Norepinephrine transporter (NET) as a predictive marker of response to PI3K/mTOR inhibition in pheochromocytoma

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Abstract:
Phaeochromocytomas (PCs) are rare highly vascularized neuroendocrine tumors derived from neural crest-derived chromaffin cells located either in adrenal medulla or sympathetic ganglia (paragangliomas). Although most cases are benign but about 10% of all PCs can become malignant and resistant to conventional chemotherapy or radiotherapy. Therefore, novel therapeutic approaches are required.

In this study, we verified the antioxidant efficacy of the dual PI3K/mTOR inhibitor BEZ235 in a unique model of bilateral PCs, MENX affected rats (Figure 1) and identified molecular read outs of drug treatment. Genome-wide transcriptome profiling of PCs from drug-treated or placebo-treated rats was conducted, and identified the Slc6a2 gene, encoding the NET protein, as a target of BEZ235, which is inhibited by drug treatment in a dose-dependent manner. Functional analyses confirmed a predictive role for NET expression in the response to PI3K/mTOR inhibition, which can be monitored using NET-selective functional positron emission tomography (PET) imaging with 18F-LMI1195. Moreover, BEZ235 reduced Slc6a2/NET expression also in PC cell line, MPC.

Material and Methods:

BEZ235: This compound was kindly supplied by Novartis Pharma and used for in vitro and in vivo studies.

Pharmacological treatment and cell culture: BEZ235 was dissolved in DMSO and diluted with PBS to prepare stock solutions of 10 µM and used at a final concentration of 1 µM. MPC cells resistant to BEZ235 do not suppress NLS and RAD001.

Results

Figure 1. MENX-affected bilateral pheochromocytomas with 100% penetrance

Figure 2. Analysis of PCC tissues from rats treated with placebo or BEZ235.

Figure 3. DW-MRI to assess the response of rat PCs BEZ235 and primary cells.

Figure 4. NVP-BEZ235 reduces Slc6a2/NET expression in rat PCs in vivo and in vitro.

Figure 6. The expression of NET in MPC and MPCR cells after BEZ235 treatment.

Conclusions:
Our findings establish PI3K/mTOR inhibition as an effective therapeutic option for PC. NET expression seems to be a predictive biomarker of the response of PC cells to a blockade of PI3K and mTOR signaling, which can be assessed by functional imaging.

References: