1416 COMMON METABOLIC ADAPTATIONS EMPOWER CD8 T CELL TISSUE RESIDENCY AND ANTITUMOR IMMUNITY

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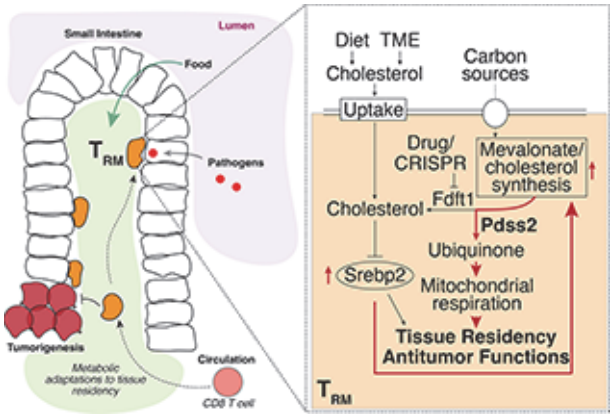
Background Lodged in tissues throughout the body, tissue-resident memory CD8 T cells (TRM) are key constituents of the memory T cell arsenal offering robust, long-term protection from reinfections. Effective anti-tumor immunity requires sustained T cell function in tissues, and tumor infiltrating lymphocytes (TIL) with characteristics of TRM maintain enhanced effector functions, predict responses to immunotherapy, and accompany better prognoses. The metabolic adaptations required for T cells to transition from an itinerant lifestyle in circulation to tissue residency in response to infections or malignancies are not well understood. We hypothesized that an improved understanding of the metabolic programs underlying tissue residency could inform new approaches to empower T cell responses in tissues and solid tumors.

Methods To define the basis for the metabolic reprogramming supporting TRM differentiation, survival, and function, we leveraged in vivo functional genomics, untargeted metabolomics, and transcriptomics of virus-specific memory CD8 T cell populations. In addition to genetic perturbations, we employed dietary and pharmacological approaches to investigate import, sensing, and utilization of lipids by TRM and TIL in their respective environments.

Results We found that memory CD8 T cells deployed a range of adaptations to tissue residency including a marked upregulation of a Srebp2-dependent production of non-steroidal metabolites, such as ubiquinone, derived from the mevalonate/cholesterol pathway. This metabolic adaptation was most pronounced in the small intestine, where TRM interface with dietary cholesterol and maintain a heightened state of activation, and was shared by functional TIL in diverse tumor types in mice and humans. Enforcing ubiquinone synthesis through Fdft1 deletion or Pdss2 overexpression promoted mitochondrial respiration, memory formation upon acute viral infection, and enhanced antitumor immunity. In addition, we found that pharmacological inhibition of Fdft1 with a fungal-derived metabolite, zaragozic acid, is able to promote increased tumor control in mouse models of colorectal cancer and melanoma in a CD8-dependent manner as a single agent or in combination with anti-PD1 treatment.

Conclusions In sum, through a systematic exploration of TRM metabolism, we reveal how these programs can be strategically coopted to potentiate CD8 T cell memory formation in the context of acute infections and power CD8 T cell function in the context of tumors (figure 1).



Abstract 1416 Figure 1

http://dx.doi.org/10.1136/jitc-2023-SITC2023.1416