Application Brief

Cell Analysis

Agilent

Trusted Answers

Regulating the Metabolism of CD8+ T Cells Protects Against Influenza Virus Infection

Introduction

T cells play a critical role in host innate immune response to pathogen infection. During infection, with the transition from naïve to effector and memory cells, host T cell activation, proliferation, and differentiation are driven by metabolic responses to meet the cellular requirements for eradicating infected cells. These metabolic mechanisms controlling host T cell response to pathogen infection are not fully understood.

With this essential role of host T cell response to combat pathogen infection, identifying checkpoints and regulators of host T cell activation represents a promising area of opportunity for developing effective therapies for infectious disease. Agilent Seahorse XF technology provides key functional measurements for live cells in real time to measure metabolic host-innate immune response to pathogen infections, and can provide insight into therapeutic targets to enhance the innate T cell response.

Study results

Combining the utility of the Agilent Seahorse XF Mito Stress Test to measure mitochondrial function with orthogonal assay methods, Champagne *et al.* have shown that the MCJ/DnaJC15 protein, a distinct cochaperone that localizes at the mitochondrial inner membrane, restrains mitochondrial respiration in CD8+ T cells (Figure 1).[1] In the absence of this natural restraint, activated CD8+ T cells have enhanced OXPHOS activity, leading to increased secretion of IFN-γ by effector CD8+ T cells (Figure 2).

MCJ-deficient memory CD8+ T cells also exhibited enhanced protection against influenza virus. MCJ deficiency interferes with the metabolic adaptation during the contraction phase of effector CD8+ T cells and results in greater antiviral protective activity of memory CD8+ T cells. This effect is indicated by increased survival and decreased viral load (data not shown).

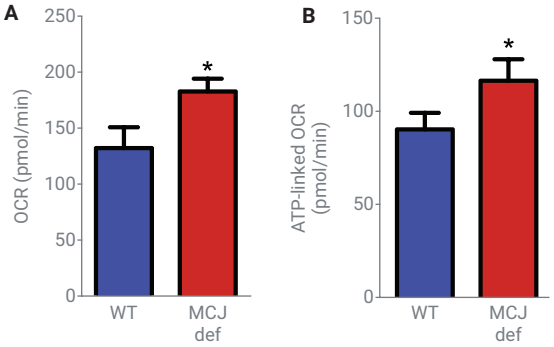

Figure 1. MCJ restrains mitochondrial respiration in naive CD8+ T cells. WT (blue) and MCJ-deficient CD8+ T cells (MCJ def, red). (A) Baseline OCR and (B) OCR linked to mitochondrial ATP production of freshly isolated cells as determined by the Agilent Seahorse XF Cell Mito Stress Test.

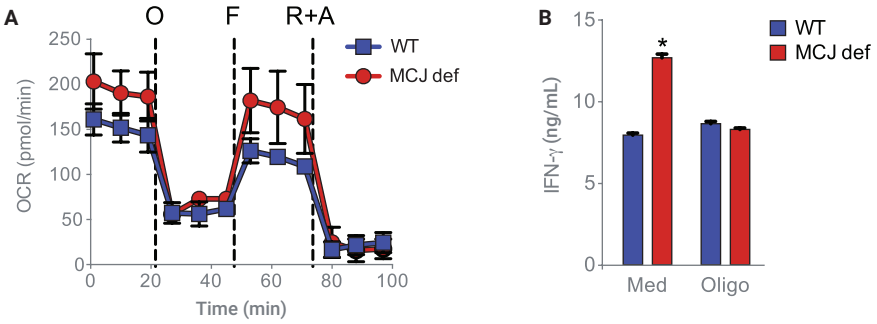

Figure 2. Increased oxidative phosphorylation in MCJ-deficient effector CD8+ T cells facilitates IFN-γ secretion. WT (blue) and MCJ-deficient CD8+ T cells (MCJ def, red) were activated with anti-CD3 and anti-CD28 for 2 days. (A) OCR of cells rested for 12 hours at baseline and in response to oligomycin (O), FCCP (F), and rotenone with antimycin (R+A) by the Agilent Seahorse XF Cell Mito Stress Test. (B) Cells were incubated with oligomycin during the last 4 hours of activation and then rested for 4 hours. IFN-γ in the supernatants was determined by ELISA.

Conclusion

Metabolism is intimately linked to many aspects of immune cell biology. By measuring the influence of metabolic programs on immune cell function, insight into how pathways and nutrients impact immune cell processes is driving discoveries of novel, innovative strategies to modulate and control immune cell fate and function. Results from this study indicate that MCJ may be a promising therapeutic target to increase the protective response of CD8+ T cells against influenza virus infection.

Reference

1. Champagne, D. P. *et al.* Fine-Tuning of CD8(+) T Cell Mitochondrial Metabolism by the Respiratory Chain Repressor MCJ Dictates Protection to Influenza Virus. *Immunity* **2016**.

www.agilent.com/chem

DE.5098726852

Printed in the USA, April 27, 2020
5994-1950EN

Agilent
Trusted Answers