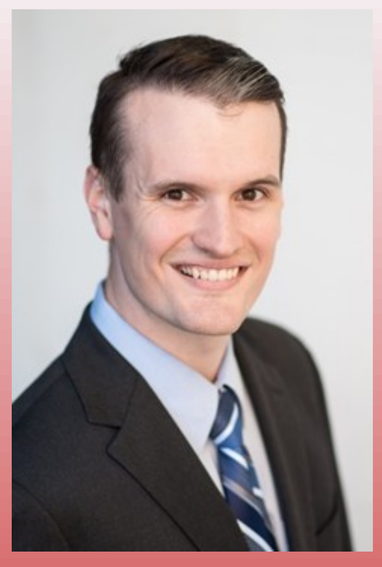
AMERICAN OTOLOGICAL SOCIETY



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John Hopkins University

"Metabolomic Profiling of Human Vestibular Schwannoma and Meningioma Before and After Radiation Therapy"

RESEARCH GRANT 2021

Amount Awarded by AOS: $44,000

Ongoing Funding: NIH National Cancer Institute Individual Postdoctoral National Research Service Award (PI: Dougherty). Amount: $69,802. Period: 2022-2023.

Dougherty MC, Shibata SB, Hansen MR. The biological underpinnings of radiation therapy for vestibular schwannomas: Review of the literature. *Laryngoscope Investig Otolaryngol*. 2021 Mar 30;6(3):458-468. doi: 10.1002/lio2.553. PMID: 34195368; PMCID: PMC8223465.

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Liu SJ, Casey-Clyde T, Cho NW, Swinderman J, Pekmezci M, **Dougherty MC**, Foster K, Chen WC, Villanueva-Meyer JE, Swaney DL, Vasudevan HN, Choudhury A, Pak J, Breshears JD, Lang UE, Eaton CD, Hiam-Galvez KJ, Stevenson E, Chen KH, Lien BV, Wu D, Braunstein SE, Sneed PK, Magill ST, Lim D, McDermott MW, Berger MS, Perry A, Krogan NJ, Hansen MR, Spitzer MH, Gilbert L, Theodosopoulos PV, Raleigh DR. Epigenetic reprogramming shapes the cellular landscape of schwannoma. *Nat Commun*. 2024 Jan 12;15(1):476. doi: 10.1038/s41467-023-40408-5. PMID: 38216587; PMCID: PMC10786948.

Dougherty MC, Syed HS, Xu L, Liu SJ, Raleigh DR, Rauckhorst AJ, Taylor EB, Hansen MR. Metabolomic profiling and stable isotope tracing of human schwannomas: A novel perspective on tumor biology and radiation response. *Neuro-Oncology Advances*. 2025 October; vdaf223, https://doi.org/10.1093/noajnl/vdaf223.

RESEARCH SUMMARY:

Although schwannomas and meningiomas are common and benign, their growth patterns are often hard to predict. Currently, surgery and radiotherapy are the only standard treatments. Since metabolites are the end products of genes and proteins, metabolomics may reveal downstream tumor features in ways that other -omics cannot. We aimed to use metabolomic profiling and stable isotope tracing to characterize primary human schwannomas and meningiomas and describe their changes following radiation in patient-derived xenografts.

Figure 1:

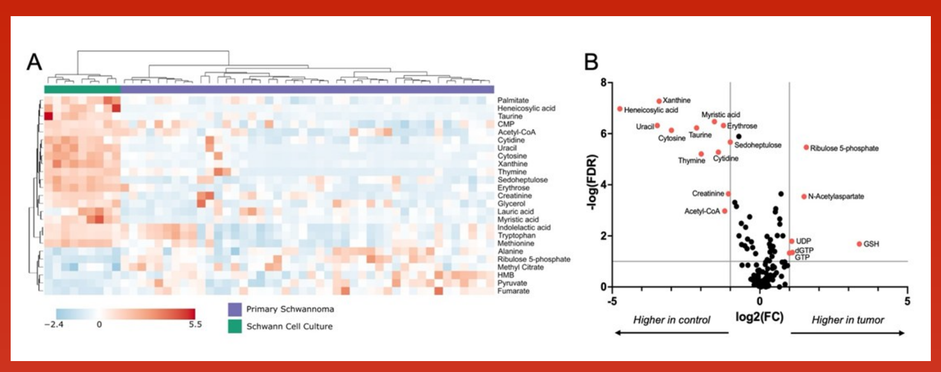
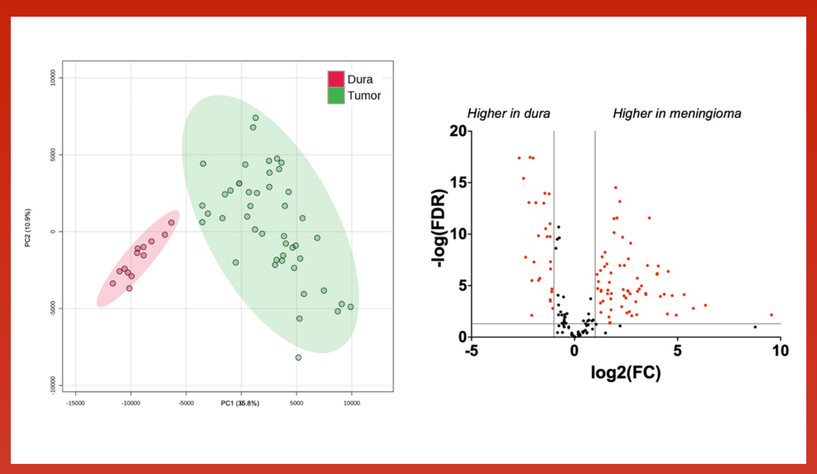


Figure 2:



OUTCOMES:

We found that the schwannoma metabolome differed significantly from that of normal cultured Schwann cells (Figure 1). In schwannoma xenografts, radiation decreased cellular proliferation and produced small but detectable changes the tricarboxylic acid cycle and nucleotide metabolism. ^{13}C-glutamine tracing showed that schwannomas can produce urea cycle intermediates, TCA cycle intermediates, CMP, and CTP from glutamine even after radiation. CMP was the only metabolite with altered glutamine-derived carbon uptake following radiation in schwannoma xenografts. In meningiomas, clear metabolic differences were identified between the tumors and the non-neoplastic dura, with 68 metabolites significantly increased and 27 significantly decreased in tumors as compared to dura (Figure 2). In contrast to schwannomas, meningioma xenografts showed unpredictable responses to radiation in terms of cellular proliferation. ^{13}C-glutamine tracing showed that meningiomas, like schwannomas, can also produce certain urea cycle intermediates. Radiation led to a slight decrease in ^{13}C-glutamine uptake in meningiomas but otherwise did not alter the metabolic pathways we tested.

FURTHER FUNDING HAS ENABLED US TO EXPAND OUR RESEARCH TO:

Further funding has enabled us to expand our research to an integrated analysis of metabolomic profiling and molecular classification based on DNA methylation profiling of schwannomas and meningiomas. So far we have found that metabolomics-based clustering of schwannomas closely resembles DNA methylation-based classification, whereas metabolomics-based clustering of meningiomas does not.

LAY SUMMARY OF FINDINGS AND IMPLICATIONS OF THIS RESEARCH:

Schwannomas and meningiomas have distinct metabolic fingerprints compared to the normal cells they originate from. Interestingly, however, even though radiation is the only proven effective non-surgical treatment for both diseases, relatively few metabolic changes were seen after we radiated human tumors implanted in mice. This means that, at least in the short term, these tumors' metabolism is fairly resistant to radiotherapy, so the long-term effectiveness of radiation must have some other explanation.