Background CD8+ T cells are vital for their protective roles against pathogens and cancer. Aging and cancer are known to promote defects in the quality and quantity of functional naive T cells thus lowering immune surveillance. Interventions aimed to improve and to sustain the quality of naive T cells are needed for cancer immunoprevention. We recently showed that the mitochondrial modulator mitophagy inducer Urolithin-A (UroA) improves immune system function by ameliorating the mitochondrial pool in Hematopoietic Stem Cells (HSCs).1 However, the direct contribution of UroA on the homeostasis and functionality of CD8+ T cells has not been investigated.

Methods We adopted in vitro assays and in vivo tumor models to investigate the contribution of UroA in improving CD8+T quality and functionality.

Results Our current study demonstrates that orally supplemented UroA reduces tumor progression in mice in a CD8+ T-cell dependent manner. We show that preexposure to UroA enriched diet is sufficient to induce a robust antitumor response identifying UroA as an immunosurveillance agent. Notably, UroA supplementation promotes expansion of naive CD8+ T cells in vivo. Furthermore, UroA improves cytokine production, mitochondrial activity in CD8+ T cells and promotes memory differentiation in vitro. Interestingly, we reveal the transcription factor FOXO1 as a non-mitochondrial target of UroA in CD8+ T indicating a novel mitophagy-independent UroA mode of action. Furthermore, we have optimized dosage and timing of UroA supplementation in vitro for long expansion of CD8+ T cells with a superior anti-tumor in the context of adoptive T cell therapy (ACT).

Conclusions Overall, our finding provide preclinical evidence supporting the therapeutic function of UroA as novel immunomodulator to improve immunosurveillance.

REFERENCE

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