Impact of Cell Proliferation Index and Tumor-Associated Fibroblasts in Vestibular Schwannoma

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Introduction

Vestibular schwannomas (VS) are benign intracranial neoplasms arising from Schwann cells of the vestibulocochlear nerve. They can cause hearing loss, dizziness, and other neurological sequelae. VS occur sporadically in most cases or through a germline inactivation of the NF2 gene. The VS tumor microenvironment (TME) is a dynamic entity consisting of complex intercellular networks between multiple cell types that regulate tumor progression. Although recent advances in scientific methods support dual functions for tumor-associated fibroblasts (TAF) in promoting and suppressing cancer growth, the role TAFs in VS is unknown.

Objectives

Determine the role of TAFs on tumor size and progression in VS.

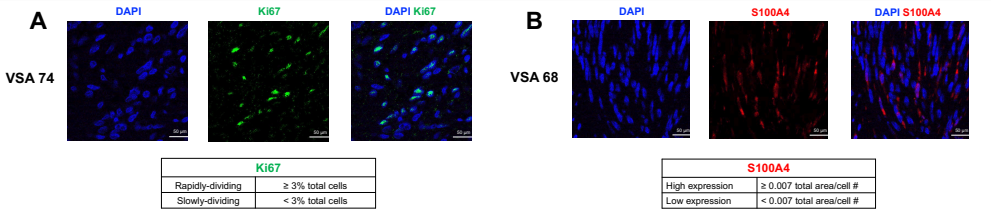
Methods

VS tumors were obtained from 76 patients undergoing VS surgery between May 2018 & December 2021. Immunohistochemistry (IHC) was performed on fixed tissue to quantify Ki67 (cell proliferation) and S100A4 (fibroblast) expression. Ki67 was categorized as slowly (<3% total cells) and rapidly-dividing (≥3% total cells) groups. S100A4 was categorized as low (<1% total area/cell count) and high expression (≥1% total area/cell count). Demographic information and hearing status (serviceable vs. non-serviceable hearing) were obtained from electronic medical records. Tumor size was categorized by maximum linear tumor dimension on pre-operative contrast-enhanced magnetic resonance imaging (small-to-medium, ≤25 mm vs. large-to-giant, >25 mm).

Results

N	76
Age at surgery	52 years (range: 17-77)
Gender	55% Female, 45% Male
Neurofibromatosis Type 2	11%
Prior Surgery	3%
Prior Radiation	8%
Prior Chemotherapy	3%
Unserviceable Hearing	61%
Max Linear Tumor Dimension	27 mm (range: 2-54 mm)

Figure 1. Patient Demographics. Patient demographics for our cohort of 76 patients



Ki67	
Rapidly-dividing	≥ 3% total cells
Slowly-dividing	< 3% total cells

S100A4	
High expression	≥ 0.007 total area/cell #
Low expression	< 0.007 total area/cell #

Figure 2 [A-B]. Ki67 Expression (Cell Proliferation Marker) and S100A4 Expression (Fibroblast Marker) on IHC. These are representative confocal images for two different VS tumors. Blue staining indicates the cell nucleus. Green staining indicates Ki67 nuclear expression while red staining indicates S100A4 cytoplasmic expression.

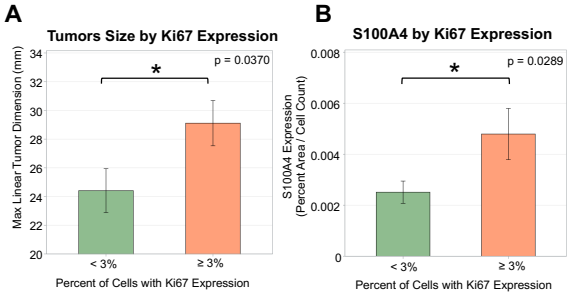
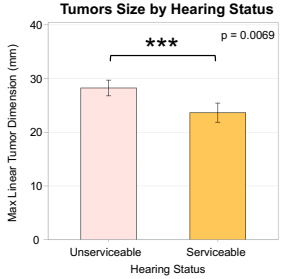


Figure 3 [A-B]. Higher Ki67 expression was associated with larger tumors and more S100A4 expression. Larger tumors have more cell proliferation and more fibroblasts, suggesting that fibroblasts may be contributing to tumor growth in VS



B

Outcome: Large-to-Giant Tumors

Variable	Odds Ratio	95% CI	p-value
Ki67 ≥3%	**3.302**	**1.152 – 9.461**	**0.0261**
Unserviceable Hearing	**3.362**	**1.149 – 9.840**	**0.0269**
S100A4 Percent Area / Cell Count ≥0.007	**1.129**	**0.268 – 4.764**	**0.8686**
NF2-Associated VS	1.145	0.159 – 8.223	0.8930
Age <30 years	7.372	0.698 – 77.868	0.0967

Figure 4. Tumor Size and Hearing Status with Ki67 and S100A4 Expression. [A] Patients with unserviceable hearing loss had larger tumors. [B] A multiple regression analysis was performed to determine independent predictors of large-to-giant tumors. Higher Ki67 expression and unserviceable hearing were independent predictors.

A

	Radiographic Growth	No Radiographic Growth	p-value
N	**21**	**3**	
Age at surgery (years)	57.2 (range: 27-73)	48.3 (range: 34-63)	0.4567
Gender	67% Female	67% Female	1.0000
Neurofibromatosis Type 2	24%	33%	1.0000
Prior Surgery	10%	0%	1.0000
Prior Radiation	33%	17%	0.5680
Prior Chemotherapy	0%	33%	0.1250
Unserviceable Hearing	57%	67%	1.0000
Max Linear Tumor Dimension (mm)	16.0 (range: 8.7-23.0)	20.1 (range: 18.4-21.4)	0.2412

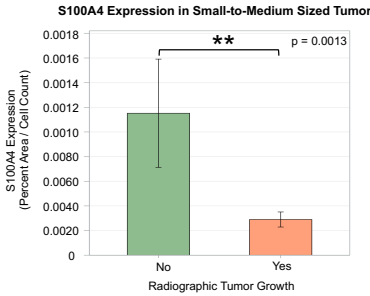


Figure 5. Fibroblast Expression in Non-Growing Tumors. [A] A subset of patients with small-to-medium sized tumors were analyzed to determine which ones were growing and not growing based on MRI. [B] Small-to-medium tumors with no growth on MRI had significantly higher S100A4 expression.

Conclusion

- Larger tumors had more proliferation and fibroblasts, compared to small tumors
- Smaller tumors with no radiographic growth had more fibroblasts, compared to growing tumors
- Fibroblasts may be ***tumor-suppressive in early VS development*** but ***tumor-promoting in later stages*** of VS development

References

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