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Metabolic reprogramming of sunitinib- and pazopanib-resistant renal cell carcinoma cells: a metabolomics approach

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Abstract

Background: Tyrosine kinase inhibitors (TKIs), such as sunitinib and pazopanib, changed the therapeutic landscape of metastatic renal cell carcinoma (RCC) [1,2]. However, TKIs resistance and disease progression within one year have been observed even in patients who initially respond to treatment [3]. Hence, understanding the metabolic mechanisms associated with TKIs resistance is of utmost importance to reverse this issue and improve RCC treatment guidelines. **Objective:** This work applied a metabolomics approach to investigate the metabolic dysregulations underlying sunitinib and pazopanib resistance in a metastatic RCC cell line (Caki-1). **Methods:** Caki-1 cell line was continuously (6 months) exposed to increasing concentrations of sunitinib and pazopanib to induce resistance. Resistance was confirmed through the MTT assay by a 4.9- and 2.8-fold increase in the IC_{50} values of sunitinib and pazopanib-resistant cells compared with the parental cells, respectively. In the metabolomics assay, eight independent passages were considered for TKI-resistant and parental cells. Intracellular and extracellular metabolites were analyzed by proton nuclear magnetic resonance (^{1}H NMR) spectroscopy. Statistical analysis comprised multivariate and univariate methods, and biological interpretation was performed through pathway analysis. **Results:** TKIs-resistant cells revealed a common reprogramming in the amino acid, glycerophospholipid, and nicotinate and nicotinamide metabolisms. Sunitinib-resistant cells were also characterized by an enhanced cellular antioxidant capacity supported by a significant increase in the intracellular levels of glutathione and myo-inositol, and a significantly higher uptake of glutamine. On the other hand, pazopanib-resistant cells exhibited marked changes in several metabolites (e.g., glucose, lactate, pyruvate, acetate, succinate, fumarate) participating in energy metabolism. **Conclusions:** Our findings demonstrate for the first time a distinct pattern of metabolic alterations associated with sunitinib and pazopanib resistance in metastatic RCC cells. Targeting these dysregulations may constitute a promising strategy to restore cell sensitivity to treatment with these TKIs.

Keywords: renal cell carcinoma; tyrosine kinase inhibitors resistance; *in vitro* metabolomics

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