Aberrant PI3K/AKT/mTOR pathway found in vestibular schwanommas may be therapeutic target

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Researchers from the University of Toronto, directed by Drs. Gelareh Zadeh and Boris Krischek, investigated gene expression in normal vestibular nerves and vestibular schwannomas (VSs). Two important discoveries were made: 1) there is negligible difference between VSs that sporadically occur and those commonly associated with neurofibromatosis Type 2 (NF2), a genetic disorder; and 2) the overexpressed PI3K/AKT/mTOR signaling pathway in these tumors may be an excellent therapeutic target. Detailed findings of this study are reported and discussed in "Gene-expression profiling elucidates molecular signaling networks that can be therapeutically targeted in vestibular schwannoma," by Sameer Agnihotri and colleagues, published today online, ahead of print, in the *Journal of Neurosurgery*.

A vestibular schwannoma (VS) is a nonmalignant, usually slow-growing tumor that originates in the region where hearing and balance nerves dwell in the skull. VSs usually arise spontaneously and appear singly. Sometimes, however, they appear bilaterally and when they do, they are generally associated with a genetic disorder, neurofibromatosis Type 2 (NF2), which is categorized by numerous noncancerous tumors of the nervous system. A VS is composed of an overabundance of Schwann cells, which normally surround nerve cells, providing insulation and support. As the tumor grows, it can press against adjacent nerves, causing loss of hearing, tinnitus (ringing in the ears), and balance problems. Some VSs become dormant, ceasing to grow. Others can

become large enough to press against other nearby nerves or brain structures, and rarely may become life threatening. Currently surgery and radiosurgery are the primary therapies used to treat VS. However, these treatments are not always viable options due to the size of the tumor(s) or, in cases of NF2, the nature of the underlying genetic condition.

Gene expression is the process by which genetic information is copied (transcribed) from DNA to RNA and then translated into gene products (mainly proteins) in the cell. Although all genes in the makeup of a particular person are found in nearly all cells in the human body, gene expression varies. Genes may be turned off or they may be turned on at varying degrees. This determines the type of cell (for example, cardiac cells or skin cells) and the cell's behavior (normal or aberrant).

A loss of function of a gene on Chromosome 22 has been postulated as the cause of VS. In this study, an international team of researchers, led by Drs. Zadeh, Agnihotri, and Krischek, examined RNA transcripts in 49 vestibular schwannomas (VSs) and seven normal vestibular nerves. The researchers found more than 4000 genes whose expression differed depending on whether the tissue sample was normal or tumor. The researchers also found previously unknown signaling pathways that regulate gene expression in VS cells, inducing the proliferation of the tumor cells and inhibiting these cells' natural death. What they did not find were significant differences between VSs that occur sporadically in the general population and those VSs that are commonly associated with NF2.

One particular signaling pathway that was consistently overexpressed in VS cells, PI3K/AKT/mTOR, was examined as a possible target for therapeutic intervention. The researchers tell us that the PI3K/AKT/mTOR is one of the most aberrant signaling pathways found in several other cancers as well. Using cells from an established

schwannoma cell line, the researchers tested two compounds—BEZ235 and PKI-587—known to inhibit both PI3K and mTOR. Application of these compounds to the cell line reduced tumor cell viability and increased cell death.

To summarize, included in this paper are the results of several interesting studies:

- The researchers conducted a gene profiling analysis of VS, which to their knowledge is the largest one completed to date. The analysis identified more than 4000 genes whose expression differs between VS (tumor) cells and normal Schwann cells.
- The researchers compared sporadic VSs with VSs associated with NF2, examining the tumors on both a molecular and clinical basis. They found no significant differences between the two groups of tumors, which means that separate therapies may not be needed.
- In an experimental setting, the researchers tested a therapeutic intervention in a VS cell line targeting the aberrant PI3K/AKT/mTOR signaling pathway. Administration of BEZ235 and PKI-587 reduced tumor growth.

The authors provide six multipaneled figures illustrating the findings of this study. A supplemental table shows the 4000+ genes found to have different expression profiles in normal vestibular nerve (Schwann) cells and VS (tumor) cells.

Future studies involving BEZ235 and PKI-587 as possible therapeutic interventions for use in vestibular schwannomas are certainly worthy of consideration, and the researchers call for additional molecular studies of VS including whole genome sequencing, copy number analysis, and methylation profiles. Nevertheless, the present findings are encouraging in the search for novel therapies for patients suffering from VS.

In speaking of the study, Dr. Zadeh said, "For vestibular schwannomas in which complete surgical resection is not possible or the patient is not a suitable candidate for surgery, and more importantly in patients whose hearing is limited and preservation of hearing is critical, nonsurgical treatment options are important. This is the first study to provide evidence that targeted therapeutics may be a very viable option to pursue in clinical studies for vestibular schwannomas."

More information: Agnihotri S, Gugel I, Remke M, Bornemann A, Patazis G, Mack SC, Shih D, Singh SK, Sabha N, Taylor MD, Tatagiba M, Zadeh G, Krischek B: Gene-expression profiling elucidates molecular signaling networks that can be therapeutically targeted in vestibular schwannoma. Laboratory investigation. *Journal of Neurosurgery*, published online, ahead of print, September 23, 2014; DOI: 10.3171/2014.6.JNS131433

An editorial on this article, entitled "Editorial. Therapeutic targeting based on gene-expression profiling in vestibular schwannomas," by Drs. Pier Paolo Peruzzi and Russell R. Lonser, is also available online in the *Journal of Neurosurgery*; DOI: 10.3171/2014.2.JNS14321

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