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The molecular biology and novel treatments of vestibular schwannomas

A review

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Vestibular schwannomas are histopathologically benign tumors arising from the Schwann cell sheath surrounding the vestibular branch of cranial nerve VIII and are related to the *NF2* gene and its product merlin. Merlin acts as a tumor suppressor and as a mediator of contact inhibition. Thus, deficiencies in both *NF2* genes lead to vestibular schwannoma development. Recently, there have been major advances in our knowledge of the molecular biology of vestibular schwannomas as well as the development of novel therapies for its treatment. In this article the authors comprehensively review the recent advances in the molecular biology and characterization of vestibular schwannomas as well as the development of modern treatments for vestibular schwannoma. For instance, merlin is involved with a number of receptors including the CD44 receptor, EGFR, and signaling pathways, such as the Ras/raf pathway and the canonical Wnt pathway. Recently, merlin was also shown to interact in the nucleus with E3 ubiquitin ligase $CRL4^{DCAF1}$. A greater understanding of the molecular mechanisms behind vestibular schwannoma tumorigenesis has begun to yield novel therapies. Some authors have shown that Avastin induces regression of progressive schwannomas by over 40% and improves hearing. An inhibitor of VEGF synthesis, PTC299, is currently in Phase II trials as a potential agent to treat vestibular schwannoma. Furthermore, in vitro studies have shown that trastuzumab (an ERBB2 inhibitor) reduces vestibular schwannoma cell proliferation. With further research it may be possible to significantly reduce morbidity and mortality rates by decreasing tumor burden, tumor volume, hearing loss, and cranial nerve deficits seen in vestibular schwannomas. *(DOI: 10.3171/2011.6.JNS11131)*

Key Words • **vestibular schwannoma** • **acoustic neuroma** • **merlin** • **Avastin** • **VEGF** • **neurofibromatosis Type 2** • **molecular biology** • **treatment** • **oncology**

Vestibular schwannomas, also known as acoustic neuromas, are histopathologically benign tumors that most commonly grow slowly from the Schwann cell sheath surrounding the vestibular branch of cranial nerve VIII.[62] They often extend into the cerebellopontine angle and can affect the sensory nerves of cranial nerve V, the lower cranial nerves, and the motor nerves of cranial nerve VII.[25,36,62] In the US, the incidence rate for all primary CNS nerve sheath tumors is approximately 1.1/100,000 person-years.[18,19,88] Studies in Denmark have shown an increase of sporadic vestibular schwannoma over the years: 7.8 per million per year between 1976 and 1983, 9.8 per million per year between 1983 and 1990, 12.4 per million per year between 1990 and 1995, 17.4 per million per year between 1996 and 2001, and 19.3 per million in 2001.[102,103,108–111] However, the authors noted that this may be due to increased diagnosis resulting from increased use of MR imaging.[103]

Neurofibromatosis Type 1, or von Recklinghausen disease, was coined in 1882 by Fredrich von Recklinghausen, who noted 5 patients with congenital neurofibromas.[118] In 1822, Wishart[122] reported on bilateral acoustic neuromas with faster progression of cerebral and spinal lesions.[119] Vestibular schwannomas are also intricately related to NF2 where the *NF2* gene, located on chromosome 22, is altered. It has also been shown that in patients with unilateral vestibular schwannoma, there is an increased risk of tumor growth with greater tumor size at initial presentation.[2,9,32,100,104] Furthermore, the presence of tinnitus at presentation increases the odds of tumor growth 3-fold.[2]

Abbreviations used in this paper: NF1 = neurofibromatosis Type 1; NF2 = NF Type 2.

This article contains some figures that are displayed in color online but in black and white in the print edition.

Recently, there have been major advances in our knowledge of the molecular biology of vestibular schwannoma as well as the development of modern and novel therapies for treating this disease. In this article, we comprehensively review the recent advances in the molecular biology and characterization of vestibular schwannomas and the development of modern treatments for vestibular schwannoma.

Etiology

In the general population, sporadic cases of vestibular schwannomas tend to arise unilaterally (95%), whereas in patients with NF2 they commonly occur bilaterally.[81] The most common symptoms associated with sporadic vestibular schwannoma include vertigo, hearing loss, facial paralysis, tinnitus, trigeminal neuralgia, and occasionally more serious complications such as hydrocephalus, malignant transformation, and brainstem compression.[8,20,24,54,75,81,99,121] Sporadic vestibular schwannomas are benign, slow-growing tumors in patients who present at a median age of approximately 50 years.[81] Conversely, NF2-associated bilateral vestibular schwannoma tumors generally have faster growth rates and a younger age of presentation.[43,94] The incidence of NF2 is about 1 in 35,000 persons, with no greater risk found in any one ethnicity.[25,64] Patients with the NF2 exhibit similar symptoms as those with the sporadic form of vestibular schwannoma but with the added genetic predisposition for ocular manifestations such as posterior subcapsular lens opacities.[62]

Neurofibromatosis Type 2 represents an autosomal dominant disorder with full penetrance associated with the *NF2* gene located on chromosome 22 band q11–13.1, which normally encodes the protein merlin (schwannomin).[64,124] Merlin is thought to play a role in the maintenance of membrane stability by interacting with cytoskeletal and integral membrane proteins.[64] It has been shown that both sporadic and NF2-related vestibular schwannomas are associated with a loss of function of merlin in Schwann cells.[3,91] Therefore, since its discovery, merlin produced by the *NF2* gene has been thought of as a classic tumor suppressor.[64] In a study of 33 patients with the *NF2* mutation, 19 of 20 alterations in the *NF2* gene were interrupted due a stop codon, frame shift, or interference with splicing causing truncation of merlin.[64]

Histopathological and Radiological Findings

Vestibular schwannomas in patients with the *NF2* gene are histologically benign.[64] It has been shown that a loss of function mutation in the *NF2* gene causes the Schwann cell function to switch from myelinating to nonmyelinating.[43] Histologically, both sporadic and NF2 tumors are composed of intersecting elongated spindle cells with long cigarlike nuclei.[43,61] Sporadic and NF2-associated schwannomas are similar barring a few differences.[62] Forty percent of NF2-associated vestibular schwannomas exhibit a nodular pattern, whereas sporadic schwannomas rarely appear this way. Furthermore, nerve fibers are often rooted into NF2-associated vestibular schwannomas, whereas they are more extracapsular in the sporadic form.[44,62] Another predominant histological feature is islands of neoplastic schwannoma cells bordered by a broad central area of eosinophilic fibrosis with large regions of tumor cells in the margins.[126] In a retrospective review of the histology of tumors after radiotherapy, it was found that the irradiated tumors were somewhat cellular with nuclear polymorphism, vascular hyalinization, and hemosiderin deposition.[56] However, the authors noted that these changes were also normal in nonirradiated vestibular schwannomas and observed that the absence of necrosis postirradiation indicates possible radioresistance.[56] It is thought that radioresistance occurs when there is only a small fraction of cells dividing in the tumor on administration of low-dose radiation.[60,126] The molecular mechanism behind radioresistance has been postulated to be related to the inhibition of ERBB2 and interference with cell-cycle arrest.[37,126]

Gadolinium-enhanced MR imaging is the gold standard for imaging investigation.[119] Other examinations include CT scanning and digital subtraction angiography.[68] On MR imaging, the cerebellopontine angle, auditory canal, and brainstem are often visualized to measure tumor size, mass effect, and potential scarring and fibrosis to cranial nerves such as the facial nerve.[56] Computed tomography scanning is beneficial for both diagnostic and surgical management. On thin-cut CT scans, expansion of the internal auditory canal is often noted. The tumor may also have thinned the bone surrounding it without any hyperostosis that may be seen with meningiomas in similar locations. Formal angiography can sometimes demonstrate feeding vessels to these schwannomas.[1,125] Additionally, the location of the surrounding major vessels can be elucidated.

Molecular Biology and Pathology

The NF2 *Gene and the Structure of Merlin*

The *NF2* gene was first identified on chromosome 22 using polymorphic DNA markers to screen for loss of chromosomal regions.[96] Studies were prompted based on previous studies of meningiomas that also presented with bilateral vestibular schwannomas. It has been postulated that the *NF2* gene acts as a tumor suppressor gene, and generally one allele is inherited in an autosomal dominant fashion.[64,96] A "second hit" is necessary to knock out the remaining normal allele to cause disease; this is often caused by a second-point mutation or loss of heterozygosity.[35,76] However, in one study, it was shown that 49% of cases were due to two sporadic mutations affecting each allele with a rate of 6.5×10^{-6}.[25,76] Individuals with NF2 also have a greater risk of developing peripheral schwannomas, meningiomas, and spinal ependymomas, which also exhibit biallelic NF2 inactivation.[40,74,92,114]

In 1993, two other groups isolated the loss of mutation to 22q12.2 using genetic linkage analysis and tumor deletion mapping.[91,112] The product of this gene was found to be a 595 amino acid "moesin-ezrin-radixin-like protein" known as "merlin" or "schwannomin," which is similar to cytoskeleton-associated proteins known as ezrin-radixin-moesin (ERM).[14,64,91] Both merlin and ERM

contain a FERM (Four-point one, ezrin, radixin, moesin)–binding domain usually on the amino terminus that allows it to mediate cell-cell attachment, cell motility, membrane receptor availability, and signal transduction (Fig. 1).[14,71,98] ERM family proteins can interact with one another using ERM-associated domains (N-ERMAD, C-ERMAD). While merlin lacks C-ERMAD, it still can bind to actin.[14,21,45,53,55,71,85,93,105] Moreover, it has been shown that merlin can affect signal transduction of Rho family GTPases such as Rac1 by associating with PAK (p21-activated kinase).[22,42,50,65,71,97,101,106]

A recent in vitro study on small interfering RNA merlin knockdowns in human Schwann cells showed that there was an accumulation of EGFRB (ERBB2, ERBB3), CD44, and nestin.[3]

Merlin Regulation

Studies in *Drosophila* indicate that merlin can exist in a folded or nonfolded state and that the unfolded state is active in vivo.[52] In the unfolded state, merlin's C-ERMAD can mediate cell-cell adhesion by binding to actin filaments, but the folded state is thought to be the tumor suppressor form.[71] It has been shown that missense mutations disrupt the folded state and its tumor suppressive function.[83] Merlin's conformational changes are promoted by PAK, which phosphorylates merlin at S518, interrupting the c-terminal domain and maintaining the folded state (Fig. 2).[49,82] This folding is accomplished by a folding of the alpha-helical portion and c-terminal portion of merlin such that it blocks the FERM binding sites.[57,71,84] Merlin's ability to act as a tumor suppressor is likely related to its ability to inhibit the Rac pathway, which has been associated with tumorigenesis (Fig. 2).[49,82,90] Understanding of this pathway may lead to the development of PAK inhibitors that would prevent PAK from phosphorylating merlin, allowing for maintenance of merlin's inhibition of the Rac1 pathway.[49]

Merlin Cell-Cell Adhesion and Contact Inhibition

In mouse studies, it has been shown that there is low merlin expression prior to tissue fusion, indicating that merlin would normally suppress cell-cell adhesion.[72] In studies of NF2 knockout mouse embryonic fibroblasts, it has been shown that fibroblasts lose contact inhibition of cell proliferation and that Rac1 (–/–) mutants were able to inhibit uncontrolled cell proliferation.[12,22,50,71,97] This finding indicates that merlin negatively regulates Rac1-mediated canonical Wnt signaling and that Rac1 is necessary for loss of contact inhibition.[12,22,50,71,97] It has also been shown that merlin interacts with CD44, a cell-surface receptor for hyaluronan (HA), and plays a role in promoting contact-dependent inhibition of proliferation and suppressing tumor growth.[78] Furthermore, increased merlin expression in Schwann cells prevents HA from binding to the CD44 receptor, preventing tumor growth in immunocompromised mice.[7] Bai et al.[7] showed that the first 50 amino acids of the C-terminal end of merlin are responsible for its inhibitory effect on the CD44-HA interaction. Morrison and coworkers[78] also showed that under normal circumstances at high cell density, merlin becomes hypophosphorylated, inhibiting cell growth, but at low cell density, merlin is phosphorylated, allowing for growth. PAK promotes release from contact inhibition through phosphorylation of merlin, causing it to remain in its folded state.[82] Merlin localizes to the cell membrane and stabilizes cadherin-dependent cell-cell junctions that inhibit receptor tyrosine kinase activation.[4,31,89,107] This also explains why merlin would normally inhibit Rac1 activation by interfering with the RTK pathway.[4,47,79]

Merlin Proliferative Activity

Hansen and colleagues[38] showed that vestibular schwannomas express Neuroregulin-1 (NRG1) and its receptors ERBB2 (also known as Her2/neu or HER2) and ERBB3 in vivo. NRG1 induces proliferation of human Schwann cells by binding ERBB2 and ERBB3 and initiating a phosphorylation cascade resulting in activation of PI3k and MAPK pathways.[6,67] Furthermore, it has been shown that NRG1, ERBB2, and ERBB3 are expressed during wallerian degeneration, a state in which there is a loss of axonal contact.[15] This indicates a potential relationship with merlin, which normally functions to inhibit cell growth by inhibition of cell-cell adhesion. Furthermore, it has been shown that Merlin normally inhibits ERBB2 activation and ERBB2-Src binding.[40] This offers an explanation for how loss of merlin would allow for Src activation and downstream phosphorylation

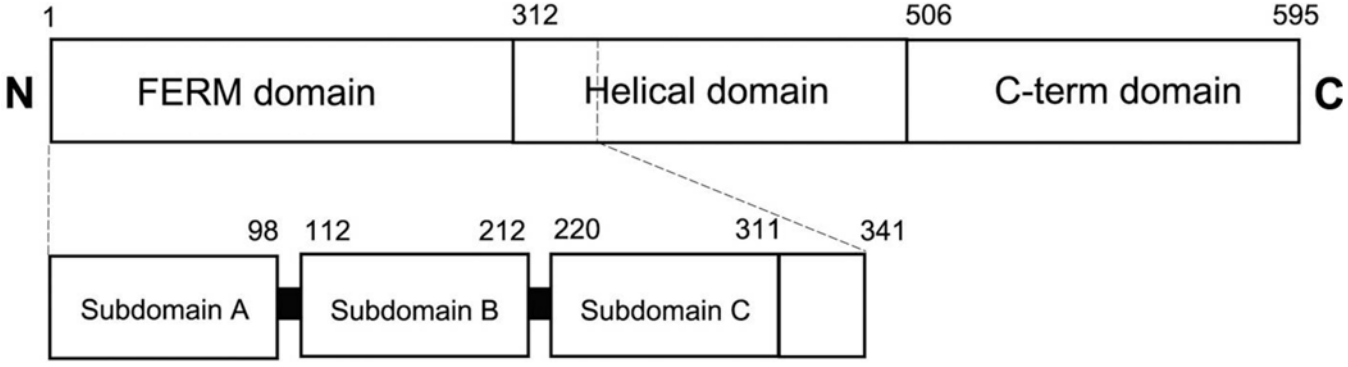

Fig. 1. Schematic of merlin domains. Merlin consists of a FERM component at the N-terminal domain, which is subdivided into subdomains A, B, and C, and a C-terminal end. The N-terminal domain is postulated to be responsible for merlin's role in cell-cell adhesion and signal transduction. Reproduced with permission from Shimizu et al.: **J Biol Chem 277:**10332–10336, 2002.

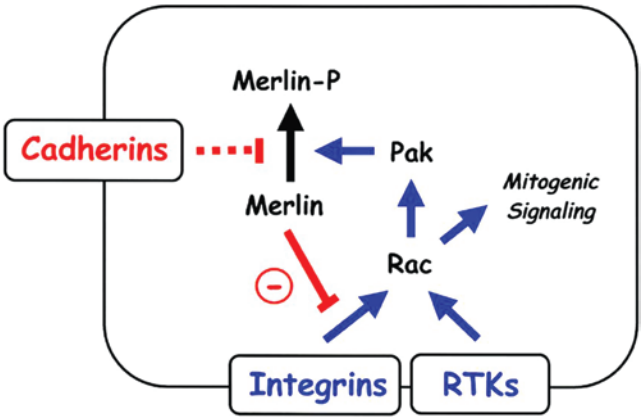

Fig. 2. Theoretical merlin signaling pathway. Merlin stabilizes cadherin interactions at the cell membrane and is inhibited from phosphorylation by cadherin binding (contact-inhibition). Accumulation of dephosphorylated merlin has an inhibitory function on the Rac pathway, further inhibiting mitogenic signaling. Once merlin is no longer bound to cadherin, PAK can phosphorylate merlin and remove the inhibition on the Rac pathway, which allows for mitogenic signaling. Reproduced with permission from Okada et al.: **J Cell Biol 171:**361–371, 2005.

of FAK and paxillin, ultimately increasing astrocyte cell growth.[40] Merlin can also bind to paxillin directly via PBD1 (exon 2).[27] Loss of exon 2 has been seen in patients with both NF2 and sporadic schwannomas.[11,13,27,33,95,120] The association between merlin and paxillin was found to be higher in confluent cells, indicating merlin's role in contact inhibition.[27,78] Paxillin plays a role in a variety of pathways including that as a mediator for RAC1 binding.[113] It has also been shown that paxillin phosphorylation is stimulated by neuregulin binding of ERBB2 and ERBB3.[26,27,66,80,116,117]

Merlin also senses cell contact by binding E-cadherin and EGFR at the cell membrane, blocking internalization of ligand-bound EGFR by sequestering it within an insoluble endosome.[22,71] Similarly, it has been shown that merlin binds β1-integrin and ERBB2 at the plasma membrane.[27] This may point to an EGFR or ERBB2 inhibitor as targeted therapy for treating vestibular schwannomas with the NF2 mutation.

Merlin Tumor Suppressor Function

Since its discovery in 1993, merlin's function has remained elusive, with only a broad association with tumor suppressor function.[71] Merlin's role as a tumor suppressor is likely due to its ability to suppress Rac1 recruitment, preventing loss of contact inhibition.[82] Furthermore, it has recently been shown that the folded form of merlin translocates to the nucleus and binds to DCAF1 and suppresses cell proliferation by inhibiting E3 ubiquitin ligase $CRL4^{DCAF1}$.[58] Li et al.[58] also showed that merlin/DCAF1 binding creates stability, indicating that merlin is not a target for degradation but actually an inhibitor of $CRL4^{DCAF1}$. They found that deletion of the merlin-binding segment for DCAF1 led to constitutive activation of the $CRL4^{DCAF1}$, further indicating that merlin plays a role in the suppression of E3 ubiquitin ligase.[58] $CRL4^{DCAF1}$ plays a role in DNA replication and movement through the G2 phase of the cell cycle, and merlin's inactivation of $CRL4^{DCAF1}$ downregulates genes promoting cell-cycle progression and upregulates genes related to apoptosis and cell-cycle arrest.[41,58,70] Expression of merlin and inactivation of $CRL4^{DCAF1}$ also inhibits integrin, PDGF signaling, and downregulated cell adhesion genes.[58] Perhaps most importantly, Li et al. also demonstrated that depletion of DCAF1 reverses the effect of merlin inactivation and suppresses growth of merlin-deficient tumors both in vitro and in vivo. Depletion of DCAF1 inhibits hyperproliferation of Schwann cells in NF2 patients, suppressing tumorigenesis in merlin-deficient cell lines.[58] Therefore, DCAF1 inhibitors may be explored as a potential treatment option for patients with NF2-associated vestibular schwannoma.

NF2 Mosaicism/Segmental NF2

Using DNA hybridization studies, one group of authors found that vestibular schwannomas show heterogeneity, perhaps due to mosaicism in which some cells are normal and others carry only one normal chromosome 22.[96] Mosaicism occurs in sporadic NF2 if de novo mutations occur after fertilization and cell division.[10,51]

Expression of VEGF

Vascular endothelial growth factor, a diffusible glycoprotein, plays a major role in the angiogenesis of brain tumors.[28] It binds to either VEGFR-1 or VEGFR-2, both of which are located on vascular endothelial cells.[28] Using quantitative real-time polymerase chain reaction and quantitative ELISA, it has been found that vestibular schwannomas express VEGFR-1 at high levels.[17,115] Patients with a larger tumor volume, recurrent tumors, and tumors with a high growth rate had higher levels of VEGFR-1 and NF2 mRNA.[17,115]

Sporadic Vestibular Schwannoma

Both sporadic and NF2 vestibular schwannomas are associated with a loss of function mutation in the 22q12 locus.[91,112] Whereas most of the genetic analysis of vestibular schwannoma is focused on patients with NF2, the genetics of sporadic vestibular schwannoma is less established. Using microarrays, one group found that 8 of the upregulated genes are involved in cell-cycle regulation, 6 in cell morphogenesis, 8 in cell development, 11 in cell differentiation, 6 in cell death, 13 in cell adhesion, 9 in extracellular matrix, and 50 in protein binding.[16]

Treatment

Novel Treatment Options

Outside of neurosurgical management of vestibular schwannomas, targeted therapy has been on the rise as possible treatment options for patients with NF2. We discuss current research on several novel treatment options for vestibular schwannoma.

Bevacizumab/Avastin

Bevacizumab (Avastin, rhuMAb VEGF), a humanized monoclonal IgG1 antibody against VEGF has re-

cently been approved for use in the treatment of various cancers, such as glioblastoma, that express high levels of VEGF.[63,123] In a case report of 2 patients, bevacizumab was infused every 2 weeks at 5.0 mg/kg body weight for 90 minutes and gradually reduced to 30 minutes.[69] The authors of the case report found that bevacizumab induced regression of progressive vestibular schwannomas by over 40% and improved hearing in one patient who was treated for 6 months. In the first patient with NF2, a 22-year-old man, MR imaging showed clear improvement of brainstem compression with decreased syrinx volume as well as improved hearing. The only initial side effects were mild epistaxis and fatigue. In the second patient, a 38-year-old man, MR imaging demonstrated resolution of the right vestibular schwannoma, but hearing improvement was absent. In this case, the patient was placed on an angiotensin I antagonist due to hypertension, a side effect of bevacizumab.[5,69]

Another study of 10 patients with NF2 and progressive vestibular schwannomas who were not candidates for traditional treatment received bevacizumab. Nine of the 10 patients exhibited a reduction in tumor size and modest improvement in hearing.[87] Despite the promise of bevacizumab as a treatment option for vestibular schwannoma, there are currently only a few case studies that can show its effectiveness. Furthermore, angiogenesis is only one aspect of tumor proliferation. Therefore, we should continue looking for other therapeutic options and proceed with caution until bevacizumab can be thoroughly examined in larger studies.

Another drug that inhibits VEGF synthesis upstream by interrupting posttranslational processing, PTC299 is currently in Phase II trials.[48] As with bevacizumab, the goal of the drug is to reduce both tumor volume and perfusion at the tumor site. The trial is currently enrolling NF2 patients with progressive growth of vestibular schwannomas and concurrent hearing loss, and restoration of hearing is being used to measure clinical outcome.[48]

Trastuzumab

Another potential molecular target is the ERBB2 receptor, which is associated with the proliferative effects of NRG1. In vitro studies have shown that trastuzumab, an ERBB2 inhibitor, reduced vestibular schwannoma cell proliferation.[15] To date, there have been no clinical trials on the effectiveness of trastuzumab compared with the standard treatment. However, a recent study has shown that trastuzumab and another ERBB inhibitor, erlotinib, inhibit growth of vestibular schwannoma xenografts in nude mice.[20]

Erlotinib

Erlotinib is an oral EGFR tyrosine kinase inhibitor that is currently available for the treatment of non–small cell lung cancer and pancreatic cancer.[46,77,86] Interestingly, in one study, treatment with erlotinib resulted in increased vestibular schwannoma cell death as measured by TUNEL staining.[20] Unfortunately, this study did not assess for merlin mutations in the tumor xenografts. In a retrospective study of 11 patients with NF2 and progressive vestibular schwannoma, the authors found that erlotinib was not associated with decreased tumor size, based on volumetric MR imaging analysis, and that erlotinib failed to improve hearing response, based on changes in word recognition score.[86] However, the authors pointed out that there were no selection criteria in place, and therefore, Phase II clinical trials would still be warranted. Moreover, they hypothesized that there may be other molecular alterations that lead to vestibular schwannoma proliferation outside of EGFR receptors.[86] The benefits of these treatment options are that they can affect multiple tumors more easily than open surgery. Furthermore, there would be fewer toxic side effects than with cytotoxic agents, making such treatment options more suitable for long-term therapy.[20,39]

Lapatinib

Lapatinib is a dual inhibitor of EGFR and HER2 approved in 2007 by the US FDA.[73] Lapatinib has shown promising effects in breast cancer metastasis to the brain, and with further research and clinical trials it may be a potential treatment option for vestibular schwannoma.[34,59] Ammoun and colleagues[4] found that lapatinib inhibited ERBB2 phosphorylation and resulted in decreased proliferation of vestibular schwannoma in vitro. Currently, there is an ongoing "Phase 0" clinical trial assessing the effects of lapatinib on tumor tissue. Enrollment requirements include: 1) being scheduled for vestibular schwannoma surgery, 2) lapatinib given before surgery, and 3) consent to have the tumor analyzed postoperatively to look for presence of lapatnib.[48] The trial is currently studying the drug's ability to reach the tumor site, and if successful, the investigators may move it to Phase II trials.[48]

PAK Inhibitor

One group used a small-molecule PAK inhibitor, IPA-3, to further elucidate the role of PAK activation on Rac1. IPA-3 is a direct, noncompetitive inhibitor of PAK1 that works by targeting its activation and its autoregulation.[23] Flaiz and associates[29,30] found that IPA-3 does block PAK, resulting in decreased Rac1 activation.

Conclusions

Vestibular schwannomas are tumors of cranial nerve VIII that are related to the *NF2* gene and its product, merlin. Merlin acts as a tumor suppressor and as a mediator of contact inhibition. Thus, deficiencies in both *NF2* genes lead to vestibular schwannoma development. Merlin is intricately involved with a number of receptors including the CD44 receptor, EGFR, and signaling pathways, such as the Ras/raf pathway and the canonical Wnt pathway. Recently, merlin has also been shown to interact in the nucleus with E3 ubiquitin ligase $CRL4^{DCAF1}$. A greater understanding of the molecular mechanisms behind vestibular schwannoma tumorigenesis has begun to yield novel therapies. With further research, it may be possible to significantly reduce the morbidity and mortality rates by decreasing tumor burden, tumor volume, hearing loss, and cranial nerve deficits seen in vestibular schwannoma.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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