Metabolic control of cancer immunity and immunotherapy

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Cancer therapy: past, present, and future

1. Surgery: Physically remove tumor mass.
1846 Anesthesia

2. Radiation: X-rays, protons, or other types of energy directly kill tumor cells
1930-1950

3. Hormone therapy: Exogenous hormones or hormone antagonists
1941, metastatic prostate cancer treated by castration or estrogen
1966 Nobel Prize: Charles Huggins

4. Chemotherapy and targeted therapy: Cytotoxic chemicals directly kill tumor cells…..
1956, methotrexate in choriocarcinoma
1988 Nobel Prize: Gertrude Elion and George Hitchings

5. Immunotherapy: T cells kill tumor cells and remember to kill again
2018 Nobel Prize: Allison and Honjo

6. Which therapy, next?
Next Nobel Prize: 2038-2048?

Cancer microenvironment holds the key to understanding tumor immunity and therapy

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W Wang and W Zou. Amino acids and their transporters in T cell immunity and cancer therapy. Molecular Cell, 3: 384-395, 2020

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W Zou, JD Wolchok and L Chen. PD-L1 (B7-H1) and PD-1 Pathway Blockade for Cancer Therapy: Mechanisms, Response Biomarkers and Combinations. Science TM, 8:328rv4, 2016

W Zou and N Restifo. Th17 cells, tumor immunity and immune therapy. Nature Reviews Immunology, 10:248-256, 2010

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Cancer microenvironment holds the key to understanding tumor immunity and therapy

Metabolic pathways in T cell immunity and cancer therapy

1: ACSL4 in CTL-mediated tumor cell ferroptosis.

2: SLC43A2 in T cell dysfunctionality in the TME.

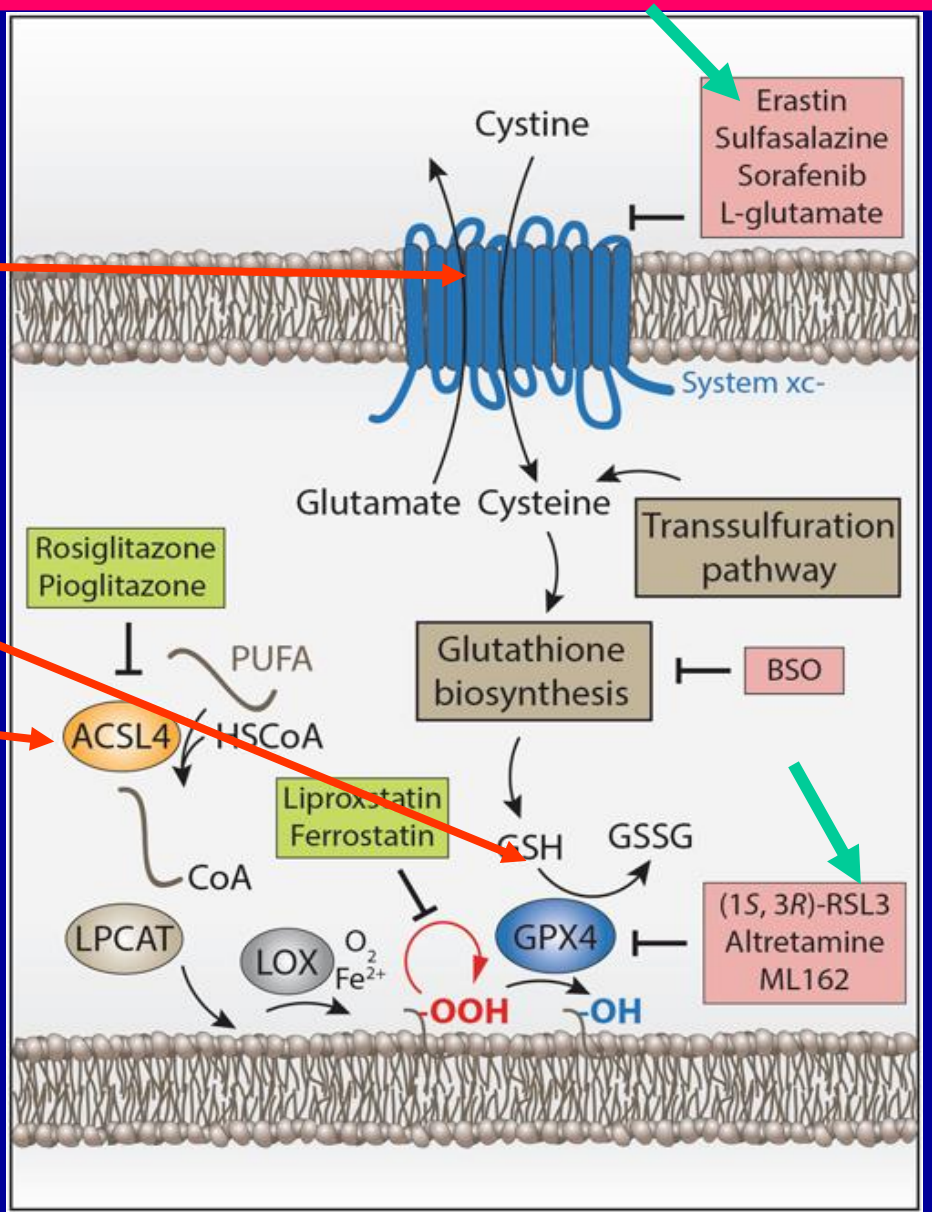
3: Immunotherapy associated hyperprogressive disease (HPD)

1: ACSL4 in CTL-mediated tumor cell ferroptosis

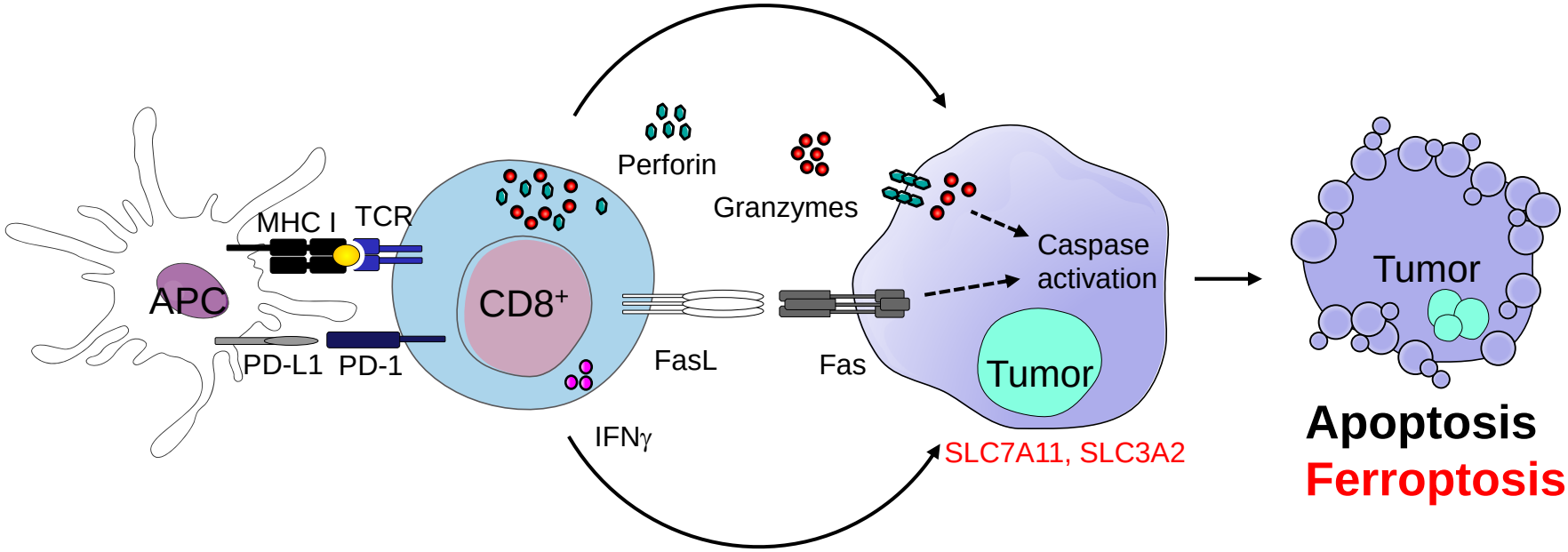
Ferroptosis: Iron-dependent, lipid peroxidation-induced cell death

- System xc-: SLC7A11 and SLC3A2, negatively regulate ferroptosis
- GPX4: negatively regulate ferroptosis
- ACSL4: positively regulate ferroptosis

Determining cell ferroptosis:
a. Lipid ROS
b. Oxidized lipid
c. Functional examination



Effector T cells, tumor cell amino acid metabolism, and ferroptosis



1. Perforin and granzymes induce tumor cell apoptosis
2. Fas and FasL induces tumor cell apoptosis
3. T cells promote tumor cell ferroptosis via IFNγ

Nature, 2019

Cancer Cell, 2022

Natural ferroptosis inducer(s) are unknown

1. T cells checkpoint therapy promote tumor cell ferroptosis via IFNγ

2. IFNγ alone fails to induce tumor cell ferroptosis

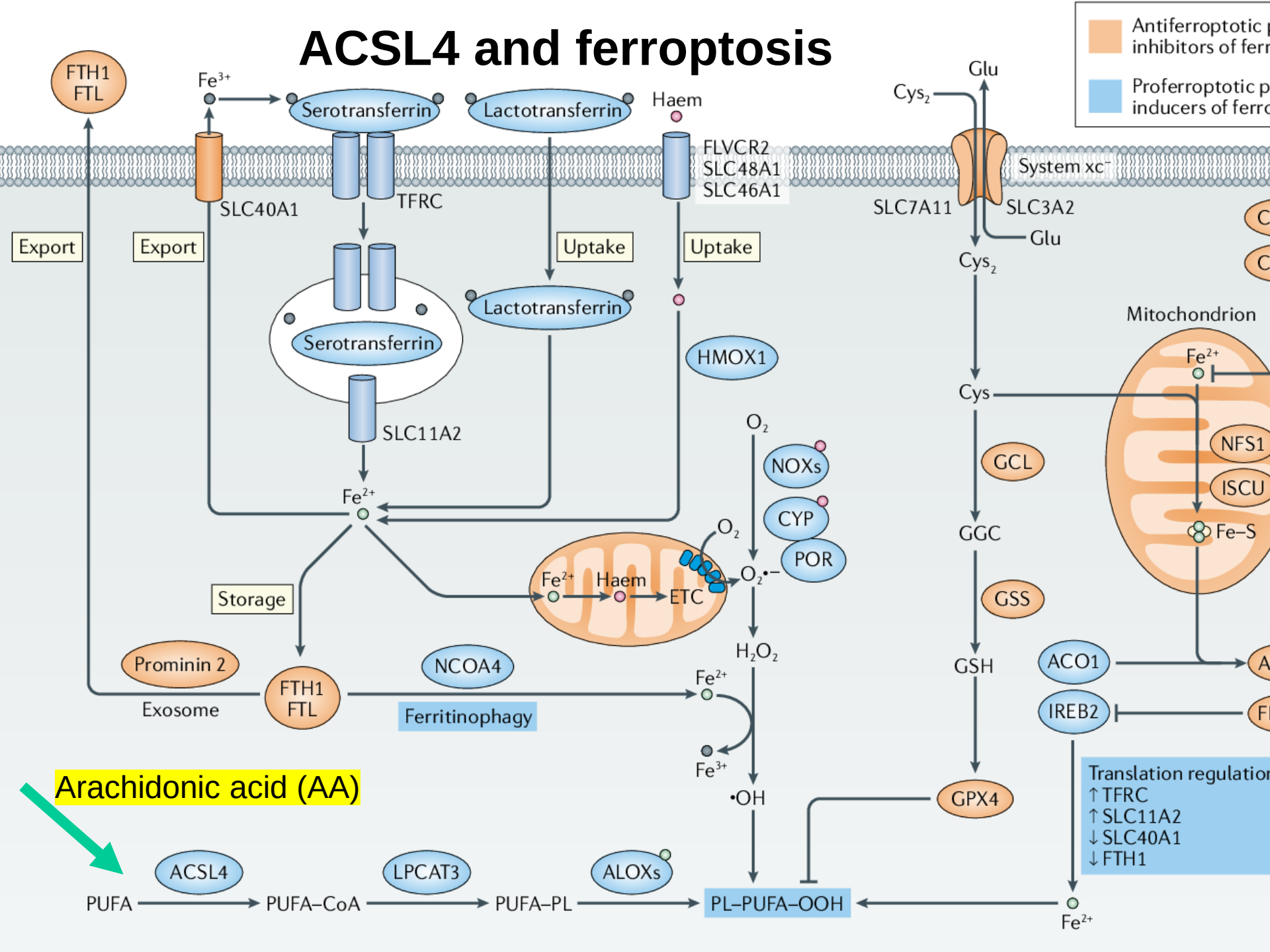
3. Diets (fatty acids) affect tumor immunity and immunotherapy

Can IFNγ in combination with fatty acids induce tumor cell ferroptosis?

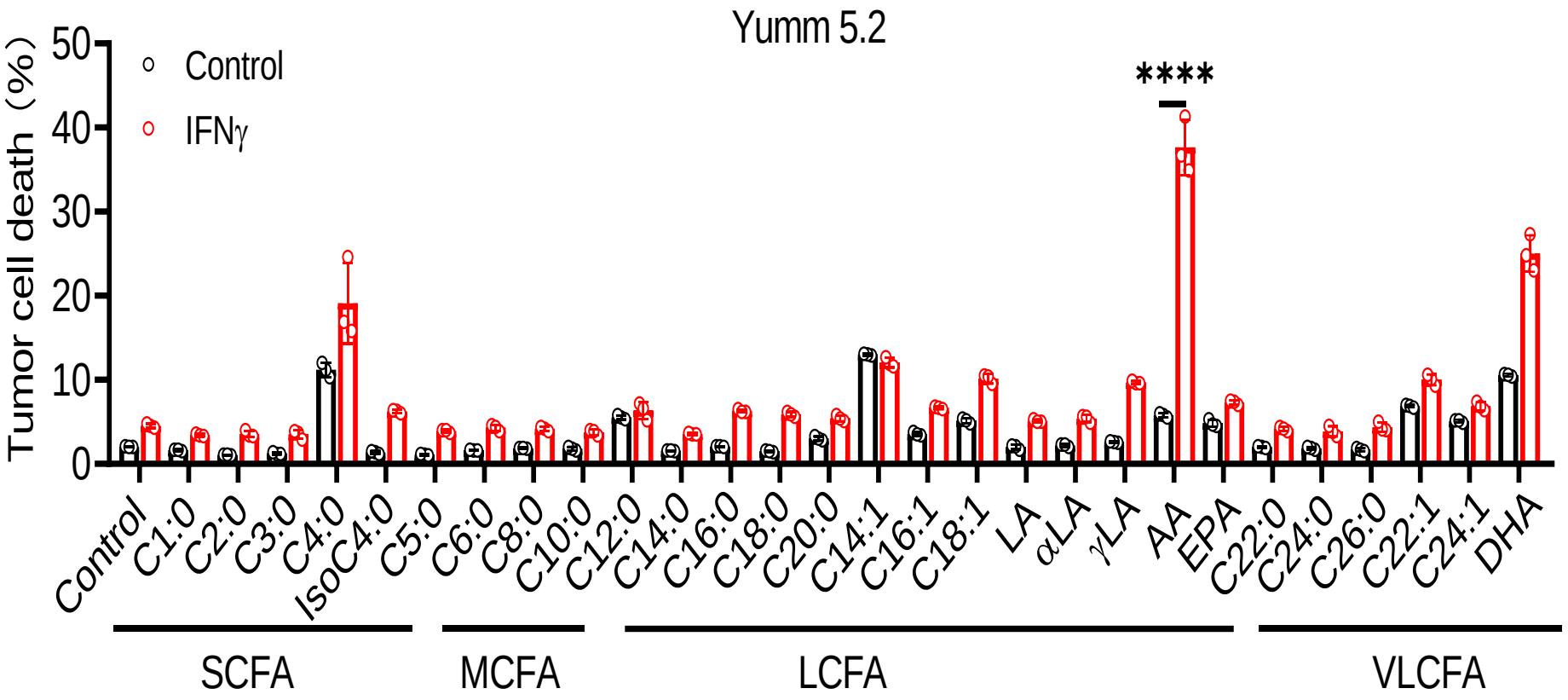
Common fatty acids

Sub Class	Common Name	Synonyms	Molecular Formula
Short-chain	Formic acid	C1:0	C1H2O1
	Acetic acid	C2:0	C2H4O2
	Propionic acid	C3:0	C3H6O2
	Butyric acid	C4:0	C4H8O2
	Isobutyric acid	C4:0	C4H8O2
	Valeric acid	C5:0	C5H10O2
Medium-chain	Caproic acid	C6:0	C6H12O2
	Caprylic acid	C8:0	C8H16O2
	Capric acid	C10:0	C10H20O2
	Lauric acid	C12:0	C12H24O2
Long-chain	Myristic acid	C14:0	C14H28O2
	Palmitic acid (PA)	C16:0	C16H32O2
	Stearic acid (SA)	C18:0	C18H36O2
	Arachidic acid	C20:0	C20H40O2
	Myristoleic acid	C14:1	C14H26O2
	Palmitoleic acid (POA)	C16:1	C16H30O2
	Oleic acid (OA)	C18:1	C18H34O2
	Linoleic acid (LA)	C18:2	C18H32O2
	Linoelaidic acid(gLA)	C18:2	C18H32O2
	α-Linolenic acid (aLA)	C18:3	C18H30O2
	Arachidonic acid (AA)	C20:4	C20H32O2
	Eicosapentaenoic acid (EPA)	C20:5	C20H30O2
Very long-chain	Behenic acid	22:0	C22H44O2
	Lignoceric acid	24:0	C24H48O2
	Cerotic acid	26:0	C26H52O2
	Erucic acid	22:1	C22H42O2
	Nervonic acid	24:1	C24H46O2
	Docosahexaenoic acid (DHA)	22:6	C22H32O2
	Docosatetraenoic acid (AdA)	22:4	C22H36O2

ACSL4 and ferroptosis



Arachidonic acid (AA) plus IFNγ induce tumor cell ferroptosis



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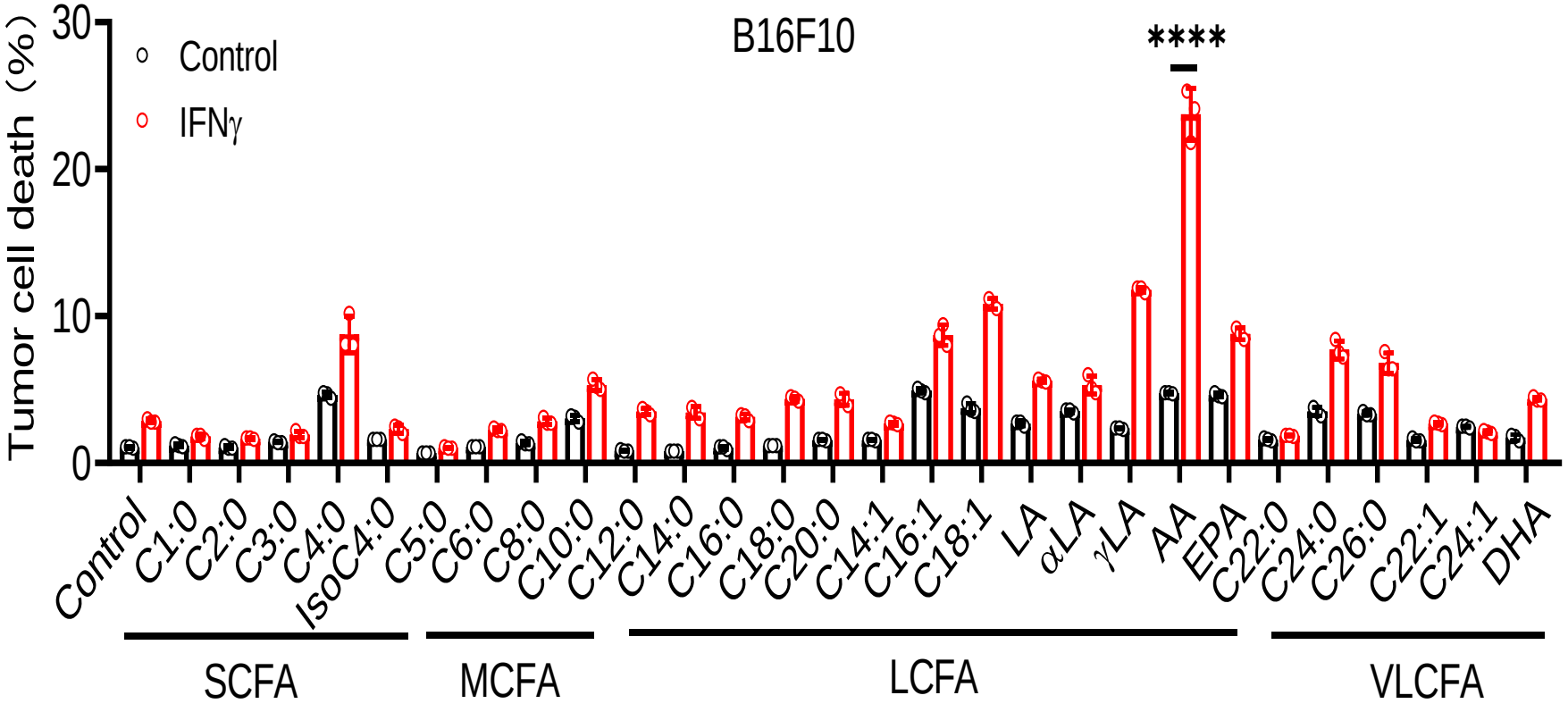

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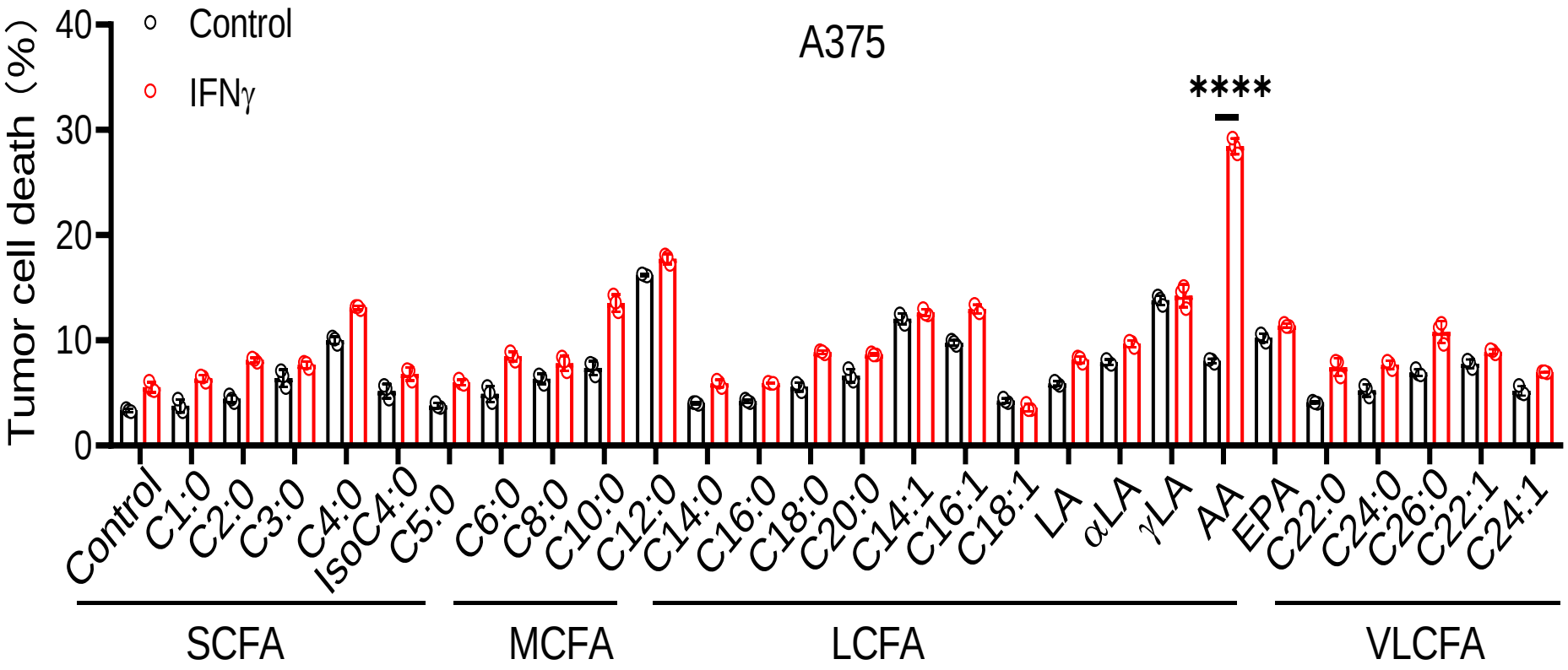
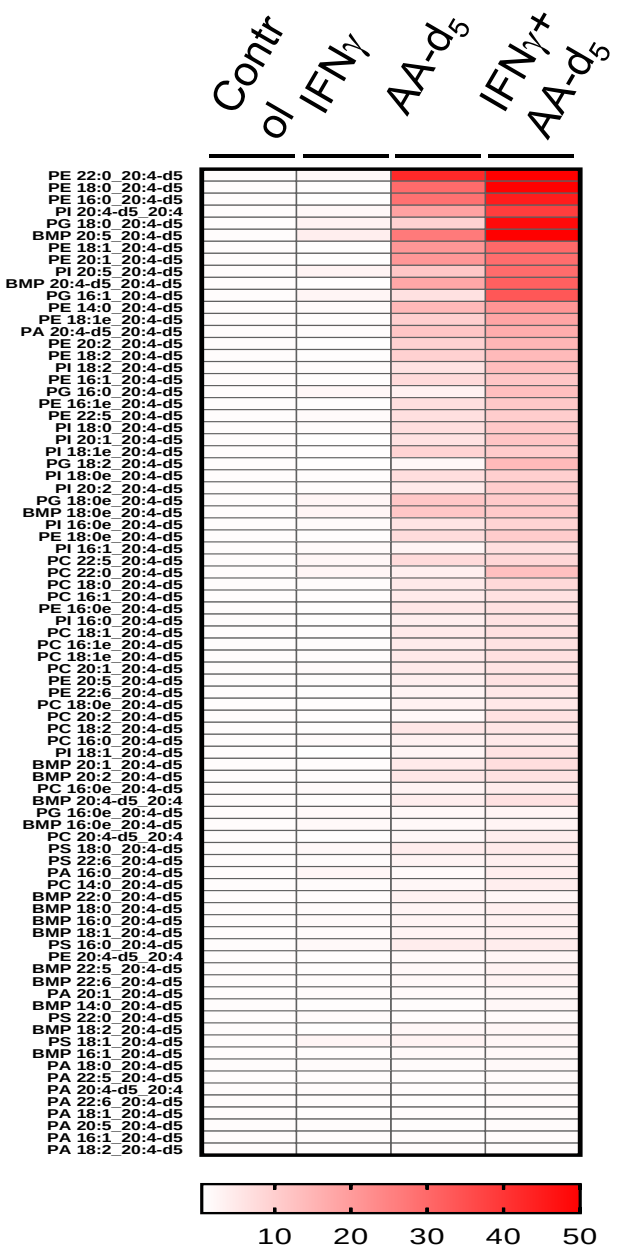
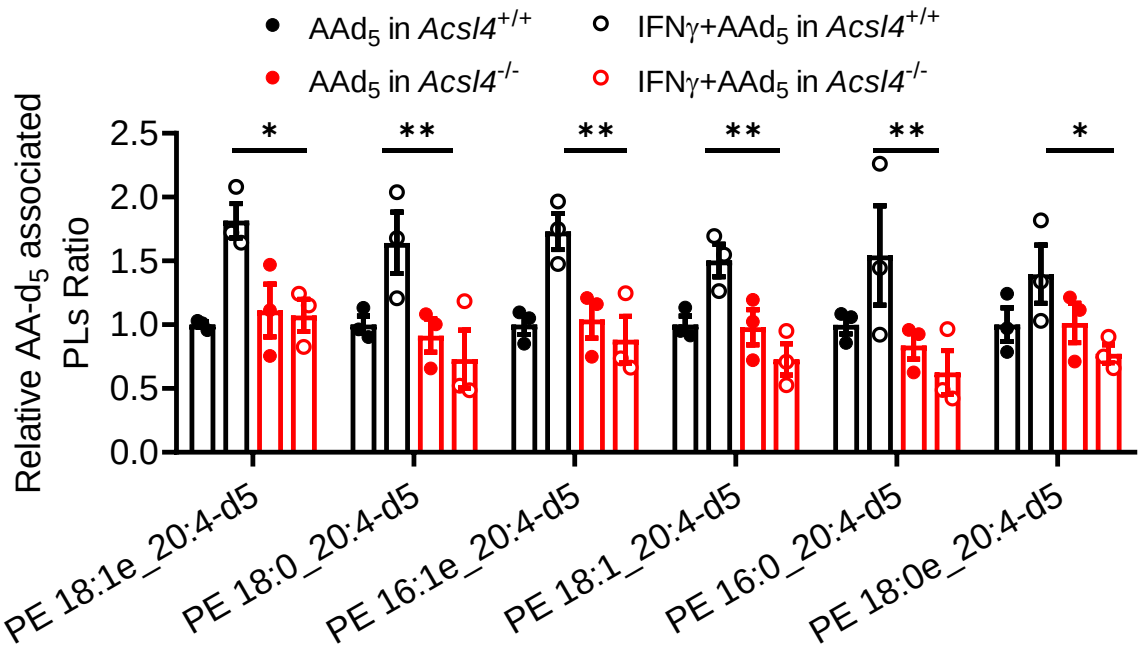
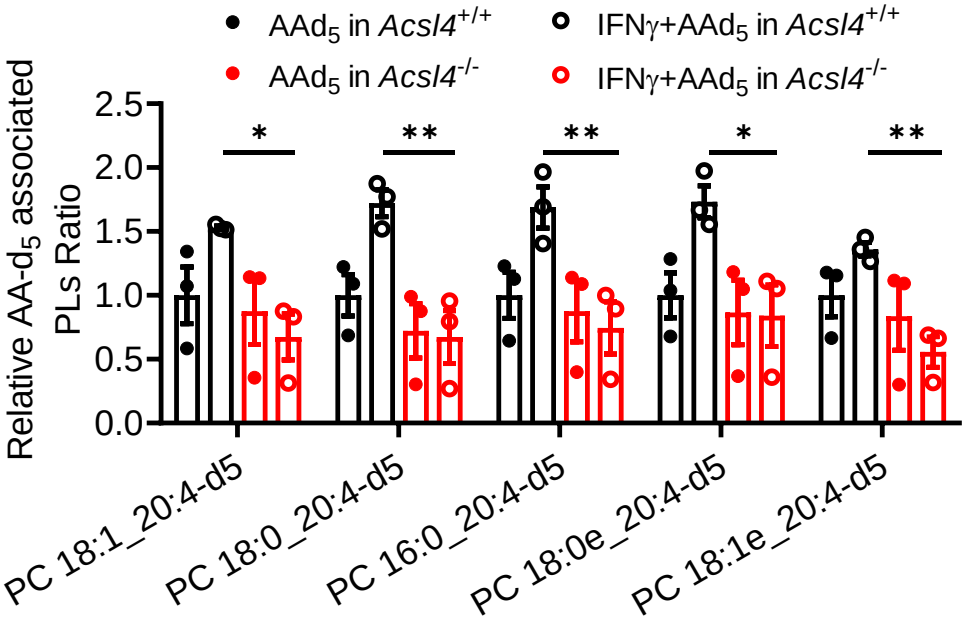


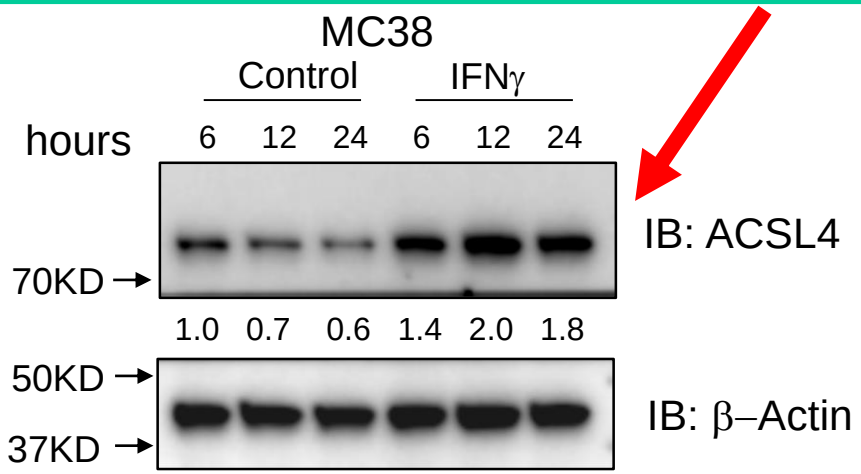
IFNγ alters ACSL4 associated phospholipids to induce tumor ferroptosis

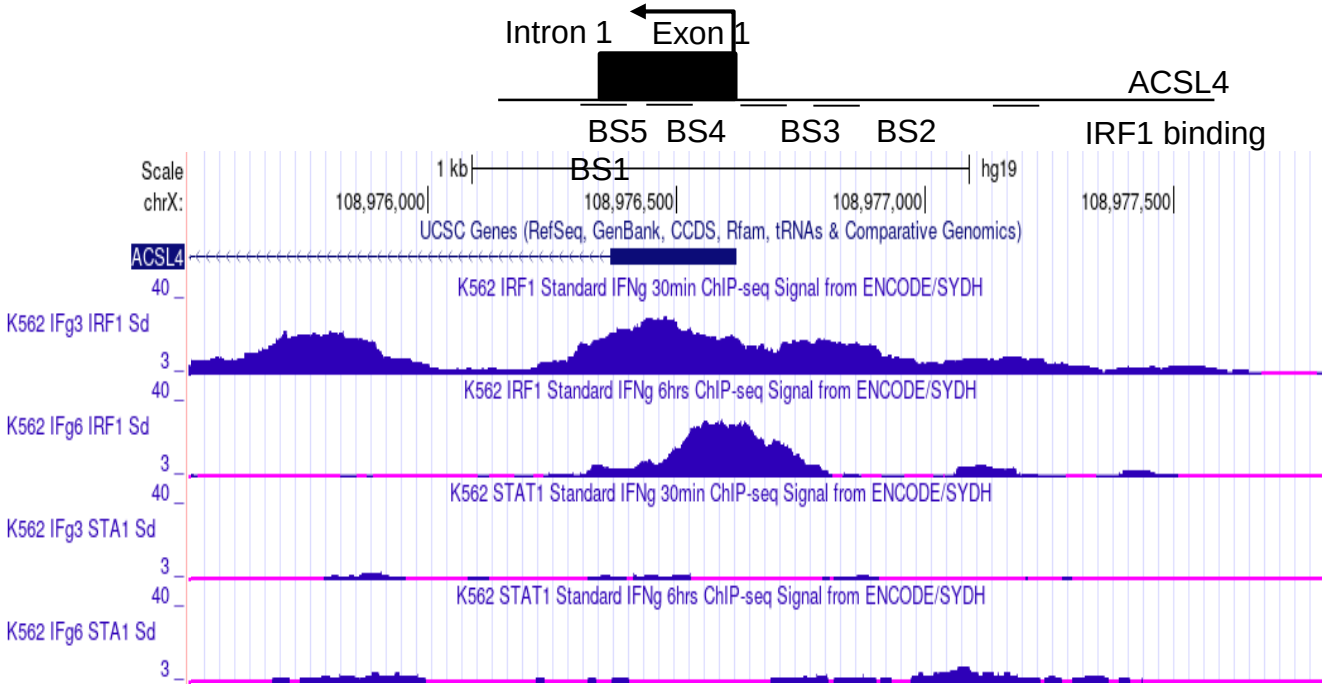


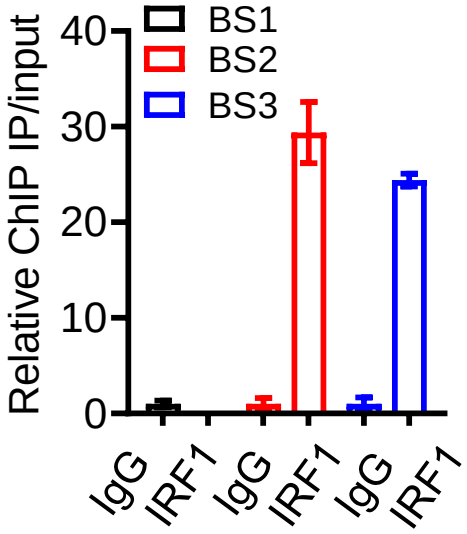




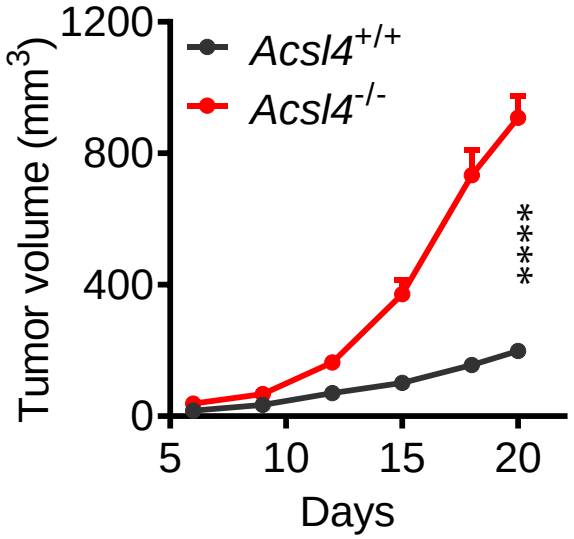
IFNγ regulates ACSL4 via STAT1 and IRF1 signaling

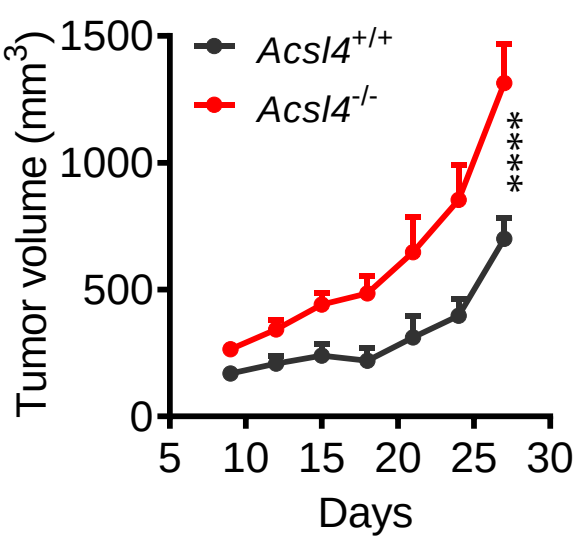


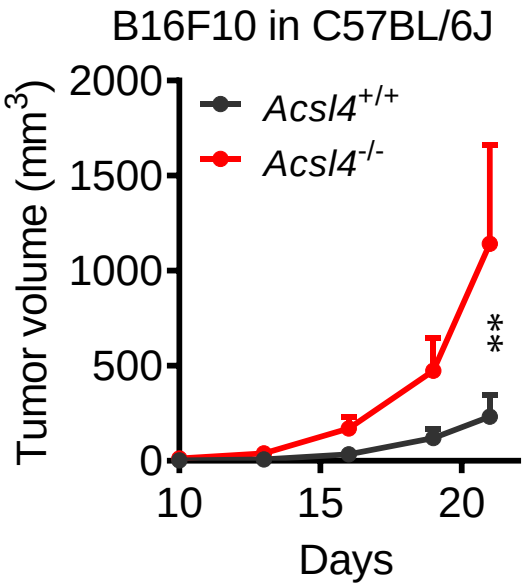


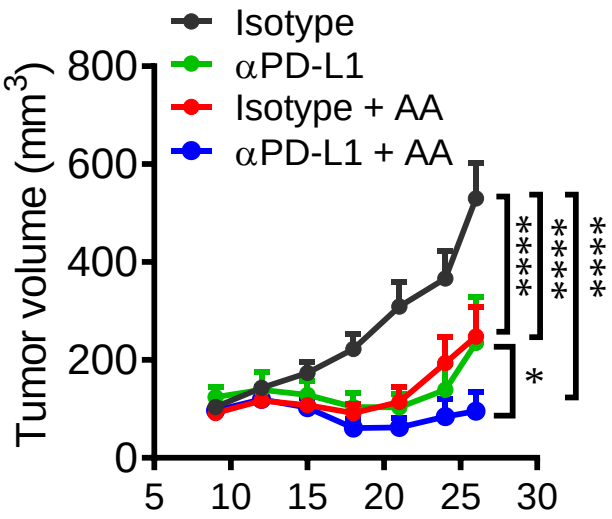


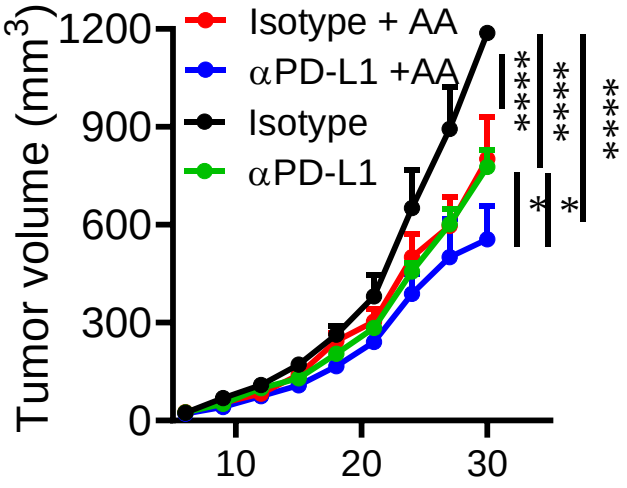
AA and ACSL4 pathway affects anti-tumor immunity

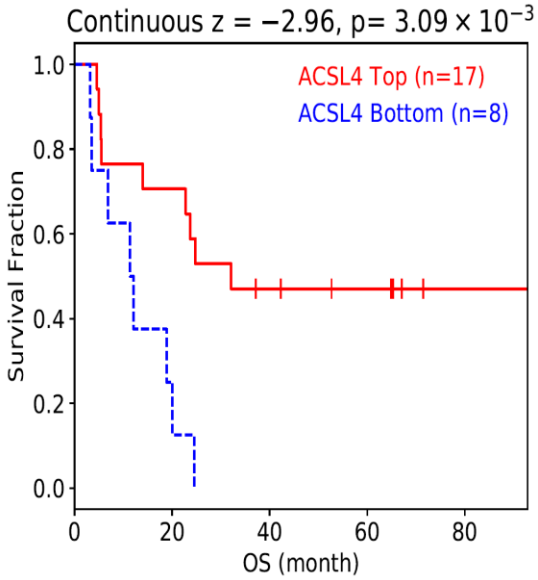






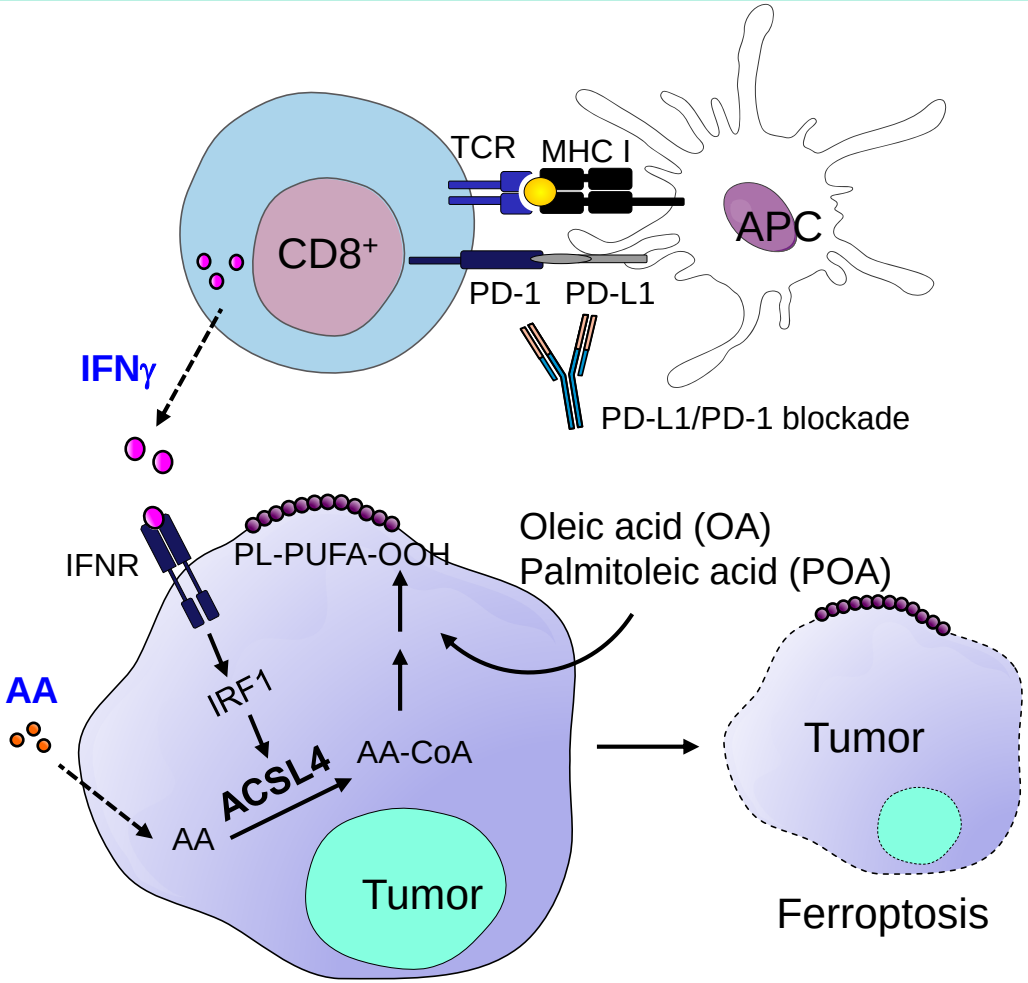






IFNγ alters ACSL4 associated phospholipids to induce tumor ferroptosis

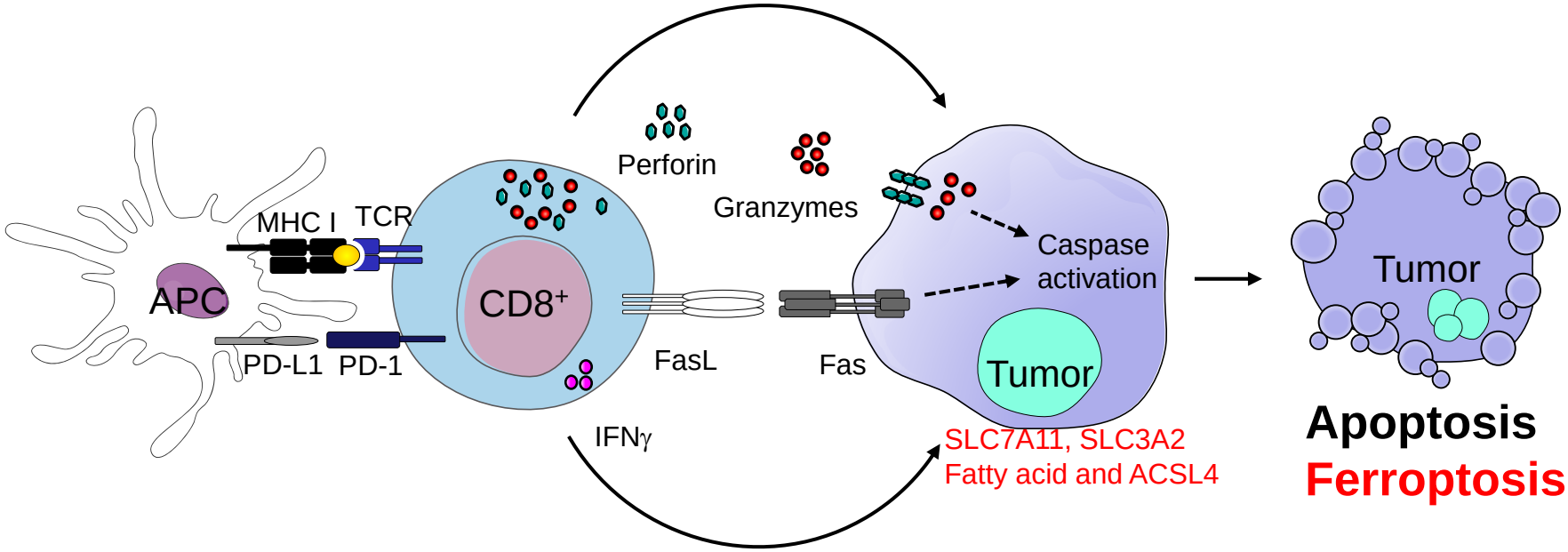
IFNγ regulates ACSL4 via STAT1 and IRF1 signaling



IFNγ plus AA (OA, POA) induce cell ferroptosis without synthetic compound

Th1: IFNγ plus IL-12; Th17: TGFβ plus IL-6; Treg: TGFβ plus IL-2

Effector T cells and tumor ferroptosis



1. Perforin and granzymes induce tumor cell apoptosis
2. Fas and FasL induces tumor cell apoptosis

3. T cells promote tumor cell ferroptosis via IFNγ

4. IFNγ plus AA (OA, POA) is an intrinsic ferroptosis mechanism

Nature, 2019

Cancer Cell, 2022

Take-home messages

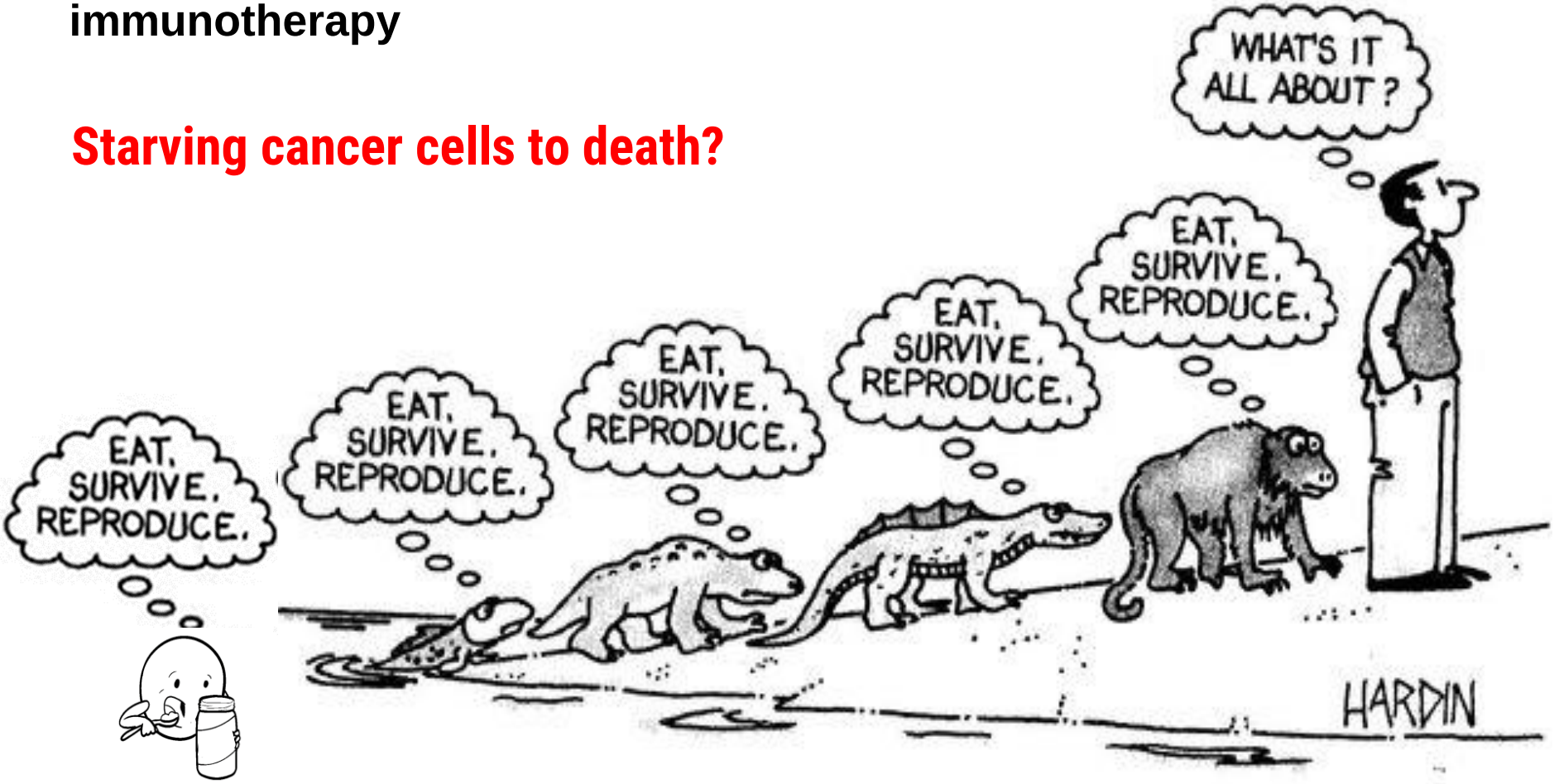
Tumor ferroptosis is a mode of action of CTLs.

Tumor ferroptosis is an immunotherapy mechanism.

2: SLC43A2 in T cell dysfunctionality in the TME.

Effect of methionine metabolism on T cell function and survival, and immunotherapy

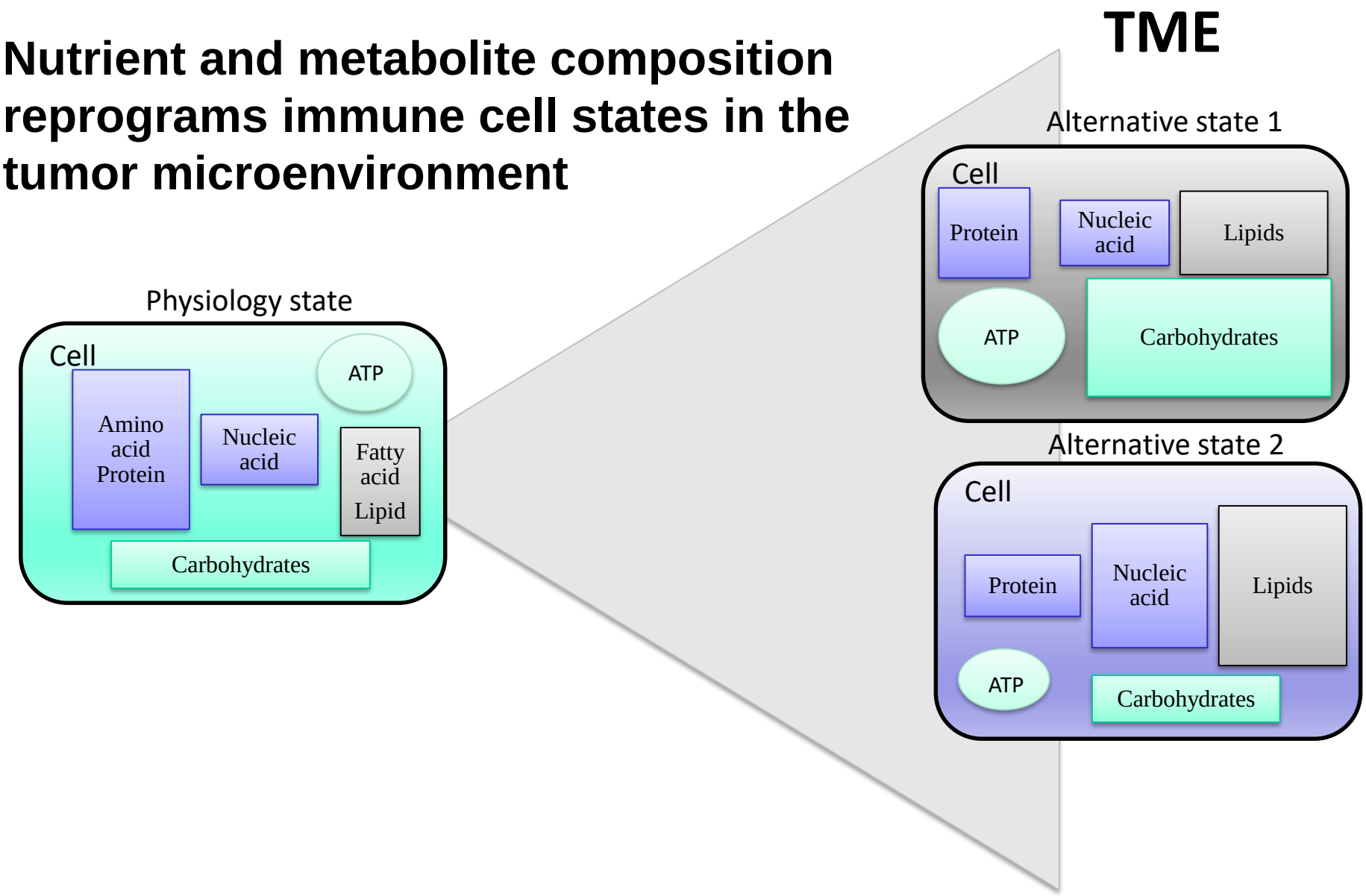
Starving cancer cells to death?



Nat. Hist., 1994, 103(6)

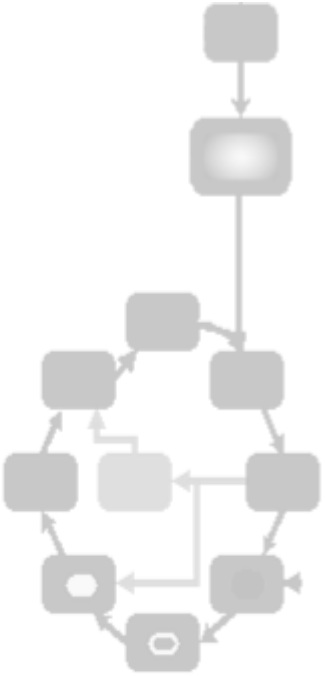
Metabolism can shape immune cell states

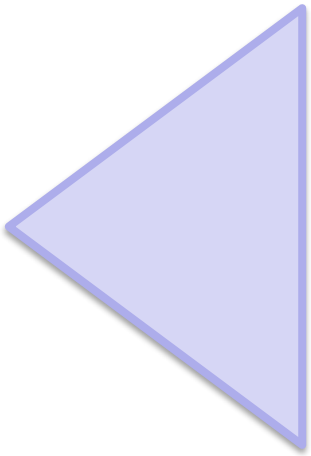
Nutrient and metabolite composition reprograms immune cell states in the tumor microenvironment



Nutrients and metabolites in the tumor microenvironment

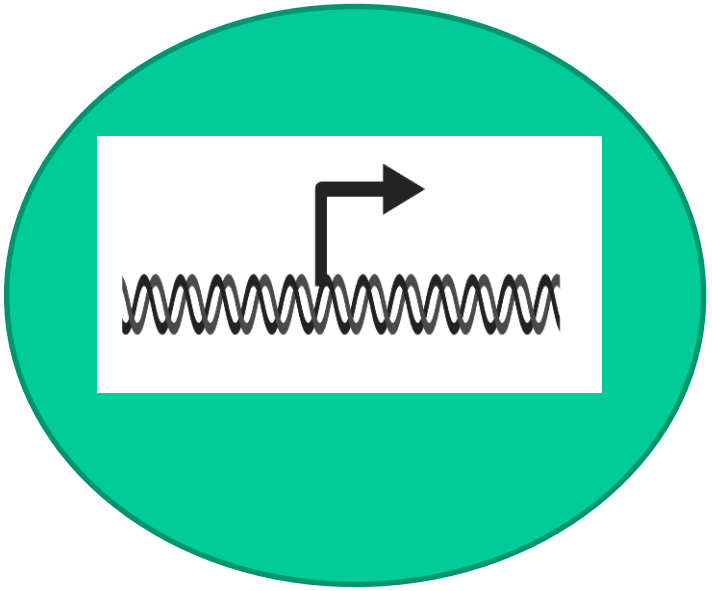
Cross-talk between metabolic and epigenetic mechanisms in T cell state in the TME



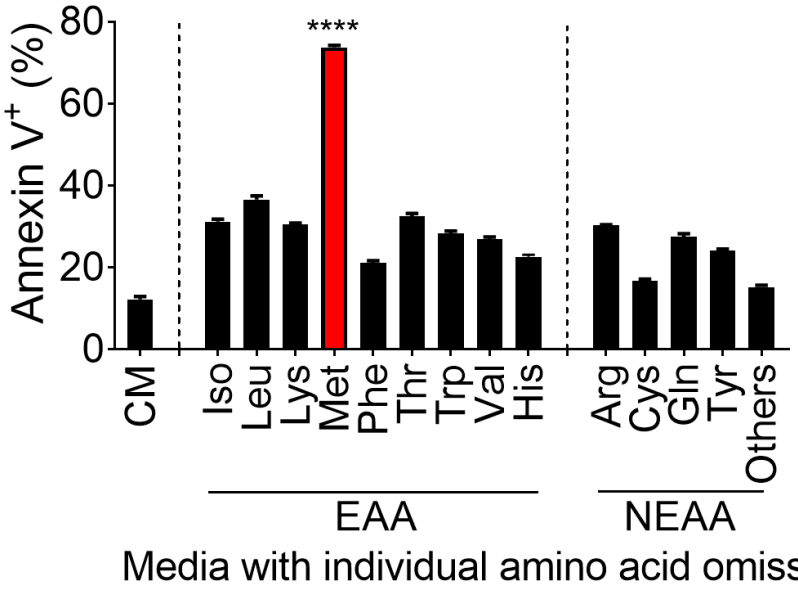


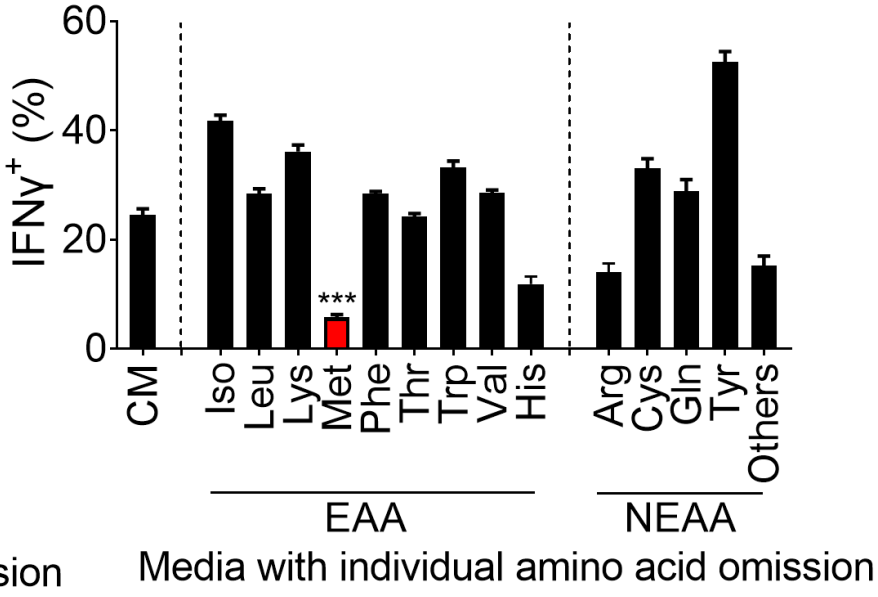
Ac-CoA
αKG
succinate
2-HG
SAM
NAD$^+$

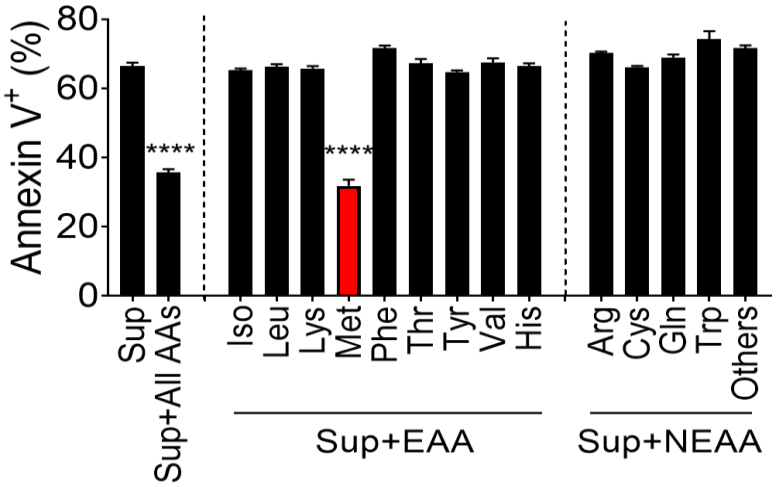
T cell dysfunction (exhaustion)

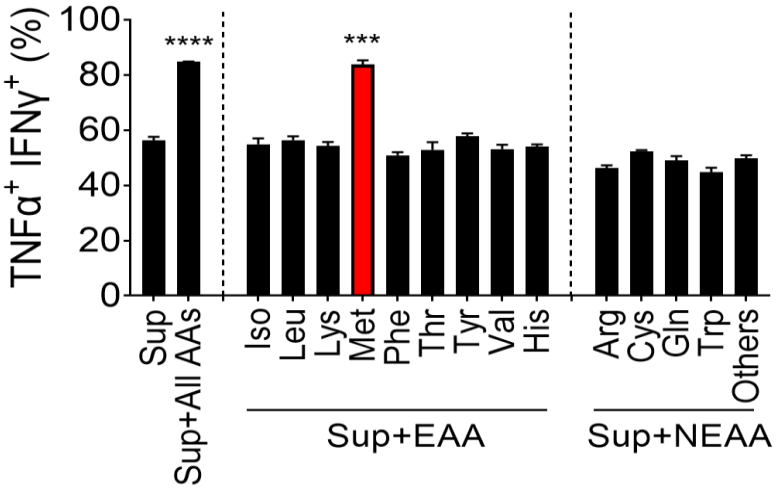


Tumor cells outcompete T cells for methionine

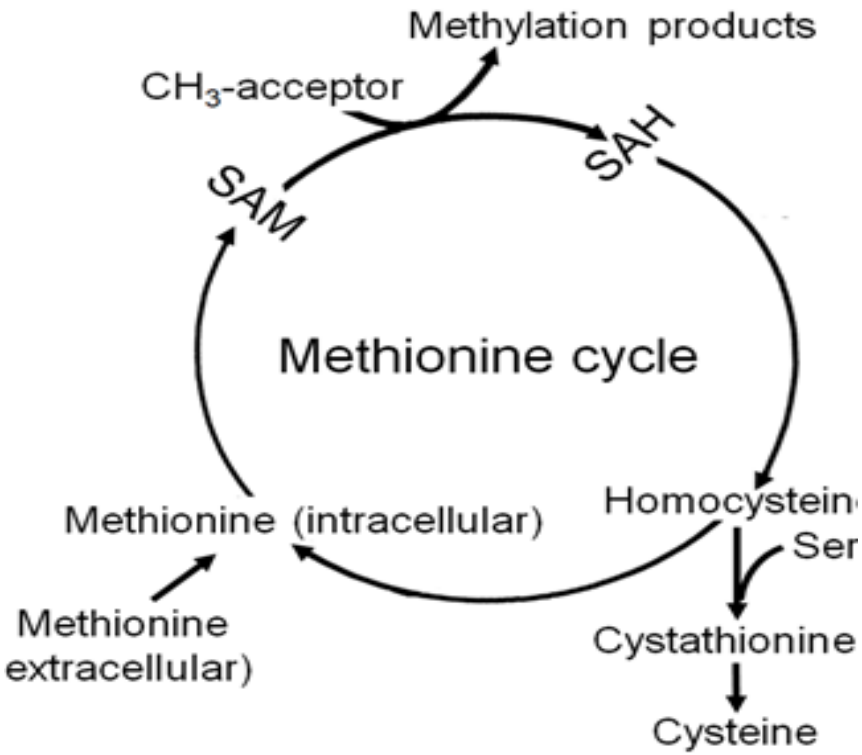


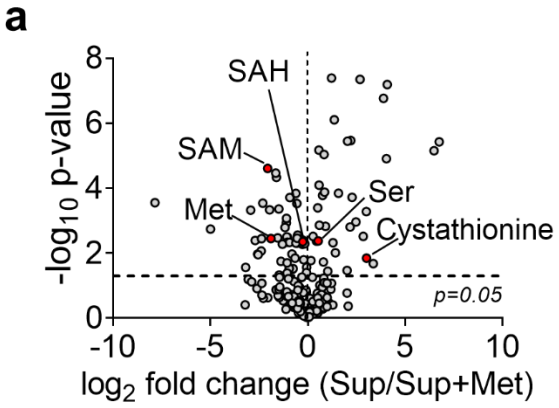


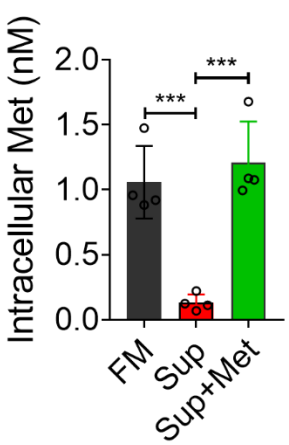


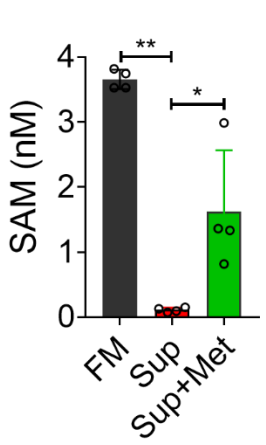


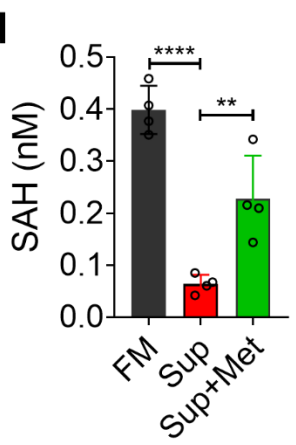
Tumor cells reduce methionine, SAM, and SAH





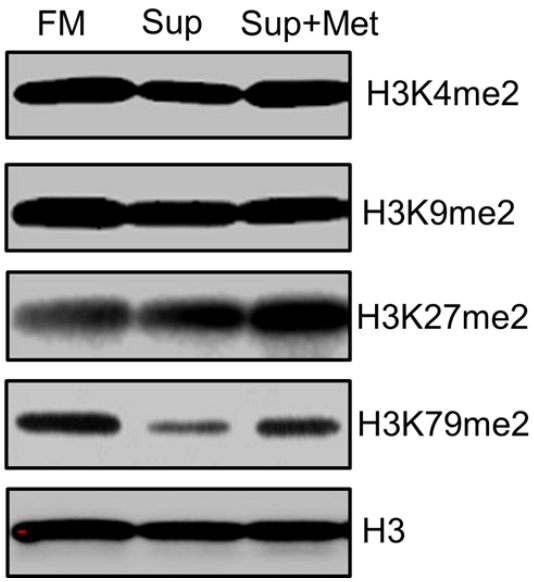






Methionine deprivation abolishes H3K79me2 in T cells

B16



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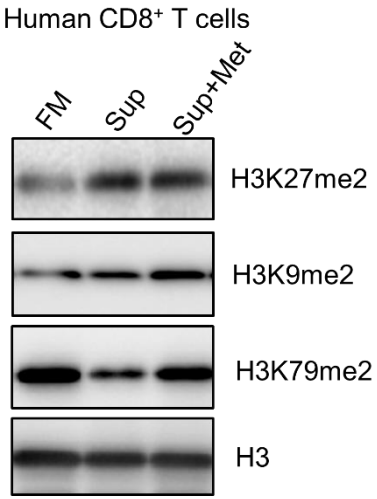
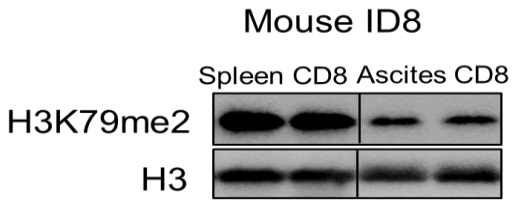
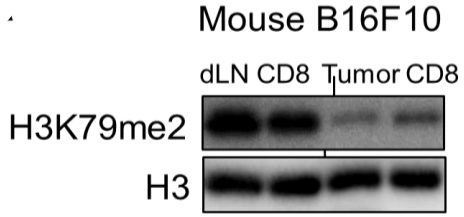
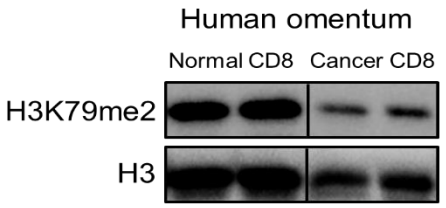


Reduced H3K79me2 in tumor infiltrating T cells

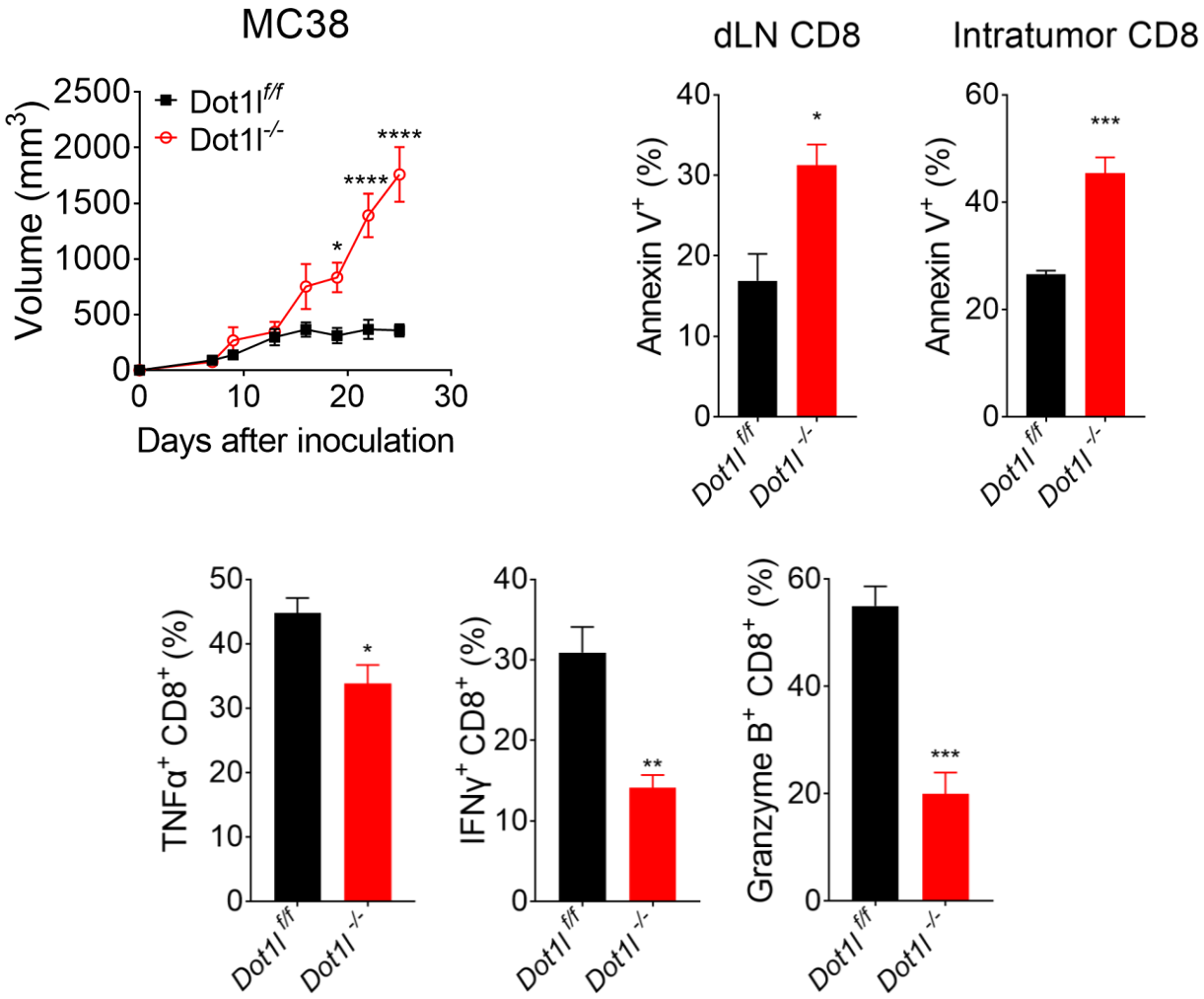




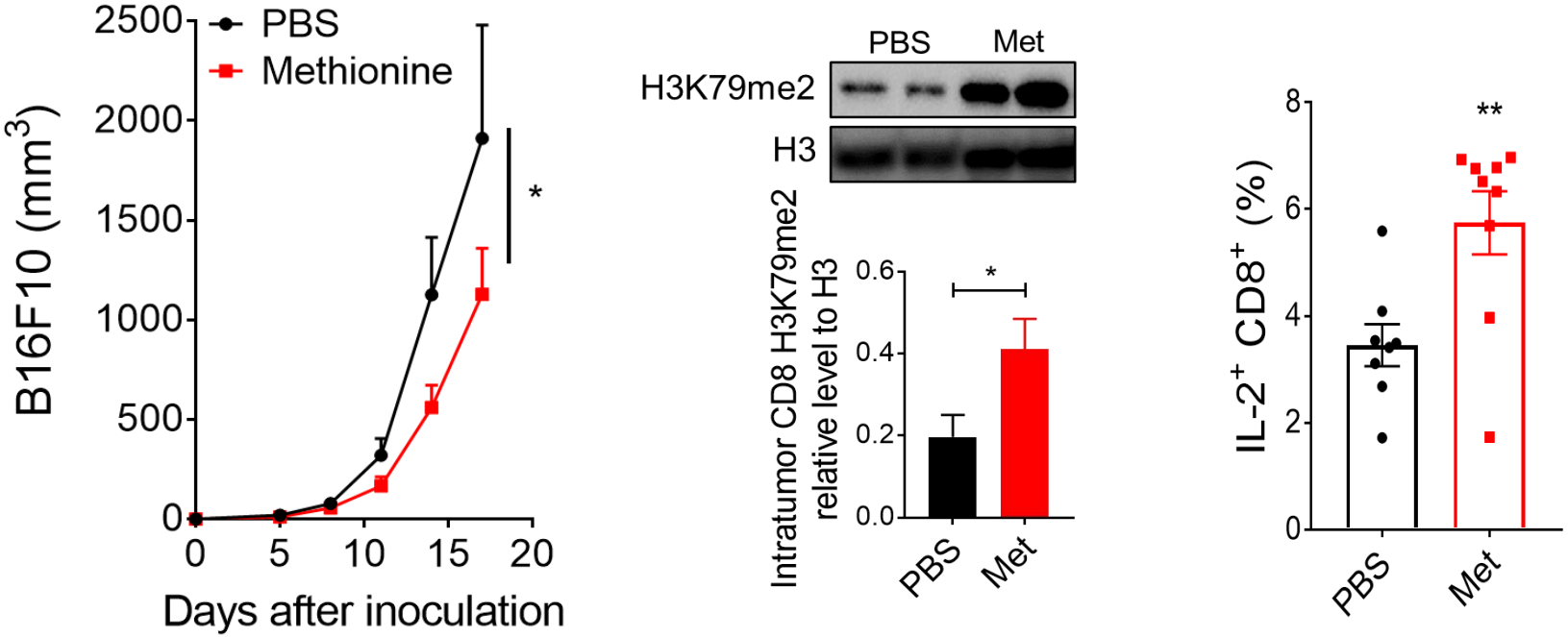


Loss of DOT1L/H3K79me2 impairs T cell anti-tumor immunity

DOT1L specific KO in T cells



Methionine supplementation recovers T cell immunity



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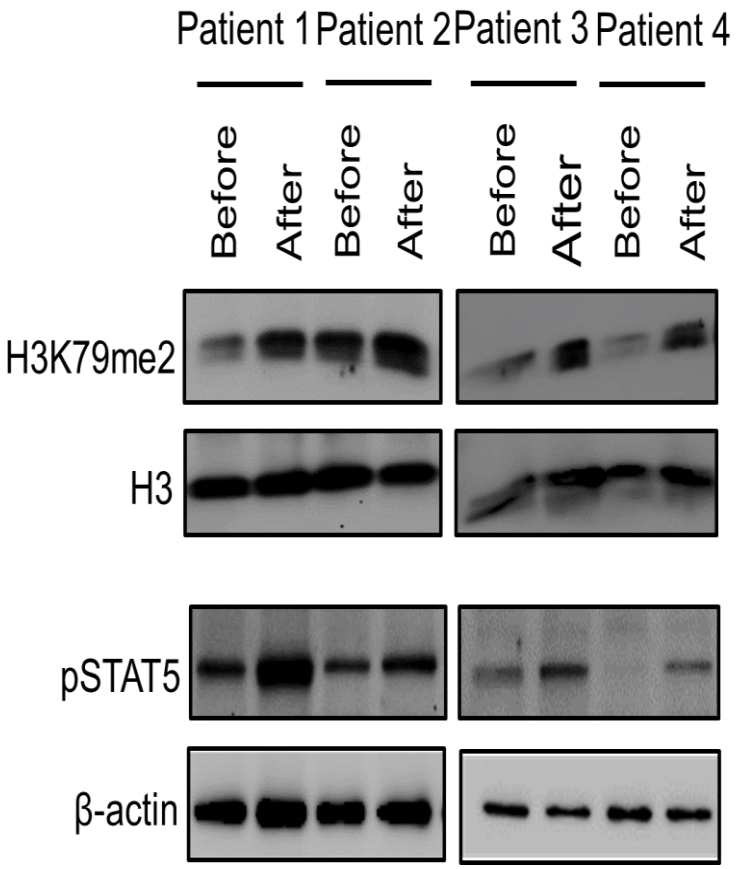

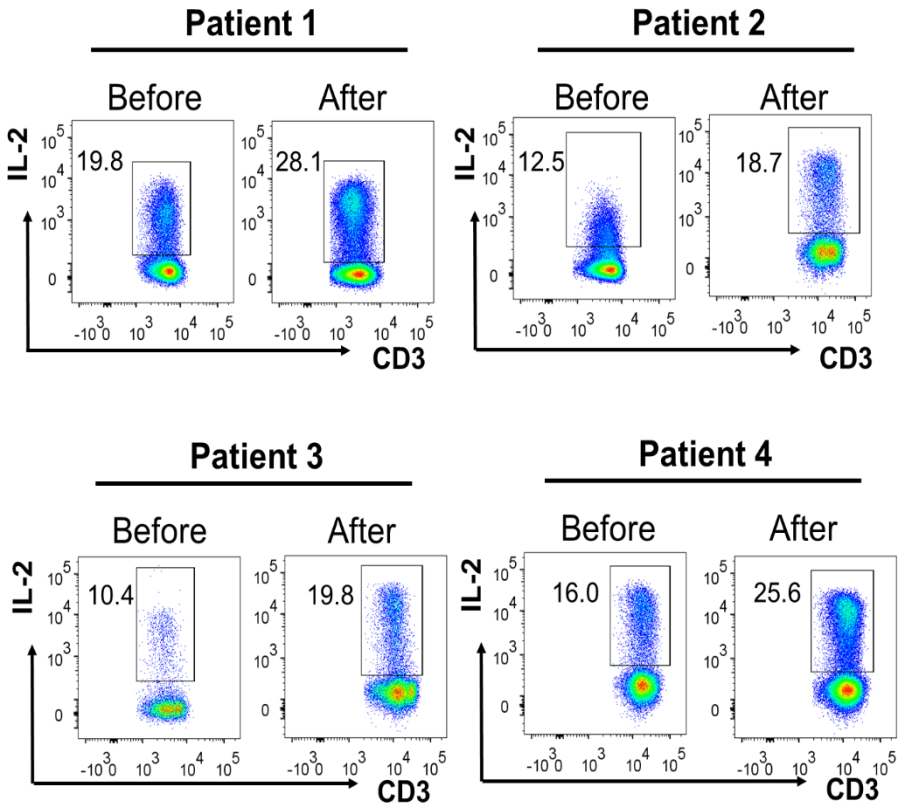

H3K79me2 targets STAT5

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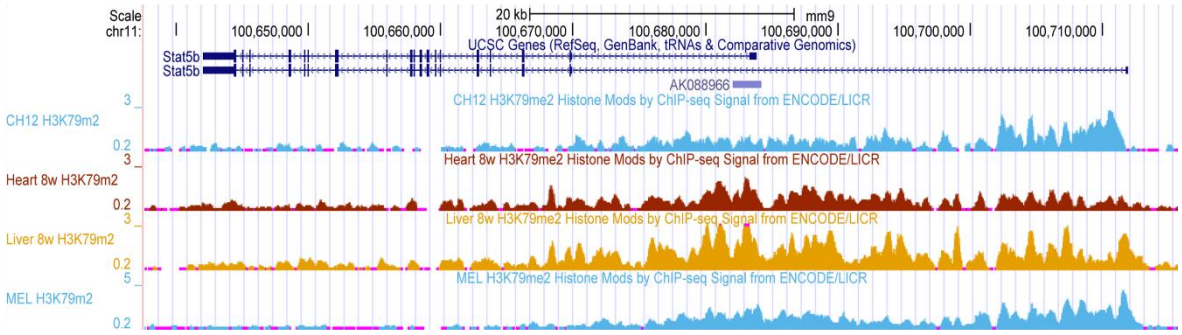

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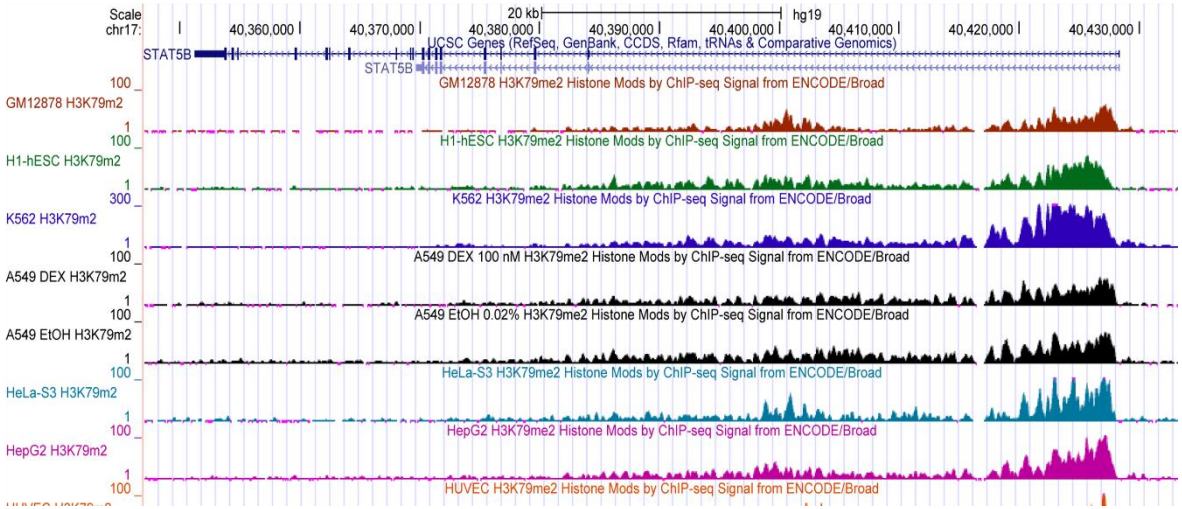

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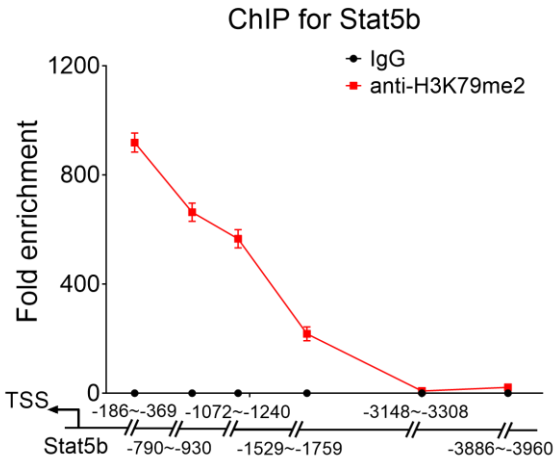

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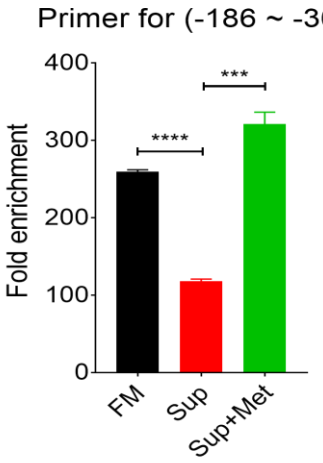
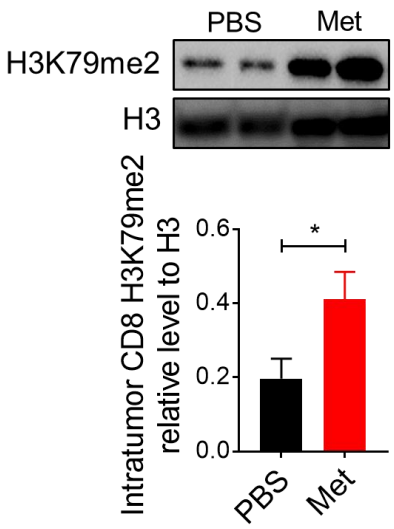
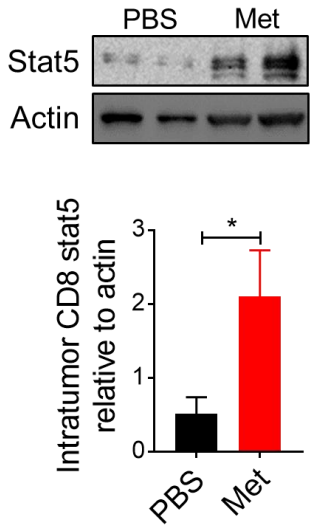
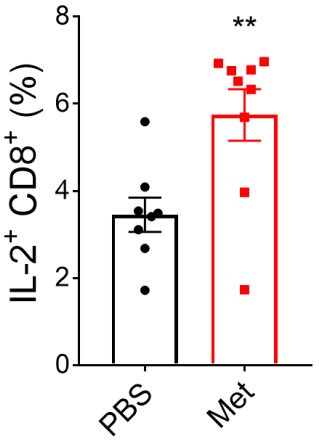


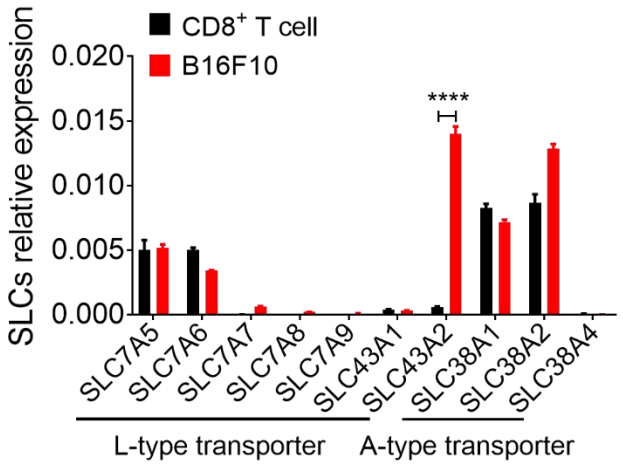
Methionine supplementation recovers T cell STAT5

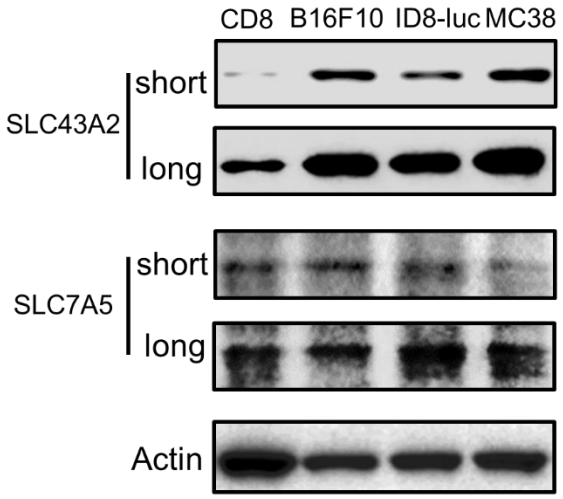


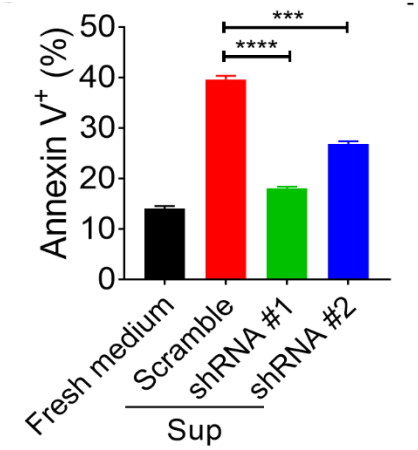


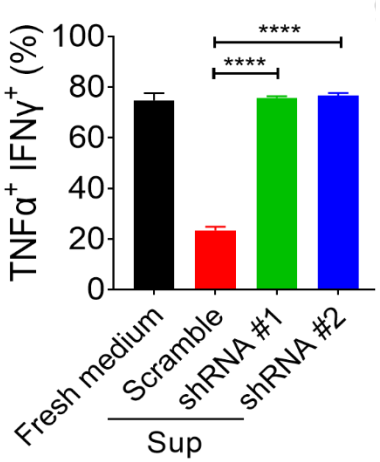


Tumors limit T cell access to methionine via SLC43A2

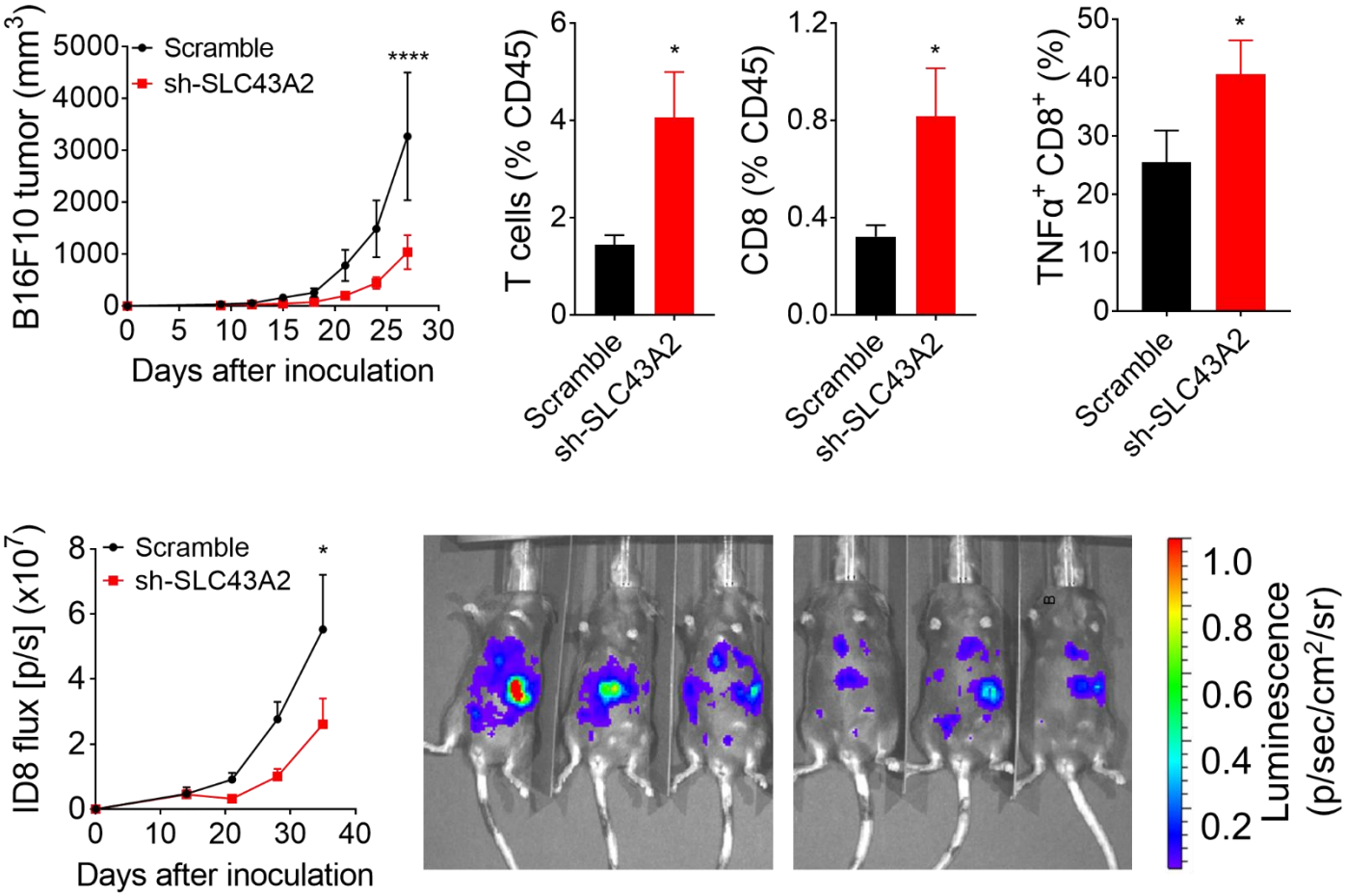




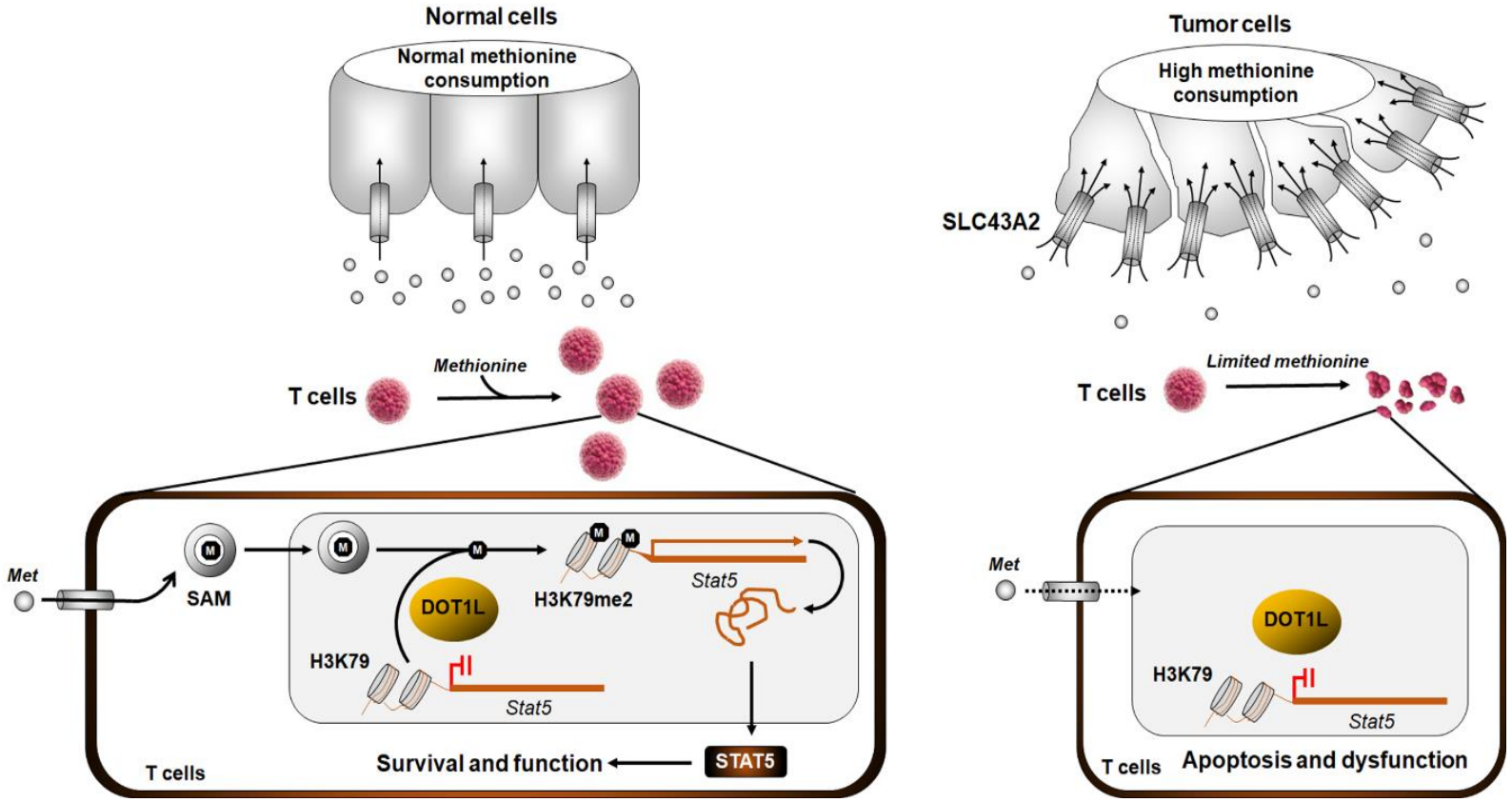




Tumors limit T cell access to methionine via SLC43A2



2: Take-home messages



- Cancer consumes and outcompetes T cells for methionine via SLC43A2.
- Cancer alters methionine metabolism and causes a loss of H3K79me2 in T cells.
- Loss of H3K79me2 impairs T cell STAT5 and function, as well as anti-tumor immunity.
- Methionine supplementation recovers T cell immunity in Tumor.
- Targeting tumor SLC43A2 rescues T cell H3K79me2 and immunity.

Nature, 2020; Molecular Cell, 2021

Starving cancer cells to death?

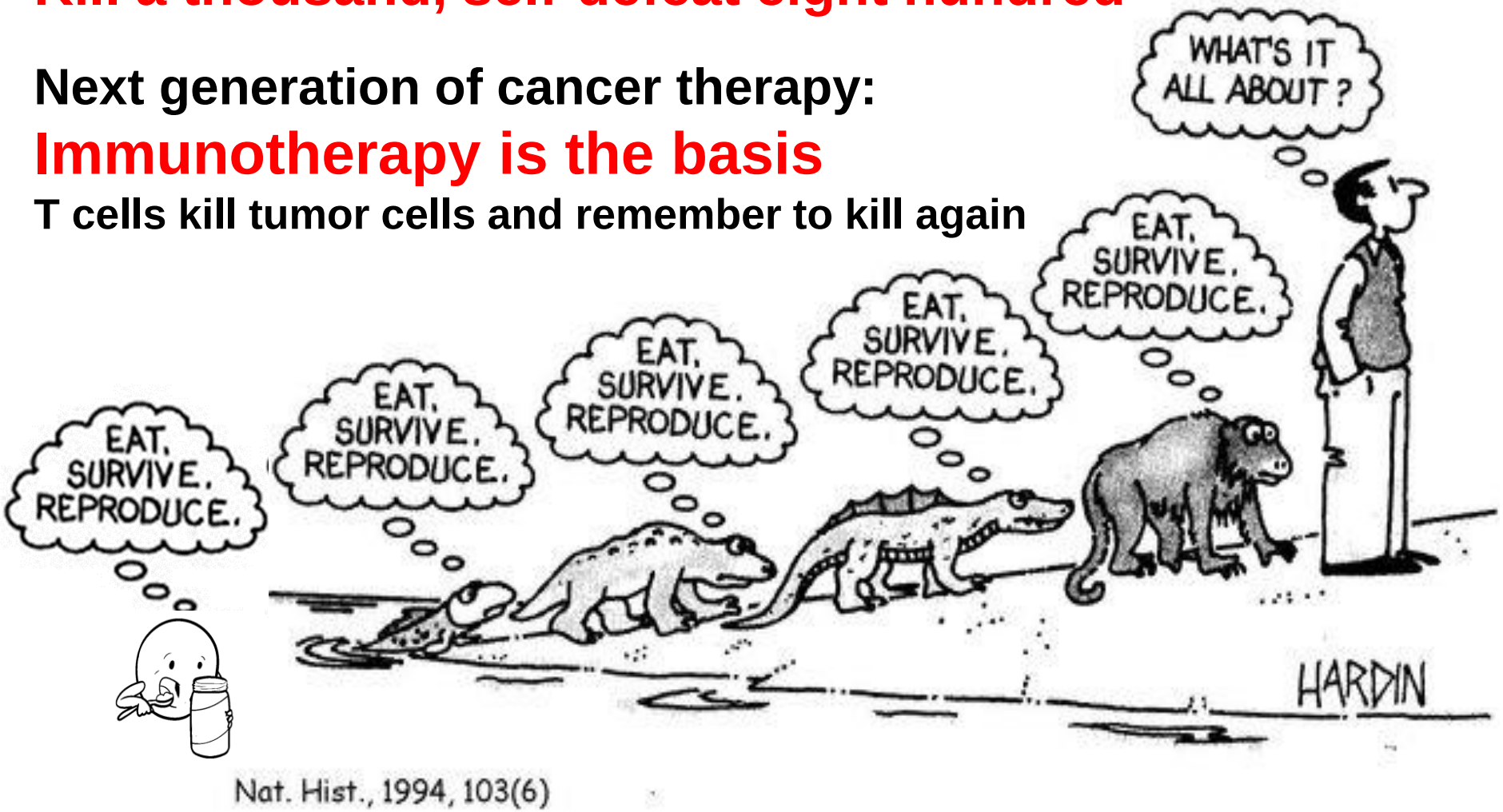
Starving T cells to death?

Kill a thousand, self-defeat eight hundred

Next generation of cancer therapy:

Immunotherapy is the basis

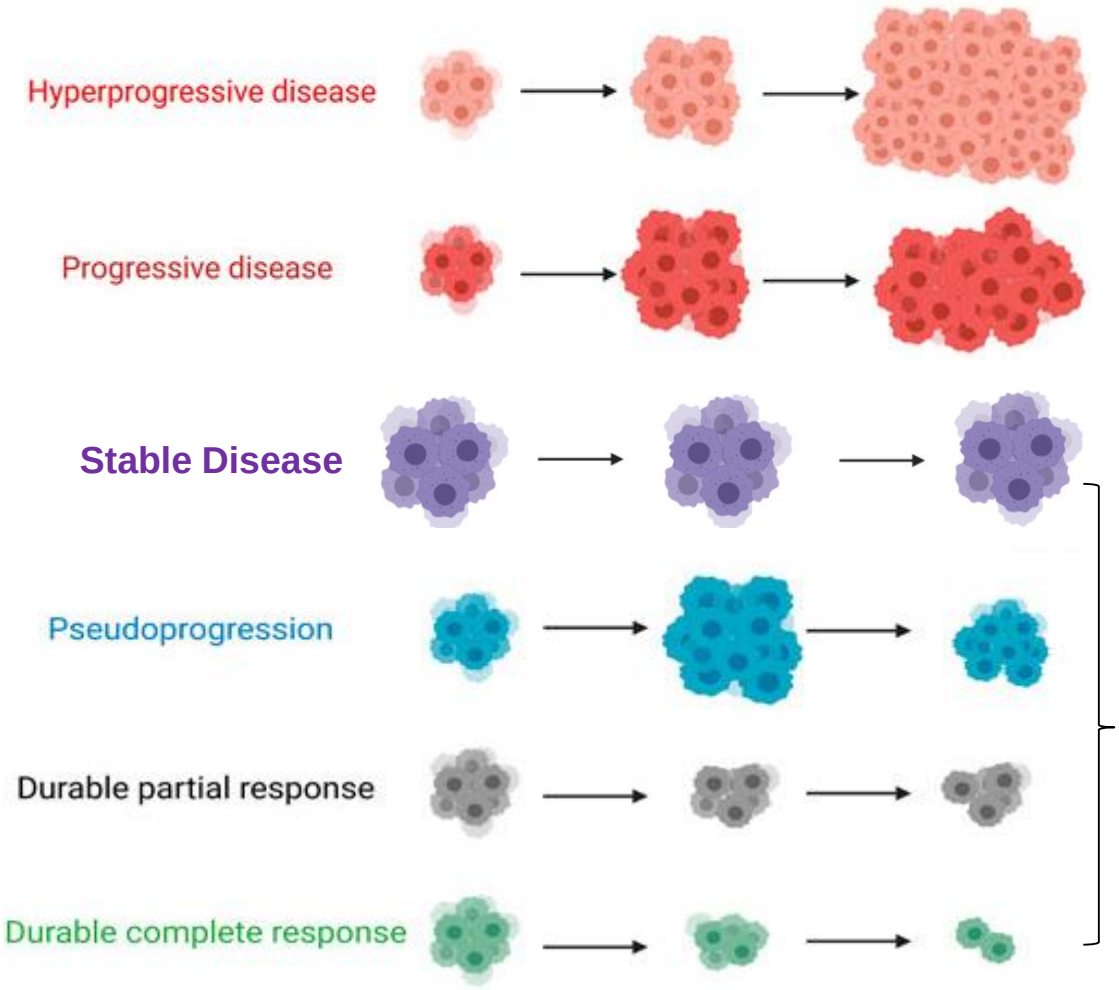
T cells kill tumor cells and remember to kill again



Nat. Hist., 1994, 103(6)

3: Clinical responses to immune checkpoint blockade (ICB) ICB-associated hyperprogressive disease (HPD)

Response **E**valuation **C**riteria **I**n **S**olid **T**umors: **Target lesions:** Maximum 5, No more than 2 from the same organ. **Non-target lesions**: All other lesions and sites of disease



Pathological immune activation?
Active progression?

Immune resistance
Passive progression

Different levels of immune activation and sensitivity

Autoimmune effects?

Liver metastases and immune resistance in human cancer

1/6 Colorectal patients

>3/4 Pancreatic patients

1/4 NSCLC patients

1/4 Melanoma patients

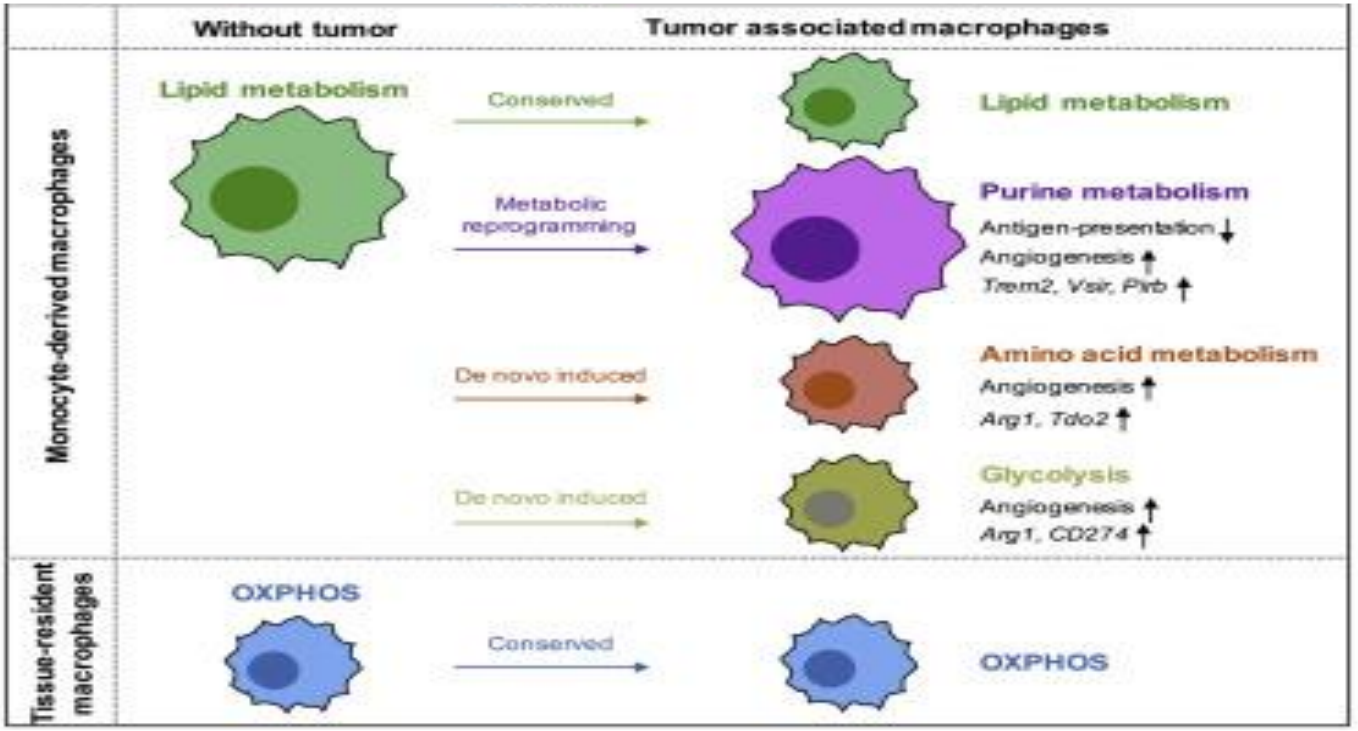
Article | Published: 04 January 2021

Liver metastasis restrains immunotherapy efficacy via macrophage-mediated T cell elimination

Jiali Yu, Michael D. Green ✉, [...] Weiping Zou ✉

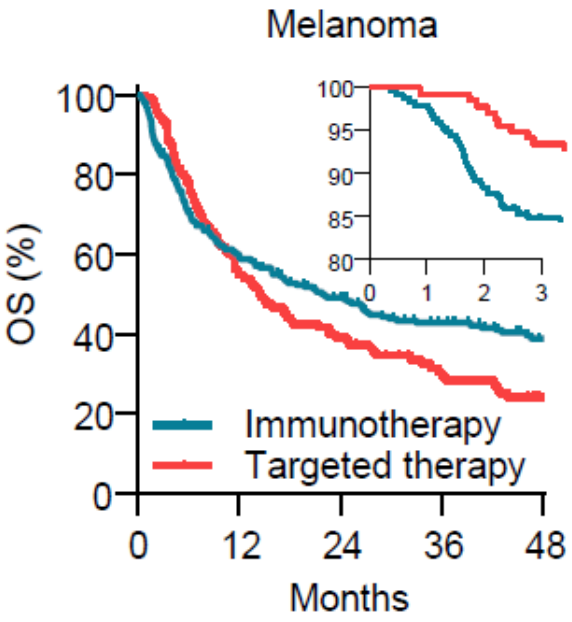
Macrophage-mediated T cell deletion in liver

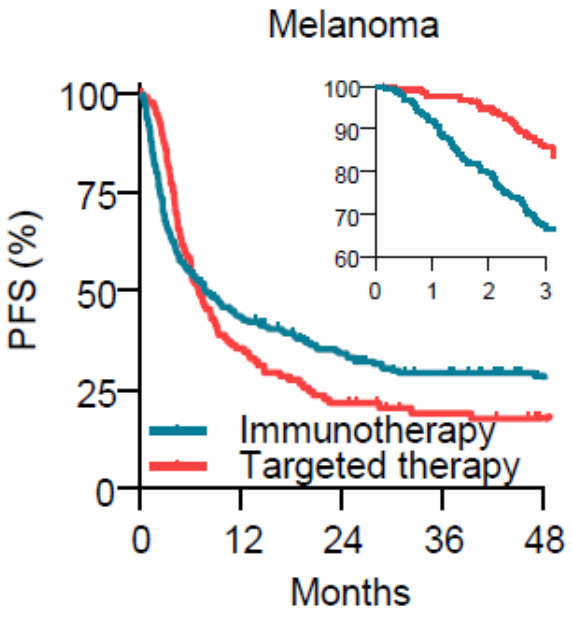
Metabolic characteristics in specific organ sites.
Purine metabolism in tumor associated macrophages.

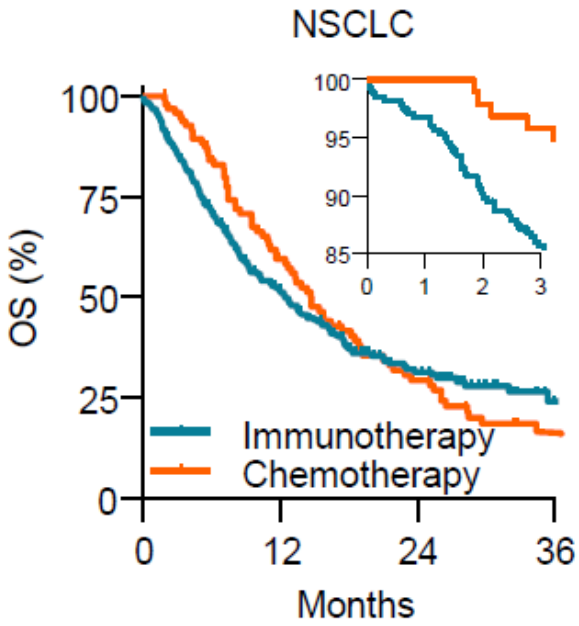


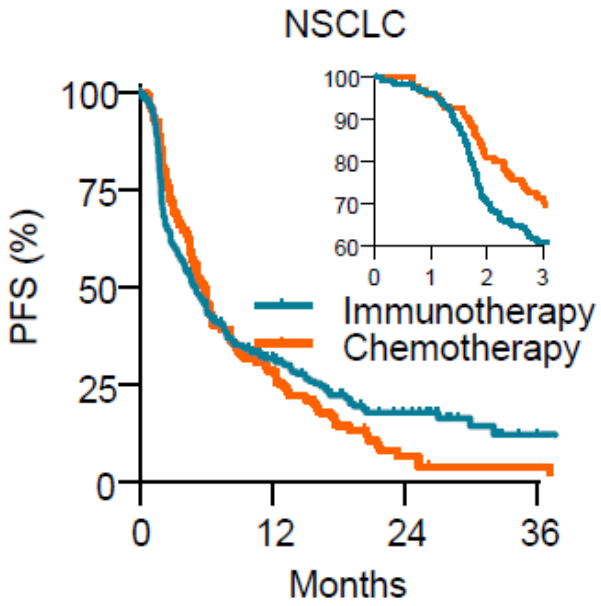
Yu J, Nat Med, 2021; Li, S, Cell Reports, 2022

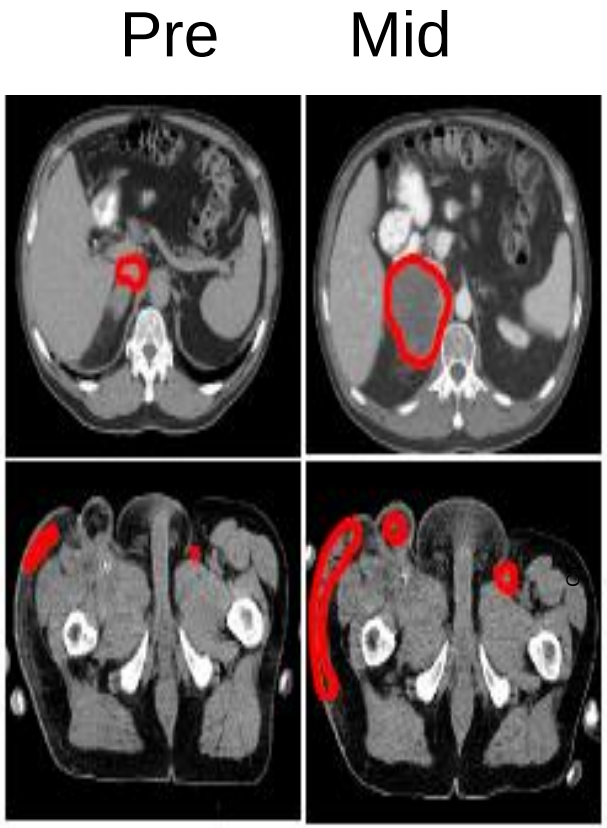
HPD occurs in patients receiving ICB











Ongoing studies on HPD

Rate of HPD?

Associated with a specific therapy?

Associated with a specific patient subset?

Animal models?

Cellular mediators?

Molecular mediators?

Clinical predictors?

Current data:

(a) HPD is a feature of ICB

(b) HPD may be caused by oncogenic signaling activation (e.g. β-catenin) and triggered by cross-talk between immunogenic and metabolic pathways.

Spranger S, Nature, 2015

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Ovarian Cancer Research Fund; Rivkin Ovarian Cancer Research Center