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Therapeutic Targeting of SDHB-Deficient Tumors

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BACKGROUND

Pheochromocytomas and Paragangliomas (PPGLs) are rare neuroendocrine tumors arising from the adrenal medulla and extra-adrenal paraganglia, respectively. About 40% of PPGLs are hereditary, and nearly half of these caused by germline mutation of a succinate dehydrogenase (SDH) subunit. Pathogenic succinate dehydrogenase subunit B (*SDHB*) mutation confers increased risk for metastasis. Unfortunately, treatments for metastatic PPGL remain palliative. Hence, discovering novel therapeutic avenues that improve the prognosis for metastatic *SDHB*-PPGL patients is an urgent unmet need.

METHODS

To explore the function of *SDHB* in cells and human PPGLs, we (i) conducted bulk mRNAseq on UOK269, a human *SDHB*-deficient renal cell carcinoma line, and *SDHB* reconstituted UOK269 (UOK269WT) cells (n=3), and (ii) interrogated gene expression in the publicly available PPGL (n=178) Cancer Genome Atlas (TCGA) database. Gene Ontology (GO) analysis identified pathways altered by *SDHB* deficiency. Additionally, we performed cell viability assays, Hoechst and Ethidium Homodimer I (EthD-I) staining, following compound treatment (t=72h), and automated image acquisition and analysis (Operetta, PerkinElmer). ANOVA or paired t-tests were used for statistical analysis, as appropriate.

RESULTS

GO analysis revealed that UOK269 cells exhibit enhanced expression of nutrient transporters, including many solute carrier (SLC) transporters; likely reflecting adaptive metabolic activity due to *SDHB* deficiency. Notably, altered SLC transporter expression is also present in human *SDHB*-deficient PPGLs (TCGA dataset). Among these, we identified SLC35F2, which demonstrates ~4-fold increased expression in *SDHB*-deficient PPGLs, as an attractive potential therapeutic target for *SDHB*-deficient PPGLs. The SLC35F2 transporter is required for cytotoxic activity of the chemotherapeutic compound YM155. Furthermore, YM155 acts by promoting DNA damage, a pathway of increased susceptibility in SDH-deficient cells. Indeed, YM155 cytotoxicity against UOK269 was ~10-fold enhanced. Importantly, chemical inhibition of SDH complex activity in UOK269WT cells with 3-NPA, to mimic *SDHB*-deficiency, conferred increased YM155 sensitivity. Finally, YM155 cytotoxicity was found to be increased against *SDHB*-deficient mouse primary renal tubule cells. Mechanically, YM155 treatment results in increased DNA damage (γ-H2AX) in *SDHB*-deficient UOK269 cells.

CONCLUSIONS

We identified SLC35F2 as a potential therapeutic target for *SDHB*-deficient tumors. Specifically, this transporter is upregulated in human *SDHB*-deficient PPGLs and is responsible for cellular import of the chemotherapeutic compound YM155. Critically, YM155 demonstrated preferential cytotoxicity towards *SDHB*-deficient cells, in part related to impaired DNA damage repair. This preferential cytotoxicity of YM155 towards *SDHB*-deficient cells was observed in both tumor cell lines and primary cell cultures. Collectively, these data indicate that *SDHB*-deficient cells exhibit unique chemical sensitivities which have potential to be therapeutically leveraged.

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