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Type	Oral communication
Session	Gene regulation, transcriptomics and epigenomics
Title	Connectivity map analysis indicates PI3K/Akt/mTOR inhibitors as potential anti-hypoxia drugs in neuroblastoma
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Motivation

Neuroblastoma (NB) is one of the deadliest pediatric cancers accounting for 15% of deaths in childhood. A large percentage of patients relapses and dies despite treatment, demanding for new personalized strategies and therapeutic targets. Pathologic hypoxia is a condition of low oxygen tension occurring in solid tumors and an unfavourable prognostic factor for NB.
Establishing new connections between hypoxia and pharmacological compounds may provide novel treatments for NB patients. Connectivity map (CMap) is an online resource designed to analyze gene pathways, uncover structure-function relationships, and investigate drug repurposing.
In the present study, we aimed to identify novel promising drugs for high-risk NB treatment by investigating connections between hypoxia-modulated genes in primary NB tumors and small molecule compounds using the CMap.

Methods

The degree of connectivity between hypoxia-modulated genes in NB tumors and compounds was measured by the CMap connectivity score. A negative connectivity score reflects the potential effect of that small molecule to reverse the signature of a specific disorder and can, thus, be used as an indicator for therapy. The gene expression profiles of SK-N-BE(2)c NB cells cultured under hypoxic conditions and treated with the mTORC complex inhibitor PP242, referred to as Mohlin dataset, was used to validate CMap findings. Gene set enrichment analysis (GSEA) was used to assess enrichment of gene sets belonging to the Hallmark (H) collection.

Results

We analyzed with CMap two sets of 34 and 21 genes up- and down-regulated, respectively, between hypoxic and normoxic primary NB tumors, recently identified by our group as hypoxia modulated genes. Analysis of 2837 compounds reported a connectivity score ranging from +78.42 to -97.04. No compounds displayed a connectivity >90, whereas 19 mainly belonging to the class of PI3K/Akt/mTOR inhibitors displayed a connectivity <-90, evidencing a clear negative connectivity between genes associated with hypoxia in NB tumors and these compounds. Because CMap does not include NB cell lines among those used to create the reference database, we needed to confirm CMap findings in NB cells. To this aim, we performed a literature search to find published gene expression profiles of NB cell lines cultured under hypoxia and treated with mTOR inhibitors. Mohlin and colleagues have recently published a dataset, hereafter referred to as Mohlin dataset, which was used to show the therapeutic efficacy of targeting PI3K and mTOR complex 2 (mTORC2) in aggressive NB cells. In this study, SK-N-BE(2)c NB cells treated with the mTORC complex inhibitor, PP242, or dimethyl sulfoxide (DMSO), as a control, were cultured under hypoxic condition for different time points, and the gene expression profile was determined by microarray analysis. Heat map representation of hypoxia-modulated genes in the Mohlin dataset showed an opposite regulation of these genes in the set of NB cells treated with the mTORC inhibitor PP242. In addition, GSEA identified fourteen negatively enriched gene sets in NB cells treated with PP242 ($p<0.05$ and qvalue<0.005), which included HALLMARK_MTORC1_SIGNALING, HALLMARK_PI3K_AKT_MTOR_SIGNALING, HALLMARK_HYPOXIA, and HALLMARK_GLYCOLYSIS, which corroborated the negative connectivity between mTOR inhibitors and hypoxia in NB cells.
Our analysis identified inhibitors of the PI3K/Akt/mTOR signaling pathway as novel candidate compounds to treat NB patients with hypoxic tumors and poor prognosis.

Info

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Figure	
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Availability	-
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