

a transwell migration assay and found that sitagliptin treatment significantly impaired their migratory capacity. However, sitagliptin did not impair the ability of T cells to functionally respond to antigen.

Conclusions These data suggest that the enzymatic activity of CD26 is important for the ability of T cells to migrate to the tumor site in order to mount an effective antitumor response. Further investigations into the mechanism behind the role of CD26 are ongoing.

Ethics Approval This study was approved by the Medical University of South Carolina's IACUC, protocol #00488

<http://dx.doi.org/10.1136/jitc-2020-SITC2020.0513>

514 DISTURBED MITOCHONDRIAL DYNAMICS REWIRE THE EPIGENETIC PROGRAM FOR CD8+ TIL EXHAUSTION

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Background Cancer immunotherapy, including checkpoint blockade and adoptive transfer of tumor-reactive T cells, represents a paradigm shift in the treatment of malignancies in recent years, and yields remarkable responses by reawakening anti-tumor immunity in established tumors. Nevertheless, a significant portion of patients are refractory to cancer immunotherapies, which may be in part due to the persistent impairment of anti-tumor effector functions in T cells, a phenomenon referred to as T cell exhaustion. Emerging evidence reveal that alterations in global chromatin accessibility and de novo DNA methylation patterns are key events to drive development of T cell exhaustion under chronic antigenic stresses. However, it remains elusive how T cells engage epigenetic reprogramming to orchestrate exhausted state.

Methods Here, we examined the mitochondrial fitness in CD8+ TILs with mitoTrackers.

Results We found that tumor-infiltrating tumor-reactive T cells with accumulation of damaged mitochondria, characterized by increased mitochondrial mass but reduced mitochondrial membrane potential and cristae, display more severe exhausted phenotypes, including decreased proliferation capacity, reduced cytokine production and up-regulation of co-inhibitory receptors. The accumulation of damaged mitochondria is in part due to the deficiency of mitophagy machinery. Importantly, we found that the accumulation of dysfunctional mitochondria is correlated to the specificity and affinity of antigen, and also supported by the PD-1 expression. Moreover, the combination of glucose deprivation, hypoxia and TCR signaling in vitro can drastically weaken T cell immunity with the accumulation of dysfunctional mitochondria as seen in TILs previously. Furthermore, T cells with accumulation of damaged mitochondria, generated artificially by Oligomycin A and Mdivi-1, also exhibit persistent exhaustion features. Ultimately, supplementation with nicotinamide riboside enhances T cell mitochondrial fitness and improved responsiveness to anti-PD-1 treatment.

Conclusions Taken together, our study suggests that mitochondrial fitness is pivotal for T cell-mediated immunity and the accumulation of dysfunctional mitochondria could result in exhaustion phenotypes in T cells. And our findings also provide pillars for better harnessing T cell immune responses with metabolic regulations for immunotherapy.

<http://dx.doi.org/10.1136/jitc-2020-SITC2020.0514>

515 METABOLIC REPROGRAMMING OF ANTITUMOR CD8+ T CELL IMMUNITY

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Background Adoptive cell transfer (ACT) therapies are successfully used in the clinic; however, a large fraction of patients remains unresponsive. The limited efficacy of this therapy is due, in part, to the terminally differentiated state of transferred T cells, which limits their proliferation and long-lasting antitumor response. Memory CD8+ T cells display specific phenotypic and functional characteristics endowing them with the ability to provide a more robust and long-lasting antitumor immune response than their terminally differentiated counterparts. The development and fitness of memory T cells was recently shown to be associated with specific metabolic pathways.

Methods We aimed to metabolically reprogram CD8+ T cells in order to generate fitter memory-like T cells prior to ACT.

Results We have found that pharmacological inhibition of the metabolic enzyme isocitrate dehydrogenase 2 (IDH2) during the priming of CD8+ T cells led to an increased memory formation and to an enhanced tumor growth inhibition upon ACT into melanoma tumor-bearing mice. Interestingly, IDH2 inhibition was associated with increased histone methylation and acetylation. We show that these histone modifications were required to induce the observed memory phenotype.

Conclusions These results suggest a novel strategy to promote stable memory T cell differentiation by epigenetic processes induced by metabolic reprogramming during T cell priming. These findings might be exploited to optimize ACT immunotherapy against cancer.

<http://dx.doi.org/10.1136/jitc-2020-SITC2020.0515>

516 CASPASE-8 REGULATED SENESENCE AS AN IMMUNE CHECKPOINT IN T LYMPHOCYTES FOR ADOPTIVE CELL THERAPY

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Background The development of immunotherapies holds great promise for the treatment of refractory infections and cancer. Current approaches, although effective in many settings, have limitations that prevent their widespread use. Hence, several aspects require improvements, including the re-wiring of T-cell fates and function. T-cell dysfunction is central to the persistence of several chronic viral infections and the progression of malignancies. Upon activation, T cells can follow several paths of differentiation, leading to terminal effector differentiation and/or exhaustion which are widely recognized as dysfunctional features limiting human immune competence. Furthermore, dysfunctional features induced during laboratory-based manipulations of T-cell products prior to adoptive cell transfer has a determining effect on outcomes. Similarly, repeated antigen encounters after transfer in vivo favors the development of T-cell dysfunction. However, the nature and underlying mechanisms of T-cell dysfunction are still incompletely understood.