The mitochondrial pyruvate carrier regulates memory T cell differentiation and antitumor function

Mathias Wenes, Alison Jaccard, Tania Wyss, Noelia Maldonado-Pe´ rez, Shao Thing Teoh, Anouk Lepez, Fabrice Renaud, Fabien Franco, Patrice Waridel, Ce´ line Yacoub Maroun, Benjamin Tschumi, Nina Dumauthioz, Lianjun Zhang, Alena Donda, Francisco Martı´n, Denis Migliorini, Sophia Y. Lunt, Ping-Chih Ho, and Pedro Romero

Speaker: Jie-Ting, Low

Advisor: Professor Michael Chan

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一、簡訴論文概要及重大發現

Glycolysis is known to participate in CD8+ T cell differentiation, but the underlying mechanism for mitochondrial pyruvate carrier to control T cell differentiation remains unknown. So, from this literature they proved that metabolic interruption might skew the differentiation of short-lived effector cells towards long-lived memory precursor cells, which can further use as CART for leukemia treatment.

Moreover, they perform in vitro simulation for tumor microenvironment using isotope tracing experiment to identify the key player in CD8 T cell memory phenotype differentiation. They discovered that acetyl-coA donor are glutamine and palmitate which indicates that glutaminolysis and fatty acid oxidation is enhanced after MPC inhibition.

The most profound discovery is that in vitro short-term inhibition of MPC for CART cells and further perform adoptive cell transfer in mice model resulted in superior and long-lasting antitumor effect.

In summary, the inhibition of MPC will results in memory T phenotype and enhances CART anti tumor efficacy by utilizing lactate in tumor microenvironment.

二、對論文內容的提問

The author suggested that the epigenetic modification is modulated by MPC inhibition through the interruption of acetyl-coA metabolism, but why H3K27me3 is induced and what is the effect for H3K27me in phenotype modulation? Is it a bivalent regulation for memory related genes?

三、論文的缺點與評論

There might be some limitations for this study because of the in vitro simulation of tumor microenvironment is difficult and too many variables to be included. Thus, although the in vitro nutrient deprived cell culture and in vivo mice model shows promising result but is it exactly the same as what we were observing through cell culture and also tracing?

Moreover, other references suggested that lactate in tumor microenvironment might dampen the effector function of CD8 T cell, while this paper suggested that lactate is important for depicting CD8 T cell function. Maybe that’s the “battle” between tumor cells and immune cells within tumor microenvironment.

However, this is an integrative way to investigate the role of a carrier protein in regulating antitumor response.

Article

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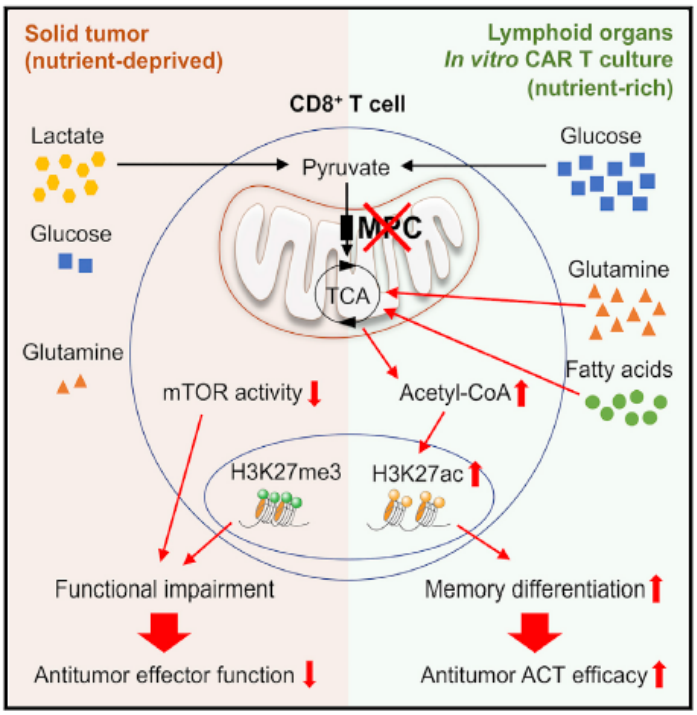
Graphical abstract



Authors

Mathias Wenes, Alison Jaccard, Tania Wyss, ..., Sophia Y. Lunt, Ping-Chih Ho, Pedro Romero

Correspondence

mathias.wenes@unige.ch (M.W.), pedro.romero@unil.ch (P.R.)

In brief

Wenes et al. show that lactate oxidation via pyruvate conversion and mitochondrial import may sustain antitumor function of cytotoxic T cells in the tumor microenvironment. In contrast, short-term inhibition of the mitochondrial pyruvate carrier in recently activated T cells promotes memory differentiation, which enhances antitumor activity upon adoptive transfer therapy.

Highlights

- Genetic and pharmacological MPC inhibition promotes memory T cell differentiation
- A metabolic-epigenetic axis enables memory T cell formation upon MPC inhibition
- Transient MPC blockade during CAR T cell manufacturing enhances antitumor efficacy
- The MPC allows lactate oxidation to sustain antitumor function of cytotoxic T cells

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