REGULATION AND ROLES OF THE POLYAMINE-HYPUSINE AXIS IN CD8+ T-CELL FATE AND FUNCTIONS

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Background CD8+ T cells play central roles in tumor immune surveillance and are major effectors in adoptive cell therapy. Thus, strategies that enhance their functions are an urgent clinical need. Metabolic reprogramming determines T cell fate and function.1 The roles of amino acid catabolism in controlling CD8+ T cell fate and function are less well understood.2,3 Glutamine is essential for nucleotide biosynthesis and as an anaplerotic fuel source for the tricarboxylic acid (TCA) cycle.

Methods Isotope tracing experiments with 13C glutamine or 13C arginine
Pharmacologic inhibition of ODC and DHPS

Results Pharmacologic inhibition of Odc using difluoromethylornithine (DFMO), or inhibition of hypusination using the pharmacologic inhibitor of Dhps, GC7, augments cytokine production in activated CD8+ T cells, including IFN-γ and TNF-α. Indeed, inhibition of Odc or Dhps augments other TRM phenotypes, including increases in CD69high;S1PR1low;CD62Llow cells that define the tissue resident memory (TRM) CD8+ T cells that play key roles in tissue and anti-tumor immunity anti-tumor reactivity. In addition, ACT of DFMO treated CD8+ T cells augments their survival in vivo and augments the generation of CD69+CD103+CD69+CXCR6+ and Ly6C+ TRMs in the bone marrow. Finally, DFMO or GC7 treatment enhances IFN-γ and TNF-α production in human CD8 T cells.

Conclusions We conclude that polyamine-hypusine axis is a metabolic check point in CD8+ TRM generation and are an actionable target to improve the anti-tumor immunity of T-cell based immunotherapies.

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REFERENCES