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Competing interests
The author declares no competing interests.

IMMUNOMETABOLISM

A reactive metabolite as an immune suppressant

Myeloid-derived suppressor cells (MDSCs) occupy sites of chronic inflammation and suppress CD8⁺ T cell function. A new study describes the transfer of the metabolite methylglyoxal (MG) to T cells, which mediates this immunosuppressive mechanism.

Vijyendra Ramesh and Jason W. Locasale

The immunosuppressive activity of MDSCs is an important yet mysterious aspect of the immune-evasive tumor microenvironment. In this issue of *Nature Immunology*, Baumann et al. uncover a novel mechanism for the MDSC-dependent metabolic and functional paralysis of CD8⁺ T cells, which involves the cytosolic transfer of the toxic dicarbonyl-molecule MG to T cells via cell-to-cell transmission[1].

The immune system is a fundamental aspect of cancer biology. Substantial effort has been dedicated to elucidating immune evasion mechanisms and designing therapeutic strategies to bolster the capacity of the immune system to eradicate cancer cells. These have resulted in several breakthroughs, including the development of checkpoint inhibitors and CAR T cell therapies, which are clinically proven in many settings and have shown great promise in curtailing the progression of a wide spectrum of cancers by boosting the activity of effector T cells[2]. The success of these therapies, however, has been highly variable, which has motivated efforts toward uncovering the mechanisms of resistance. Targeting the metabolism of immune cells has emerged as an intriguing but poorly understood possibility for influencing immunotherapy[2].

One attractive approach to overcoming resistance to immunotherapy is to define the endogenous mediators of immunosuppression through understanding the cellular composition of the tumor microenvironment (TME). Within the TME, there exist populations of immune cells, including MDSCs, that secrete cytokines and chemokines that temper immune activation and surveillance, which can in turn promote tumor progression. MDSCs encompass a heterogeneous population of cells derived from myeloid precursors, including monocytes (M-MDSCs) and polymorphonuclear cells (PMN-MDSCs), stimulated by factors provided by stromal cells during chronic inflammation[3]. MDSCs are unified, however, unified by their ability to suppress T cell function. The number of circulating MDSCs has been shown to correlate with poor disease prognosis, immune suppression and poor responsiveness to checkpoint inhibition and anticancer vaccination[3]. Identifying MDSCs and suppressing their activity, however, is challenging, due to a lack of expression of bona fide molecular signatures and cell-surface markers and, consequently, a poor understanding of their exact immunosuppressive mechanisms[3]. In the study by Baumann et al., the authors have uncovered a specific metabolic signature to unequivocally identify MDSCs among other immune cells, along with a novel metabolic mechanism involving the reactive metabolite MG, which may underlie their suppression of CD8⁺ T cells. Thus, these findings have implications for targeting the function of MSDCs to promote responses to current standard-of-care immunotherapies.

To identify vulnerabilities specific to MDSCs, Baumann et al. first compared the expression of genes in monocytes and cells exhibiting an MDSC-like phenotype that showed no obvious differences in the expression of surface markers and immunosuppressive mediators. Instead, the MDSC-like cells exhibited reduced expression of genes involved in the metabolism of glycolysis, corresponding to a decreased central carbon metabolism (Fig. 1). MDSC-like cells isolated from patients with cancer showed a similar metabolic profile, prompting the authors to investigate whether this phenotype was involved in the suppression of CD8⁺ T cells. Indeed, coculturing T cells with MDSCs but not monocytes after activation with costimulatory signals suppressed TCR signaling, which led to the metabolic and functional paralysis of T cells, characterized by reduced central carbon metabolism and reduced expression of cytokines and release of granzyme B. This finding is consistent with studies demonstrating the influence of nutrient availability and metabolism on antitumor T cell function[4,5]. Interestingly, this interaction seems to require the physical association of both cell types, which, with further investigation, was found to involve a transfer of cytosolic constituents from MDSCs to T cells, a phenomenon that was also observed in vivo. While investigating the aspect of MDSC metabolism that was responsible for T cell suppression, Baumann et al. found that, upon treatment with dimethylbiguanide (DMBG), MDSCs failed to carry out their function.

Among their other functions, such as targeting electron transport chain complex I, DMBG, or metformin, and related guanidine-containing molecules[6] are nucleophilic scavengers of reactive dicarbonyl compounds, including MG, that are generated during cellular metabolism and form molecular adducts with the amino groups on nucleic acids and lysine and arginine residues in proteins, thus disrupting their function[7]. MG adducts are commonly referred to as

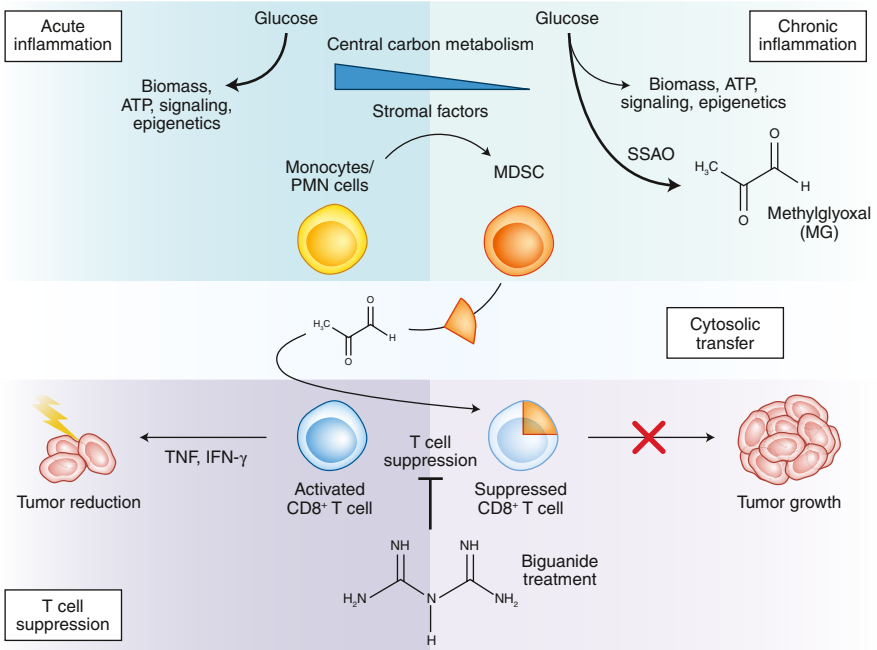

Fig. 1 | Methylglyoxal as an immune suppressant in the tumor microenvironment. The tumor microenvironment can reprogram myeloid-derived monocytic and polymorphonuclear cells as myeloid-derived suppressor cells (MDSCs), with the help of stromal factors, which results in a global suppression of central carbon metabolism. This reprogramming involves increased levels of the electrophilic, carbonyl-rich metabolite methylglyoxal (MG), generated by the activity of the enzyme SSAO. MDSCs physically interact with CD8+ effector T cells within the tumor microenvironment, to which they transfer cytosolic contents, including MG. This transfer initiates the metabolic and functional paralysis of activated CD8+ T cells, which leads to a loss of cytokine production and tumor immune evasion. Neutralizing MG by using nucleophilic scavengers such as biguanides can abrogate this mechanism of immune suppression, suggesting a potential use for these molecular agents in the reversal of resistance to immunotherapies such as checkpoint inhibitors.

advanced glycation end products (AGEs) and may be involved in aging, the pathogenesis of type 2 diabetes, neurodegenerative disorders and cancer-associated processes[7,8]. MG is primarily produced as a byproduct of glycolysis due to fragmentation of the metabolites glyceraldehyde-3-phosphate and dihydroxyacetone phosphate[7], which can be more pronounced during conditions such as hyperglycemia[7] or aerobic glycolysis[9]. MG can also be produced by the deamination of aminoacetone, derived from acetyl-CoA and glycine, which is catalyzed by the enzyme SSAO (semicarbazide-sensitive amine oxidase)[10]. Cells actively detoxify MG and related dicarbonyls with the help of enzymes such as glyoxalase, the activity of which is dysregulated in several of the pathologies mentioned[7].

Using high-resolution mass spectrometry, Baumann et al. found that MDSCs accumulate MG[1], which could be due to increased metabolic flux through SSAO (Fig. 1) and decreased activity of detoxifier glyoxalase I. This finding was confirmed to occur in MDSCs isolated from human and mouse tumors and inflamed mouse central nervous system tissue. Furthermore, analyzing MG accumulation in other immune cell types revealed that it was specific to MDSCs, suggesting that MG could be used as a biomarker to unequivocally identify these cells at sites of chronic inflammation. Subsequently, T cells were shown to accumulate MG following coculture with MDSCs. Treatment with DMBG was shown to reduce MG accumulation and restore glycolytic metabolism in MDSCs and T cells as well as T cell antigen receptor signaling in T cells. To investigate the downstream consequence of MG transfer to T cells, Baumann et al. measured the level of L-arginine, a target of MG-adduction known to be required for T cell activation. Indeed, as revealed by mass spectrometry, coculture with MDSCs led to a decrease in intracellular concentrations of free L-arginine in T cells, with a concomitant increase in the abundance of the MG-arginine adducts argpyrimidine and hydroimidazolone. Finally, treatment with DMBG was shown to increase the efficacy of anticancer vaccination and anti-PD-1 checkpoint inhibition in a mouse model of melanoma by boosting the functionality of CD8+ T cells.

These new observations suggest that MDSCs may have an immunosuppressive function, mediated by metabolism, which involves generating and transferring of MG to T cells, the targeting of which can boost immune activation in cancer settings in concert with checkpoint inhibition. The implications for the use of MG both as a biomarker and as a target for therapy are intriguing. Nevertheless, questions regarding the molecular mechanism remain. The targets of MG are unclear, and other studies have linked MG with other proliferative pathways, such the redox response involving KEAP1–NRF2[11] and the Hippo signaling pathway[12]. While Baumann et al. conclude from the labeling patterns in the isotope tracing experiments that glycolysis does not produce the relevant MG, other interpretations of the data may be consistent with MG being derived from glucose, such as the consideration of fluxes in isotope exchange. Furthermore, the accumulation of metabolites in upper glycolysis (defined as the metabolic reactions upstream of the rate-limiting enzyme GAPDH) is observed during conditions of reduced glycolytic rate[9]. Such mechanisms would provide further support for the existence of cellular communication mechanisms that link glucose and central carbon metabolism to effector functions in a complex multicellular environment such as that found in tumors. ❐

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Competing interests

J.W.L. advises Nanocare Technologies, Raphael Pharmaceuticals and Restoration Foodworks.