Metabolic pathways in clear cell renal cell carcinoma: possible therapeutic targets


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Objective. Clear cell Renal Cell Carcinoma (ccRCC) is characterized by cells filled with lipid and glycogen. The bi-allelic inactivation of VHL gene prevents degradation of HIF1a and HIF2a that activate specific hypoxia-inducible genes, involved in the development of metabolic alterations responsible of the “clear” cytoplasm. The activation of glycolysis and lactate production even in the presence of oxygen, the alteration of mitochondrial oxidative metabolism, and the switch of glutamine metabolism that supply Krebs cycle to support lipogenesis, are present in ccRCC and can be potential therapeutic targets. Interestingly, PPAR pathway, involved in fatty acid metabolism, seems to be negatively regulated by Annexin A3 protein [J Biochem 2012, 152, 355] that we have previously evidenced as downregulated in RCCcc cells [Am J Pathol 2010, 176, 1660].

Our aim was to investigate whether: 1) lipid and glycogen storages were differently modulated on the basis of histopathological features; 2) the viability of ccRCC cells were differently affected by specific metabolic pathway inhibition; 3) Annexin A3 was involved in lipid storage of ccRCC cells.

Materials and Methods. Primary cell cultures established from ccRCC of different Fuhrman grade and normal cortex tissue were used. Lipid and glycogen storages were evaluated in cultures and corresponding tissues by Oil Red “O” and PAS staining. MTT assay was used to analyze the viability of primary cell cultures after 72 h of treatment with specific inhibitors of lipid (etomoxir) or glucose (2DG) metabolism, and after culture in glutamine depleted media.

Results. The lipid storages were more abundant in lower grade (G2) than in higher grade (G3-G4) ccRCC primary cultures and corresponding tissues. The glycogen storages were more abundant in higher grade (G3-G4) ccRCC cultures and tissues. The viability of low grade (G2) ccRCC cultures was affected by treatments that interfered with lipid metabolism (etomoxir and glutamine depletion). Higher grade (G3) ccRCC cultures were
affected by treatments that interfered with glucose metabolism (2DG). Also transcriptomic and miRNA profiles of our ccRCC primary cultures were consistent with the cytological phenotype. Annexin A3 gene, silenced by siRNA, induced in ccRCC cell an increase of lipid storage with a decrease of cell viability.

Discussion. The data evidenced different metabolic storages in ccRCC cells and different impact of glucose and lipid metabolism on cell viability, in relation to histopathological grading of corresponding tumor tissues. The involvement of Annexin A3 protein in modulation of lipid storage in ccRCC cells may shed light on the molecular mechanisms involved in metabolic reprogramming of ccRCC.

Conclusions. These results might be useful to develop an approach to “personalized medicine” for ccRCC, targeting metabolic pathways highly represented in specific ccRCC grades.