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Glutamine and the Tumor Immune Microenvironment

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Metabolic dysregulation is a hallmark of renal cell carcinoma (RCC) and is the common link among the most prevalent forms of RCC in which interruption of the Krebs cycle and preference for aerobic glycolysis dominate [1]. The metabolic pathway alterations that lead to aerobic glycolysis have several actionable targets with therapeutic potential, some of which have been evaluated in preclinical models [2]. Disruption of tumor metabolic activity can potentially be accomplished by inhibiting glucose uptake, along with several other enzymes along the aerobic glycolysis pathway, which would theoretically starve tumor cells and lead to tumor senescence. In the cancer setting, tumor-intrinsic glutamine metabolism is well documented, but its effects on the immune microenvironment are not well studied.

In this issue of *European Urology*, Fu et al. [3] report on their evaluation of the effects of extracellular glutamine depletion on the immune microenvironment. Using The Cancer Genome Atlas (TCGA) data, the authors identified a glutamine signature (GlnS) and showed that a high signature (ie, high glutamine consumption) was associated with poor overall and cancer-specific survival. To understand its effects on the immune microenvironment, they studied cytotoxic $CD8^+$ T cells from tumor specimens using flow cytometry and found that high-GlnS tumors had lower expression of IFNγ, GZMB, and PRF1, indicating lower effector T-cell cytotoxic function. Confirming these findings in both in vitro and in vivo models, the authors further showed that disruption of the glutamine pathway using knockdown of SLC1A5 (glutamine transporter) or GLS (glutaminase) led to a decrease in intracellular glutamine concentration and increases in the proliferation and effector function of cytotoxic $CD8^+$ T cells. To help define the mechanism of lower cytotoxicity, the authors identified that high-GlnS tumors had higher levels of immunosuppressive T regulatory cells (T-reg). Knockdown of GLS and SLC1A5 reduced glutamine and led to reduced T-reg proliferation and function. Mechanistically, this immunosuppressive effect may be mediated by IL-23 secretion by M2 macrophages. Glutamine deprivation is directly responsible for IL-23 secretion by macrophages via activation of the HIF1α pathway. IL-23 levels correlated with both poor outcome and as high GlnS and T-reg signatures in the TCGA data. Addition of IL-23 to T-regs in vitro induced proliferation and activation of PD-1 and CD69, all leading to suppressed proliferation of effector CD4 and CD8 T cells. Blocking of IL-23 ex vivo with guselkumab (anti-IL-23A monoclonal antibody) appears to inhibit T-regs, lower IL-10, and increase GZMB, leading to a decrease in the metastatic potential of tumors in a syngeneic mouse model.

The results of this study are highly intriguing as more evidence points to the importance of the tumor microenvironment in dictating overall effector immune function. Understanding the role of glutamine in this process adds to the growing complex picture of tumor–host interactions. Glutaminase inhibitors are in clinical development and prevent the conversion of glutamine to glutamate for shuttling into the Krebs cycle via reductive carboxylation [4,5]. Inhibition could alter tumor metabolism and make cells less dependent on these pathways. It is possible that less uptake would increase extracellular concentrations and in turn reactivate the immune response. Ongoing protocols are evaluating PD-1 inhibition in conjunction with CB-839 in clear cell RCC (NCT02771626). However, in the low-glutamine tumors, it is possible that other metabolic factors impact the microenvironment. As there may be contrasting roles of HIF1 and HIF2 with glutamine metabolism, the picture becomes even more confusing [6]. Blocking the downstream immune effects of glutamine addiction via

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IL-23 may be more viable option, as this might exploit the metabolic dysfunction to improve immune function. Various IL-23 inhibitors have been clinically approved or are in development for several autoimmune disorders such as psoriasis. To the best of our knowledge, these agents have not been studied in cancer but could be an interesting area of further investigation.

Conflicts of interest: The authors have nothing to disclose.

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