

POSTER PRESENTATION

Open Access

Modulating immunometabolism of tumor specific mouse and human lymphocytes to enhance T cell based therapy for cancer

Madhusudhanan Sukumar^{1*}, Jie Liu², Shashank J Patel³, Christopher A Klebanoff¹, Gautam Mehta², Rahul Roychoudhuri¹, Joseph Crompton¹, David Clever¹, Luca Gattinoni⁴, Pawel Muranski⁵, Toren Finkel⁵, Nicholas Restifo¹

From 30th Annual Meeting and Associated Programs of the Society for Immunotherapy of Cancer (SITC 2015) National Harbor, MD, USA. 4-8 November 2015

Tumor cells and tumor infiltrating lymphocytes (TIL) competes for glucose and other metabolites within the tumor microenvironment for their survival. Glucose consumption by tumors metabolically restricts T cell's ability to produce effector cytokines and therefore approaches to improve the overall metabolic fitness of TIL may improve tumor regression in cancer patients. Long-term survival and anti-tumor immunity critically depends on their metabolic fitness but approaches to select metabolically robust T cells for adoptive immunotherapy remains less clear. Here we introduce a simple and clinically translatable method using a lipophilic cationic dye (tetramethylrhodamine methyl ester-TMRM) to identify and isolate metabolically-robust T cells based on mitochondrial membrane-potential ($\Delta\Psi_m$). Cells with lower membrane-potential (low- $\Delta\Psi_m$) had a molecular profile characteristic of memory precursors and displayed an enhanced ability to enter the memory pool as compared to cells displaying higher mitochondrial potential (high- $\Delta\Psi_m$) characteristic of short-lived effectors. Interestingly, we also found that multiple distinct negative inhibitory receptors such as programmed death-1 (PD-1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), B- and T-lymphocyte attenuator (BTLA), Lymphocyte-activation gene 3 (LAG-3) and T cell immunoglobulin mucin receptor 3 (TIM-3) were enriched in the high- $\Delta\Psi_m$ subset compared to the low- $\Delta\Psi_m$ subset. Comprehensive metabolic and gene expression profiling demonstrated global features of metabolic fitness in low $\Delta\Psi_m$ sorted CD8⁺

T cells—including reduced glycolysis, enhanced fatty-acid oxidation and robust spare respiratory capacity. Transfer of low- $\Delta\Psi_m$ T cells was associated with superior long-term in vivo persistence as evidenced by 100 fold increase in the frequency of T cells 300 days after adoptive transfer, augmented autoimmunity and an enhanced capacity to eradicate established cancer compared with high- $\Delta\Psi_m$ cells. High- $\Delta\Psi_m$ T cells exhibited elevated ROS levels, increased effector cytokines and had up-regulation of genes involved in DNA replication, DNA repair and cell-cycle arrest genes compared to low- $\Delta\Psi_m$ T cells. Surprisingly, use of Ψ_m to enrich for cells with superior metabolic features was observed within central-memory (T_{CM}) and effector (Tc17, Th1, Th17) T cells as well as long-term hematopoietic stem cells (LT-HSC). Finally, we also demonstrate that mitochondrial membrane potential based sorting can identify CD45RO⁺ CCR7⁺ human CD8⁺ T cells. These findings demonstrate that metabolic-sorting serves as a complementary strategy to the use of conventional cell surface markers for identifying cells with the capacity for long-term survival and ongoing effector function after adoptive-transfer. This novel metabolism-based approach may be broadly applicable to therapies involving transfer of hematopoietic stem cells or lymphocytes for treatment of viral-associated illnesses and advanced cancer.

Authors' details

¹Center for Cancer Research, NCI/NIH, Bethesda, MD, USA. ²National Institutes of Health, Rockville, MD, USA. ³Center for Cancer Research, NCI/NIH, Rockville, MD, USA. ⁴Experimental Transplantation and Immunology Branch, NCI/NIH, Bethesda, MD, USA. ⁵NIH, Bethesda, MD, USA.

¹Center for Cancer Research, NCI/NIH, Bethesda, MD, USA
Full list of author information is available at the end of the article

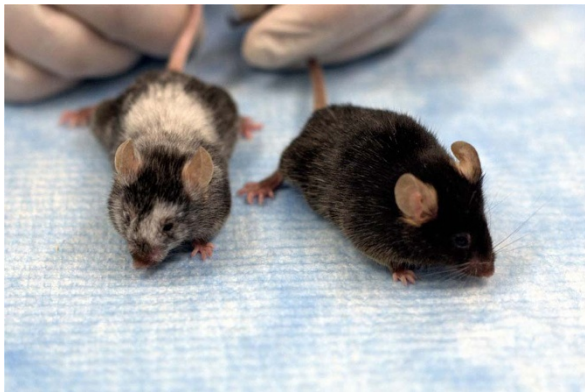


Figure 1

Published: 4 November 2015

doi:10.1186/2051-1426-3-S2-P325

Cite this article as: Sukumar *et al.*: Modulating immunometabolism of tumor specific mouse and human lymphocytes to enhance T cell based therapy for cancer. *Journal for ImmunoTherapy of Cancer* 2015 **3**(Suppl 2): P325.

**Submit your next manuscript to BioMed Central
and take full advantage of:**

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at
www.biomedcentral.com/submit

 **BioMed** Central