Molecular Pathogenesis of Vestibular Schwannomas: Insights for the Development of Novel Medical Therapies

Patogeneza molekularna osłoniaka przedsionkowego: przegląd opracowania nowych metod terapeutycznych

Craig Miller, Suzu Igarashi, Abraham Jacob

Otolaryngol Pol 2012; 66 (2): 84-95

SUMMARY

Vestibular schwannomas (VS), benign intracranial tumors originating from the vestibulocochlear nerve, usually present with hearing loss, tinnitus, and balance dysfunction. Rarely, however, if untreated, these neoplasms can cause significant patient compromise – resulting in facial paralysis, brainstem compression, and even death. Those with vestibular schwannomas currently choose between surgery and stereotactic radiation therapy as available treatment options. Unfortunately, no medical therapies are presently U.S. Food & Drug Administration approved, representing an urgent and unmet clinical need. Recent breakthroughs in research have discovered key cell surface receptors and intracellular signaling pathways that drive vestibular schwannoma tumorigenesis, proliferation, and survival. A number of promising inhibitors targeting these signaling molecules have also now shown efficacy in preclinical VS cell culture models and animal experiments, with some recently entering human clinical trials. In this review, we summarize ErbB receptor signaling, PDGF receptors, MAP kinase signaling, AKT, p21-activated kinase signaling, mTOR, and VEGF signaling in the context of vestibular schwannoma drug development efforts worldwide. Today, it is truly an exciting time as our specialty stands on the verge of major breakthroughs in the development of medical therapies for VS.

Hasła indeksowe: osłoniak przedsionkowy, neurofibromatoza typ 2, NF2, AKT, EGFR, PDGF, VEGF, merlina

Key words: Vestibular Schwannoma, Neurofibromatosis type 2, NF2, AKT, EGFR, PDGF, VEGF, PAK, Merlin

Otrzymano/Received:
09.01.12
Zaakceptowano do druku/Accepted:
13.02.12

Department of Surgery, Division of Otolaryngology; The University of Arizona

Zależności finansowe:
National Institute of Deafness and Other Communication Disorders [ABJ – K08 DC009644-01A1; Children's Tumor Foundation [ABJ – DDI 2007-05–2], and the Triological Society [ABJ – GRT00011359]
Konflikt interesu/Conflicts of interest:
Autorzy pracy nie zgłaszają konfliktu interesów.

Adres do korespondencji/
Address for correspondence:
imię i nazwisko: Abraham Jacob
adres pocztowy:
Department of Surgery
Division of Otolaryngology
The University of Arizona
1515 North Campbell Avenue
P. O. Box 245024
Tucson, Arizona 85724
tel. 520-626-3553
fax 520-626-6995
e-mail ajacob@surgery.arizona.edu

Vestibular Schwannomas: Introduction & Clinical Background

Vestibular schwannomas (VS) are benign, intracranial tumors arising from Schwann cells of the 8th cranial nerve. These neoplasms often present with tinnitus, hearing loss, facial hypesthesia, facial weakness, and disequilibrium [1]; however, in rare cases, catastrophic complications such as brainstem compression, stroke or even death can occur. VS constitute about 6% of intracranial neoplasms [2], have an incidence of approximately 9–13 per million people per year [3–6], and are clinically categorized as unilateral sporadic, NF2-associated, cystic, or malignant schwannomas. They are disease-defining tumors in patients with neurofibromatosis type 2 (NF2).

NF2 is an autosomal-dominant familial syndrome characterized by the development of vestibular schwannomas, meningiomas, ependymomas, spinal schwannomas, gliomas, and posterior subcapsular lenticular opacities. This disorder is caused by biallelic loss of the *NF2* gene on the long arm of chromosome 22. *NF2* codes for the tumor suppressor protein merlin (moesin, ezrin, and radixin-like protein) [7, 8], and while 50% of individuals with NF2 have an affected parent with the disease, the remaining 50% have *de novo* gene mutations [9]. Patients with germ-line mutations in NF2 develop bilateral VS (Fig. 1A); however, unilateral, sporadic tumors are far more common, making up 95% of VS (Fig. 1B). Whether the neoplasms are sporadic or due to neurofibromatosis type 2, *NF2* gene mutations are present in nearly 100% of VS tumors.

The majority of vestibular schwannomas are histologically benign, composed of spindle-shaped cells that have elongated, palisading nuclei (Fig. 2.). Hypercellular regions are described as Antoni type A, whereas areas with fewer cells and looser architecture are designated Antoni type B Fortunately, nuclear atypia and mitoses are rarely seen in vestibular schwannomas, and in contrast to neurofibromas and malignant peripheral nerve sheath tumors (MPNSTs) in patients with neuro-

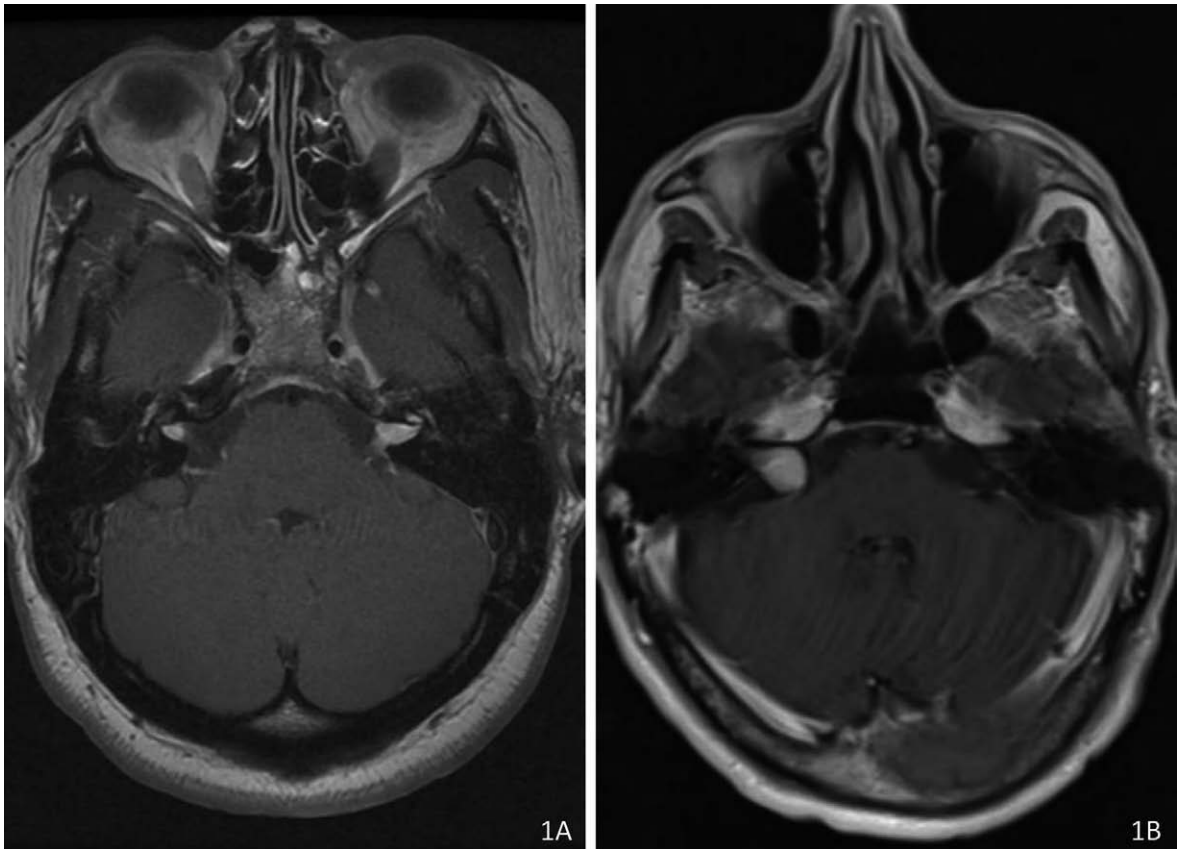

Fig. 1. Vestibular schwannoma magnetic resonance imaging. (A) Contrast-enhanced, T1-weighted MRI demonstrating bilateral enhancing internal auditory canal lesions characteristic of patients with Neurofibromatotis type 2. (B) Contrast enhanced T1-weighted MRI demonstrating a typical medium-sized sporadic vestibular schwannoma.

fibromatosis type 1, inflammation and abnormalities in tumor microenvironment have not been implicated in the pathogenesis of VS. Small tumors have a lower mitotic index than larger tumors, with the average growth rate for VS being approximately 1–2 mm per year [10–12]. While they are extremely rare, malignant vestibular schwannomas, known as triton tumors, grow rapidly and are usually lethal [13].

Vestibular schwannomas cause significant patient compromise due to their critical intracranial location. Sensorineural hearing loss is present in nearly 95% of VS patients [14], likely resulting from auditory nerve compression, infiltration of the auditory nerve, and/or vascular compromise. Fewer than 5% of total patients suffering sudden hearing loss have VS as the cause, but among patients known to have VS, 20–30% report sudden deterioration in hearing sometime during their clinical course [15, 16]. Tinnitus is the second most common symptom, present in about 75% of afflicted individuals [17]. Vestibular symptoms (~60%), facial hypesthesia/dyesthesia (~10%) and facial weakness (~5%) are less common [16]. Prior to the advent of advanced imaging, neurosurgeons made the clinical diagnosis of cerebellopontine angle tumors by a characteristic constellation of symptoms including unilateral hearing loss, tinnitus, imbalance/vertigo, facial numbness, facial weakness, blindness, and mental status changes. Today, the gold standard for diagnosis is an MRI scan of the brain (with and without IV contrast) employing fine cuts through the internal auditory canal

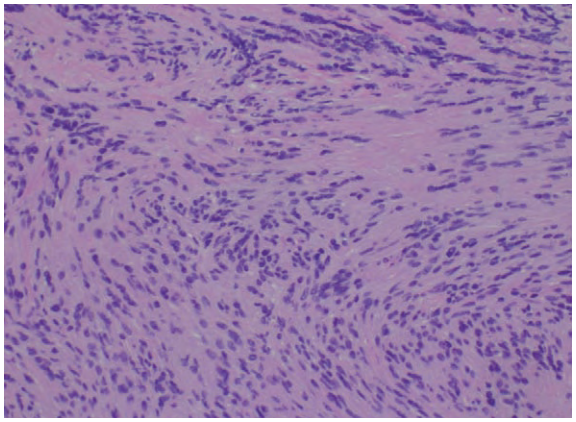

Fig. 2. Vestibular schwannoma histology. Hematoxylin and eosin stained vestibular schwannoma tumor specimen demonstrating Antoni A and Antoni B cytoarchitecture characteristic of these neoplasms.