Biallelic mutations in the neurofibromatosis 2 (NF2) gene are linked to schwannoma and meningioma tumorigenesis. Cells with NF2 mutations exhibit elevated levels of phosphorylated extracellular signal-regulated kinase (ERK) and aberrant cell-cell and cell-matrix contacts. The NF2 gene product, merlin, associates with adherens junction protein complexes, suggesting that part of its function as a tumor suppressor involves regulating cell junctions. Here, we find that a novel PDZ protein, called erbin, binds directly to the merlin-binding partner, EBP0, and regulates adherens junction dissociation through a MAP kinase-dependent mechanism. Reducing erbin expression using a targeted siRNA in primary cultures of Schwann cells results in altered cell-cell interactions, disruption of E-cadherin adherens junctions, increased cell proliferation, and elevated levels of phosphorylated ERK, all phenotypes observed in cells that lack merlin. Reduction of erbin expression also results in the dissociation of merlin from adherens junction proteins and an increase in the levels of phosphorylated merlin. These phenotypes can be rescued if cells with reduced levels of erbin are treated with a pharmacological inhibitor of ERK kinase. Collectively, these data indicate that erbin regulates MAP kinase activation in Schwann cells and suggest that erbin links merlin to both adherens junction protein complexes and the MAP kinase signaling pathway.

Neurofibromatosis 2 (NF2) is an autosomal dominant disease characterized by the development of multiple tumors, including schwannomas (especially of the vestibular branch of the eighth cranial nerve), meningiomas, and ependymomas (1). Both NF2 and spontaneous schwannomas demonstrate loss of heterozygosity of the NF2 gene located on human chromosome 22 (2–6). Although mice that are Nf2-null die at early embryonic stages, heterozygotes are viable and develop metastatic disease (7, 8). Mice with Schwann cell-targeted expression of mutant merlin proteins or biallelic loss of Nf2, however, develop schwannomas that resemble the tumors seen in NF2 patients (9, 10). Collectively, these data indicate that Nf2 functions as a tumor suppressor gene.

The mechanism by which the Nf2 gene product, merlin (also called schwannomin), regulates cell growth is not well understood. Merlin is a member of the band 4.1 superfamily of proteins that link the actin cytoskeleton to transmembrane proteins. Within this family, merlin shares the highest degree of homology with a subgroup of proteins that includes ezrin, radixin, and moesin ("ERM proteins"), which interact with transmembrane proteins, such as the CD44 glycoprotein, through their N-terminal FERM (Four-point-one, ERM) domains (11, 12). The FERM domains of ERM proteins and of merlin also interact with a number of intracellular partners, including the C-terminal sequence of the sodium/hydrogen exchanger regulatory factor-1 (NHERF1; also called EBP50), that, through two PDZ (PSD95/Disc Large/Zona occludens-1) domains, link ERM proteins and merlin to other transmembrane and intracellular proteins (12).

Merlin also interacts, either directly or indirectly, with a number of proteins that may influence cell growth regulation in Schwann cells and other cells, including paxillin, erbB2, p21-activated kinase, and components of cadherin-mediated cell junctions (13–17). In Nf2-deficient mouse embryo fibroblasts, Nf2 deficiency led to piling-up of cells, hyperproliferation, increased ERK phosphorylation, and defective cadherin-mediated cell-cell interactions characterized by mislocalization of β-catenin, α-catenin, and N-cadherin (17). These data support a model for merlin function that includes integrating signals that regulate cell proliferation with signals that influence cell-cell and cell-extracellular matrix interactions.

A protein that could link merlin to both MAP kinase signaling, erbB2, and cadherin-mediated cell junctions is the recently discovered PDZ protein, erbin. Originally described as an erbB2-interacting protein, erbin contains 16 leucine-rich repeats and a single PDZ domain in its C terminus (18). Because of this unique composition of domains, erbin is regarded as a member of the LAP (for leucine-rich repeat and PDZ) protein superfamily (19). Erbin has been implicated in regulating cell polarity and in basolateral targeting of its binding partners (20). The PDZ domain of erbin binds with high affinity to members of the p120-catenin family that are implicated in regulating cadherin turnover, including δ-catenin and ARVC (armadillo repeat gene deleted in yelagardiofacial syndrome) (21). Erbin also interacts with p0071 (also called plakophilin-4),
another p120 family member, in cell-cell junctions of epithelial cells (22–24). Although the erbin PDZ domain may associate with β-catenin, it only does so in vitro with very low affinity (21). Interestingly, erbin inhibits ERK activation through its leucine-rich repeat domain (25). This effect appears to depend on indirect interactions between erbin and active, GTP-bound Ras that disrupt the binding of Raf1 to Ras and subsequent activation of ERK.

Given that both erbin and merlin associate with proteins constituting adherens junctions as well as erbB2, and that loss of either protein results in increased ERK phosphorylation, we tested the possibility that erbin and merlin interact with one another. We report here that erbin is expressed in myelinated peripheral nerve fibers by Schwann cells and interacts indirectly with merlin and directly with the C terminus of EBP50. Merlin dissociates from adherens junction protein complexes in Schwann cells with reduced erbin expression. This effect can be reversed using a pharmacological inhibitor of MEK, indicating that erbin links merlin to adherens junction protein complexes through a MAP kinase-dependent mechanism.

MATERIALS AND METHODS

Cell Culture—Schwann cells were isolated from sciatic nerves of 3-day-old rat pups (26), purified by anti-Thy 1.1 immunoselection, and expanded for 6–7 passages on 10-cm plates coated with poly-L-lysine (Sigma) in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal bovine serum, 2 μg forskolin (Sigma), and 5 ng/ml recombinant human HRG-β1 (EGF domain; R&D Systems). For cell growth assays, cells were grown in the absence of added neurotrophins to increase the proportion of Schwann cells and reduced erbin expression. This effect can be reversed using a pharmacological inhibitor of MEK, indicating that erbin links merlin to adherens junction protein complexes through a MAP kinase-dependent mechanism.

Immunoprecipitations—Total protein extracts were made in 85 mM NaCl, 150 mM Tris-HCl, 1% Triton X-100, pH 7.5, supplemented with protease inhibitors as previously described (27). Mean numbers of cells were determined from at least three cultures per condition. Significance was determined using a Student’s t test.

RESULTS

Erbin Is Expressed by Schwann Cells in Myelinated Peripheral Nerves—In peripheral nerves, β-catenin is expressed in the outer cytoplasmic loops of Schwann cells, in Schmidt-Lanterman incisures, and flanking axons at the paranodes, with only diffuse expression at the node of Ranvier (28). We therefore tested whether erbin localized to the nodes or paranodes of teased sciatic nerve fibers by double-labeling immunohistochemistry with anti-erbin and anti-β-catenin antibodies. Erbin and β-catenin co-localized at incisures and at paranodes in a pattern consistent with expression by Schwann cells at these locations (Fig. 1, A and B). Erbin was also weakly expressed at the abaxonal membrane, especially near incisures (Fig. 1B, arrowheads, middle panel). To verify that erbin is expressed by Schwann cells, we examined erbin expression in primary Schwann cell cultures derived from neonatal rat sciatic nerves. Erbin was diffusely expressed near the membrane (arrowheads, Fig. 1C) and throughout the cytoplasm (arrow, Fig. 1C, middle panel) of Schwann cells where it partially co-localized with β-catenin.
Reducing Erbin Expression Alters Schwann Cell Proliferation and Cell-Cell Interactions—Using a previously described erbin siRNA construct (25) we found that we could reduce erbin expression in primary cultures of Schwann cells by 50–80% as determined by scanning densitometry of Western blots probed with an erbin antibody (Fig. 2A). Neither an empty vector, an irrelevant siRNA (against glyceraldehyde-3-phosphate dehydrogenase; not shown), nor a scrambled erbin siRNA (Fig. 2A, right panel) had any effect on erbin expression. Schwann cells with reduced erbin levels tended to pile up on top of one another, had a more flattened appearance than cells in control cultures, and failed to form typical cell-cell contacts in confluent cultures (Fig. 2, compare B and D with C and E). Consistent with this observation, we found that β-catenin became dissociated from E-cadherin (but not N-cadherin) in erbin siRNA-treated cells (Fig. 2, F and G) even though the absolute levels of E-cadherin and β-catenin were unaffected by the reduction of erbin (Fig. 2H).

Many of the cells that piled-up in the erbin siRNA-treated cultures became detached and floated in the culture dish. By 55 h post-transfection, 40–50% of cells treated with erbin siRNA were floating in the culture dish as compared with control cultures where fewer than 5% of cells were floating. This occurred in cultures grown on both poly-L-lysine and laminin-coated plates (data not shown). We therefore tested if cells became detached due to cell death by performing trypan blue exclusion assays and cell counts on both attached cells and floating cells at 24, 48, and 55 h post-transfection. There were 20–30% more live Schwann cells (determined by counting both attached and detached cells that excluded trypan blue; Fig. 3A) in the erbin siRNA cultures than in the control cultures. Consistent with this observation, we observed a 15–25% increase in the numbers of cells expressing Ki-67 (Fig. 3B) and a dramatic (>4-fold) increase in the expression of cyclin D1 (Fig. 3C), indicating that reduced erbin expression leads to increased Schwann cell proliferation. Reducing erbin expression also caused an increase in the levels of phosphorylated ERK (40–60% above controls, normalized to the levels of total ERK protein).

The majority of the detached cells found in the medium 55 h post-transfection were alive (Fig. 3D). However, 24 h later, nearly all of these cells incorporated trypan blue, suggesting that they died as a result of anoikis (data not shown). To determine if a greater number of the floating cells had incorporated erbin siRNA than those that were still attached, we repeated these experiments using a fluorophore-tagged erbin siRNA construct. Over 90% of the cells, both attached and floating, had taken up the siRNA 24 h post-transfection (data not shown). Moreover, immunocytochemistry revealed that at 50 h post-transfection, erbin expression had been reduced to a similar degree in all the cells that had taken up the siRNA construct (data not shown), thus ruling-out the possibility that the floating cells were for some reason more likely to have taken-up the erbin siRNA at the time of transfection. Together, these data indicate that reducing the levels of erbin in Schwann cells promotes Schwann cell proliferation in conjunction with a disruption of normal cell-cell contacts.

The Phenotypes of Schwann Cells with Reduced Levels of Erbin Can Be Reversed with an MEK Inhibitor—Erbin has been implicated in regulating the activation of ERKs by interfering with the binding of Raf-1 to activated Ras (25). As shown above, Schwann cells with reduced erbin expression had increased levels of phosphorylated ERK compared with controls (Fig. 3C). To determine if the phenotypes of Schwann cells with reduced erbin expression could be reversed by lowering ERK activation, we tested the effects of a MEK inhibitor, U0126, on Schwann cells treated with erbin siRNA. After 24 h in the presence of 25 μM U0126, ERK phosphorylation was dramatically reduced in cells that had been grown in the presence of erbin siRNA (Fig. 4A). Furthermore, blocking MEK reversed the dissociation of β-catenin from E-cadherin (Fig. 4B), as well as the piling-up phenotype observed in cultures treated with the erbin siRNA alone (Fig. 4, C and D), with many cells (>40%) regaining cell-cell contacts. Increased proliferation and the detachment of live, erbin siRNA-treated cells were also markedly reduced following treatment with U0126 (Fig. 4, C and D).
These data indicate that the phenotypes of Schwann cells with reduced levels of erbin depend on increased MAP kinase activity.

Merlin Associates with Erbin in Schwann Cells—Given that merlin is known to localize to adherens junctions in other cell types (17), that merlin and erbin are expressed by Schwann cells and co-localize to the paranodes and Schmidt-Lantermann incisures of peripheral nerve fibers (29), and that loss of merlin or erbin cause the dissociation of adherens junctions (17), we postulated that erbin may play a role in linking merlin to the complex of proteins that constitute adherens junctions in Schwann cells. To test if erbin and merlin co-localize with one another in Schwann cells, we analyzed merlin and erbin localization in Schwann cell cultures by immunocytochemistry. Merlin has been reported to localize to the Schwann cell membrane and adjacent cytoplasm, filopodia, ruffling membranes, and microspikes (13) but is absent from the Schwann cell tips, a region that is highly immunoreactive for N-cadherin (30). We report here that erbin (Fig. 5A) co-localized with merlin (Fig. 5B) near the cell membrane and throughout Schwann cell cytoplasm (Fig. 5, A–C). In agreement with this finding, erbin co-immunoprecipitated with merlin and $\beta$-catenin in Schwann cells grown at both confluent (not shown) and subconfluent densities (Fig. 5, D and E). Interestingly, although Schwann cells also express ezrin, we were unable to co-immunoprecipitate ezrin with erbin (Fig. 5E) suggesting that erbin does not
Role of Erbin in Schwann Cell Adherens Junctions

Loss of Erbin Results in Increased Merlin Phosphorylation and the Dissociation of Merlin from Adherens Junction Protein Complexes—We next tested the possibility that erbin links merlin to proteins in Schwann cell adherens junctions. Reducing erbin expression using the erbin siRNA had no significant effect on total levels of merlin, the levels of CD44, which interacts with merlin (31), or, as shown above, on levels of β-catenin (Fig. 5F). The expression of EBP50 was slightly elevated (between 1.2- and 1.4-fold; Fig. 5F). This latter finding is interesting in light of the fact that EBP50 phosphorylation is elevated in cells that lack merlin (32).

Although total merlin levels do not appear to change significantly in the presence of erbin siRNA (with total signal from all bands being only 5–12% lower in siRNA-treated cultures compared with controls), a slower mobility merlin band was in far greater abundance (60–80%) than a band with faster mobility (Fig. 5F). When Schwann cell lysates were treated with λ-protein phosphatase, the merlin band with slower mobility was abolished confirming that this band represents a phosphorylated form of the protein (Fig. 5F, lower panel). These findings are interesting in light of the fact that the activity of merlin as a tumor suppressor protein has been linked to its phosphorylation status (14, 31, 33–35), and because loss of erbin in Schwann cells results in increased cell proliferation, as shown above. Merlin appears to suppress cell growth only when it is hypophosphorylated (31). Thus, loss of erbin appears to promote the growth-permissive state of merlin.

In untreated Schwann cells (not shown) and cells treated with control siRNAs, β-catenin co-immunoprecipitated with merlin (Fig. 5G). However, little or no β-catenin co-immunoprecipitated with merlin in cells with reduced erbin expression (Fig. 5G). E-cadherin similarly failed to co-immunoprecipitate with merlin in the erbin siRNA-treated cells (data not shown). In contrast, interactions between merlin and EBP50 (Fig. 5G), merlin and CD44 (Fig. 5G), and β-catenin and EBP50 (Fig. 5F) were unaffected in Schwann cells with reduced erbin expression. Collectively, these data suggest (a) that erbin links merlin to adherens junction protein complexes and (b) that intracellular pools of EBP50, which bind β-catenin, may be distinct from pools of EBP50 that interact with merlin.

Erbin Forms a Complex with EBP50 and Merlin—To test if erbin binds directly to erbin, we examined interactions between merlin and erbin fusion proteins in vitro. We were unable, however, to find any conditions under which merlin bound directly to erbin (data not shown), suggesting that merlin associates indirectly with erbin in Schwann cells. One possible way that merlin could be linked to erbin is via EBP50. We found that erbin and merlin co-immunoprecipitate with EBP50 in Schwann cell lysates (Fig. 6A). Furthermore, EBP50 was precipitated from Schwann cell lysates using erbin-GST fusion proteins encompassing the domain adjacent to the PDZ domain (Fig. 6, B and C).
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FIG. 5. Erbin associates with merlin and is required for the interaction between merlin and adherens junction proteins. A–C, confocal images of a Schwann cell in vitro double labeled with anti-erbin (A) and anti-merlin (B) antibodies. Co-localization of the two proteins is evident in the merged image (C), where the nucleus is labeled with Hoechst 33342. D, co-immunoprecipitation assay showing that Schwann cell lysates immunoprecipitated with a merlin antibody (IP) also pull-down erbin and β-catenin. E, co-immunoprecipitation assay using an anti-erbin antibody. Note that while merlin co-immunoprecipitated with erbin, ezrin did not. F, effects of erbin siRNA on the levels of proteins associated with merlin. Actin was used as a loading control. Note that there was a slight increase in EBP50 in cells treated with the erbin siRNA as compared with cells treated with a control vector. In the lower panel, lysates were pretreated with λ-phosphatase, demonstrating that the higher molecular weight band that accumulates in the erbin siRNA-treated cultures is a phosphorylated form of merlin. G, Western blot analysis of a merlin co-immunoprecipitation experiment following treatment with the erbin siRNA. Note that merlin no longer associates with β-catenin, but still interacts with CD44 and EBP50. H, co-immunoprecipitation assay showing that β-catenin still interacts with EBP50 following treatment with the erbin siRNA.

We find that erbin is expressed by Schwann cells in myelinated peripheral nerves and indirectly associates with merlin. Reducing erbin expression in Schwann cells results in phenotypes that are similar to those of both human schwannoma cells and mouse embryo fibroblasts that lack merlin (17, 36), including altered cell-cell contacts, disruption of adherens junction proteins, increased cell proliferation, and elevated ERK phosphorylation. These phenotypes can be rescued using a MEK inhibitor, indicating that elevated MAP kinase activity is required for the phenotypes induced by erbin siRNA. Previous studies demonstrated that erbin binds directly to δ-catenin and other p120-catenin family members with high affinity, and we have found that δ-catenin and erbin co-immunoprecipitate in Schwann cell lysates, thus linking erbin to adherens junctions. Here, we find that erbin also binds directly to EBP50. We propose, therefore, that erbin links merlin to adherens junction protein complexes through EBP50, and that these interactions are stabilized through the ability of erbin to regulate MAP kinase activity, likely by preventing interactions between Raf1 and Ras-GTP (25).

Erbin was originally described as an erbB2-interacting protein (19, 37). ErbB2 is a member of the epidermal growth factor family of receptor tyrosine kinases and is essential for Schwann cell differentiation, growth, and survival (37–41). At least part of the survival signal that is transduced by erbB2 in Schwann cells involves activation of the mitogen-activated protein (MAP) kinase pathway (42). Because loss of both erbin and merlin result in elevated MAP kinase signaling, and because an MEK inhibitor can revert virtually all of the phenotypes seen in Schwann cells with reduced erbin expression, it is possible that erbin may coordinate MAP-kinase-dependent signaling between erbB2, merlin, and β-catenin. Consistent with this idea, merlin associates with erbB2 in Schwann cells through interactions with paxillin (13), and merlin can inhibit the activation of the Ras-ERK pathway, possibly through interactions with the Grb2-binding protein, magicin (43–45). The indirect interactions between merlin and erbin demonstrated in the current study provide another mechanism by which

DISCUSSION

We find that erbin is expressed by Schwann cells in myelinated peripheral nerves and indirectly associates with merlin. Reducing erbin expression in Schwann cells results in phenotypes that are similar to those of both human schwannoma cells and mouse embryo fibroblasts that lack merlin (17, 36), including altered cell-cell contacts, disruption of adherens junction proteins, increased cell proliferation, and elevated ERK phosphorylation. These phenotypes can be rescued using a MEK inhibitor, indicating that elevated MAP kinase activity is required for the phenotypes induced by erbin siRNA. Previous studies demonstrated that erbin binds directly to δ-catenin and other p120-catenin family members with high affinity, and we have found that δ-catenin and erbin co-immunoprecipitate in Schwann cell lysates, thus linking erbin to adherens junctions. Here, we find that erbin also binds directly to EBP50. We propose, therefore, that erbin links merlin to adherens junction protein complexes through EBP50, and that these interactions are stabilized through the ability of erbin to regulate MAP kinase activity, likely by preventing interactions between Raf1 and Ras-GTP (25).

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merlin could influence Ras-ERK signaling.

Although EBP50 can, itself, directly interact with β-catenin (46), theoretically bridging merlin to β-catenin, our findings indicate that erbin is required to maintain the association between merlin and adherens junction proteins, but not the interaction between merlin and EBP50. Because erbin binds to EBP50 and because EBP50 binds directly to β-catenin, it is possible that erbin functions in part to physically stabilize adherens junction protein complexes that associate with merlin. The effects of erbin on MAP kinase signaling, however, could also influence adherens junction stability as well as the affinity of merlin for different binding partners. Consistent with our results, previous studies found that the activation of at least some members of the Ras family, which leads to elevated MAP kinase activity, can promote the dissociation of E-cadherin from β-catenin in other cell types (47, 48). Furthermore, the finding that erbin can influence merlin phosphorylation in a MAP kinase-dependent manner suggests that erbin may indirectly influence merlin activity and its interactions with other proteins.

The observation that erbin loss leads to the dissociation of E-cadherin adherens junctions is interesting in light of the unique functions attributed to E-cadherin in Schwann cells. In the non-compacted areas of myelinated peripheral nerve, E-cadherin mediates the formation of adherens junctions between membrane lamellae of the same cell and are referred to as “autotypic” (28) or “reflexive” (49) adherens-type junctions. Mice lacking E-cadherin in peripheral nerves are devoid of electron-dense structures in the outer mesaxon of myelinated fibers and have a widened gap in the outer mesaxon between the two opposing membranes of the same Schwann cell (50). We predict that erbin is required to maintain stable homotypic adherens junctions at the paranode and could, therefore, significantly influence the integrity of non-compacted myelin. Our findings could further implicate erbin in regulating Schwann cell behaviors following peripheral nerve injury or other insults, when Schwann cells proliferate and undergo a series of changes in cell-cell and cell-matrix adhesion during the course of Wallerian degeneration and regeneration, then re-establish

**FIG. 6.** Erbin binds directly to EBP50. A, co-immunoprecipitation assay of Schwann cell lysates showing that an anti-erbin antibody co-immunoprecipitates EBP50. B, diagram of erbin GST proteins used in protein-protein interaction assays. C, Western blot of proteins eluted from GST-erbin fragments incubated with Schwann cell lysates, as indicated in B, showing that EBP50 binds to a domain within amino acids 914–1240 of erbin. Lys, total cell lysates; GST, pull-down with GST alone. D, Western blot from an in vitro binding assay showing full-length EBP50 binds directly to amino acids 914–1240 of erbin. E, diagram of EBP50 protein fragments used in the in vitro binding assays. F, in vitro binding assay showing that full-length erbin binds to carboxyl tail of EBP50.

**FIG. 7.** The dissociation of merlin from β-catenin and aberrant merlin phosphorylation are rescued by a MEK inhibitor. A, co-immunoprecipitation assay showing that the association between β-catenin and merlin are re-established if cells with reduced levels of erbin are treated with U0126. Note that the MEK inhibitor alone has no effect on β-catenin-merlin interactions. B, Western blot showing that U0126 reduces the increased levels of hyperphosphorylated (upper arrow) as compared with hypophosphorylated (lower arrow) merlin. Me2SO was added to control cultures without U0126 as a vehicle control.
stable cell junctions and quiescence following repair (51). Indeed, E-cadherin is up-regulated at points of Schwann cell–Schwann cell contact in peripheral nerves as they recover from nerve injury (52). Future studies will reveal the contribution of Schwann cell contact in peripheral nerves as they recover from nerve injury.

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Role of Erbin in Schwann Cell Adherens Junctions

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Erbin Regulates Mitogen-activated Protein (MAP) Kinase Activation and MAP Kinase-dependent Interactions between Merlin and Adherens Junction Protein Complexes in Schwann Cells

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