ORT_12 - Influence of carbonic anhydrase IX and cyclooxygenase-2 on immune checkpoint

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Introduction: Clear cell renal cell carcinoma (ccRCC) presents a complex tumor microenvironment with the presence of infiltrated immune cells, and at the same time immunosuppressive due to the production of cytokines. And the constitutive expression of the metalloenzyme carbonic anhydrase IX in ccRCC, independent of hypoxia, occurs in 94-97% of cases and making CAIX an interesting target for the development of antitumor drugs against ccRCC. Several types of tumors including ccRCC are capable of expressing the programmed cell death receptor- 1 (PD-L1) which, when interacting with the programmed cell death receptor-1 (PD-1), located mainly in T lymphocytes (LT), favors the exhaustion of these cells that become incapable of curbing tumor development. Also, COX-2 positive expression was described by other studies in about half of the evaluated samples of ccRCC.

Objectives: In this project, we aim to evaluate whether blocking CAIX with monoclonal antibodies is capable of modulating PD-L1 and COX-2 expression levels in clear cell renal cell carcinoma tumor cell lines, enabling an indirect regulatory response to the LT depletion process via PD-L1/PD-1 checkpoint blockade and COX-2- mediated tumorigenesis.

Methodology: For this study, renal tumor cells (SKRC 52 and SKRC 59, both positive for CAIX and PD-L1) were used as models of renal cancer. The baseline levels of CAIX, PD-L1, and COX-2 expression were evaluated through immunohistochemistry. Subsequently, the effect of CAIX inhibition using different anti-CAIX monoclonal antibodies on PD-L1 and COX-2 expression was assessed through immunofluorescence.

Results: We have established compelling evidence indicating an upregulation of CAIX, PD-L1, and COX-2 in the examined cellular lineages. Remarkably, we have observed an interplay between the CAIX/PD-L1 and CAIX/COX-2 axes, where the blockade of CAIX engenders a diminution in the expression levels of PD-L1 and COX-2.

Conclusion: The augmented CAIX expression may be inherently linked to programmed cell death ligand-1, thereby instigating an augmentation of its expression, which, in turn, fosters the process of T lymphocyte exhaustion, ultimately fueling tumorigenesis and its subsequent progression. A correlative association has been unveiled between the levels of CAIX and COX-2 expression, propounding that individuals harboring CAIX and COX-2 positive renal tumors could reap potential therapeutic benefits from CAIX inhibitors. Furthermore, the use of anti-CAIX therapies alongside other anti-tumor treatments has the potential to improve therapeutic effectiveness against renal tumors.

Keywords: CAIX; Renal carcinoma; Solid tumors