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From bench to bedside: Advancing towards therapeutic treatment of vestibular schwannomas

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Abstract

Vestibular schwannomas are rare intracranial tumors originating from Schwann cells of the vestibular nerve. Despite their benign nature, these tumors can exert significant mass effects and debilitating symptoms, including gradual hearing loss, vertigo, facial nerve dysfunction, and headaches. Current clinical management options encompass wait-and-scan, surgery, radiation therapy, and off-label medication. However, each approach exhibits its own challenges and harbors limitations that underscore the urgent need for therapeutic treatments. Over the past 2 decades, extensive elucidation of the molecular underpinnings of vestibular schwannomas has unraveled genetic anomalies, dysregulated signaling pathways, downstream of receptor tyrosine kinases, disrupted extracellular matrix, inflammatory tumor microenvironment, and altered cerebrospinal fluid composition as integral factors in driving the development and progression of the disease. Armed with this knowledge, novel therapeutic interventions tailored to the unique molecular characteristics of those conditions are actively being pursued. This review underscores the urgency of addressing the dearth of Food and Drug Administration–approved drugs for vestibular schwannoma, highlighting the key molecular discoveries and their potential translation into therapeutics. It provides an in-depth exploration of the evolving landscape of therapeutic development, which is currently advancing from bench to bedside. These ongoing efforts hold the promise of significantly transforming the lives of vestibular schwannoma patients in the future.

Key Points

- Lack of targeted therapy for vestibular schwannomas hinders disease management.
- Key culprits of disease are receptor tyrosine kinases (RTK)-driven signaling, angiogenesis, and inflammation.
- Clinical trials seek approval for anti-RTK, anti-angiogenic, and anti-inflammatory therapies.

Vestibular schwannomas (VSs) originate from myelinating Schwann cells in the vestibular division of the vestibulocochlear (eighth cranial) nerve (Figure 1). These tumors are the most prevailing neoplasms found at the cerebellopontine angle in adults and constitute 8% of all intracranial tumors.[1] Recent epidemiological data indicate an annual incidence rate of 3–5 cases per 100 000 individuals, primarily diagnosed in adults in their 60s or 70s.[2,3] The primary risk factor for VSs is having a family history of NF2-related schwannomatosis (referred hereafter as NF2) or a personal history of NF2-related

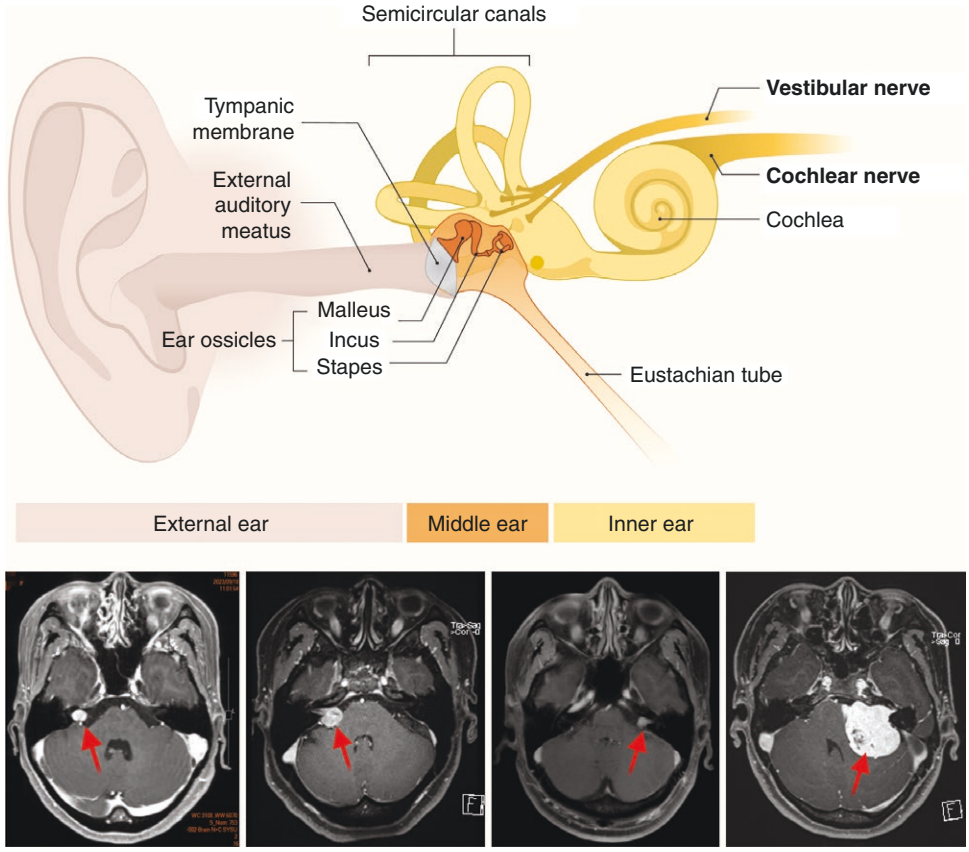

Figure 1. Anatomical presentation of vestibular schwannomas (VSs). Illustration of the anatomical sites of vestibular and cochlear nerves where VSs often develop behind the inner ear along with magnetic resonance imaging scans marking VS tumors.

tumors. NF2 is a rare autosomal dominant disorder caused by pathogenic variants within the neurofibromin 2 (*NF2*) gene leading to the development of various kinds of tumors in the nervous system, including bilateral VSs.[4] While benign, VS poses a risk to intracranial structures due to its mass effect. Over 60% of patients experience progressive hearing loss and tinnitus, with larger tumors potentially causing hydrocephalus and brainstem compression, resulting in symptoms like facial nerve dysfunction, vertigo, and headaches.[5]

VSs are typically diagnosed due to otological symptoms such as sensorineural hearing loss, unilateral tinnitus, and vertigo.[5,6] Magnetic resonance imaging (MRI) scans are routinely performed for diagnosis, monitoring tumor growth and assessing symptomatic changes.[7] Current management strategies are limited to wait-and-scan, surgery, and radiation therapy in both NF2-related and sporadic VSs, with conservative approaches preferred in elderly patients due to comorbidities.[8] However, these existing options pose particular challenges such as the risk of unexpected tumor growth during the wait-and-scan approach, chances of hearing loss, facial paralysis, cerebrospinal fluid (CSF) leak, intracranial bleeding and stroke in surgical resection, and likelihood of subsequent tumor growth after radiation therapy.[8,9]

Despite advancements in molecular understanding in recent years, therapeutic options for VSs remain limited with the exception of few off-label Food and Drug Administration (FDA)-approved medications.[10,11] This review underscores the pressing necessity for the development of therapeutic treatments for VSs. We first present an up-to-date molecular understanding of VSs, integral to the development of novel therapies and optimizing current management strategies. We subsequently summarize progress in therapies tailored for VSs, discuss ongoing preclinical and clinical trials, and highlight off-label medication use. Finally, we conclude by addressing challenges in advancing therapeutic options for clinical application.

Molecular Basis of VSs

The exploration of the molecular basis of VSs has experienced exponential growth in recent decades. Here, we present key molecular events, including genetic anomalies, dysregulated signaling pathways, disrupted extracellular matrix (ECM), inflammatory tumor microenvironment (TME), and altered CSF composition, involved in the development and progression of VSs (Figure 2).

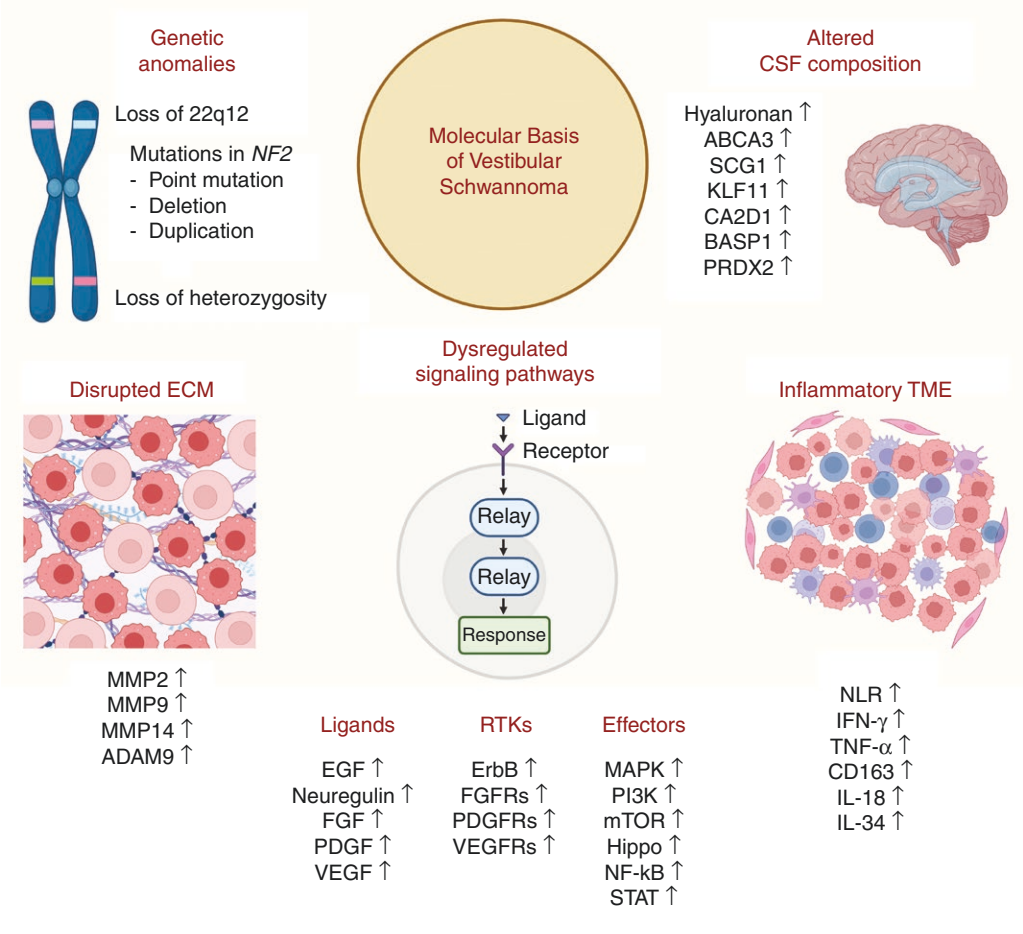

Figure 2. Molecular basis of vestibular schwannomas (VSs). The genetic anomalies, dysregulated signaling pathways, disrupted extracellular matrix (ECM), inflammatory tumor microenvironment (TME), and altered cerebrospinal fluid (CSF) composition that contribute to the development and progression of VSs. Key molecular events involved in VSs are highlighted.

Genetic Anomalies

The most frequent chromosomal aberration in VSs is the loss of genetic material from chromosome 22q, the region that harbors *NF2* tumor suppressor gene.[12] The fact that most VS cases are sporadic underscores the high mutation rate of the NF2 gene, aligning with findings in NF2-related meningiomas and other non-VS tumors. The most common types of mutations observed in *NF2* gene are either point mutations or complex rearrangements such as single or multi-exon deletions or duplications.[13] Moreover, loss of heterozygosity is prevalent in most sporadic VSs. The second functional *NF2* allele gets inactivated through identical point mutations as those found in the germline, significant deletions or duplications encompassing single or multiple exons, complete loss of chromosome 22 or the 22q12 locus, or via mitotic recombination. Larger deletions may encompass other genes adjacent to the *NF2* gene, potentially contributing to tumor growth and progression.[14] Alternatively, epigenetic modifications such as methylation of CpG islands in the promoter region of NF2 gene may lead to inactivation of NF2 in sporadic cases.[15] Of note, indel mutations found in SOX10 transcription factor are enriched in schwannomas arising from non-vestibular cranial nerves, but are absent in NF2-driven VSs.[16] Overall, genetic anomalies in the *NF2* gene play a crucial role in the development of VSs.

Dysregulated Signaling Pathways

The *NF2* gene encodes Merlin that belongs to the ERM (ezrin, radixin, moesin) family of cytoskeleton linker proteins. These proteins possess a conserved N-terminal FERM domain, an α-helical region, and a charged hydrophilic-COOH tail.[17] Merlin is expressed in 2 major isoforms: isoform 1 (exon 16 skipping) and isoform 2 (exon 16 retention), both acting as tumor suppressor and maintaining the structural integrity of Schwann and other cells in the nervous system.[18] Therefore, mutations in the *NF2* gene and/or loss of Merlin are crucial in both sporadic and NF2-related bilateral VS development. Merlin's activity is regulated by phosphorylation at Ser518: dephosphorylated Merlin acts as a growth inhibitor through a closed conformation formed by intramolecular association of its N-terminal domain and carboxy-terminal

domain, whereas phosphorylated Merlin lacks proper folding and function.[19] Merlin plays a crucial role in cell membrane stability through binding integral membrane proteins and spectrin actin cytoskeleton, while also mediating cell contact inhibition. Its growth-suppressive role involves modulating intracellular signal cascades associated with tumor development, including Ras/Raf/MAPK, PI3K/Akt/mTORC1, Hippo, and NF-kB signaling pathways. Additionally, Merlin is suggested to play key roles in mediating cell-cycle progression.[20] Myosin phosphatase targeting subunit 1 (MYPT1) protects Merlin by keeping it in a dephosphorylated state. During oncogenic transformation, the C-kinase-potentiated protein phosphatase-1 inhibitor of 17 kDa (CPI-17) inhibits MYPT1 that leads to Merlin phosphorylation.[21] Notably, CPI-17 is upregulated in more than 90% of sporadic VSs, correlating with Merlin's phosphorylation and cell proliferation during VS progression.[22] Alternatively, activation of RTKs and integrin signaling promote Merlin's phosphorylation through downstream effectors like p21-activated kinase-1 (PAK1) (Figure 3A), whereas genetic disruption of PAK1 reduces schwannoma size, restores hearing, and prolongs lifespan in vivo.[23] Here, we summarize the *NF2*/Merlin-related molecular mechanisms in VS development and progression in terms of oncogenic signal transduction, and downstream signaling mechanisms through effectors.

Oncogenic signal transduction through RTKs.—Overexpression of oncogenic growth factors, such as epidermal growth factor (EGF), neuregulin, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF), and/or hyper-activation of RTKs, such as ErbB family receptors, PDGFRs, FGFRs, and VEGFRs, are implicated in driving sporadic and NF2-related VS progression.[20] EGF is elevated in almost all NF2-related VS cases whereas neuregulin is upregulated in 86% of sporadic VS cases and 19% of NF2-related VS cases.[24] EGFR is upregulated in 68% of cases (62% in sporadic and 75% in NF2-related VSs), ErbB2 in 84% (76% in sporadic and 94% in NF2-related VSs), and ErbB3 in 34% of VSs.[24] PDGF family of ligands act via 2 RTKs (PDGFR-α and -β) and regulate cell growth, stemness, and tumorigenesis in schwannoma cell lines.[25] Hence, targeting these oncogenic factors is a promising approach for VS treatment.

FGF works as an angiogenic cytokine and a mitogen that promotes the proliferation and invasion of cells derived from sporadic VSs in vitro, highlighting the importance of targeting FGF in VS treatment.[26] However, it has been shown to protect auditory neurons from acoustic trauma and aminoglycoside ototoxicity as its expression is 3.5-fold higher in tumors from VS patients with good hearing compared to those with poor hearing.[27] Additionally, post-treatment data indicate that FGF plasma concentration increases as the patient's hearing improves, suggesting alternative mechanisms regulating tumor growth and hearing downstream of FGF, and a poor correlation between tumor volume and hearing outcome in VS patients.[27] Therefore, targeting FGF needs careful consideration to balance its potential tumor-promoting effects with its protective role in hearing preservation.

Pro-angiogenic VEGF regulates blood vessel growth and sprouting, and contributes to develop an immune-suppressed TME.[28] In VS tissues, there is a notable increase in the expression of VEGF, VEGFR-1/Flt, VEGFR-2/Flk, and the co-receptor NP1 compared to the normal vestibular nerve.[29] Recurrent and preoperatively irradiated tumors also exhibit significantly higher VEGF levels than primary VSs, suggesting that angiogenesis plays a key role in tumor growth in VSs.[30] In addition, VEGF expression along with that of FGF is positively correlated with factors such as tumor volume, tumor growth index, and microvessel density in VSs.[31] Despite these findings, conflicting evidence suggests that although tumors with high proliferation and elevated VEGF receptor levels are certainly more common than those with low proliferation and reduced VEGF receptor levels, the expression of VEGF and its receptors does not directly correlate with proliferation indexes (Ki-67) or tumor growth features.[30] Therefore, these parameters should be critically assessed while targeting VEGF in VS treatment.

Downstream effector signaling.—Various signaling pathways play a role in both sporadic and NF2-related VSs. Ras, a G-protein downstream of RTKs, shifts between inactive GDP-bound and active GTP-bound states, impacting cell proliferation and division. Active Ras triggers downstream effectors in Ras/Raf/MAPK and Ras/PI3K/Akt pathways, driving cellular transformation and tumorigenesis. In addition, Ras activation triggers Rac/Cdc42 and their downstream PAK1.[32] Merlin counteracts Ras-induced transformation through various mechanisms: hindering GRB2 expression, dampening Ras and Rac activation, inhibiting PAK1 activation at focal adhesions, and releasing Rac1 negative regulator Rich1 via angiomotin competition[33] (Figure 3A). Although CPI-17 promotes Merlin phosphorylation and subsequent inactivation by inhibiting MYPT1, it activates other ERM proteins essential for Ras activation and subsequent transformation.[34] This dysregulation of Merlin intensifies Ras signaling and tumor growth.[21] In addition, Rac leads to Merlin inactivation through PAK1 which directly phosphorylates Merlin at Ser518, weakening its cytoskeleton interaction and inhibiting its tumor suppressive functions.[35] Therefore, dysregulated Ras signaling in VSs provides multiple targetable axes to treat the disease in clinics.

The aberration in the Hippo signaling and consequent activation of Yes-associated protein (YAP) promote cell proliferation in VSs.[36] Merlin directly activates STE20-like protein (MST1/2), which, in turn, phosphorylates large tumor suppressor homolog 1/2 (LATS1/2). Activated LATS1/2 directly phosphorylates YAP and its transcriptional co-activator TAZ leading to ubiquitination-mediated degradation and resulting in the inhibition of Hippo signaling. In Merlin's inactive state, YAP/TAZ relocates to the nucleus and binds with TEAD, triggering the transcription of pro-proliferation and anti-apoptotic genes.[37] Alternatively, E3 ubiquitin ligase CRL4DCAF1 targets and destabilizes LATS1/2 to activate YAP, but Merlin's nuclear translocation and high-affinity binding to CRL4DCAF1 inhibit this axis[38] (Figure 3B). Pharmacological inhibition of NEDD8-activating enzyme, a CRL4DCAF1 activator,

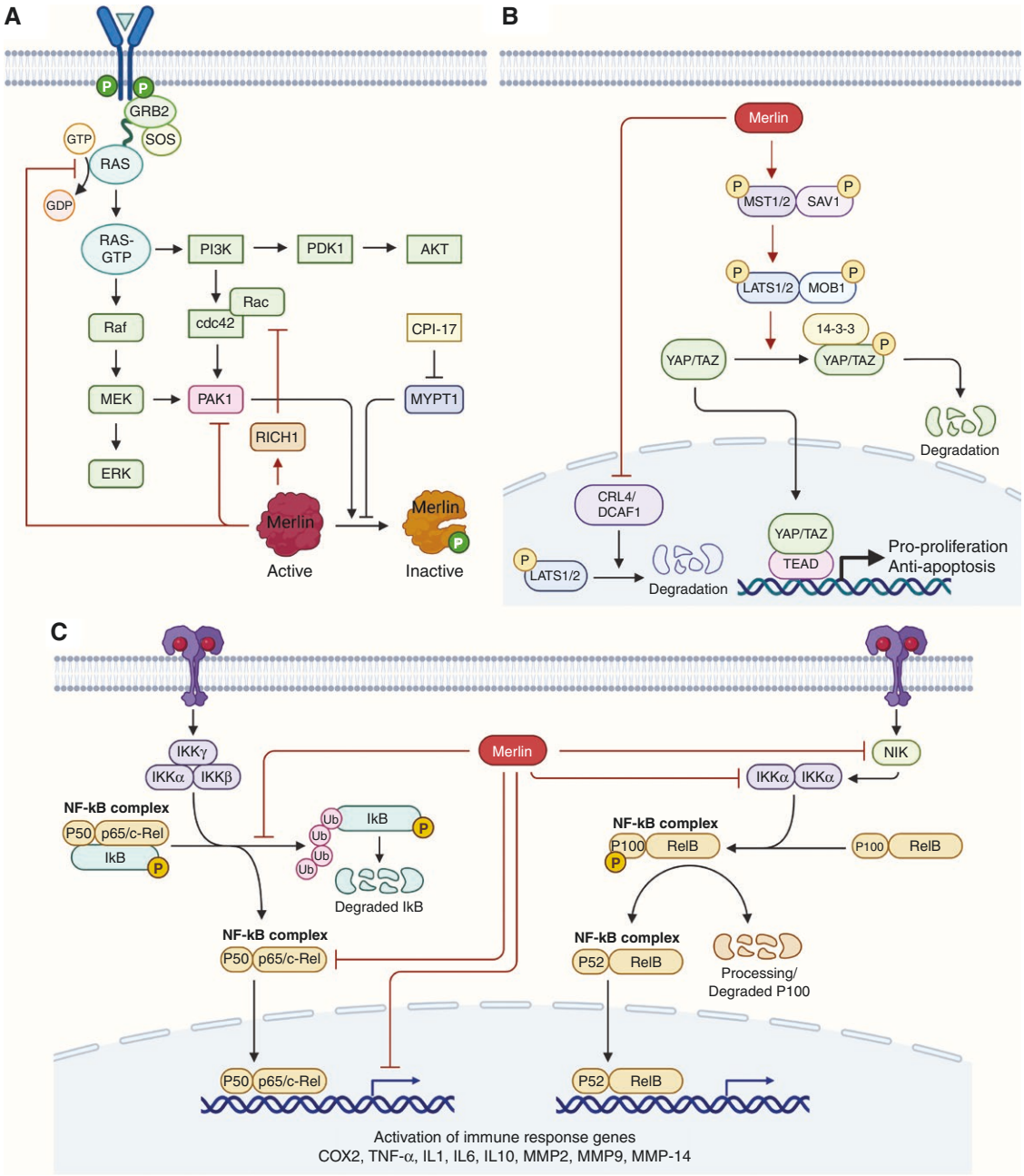

Figure 3. Inhibition of Ras, Hippo, and NF-κB signaling by Merlin. (A) Merlin's role in inhibiting Ras signaling: Ras, a G-protein, shifts between inactive GDP-bound and active GTP-bound states, impacting cell proliferation and division. Active Ras connects with multiple effectors, initiating downstream signaling like Ras/Raf/MAPK and Ras/PI3K/Akt pathways, driving cellular transformation and tumorigenesis. Ras activation also triggers Rac/Cdc42 and their downstream PAK1, which phosphorylates Merlin and inactivates it. MYPT1 protects Merlin by keeping it in a dephosphorylated state, while CPI-17 inhibits MYPT1, leading to Merlin phosphorylation. Merlin counteracts Ras-induced transformation through various mechanisms. (B) Merlin's role in inhibiting Hippo signaling: Merlin directly activates STE20-like protein (MST1/2), which, in turn, phosphorylates large tumor suppressor homolog 1/2 (LATS1/2). Merlin also inhibits the CRL4/DCAF1 complex-mediated degradation of LATS1/2. Activated LATS1/2 directly phosphorylates YAP and its transcriptional co-activator TAZ, leading to ubiquitination-mediated degradation and resulting in the inhibition of Hippo signaling. (C) Merlin's role in inhibiting NF-κB signaling: NF-κB comprises homo- and heterodimeric proteins (p65/RelA, c-Rel, p50/p105 [NF-κB1], and RelB and p52/p100 [NF-κB2]) within cells, residing in nonstimulated cell cytoplasm bound to IκB. Inflammatory cytokines or growth factors activate NF-κB signaling, inducing the transcription of genes involved in numerous cellular processes. Merlin inhibits NF-κB signaling by blocking p65, NIK, IKKα, TNF-α-induced IκB degradation, and NF-κB–DNA binding, subsequently inhibiting transcription.

triggers inhibitory YAP phosphorylation in *NF2*-mutant tumor cells.[39] These findings suggest that pharmacological targeting of Hippo signaling may limit VS tumor growth.

NF-κB transcription factor governs cell growth, apoptosis, inflammation, and malignant transformation. It comprises homo- and heterodimeric proteins (p65/RelA, c-Rel, p50/p105 [NF-κB1], and RelB and p52/p100 [NF-κB2]), residing in nonstimulated state bound to IκB. Inflammatory cytokines or growth factors activate NF-κB signaling, inducing transcription of genes involved in myriad of cellular processes.[40] Merlin inhibits NF-κB signaling by blocking p65, NIK, IKKα, TNF-α-induced IκB degradation, and NF-κB–DNA binding and subsequent transcription,[41] whereas in the absence of Merlin, overexpressed NIK and IKKα drive NF-κB-dependent transcription[42] (Figure 3C). In VSs, increased NF-κB activity also boosts a feed-forward loop of HGF to c-Met, enhancing tumor cell proliferation.[43] Hyperactive NF-κB signaling promotes COX2 and STAT1 expression as well as induces the release of factors tied to VS growth and progression like MMP-2, MMP-9, MMP-14, IL-1, IL-6, and TNF-α.[20] In particular, COX2 is upregulated in most of the VS tissue samples (96.67%), correlating with higher proliferation rate.[44] Hence, targeting NF-kB signaling and/or its downstream functional targets is suggested to be a promising therapy against VSs.

Disrupted ECM

Matrix metalloproteinases (MMPs) are zinc- and calcium-dependent proteolytic enzymes that remodel ECM and play fundamental roles in tumor progression, invasion, and angiogenesis.[45] VSs exhibit elevated expression of MMP-2 and MMP-9, linked to increased tumor growth rate.[46] MMPs can degrade collagen, fibronectin, and laminin in the ECM contributing to cyst formation. Cystic VSs also express elevated levels of MMP-2 and MMP-9 compared to solid tumors.[47] In addition, MMP-14 is also upregulated in VSs, and its proteolytic activity correlates with sensorineural hearing loss and poor surgical outcomes.[48] ADAM9, a membrane-anchored ECM modulating protein, is associated with an aggressive tumor state and poor prognosis in cancer. ADAM9 is significantly upregulated at the mRNA level in VSs and correlates with the degree of functional hearing impairment.[49] Hence targeting ECM modulators such as MMP-2, MMP-9, MMP-14, and ADMA9 offers a promising approach for the treatment of VSs.

Inflammatory TME

Growing evidence suggests that solid tumors exhibit tumor-associated inflammation contributing to cancer progression and metastasis. An increase in VS tumor volume involves not only cell proliferation but also processes like intratumoral hemorrhage, cyst formation, and inflammation.[50] Preoperative peripheral blood neutrophil-to-lymphocyte ratio (NLR) reflects systemic inflammation with elevated pro-inflammatory and angiogenic cytokines, contributing to tumor progression, immunosuppression, and stroma formation, and works as a promising negative prognostic biomarker in cancer. In the context of VSs, patients with actively growing tumors exhibit an elevated NLR compared to those with stable disease.[51] In response to stimuli, 2 types of tumor-associated macrophages (TAMs) are derived from monocytes. Classically activated M1-type macrophages aid host defense through releasing pro-inflammatory cytokines whereas alternatively activated M2-type macrophages surface later to suppress destructive immunity, and promote repair, fibrosis, and angiogenesis. But M2 macrophages can contribute to tumor progression and poor prognosis through the secretion of different factors and cytokines including VEGF and MMP-9.[52] Interestingly, macrophages, not tumor cells, actively proliferate in growing VSs, with high TAM density positively linked to VEGF production and microvessel development.[53] CD163, an M2 marker, is elevated in fast-growing VSs, correlating with increased microvessels. In addition, the levels of both the macrophage colony-stimulating factor and its synergistic cytokine IL-34 are increased in fast-growing VSs, stimulating macrophage polarization into an M2 type.[54] In line with these findings, a recent single-cell sequencing study has identified significant tumor heterogeneity in VS phenotypes, particularly noting that a nerve injury-like state is associated with larger tumor sizes in VSs. In this context, tumor-associated injury-like Schwann cells exhibit an antigen-presenting state that recruits myeloid cells (macrophages) via colony-stimulating factor 1 signaling, thereby orchestrating an inflammatory TME and promoting tumor growth.[55] Furthermore, immune cell infiltration following radiotherapy in VSs has been attributed to metabolic and epigenetic reprogramming that plays a pivotal role in orchestrating inflammatory TME. Genome-wide CRISPRi screens and targeted metabolite profiling have identified key epigenetic regulators such as histone demethylases KDM1A and KDM5C as critical factors influencing radiotherapy resistance, offering a promising avenue for potentially manipulating treatment outcomes in VSs.[56] Therefore, remodeling inflammatory TME could be a promising approach for VS therapy.

Altered CSF Composition

VSs originate from Schwann cells in nerve rootlets exposed to CSF, potentially altering CSF composition via protein secretion or metabolic changes.[57] These alterations corroborate with VS tumor growth, offering diagnostic and therapeutic targets. For instance, elevated hyaluronan (HA) in CSF directly correlates with tumor growth as increased HA levels are observed in NF2-related VS cases compared to controls.[58] Mechanistically, HA binds CD44 on Schwann cells and triggers uninterrupted proliferation, but Merlin disrupts HA-CD44 interaction to keep cell proliferation in check.[59] In addition to HA, other CSF factors such as ATP-binding cassette subfamily A member 3, secretogranin-1, Krueppel-like factor 11, voltage-dependent calcium channel subunit alpha-2/delta-1, brain acid soluble protein 1, and peroxiredoxin-2 are also reported to correlate with VS tumor growth.[60] Although still in infancy, therapeutic modulation of CSF factors holds great promise for the treatment of cancers of brain origin including VSs.

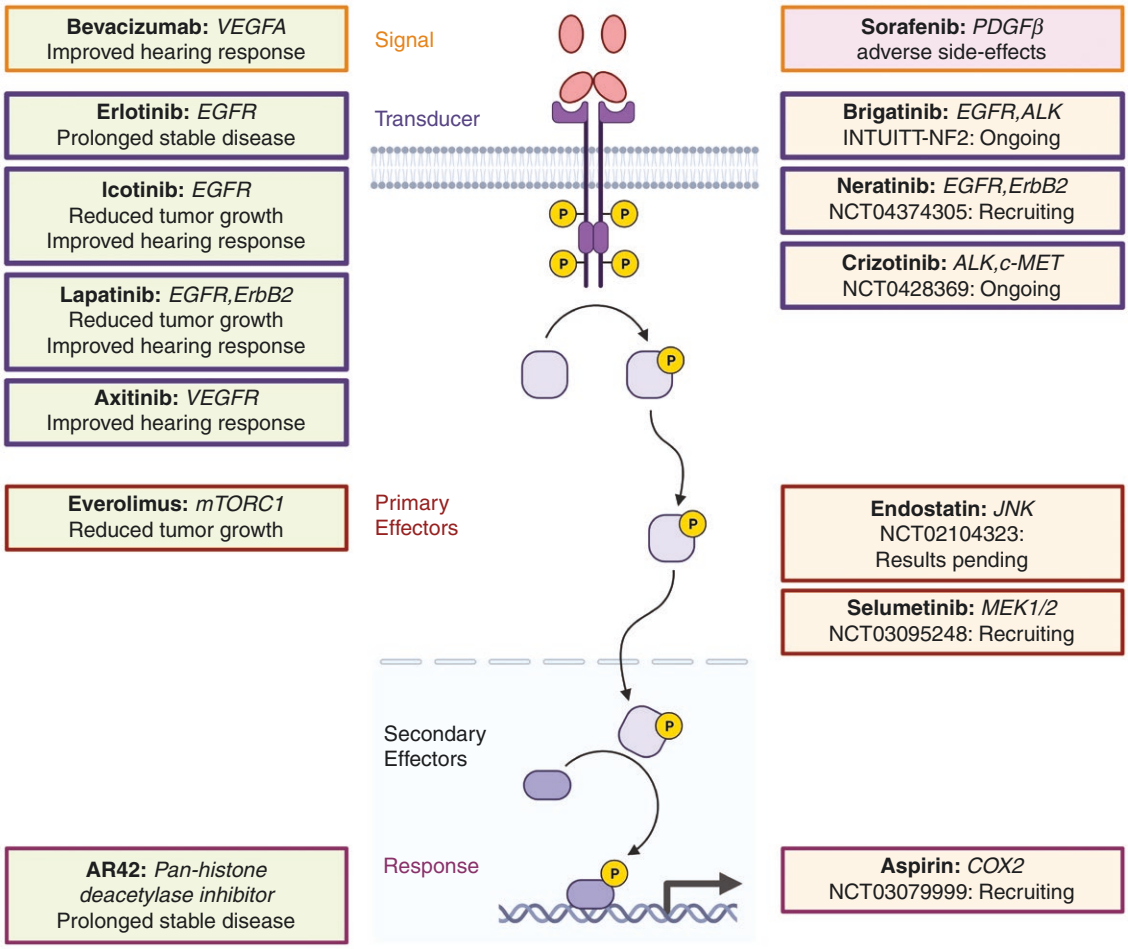

Figure 4. Therapeutic advancements in clinical management of vestibular schwannomas (VSs). Various therapeutics that target different levels of signaling cascades including signals, transducers, effectors, and response elements have been tested in clinical trials for the management of VSs. The therapeutics are listed along with their targets, and the outcomes of completed clinical trials are also provided.

Therapeutic Advancements in Clinical Management of VSs

Recent advances in understanding the molecular basis of VSs have contributed greatly in devising therapeutic strategies, though the progress has been slow. Here, we provide an overview of both preclinical investigations and clinical trials conducted thus far for VS treatment. Ongoing or recruiting trials are categorized according to the specific biological targets of the therapeutic agents (Figure 4).

Anti-RTK Therapy

Erlotinib, an EGFR inhibitor, holds FDA approval for non-small cell lung cancer and pancreatic cancer. A retrospective study of 11 subjects with NF2-related progressive VSs, who were treated daily with 150 mg erlotinib due to surgical limitations, has reported no association between treatment and hearing or radiographic responses, though a subgroup of patients experienced prolonged stable disease.[61] Icotinib, an FDA-approved oral EGFR inhibitor for non-small cell lung cancer, has been tested in a phase II clinical trial involving 11 NF2 subjects. Treatment with icotinib at 375 mg orally daily resulted in a radiographic response with ≥20% tumor volume reduction and a hearing response of 43%. Unfortunately, accompanying adverse effects including rash (90%), diarrhea (50%), myalgia (20%), and nausea (20%) undermined the use of icotinib for VSs.[62] Lapatinib, a dual EGFR/ErbB2 inhibitor with FDA approval for HER2-overexpressing metastatic breast cancer, has completed a phase II trial in 17 subjects with NF2-related progressive VSs. Results show that a continuous 4-week regimen of 900 mg/m^2 (up to 750 mg twice a day for pediatric patients and 1500 mg daily for adults) yields a radiographic response with 23.5% of patients exhibiting volumetric response and 30.8% of patients experiencing increase in hearing response.[63] Neratinib, another dual EGFR/ErbB2 inhibitor, possesses FDA approval for combination therapy treatment of metastatic breast cancer.[64] A clinical trial (NCT04374305) is actively recruiting subjects with NF2-related VSs under the Innovative Trial for Understanding the Impact of Target Therapies in NF2

(INTUITT-NF2) platform. Trastuzumab, an ErbB2 inhibitor with FDA approval for metastatic HER2-overexpressing breast cancer, displays reduced VS cell proliferation in vitro[65]; however, in vivo and clinical data are lacking.

Brigatinib is a multi-RTK inhibitor that has been shown to target focal adhesion kinase (FAK1) in an in vivo model of NF2.[66] It is presently being tested in clinical trials simultaneously across various NF2-associated tumor types, including progressive VS, non-VS, meningiomas, and ependymomas under the INTUITT-NF2 platform. Crizotinib is a known inhibitor of RTKs, ALK, and c-MET with FDA approval in non-small cell lung cancer treatment. It augments DNA damage and radiosensitivity in VSs.[67] A phase II clinical trial of crizotinib in children and adults with NF2 and progressive VS has completed the initial recruitment phase (NCT04283669).

Sorafenib, a PDGFβ inhibitor, has exhibited VS tumor growth inhibition in vitro. A phase 0 trial enrolled 5 adult subjects with NF2-related peripheral schwannomas and treated them with sorafenib at 400 mg twice a day for 10 days and a single 400 mg dose on day 11. Despite sorafenib detection in tumor tissue for all patients, pharmacodynamic effects remained below expectations in this trial, with low intratumoral concentrations of sorafenib and adverse side effects experienced by all subjects.[68] Nilotinib, a second-generation RTK inhibitor that targets both PDGF signaling and the BCR-ABL oncoprotein, has displayed efficacy against VS growth in vitro.[69] Although a clinical trial (NCT01201538) was previously initiated to assess the efficacy of nilotininb against VSs, it was halted midway due to the death of the principal investigator.

Anti-effector Signaling Therapy

Everolimus, an mTORC1 inhibitor, holds approval for the treatment of various malignancies with anti-angiogenic effects extending beyond VEGF inhibition.[70] Generally well-tolerated with minimal severe toxicities,[71] previous trials (NCT01419639, NCT01490476) on NF2-related VS patients yielded inconclusive results, with no decrease in tumor size or hearing response.[72,73] A 4-year study involving 4 subjects suggests potential VS growth rate reduction with everolimus,[74] highlighting the challenges of conducting prolonged clinical trials, particularly in rare diseases like NF2. AR-42, a pan-histone deacetylase inhibitor, inhibits VS cell growth by inducing cell-cycle arrest and apoptosis both in vitro and in vivo.[75] A pilot study with 4 VS subjects found high tumor retention, a decrease in p-AKT levels in tumors, and no high-grade toxicities associated with AR-42 treatment.[76] Recently, a phase 1 trial (NCT01129193) involving NF2-related solid tumors has established AR-42's being safe and tolerable, with 53% of subjects experiencing stable disease.[77] AR-12, a phosphoinositide-dependent kinase-1 (PDK1) inhibitor, reduces AKT phosphorylation and activation, and subsequent tumor growth in vivo.[78] Further clinical studies are essential to assess AR-12's safety and efficacy for VS treatment. Selumetinib, a MEK1 and 2 inhibitor, effectively reduces ERK1/2 activity and proliferation in VSs. In a preclinical study, combining selumetinib with nilotinib heightened the inhibitory impact on PDGFR and downstream RAF/MEK1/2/ERK1/2 pathways.[38] A clinical trial (NCT03095248) is actively recruiting patients to explore selumetinib's effects on NF2-related tumors.

Anti-angiogenic Therapy

Bevacizumab, an anti-VEGFA monoclonal antibody, not only lessens tumor vasculature and vasogenic edema, but also mitigates hearing loss and reduces tumor size in NF-related progressive VS.[79] Bevacizumab underwent a multicenter phase II clinical trial to assess its efficacy in 14 subjects with NF2-related VS. Here, 36% of subjects achieved a sustained hearing response (lasting more than 3 months) and 43% experienced radiographic responses in target VSs.[80] Another multicenter phase II trial examined high-dose bevacizumab (10 mg/kg) in children and adult subjects (NCT01767792). Surprisingly, no heightened benefits emerged in comparison to the standard dose (7.5 mg/kg) for treating adults with NF2-related VS accompanied by hearing loss. Notably, pediatric subjects showed minimal hearing response benefits (14%) and no radiographic responses (0%) at 6 months.[81] PTC299, a VEGF inhibitor binding to untranslated VEGF mRNA regions.[82] has undergone a phase II clinical trial (NCT00911248). However, the trial was terminated before completion for an undisclosed reason. A clinical trial (NCT02129647) evaluating a VEGFR inhibitor named axitinib in subjects with NF2-related progressive VS has indicated modest hearing and radiographic responses that are inferior to those achieved with bevacizumab. In addition, increased drug toxicity was observed.[83] Endostatin, another potent angiogenesis inhibitor that primarily targets the JNK pathway, has already been tested in an NF2-related trial (NCT02104323), but outcomes are pending reporting.[84]

Anti-inflammatory Therapy

Aspirin is an anti-inflammatory drug that irreversibly inhibits COX2. Although in vitro and small retrospective studies suggest that aspirin reduces VS growth rate, a recent meta-analysis has concluded that evidence is insufficient for recommending aspirin in VS patients.[85] An ongoing placebo-controlled clinical trial (NCT03079999) is aimed at investigating aspirin's impact on VS patients and is currently recruiting subjects. Curcumin possesses anti-inflammatory and anti-tumorigenic properties through regulating multiple pathways including Merlin regulation. It synergizes with heat shock protein inhibition to suppress schwannoma cell growth in vitro.[86] However, no clinical study has been conducted so far to test the effect of Curcumin in patients.

Off-Label Medications for VS Treatment

As conventional options for VS treatment are restricted to wait-and-scan, surgery, and radiotherapy, off-label use of targeted therapies is progressively gaining prominence. Anti-angiogenic bevacizumab is currently favored in treating VSs due to its superior outcomes compared to other targeted therapies like lapatinib and everolimus.[87,88] The major constraint associated with bevacizumab therapy

is the potential need for long-term treatment due to tumor regrowth post-treatment cessation, coupled with significant adverse effects including proteinuria, delayed wound healing, bleeding, hypertension, and premature ovarian insufficiency in reproductive-age females.[89] Off-label intracisternal irrigation with papaverine (a vasodilator) during VS surgery enhances immediate postoperative and comparable long-term facial nerve outcomes without notable complications.[90] Nimodipine is a calcium channel blocker and approved treatment for cerebral vasospasm following a subarachnoid hemorrhage.[91] Its off-label use during surgery promoted peripheral facial nerve regeneration after surgical trauma in VS patients.[92] It has also been occasionally used in Germany as an off-label medication during surgery and shown to improve hearing response post-surgery.[93] A phase III randomized trial is underway to assess whether prophylactic nimodipine provides neuroprotection and preserves hearing in VS surgery.[94]

Challenges and Future Perspectives

The translation of molecular discoveries into effective clinical strategies for VSs is confronted with substantial challenges. Foremost among these challenges is the rarity of the disease coupled with restricted number of patients requiring therapeutic intervention, which results in a limited pool of patients available for enrollment in clinical trials.[8,95] Additionally, obtaining an adequate amount of tumor tissue for molecular analysis becomes problematic, particularly in cases where surgery is not pursued or when tumors remain small. As the primary objective of transitioning towards therapeutic treatments for VSs is to mitigate the complications associated with conventional management options, the poor correlation between tumor size and hearing loss complicates matters.[96] Therefore, the pursuit of improved biomarkers that individually address tumor growth and hearing loss remains an unmet need in the field. Moreover, the validation of biomarkers identified through molecular profiling demands comprehensive large-scale studies, including prospective clinical trials, to establish their significance in clinical contexts and their correlation with treatment outcomes. The presence of patient-to-patient and intratumor heterogeneity adds another layer of complexity,[4,97] requiring an in-depth understanding through techniques such as single-cell sequencing to delineate the transcriptional networks, and identify biomarkers and therapeutic targets.[98] Furthermore, molecular findings suggest that different signaling pathways come into play during various stages of tumor growth in VSs. The development of in vitro and preclinical in vivo models of tumor growth also becomes imperative. The existing models fall short of fully replicating the true essence of tumor growth and molecular characteristics.[20] Considering that Merlin is a protein implicated in multiple signaling pathways, targeting a single pathway may not offer the most optimal solution. Additionally, the clinical targeting of certain signaling pathways encounters limitations. For instance, targeting PAK1 with generalized PAK inhibitors is not feasible, as the inhibition of PAK2 is shown to result in significant cardiotoxicity in mouse models.[99] Therefore, the development of robust selective inhibitors for PAK1 presents a distinct clinical challenge. Furthermore, a majority of targeted therapies in clinical trials necessitate systemic drug administration, resulting in side effects overtime.[100] Therefore, there is a critical need to identify and/or devise single-dose therapeutic strategies, considering the slow nature of VS tumors, to mitigate the occurrence of side effects.

Amidst these challenges lie promising opportunities for the future of VS treatment. Collaborative data sharing and conducting conjugated multicenter clinical trials can limit the challenges associated with a low number of patients. Uncovering additional molecular mechanisms involved in VSs is a key avenue of research, enhancing our understanding of the disease. Investigating molecular subtypes and their implications can refine treatment strategies, leading to personalized therapies based on individual molecular profiles.[101] Notably, patient stratification based on molecular profiling has recently identified distinct immunogenic and proliferative tumor subgroups in VSs. These subgroups exhibit notable differences in immune, stromal, and cell enrichment, highlighting distinct therapeutic vulnerabilities and reinforcing the principles of personalized medicine.[102] Similarly, single-cell sequencing and deconvolution analyses have confirmed substantial tumor heterogeneity in VS phenotypes with the presence of nerve injury-like inflammatory TME being associated with large tumor size. These findings underscore the importance of personalized medicine tailored to individual disease characteristics.[55] The discovery of reliable biomarkers for treatment prediction and disease monitoring can revolutionize patient care. In this regard, the levels of circulating biomarkers, in addition to utilizing advanced imaging methods, could also serve as convenient and dependable indicators for predicting subsequent tumor growth.[103] Advances in targeted therapies, exploration of combination and/or sequential strategies, and combining therapies with existing management options offer new frontiers for enhancing treatment outcomes.

In summary, the establishment of preclinical models, rigorous clinical trials, and the promotion of collaborative data sharing can lead to the effective validation of innovative treatments. With these coordinated efforts, the future holds the promise of more effective treatments for VSs, ultimately resulting in improved patient outcomes.

Keywords

angiogenesis | inflammation | receptor tyrosine kinases (RTKs) | targeted therapy | vestibular schwannoma

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Study conception and design: Q.H. and S.Y. Drafted the manuscript: S.G., X.Z., W.C., and U.R. Critically revised the manuscript: A.Z., F.A., Q.H., and S.Y. Figures and visualization: U.R., and S.Y. All authors read and approved the final manuscript.

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