KIDNEY CANCER

IL-23 links glutamine addiction and immune function

the study reveals a previously uncharacterized immunoregulatory role for IL-23 in glutamine-addicted ccRCC

A key metabolic hallmark of clear cell renal cell carcinoma (ccRCC) is glutamine addiction, which depletes the local microenvironment of this metabolite. However, the influence of tumour glutamine metabolism on the ccRCC immune contexture is unclear. A new study now offers mechanistic insight into how macrophage-derived interleukin-23 (IL-23) orchestrates immune infiltration in glutamine-addicted ccRCC tumours.

Using The Cancer Genome Atlas (TCGA) data and tumour samples from patients, Fu and colleagues initially found that a 41-gene glutamine metabolism signature — indicative of tumour glutamine metabolism — was associated with poor overall survival (OS) and cancer-specific survival (CSS), decreased tumour-infiltrating CD8⁺ T cell cytotoxicity, and increased regulatory T (T_{reg}) cell-associated gene expression in ccRCC tumours. Interestingly, IL-23 expression was positively correlated with both glutamine metabolism and T_{reg} cell signatures and was associated with poor OS and CSS. Collectively, these data suggested that glutamine addiction dampens T cell-mediated antitumour cytotoxicity via T_{reg} cell

activation and implicated IL-23 as the missing link between glutamine metabolism and T_{reg} cell responses.

The role of IL-23 in regulating T_{reg} cell function was then investigated. In co-culture experiments, recombinant IL-23 treatment increased T_{reg} cell proliferation and activation, elevated T_{reg} cell-derived transforming growth factor- β (TGF β) and IL-10 expression, and enhanced T_{reg} cell-dependent suppression of responder CD4⁺ and CD8⁺ T cell proliferation, inferring that IL-23 enhances T_{reg} cell immunosuppressive functionality. Flow cytometry and immunofluorescence assays identified macrophages as the predominant source of IL-23 in human ccRCC tumours. Furthermore, culture of murine peritoneal macrophages and isolated human tumour-infiltrating macrophages under glutamine-deficient conditions increased IL-23 secretion, suggesting that glutamine deprivation in the glutamine-addicted ccRCC tumour microenvironment promotes IL-23 secretion. Subsequent experiments identified a role for hypoxia-inducible factor 1 α (HIF1 α) in IL-23 induction in glutamine-deprived macrophages.

The therapeutic effects of IL-23 blockade were subsequently assessed. Treatment of tumour-bearing mice with an anti-IL-23A antibody prolonged survival and reduced tumour and metastatic burden; these therapeutic effects were mitigated in mice bearing tumours with knockdown of glutamine metabolism genes *Slc1a5* or *Gls*. Flow cytometry profiling of tumour-infiltrating lymphocytes showed that

anti-IL-23A therapy decreased T_{reg} cell infiltration and increased activated CD8⁺ T cell counts, indicative of enhanced antitumour cytotoxicity. Furthermore, anti-IL-23A antibody therapy synergistically enhanced the antitumour effect of an anti-programmed cell death 1 (PD-1) antibody, highlighting the potential for IL-23 blockade to improve the efficacy of immune checkpoint inhibition in ccRCC.

Fu et al. also developed a novel in vitro culture system incorporating bulk single-cell suspensions from resected ccRCC tumours to simulate the in vivo tumour immune contexture. “This model is easy to handle and can maintain the proportions and phenotype of leukocyte subsets during short-time culture,” explains author Jiejie Xu. In this system, treatment with the FDA-approved anti-IL-23A antibody guselkumab decreased T_{reg} cell proliferation, increased CD8⁺ T cell cytotoxicity and induced tumour cell death.

Overall, the study reveals a previously uncharacterized immunoregulatory role for IL-23 in glutamine-addicted ccRCC tumours and highlights therapeutic opportunities for IL-23 blockade in this context, either alone or in combination with immune checkpoint inhibitors. “Further investigation of the impact of IL-23 on other immune or stromal cells is still needed to improve our understanding of the biological functions of IL-23,” concludes Xu.

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ORIGINAL ARTICLE Fu, Q. et al. Tumour-associated macrophage-derived interleukin-23 interlinks kidney cancer glutamine addiction with immune evasion. *Eur. Urol.* <https://doi.org/10.1016/j.eururo.2018.09.030> (2018)