O04 Metabolic reprogramming and epigenetic landscape: an interplay to renal cell carcinoma aggressiveness promotion

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Introduction & Objectives: Renal cell carcinomas (RCC) are the most lethal of the common urological cancers, despite the major improvements in adjuvant therapies. Recently, metabolic reprogramming and epigenetic deregulation were recognized as cancer hallmarks and their interactions have been associated with cancer aggressiveness. RCC display a characteristic Warburg effect, producing high lactate levels, which is transported to a pseudo-hypoxic microenvironment by monocarboxylate transporters (MCTs). Additionally, metabolites fluctuations derived metabolic reprogramming dictate an epigenetic plasticity in cancer cells. Thus, firstly, we assessed MCTs expression, as well as their association with VHL expression in RCC. In addition, the effects of lactate in epigenetic mechanisms modulation of RCC were also evaluated.

Materials & Methods: A total of 200 ccRCC primary tumors and 25 normal kidney tissues derived from patients at the Portuguese Oncology Institute of Porto were used for MCT1, MCT4, VHL, HIF-1α, SIRT1 and SIRT6 protein expression's assessment. The lactate effects on epigenetic enzymes and cell phenotype were evaluated in normal kidney and RCC cell lines. Cells were also exposed to nicotinamide (NAM) – sirtuin inhibitor- and alpha-cyano-4-hydroxycinnamate (CHC) – MCT inhibitor – to investigate *in vitro*, as well as *in vivo* effect by CAM model assay in kidney cells.

Results: MCT1, MCT4, HIF-1α expression was upregulated in ccRCC, whereas VHL was downregulated, with concomitant with increased methylation levels. Lactate inhibited SIRT1 and SIRT6 both in RCC cells and normal kidney cells, increasing H3K9 and H4K16 acetylation. Cells exposed to lactate displayed pronounced glycolytic phenotype, increased cell migration and invasion. NAM treatment paralleled lactate effects, promoting cell aggressiveness, whereas CHC reversed them. In *in vivo* CAM model, lactate and NAM treatment associated with increased tumors' size, while CHC associated with diminished tumors growth. Primary RCC disclosed HIF-1a upregulation, whereas SIRT1 and SIRT6 expression was downregulated comparing with normal tissues.

Conclusions: In RCC, MCTs overexpression along with increased lactate levels, promote tumor cell aggressiveness and modulates normal cell phenotype inducing malignant-like features, through SIRTs downregulation. Therefore, tumor metabolism might be a promising therapeutic target in RCC.