**HOW CAN WE MODEL MUTATIONS IN ANCIENT CONSERVED HUMAN DISEASE GENES? A CASE STUDY IN *C. ELEGANS***

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**Abstract**

* **Background**: The conserved B-subunit of succinate dehydrogenase (SDH) participates in the TCA cycle and mitochondrial electron transport. The Arg230His mutation in SDHB causes heritable pheochromocytoma/paraganglioma (PPGL).
* **Objectives**: Simple animal models can be useful in the study of rare diseases thus we generated an *in vivo* PPGL model (SDHB-1 Arg244His; equivalent to human Arg230His) in the nematode *C. elegans*.
* **Methods**: LC-MS, Seahorse and RNAseq were used to characterize the metabolism of *sdhb-1(Arg244His)* and *sdhb-1(-)* mutants. The number of functional mitochondria was determined by Mitotracker. ROS levels were measured by CellRoxGreen, expression of HIF-1 targets was determined by semi-quantitative RT-PCR.
* **Results**: Arg244His mutants manifest delayed development, attenuated ATP production and reduced mitochondrial number. Although succinate is elevated in both missense and null *sdhb-1* mutants, transcriptomic comparison suggests that only Arg244His worms elevate lactate/pyruvate levels, pointing to ‘Warburg’-like aberrant glycolysis. Accordingly, in Arg244His mutants increased expression of lactate dehydrogenase *(ldh-1)* was observed, which could be inhibited by LDHA inhibitors and caused arrested development. Besides *ldh-1/LDHA*, elevated expression of other hypoxia target genessuch as *pvf-1/VEGFA* and *Y48G10A.3/NDGR1* were detected in point mutants. In addition*,* Arg244His mutants displayed elevated ROS levels.
* **Conclusion**: Characterization of our novel nematode PPGL model revealed rewired metabolism, hypoxia activation and increased ROS levels, characteristics of PPGL tumors, which can be observed in patients. We showed that our model is druggable and can be used after optimalization for high-throughput screening of drug candidates.

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