**Additional information on proteins of which expression was affected by DIO1 in renal cancer cells.**

Transketolase (TKT) is one of the PPP enzymes that generates ribose-5-phosphate (R5P) and NADPH [1]. Cancer cells require R5P for nucleotide synthesis, while NADPH is used in reductive detoxification needed for protection against oxidative stress. R5P is synthesized in the oxidative phase of the PPP in which glucose-6-phosphate dehydrogenase (G6PD) oxidizes G6P, generating NADPH and subsequently R5P. In the non-oxidative PPP phase, glyceraldehyde-3-phosphate and fructose-6-phosphate are converted to R5P. Activation of TKT leads to reversal conversion of R5P to F6P and G6P with generation of NADPH, contributing to redox homeostasis [1]. In ccRCC tumors, the metabolism of sugars is rerouted towards PPP, providing both substrates for anabolic reactions as well as antioxidative protection [2].

Nicotinamide phosphoribosyltransferase (NAMPT) is a critical enzyme of the first-rate limiting step in conversion of nicotinamide to NAD+, essential for many metabolic pathways, including NADP synthesis. Decreased expression or inhibition of NAMPT attenuates glycolysis downstream of glyceraldehyde 3-phosphate dehydrogenase, increases the activity of the non-oxidative PPP branch, and results in attenuation of the TCA cycle [3]. In ccRCC cells, NAMPT inhibition attenuates their growth [4], underscoring the significance of this enzyme for cancer cell survival.

IDH2 is a mitochondrial isoform of isocitrate dehydrogenase. In hypoxic conditions, activation of IDH2 leads to reductive carboxylation of α-ketoglutarate, supporting citrate production at the expense of NADPH that donates hydrogen for α-ketoglutarate reduction. This is the major source of citrate synthesis from glutamine [5]. In ccRCC cells, citrate is further utilized for FFA synthesis that leads to lipid accumulation in cytosol and contributes to the clear cytosolic appearance of ccRCC cells [6]. Finally, ccRCC cells are highly dependent on extracellular amino acids [7]. To sustain their high amino acids demands, ccRCC cells express increased levels of amino acid transporters [8,9].

NDUFA3 subunit of mitochondrial complex I (NADH\_ubiquinone oxidoreductase). Complex I is one of the elements of the respiratory chain that contributes to the H+ gradient across mitochondrial inner membrane [10]. It catalyzes the first step of NADH oxidation. In ccRCC the expression of mitochondrial complex I is decreased [11]. Suppression of mitochondrial complex I activity reduces NAD+/NADH ratios in breast cancer cells and enhances their metastatic potential. In contrast, enhanced complex I activity reduces metastatic growth by inducing autophagy via mTORC/Akt involving mechanism [12].

CYP4F11 belongs to the family of cytochrome P450 monooxygenases that catalyze metabolism of fatty acids [13].

ANPEP belongs to the family of zinc metalloenzymes that preferentially cleave amino acids at neutral N-terminus of the protein. The levels of aminopeptidase N are elevated in cancers and often correlate with worse prognosis for patients. ANPEP actively contributes to cancer progression by promoting angiogenesis, migration and invasion of cancer cells. Inhibition of ANPEP activity by small compounds as well as targeting antibodies inhibits tumor progression in mouse models. Hence, ANPEP is considered as an important therapeutic target for treatment of many cancers [14]. In our study, DIO1 expression reduced ANPEP levels by nearly 9-fold (Table 2).

Depletion of TBC1D2 and NMI impairs biogenesis of autolysosomes and autophagy induction, respectively [15].

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