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Targeting glutamine metabolism and PD-L1:

A novel anti-tumor pas de deux

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In this issue of Molecular Cell, Park et al. (2020) find that the dual targeting of glutamine metabolism and the PD-L1 checkpoint inhibitor augments anti-tumor immunity. Mechanistically, decreased glutamine availability attenuated S-glutathionylation of SERCA, resulting in an increase in cytosolic calcium, enhanced NF-κB activity and upregulation of programmed death-ligand 1.

Tumors are often able to adapt to their environment, undergoing proliferation in regions where the supply of nutrients is limited and gas exchange is suboptimal. The success of anti-tumor strategies requires that the designed therapies are able to target tumor growth in physical conditions that differ in oxygen concentration, interstitial pressure, acidity and nutrient availability. Furthermore, the efficacy of immunotherapies, aimed at harnessing the power of endogenous or adoptively-transferred anti-tumor immune cells, will be significantly improved
by promoting the function of immune cells in metabolically heterogeneous tumor environments.

Recent studies have documented the heterogeneous regional depletion of nutrients within a tumor. Interestingly, mass spectrometry evaluations of several distinct tumors have shown that 5 amino acids—arginine, asparagine, aspartate, serine and glutamine—are selectively depleted in the core, as compared to the periphery (Lee et al., 2019; Pan et al., 2016). These changes significantly impact individual cells within the tumor, resulting in changes in chromatin organization, macropinocytosis, and immune cell localization, amongst others (Lee et al., 2019; Pan et al., 2016). Furthermore, tumor heterogeneity has been shown to dramatically alter the responsiveness of individual tumor cells to therapy; Upon inhibition of the mammalian target of rapamycin complex 1 (mTORC1) kinase, integrating cues from nutrients to control cell growth, the growth of pancreatic ductal adenocarcinoma cells at the outer nutrient-replete regions was significantly decreased but notably, the percentage of Ki67+ cells in the hypovascularized, amino acid-starved interior regions of the tumor were markedly increased (Palm et al., 2015). Thus, tumor heterogeneity, resulting at least in part from alterations in amino acid availability, serves as a nutritional cue that can modulate the outcome of anti-tumor therapies.

Amongst the amino acids that are selectively depleted in the core of several solid tumors (Lee et al., 2019; Pan et al., 2016), glutamine often plays a key role. The importance of glutamine homeostasis in cell growth is supported by the presence of at least 14 glutamine transport solute carriers (in the SLC 1, 6, 7, and 38 families). These characteristics have driven research aimed at targeting glutamine metabolism as a strategy to inhibit tumor growth. Indeed approaches blocking glutamine uptake via the ASCT2/SLC1A5 transporter (Schulte et al., 2018) and abrogating glutaminase (GLS) activity and downstream glutaminolysis (Gross et al., 2014; Leone et al., 2019) have been successful in preclinical studies. Moreover, CB-839, a noncompetitive inhibitor of GLS1, is currently undergoing clinical trials in several malignancies (clinicaltrials.gov). Notably though, it is not known whether inhibiting glutamine metabolism in
peripheral versus interior regions of a tumor, distinguished by high and low glutamine concentrations, respectively, results in different outcomes.

In this issue of *Molecular Cell*, Park et al. (2020) find that interventions decreasing glutaminolysis result in alterations in the phenotype of multiple lung cancer and colorectal cancer cell lines, both *in vitro* and *in vivo*. Most notably, the authors detected a significant increase in the expression of the programmed death-ligand 1 (PD-L1). Consistent with the lower concentration of glutamine in the core of a tumor, the majority of tumor cells in this region were PD-L1+ as compared to the periphery where less than 20% of cells expressed this antigen. Since PD-L1 functions as a checkpoint inhibitor, counteracting T cell receptor signals upon binding to the PD-1 receptor on activated T cells, these exciting data suggest that decreased T cell activity in the core of the tumor, as compared to the periphery, is due not only to a harsh metabolic environment but to signaling through the PD-1-PD-L1 axis.

Mechanistically, inhibition of glutamine metabolism, whether via glutamine depletion, V-9302-mediated inhibition of ASCT2 transporter activity (Schulte et al., 2018), or inhibition of GLS1, resulted in a loss of intracellular glutathione (GSH). GSH directly upregulated PD-L1 expression as supplementation with GSH, under conditions of glutamine deprivation, attenuated PD-L1 upregulation. The impact of GSH on PD-L1 was not due to decreased GSH synthesis as depletion of cysteine, also required for GSH synthesis, did not impact PD-L1 levels. Rather, decreased GSH levels were due to the export of glutathione S-conjugates through the multi-drug resistance associated protein 2 (MRP2).

Low glutamine levels are known to contribute to endoplasmic reticulum (ER) stress and thus, as expected, the authors detected increased levels of the ER stress marker CHOP. ER stress occurs under conditions of altered calcium homeostasis, regulated in large part by the sarcoplasmic reticulum (SR) Ca²⁺-ATPase pump (SERCA) which normally transports Ca²⁺ back into the SR/ER from the cytosol. Indeed, the authors found that SERCA activity was severely attenuated under conditions of glutamine deprivation and this was due to a low glutathionylation of SERCA2. In turn, aberrant SERCA activity increased cytosolic calcium and
activation of the calcium/calmodulin-dependent protein kinase II (CAMKII). These conditions lead to aberrant NF-κB signaling and notably, in this study, aberrant NF-κB activity was associated with PD-L1 expression while silencing of NF-κB significantly attenuated the glutamine deprivation-induced upregulation of PD-L1. Moreover, the authors found that NF-κB activity within a tumor, assessed as a function of p65 nuclear localization, was significantly higher in the glutamine-deprived core than in the periphery. As NF-κB activity, due to oncogenic mutations or the inflammatory tumor environment, promotes tumor cell proliferation, angiogenesis and metastasis, it will be critical to determine whether an augmented NF-κB activity is a common feature of glutamine-poor tumor regions. This would expand the potential range of NF-κB-dependent cancer vulnerabilities (Figure 1).

The authors’ demonstration that inhibition of glutamine metabolism is coupled to PD-L1 expression opens new avenues for targeted anti-tumor therapies. The authors specifically evaluated the effects of the ASCT2 antagonist V-9302 and an anti-PD-L1 antibody therapy on tumor growth. While V-9302 alone did not alter tumor progression in in immunocompetent BALB/c mice, pointing to a negative interplay between the immune system and V-9302, the combined effect of V-9302 and anti-PD-L1 antibodies significantly reduced tumor growth. The combined therapy increased the influx of CD8+ T cells into the tumor and cell death was mediated by an NF-κB-induced upregulation of Fas/CD95 on tumor cells (Figure 1).

It is interesting to note that V-3902/anti-PD-L1 therapy did not significantly alter the influx of other immune cells into the tumor. The CD8+ T cells detected in tumors of V-9302/anti-PD-L1 antibody-treated mice harbored cytolytic activity, as monitored by granzyme B release, but it will be important to compare the activities of T cells in the core and periphery of the tumor. Furthermore, it will be critical to directly evaluate the impact of V-9302 on both CD4 and CD8 T cell function. The mitigating effects of V-9302 on tumor growth in immunocompetent mice suggest a negative impact of this SLC1A5 antagonist on immune cell function. However, Leone et al reported that treatment with an allosteric inhibitor of both GLS1 and GLS2 did not adversely affect the anti-tumor activity of CD8+ TILs (Leone et al., 2019). The
potential discrepancy may be explained by the type of tumor studied but also by the specific role of CD8 effectors in the elimination of these specific tumors. Indeed, Nakaya et al determined that while the knockout of ASCT2 did not result in any obvious effects on CD8+ T cells, it dramatically impacted CD4 T cell function, and especially Th1 differentiation (Nakaya et al., 2014). Furthermore, Johnson et al. identified GLS1 as being critical for the differentiation of CD4 T cells to a Th17 fate and induction of a rapid exhaustion of Th1 differentiated cells (Johnson et al., 2018). Finally, as glycolysis-mediated repression of SERCA activity was previously shown to result in sustained T cell effector function (Ho et al., 2015), it will be of interest to determine whether the decreased SERCA activity detected in glutamine-deprived tumor cells also characterizes T effectors infiltrating into that environment. Studies of the cross-talk between glutamine-, SERCA- and glucose-mediated signals will allow these issues to be addressed.

The present study from Park and colleagues elegantly identifies a vulnerability in the glutamine-poor tumor microenvironment that can be exploited by anti-PD-L1 antibody treatment. One hypothesis that arises from this exciting study is that external manipulations blocking glutamine uptake can decrease intratumoral heterogeneity, thereby providing a tumor environment wherein infiltrating anti-tumor T cells harbor equivalent activity in the interior and peripheral regions of the tumor. This is critical as anti-tumor chimeric antigen receptor (CAR)-T cells have been shown to exhibit extensive functional in vivo heterogeneity, both across and within anatomical sites (Cazaux et al., 2019). Further work will reveal the choreography that can couple glutamine deprivation to anti-PD-L1 antibody therapy in a novel anti-tumor pas de deux.

References


