Metabolic regulation of immune cell fate decisions

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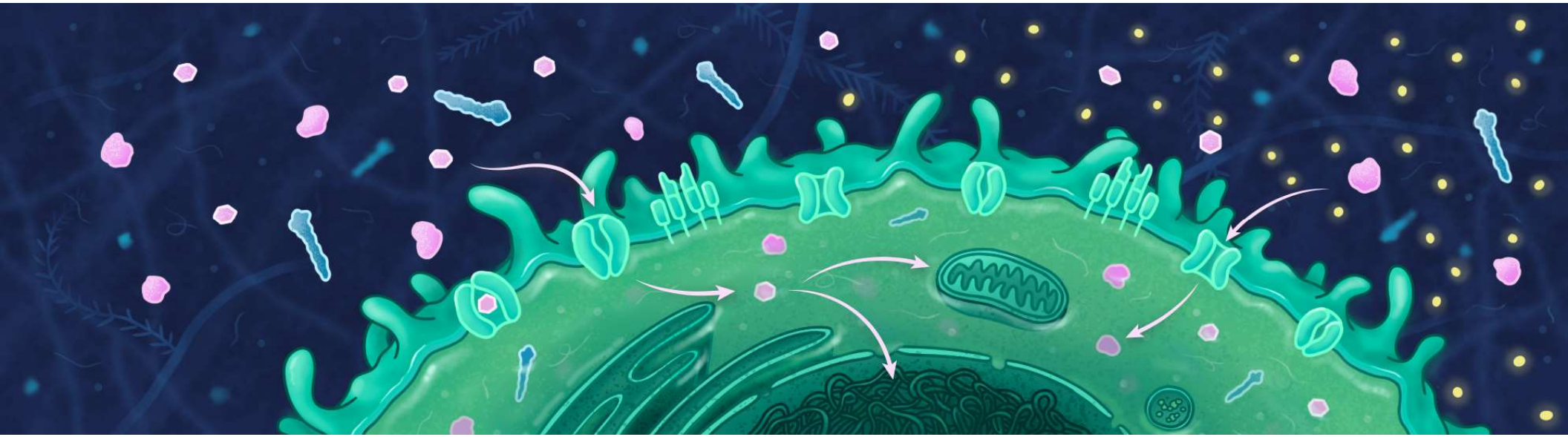
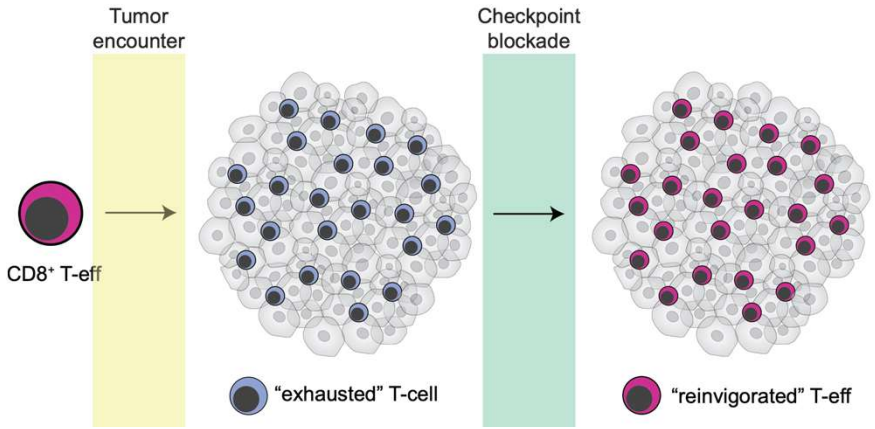


Disclosures

- Advisory: Immunai

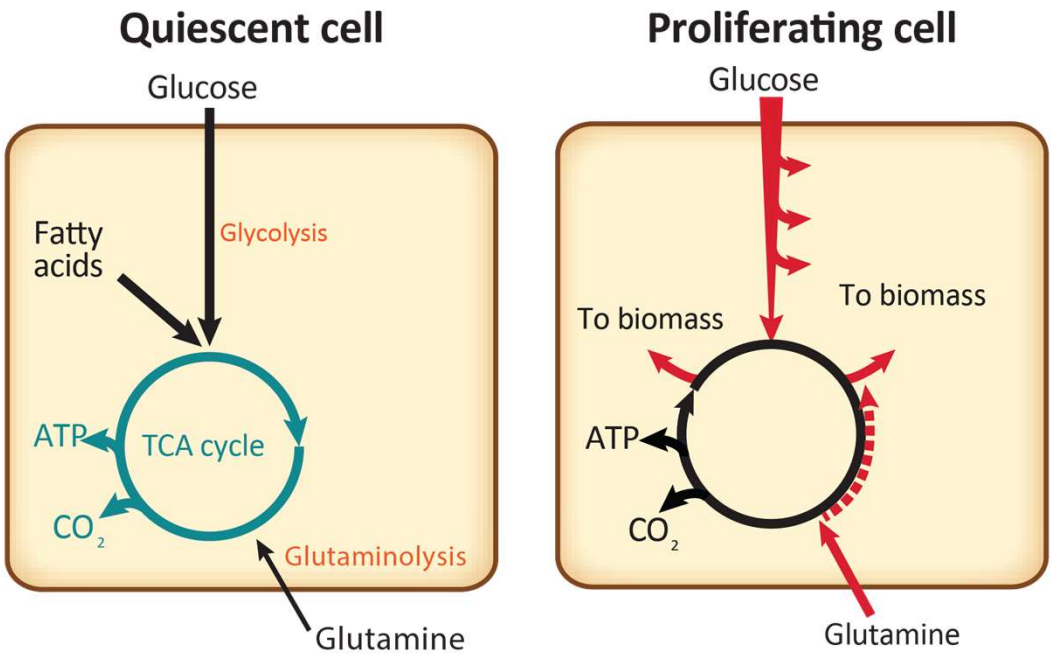
An evolving view of intratumoral T-cell dysfunction

Old paradigm:
Checkpoint blockade reinvigorates tumor-resident T-eff

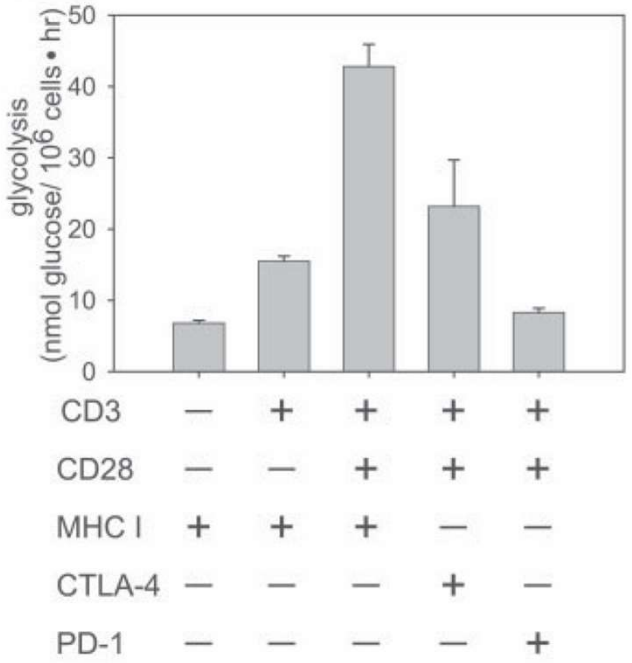


Im et al, ***Nature*** 2016
Huang et al, ***Nature*** 2017
Siddiqui et al, ***Immunity*** 2019
Miller et al, ***Nat Immunol*** 2019
Chen et al, ***Immunity*** 2019
Yost et al, ***Nat Med*** 2019

Cellular metabolism as a driver of proliferation

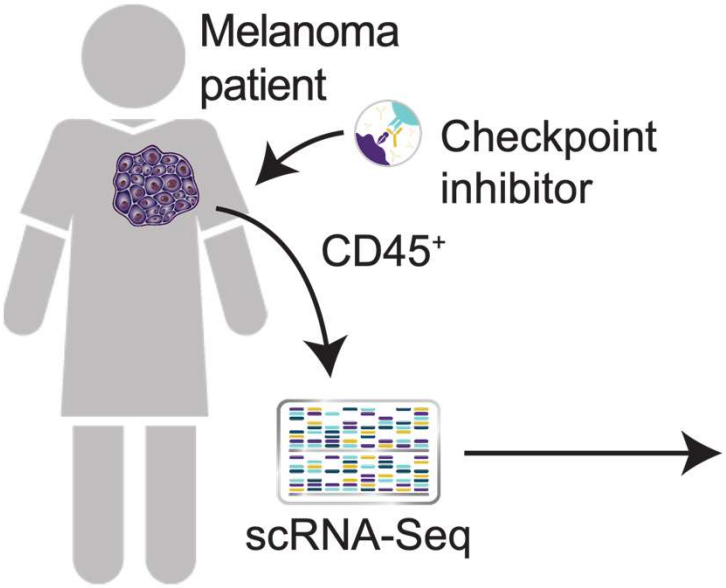


Finley et al, ***Cancer Cell*** 2013



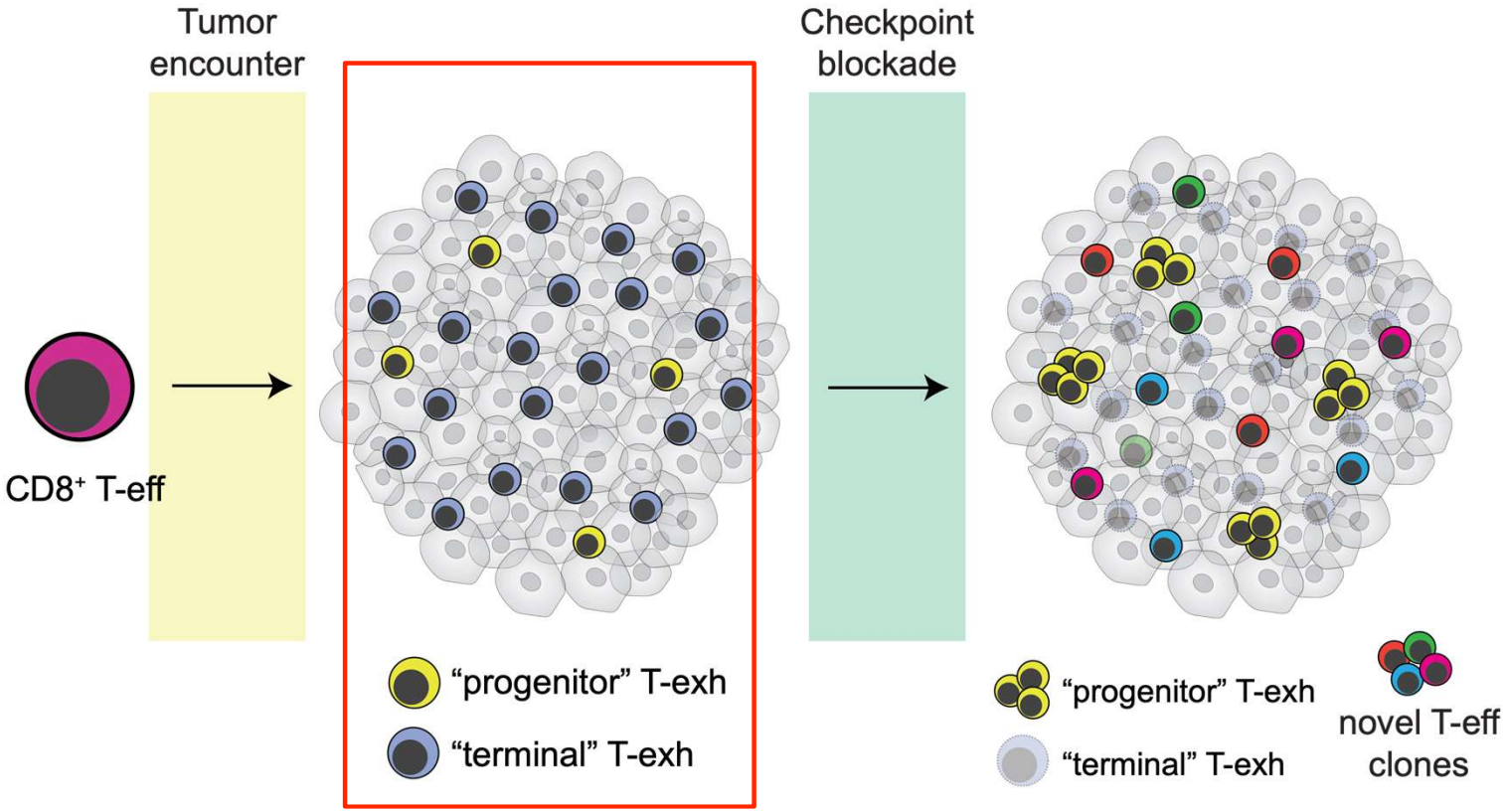
Frauwirth et al, ***Immunity*** 2002

Single-cell analysis of TILs suggests distinct metabolic features of exhausted T-cell subsets

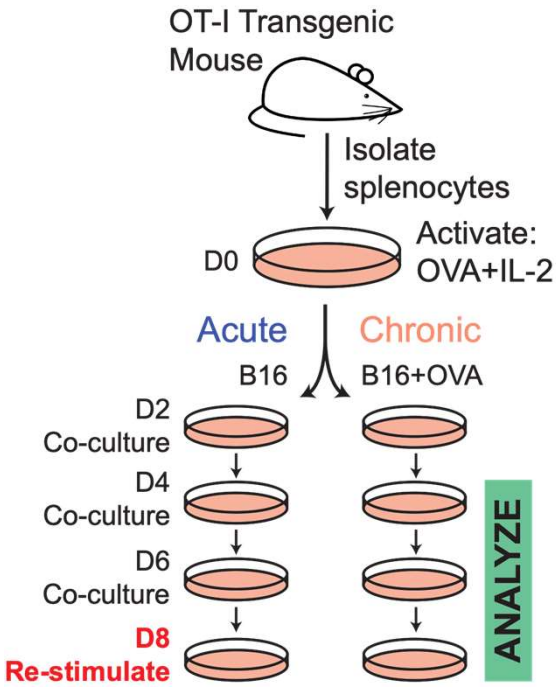


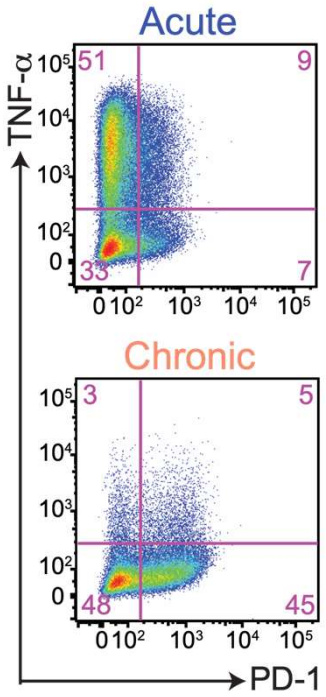
Sade-Feldman et al, *Cell* 2018

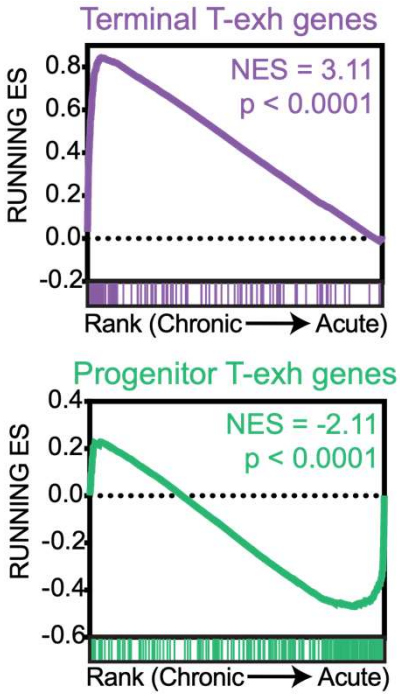
Metabolic analysis of TILs largely profiles terminally exhausted cells

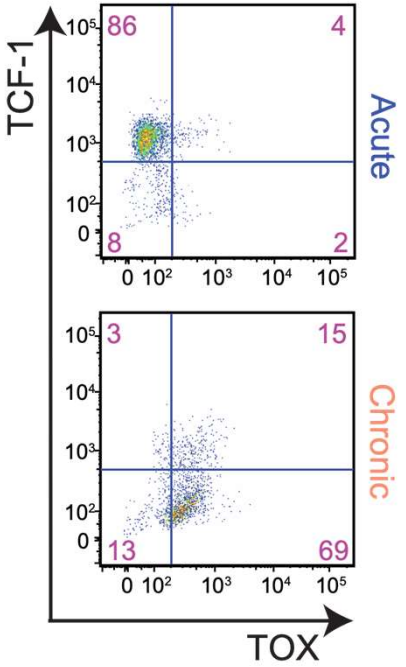


A novel *in vitro* platform generates dysfunctional T-cells

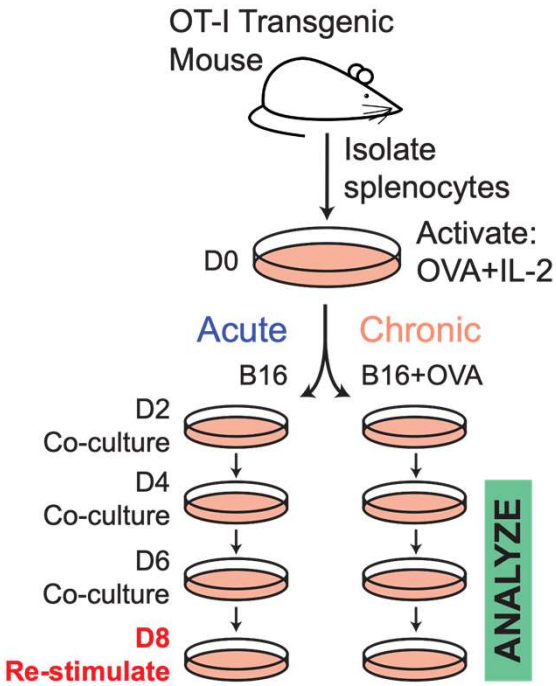


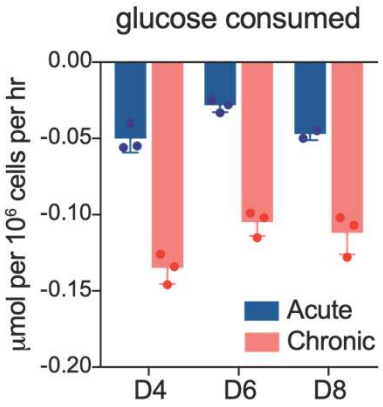


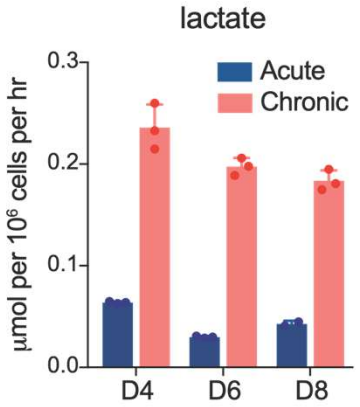


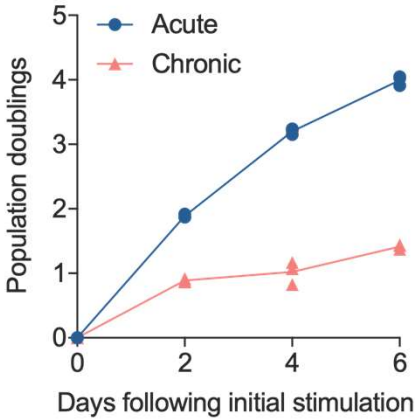


Chronically stimulated T-cells exhibit high rates of aerobic glycolysis but cannot proliferate

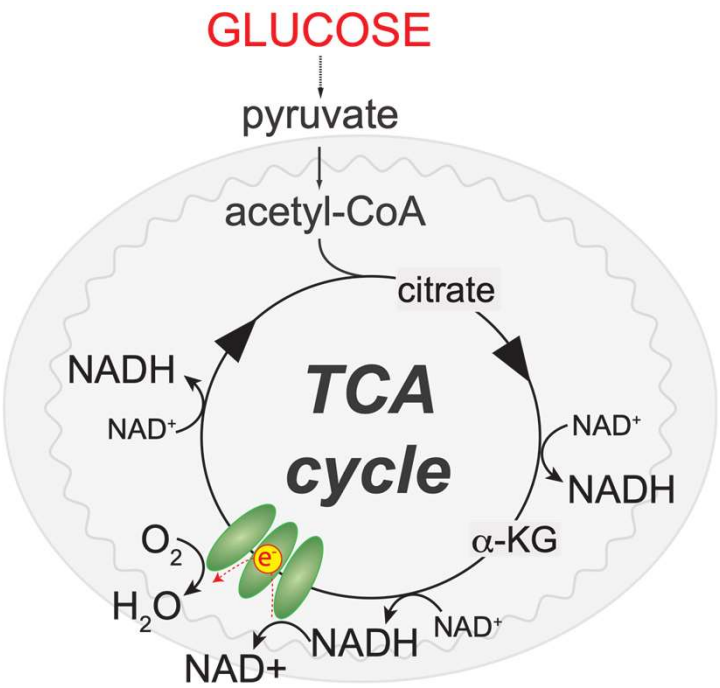


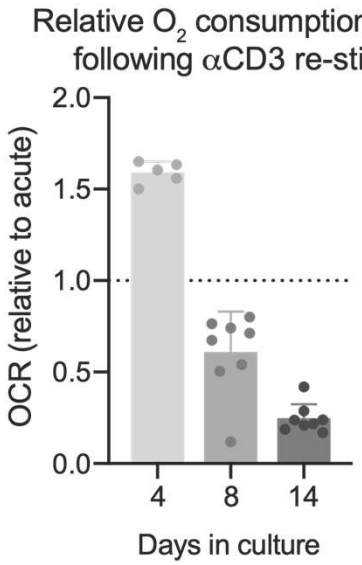


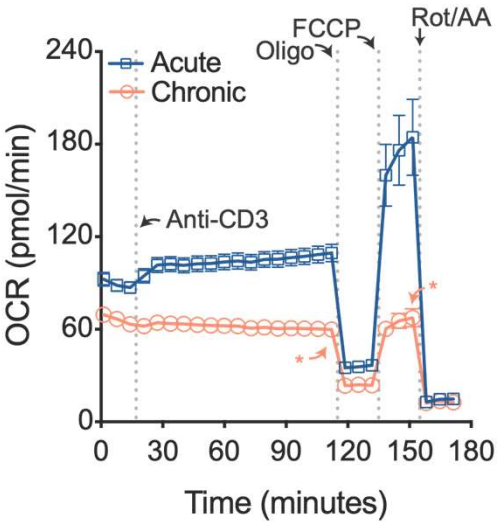




Chronic T-cell stimulation suppresses mitochondrial oxidative phosphorylation

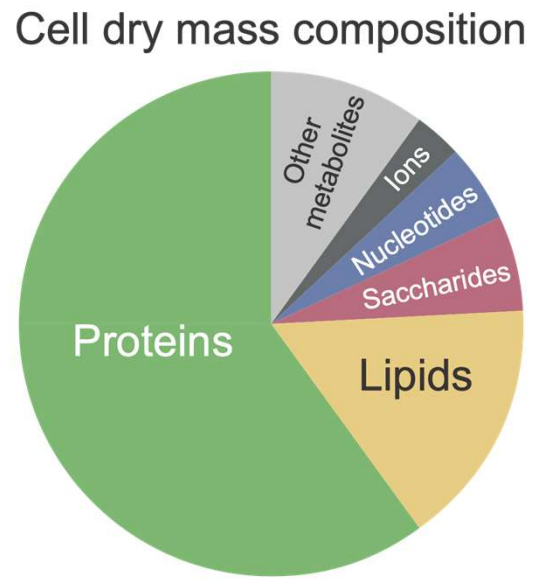






1. How is mitochondrial dysfunction blocking proliferation?
2. What is responsible for impaired mitochondrial oxygen consumption?

Early chronic stimulation induces a proliferative, but not a growth defect



Palm and Thompson, ***Nature*** 2017

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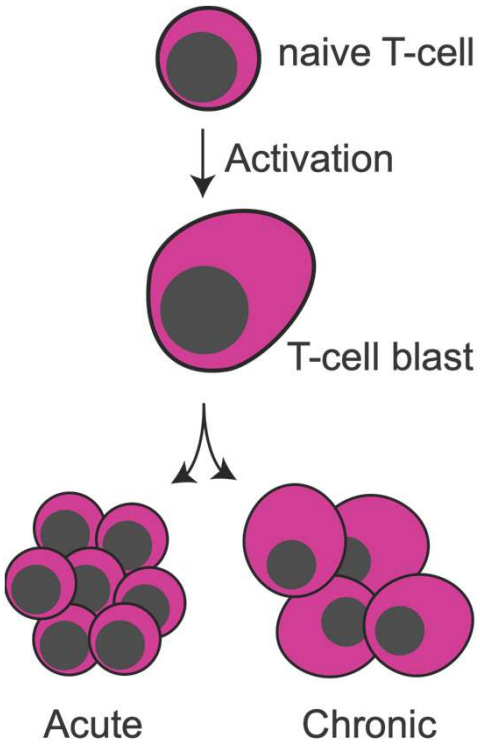
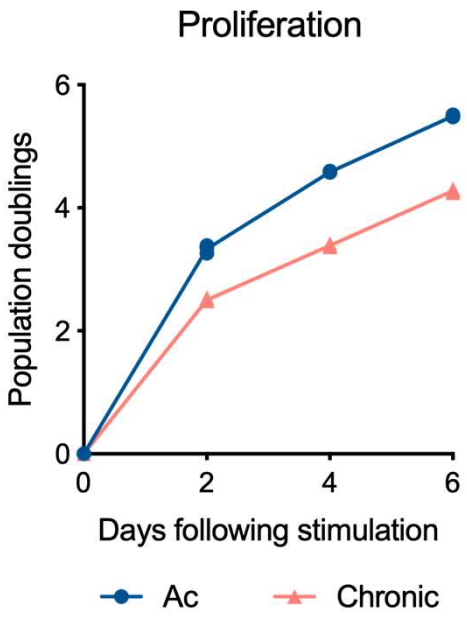
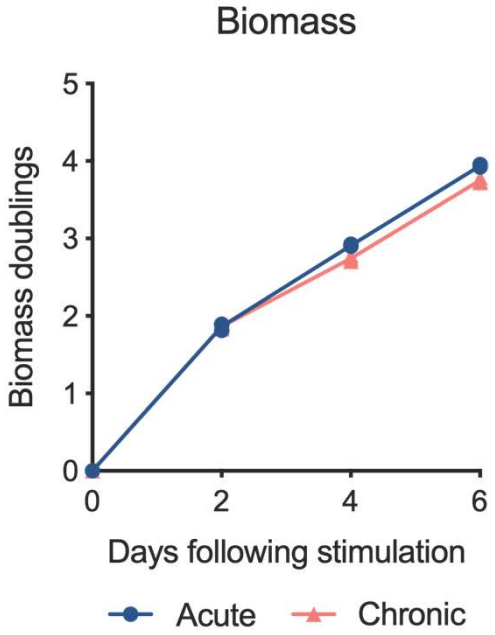
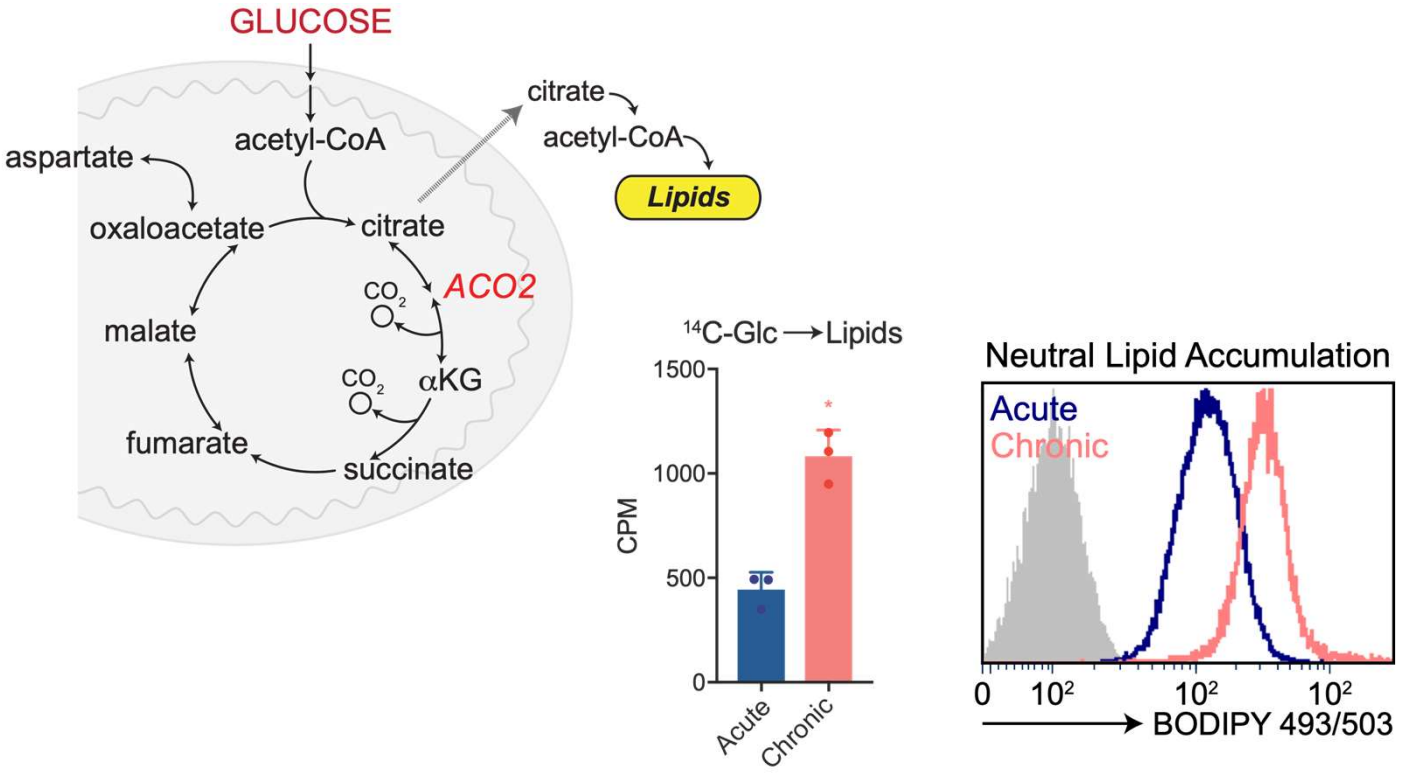


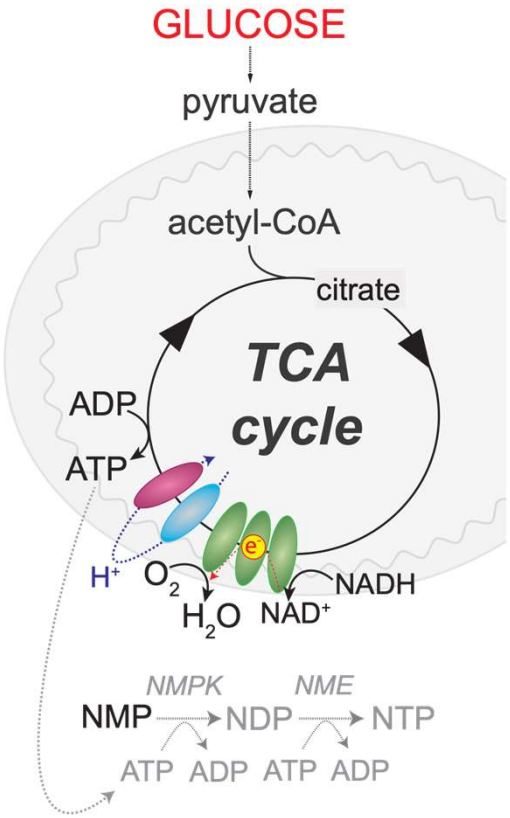


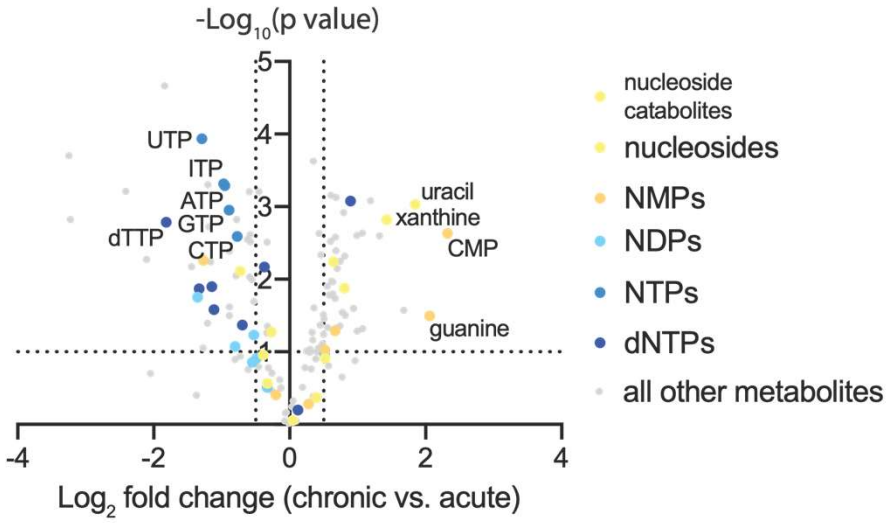


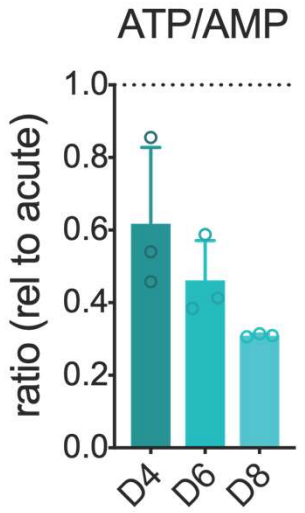
Lipid synthesis is not limiting for T-cell proliferation during chronic stimulation



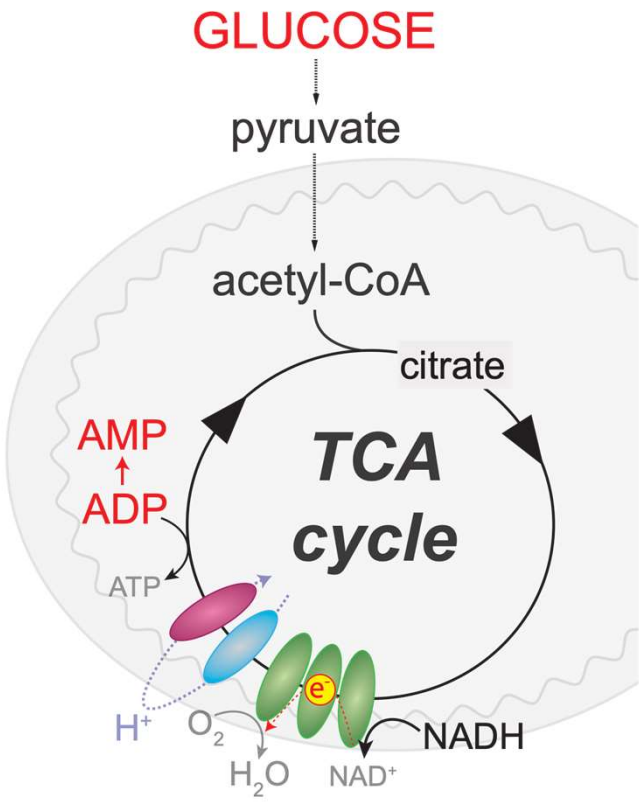
Impaired NTP generation during chronic T-cell stimulation

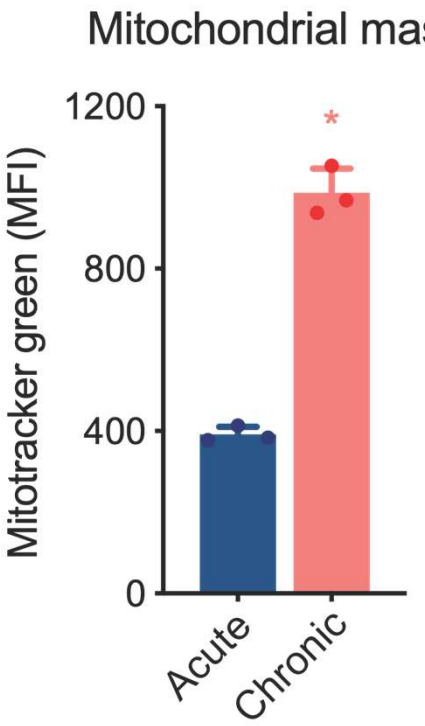


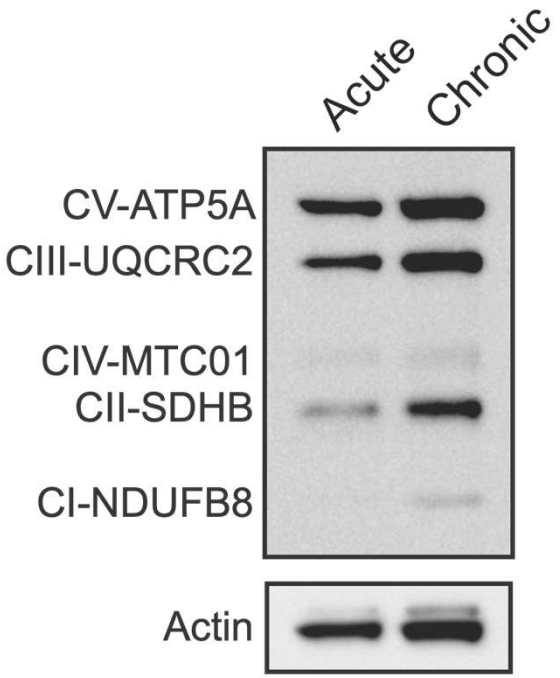




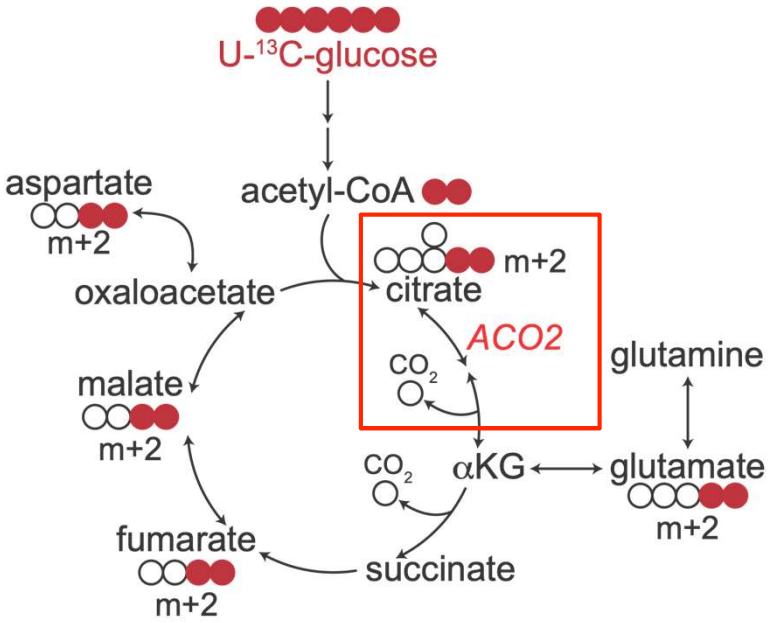
Chronically stimulated T-cells have sufficient mitochondrial mass

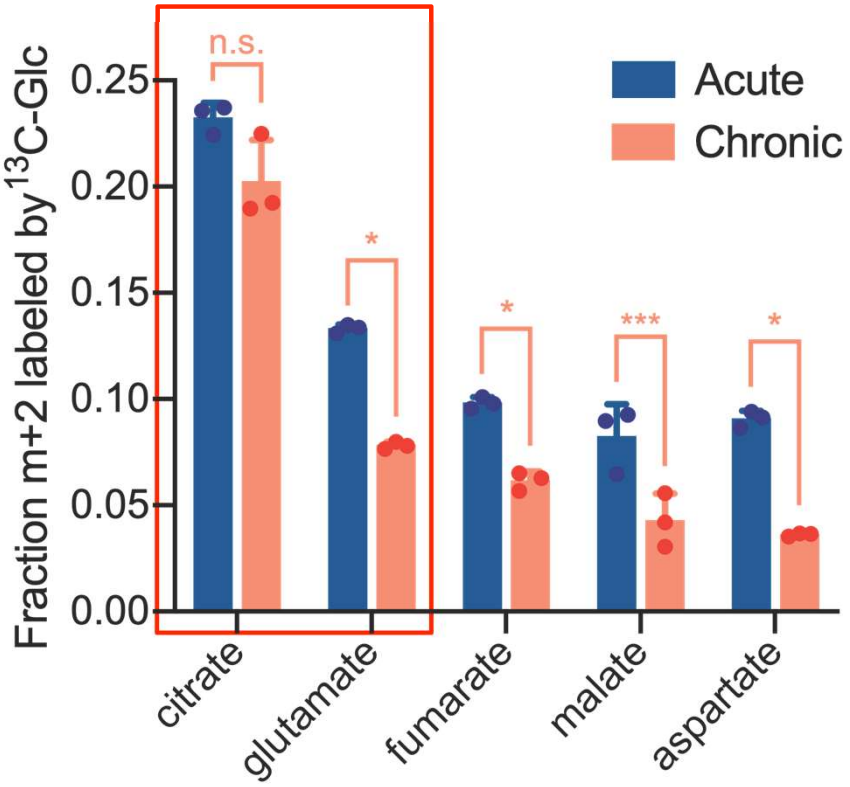




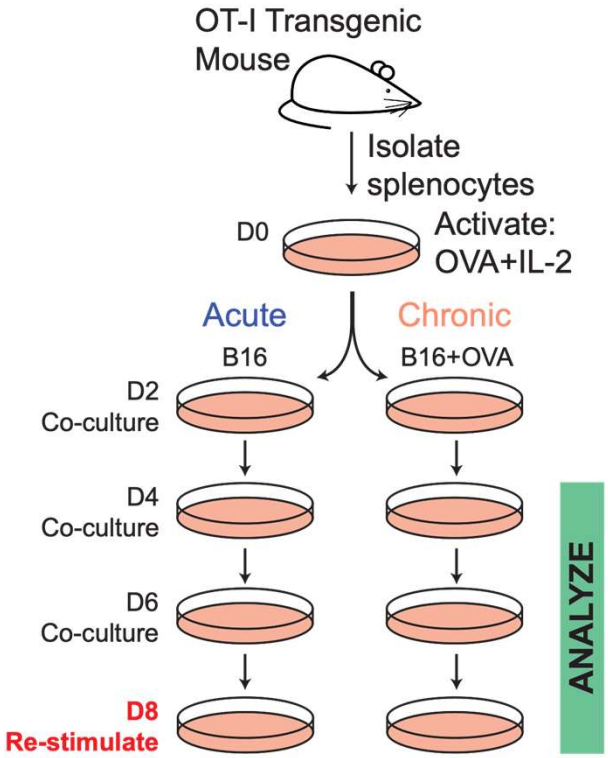


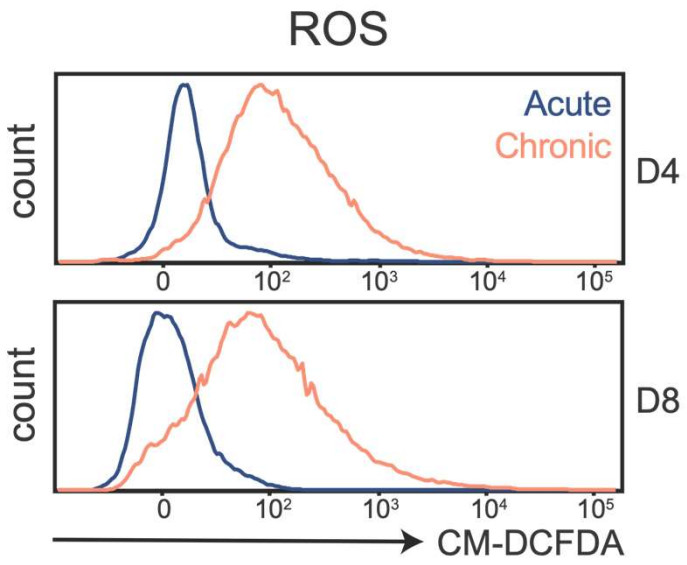
Chronically stimulated T-cells exhibit decreased mitochondrial oxidation of glucose-derived carbons

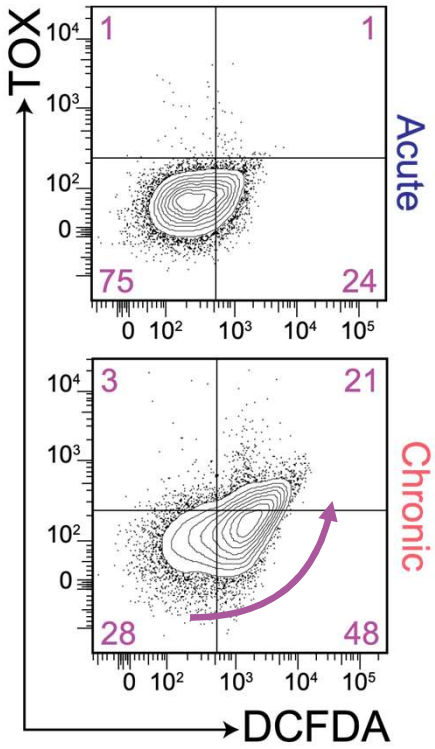




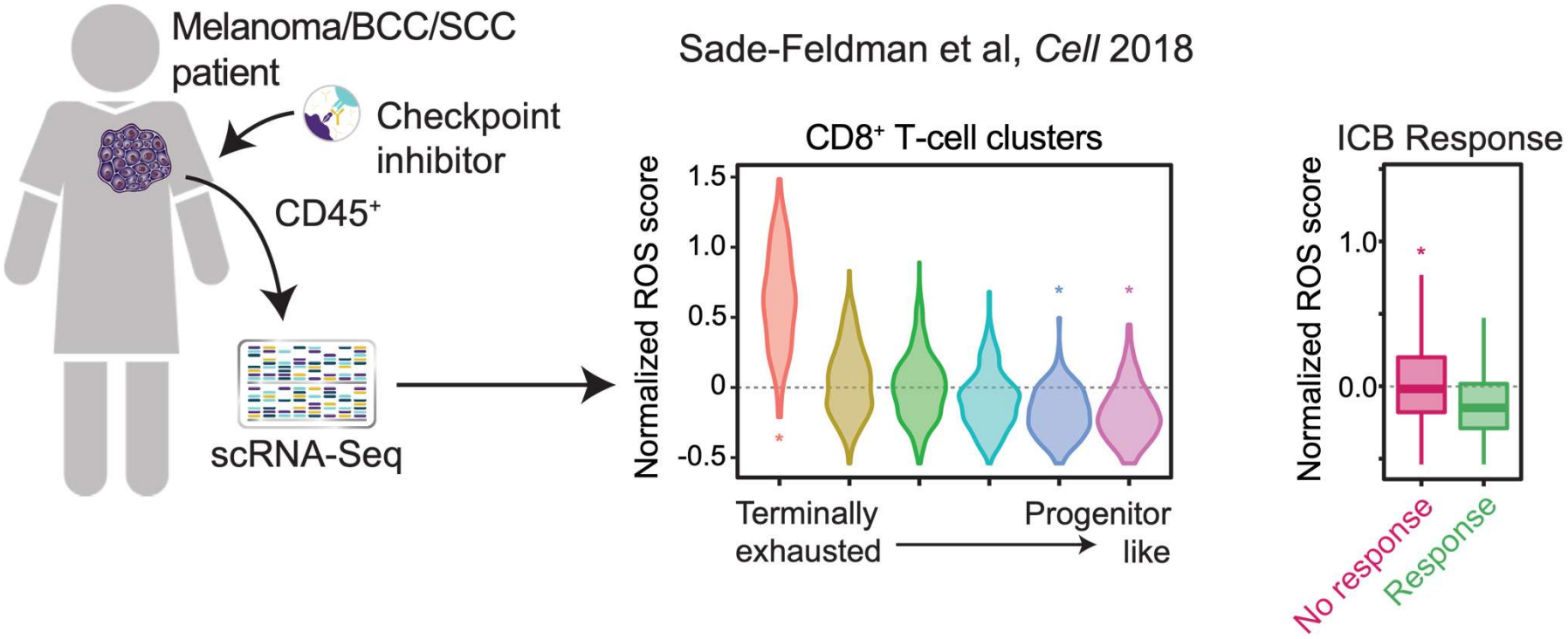
Chronically stimulated T-cells rapidly accumulate reactive oxidation species



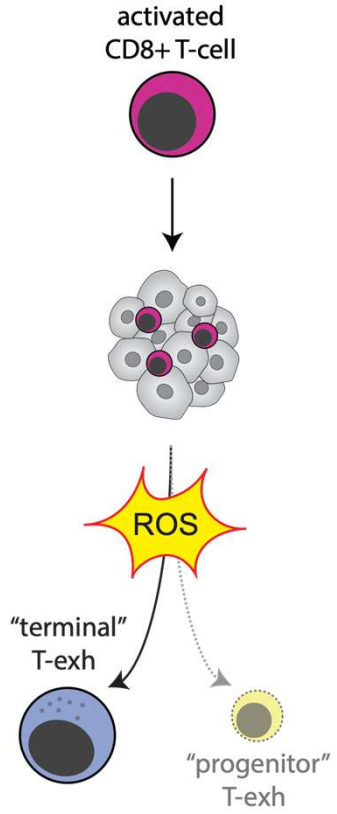


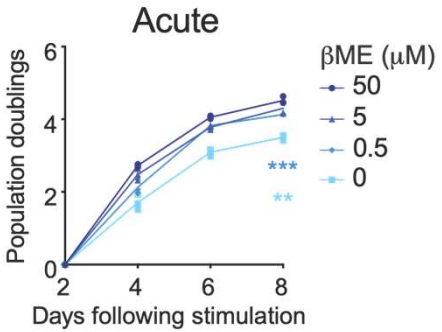


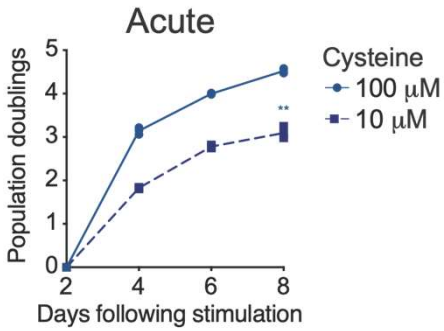
Single-cell TIL analysis shows an association between oxidative stress genes and terminal T-cell exhaustion

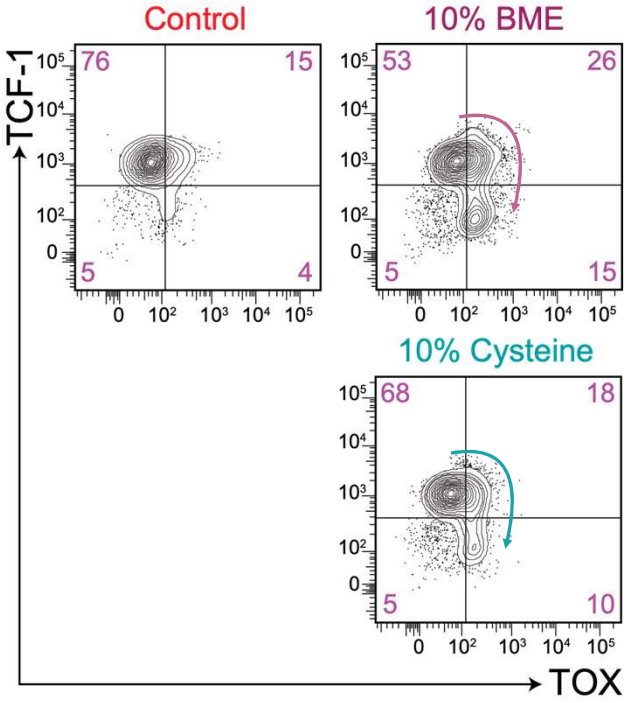


ROS-dependent mitochondrial inactivation impairs T-cell self-renewal and activate TOX expression









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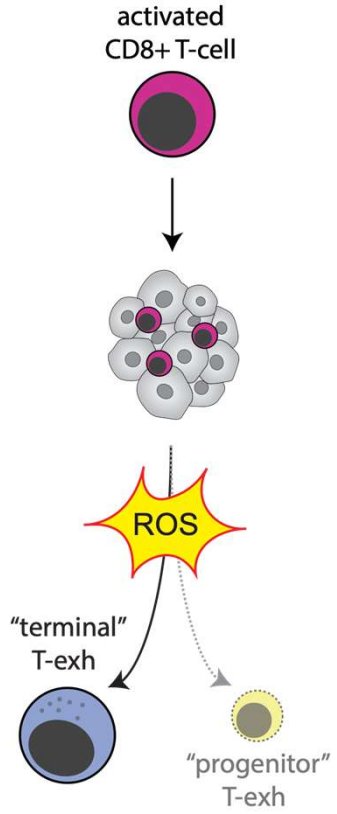
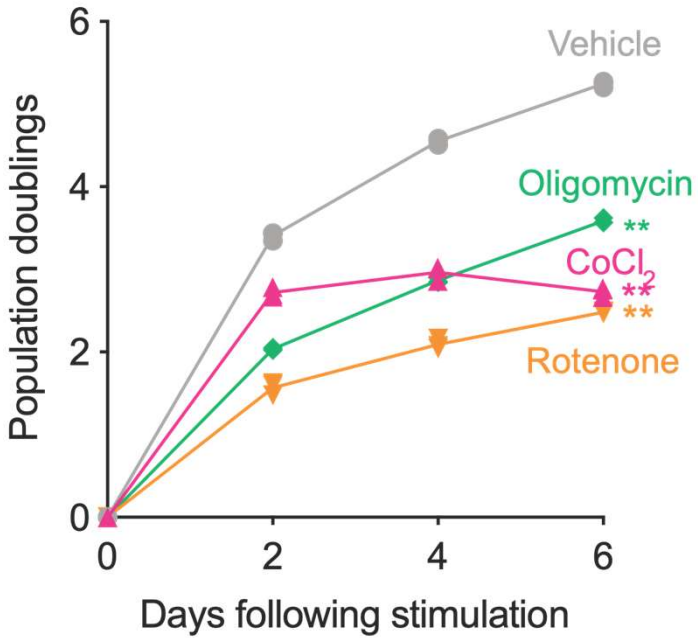
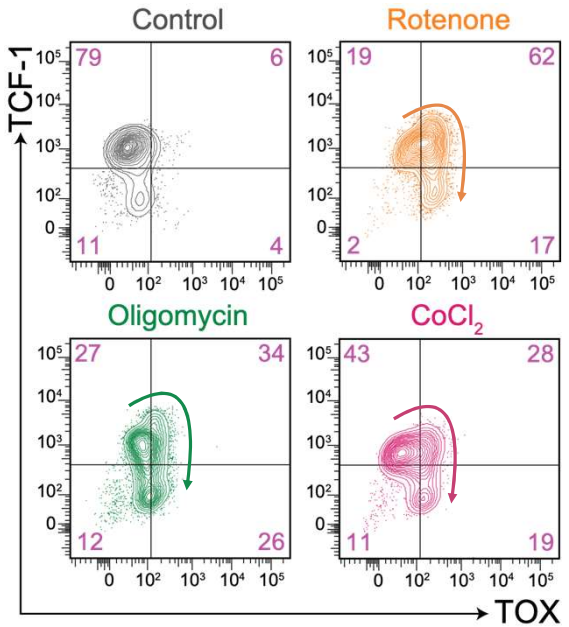
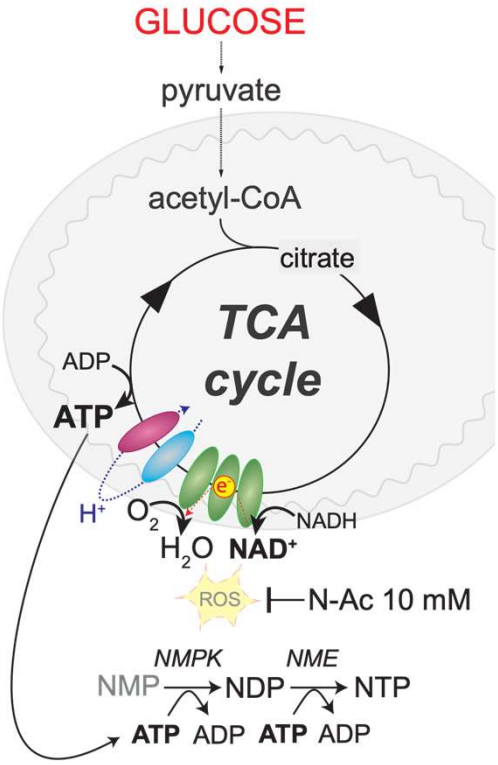
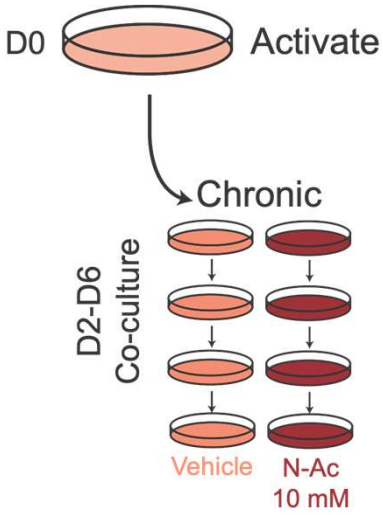




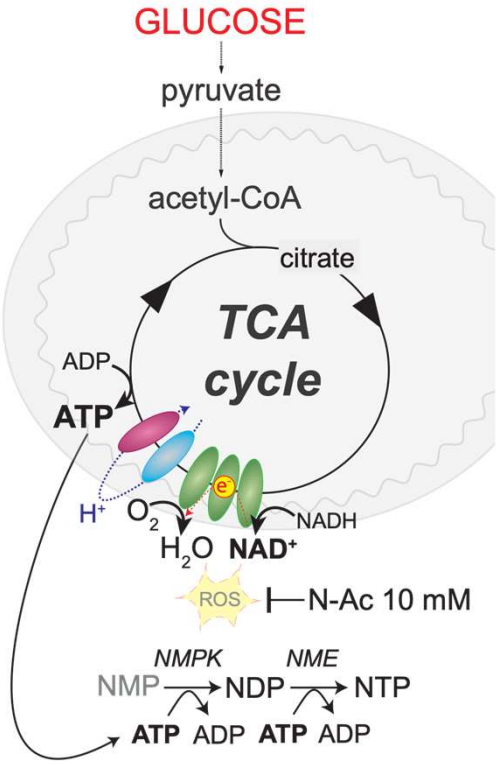


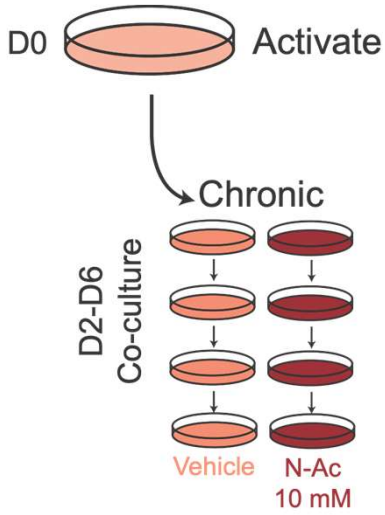
Buffering oxidative stress restores NTP synthesis during chronic T-cell stimulation

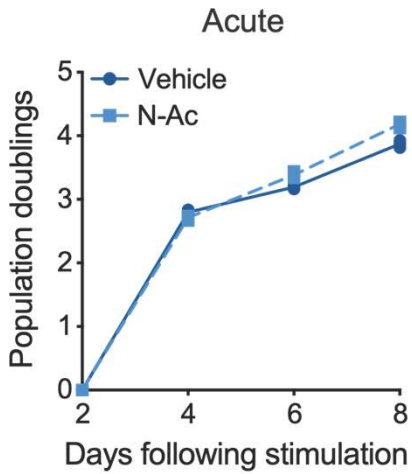


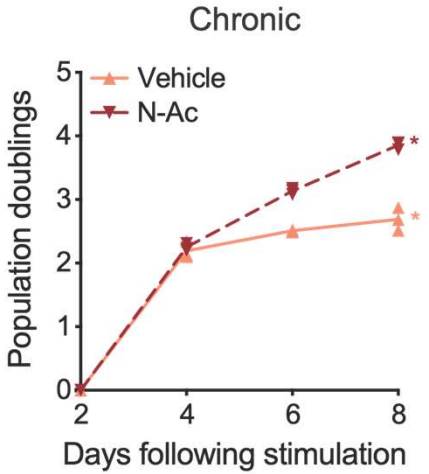


N-acetylcysteine supplementation restores proliferation during chronic T-cell stimulation

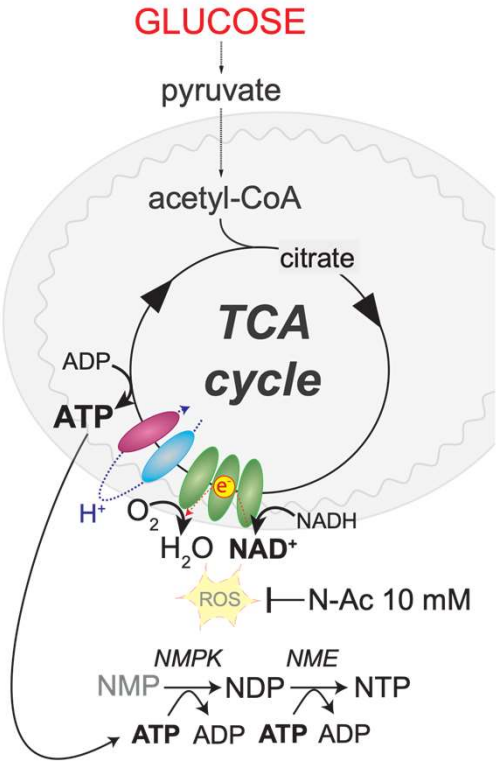


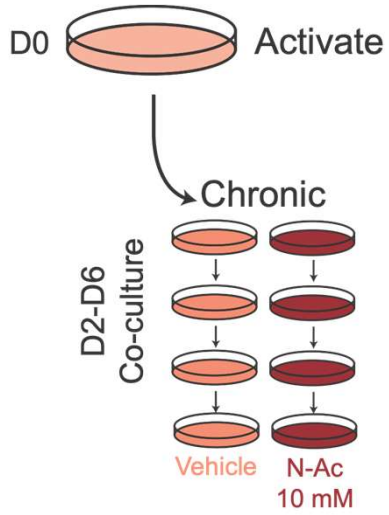


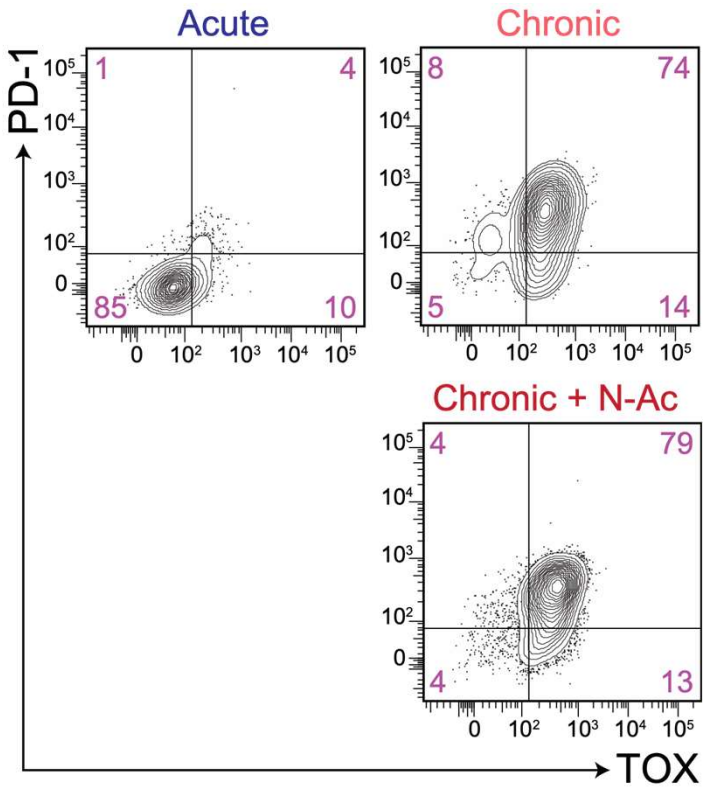




N-acetylcysteine supplementation restrains terminal T-cell differentiation by maintaining a “progenitor-like” T-cell population







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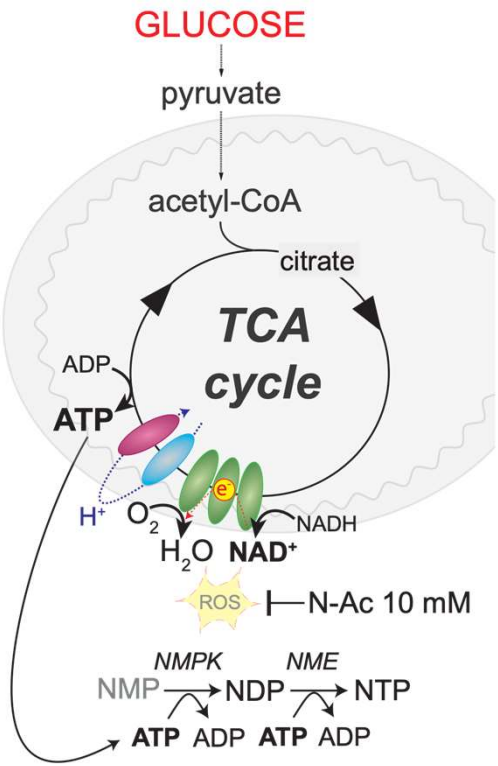
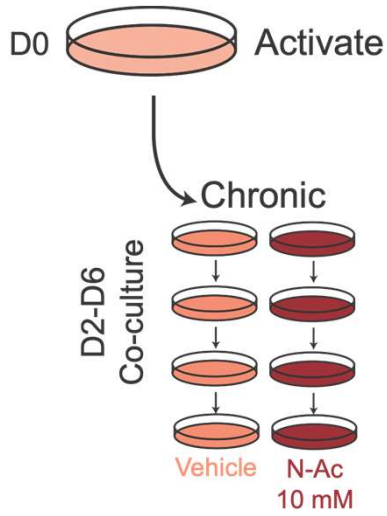
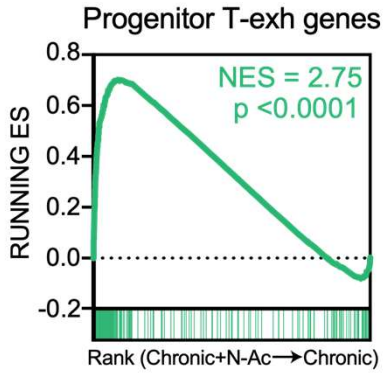
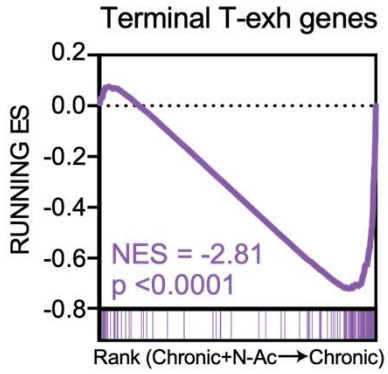
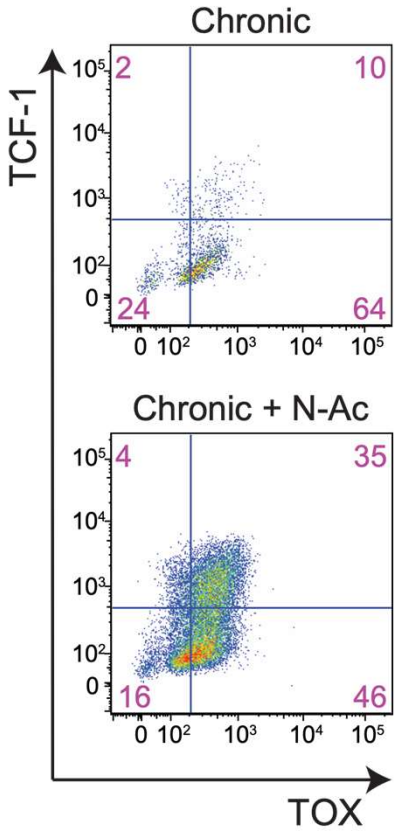


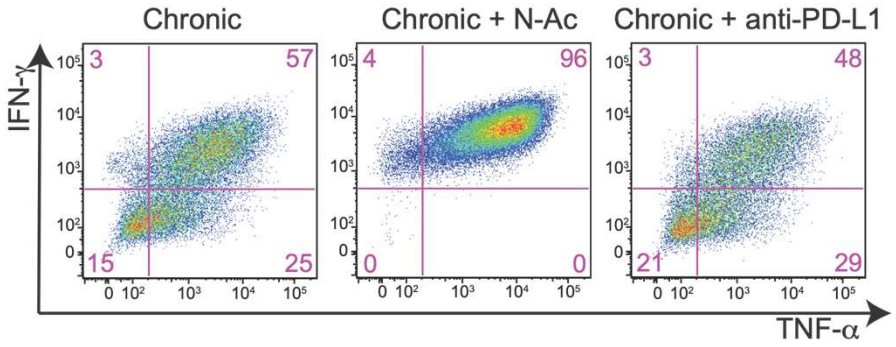


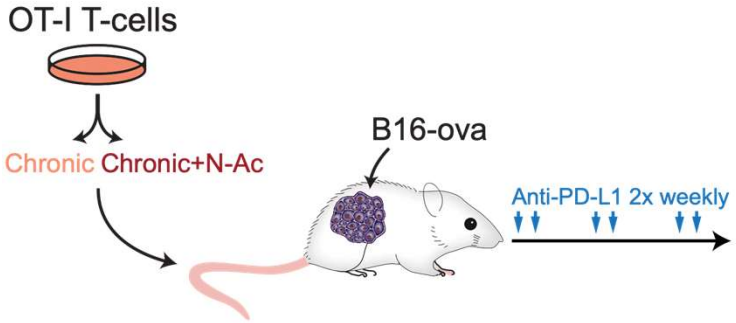


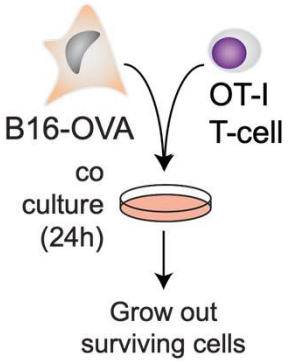


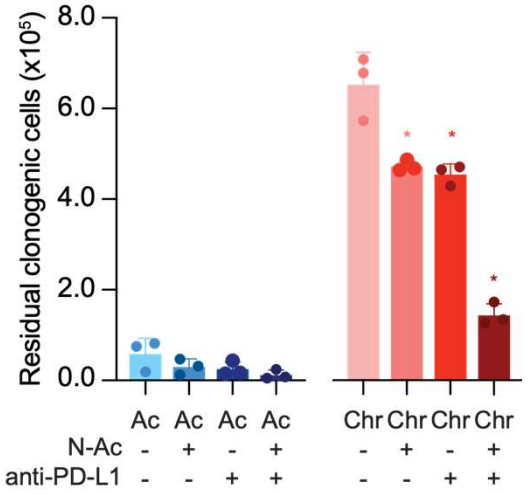


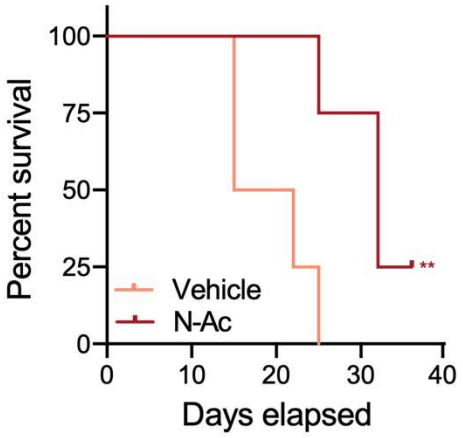
N-acetylcysteine-treated T-cells retain effector capacity

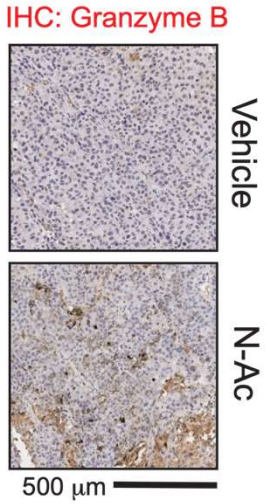




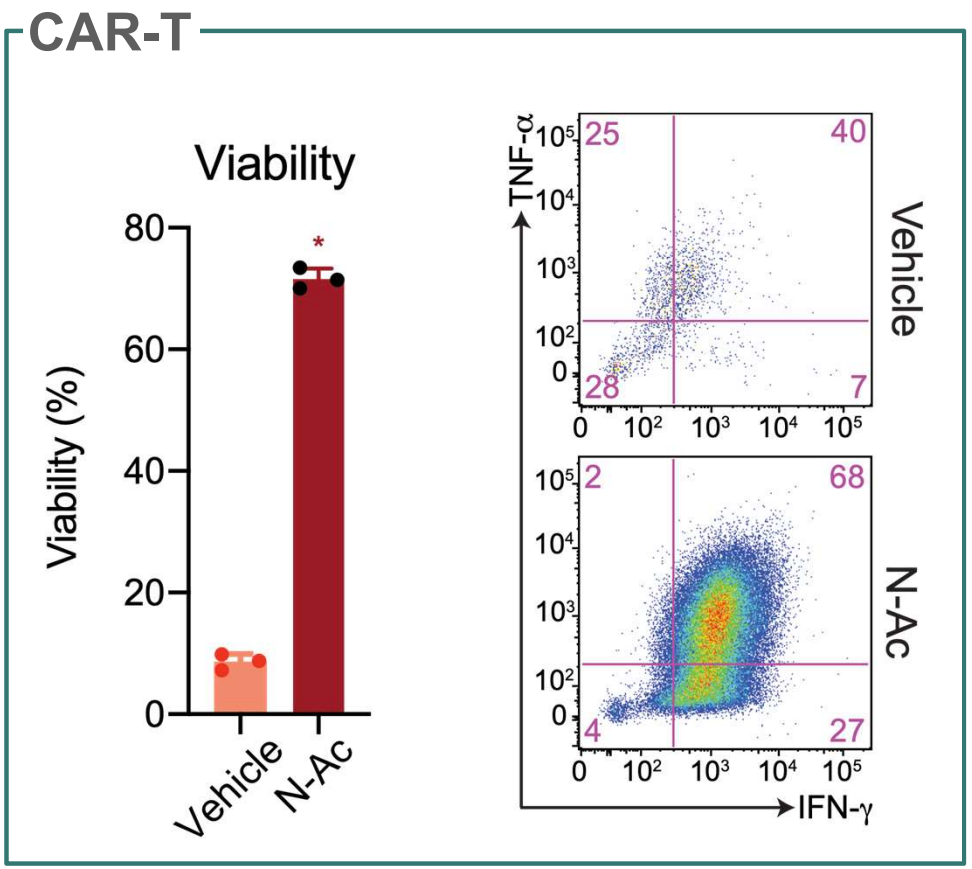


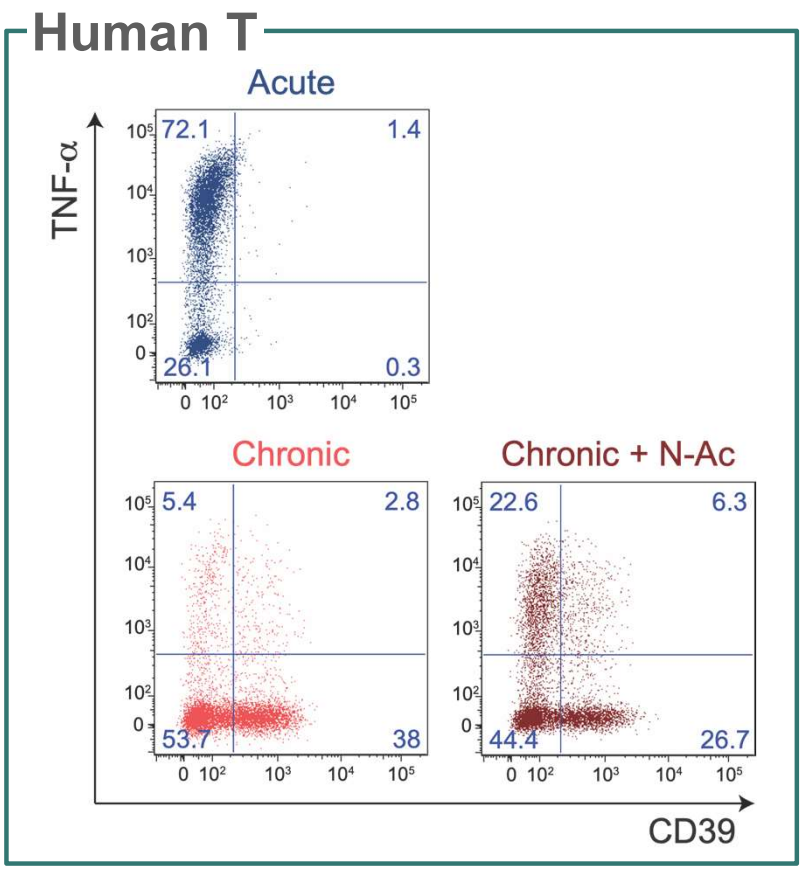






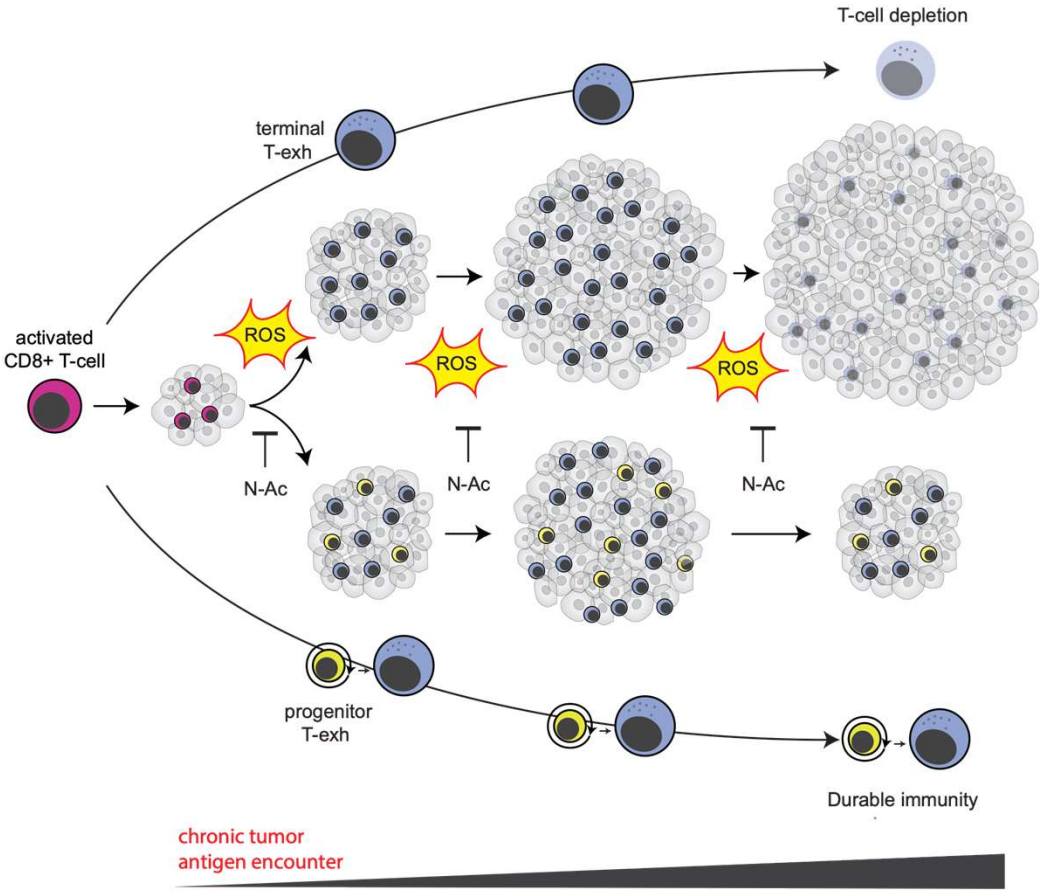
CAR-T, human T-cell function are limited by ROS





Metabolic control of T-cell dysfunction

- Altered metabolism is an **upstream** regulator of intratumoral T-cell fate decisions
- You can change phenotype by changing metabolism - **even if all other inputs remain present**
- Metabolism is a key regulator of not only T-cell function but also **T-cell state**

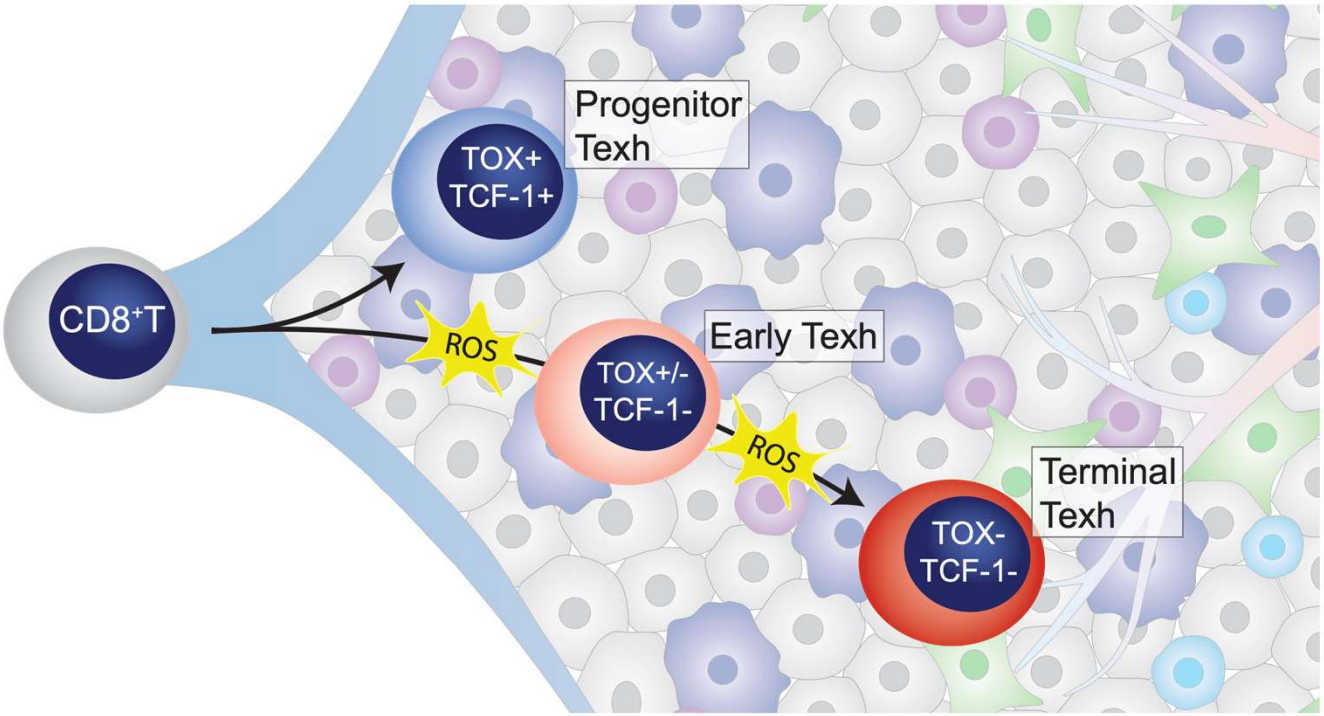


Vardhana et al, ***Nat Immunol***, 2020

Future Directions: metabolic control of immune cell fate decisions

1. How do changes in cellular metabolism activate the T-cell exhaustion program?

2. How does the tumor-specific nutrient environment affect intratumoral T-cell metabolism and differentiation?



Thank you

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