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Succinate Accumulation Is Not Sufficient for Tumorigenesis in Mouse Chromaffin Cells But Dual Loss of SDHB and NF1 Yields SDHx-like Pheochromocytomas

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BACKGROUND: Inherited pathogenic Succinate Dehydrogenase (SDHx) gene mutations cause the hereditary pheochromocytoma and paraganglioma tumor syndrome. Syndromic tumors exhibit elevated succinate, an oncometabolite proposed to drive tumorigenesis via DNA and histone hypermethylation, mitochondrial expansion and pseudohypoxia-related gene expression. It remains unproven whether oncometabolites are sufficient to drive tumorigenesis or whether it is feasible to generate an SDHx pheochromocytoma mouse model.

METHODS: To interrogate the prevailing hPPGL tumorigenesis model we disrupted mouse adrenal medulla Sdhb and Nf1 expression (independently and in conjunction) and evaluated pheochromocytoma formation and molecular phenotype. We conditionally knocked out Sdhb in catecholaminergic cells (TH-Cre) and rigorously tracked the SDHB-/- population using a GFP-based Cre-reporter system. Additionally, we utilized a sophisticated mass spectrometry technique (DESI-MS) to measure the spatial distribution of succinate in intact adrenal glands.

RESULTS: Aged SDHB-deficient mice do not develop tumors despite the succinate accumulation, histone methylation and mitochondrial pathology showing that these conditions are insufficient for tumorigenesis. These data suggested that a “second-hit” is required to initiate tumorigenesis in SDHB-/- chromaffin cells. Towards this end, we developed a double knockout mouse with co-deletion of the NF1 tumor suppressor. The SDHB/NF1 mice

develop pheochromocytomas with high levels of succinate as well as many other aspects of human SDHx tumors such as histone methylation, loss of 5-hydroxymethylcytosine and large clusters of swollen mitochondria. Unexpectedly, in vivo depletion of the 2-oxoglutarate (2-OG) dioxygenase cofactor ascorbate reduced SDHB-deficient cell survival, indicating that the lineage-restricted pattern of SDHx tumors may be determined by cellular ascorbate levels.

CONCLUSION: Contrary to the prevailing oncometabolite model, succinate accumulation and 2-OG-dependent dioxygenase inhibition are insufficient for mouse pheochromocytoma tumorigenesis, which requires additional growth-regulatory pathway dysregulation. This work describes the first mouse model for SDHx pheochromocytoma which recapitulates most essential aspects of the human disease.

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