Tumor cells and memory T cells converge at glycolysis

Therapeutic implications

Swathi Karthikeyan, Jean-Francois Geschwind, and Shanmugasundaram Ganapathy-Kanniappan*

Department of Radiology & Radiological Sciences; Johns Hopkins University School of Medicine; Baltimore, MD USA

In the immune system, activation of naïve T (T_n) cells into effector T cells (T_{eff}) involves a metabolic switch to glycolysis to promote rapid proliferation and differentiation. In the October issue of *The Journal of Clinical Investigation*, Sukumar et al. have demonstrated that in CD8⁺ memory T (T_{ems}) cells glycolytic phenotype contributes to the shortened lifespan of T_{ems} . Conversely, inhibition of glycolysis in T_{ems} not only extended their viability but also augmented desirable properties. Notably, they also demonstrate that glycolytic inhibition during the ex vivo clonal expansion of tumor-specific T_{ems} enhanced their antitumor function. Overall, the data suggest that an antiglycolytic strategy targeting the T_{ems} could enhance antitumor immune response. On the other hand, cancer cells have long been known to exhibit metabolic reprogramming which involves a shift toward glycolysis (the conversion of glucose into lactate) to facilitate uninterrupted growth. Interestingly, antiglycolytic treatment of cancer cells has been known to trigger antitumor immune response as well. Taken together, it is probable that a strategy involving concurrent inhibition of glycolysis in tumor cells and T_{ems} could promote a dual attack on cancer by inducing an effective antitumor immune response and an immunogenic chemotherapy.

as T cell (or lymphocyte)-associated factors and tumor-associated factors.² The former includes immune suppressor elements such as regulatory T (T_{Reg}) cells and myeloid derived suppressive dendritic cells among others. Whereas, the tumor-associated factors include metabolic alterations that contribute to the acidic (lactate) microenvironment, hence hostile to the invading antitumor immune cells (e.g., T cells), and the altered expression of antigens (e.g., MHC) to escape immune detection.³

Almost two decades ago, Rosenberg et al.⁴ documented the first tangible evidence indicating that systemic administration of modified immune cells in patients can affect tumor progression. Extensive investigations by Rosenberg's laboratory and others have delineated a wealth of information on the potential implications of ex vivo or in vitro expansion of tumor-associated antigen-specific T cells for further transfer to patients, a process known as adoptive therapy.² Clinically, the adoptive therapy showed impressive outcomes in selected tumor types. As discussed, the concept of modulating T cell immunity against tumors per se is not completely unknown.⁵ However little is known about the metabolic reprogramming in such immune cells (e.g., T_{ems} , T_{eff}) and the ramifications of such altered metabolic phenotype. Sukumar et al.⁶ have elegantly demonstrated that experimental manipulation of energy metabolism in T_{ems} promotes antitumorigenic effects. Methodically Sukumar et al. show that the rate of glucose uptake differs between short-lived effectors T cells and the memory T cell precursors. Importantly they also document

Keywords: glycolysis, cancer, T cells, immunotherapy, chemotherapy

*Correspondence to: Shanmugasundaram Ganapathy-Kanniappan;
Email: gshanmu1@jhmi.edu

Submitted: 01/15/2014

Accepted: 02/09/2014

Published Online: 02/20/2014

<http://dx.doi.org/10.4161/cbt.28160>

Comment on: Sukumar M, Liu J, Ji Y, Subramanian M, Crompton JG, Yu Z, Roychoudhuri R, Palmer DC, Muranski P, Karoly ED, et al. Inhibiting glycolytic metabolism enhances CD8⁺ T cell memory and antitumor function. *J Clin Invest* 2013; 123:4479–88; PMID:24091329; <http://dx.doi.org/10.1172/JCI69589>

The ability to escape immune surveillance through immunosuppressive networks is one of the hallmarks of cancer.¹ The principal factors involved in challenging the efficiency of antitumor-immune cells or T cells have broadly been classified

for the first time that the short-lived effector T cells rely on glycolysis as evident by increased lactate production and a corresponding decrease in mitochondrial respiration and oxygen consumption. To further validate the hypothesis that glycolysis could contribute for the shortened lifespan of CD⁺ T cells Sukumar et al. inhibited glycolysis in CD8⁺ T cells using sublethal dose of 2-deoxyglucose (2-DG). Remarkably, the glycolytic inhibition enhanced the formation of memory CD8⁺ T cells. It is intriguing that despite the oxygen availability effector T cells switched to a glycolytic phenotype mimicking the aerobic glycolysis of cancer cells. Paradoxically, the metabolic reprogram (i.e. glycolytic phenotype) which is attributed to the shortened life span of effector T cells has long been known to facilitate uncontrolled proliferation in cancer cells. Further investigations on the molecular networks of glycolytic switch could advance our current understanding of tumor metabolism.

Significantly, the antiglycolytic strategy in memory CD8⁺ T cells also improved their antitumor function, a paradigm that could impact current cancer therapies. However, it is imperative to recognize whether a single therapeutic approach, like metabolically modified immune cells, could be effective in eradicating cancer cells. Noteworthy, Zou³ opined that although the “proof of principle” for improving antitumor immunity in cancer patients has been verified, the complete eradication of aggressive or hypoxic malignancies by sheer supplementation of the immune elements (e.g., adoptive transfer of T cells, cytokines) might not be sufficient.

From the tumor metabolism perspective, cancer cells have been known to switch to glycolysis even in the presence of oxygen (aerobic glycolysis) and/or functionally active mitochondria.⁷ This metabolic alteration which is frequent in cancer cells has been envisaged as potential target for therapeutic intervention.⁸ Interestingly, recent reports have documented a differential response of cancer cells to the inhibition of glycolysis. While some undergo apoptosis the others survive by switching to oxidative phosphorylation (OxPhos) where they can rely on

mitochondrial respiration.⁹ However, antiglycolytic treatment has been known to at least sensitize cancer cells to other therapeutics.¹⁰ It has been widely accepted that the accumulation of lactate and a subsequent change in the pH of the tumor microenvironment (due to an increase in H⁺ concentration) impede the immune reaction. The glycolytic phenotype, a characteristic feature of altered energy metabolism, is a prerequisite to accomplish this microenvironment-mediated effect. Thus inhibition of tumor glycolysis can be used to alter tumor proliferative potential or at the least could enforce them to switch to OxPhos which then will result in a less acidic microenvironment due to a reduction in the lactate output. Such an alteration will (1) prevent lactate-mediated anti-immune effects and (2) modify the pH (less H⁺) leading to the removal of blockade against the tumor-infiltrating T cells. In fact recent preclinical data indicate that this indeed is a viable approach. Ohashi et al.¹¹ have shown that lactate accumulation upregulated the expression of arginase-1 in macrophages eventually affecting the proliferation and activation of T cells. A reduction in the lactate output by the glycolytic inhibitor, dichloroacetate blocked the tumor progression. Similarly, Rivoltini's laboratory have shown, using a specific proton-pump inhibitor, that the acidic pH (increased concentration of H⁺) of the tumor microenvironment is hostile to infiltrating immune cells which affects their function.¹² Convincingly, the glycolytic inhibition alters the tumor microenvironment and improves the effectiveness of antitumor immunotherapy.

Understandably, targeting a process or pathway (glycolysis) that is critical for cancer cells' proliferation and their defense against scavenging immune cells will be an effective therapeutic strategy. Recent reports support this notion, for instance, Beneteau et al.¹³ show that targeting glycolysis through 2-deoxyglucose combined with etoposide promoted tumor-specific T-cell activation. Similarly, Ohashi et al.¹¹ also suggested the possibility of targeting glycolysis for a new immunogenic chemotherapy. In summary, due to the differential impact of glycolytic switch in cancer cells and T_{ems}, a concomitant inhibition

of glycolysis in tumor cells and T_{ems} could promote tumor destruction (chemotherapy) while extending the life-span of T_{ems} (improved immune response). Since the two hallmarks of cancer “altered energy metabolism” and “evasion of immune surveillance” are fundamentally linked¹⁴ and aerobic glycolysis is the common metabolic phenotype shared by both, its inhibition is likely to trigger a dual attack on cancer by inducing an effective antitumor immune response and an immunogenic chemotherapy. Further research focusing on the molecular regulation of glycolytic switch in cancer cells and T-cell activation would enable us to understand the differential impact of glycolysis in tumor cells and T cells.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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