ECM ligand is often recognized by multiple integrins. For example, at least 7 integrins are capable of binding laminin-1, and 9 integrins have been reported to bind fibronectin (12). Integrins mediate interactions with cell surface ligands such as cell adhesion molecules in the Ig superfamily, and ADAMs family disintegrins. Integrins also serve as docking sites for viruses and bacteria, and play a role in sperm binding to eggs (13). The list of integrin ligands continues to grow, and, based on the sequence of the human genome, reports of novel integrins are likely (14, 15).

At first glance, it appears that there is a great deal of overlap in integrin function. However, the apparent redundancy has not been reflected in studies of knockout mice lacking integrin genes. Twenty of 22 subunit knockouts show striking phenotypes and 10 are lethal (16-18). These and other studies have implicated integrins in a wide array of cellular processes, including cell adhesion, cell spreading, cell migration, cellular polarization, axon outgrowth, synapse formation, myoblast fusion, apoptosis, cell division, phagocytosis, and changes in gene expression. Physiological processes thought to require integrin function include thrombosis, inflammation, synaptic plasticity, angiogenesis, vasculogenesis, fertilization, tissue repair, tumor cell metastasis, and a variety of developmental events.

Both alpha and beta subunits span the membrane once, and most have relatively short cytoplasmic domains (except for the beta-4 subunits). Recent x-ray crystallographic studies of integrin extracellular domains as well as previous structure function results indicate that both alpha and beta subunits contribute to the ligand binding site in most integrins (19, 20). A seven-bladed beta-propeller in the alpha subunits and a “metal ion-dependent adhesion site” (MIDAS) metal binding site in the beta subunits, along with divalent cations, are crucial elements of ligand interaction (19, 21). Integrins recognize several well characterized amino acid motifs, such as RGD in fibronectin, vitronectin and other matrix proteins.

Upon binding ligand, integrins are known to cluster into point contacts that mature to become focal contacts or focal adhesions (22). This clustering is an important aspect of “outside-in” signal transduction, since signaling can be induced by treatment of cells with anti-integrin antibodies. Part of this clustering is brought about by the proximity of multiple ligands present in polymeric matrix networks. The focal adhesion that is assembled is a specialized multiprotein anchorage complex that links to actin stress fibers. Focal adhesions contain a complex array of interacting proteins, such as talin, alpha-actinin, vinculin, and paxillin. Integrin beta subunit cytoplasmic domains interact with Focal Adhesion Kinase (FAK) and activate the kinase upon ligand binding (2, 3, 23, 24). Once integrins bind their ligands, they are thought to assemble a signaling complex that includes FAK, SRC, GRB2, p130CAS, SHC, integrin-linked kinase, paxillin, calreticulin, caveolin-1 and other signaling elements that are still being identified. Integrins can activate the MAP kinase pathway and increase intracellular pH and Ca2+. The complex web of intracellular signaling events initiated by integrin receptors is also thought to involve the small GTPases rho, rac, and cdc42. These proteins are important regulators of actin polymerization dynamics during movement of filipodia and lamellipodia (22). Recently evidence has been presented that integrins may signal to induce apoptosis in the absence of ligand (25). It has become clear that the signaling pathways used by integrins are the same ones used by many other factors, and we are just beginning to understand the complex crosstalk between receptor systems (26).

Integrins can associate within the membrane (in cis) with other transmembrane receptors (27). These receptors are believed to bind ligands and signal via the associated integrin. This widens the repertoire of ligands that use integrins. These include tetraspan receptors such as CD-9, which can mediate fertilization, neurite outgrowth and myoblast fusion (13, 28, 29), and integrin-associated protein (IAP), a thrombospondin/p84 receptor that may play a role in memory and learning (30).

Integrin binding affinity and specificity is regulated via “inside–out” signaling mechanisms that are thought to involve small GTPases (such as R-ras) and alter associations between alpha and beta subunit cytoplasmic domains (3, 21, 31). Factors that bind to other receptors can stimulate integrins via this mechanism. Regulatory conformational changes can also be induced by ligand binding. In addition, expression is regulated at the transcriptional level. For example, cells can respond to the composition of the underlying ECM and modify integrin expression (32). Because of this regulation, integrin binding specificity is context specific – the same receptor can bind different ligands when expressed in different cells.

3. INTEGRINS IN THE NERVOUS SYSTEM

In studies of the nervous system, beta-1 family integrin receptors were first identified as mediators of neurite outgrowth on ECM components more than ten years

Table 1. Integrins and Their Ligands

Integrin	Ligands
Alpha-1 beta-1	**collagens**, laminin-1
Alpha-2 beta-1	chondroadherin, **collagens**, echovirus, integrin alpha-3, laminin-1
Alpha-3 beta-1	collagens, fibronectin, integrin alpha-2, integrin alpha-3, **laminin-5**, invasin, thrombospondin-1
Alpha-4 beta-1	ADAM-28, **fibronectin (LDV)**, integrin alpha-4, intercellular adhesion molecule-4, invasin, junctional adhesion molecule-2, osteopontin, thrombospondin-1, tissue transglutaminase, **vascular cell adhesion molecule-1**, von Willibrand factor
Alpha-5 beta-1	ADAM-15, **fibronectin (RGD)**, invasin, L1 cell adhesion molecule, osteopontin, thrombospondin-1
Alpha-6 beta-1	ADAM-3, ADAM-9, fertilin-beta-(ADAM-2), invasin, **laminin-1**, laminin-5, papilloma virus
Alpha-7 beta-1	**laminin-1**, laminin-2/4
Alpha-8 beta-1	fibronectin (RGD), **nephronectin**, osteopontin, poem, tenascin, vitronectin
Alpha-9 beta-1	ADAM-12, ADAM-15, coagulation factor XIII, collagens, laminin-1, osteopontin, tenascin, tissue transglutaminase, vascular cell adhesion molecule-1, von Willibrand factor
Alpha-10 beta-1	**collagens**
Alpha-11 beta-1	**collagens**
Alpha-v beta-1	agrin, fibronectin (RGD), L1 cell adhesion molecule, osteopontin, transforming growth factor-beta-1, **vitronectin**, von Willibrand factor
Alpha-L beta-2	**intercellular adhesion molecules** 1, 2, 3, 4, 5
Alpha-M beta-2	complement factor C3bi, coagulation factor X, fibrinogen, intercellular adhesion molecule-1, neutrophil inhibitory factor
Alpha-X beta-2	fibrinogen, complement factor C3bi
Alpha-D beta-2	vascular cell adhesion molecule-1, intercellular adhesion molecule-3
Alpha-v beta-3	ADAM-15, ADAM-23, adenovirus, bone sialoprotein, fibrinogen, fibronectin, HIV tat protein, L1 cell adhesion moleculeCAM, matrix metalloproteinase-2, platelet/endothelial cell adhesion molecule-1, nephronectin, osteopontin, prothrombin, tenascin, thy-1, thrombospondin-1, **vitronectin**, von Willibrand factor
Alpha-IIB beta-3	**fibrinogen**, decorsin, fibronectin (RGD), intercellular adhesion molecule-1, thrombospondin-1, variabilin, vitronectin, von Willibrand factor
Alpha-6 beta-4	**laminin-1**, laminin-5
Alpha-v beta-5	**vitronectin**, osteopontin, bone sialoprotein, HIV tat protein, prothrombin, transforming growth factor-beta-1, nephronectin, ADAM-9
Alpha-v beta-6	**fibronectin (RGD)**, foot and mouth virus, nephronectin, tenascin, thrombospondin-1, transforming growth factor-beta-1,
Alpha-4 beta-7	fibronectin (LDV), **mucosal adhesin cell adhesion molecule-1 (MadCAM-1)**, nephronectin, vascular cell adhesion molecule-1,
Alpha-E beta-7	integrin alpha-E
Alpha-v beta-8	collagen IV, fibronectin, laminin-1, transforming growth factor-beta-?

ago using blocking antibodies *in vitro* (33). Since that time, it has become clear that integrins also play important roles in neuroblast migration, synapse formation, glial cell development, and neural disease (34, 35). Below, we summarize recent studies related to different phases of neuronal life.

3.1. Migration of Neuroblasts

Neuroblasts in the developing organism move from germinal or proliferative zones to their final destinations using various modes of migration. In the retina, migration involves a somal translocation over a relatively short distance (36). Migration of neuroblasts along radial glia in the brain (37), and tangential migration in chains of cells from the subventricular zone (38) illustrate longer distance migrations, with neural crest cells highlighting the extremes of migration (39). Integrins have been implicated in all types of neuroblast migration (Table 2). However, as described below, not all of the data are consistent.

The role of integrin subunit beta-1 in the retina has been studied extensively. Blocking anti-beta-1 antibodies were shown to inhibit the radial movement of nascent chick retinal ganglion cells from the ventricular zone to the vitreal border (40), while expression of antisense beta-1 mRNA from replication incompetent retroviruses inhibited tangential migration of chick retinoblasts (41). Blocking beta-1 antibody injected into the developing retina resulted in the formation of photoreceptor rosettes in Xenopus and severely disrupts normal eye morphogenesis in the chick, which may be due to migration defects (42, 43). However, not all studies confirm a role for beta-1 integrin in retinal migration. Retinal precursors in chicken embryos transfected with a dominant negative beta-1 construct migrated appropriately, although axon and dendrite elongation by retinal ganglion cells was inhibited (44).

Integrins have also been implicated in radial and tangential migration in brain neuroblasts. Expression of antisense beta-1 mRNA from replication incompetent retroviral vectors inhibited migration, as well as survival, of chick tectal neuroblasts (45). Furthermore, radial migration of a population of chick tectal cells from the ventricular zone to the tectal plate was inhibited by expression of antisense alpha-6 message (46). The alpha-6 subunit is also required for chain migration of forebrain derived neural precursors *in vitro* (47). Integrin subunits alpha-1, alpha-v and beta-1 support tangential migration of neural precursors from the subventricular zone to the olfactory bulb along the rostral migratory stream (48). In a study of cortical neuronal migration, roles for two alpha subunits known to pair with beta-1 were identified. Antibody blockade of alpha-3 slowed neuronal migration along radial glia *in vitro*, but did not result in detachment from the glia. Alternately, blocking the function of an integrin found mainly on the radial glia, alpha-v, resulted in not only a reduced migration rate, but also detachment of neurons from glia (49). The above results suggest important roles for alpha-3, alpha-6 and alpha-v integrins during cortex lamination. Although these subunits are part of the beta-1 family of integrins, in beta-1 chimeric mice, cortex neurons lacking expression of the subunit appear to develop and migrate normally (50). While mice lacking beta-1 in neural tissue exhibited extensive disruption in cortical lamination and foliation with similar results in the cerebellum, only minor abnormalities were found in neuronal migration during corticogenesis (51). In studies using function-blocking antibodies to the beta-1 subunit and the cell adhesion molecule L1 in mouse cerebellar slice culture (52), granule cell migration was inhibited when antibodies to both beta-1 and L1 were used. Use of either antibody alone did not inhibit migration. These results suggest that L1 and beta-1 integrins cooperatively regulate radial migration, and provide an explanation for the results obtained using beta-1 chimeric mice.

Recent studies have provided insight into the role of alpha-3beta-1 in the reelin signal transduction pathway. The Cajal-Retzius cells of the cerebral cortex secrete reelin, which slows neuronal migration along radial glia and causes detachment of neurons from glia (53). In alpha-3beta-1 mutant embryos, reelin application was unable to reduce the rate of migration and did not result in neuronal detachment from glia. Furthermore, alpha-3beta-1 may protect reelin from self-degradation (54). Reelin, alpha-3 integrin subunit and a cytosolic component of the reelin signaling pathway, Dab1, are present in human neural stem cells suggesting that these cells can use the reelin signal transduction pathway to regulate their migration (55). This work on integrins in the reelin pathway lends further evidence to support an integral role for the beta-1 integrin subunit in neuroblast migration.

Many studies have implicated integrins in neural crest migration. A number of ECM molecules are known to line the paths neural crest cells follow during their migration from the dorsal neural tube to their destinations in the mature organism. Recent work has addressed the cast of integrins expressed by the neural crest cell populations that allow for interaction with various ECM molecules. On laminin-1, neural crest cell migration is mediated predominantly by alpha-1beta-1, which binds both the E1' and E8 cell-binding domains of laminin (56). In an *in vitro* study of avian neural crest cells, although most known fibronectin receptors were expressed, only alpha-4beta-1, alpha-vbeta-3 and alpha-8beta-1 seemingly participate in migration. This study revealed apparent functional compensation among the integrins since use of multiple function-blocking antibodies was necessary to fully inhibit neural crest cell migration (57). More recent work has emphasized the importance of the alpha-4beta-1 integrin heterodimer in avian neural crest cell migration by demonstrating expression of this integrin in migrating, but not premigratory cells (58). Integrin alpha-4 mRNA and alpha-4 protein expression were found in both cranial and trunk migrating neural crest cells in chicken and mouse respectively. Blocking antibody and peptide were used to demonstrate a reduced capacity of neural crest cells to migrate when alpha-4 function was impaired (59).

Despite the apparent roles for alpha-1 and alpha-4 in neural crest cell migration suggested by the above studies, mutant mice lacking alpha-1 or alpha-4 still form tissues derived from neural crest cell populations (60, 61). A study of alpha-4 and alpha-5 deficient embryos defined a role for alpha-4 in cell survival, but not motility during neural crest cell migration. Further, although alpha-5 null cells exhibited delayed migration when plated on fibronectin *in vitro*, they develop normally in an *in vivo* environment (62). Using chimeric mice it has been possible to examine the behavior of cells that lack beta-1 expression *in vivo* (50). Neural crest cells lacking beta-1 migrated normally, a surprising finding in light of previous results. The difference in results from perturbations with antibodies, peptides, or antisense and some null mouse studies may be explained by compensatory changes in expression that are activated in mutant mouse cells, though such up-regulation has yet to be demonstrated. In fact, in alpha-4 null cells there was no up-regulation of beta-1, beta-3, alpha-3, alpha-5, or alpha-v (62). This analysis was performed *in vitro* and as such may not reflect functional compensation by up-regulation of some critical subunits occurring *in vivo.*

Table 2. Neuronal Integrins

Integrin	Distribution in Nervous System	Putative Function
Alpha-1 beta-1	Brain, Retina, Neural Crest	neural crest cell migration
Alpha-2 beta-1	Retina (Neuroblasts)	
Alpha-3 beta-1	Brain (Cerebellar Dendrites, Cortex Neuroblasts), Retina, Motor Neuron Active Zones, Muscle (Postsynaptic)	cortex neuroblast migration on radial glia, LTP, reelin receptor
Alpha-4 beta-1	Brain, Retina (Neuroblasts, Retinal Ganglion Cells), Neural Crest	neural crest migration, sympathetic and sensory axon outgrowth
Alpha-5 beta-1	Brain (Hippocampal Dendrites)	LTP
Alpha-6 beta-1	Brain, Retina (Neuroblasts, Retinal Ganglion Cells),	neuroblast migration, axon extension
Alpha-7 beta-1	Brain, Motor Neurons, Sensory Neurons, Muscle	synapse formation (neuromuscular junction), motor and sensory axon
Alpha-8 beta-1	Brain (Hippocampal Dendritic Spines), Inner Ear Hair Cells, Retina (Retinal Ganglion Cells)	
Alpha-9 beta-1	Muscle (Postsynaptic)	
Alpha-v beta-1	Muscle (Postsynaptic)	Ach receptor clustering, agrin receptor
Alpha-v beta-3	Brain (Radial Glia), Retina (Neuroblasts)	
Alpha-v beta-8	Brain (Cerebellar And Hippocampal Dendrites)	

While many of the mice null for integrin subunits (i.e. alpha-4, alpha-5 and beta-1) do not present the phenotypes that might have been anticipated based on previous experimentation, disruption of some subunit genes has resulted in severe phenotypes. Mutant mice lacking the integrin subunit alpha-6 die at birth with severe skin blisters, and show abnormal organization of the cerebral cortex and retina. Ectopic neuroblast-like outgrowths were observed in the brain, the nerve fiber layer of the retina and in the vitreous humor. Neuroblasts fail to stop migrating, an effect possibly due to altered laminin deposition on radial glia since laminin persists longer in the mutant brains (63). Targeted mutation of the alpha-3 gene resulted in abnormal cortical layering and cell aggregate formation due to a switch in adhesive preference so that neurons preferred to adhere to other neurons rather than glial cells (49). Investigation of mouse embryos null for both alpha-3 and alpha-6 revealed further defects in cortex organization as well as retinal, limb and digit abnormalities (64). Genetic studies of C. elegans may clear up some of the confusion arising from null mouse studies since fewer subunits have been identified in this organism. In C. elegans mutant for the alpha integrin subunit gene, ina-1, long-distance neuronal migration is disrupted (65). Although perturbations with antibodies, peptides, and antisense must be interpreted with caution in light of the results from mouse genetics, the preponderance of evidence points to a key role for integrins in neuroblast migration.

Investigations into the mechanism of adherent (nonneuronal) cell migration have important implications for understanding the migration of neuroblasts. This topic has been extensively reviewed (for recent review see (66)), and will only be treated briefly here. Progress is being made on understanding the precise interactions between integrins and the cytoskeleton. For example, in fibroblasts, integrins are preferentially bound to the cytoskeleton at the leading edge of lamellapodia, providing stability to the integrin – fibronectin interaction. Further back on the lamellapodia, the integrin – ECM linkage is weakened, correlating with a dissociation of the integrin-cytoskeletal association (67). This position-dependent binding of integrin to the cytoskeleton may confer directionality to cell migration. As the cell migrates, integrins once located at the leading edge are found on the backside of the lamellapodia. In neutrophils, these integrins appear to be recycled by endocytosis and relocated by direct transport to a region just behind the leading edge (68). A similar mechanism in migrating neuroblasts is suggested by Thelen *et al.* (mentioned above), who showed that L1 and integrins promote migration through a mechanism involving endocytosis (52).

Alpha-4 integrins appear to have somewhat unique functions in nonneuronal cell migration. Recent studies show that alpha-4 integrins increase migration and decrease cell spreading and focal adhesion formation relative to other integrins (69). Unlike other integrins, alpha-4 is not usually localized to focal adhesions, and instead is thought to allow less stable, transient adhesion to bring about lamellapodial protrusion in a focal adhesion independent mechanism (70). This activity is mediated by the alpha-4 cytoplasmic domain, since transfer of this domain to other alpha- subunits increases migration and decreases spreading and focal adhesion formation (69, 71). The unique signaling properties of alpha-4 have been traced to a 9 aa motif (E(X2-3)R(X4)Y)n the cytoplasmic domain, which binds to the signaling adaptor protein paxillin (70, 72). Phosphorylation on a serine in the alpha-4 cytoplasmic domain, possibly by protein kinase A, inhibits the interaction with paxillin (73). This motif is evolutionarily conserved and is distinct from other motifs recognized by paxillin, which allows paxillin to mediate formation of a signaling complex that includes focal adhesion kinase (FAK) and other proteins. FAK has also been implicated in migratory events (74). Recent work by Ginsberg's group

has shown that a 100 aa fragment of paxillin functions in a dominant negative fashion to selectively inhibit alpha-4-mediated cell migration in CHO cells (75). Paxillin has also been shown to associate with alpha-4 in DRG neurons and PC12 cells, and paxillin has been implicated in neurite outgrowth (76). Previous studies have shown that tyrosine phosphorylation of paxillin increases after neurite outgrowth on laminin, and paxillin redistributes to the cytoskeletal fraction (77). Thus, paxillin association with the cytoplasmic domain of alpha-4 is crucial for alpha-4 signaling in both neural and nonneuronal cells.

3.2. Axon and Dendrite Outgrowth

Integrin-ECM interactions and their effects on outgrowth have been studied intensely *in vitro* (78-81), but activities suggested by these experiments have thus far not produced the anticipated phenotypes in knockout mice. Despite a previously identified role for the alpha-1beta-1 integrin as an important laminin receptor mediating neurite outgrowth in sensory neurons (82), no outgrowth defects were reported in alpha-1 null mice (60). No retinal pathfinding errors were noted in the alpha-6beta-1 knockout animal (63) in apparent contradiction to earlier evidence for a role in retinal axon outgrowth (83). The availability of multiple guidance systems able to compensate for missing integrins may account for the lack of observed outgrowth phenotypes in the null mice (84). It is also conceivable that subtle phenotypes are present in the null mice, but have yet to be characterized. Further analysis of axonal and dendritic projections may eventually clarify the relationship between *in vitro* and *in vivo* work.

Genetic studies conducted in other organisms have better reflected the roles for integrins in axon and dentrite outgrowth. A study of retinal development in Drosophila integrin mutants showed disrupted omatidium structure (85). Multiple errors in axon pathfinding were identified in Drosophila null mutants lacking integrin alpha subunits alpha-PS1 and alpha-PS2, with loss of the RGD-dependent alpha-PS2 resulting in more damage than loss of alpha-PS1, a laminin-binding integrin (86). Mutant CNS longitudinal axons appear wavy and disconnected and defective motor neuron axons either fail to turn at choice points, make improper turns, or extend beyond stopping points. Hoang and Chiba propose a model where integrins act as a “speed control” device in growth cones (86). By this model, integrin expression must be high enough to generate sufficient adhesion so that the growth cone proceeds slowly, which allows it to recognize guidance cues. Also in Drosophila, CNS axons were more likely to make pathfinding errors when reduced expression of the midline growth cone repellent slit was combined with reduced expression of integrin genes alpha-PS1, alpha-PS2, alpha-PS3/4 and beta-PS1. Similar results were seen when integrin ligands laminin A or Tiggrin were reduced in combination with Slit, but not with reduced expression of the midline attractant Netrin (87). These results suggest an important role for integrins in midline axon guidance. Xenopus retinal ganglion cells expressing a dominant negative integrin beta-1 subunit exhibited inhibition of both axon and dendrite process outgrowth, while retinal pathfinding errors resulted from injection of blocking antibodies to both beta-1 and N-cadherin (44). C. elegans mutants lacking the alpha- integrin subunit INA-1 show defective axon fasciculation, suggesting possible roles in fascicle formation or axon-axon interactions needed for bundling (65).

Integrin signaling in neurons. It is well established that nerve growth factor (NGF) stimulates integrin-dependent axon outgrowth, but the mechanism connecting these systems is less understood. NGF was shown to stimulate the accumulation of beta-1 integrins at the tips of growth cone filopodia of sympathetic neurons grown in the absence of an ECM substrate. Myosin inhibitors blocked this effect (88). Later work showed the movement of beta-1 to the filipodia to occur by diffusion as well as directed transport (89). The navigating axon can modify its actions in response to ECM, but also to diffusible factors in an integrin-dependent manner. While increasing gradients of netrin-1 attracted Xenopus retinal neurons cultured on glass, fibronectin, or poly-D-lysine, growth cones turn away from netrin-1 when cultured on laminin-1 (90). This change in response to laminin likely results from the cis interaction between a beta-1 integrin receptor, possibly alpha-6beta-1, and the 67 kDa laminin receptor to lower cAMP in the growth cone. Retinal ganglion cell growth cones may turn down the optic nerve in response to laminin-1 and netrin-1 at the optic nerve head. Further evidence for synergy between integrin and secreted factors was provided by Stevens and Jacobs as mentioned above (87). These results suggest a role for soluble factors in coordination with ECM bound integrins in proper axonal navigation.

Of particular interest in understanding process outgrowth is the interaction between integrins and their extracellular ligands as well as the cytoskeleton. Post-translational changes in integrin alpha-6beta-1 levels on the cell surface mirrored changes in the concentration of substrate-bound laminin, with decreased available laminin resulting in an increased presence of alpha-6beta-1 levels and vice versa (32). Through this regulation, neurons maintain an intermediate level of adhesion facilitating movement of the growth cone over varying concentrations of ECM. A link between integrin cytoplasmic domains and the cytoskeleton is required to provide the traction needed for filopodial advance. Work done by Smilenov *et al.* suggests a model where integrins in the focal adhesion act as a “molecular clutch” (91). In fibroblasts, ligand binding is not required for integrins in focal adhesions to associate with the cytoskeleton. A GFP-integrin fusion protein was used to track focal adhesions as they moved along actin cables in stationary fibroblasts. This movement was driven by either contraction or retrograde flow of the associated actin fibers. In contrast, the focal adhesions were stationary in the leading edge of moving cells (91). These results, when combined with other studies (92, 93), suggest a model for integrin function in filipodia with multiple points of regulation, including: integrin localization, actin retrograde flow and assembly, and integrin association with either the ECM or the actin cytoskeleton. Work done by Grabham and colleagues supports this model (89). Treatment with the soluble neurotrophin NGF results in the

coupling of beta-1 integrin to the retrograde flow of actin as monitored by single particle tracking. This suggests that NGF increases the association between the ECM and the actin cytoskeleton via integrins thereby increasing the traction needed for progression of the axon growth cone. Presumably, similar mechanisms are in operation during neuroblast migration.

Another role for integrins in filipodia may involve growth cone turning. High speed confocal imaging demonstrated differential calcium transients in response to varied substrates, indicating a signaling mechanism by which the growth cone is aware of the substrate environment. The integrin subunit beta-1 is sufficient (though not necessary) to generate these transients as determined using function-blocking antibodies. When calcium transients occur in the filipodia on only one side of the growth cone, turning of the growth cone results (94). Growth cone turning may also occur in response to inhibitory cues in the extracellular environment. One of these inhibitory matrix proteins is the condroitin sulfate proteoglycan (CSPG) aggrecan. In embryonic sensory neurons, integrins are involved in neuronal adaptation to aggrecan in the local environment. Integrins alpha-6beta-1 and alpha-3beta-1 were upregulated when cells were plated on laminin and aggrecan as compared to laminin alone. The ability to extend neurites in the presence of aggrecan was dependent on the amount of integrin present, with high levels of alpha-3 and alpha-6 expression reflecting enhanced neurite outgrowth (95). In contrast, in the human neuronal cell line SH-SY5Y, contact with the CSPG aggrecan did not increase the level or change the distribution of integrins. Blocking beta-1 antibody did not change growth cone turning in response to aggrecan indicating that growth cone turning is not integrin dependent in SH-SY5Y cells (96).

When integrins bind to ECM proteins, an intracellular signaling cascade is activated and can result in the cytoskeletal changes needed to modulate growth cone structure, neurite outgrowth and axon pathfinding. PC-12 cells lacking vinculin show reduced neurite outgrowth, with less stable lamellapodia and filopodia (97). Colocalization of vinculin and beta-1 integrin, along with paxillin, talin, FAK and RhoA, is seen in point contacts of the tip and central domain of filipodia in rat dorsal root ganglia explants cultured on laminin. The localization of vinculin suggests that it may link laminin bound integrins to the cytoskeleton, serving as an anchor to allow filipodial advance (98). FAK is localized to both growth cones and cell bodies, with FAK levels and FAK phosphorylation down-regulated in the adult as compared to embryonic brain (99, 100). Phosphorylation of FAK as well as paxillin increases during neurite outgrowth. Studies in the neuroblastoma cell line N1E-115 have examined the signaling pathways involved in neurite outgrowth in response to serum starvation. When plated on laminin, the neurite outgrowth is integrin-dependent since beta-1 blocking antibody inhibited the outgrowth and occurs in response to transient activation of integrin-linked kinase (ILK) (101). In studies using dominant-negative constructs, loss of Ras, Rac1, Cdc42, PI3K or ILK blocked neurite outgrowth (102). Using a number of mutants, Sarner *et al.* established the hierarchy of a signal transduction pathway capable of activating outgrowth (102). Ras lies at the top of this pathway, signaling to PI3K. Both are upstream of Cdc42 activation of Rac1. Requirement for the small GTPase Rac1 in promoting integrin-dependent neurite outgrowth was also found in embryonic chicken motor neurons when grown on laminin or fibronectin using blocking beta-1 antibody. Constitutively-active Rac1 resulted in actin filament accumulation in growth cones, while a decrease was seen in response to dominant-negative Rac1 (103). More studies attempting to elucidate the mechanism behind integrin dependent activation of neurite outgrowth and axon navigation identified a role for the signaling molecules cyclin-dependent kinase 5 (cdk5) and NCK-interacting kinase (NIK). Laminin enhanced cdk5 activity and neurite outgrowth in SHSY5Y cells in an alpha-1beta-1 dependent manner, as activation was prevented by treatment with anti-alpha-1beta-1 antibody (104). NIK was found to interact with beta-1 integrin and is highly expressed in the developing mouse nervous system. Genetic studies in C. elegans demonstrated interactions between NIK (MIG-15), INA-1 alpha integrin and Rac (105). Calcium ion is also thought to play a key role in signal transduction by growth cone integrins (106). Another cation, manganese, was found to induce integrin subunit beta-1 and alpha-v dependent neurite outgrowth in PC12 cells. Manganese treatment upregulated surface expression of alpha-v, which may contribute to the enhanced neurite outgrowth observed (107).

Integrins and CAMs. Recent work has also focused on cross-talk between integrins and other surface receptors in the process of neurite extension. N-cadherin and beta-1 integrin mediated adhesion and neurite outgrowth of chick retinal cells is inhibited by recombinant chicken neurocan, a chondroitin sulfate proteoglycan. This inhibition occurs via the cell surface glycosyltransferase GalNAcPTase, which is located in the ganglion cell layer and inner nuclear layers. Neurocan is localized to the inner plexiform layer and could prevent ganglion cells from projecting their axons into the other layers of the retina (108). A related study provides a mechanism by which the coordinate regulation of N-cadherin and beta-1 integrin by neurocan could occur. Treatment with a peptide resembling the juxtamembrane region of N-cadherin inhibited both N-cadherin and beta-1 function. Functional inhibition was accompanied by an increase in association of Fer tyrosine kinase with the integrin cytoplasmic domain, which was reflected by a decrease in Fer associated with the cadherin cytoplasmic domain (109). Dominant-negative expression of the non-receptor protein tyrosine phosphatase PTP1B inhibits N-cadherin and beta-1 dependent neurite outgrowth in PC12 cells. Neurite outgrowth was also inhibited in embryonic chick retinal cells when treated with PTP1B antisense RNA (110) (for further review see (111)). Cross-talk has also been documented between integrins and EGF receptors. Co-stimulation of these receptors activates Pyk2/FAK and promotes neurite outgrowth via paxillin induced cytoskeletal changes (112).

Recently it has been shown that sympathetic nerves use alpha-4beta-1 integrins to extend neurites on VCAM-1, which is expressed along the pathway axons follow to the myocardium. Blocking either VCAM-1 or alpha-4 integrins resulted in fewer sympathetic fibers innervating the heart

without an increase in cell death (Wingerd *et al.*, In Press). These results provide evidence that VCAM-1 can act as a neurite promoting molecule, and that alpha-4beta-1 mediates axon extension *in vivo.*

3.3. Synapse Formation

Integrins of the beta-2 family are known to be key components of the "immune synapse " (113). This adhesive structure that forms between T cells and other cells is crucial to the function of the immune system. Cell adhesion molecules have long been implicated in neuronal synapses (114-116). Exciting new evidence is emerging that suggests a function for integrins at neuronal and neuro-muscular synapses as well. Integrins appear to be important not only for synaptogenesis, but also for the modulation of synaptic strength that occurs during memory and learning.

3.3.1. Neuromuscular Junction

Formation of the neuromuscular junction (NMJ), perhaps the best understood synapse, is thought to involve integrin alpha-7beta-1. The alpha-7 subunit is synthesized by muscle and the alpha-7A and alpha-7B isoforms are localized to synaptic regions. A third isoform, alpha-7C, is found all over the muscle surface (117). A key event in formation of the neuromuscular synapse is the clustering of acetylcholine (Ach) receptors on the muscle surface. It is thought that laminins (Ln2 or Ln1) in the synaptic basal lamina interact with alpha-7beta-1, and this leads to a "priming" of the muscle in an unknown way that facilitates the clustering of AchRs by agrin, a proteoglycan made by motor neurons (118). In support of this model, blocking antibodies to alpha-7 integrin inhibit the acetylcholine receptor clustering activity of laminin and agrin (119).

Other integrins may also act at the NMJ. alpha-3, alpha-9 and alpha-v subunits have been detected in the postsynaptic membrane, and alpha-vbeta-1 has been shown to possess an agrin binding activity (117, 120, 121). Antibodies that block beta-1 and alpha-v inhibit the ability of agrin to cluster Ach receptors, and heterologously expressed alpha-vbeta-1 imparts cell adhesion to purified agrin (121). However, MuSK (a tyrosine kinase receptor), and alpha--dystroglycan have also been touted as agrin receptors, and neuromuscular defects in the alpha-v knockout mouse have yet to be reported. On the presynaptic side, alpha-3 subunit immunoreactivity has been detected in Xenopus motor nerve terminal active zones and nerve terminals of the Torpedo electric organ (120, 122). Active zone integrins may serve to cluster synaptic vesicles in response to laminin isoforms (containing the beta-2 S-laminin subunit) and other basal lamina molecules that induce presynaptic specialization. Finally, ECM components have been shown to influence Ach release in cultured Xenopus motor neurons (123).

3.3.2. CNS Synapses

In the central nervous system, integrins of the beta-1 family appear to be widely expressed not only in developing neurons and glia, but also in the adult (45, 124, 125). A survey of integrin mRNA localization in adult brain by *in situ* hybridization detected mRNAs encoding alpha-1, alpha-3, alpha-4, alpha-5, alpha-6, alpha-7, alpha-8, alpha-v, beta-1, beta-4, and beta-5 in both neurons and glia in various brain regions (125). beta-3 mRNA has also been detected by RT-PCR (126). Some subunit mRNAs, such as alpha-3, are broadly expressed in many brain regions, whereas others are narrowly distributed. For example, alpha-4 mRNA was detected only in discrete regions of the limbic forebrain. Integrin protein immunoreactivity has also been detected in brain for the alpha-1, alpha-3, alpha-5, alpha-8, alpha-v, beta-1, beta-3, beta-5 and beta-8 subunits (45, 124, 127-135). In some cases, integrin subunit protein staining is seen in regions where the mRNA is not detected (*e.g.*, alpha-8, (132)), indicating that distribution may be wider than revealed by *in situ* hybridization.

While in general integrins are found all over the neuronal surface, and at internal, cytoplasmic locations, several appear to be playing a role at the synapse. In the adult rat brain, alpha-8 immunoreactivity was detected in hippocampus, olfactory bulb, substantia nigra, ventral tegmental area, and superior olivary complex. Immunoreactivity was found mostly on cell bodies and dendrites, and only occasionally on axons in fiber tracts. alpha-8 was especially prominent in hippocampus, where EM analysis showed immunoreactivity in the postsynaptic densities of dendritic spines (132). During development, levels of expression increase at times of synapse formation, suggesting a possible role for the alpha-8beta-1 heterodimer in synaptogenesis. The ligand recognized by this integrin is not yet clear, but tenascin-C is expressed in an overlapping pattern and has been observed on CA3 pyramidal cells in adult rat hippocampus (136). However, *in vitro* binding studies suggest that the RGD that serves as the alpha-8beta-1 binding site may be a cryptic site that is only exposed upon proteolysis (137). Given its postsynaptic localization, it is also possible that alpha-8beta-1 interacts with some unknown membrane protein on the presynaptic cell.

Whether alpha-8 null mice exhibit synaptic defects has not yet been reported. Most of the alpha-8 knockouts die around birth due to kidney failure (138). Interestingly, those that survive show balance defects due to defective stereocilia in the sensory hair cells of the inner ear. The authors propose that alpha-8beta-1 in the apical membrane of the hair cells must interact with matrix to differentiate properly and assemble cytoskeletal elements crucial to function.

Integrin alpha-vbeta-8 has also been localized to synapses by immuno-EM (139). Immunoreactivity was observed in postsynaptic densities as well as on presynaptic membrane and glial processes in the hippocampus and cerebellum. beta-8 was also detected by western blotting in synaptosomal fractions. This localization is interesting because the beta-8 cytoplasmic domain is quite different from other beta subunits, and it may send different signals across the membrane, possibly even mediating anti-adhesive signaling in synaptic plasticity. The beta-8 null mice die at E11.5 or perinatally due to defects in vascular morphogenesis. The perinatal animals have defects in the organization of radial glia, but effects on synapses have not yet been reported (140). Again, the ligand recognized is not

clear, but one intriguing possibility is that this integrin functions in part by binding and activating TGF-beta-1 (14).

Another alpha-v integrin, alpha-vbeta-3, has been implicated in synaptic maturation in cultured hippocampal slices (134). An activity dependent maturation event has been documented that results in a decreased glutamate release and a change in the NMDA receptor subunit composition. RGD peptides and function-blocking anti-beta-3 antibodies inhibit this maturation of the synapse. The authors speculate that integrin interactions with a ligand (possibly the transmembrane cell adhesion molecule L1) might decrease the size of the active zone and send a signal to switch the subunit composition of the postsynaptic NMDA receptor. Again there is a need to analyze synaptic function in alpha-v and beta-3 knockout animals, which are fertile but have reduced viability due to blood clotting and osteoclast defects (141, 142).

The alpha-5 subunit, which pairs with beta-1 and acts as a fibronectin receptor, has also been localized to dendrites and cell bodies in adult brain, and may play a role in synaptic plasticity (see below). It is expressed in hippocampus, especially in pyramidal neurons, and blocking antibodies inhibit the consolidation of long-term potentiation (129, 130, 143). alpha-5 immunoreactivity appears late in development and was localized to the apical dendrites of both pyramidal neurons of the hippocampus and Purkinje cells of the cerebellum, but not basal dendrites. This polarized distribution suggests an as yet unexplored selective trafficking event for this subunit. Further studies at the EM level should reveal whether how this integrin is distributed in regard to synaptic contacts in these regions.

Another synaptic integrin is the alpha-3beta-1 heterodimer, which binds the reelin protein that is missing in reeler mice (see above) (144). ImmunoEM studies in adult nonhuman primate cortex have demonstrated a colocalization between reelin and alpha-3 integrins on postsynaptic densities of apical dendritic spines. As with the alpha-5 integrins, antibodies to alpha-3 inhibit LTP in hippocampal slices, making alpha-3 integrins (and reelin) good candidates for playing a role in memory and learning.

3.4. Synaptic Plasticity and Memory and Learning

It is becoming clear that a variety of cell adhesion molecules are localized to the synapse and play a role in modifying synaptic strength during learning and memory. These include cadherins, NCAM, L1, Thy-1, integrin associated protein, and integrins (114, 116, 145, 146). Pioneering studies by Lynch and coworkers demonstrated that integrin inhibiting RGD peptides blocked the stabilization (but not establishment) of long-term potentiation in hippocampus (147-150). The same inhibition is seen using disintegrins from snake venom (143). RGD peptides also block kindling in hippocampal slices (151). Since a number of integrins bind RGD peptides, it was not clear which integrins were involved in the stabilization of LTP. Early biochemical experiments showed that a 55 kDa protein that reacted with anti-alpha-5 antibodies was bound to RGD columns, which was probably a fragment of the alpha-5 subunit. More recent experiments using blocking antibodies have implicated two RGD binding integrins in LTP: alpha-3beta-1 and alpha-5beta-1.

Function-blocking antibodies to alpha-5 had no effect on the initial potentiation observed in CA1 hippocampal LTP, but decreased the magnitude of potentiation by 30% after 45 minutes (143). Interestingly, antibodies that block the function of alpha-v resulted in less than a 20% decrease, suggesting that alpha-vbeta-8 and alpha-vbeta-3 are not involved in the stabilization of LTP. Addition of echistatin and or triflavin, two snake disintegrins that bind multiple integrins, had a greater effect, implicating other integrins in LTP stabilization. Integrins known to be expressed in the CA1 hippocampal field are: alpha-vbeta-8, alpha-vbeta-5, alpha-vbeta-1, alpha-8beta-1, and alpha-3beta-1. Further studies have shown the integrin alpha-3 subunit is present in synaptic membranes from hippocampus (128). Furthermore, blocking antibodies to alpha-3 caused a “small but reliable decay” in LTP, and made the LTP more susceptible to disruption by theta pulse stimulation. It is possible that combinations of integrins and other cell adhesion molecules work together, perhaps in different steps or phases, to consolidate LTP, as occurs in cell spreading and neurite extension.

Exactly how integrins bring about the stabilization of LTP is not known, but they are thought to mediate physical changes in spine morphology that are known to accompany LTP (e.g. (152)). Alternatively, or in combination, signal transduction events mediated by integrins might lead to altered cytoskeletal or membrane topology that strengthens the synapse. Along these lines, Murase and Hayashi have reported that expression of the integrin beta-1 subunit is increased by seizure activity, indicating that activity may alter synapses by altering integrin levels (124). Integrins can give rise to calcium influx (e.g. (153)), and can influence NMDA receptor function (154), so integrin signaling and association with other proteins may be involved in addition to physical modulation of the synapse.

Studies of Drosophila also indicate that integrins play a role in learning and memory. A mutant defective in short term memory called volado (Chilean slang for absent-minded) maps to fly alpha integrin gene (alpha-PS3, (155)). The volado gene encodes two alpha-?subunit isoforms that are expressed in mushroom body neurons implicated in learning and memory. The mutation results in a 50% decrease in short term memory. Interestingly, synapses in the mutant appear to be larger and show increased evoked currents (156). Furthermore, the mutant phenotype can be rescued by conditional expression of the gene, indicating that the defect is not due to some developmental anomaly. volado mutants are defective in calcium and activity-dependent synaptic plasticity. This defect can be mimicked by the addition of RGD peptides.

Some of the integrins that have been localized to synapses may function via lateral association in the

membrane with the integrin-associated protein (IAP/CD47). IAP is a 50 kDa membrane glycoprotein the associates with integrins. It is known to regulate the function of alpha-vbeta-3 integrins in placenta and platelets, and it acts as a receptor for thrombospondins as well as P84/SHPS-1/SIRP-alpha, an adhesive membrane protein found at synapses (30, 157). Interestingly, IAP mRNA was found to be 4-fold higher in the hippocampi of rats that performed better in a memory test (158). Furthermore, IAP null mice were impaired in a memory retention behavioral test and manifested a significant reduction in the magnitude of long-term potentiation (146). These data indicate that additional integrin functions at the synapse, but the integrins involved, and the mechanism of the effect, remain unclear. One model suggests that signals transduced by IAP ligation via an integrin are important for memory and learning. This would be consistent with the finding that decreased FAK phosphorylation and defective LTP are observed in mice lacking the tyrosine kinase Fyn (159). It is known that FAK phosphorylation is regulated by neurotransmitters (160), which could link integrin signaling to changes in synaptic activity.

3.5. Glial Integrins

Glial Cells and Integrins in the CNS and PNS. In both the PNS and CNS glial cells play key roles in the proper development and maintenance of the nervous system. Glia support the nervous system by providing structural support and regulating homeostasis (161, 162). Most glia fall into one of three categories: 1) Those that form scaffolds for migrating neurons (astrocytes and radial glia); 2) Myelinating glia that ensheathe neurons in the PNS (Schwann cells), and in the CNS (oligodendrocytes); and 3) Microglia which act as phagocytic and antigen presenting cells that interface with the nervous system. In order for the glia to perform their various functions, precise coordination between the glia, neurons, and the ECM is required (163). In general, glia use integrins to control proliferation, cell death, migration, and differentiation (Table 3).

Glial integrins in the central nervous system. Within the brain and spinal cord, each type of glia expresses a slightly different array of integrins. Astrocytes are known to express alpha-1beta-1, alpha-3beta-1, alpha-5beta-1, alpha-6beta-1,?alpha-8beta-1, alpha-vbeta-3, alpha-vbeta-5, alpha-6beta-4, and alpha-vbeta-8. (164-169). With the exception of alpha-8beta-1, all the beta-1 integrins expressed are capable of binding laminins. The alpha-v integrins bind to vitronectin and Thy-1 (169-171). These ligands provide a supportive microenvironment that allows astrocyte attachment, migration, and differentiation (164, 172). The three alpha-v integrins have very different roles in astrocytes adhesion and migration. alpha-vbeta-5 is responsible for binding vitronectin and alpha-vbeta-8 allows migration. Milner *et al.* speculate that alpha-vbeta-8 plays a role in cell shape, which relates to migration (172). In addition, because alpha-vbeta-8 is detected on glia at synapses (168), it may have some role in neuronal plasticity. alpha-vbeta-3 is used by astrocytes to adhere to osteopontin deposited by microglia following CNS injury (173).

The myelinating cells of the CNS, oligodendrocytes, express alpha-6beta-1, alpha-vbeta-1, alpha-vbeta-3, alpha-vbeta-5, alpha-vbeta-8 (170, 174). These integrins most likely bind to tenacin-c, thrombospondin, or vitronectin which are expressed in the developing brain during the time of oligodendrocyte precursor migration (175-177).

Oligodendocyte precursors migrate throughout the CNS from restricted areas within the ventricular and subventricular zones. Like some cortex neuroblasts, these cells appear to use alpha-v integrins to move from place to place. Milner *et al.* have shown that alpha-vbeta-1 mediates oligodendocyte migration *in vitro*, and a shift in expression to alpha-vbeta-5 correlates with differentiation and cessation of migration (178). The alpha-v integrin also associates with beta-3 and beta-8 subunits in a fashion that is regulated with differentiation and influenced by the presence of axons (174). Blaschuk *et al.* have shown that when alpha-vbeta-3 was constitutively expressed in the oligodendrocyte cell line CG-4 proliferation increased and the cells did not differentiate (179). They also showed that blockade of the alpha-vbeta-5 integrin inhibited differentiation. In the tenascin-C (alpha-vbeta-3 ligand) knockout mouse there is an increase in oligodendrocyte migration along the optic nerve, as well as a decrease in proliferation (180). The alpha-vbeta-3 integrin is activated though a PKC-dependent pathway initiated by the PDGF receptor in oligodendrocytes. PDGF can stimulate oligodendrocytes to proliferate only when an alpha-vbeta-3 substrate is provided (181). Thus far the alpha-v integrins have been shown to play several key roles in migration, proliferation, and differentiation. Surprisingly, no nervous system defects have yet been reported in the alpha-v null mutation (182).

Myelination. Once in the proper location the oligodendrocytes must myelinate the neuronal processes they contact. This requires the alpha-6beta-1 integrin (183). Cultured oligodendrocytes that were transfected with a dominant negative beta-1 integrin construct were transplanted into spinal cord lesions. The oligodendrocytes with the dominant negative construct were unable to remyelinate axons, while control cells were able to remyelinate properly. The dominant negative cells still expressed normal amounts of myelin basic protein, but had diminished myelin membrane formation both *in vivo* and *in vitro*. In contrast, a conditional knockout of the beta-1 integrin in neuronal and glial cells did not manifest any defects in myelination (51). However, it was reported that the endfeet of radial glia failed to bind to the meningeal basement membrane. alpha-6beta-1 has also been shown to mediate oligodendrocyte binding to laminin produced by astrocytes, which keeps the oligodendrocytes from undergoing apoptosis (184). These adhesion events play crucial roles in demyelinating diseases such as multiple sclerosis (see section 3.6).

Microglia are the macrophages of the CNS, and function by phagocytosing dead neurons and clearing debris. Upon activation by various cytokines, the microglia

Table 3. Glial Integrins

Integrin	Glial Type	Putative Function
Alpha-1 beta-1	Astrocytes, Schwann Cells	Remyelination After Injury
Alpha-2beta-1	Schwann Cells	
Alpha-3beta-1	Astrocytes	
Alpha-4beta-1	Schwann Cells, Microglia	PNS glial cell survival
Alpha-5beta-1	Schwann Cells	PNS glial cell proliferation
Alpha-6beta-1	Astrocytes, Oligodendrocytes, Schwann Cells	Schwann cell migration, oligodendrocyte myelination
Alpha-7beta-1	Schwann Cells	
Alpha-8beta-1	Schwann Cells	
Alpha-9beta-1	Schwann Cells	
Alpha-vbeta-1	Oligodendrocytes	Oligodendrocyte Migration
Alpha-Mbeta-2	Microglia	Microglial Migration
Alpha-Lbeta-2	Microglia	Microglial Target Recognition
Alpha-vbeta-3	Astrocytes, Oligodendrocytes, Schwann Cells	Oligodendrocyte Proliferation
Alpha-6beta-4	Astrocytes, Schwann Cells	
Alpha-vbeta-5	Astrocytes, Oligodendrocytes	Oligodendrocyte Proliferation
Alpha-vbeta-8	Astrocytes, Schwann Cells, Synaptic Glia	

migrate very rapidly to sites of neuronal injury, or other stimuli (e.g. beta--amyloid protein) (185-187). Increased mobility requires efficient adhesion at the leading edge of the cell and deadhesion at the trailing edge (91, 188). Once activated, microglia begin to deramify to form a more ameboid cell shape, and increase alpha-Mbeta-2 integrin (aka. MAC1) expression to facilitate migration. The microglia then bind to their target using alpha-Lbeta-2 and alpha-4beta-1. These integrins are known to mediate cell:cell interactions by homophilic binding and binding to ICAM-1 and VCAM-1.

Glial Integrins in the peripheral nervous system. There are three types of glia that are located in the peripheral nervous system: Schwann cells (myelinating, and non-myelinating), satellite cells, and enteric glial cells (62). Myelination in the peripheral nervous system is carried out by Schwann cells, which express alpha-1beta-1, alpha-2beta-1, alpha-6beta-1, alpha-4beta-1, alpha-5beta-1, alpha-vbeta-3, alpha-vbeta-8, alpha-6beta-4 and possibly alpha-7beta-1, alpha-8beta-1, and alpha-9beta-1 (174, 189). Schwann cells migrate and proliferate along axons, and begin to differentiate by forming a myelin sheath around peripheral nerve axons. The microenvironment of the Schwann cells is very important for proliferation, migration and differentiation. The basal lamina surrounding axons is crucial to the myelination process (190).

Haack and Hynes transplanted neural crest cells from alpha-4 and alpha-5 null mice into chicken embryos and monitored the migration, proliferation, differentiation and rate of apoptosis of the mutant cells (62). The results indicate that alpha-5 integrins are required for glial proliferation, and alpha-4 integrins are required for survival. Loss of either integrin did not affect differentiation or migration, as the glia were still able to migrate (both *in vitro* and *in vivo*), and myelinate axons.

The laminin receptor integrins alpha-6beta-1 and alpha-6beta-4 have been shown to play an important role in Schwann cell migration and myelination. Schwann cells are also capable of making laminin-1 and laminin-2 and using their alpha-6beta-1 integrins to adhere to and migrate along acellular nerve segments (191). alpha-1beta-1, another laminin receptor, has been detected mostly on non-myelinating Schwann cells were it is thought to play a role in remodeling after nerve injury (192). Function-blocking antibodies against the beta-1 integrin can block myelination *in vitro* (193). More recently Feltri *et al.* generated a Cre-loxP conditional knockout of the beta-1 integrin in Schwann cells, and showed that these cells are still capable of populating nerves, proliferating, and surviving normally (194). However, the mutant cells were unable to segregate and bundle axons and were unable to completely myelinate and maintain myelinated segments of axons. Poderatz *et al.* (195) observed the same result using function-blocking beta-1 antibodies. This result is somewhat contrary to the results obtained by Haack and Hynes, and clarification will require further experimentation (62). The beta-1 conditional knockout mice produced by Feltri *et al.* resemble dystrophic mice that lack laminin-2 (196). Dystrophic mice have served as a model for the study of congenital muscular dystrophy (see section 3.6). The beginning of the beta-1 signaling pathway in Schwann cells has been dissected, and the major signaling complex contains FAK, paxillin, and fyn (197). Further experiments will help to gain a better understanding of the cell-cell and cell-ECM signaling events that are necessary for proper myelination to occur.

3.6. Integrins in Neural Disease

Integrins play a significant role in immune surveillance and tissue repair during infection and injury, and may be expressed by both circulating and extravasating immune cells, as well as endothelial cells. The functions of integrins in the immune system have been described in many reviews and primary reports (198, 199). Below, we discuss recent literature on integrin involvement in neural disease (Table 4).

3.6.1. Pathogenic Infection

Integrin receptors facilitate the extravasation, migration, and retention of immune cells, such as neutrophils and lymphocytes, into pathogenically compromised neural tissue. In most cases of pathogenic infection, the damage to neural tissues is often a consequence of immune cell response to the pathogenic antigen in the nervous system, and not directly associated with the invading pathogen. Pathogenic infection stimulates integrin expression on immune and endothelial cells, which may result in altered adhesion, cell trafficking, and cytokine release.

Bacterial, Parasitic, and Fungal Infection. The immune system responds to infection in the brain by mobilizing leukocytes. Integrins alpha-Lbeta-2, alpha-Mbeta-2 and alpha-4beta-1 on leukocytes bind to ICAMs and VCAMs on inflamed endothelium, bringing about extravasation of the immune cells into brain tissue. Studies of Lyme disease (200), Chagas disease have shown clear roles for these integrins (201-203). In meningitis, extravasation of neutrophils into the CNS contributes to brain injury. In a rabbit model of Group B Streptococcal meningitis, extravasated neutrophils in cerebral spinal fluid (CSF) showed a significant increase in beta-1 and beta-2 integrin expression (204). Moderate hypothermia early in infection of Group B Streptococcal meningitis resulted in decreased expression of beta-1 integrins on CSF neutrophils and decreased immune cell deposition in the neural parenchyma. beta-2 expression was also decreased but not significantly. This suggests that the pyretic condition caused by systemic infection may facilitate the upregulation of integrins involved in immune cell extravasation.

Since the immune response can damage the nervous system, it may be possible to treat patients with molecules that block integrin function and preclude leukocyte extravasation. Recent research in this area has yielded mixed results. In a rat model of *Haemophilus influenzae* type b (Hib) infection and meningitis, preliminary experiments using a monoclonal antibody against integrin alpha-M for *in vivo* pre-treatment show that while there was a slight decrease in the number of immune cells in the meninges, overall incidence of meningitis in infected rats was not decreased (205). Further research is required to assess the soundness of this potential treatment.

Cryptococcus neoformans is an opportunistic fungus that first infects the lungs and then disseminates to the CNS, causing meningoencephalitis (206). Analysis of mice infected with *C. neoformans* and treated with an antibody for alpha-M showed a partial, yet reproducible, reduction in the fungal loads in the brain. Furthermore, this treatment also significantly decreased the number of live fungal organisms circulating in the blood (207). Interestingly, treatment with antibody for beta-2 increased the fungal load in the brain. Blocking the beta-2 action during infection may render the disease more severe, since cryptococcal polysaccharides have been shown to bind beta-2 integrin and inhibit leukocyte migration into affected tissue, thereby allowing the infection to progress more rapidly (208).

Viral Infection. Viral infections elicit both humoral and cell-mediated immune responses in the host. Activated T-lymphocytes, key players in the cell-mediated immune response, are thought to play a significant role in pathogenesis, due to their ability to invade the CNS and secrete proinflammatory cytokines. During viral infection, integrins appear to be involved in directed movement of the host lymphocytes towards the compromised tissue. Also, integrins may be used as receptors by some viruses to gain entry into a cell and integrins may facilitate other post-attachment events during viral infection (Table IV) (209, 210).

When human peripheral blood lymphocytes were infected with Human T-Lymphotrophic Virus-1 (HTLV-1), expression of alpha-4beta-1 and alpha-5beta-1 integrins on the lymphocytes increased. The addition of function-blocking antibodies inhibited adhesion of infected cells to fibronectin (211), indicating that HTLV-1 infection may promote the abnormal adhesion and localization of T-cells in the CNS. Integrin-mediated cell adhesion also affects the expression of cytokine-induced matrix metalloproteinases-9 (MMP–9) from human astrocytes exposed to T-lymphocytes activated by HTLV-1. Antibodies to integrin subunits (alpha-1, alpha-3, alpha-5, and beta-1) resulted in decreased MMP-9 expression in astrocytes in contact with infected T-lymphocytes (212). It is thought that inhibition of integrin-mediated cell adhesion blocks cytokine secretion from activated T-lymphocytes, and thus, prevents metalloproteinase expression from astrocytes. This report highlights the dynamic interaction between virally infected T-cells and the CNS, and emphasizes how host neural cells may facilitate the inflammatory process.

A common consequence of Simian Immunodeficiency Virus (SIV) and Human Immunodeficiency Virus (HIV) infection is encephalitis, which is characterized by lesions comprising multinucleated giant cells, invading macrophages, gliosis, and microglial nodules and is followed by progressive motor and cognitive dysfunction (213). In the brains of SIV-infected Rhesus monkeys with impaired CNS function (CNS function was assessed by analysis of sensory evoked potentials), there were 5-fold more T-cells versus non-infected controls. Furthermore, T-cells in the brain and CSF showed high levels of alpha-L expression, suggesting a functional association between increased integrin expression and SIV-related CNS impairment (214).

Replication of macrophage-tropic HIV-1 was upregulated in human macrophages that were co-cultured

Table 4. Integrins in Neural Disease

Neural Disease	Integrin	Putative Function
Infectious diseases		
Meningitis, encephalitis, lyme disease, viral infection	**Alpha-4beta-1, alpha-lbeta-2**	Extravasation of leukocytes; Incorporation of integrins into viral coats
Demyelinating diseases		
Multiple sclerosis, guillain-barre syndrome	**Alpha-4beta-1, alpha-lbeta-2**	Extravasation of leukocytes
Muscular dystrophy	**Alpha-7beta-1**	Formation of neuromuscular junction
	Alpha-?beta-1	Schwann cell myelination
Cancer		
	Alpha-1beta-1, alpha-2beta-1, Alpha-3beta-1, alpha-5beta-1, Alpha-6beta-1, alpha-vbeta-3, alpha-vbeta-5	Metastasis of gliomas, neuroblastomas
	Alpha-vbeta-3, alpha-vbeta-5	Tumor angiogenesis
Injury		
Ischemia	**Alpha-vbeta-3**	Astrocyte activation
	Alpha-1beta-1, alpha-6beta-4	Microvessel response to ischemia
Regeneration and repair	**Alpha-1beta-1, alpha-4beta-1, alpha-5beta-1, alpha-7beta-1**	Regeneration of axons by peripheral neurons
	Alpha-dbeta-2	Monocyte/macrophage migration into injured spinal cord
Neurodegenerative diseases		
Alzheimer's disease	**Alpha-4beta-1, alpha-lbeta-2**	Microglial response to amyloid plaques
	Alpha-5beta-1	Neuronal internalization and degradation of β-amyloid
Retinal diseases		
Macular degeneration, proliferative diabetic retinopathy	**Alpha-vbeta-3, alpha-vbeta-5**	Retinal angiogenesis
Autoimmune anterior uveitis	**Alpha-4beta-1**	Extravasation of leukocytes
Proliferative sickle cell retinopathy	**Alpha4beta-1**	Vessel occlusion

with brain microvascular endothelial cells. This upregulation required cell-cell contact, as addition of antibody against alpha-Lbeta-2 blocked viral replication (215). These data highlight the significance of the blood-brain-barrier (BBB) during viral infection. During virion budding, HIV-1 may incorporate functional host membrane receptors, such as integrins, in a selective and non-random mechanism that is not well understood (216). Infectivity of non-susceptible cells by HIV-1 was increased when HIV-1 virions acquired alpha-Lbeta-2 and alpha-4beta-1 integrins (217). This work has important implications for the *in vivo* spread and transmission of HIV-1.

3.6.2. Demyelinating Diseases

Immune-mediated diseases of the CNS and PNS, such as Multiple Sclerosis (MS) and Guillain Barre Syndrome (GBS), respectively, are responsible for the majority of adult inflammatory and demyelinating nervous system impairment. The mechanism of neuropathogenesis possibly involves autoimmunity and is characterized by T-lymphocyte infiltration into the nervous system through the BBB, macrophage-mediated demyelination, axon loss, inflammation, and disease (For extensive review, see (218)). Common animal models used to study these inflammatory, demyelinating diseases are experimental autoimmune encephalomyelitis (EAE), Semliki Forest virus-induced demyelination (SFV), and experimental autoimmune neuritis (EAN). There is growing evidence that integrins play a critical role in both immune cell recruitment and pathogenesis (219), and targeting of integrins holds promise as a therapeutic approach to immune-mediated disorders of the nervous system.

Multiple Sclerosis. During bouts of MS, alpha-4beta-1 and beta-2 integrins on leukocytes bind VCAM-1 and ICAMs on inflamed endothelial cells during the extravasation of leukocytes out of blood vessels. Blocking antibodies to these integrins inhibit disease progression in animal models of Multiple Sclerosis. This has lead to the development of antibody therapeutics, and small molecule inhibitors of integrins (220, 221). An alpha-4 peptide inhibitor (CS-1 mimic) was shown to abrogate both clinical signs and T-cell invasion of the CNS in passively induced EAE. The same inhibitor reduced clinical signs, but was unable to prevent recruitment of T-cells into the CNS (222). Antibodies to alpha-4? can block this migration *in vitro* and *in vivo*, suppressing both clinical and pathologic features of EAE in the guinea pig and mouse (223). Therapeutic alpha-4 antibody targeting in MS patients is currently clinical trials (e.g. (224)). VCAM-1 in murine spinal cord white matter microvasculature was shown, in a direct *in vivo* experiment, to capture T-cells via the alpha-4 integrin (225). A novel spinal cord window technique was employed to visualize T-cell microcirculation by intravital fluorescence videomicroscopy. Addition of blocking antibodies for alpha-4 and VCAM-1 significantly reduced the number of captured T-cells in the BBB microvasculature.

Alpha-4 also pairs with beta-7 integrin, and there is evidence that this heterodimer also plays a role in EAE disease progression. In the chronic phase of a non-remitting form of EAE, treatment with antibody against beta-7 diminished disease progression. In addition, when antibodies to alpha-4 and beta-7 were administered simultaneously, remission occurred more rapidly and completely (226). Recently, selective alpha-4beta-7 antagonists have been described that may prove to be effective therapeutics (227).

Other integrins may also be feasible drug targets. Recently, adhesion of T-cells from human MS patients on collagen IV (the major constituent of basement membranes found in the BBB) was shown to be inhibited by blocking antibodies against alpha-1beta-1. Partial inhibition was seen with anti-alpha-2beta-1 antibody. Irradiation of these pathogenic T-cells was performed and resulted in significantly decreased adhesion to collagen IV, suggesting an attenuation of these inflammatory T-Cells, which may be used for vaccination therapy (228). However, efforts to develop this approach must take into account the probability of causing further autoimmune problems. Another potential therapy is aimed at preventing demyelination and facilitating remyelination. MS pathogenesis is characterized by dying oligodendrocytes and loss of myelination. Corley *et al.* reported that mouse astrocytes promoted oligodendrocyte survival *in vitro* via an alpha-6 integrin and laminin dependent interaction (184). Neurological injury may be prevented if this oligodendrocyte survival mechanism can be enhanced *in vivo.*

Guillain-Barre Syndrome. While MS is a disease of the CNS, Guillain-Barre Syndrome (GBS) is a similar inflammatory, demyelinating syndrome of the peripheral nervous system (PNS) (229). When integrin expression profiles in EAE and GBS were compared, inflammation and demyelination appeared to downregulate alpha-2beta-1 and alpha-6beta-4 on Schwann cells (218, 230). Further, when axonal loss was present, alpha-5beta-1 was expressed de novo on Schwann cells, which may be indicate a neuronal repair function for alpha-5beta-1. With regard to clinical detection of GBS, Sessa *et al.* reported that myelin-associated alpha-6beta-4 fragments were found in the serum of GBS patients and may provide a marker for disease damage and severity (231). Pathogenesis also appeared to involve alpha-4beta-1 integrins, as injection of neutralizing antibodies against alpha-4beta-1 into EAN rats significantly decreased disease severity (232). Interestingly, in an adhesion assay in which lymphocytes from human GBS patients were seeded onto VCAM-1-coated wells, addition of Interferon-beta (IFN-beta) caused lymphocyte adhesion to decrease rapidly without a concomitant decrease in alpha-4beta-1 or alpha-Lbeta-2 expression. This suggests a mechanism whereby IFN-beta may induce a conformational change, resulting in inactivation of the integrin (233). IFN-beta is currently used as an effective therapy for MS and may provide potential clinical benefit for GBS patients (234).

Muscular Dystrophy. One form of congenital Muscular Dystrophy (MD) is caused by a deficiency of Laminin-2 (Ln-2). This results not only in degeneration of muscle, but also demyelinating neuropathies in the CNS and PNS (235). As mentioned above, deposition of Ln-2 in the basement membrane appears to be critical for Schwann cell myelination of motor neurons. Ln-2 deficiency may disturb this interaction and result in demyelination. alpha-7beta-1, another laminin-binding integrin, has been shown to play a role in the formation of the postsynaptic membrane of the neuromuscular junction (NMJ) and alpha-7 homozygous null mice develop a muscular dystrophy-like disorder (236). In dystrophic mice, enhanced expression of alpha-7beta-1 integrin partially restored the structure of the postsynaptic membrane at the NMJ and slowed the progression of muscle disease (237).

3.6.3. Cancer

A great deal of experimental evidence has been reported that underscores the significance of integrins in tumor growth and metastasis. In the process of neovascularization and metastasis, tumor cells must interact with the extracellular matrix proteins and cell-surface molecules in a manner that facilitates adhesion, migration, and survival. These events are thought to be mediated by integrins (For review, see (238)). While cancer is not of course specific to the nervous system, there are some special considerations that apply to CNS cancers where integrins may play a role. These are highlighted below.

Tumor growth depends on the generation of new blood vessels. Many tumors that arise in the nervous sytem are highly angiogenic. The integrins alpha-vbeta-3 and alpha-vbeta-5 show increased expression on new vessels and have been implicated in tumor neovascularization. These integrins are expressed on the vasculature associated with highly metastasizing neuroblastomas (169, 239), and

menangiomas (240). Early work showed that inhibitors of alpha-vbeta-3 and alpha-vbeta-5 could block tumor angiogenesis in several models (241). More recent work has shown that orthotopic brain tumors are markedly reduced after treatment with an alpha-v peptide antagonist (242), via induction of apoptosis in brain tumor cells and brain capillary cells (243). Furthermore, an anti-alpha-vbeta-3 antibody is currently being tested in a Phase I clinical trial, after being reported to induce apoptosis in newly generated vascular cells (244). In addition, an inhibitor of MMP-2 disrupted MMP-2 binding to alpha-vbeta-3 and prevented angiogenesis and tumor growth (245), highlighting the role of receptor-protease complex formation and synergy in vessel growth. These treatments may be especially relevant to cancers of the nervous system.

The role of alpha-vbeta-3 and alpha-vbeta-5 integrins in angiogenesis has been clouded by recent studies of mutant mice. Surprisingly, beta-3 or beta-3/beta-5 null mice not only supported tumor growth, they also showed enhanced neovascularization. In a compensatory mechanism, vessel growth may be mediated by other reported integrins such as alpha-1, alpha-2, and alpha-5, which have also been shown to play a role in angiogenesis (246). Alternatively, recent results suggest that unligated integrins can induce cell death. If the inhibitors of the integrins induce apoptosis, similar to unligated integrins, then the vascular endothelium in the knockout would be less prone to apoptosis and would show increased growth (25). Thus, alpha-vbeta-3 might be upregulated on angiogenic blood vessels to act as a sort of sensor. It would kill off endothelial cells that lacked matrix contact and thereby bring about vessel pruning to allow proper morphogenesis.

The alpha-vbeta-3 integrin may also be useful as a target for delivering specific drugs to the tumor vasculature. Hood *et al.* recently described a cationic nanoparticle that was coated with an alpha-vbeta-3 ligand (247). When a mutant raf gene was incorporated in the particle, systemic injection resulted in apoptosis of the tumor endothelium, leading to regression of the tumor.

Astrocytes account for nearly 40% of the CNS in the adult human brain, and as such, tumors of the CNS are generally of glial cell origin (248, 249). In contrast to the invasion mechanism of other malignancies, in which metastasis occurs via the vessel and/or lymphatic system away from the primary tumor, glioma invasion occurs mostly locally, infiltrating deeply into the surrounding neural tissue, via active invasion and degradation of the extracellular matrix (ECM) (250).

Malignant PNS-specific tumors that arise from glia are characterized by upregulation of alpha-6beta-1 and downregulation of alpha-6beta-4 and alpha-2beta-1 (189). Additionally, the integrins alpha-2beta-1, alpha-3beta-1, alpha-5beta-1, alpha-6beta-1, alpha-vbeta-3, and alpha-vbeta-5 have reported involvement in adhesion, migration, and invasion by gliomas. Protease regulation, angiogenesis, and survival of gliomas appeared to be mediated only by alpha-vbeta-3 (251). Furthermore, alpha-vbeta-3 expression was also observed in the periphery of high-grade glioma tissue, most notably in the glioma cells and vasculature, which suggests a role for alpha-vbeta-3 in glioma angiogenesis and migration. Also, MMP-2 was co-localized with alpha-vbeta-3 expression in the same cells, pointing to a role in matrix degradation (252). Interestingly, analysis of five different glioma cell lines showed an absence of beta-3 integrin and strong presence of beta-1, beta-5, beta-6, and beta-8 integrins, suggesting an alteration of integrin phenotype in cultured cells. The beta-8 expression is noteworthy, as it appears to be the first report in relation to glioma integrin expression and may act as a receptor for ECM proteins in gliomas. *In vivo* analysis from the same study showed that beta-5 integrin was correlated with tumor aggressiveness (253).

3.6.4. Injury, Repair and Regeneration

Following injury to the nervous system, a reorganization of cells and tissue occurs in a concerted attempt to limit the injury and facilitate the repair of tissue damage. The de novo expression of proteins causes proliferation and migration of cells, such as microglia, astrocytes, and recruited leukocytes, as the repair process ensues. PNS neurons are capable of regenerating axons but CNS neurons are not. Integrins are believed to play a role in these processes.

Ischemia. Studies of integrin expression post-ischemia have shown that alpha-vbeta-3 integrin is upregulated rapidly on astrocytes. Also upregulated is the matrix protein osteopontin (OPN), which binds alpha-vbeta-3 and may promote healing and tissue remodeling (173). In contrast, integrin alpha-1beta-1 and alpha-6beta-4 expression on cerebellar microvessels was downregulated after ischemic insult (254). alpha-6beta-4 expression was also detected on astrocytes at the interface with microvessels, near the ECM. This points to a disruption of the astrocyte-matrix interaction (167), which may be the presumptive glial scar that forms to separate injured tissue from uninjured tissue. Since inflammation contributes to ischemic injury, Becker *et al.* investigated whether blockade of integrin alpha-4beta-1 would ameliorate the damaging consequences of ischemia-induced inflammation (255). Treatment with an alpha-4 antibody decreased infarct size in focal cerebral ischemia in rats and resulted in a higher number of circulating lymphocytes. Furthermore, the protection conferred by alpha-4 antibody appeared to be independent of blood pressure, since little difference was noted in the cerebroprotection of normotensive and hypertensive rats (256). Thus, another application of alpha-4 antagonists may be to prevent leukocyte entry into the nervous system during ischemia.

Repair and Regeneration. Regeneration of axons is a topic of great interest and extensive research. Recent work has identified roles for three integrin alpha subunits in regeneration of peripheral neurons. Integrin alpha-5beta-1 was found on regenerating rat sciatic nerve following crush injury and this integrin may be involved in contact guidance of neurons following injury (257). A number of injury models have demonstrated upregulation of integrin

alpha-7 in regenerating peripheral motor and sensory neurons, but not in CNS neurons. Reduced axon regeneration was seen in alpha-7 null mice (258). Following crush injury, strong alpha-4 immunoreactivity was seen on regenerating on mouse sciatic nerve. This study also determined that the alpha-4 cytoplasmic domain is required for neurite outgrowth in transfected PC12 cells and that paxillin may be involved in the signal cascade from ECM to integrin to enhanced neurite outgrowth (76).

Neural and microglial integrin expression increases after transection of the mouse facial nerve. The neuronal beta-1 integrin expression was strongly induced by axotomy and is associated with the onset of axon regeneration. From a development perspective, beta-1 integrin is essential for neuronal adhesion and neurite outgrowth on laminin *in vitro* (78, 81, 259), which suggests a role for beta-1 integrin in adhesive and axon regrowth events in neural repair and regeneration (260). Activated microglia upregulate an extensive profile of integrins, which are likely involved in adhesion, endocytosis, phagocytosis, and break down of cellular debris during repair (see 3.6 Glial Integrins). Similarly, the tissue repair and regeneration process alters integrin expression on lymphocytes and vessel endothelium, most likely as a means to promote immune cell influx into the damaged tissue. However, the inflammatory response of infiltrating immune cells causes considerable damage to the nervous system. In a spinal cord injury model, treatment with antibody against integrin alpha-D resulted in a significant decrease in the number of monocyte/macrophage cells at the injury site (261).

Demonstrations of regeneration in the CNS have been harder to come by, as CNS neurons lack the capacity to regenerate after injury, unlike PNS neurons. This is thought to be influenced by the absence of growth-promoting factors in the CNS matrix. Investigation into the reasons behind reduced regenerative ability in adult CNS neurons as compared to younger neurons has unveiled some integrin links. In a study of chick retinal ganglion cell process regrowth under severe conditions, it was found that younger (E7) RGCs were better able to regrow processes as compared to more mature RGCs (E10). Process regrowth on thrombospondin was integrin-dependent, while regrowth was not integrin-dependent on laminin (262).

Ivins *et al.* suspected that depressed integrin activation in adult neurons may hinder regeneration and tested the ability of manganese and R-ras to enhance activation (263). Manganese was able to enhance neurite extension of retinal neurons on laminin-1 and collagen IV in an alpha-6beta-1-dependent manner. A constitutively active form of the small GTPase R-ras was also able to promote strong, alpha-6beta-1-dependent outgrowth on laminin 1.

Another study sought to determine if the failure of adult CNS neurons to regenerate is due to a change in the level of integrin expression over developmental time. Indeed, adult neurons have been shown to regenerate robustly on permissive substrates *in vitro* (264, 265). Furthermore, embryonic neurons exhibit process outgrowth when transplanted into the injured adult CNS, implicating intrinsic differences in the repair and regeneration capacity in adult and embryonic neurons, as well as permissive changes in the injured CNS milieu. It was of interest to determine whether altering the integrin profile of adult neurons to mimic young neurons might affect regeneration capability. Adenoviral expression of transgenic integrin subunits in DRG sensory neurons restored integrin levels in the adult neurons to that of embryonic neurons (266). Transfection of alpha-1 resulted in increased neurite outgrowth on laminin, while alpha-5 transfection gave enhanced neurite outgrowth on fibronectin *in vitro*, under conditions similar to those found in injured, adult CNS. Integrin alpha-1 transfected-cells plated on laminin produced similar levels of outgrowth as P0 neurons. This is an exciting result. Rejuvenation of integrins may be a key strategy in stimulating neuronal regeneration in the adult nervous system.

3.6.5. Neurodegenerative Disease

Some studies implicate integrins in neurodegenerative disease, or immune responses to the disease. There is evidence for the localization of integrins in microglia of Alzheimer's Disease (AD) brain tissue (267, 268), which suggests an inflammatory response in AD brain tissue. The implication of an inflammatory response was further supported by localization of alpha-4beta-1 and alpha-Lbeta-2 in activated microglia adjacent to amyloid deposits (269). alpha-4 was also observed in neuritic plaques in the brain tissues of AD and Down's Syndrome (DS) patients. Aged control brain tissue also showed alpha-4 immunoreactivity, although this was limited to hippocampal and neocortical neurons (270). Thus, while alpha-4 immunoreactivity may be correlated with AD and DS, there is also an apparent age-related expression of alpha-4 in the brain. Evidence to support the relationship between inflammation and neurodegenerative progression is building, as beta--amyloid activates microglial cells and initiates a release of neurotoxic substances, which causes further neuronal damage (115). Also**?**beta-1 integrin co-localizes with and mediates cell-adhesion to beta-amyloid precursor in neurons and astrocytes (271, 272). When transfected into a human neuroblastoma cell line, alpha-5beta-1 integrin appears to mediate the internalization and degradation of exogenous beta-amyloid, as well as protect cells from apoptosis (273). Interestingly, a recent study found that integrin antagonists increase uptake of Abeta-1-42 in cultured hippocampal slices (274). This result contrasts with those of Matter *et al.*, who found that RGD peptides inhibit uptake in cultured cells (273). The mechanism of this effect in slices is not clear, but it may relate to effects on the actin cytoskeleton that increase endocytosis. While expression of alpha-5beta-1 has been reported in primary hippocampal neurons, examination of alpha-5beta-1 integrin in brain tissue of AD patients would provide more insight into the role of integrins in AD (272).

3.6.5. Retinal Disease

Some causes of blindness, such as macular degeneration or proliferative diabetic retinopathy are due to

improper growth of vessels into the retina (e.g. (275)). As described in sections 3.7.3, alpha-vbeta-3 and alpha-vbeta-5 integrins are thought to mediate angiogenesis. Systemic treatment with cyclic peptide antagonists of alpha-vbeta-3 and/or alpha-vbeta-5 can block retinal neovascularization in animal models, and they are promising as potential treatments of human disease (276, 277). In an effort to minimize systemic side effects of alpha-vbeta-3 and alpha-vbeta-5 inhibition (such as inhibited wound healing) topical application of the peptide antagonist to the eye was tested. Neovascularization associated with proliferative retinopathy was inhibited in a dose-dependent manner up to a maximum of 50% (277).

Sickle cell disease can cause secondary organ damage via erythrocyte-mediated vessel occlusion (278). With respect to the retina, this damage is called proliferative sickle cell retinopathy and is characterized by hypoxic retinal tissue and neovascularization. Concurrent with the retinal pathology is a pronounced inflammatory response, as sickle cell disease patients have high circulating cytokine levels, high immune cells counts, and erthrocytes that are alpha-4beta-1-positive. Treatment with an alpha-4beta-1 peptide antagonist inhibited erythrocyte retention in the retinal vasculature (279).

With respect to inflammation, EAE (described earlier as a model for MS) may also be used as a model for the ocular disease, autoimmune anterior uveitis. Infiltrating T-lymphocytes into EAE retinae were alpha-4-positive (280), consistent with inflammatory T-cells observed in the CNS. This inflammatory integrin expression on lymphocytes differs from non-inflammatory tissue remodeling and maintenance in the retina, which involves clearance of apoptotic cells and cell debris. Noninflammatory macrophages and retinal pigmented epithelia accomplish this phagocytosis-mediated event in part via alpha-vbeta-3 and alpha-vbeta-5 integrins (220, 281).

4. CONCLUSION

Recent studies have expanded our understanding of the importance of integrins in neural development, function and disease. Additional functions in the nervous system continue to be discovered. One particular challenge that remains is to resolve the seemingly contradictory interpretations of knockout mouse phenotypes in regard to other perturbation strategies. In addition, functions of specific integrin heterodimers need to be determined, and relevant integrin ligands need to be identified and characterized. A new generation of anti-integrin drugs are emerging that will prove useful not only in treating disease (particularly autoimmune and inflammatory diseases), but also in deciphering normal integrin functions via pharmacological perturbation experiments. There is much to be done.

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