A druggable *in vivo* model of paraganglioma

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Abstract

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). In *C. elegans*, we generated an *in vivo* PPGL model (SDHB-1 Arg244His; equivalent to human Arg230His) which manifests delayed development, shortened lifespan, attenuated ATP production and reduced mitochondrial number. Although succinate is elevated in both missense and null *sdhb-1(gk165)* mutants, transcriptomic comparison suggests very different causal mechanisms that are supported by metabolic analysis where only Arg244His (not null) worms elevate lactate/pyruvate levels, pointing to a missense-induced, 'Warburg'-like aberrant glycolysis. *In silico* predictions of the SDHA-B dimer structure demonstrate that Arg230His modifies the catalytic cleft despite the latter's remoteness from the mutation site. We hypothesize that Arg230His SDHB mutation rewires metabolism, reminiscent of metabolic reprogramming in cancer. Our tractable model provides a novel tool to investigate the metastatic propensity of this familial cancer and our approach may illuminate wider SDH pathology.