ARTICLE | VOLUME 32, ISSUE 3, P420-436.E12, SEPTEMBER 01, 2020

Sirt2 Inhibition Enhances Metabolic Fitness and Effector Functions of Tumor-Reactive T Cells

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Published: August 07, 2020 • DOI: https://doi.org/10.1016/j.cmet.2020.07.008 •

Highlights

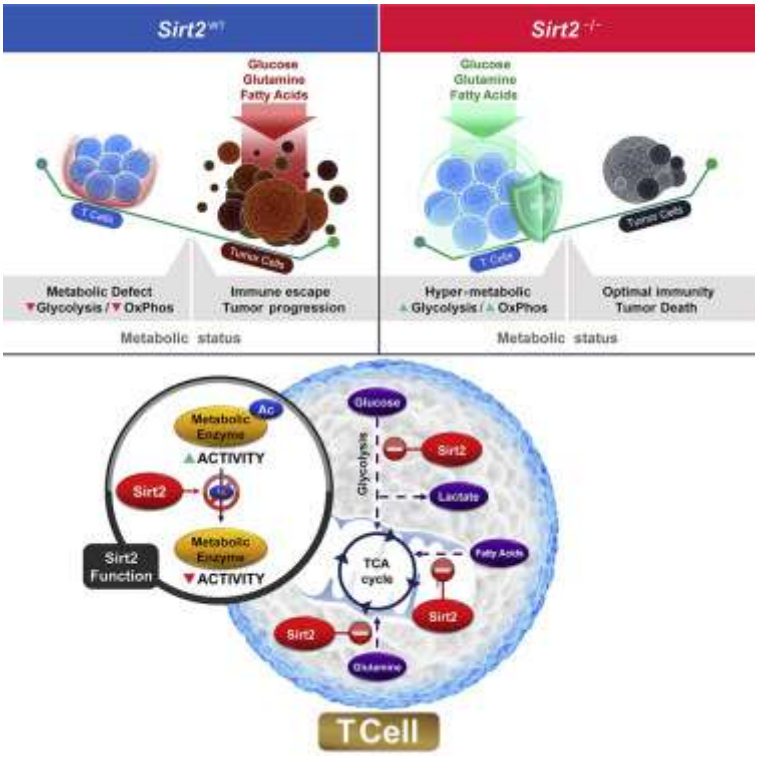
- Sirt2, an NAD $^{+}$-dependent deacetylase, is overexpressed in TILs
- Sirt2 interaction with key metabolic enzymes regulates T cell metabolism
- Sirt2-deficient T cells exhibit enhanced glycolysis and oxidative phosphorylation
- Sirt2 inhibition enhances effector functions of tumor-reactive T cells

Summary

Dysregulated metabolism is a key driver of maladaptive tumor-reactive T lymphocytes within the tumor microenvironment. Actionable targets that rescue the effector activity of antitumor T cells remain elusive. Here, we report that the Sirtuin-2 (Sirt2) NAD $^{+}$-dependent deacetylase inhibits metabolism and impairs T cell effector functions. Remarkably, upregulation of Si ... hu... infiltrating lymphocytes (TILs) negatively correlates with response to TIL therap... va...

non-small-cell lung cancer. Mechanistically, Sirt2 suppresses T cell metabolism by targeting key enzymes involved in glycolysis, tricarboxylic acid-cycle, fatty acid oxidation, and glutaminolysis. Accordingly, Sirt2-deficient murine T cells exhibit increased glycolysis and oxidative phosphorylation, resulting in enhanced proliferation and effector functions and subsequently exhibiting superior antitumor activity. Importantly, pharmacologic inhibition of Sirt2 endows human TILs with these superior metabolic fitness and effector functions. Our findings unveil Sirt2 as an unexpected actionable target for reprogramming T cell metabolism to augment a broad spectrum of cancer immunotherapies.

Graphical Abstract



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Keywords

T cells • metabolic checkpoint • Sirt2 • deacetylase • glycolysis • OxPhos • FAO • glutaminolysis • ulated metabolism • antitumor immunity

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Article Info

Publication History

Published: August 7, 2020
Accepted: July 15, 2020
Received in revised form: May 21, 2020
Received: November 22, 2019

Identification

DOI: https://doi.org/10.1016/j.cmet.2020.07.008

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