CellPress

Cancer Cell

Spotlight

Glucose makes T_{reg} lose their temper

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https://doi.org/10.1016/j.ccell.2021.03.001

Competition for glucose regulates the balance between cancer and immune responses. New findings published in *Nature* show that regulatory T cells (T_{reg}) shape their metabolism to avoid glucose competition, thus maintaining their stability and sustaining tumor progression. This research suggests hijacking the "eating habits" of T_{reg} could improve cancer therapy.

Within a solid tumor, there is a complex interaction among cancer, stromal, and immune cells. Checkpoint blockade therapies, such as those using anti-CTLA-4 and anti-PD-1 antibodies, aim at tilting the balance between cancer and immune cells in favor of the latter in order to reinvigorate the immune response and clear the cancer. The ability of the immune system to control tumors is curbed, however, by the many strategies employed by cancer cells to evade the immune response. For instance, tumor-infiltrating $CD8^+$ T cells require glucose to support their function and kill cancer cells. Similarly, cancer cells utilize glucose and engage in a competition with T cells to acquire it, effectively reducing glucose availability and in turn dampening the anti-cancer response (Chang et al., 2015; Ho et al., 2015). Regulatory T cells (T_{reg}) also infiltrate tumors and, seconding their physiological role, suppress the immune response against cancer. Unlike $CD8^+$ T cells, T_{reg} are less reliant on glucose because their master transcriptional regulator FOXP3 rewires their metabolism toward mitochondrial pathways and away from aerobic glycolysis, thus allowing T_{reg} to thrive in the tumor microenvironment (TME) (Angelin et al., 2017) (Figure 1A). It is important to understand the metabolic requirements of cancer and immune cells, and the mechanisms underlying their metabolic adaptation to the TME, in order to discover vulnerabilities of tumors and enhance the current therapeutic options. In the latest issue of *Nature*, Zappasodi et al. and Watson et al. shed new light on the metabolic profile of tumor-infiltrating T_{reg}. They demonstrate that T_{reg} appear to avoid competition for glucose within the tumor by rewiring their metabolism to utilize alternative carbon sources, which in turn supports their immune-suppressing functions. The authors show that tampering with the fuel choices of tumor-infiltrating T_{reg} enhances the efficacy of checkpoint blockade therapies against cancer (Watson et al., 2021; Zappasodi et al., 2021).

Through analysis of human melanoma samples, Zappasodi et al. find that a negative correlation between expression of glycolytic genes and immune cell infiltrates could mostly be alleviated following anti-CTLA-4 checkpoint blockade therapy. However, within the tumors, even after anti-CTLA-4 checkpoint blockade, expression of genes associated with lactate metabolism (e.g. *LDHA* and *SLC16A1*, which encode the transporter MCT1) remains inversely correlated to immune cell infiltrates. This result hints that in highly glycolytic tumors, the efficacy of anti-CTLA-4 checkpoint blockade may be hampered. To explore this, Zappasodi et al. use a series of murine tumor models whereby metastatic growth after surgical resection of primary tumors was monitored. This supports the concept that aerobic glycolysis and lactate production influenced anti-CTLA-4 therapy, genetic attenuation of lactate dehydrogenase (LDHA-KD) in tumor cells, enhances the efficacy of CTLA-4 blockade while also improving memory T cell responses to secondary tumor exposure. Consistent with previous literature, immunosurveillance was enhanced in LDHA-KD tumors (Brand et al., 2016). Uniquely, however, T_{reg} isolated from LDHA-KD tumors treated with anti-CTLA-4 have increased inflammatory cytokines (IFN-γ and TNF), suggesting that the classical inflammation-suppressing roles of T_{reg} are destabilized following CTLA-4 inhibition. This effect on T_{reg} is reversed through the addition of exogenous lactate into the TME or through using hyper-glycolytic tumor cells, and this result indicates that T_{reg} phenotypic stability is reinforced by tumor cell aerobic glycolysis. Exploring this further, Zappasodi et al. find that CTLA-4 blockade directly enhances glucose uptake and IFN-γ production. Crucially, in low-glucose conditions, CTLA-4 blockade has no impact on T_{reg} suppression of effector T cell proliferation, thus implicating T_{reg} glucose utilization as the cause of the destabilized phenotype. Collectively, this research indicates that the concentrations of lactate and glucose within the TME could be critical in determining the function of T_{reg} and the efficacy of anti-CTLA-4 therapy (Figure 1B).

The study by Watson et al. provides context around T_{reg} stability in highly glycolytic TME and reinforces the concept that induction of glucose uptake in T_{reg} destabilizes their function. The authors observe that tumor-infiltrating T_{reg} are less prone to utilizing glucose as compared to cells resident in other tissues. Through comprehensive experiments, Watson et al. demonstrate that glycolysis engagement inversely correlates with T_{reg} suppressive function and that tumor-infiltrating T_{reg} preferentially use lactate to support their metabolic needs. Lactate-derived carbons feed into the tricarboxylic acid (TCA) cycle to support mitochondrial function and

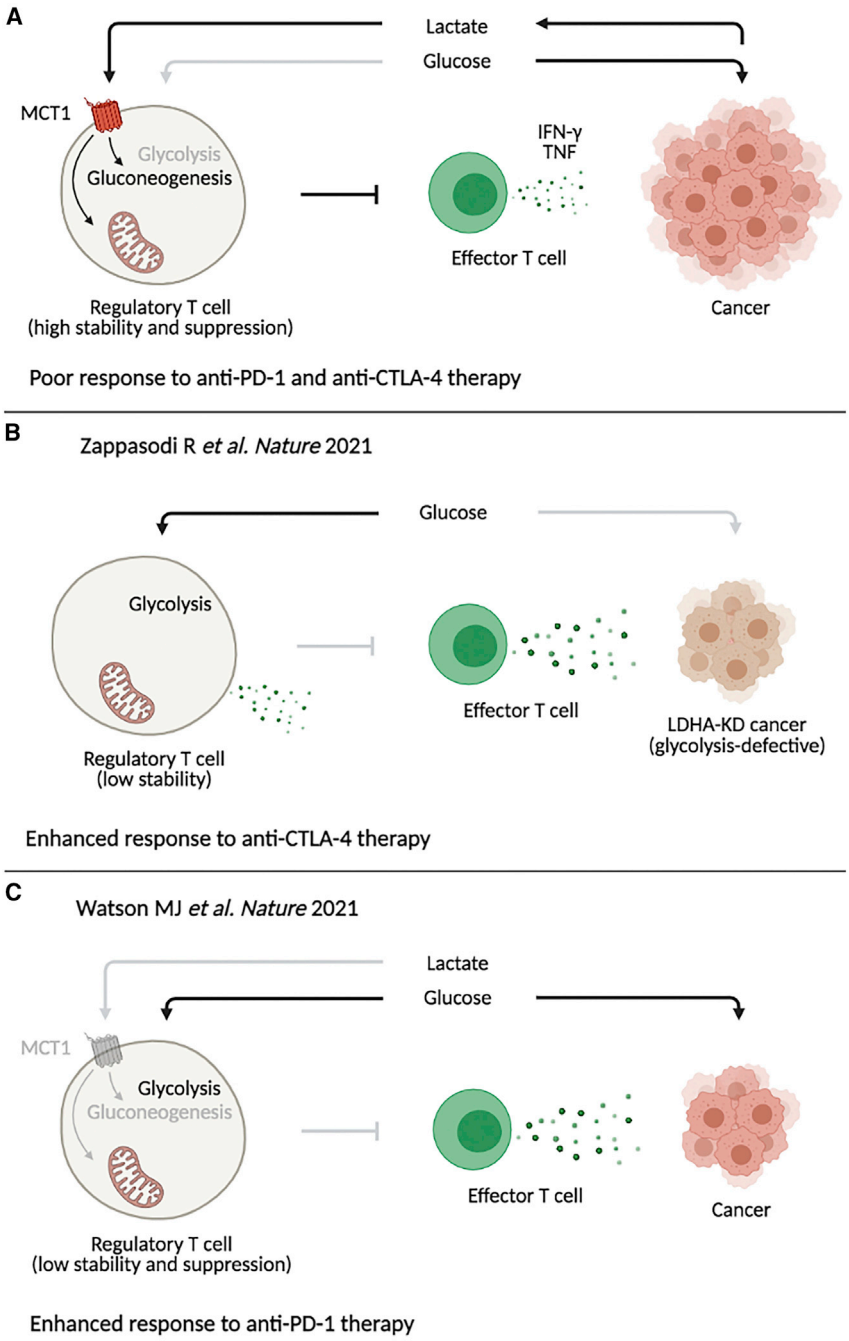

Figure 1. The interplay between cancer, effector and regulatory T cells

Within the tumor, regulatory T cells (T_{reg}) suppress the activity of effector T cells, ultimately favoring tumor growth. Cancer cells use glucose to feed their growth and secrete lactate as a "waste product" of glycolysis. Watson et al. show that lactate is utilized by T_{reg} to sustain their suppressive function. When lactate utilization is impaired, T_{reg} rely on glucose metabolism, resulting in loss of their stability and function—and in enhanced anti-tumor response by effector T cells. Adding to these data, Zappasodi et al. show that defective glycolysis in cancer cells increases the availability and utilization of glucose by T_{reg}, ultimately resulting in impaired stability and suppression, as well as production of anti-tumor cytokines.

replenish glycolytic intermediates to sustain synthesis of biomass and proliferation. When impaired in their ability to take up lactate from the TME, T_{reg} are forced to rely on glucose utilization, which in turn compromises their suppressive function and ultimately confers tumors with higher susceptibility to anti-PD-1 checkpoint blockade therapy (Figure 1C).

The work of Watson et al. and Zappasodi et al. provides convincing evidence that the TME is a driving force in manipulating intratumoral T_{reg} function, and this work highlights the potential for targeting T_{reg} metabolism to optimize cancer therapy. This could be achieved by impairing tumor glucose utilization and lactate production, or by specifically targeting T_{reg} through, for example, limiting lactate uptake with bi-specific antibodies directed at MCT1 expressed on T_{reg}. The TME is complex, and substantial heterogeneity exists in metabolite levels between tumors (Reznik et al., 2018). Recent work highlighting the role of lipid metabolism in T_{reg} function within the TME suggests that in addition to targeting lactate and glycolysis, there may be other key metabolic vulnerabilities to target within T_{reg} to improve cancer immunotherapy (Lim et al., 2021; Wang et al., 2020). These works raise wider questions around mechanisms underlying the fuel choices of T_{reg} and their suppressive function, as well as how this fits into the wider context of immune cell metabolism. For example, how does the FOXP3-imprinted transcriptional landscape of T_{reg} allow them to adapt their metabolism to thrive in the TME, while other tumor-infiltrating T cells fail to cope with it, and could these factors be co-opted to boost the function of other tumor-infiltrating T cells? The findings of Watson et al. and Zappasodi et al. could also prove interesting beyond the oncology field. Could either restricting glucose utilization or enhancing lactate consumption enhance the stability and suppressive function of T_{reg} for adoptive cell therapy or *in situ* treatment of inflammatory diseases (Ferreira et al., 2019)? These papers put the metabolic microenvironment front and center for T_{reg} function, highlighting the success of tumors in co-opting T_{reg} for nefarious purposes, but also raising the potential for manipulating metabolism as a mean to optimize immunotherapy.

DECLARATION OF INTERESTS

E.L.P. is an SAB member of Immunomet and a founder and advisor of Rheos Medicines. A family member of E.L.P. is a founder and advisor of Rheos Medicines.

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