Gene Expression, Pathway Analysis, and Drug Discovery of Neurofibromatosis 2 Vestibular Schwannomas

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Introduction: Neurofibromatosis 2 (NF2) is a rare genetic disorder characterized by benign nerve tumors, most notably vestibular schwannomas (VS), which usually result in tinnitus, vertigo, and deafness. These schwannomas arise through biallelic mutation of the gene which encodes the protein merlin. Merlin is an important tumor suppressor gene that regulates cell shape, growth, and adhesion in addition to general regulation of division (1). Sporadic vestibular schwannomas (SVS) are phenotypically similar, but almost always unilateral (2). The goal of this study is to further understand the genetic and pathway mechanisms relative to a normal nerve (NN) biopsy and sporadic vestibular schwannoma type neoplasm. We analyzed 74 samples and found significant differences between SVS and NF2 based on RNA expression profiling microarrays with NN Vestibular Nerve biopsies as our control.

Objectives: The goal of this study is to better understand the underlying pathology of NF2 related vestibular schwannomas and SVS through genetic and pathway analysis of 74 tumor samples from the Gene Expression Omnibus. Another goal is to screen for initial drug candidates that may counteract NF-2KD cell activity through the iLINCS database.

Methods: The 74 samples were put through full transcriptome pathway analysis (FTPA) as well as targeted pathway analysis (TPA) via 3-POD software and data sets from Gene Expression Omnibus (GEO). For the FTPA the genes were run through GSEA which identified leading edge genes. FTPA and TPA used enrichR to identify significantly up and downregulated pathways.

Results: NF-2 was found to have 335 significantly upregulated pathways, and 554 downregulated pathways while SVS was found to have 823 upregulated pathways and 387 downregulated pathways. In addition, many of these pathways are modified in opposition to one another and have marked involvement and regulation of immune responses. While phenotypically similar, the underlying character of sporadic vestibular schwannomas is markedly different from the profile of NF-2 tumors and will

thus most likely require very different drug treatments. NF-2 tumors are always bilateral and seem to focus on cell and molecular pathway activation and apoptotic inhibition, with one goal possibly being immunological avoidance. Initial drug discovery screens through iLINCS, enrichr, and GEO databases show Aspirin, Penciclovir, and Nafcillin as top candidates to counter NF-2KD cell activity.

References

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