DTX1

The study titled “Differential Expression of Proteins and Genes at the Tumor-Brain Interface in Invasive Meningioma,” published in *Genes Chromosomes Cancer* in November 2024, provides valuable insights into the molecular characteristics of invasive meningiomas, focusing on gene and protein expression at the tumor-brain interface [1)]

The research explores the differential expression of genes in the invasive edge of tumors versus the main tumor body, which has been largely unknown up to now.

Strengths of the Study:

1. **Innovative Approach**: Using the NanoString pan-cancer panel for gene expression analysis is a robust technique that allows for evaluating a large number of genes across different tumor samples. This method enabled the identification of six candidate genes (DTX1, RASGRF1, GRIN1, TNR, IL6, and NR4A1), which are implicated in meningioma invasiveness.

2. **Correlations with Protein Expression**: Immunohistochemistry findings for DTX1 and RASGRF1 corroborated with gene expression results, providing strong evidence of these proteins’ involvement in tumor invasiveness. The inclusion of Ki-67, a well-established marker of cell proliferation, adds depth to the analysis, linking higher expression levels of DTX1 and RASGRF1 to both invasiveness and proliferative activity in the tumor.

3. **Pathway Analysis**: The pathway analysis linking DTX1 and RASGRF1 to key biological processes like cell-cell adhesion and major signaling pathways (Notch, RAS, MAPK, Rho) provides a mechanistic framework to understand how these proteins contribute to brain invasion. These pathways are crucial for cell migration, invasion, and adhesion, which are central to tumor progression.

4. **Clinical Implications**: The findings suggest that DTX1, RASGRF1, and Ki-67 could serve as potential biomarkers for identifying meningiomas with a higher likelihood of brain invasion. This could aid in better prognosis and therapeutic decisions for patients with invasive meningiomas.

Weaknesses and Limitations:

1. **Sample Size**: The study, while informative, involved a relatively small cohort, particularly for the expanded validation of DTX1 and RASGRF1 (21 invasive and 15 noninvasive meningiomas). A larger sample size would strengthen the generalizability of the results and reduce the potential for bias in detecting significant findings.

2. **Inconclusive Results for DTX1**:

The study highlighted a less definitive role for DTX1, especially in meningiomas that were in close contact with the brain but did not show invasion. While increased expression was noted at the invasive edge and in non-invasive tumors with brain contact, further exploration is needed to understand whether DTX1 acts as a universal marker for invasiveness or if its role is more complex.

3. **Mechanistic Insights**:

While the pathway analysis identified important signaling pathways, the study does not delve deeply into the mechanisms by which DTX1 and RASGRF1 modulate brain invasion. Understanding how these proteins interact at the cellular and molecular levels, and whether they directly influence tumor cell

behavior, would provide a clearer picture of their role in meningioma pathogenesis.

4. **Lack of Functional Validation**:

The study is based on gene and protein expression profiling, but it lacks functional validation of how the overexpression of DTX1 and RASGRF1 specifically contributes to tumor invasion. Further in vitro or in vivo studies are needed to confirm the causative role of these proteins in meningioma invasiveness.

Conclusion:

This study represents an important step toward understanding the molecular underpinnings of invasive meningiomas and the role of specific genes and proteins in the brain invasion process. The identification of DTX1, RASGRF1, and Ki-67 as potential biomarkers for brain-invasive meningiomas has promising clinical implications, although the small sample size and inconclusive findings regarding DTX1 highlight the need for further research to validate and expand upon these findings. Future studies with larger cohorts and functional assays will be essential to fully elucidate the role of these proteins in meningioma invasion and progression.

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Senglek K, Teerapakpinyo C, Jittapiromsak N, Jittapiromsak P, Lertparinyaphorn I, Thorner PS, Shuangshoti S. Differential Expression of Proteins and Genes at the Tumor-Brain Interface in Invasive Meningioma. Genes Chromosomes Cancer. 2024 Nov;63(11):e70007. doi: 10.1002/gcc.70007. PMID: 39535842.