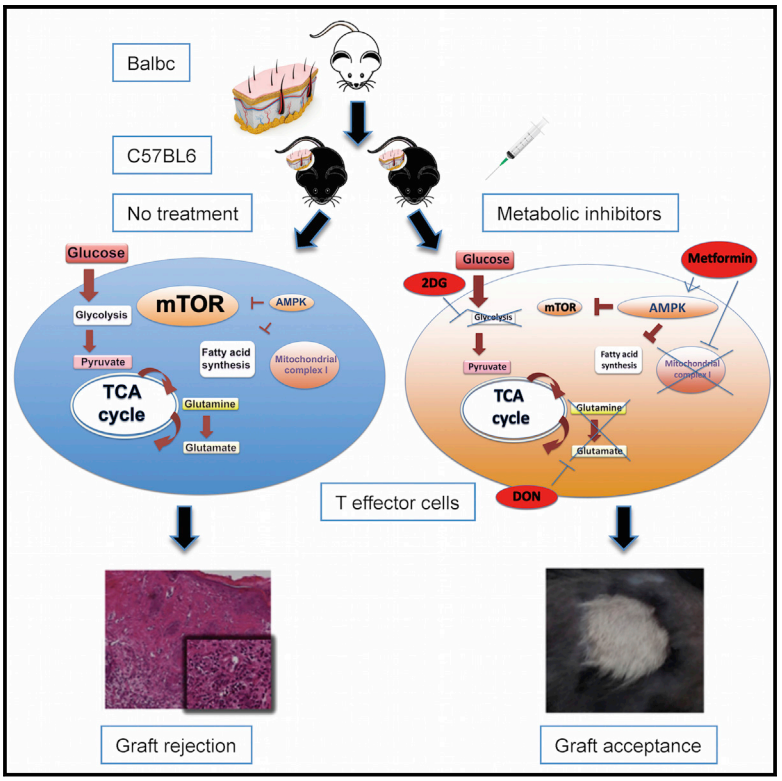
Article

Cell Reports

Preventing Allograft Rejection by Targeting Immune Metabolism

Graphical Abstract



Authors

Chen-Fang Lee, Ying-Chun Lo, Chih-Hsien Cheng, ..., Michael J. Wolfgang, Gerald Brandacher, Jonathan D. Powell

Correspondence

poweljo@jhmi.edu

In Brief

Lee et al. demonstrate that simultaneously blocking glycolysis and glutamine pathways can effectively inhibit allo-specific T cell responses while preserving mechanisms of immune regulation. Such a regimen represents a paradigm-shifting approach toward inhibiting acute rejection and promoting allograft survival.

Highlights

- Metabolic reprogramming is crucial for effector T cell differentiation and function
- Blocking glycolysis and glutamine metabolism can prevent allograft rejection
- Targeting effector cell metabolism preserves mechanisms of immunoregulation
- Targeting metabolism represents a paradigm-shifting approach to transplantation

Lee et al., 2015, Cell Reports *13*, 760–770
October 27, 2015 ©2015 The Authors
http://dx.doi.org/10.1016/j.celrep.2015.09.036

OPEN ACCESS
CellPress

Cell Reports
Article

Preventing Allograft Rejection by Targeting Immune Metabolism

Chen-Fang Lee,[1,2] Ying-Chun Lo,[1] Chih-Hsien Cheng,[1,2] Georg J. Furtmüller,[3] Byoungchol Oh,[3] Vinicius Andrade-Oliveira,[1] Ajit G. Thomas,[4] Caitlyn E. Bowman,[5] Barbara S. Slusher,[4] Michael J. Wolfgang,[5] Gerald Brandacher,[3] and Jonathan D. Powell[1,*]

[1]Sidney-Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD 21231, USA
[2]Chang-Gung Transplantation Institute, Department of Liver and Transplantation Surgery, Chang-Gung Memorial Hospital, Chang-Gung University College of Medicine, Taoyuan 333, Taiwan
[3]Vascularized Composite Allotransplantation Laboratory, Department of Plastic and Reconstructive Surgery, Johns Hopkins University School of Medicine, Baltimore, MD 21231, USA
[4]Department of Neurology and Brain Science Institute, NeuroTranslational Drug Discovery Program, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA
[5]Department of Biological Chemistry, Center for Metabolism and Obesity Research, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA
*Correspondence: poweljo@jhmi.edu
http://dx.doi.org/10.1016/j.celrep.2015.09.036

SUMMARY

Upon antigen recognition and co-stimulation, T lymphocytes upregulate the metabolic machinery necessary to proliferate and sustain effector function. This metabolic reprogramming in T cells regulates T cell activation and differentiation but is not just a consequence of antigen recognition. Although such metabolic reprogramming promotes the differentiation and function of T effector cells, the differentiation of regulatory T cells employs different metabolic reprogramming. Therefore, we hypothesized that inhibition of glycolysis and glutamine metabolism might prevent graft rejection by inhibiting effector generation and function and promoting regulatory T cell generation. We devised an anti-rejection regimen involving the glycolytic inhibitor 2-deoxyglucose (2-DG), the anti-type II diabetes drug metformin, and the inhibitor of glutamine metabolism 6-diazo-5-oxo-L-norleucine (DON). Using this triple-drug regimen, we were able to prevent or delay graft rejection in fully mismatched skin and heart allograft transplantation models.

INTRODUCTION

Advances in immunosuppressive regimens have played an essential role in driving forward the field of organ transplantation (Sayegh and Carpenter, 2004). However, long-term use of immunosuppressants results in a broad range of co-morbidity. For example, calcineurin inhibitors are associated with hyperlipidemia, hyperglycemia, neuro- and nephrotoxicity, and an increased risk of malignancy (Arnold et al., 2013; Crutchlow and Bloom, 2007; Guba et al., 2004; Hoorn et al., 2012; Roodnat et al., 2014). In addition, such agents inhibit negative regulatory and tolerance-inducing responses (Wu et al., 2012). That is, the calcineurin inhibitors are truly immunosuppressive in that they inhibit both activating and inhibitory signaling pathways (Powell and Zheng, 2006). As such, whereas the ultimate goal of anti-rejection strategies is to induce immune tolerance in the absence of long-term immunosuppression, current treatment regimens thwart this goal by inhibiting the induction of tolerance. Therefore, new approaches to preventing graft rejection are required.

Recently, metabolic signaling pathways have been shown to play critical roles in dictating the outcomes of T cell responses (Pollizzi and Powell, 2014; Waickman and Powell, 2012; Yang and Chi, 2012). The coordination of metabolism reprogramming and T cell function reflects the ability of how low-frequency antigen-specific naive T cells rapidly expand in response to a pathogen (Powell et al., 2013). In the presence of oxygen, naive or resting T cells rely on mitochondrial oxidative phosphorylation (OXPHOS) to generate energy necessary for immune surveillance (Pearce et al., 2013). In contrast, both $CD4^+$ and $CD8^+$ effector T cells employ aerobic glycolysis to meet their biosynthetic demands (Jones and Thompson, 2007; Pearce et al., 2013). This use of glycolysis in the presence of oxygen was first described by Otto Warburg in cancer cells (Warburg, 1956) and was subsequently found to be important in activated T cells (Warburg et al., 1958). It has been proposed that aerobic glycolysis permits the generation of the substrates necessary for the generation of amino acids, nucleic acids, and lipids, all of which are crucial for activation and proliferation (Vander Heiden et al., 2009). Essential for this activation-induced glycolytic response is glucose uptake (Cham et al., 2008; Cham and Gajewski, 2005). Indeed, the increased expression of the glucose transporter GLUT1 on the cell surface is a critical aspect of T cell receptor (TCR)-induced activation (Jacobs et al., 2008). Similarly, the uptake and metabolism of amino acids, especially glutamine, is essential for T cell activation (Carr et al., 2010). Glutamine deprivation blocks T cell proliferation and cytokine production (Carr et al., 2010). While the considerations depicted above reflect the metabolic needs of T cells during activation and