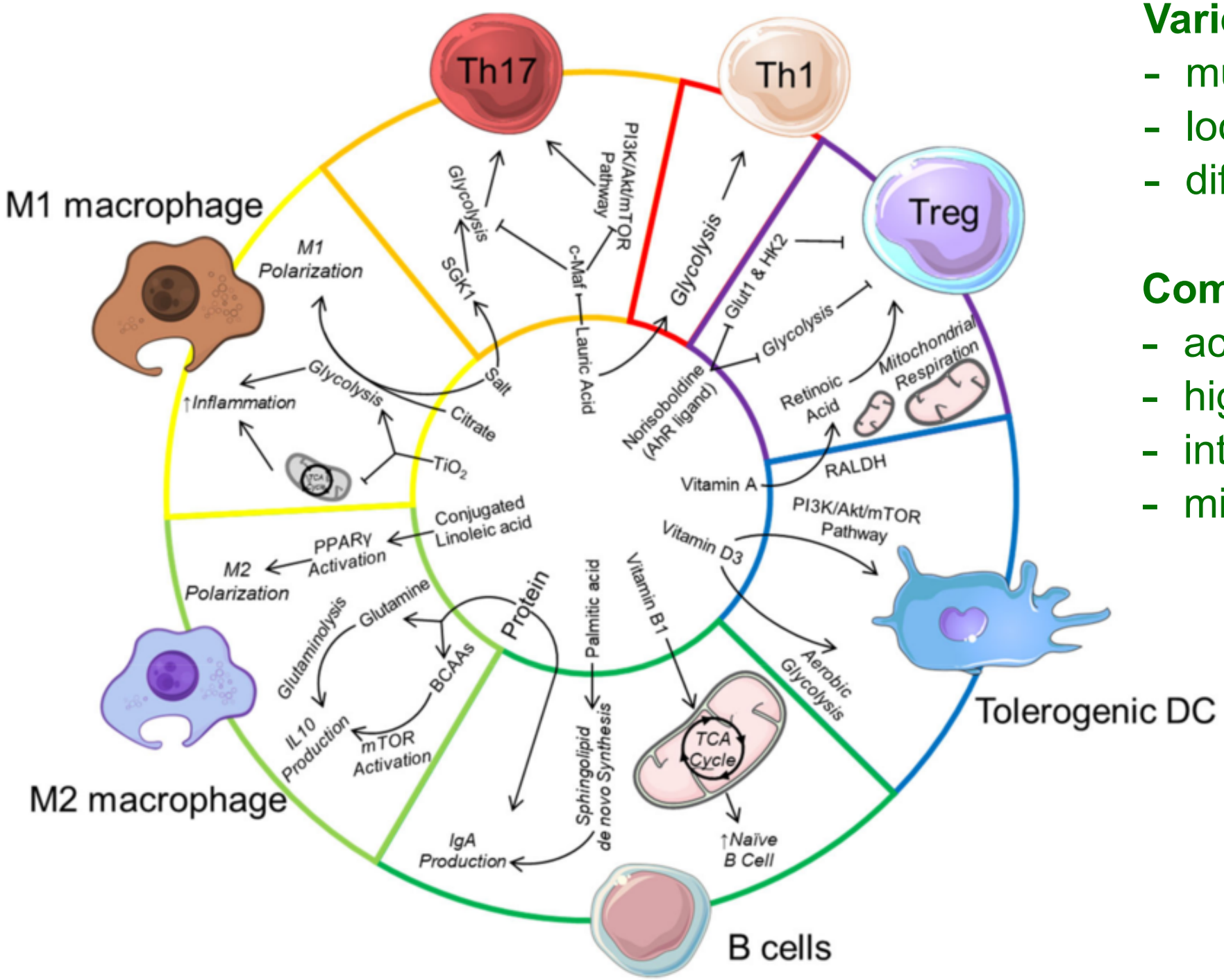
Metabolic reprogramming of immune cells

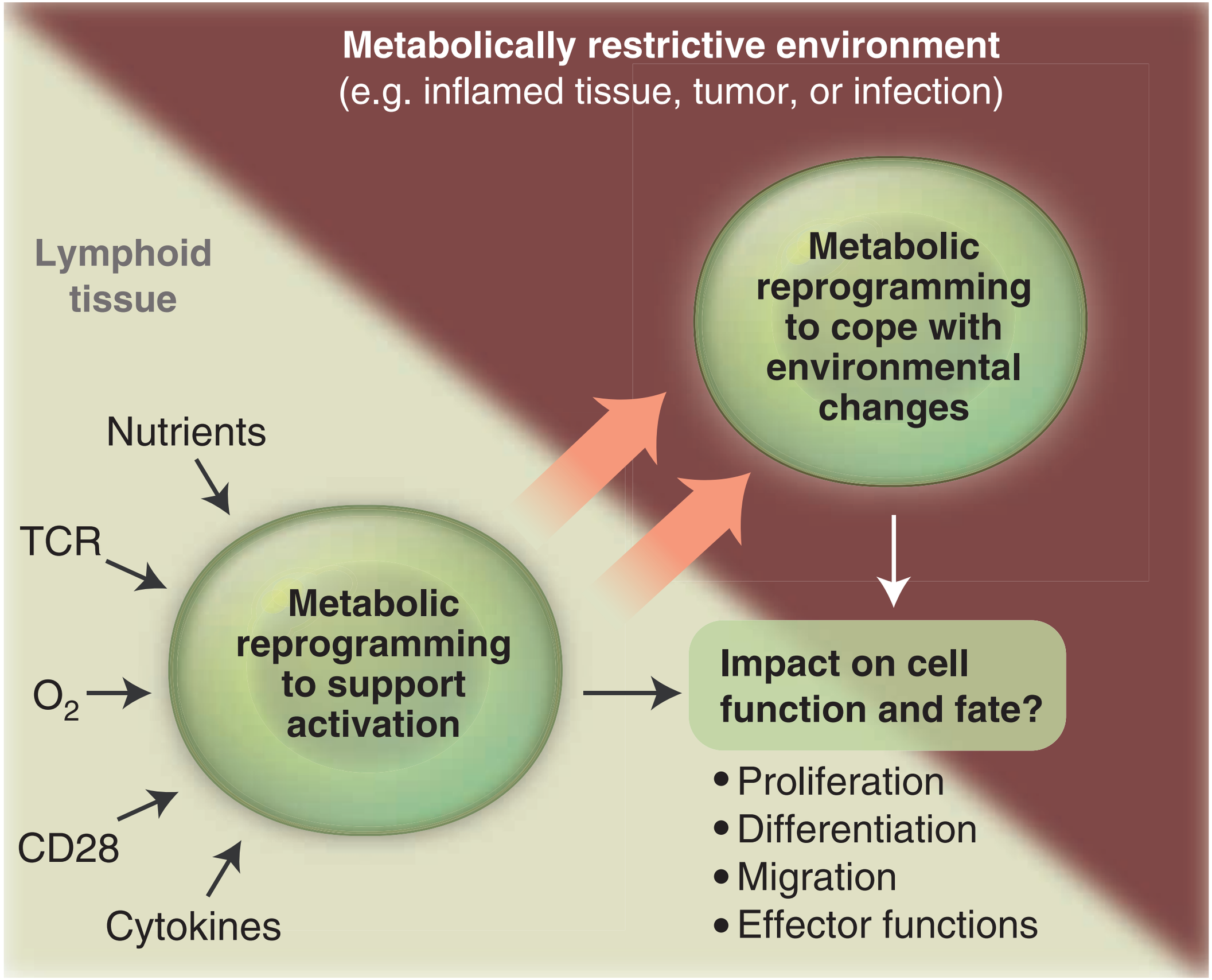
Also known: *IMMUNOMETABOLISM*

Immunometabolism across the immune system



Variety of cell types
- multiple phenotypes
- local microenvironments
- different functions

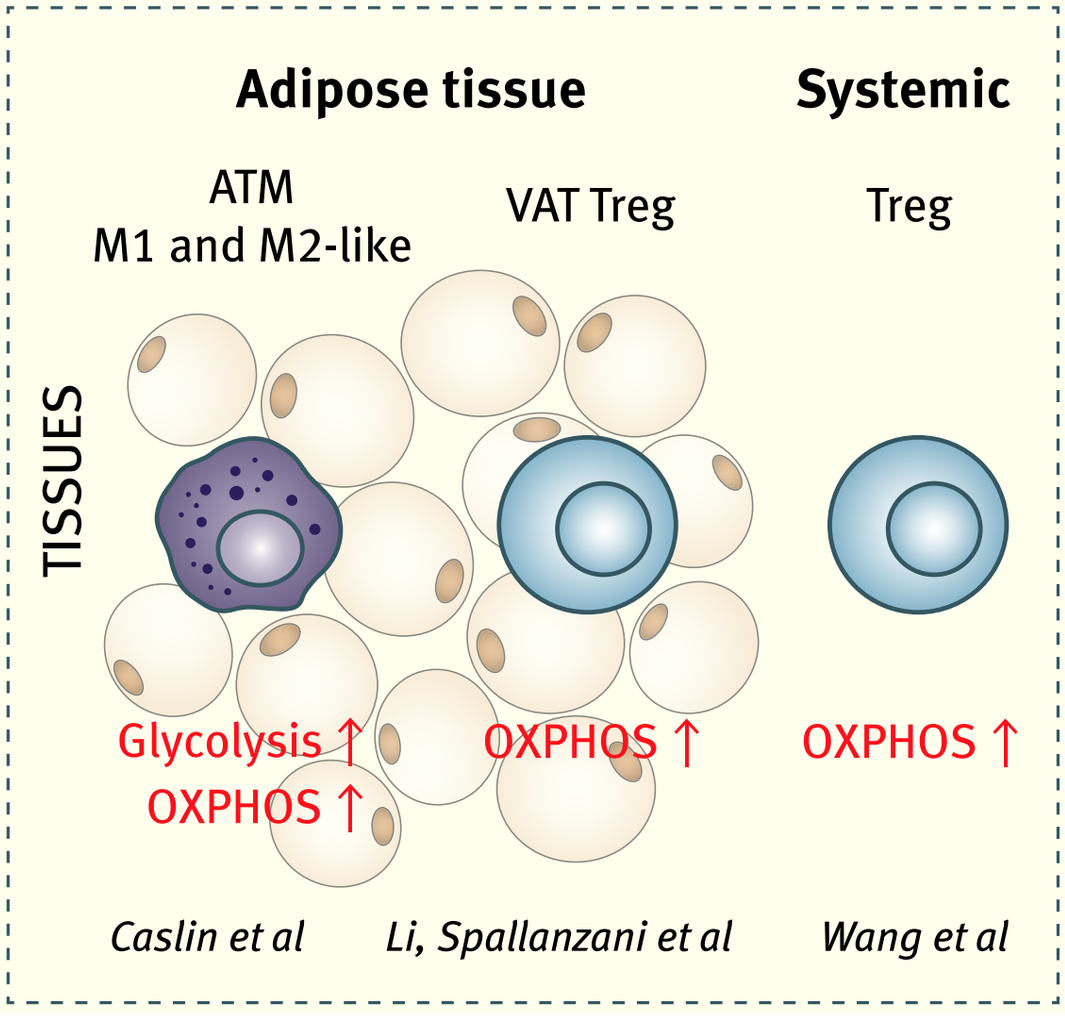
Common denominators
- actionable
- highly plastic
- interactive
- migrate and adapt



Pearce et al, ***Science****, 2013*

Immunometabolism or metabolic immunology

- Pathogenic defense is necessary for survival
- The body's immune response involves key changes to metabolic processes
- Immune mediators, such as cytokines, also dictate changes in metabolism



Early observations that inflammatory cytokines are induced in obese adipose tissue and that these cytokines contribute to metabolic disease

Makovski et al, ***Immunol Rev****, 2020*

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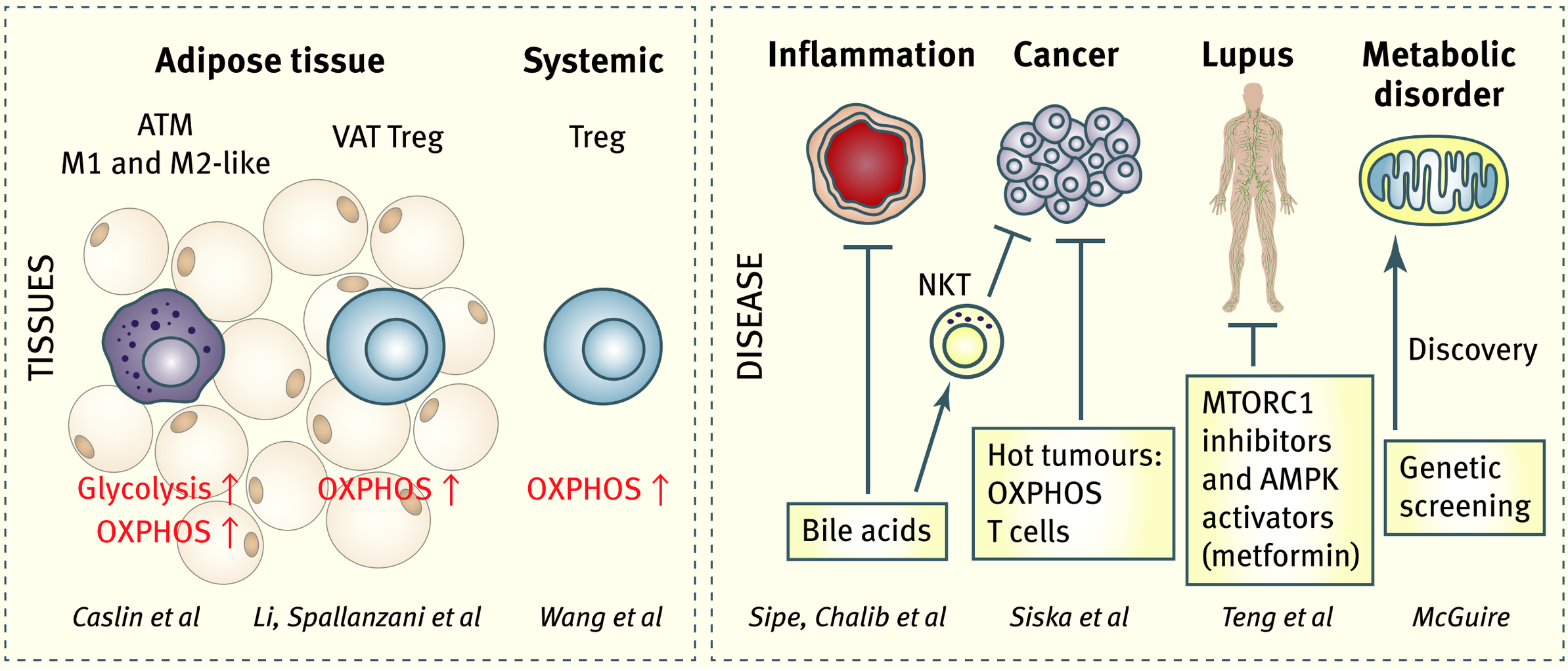
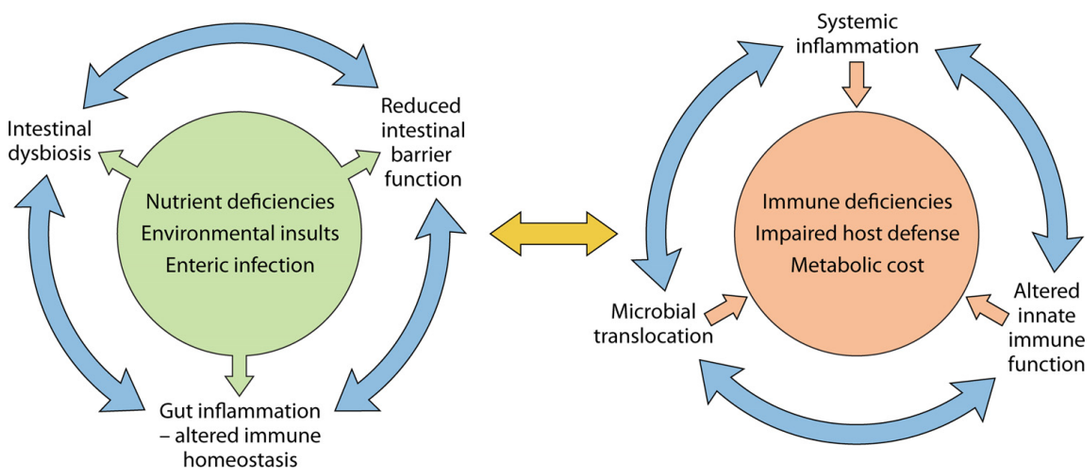


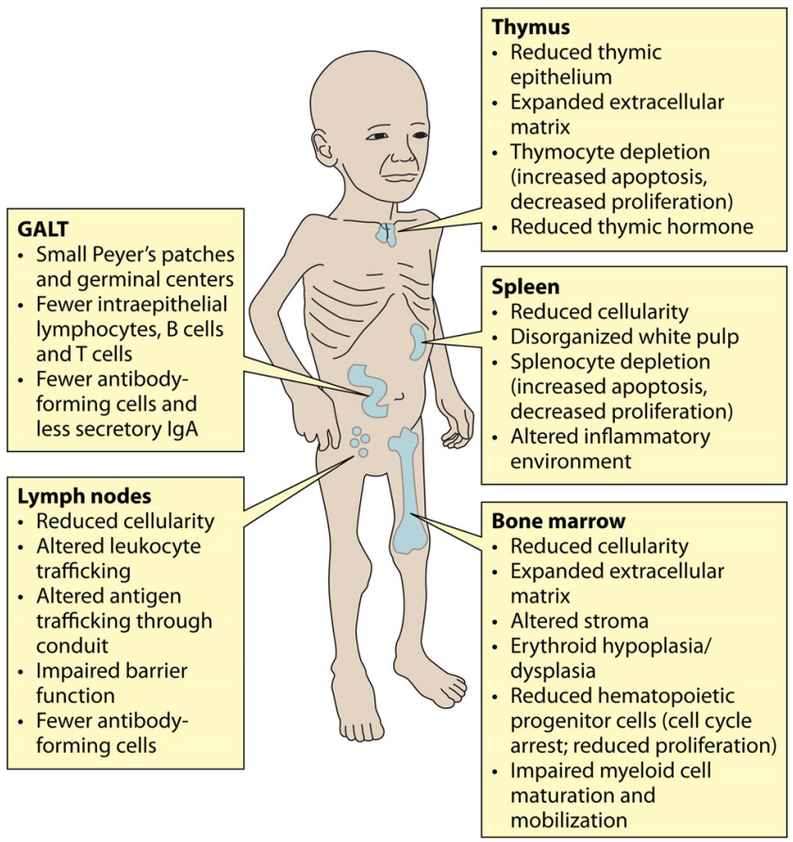
Early observations that inflammatory cytokines are induced in obese adipose tissue and that these cytokines contribute to metabolic disease

Makovski et al, ***Immunol Rev****, 2020*

Impact of Childhood Malnutrition on Host Defense and Infection

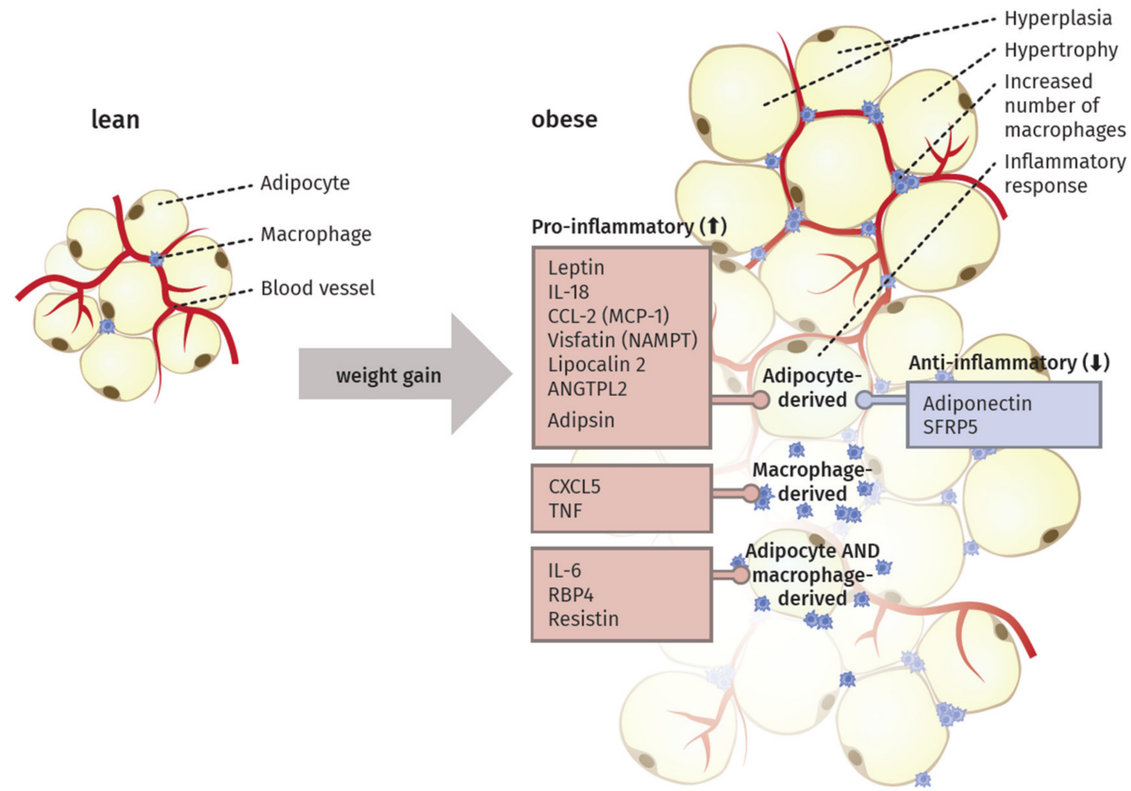
Marwa K. Ibrahim,[a] Mara Zambruni,[b,c] Christopher L. Melby,[d]
Peter C. Melby[b,c,e,f,g,h]





Increased Adipose Tissue Expression of Tumor Necrosis Factor-α in Human Obesity and Insulin Resistance

Gökhan S. Hotamisligil,* Peter Arner,‡ José F. Caro,§ Richard L. Atkinson,‖ and Bruce M. Spiegelman
**Dana Farber Cancer Institute and Department of Cell Biology Harvard Medical School, Boston, Massachusetts 02115; ‡Karolinska Institute, Department of Medicine Huddinge University Hospital S-141 86 Huddinge, Sweden; §Jefferson Medical College, Department of Medicine, Philadelphia, Pennsylvania 19107; and ‖Medical College of Wisconsin, Department of Medicine Madison, Wisconsin 53706*



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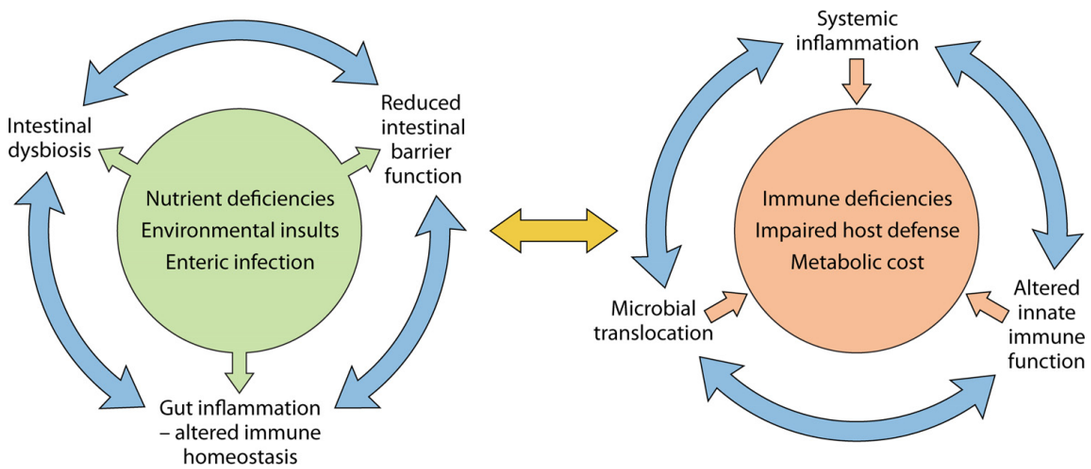

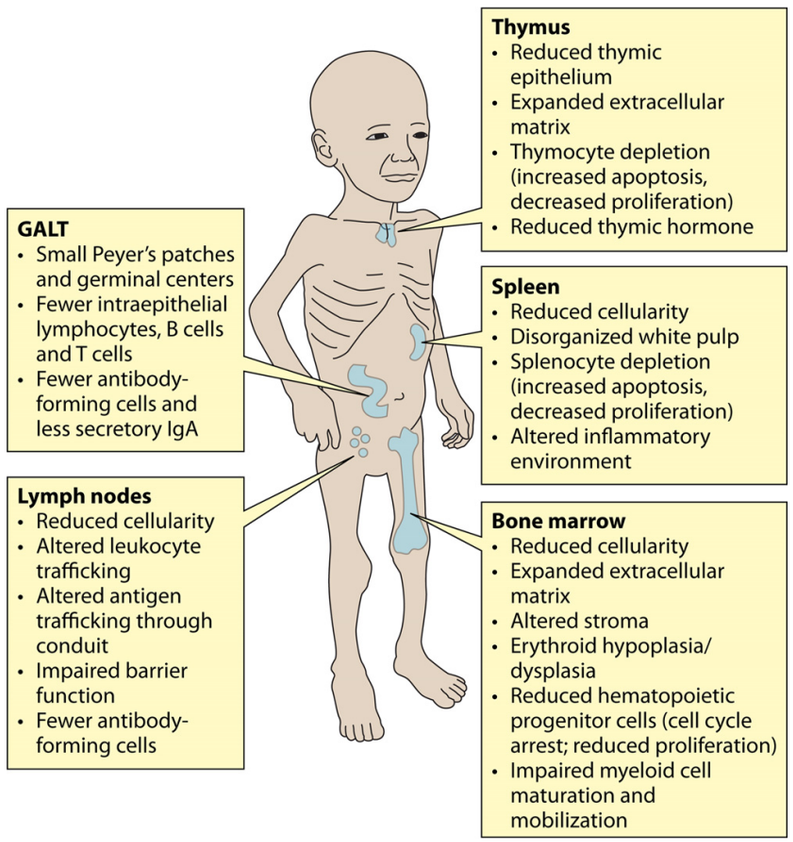

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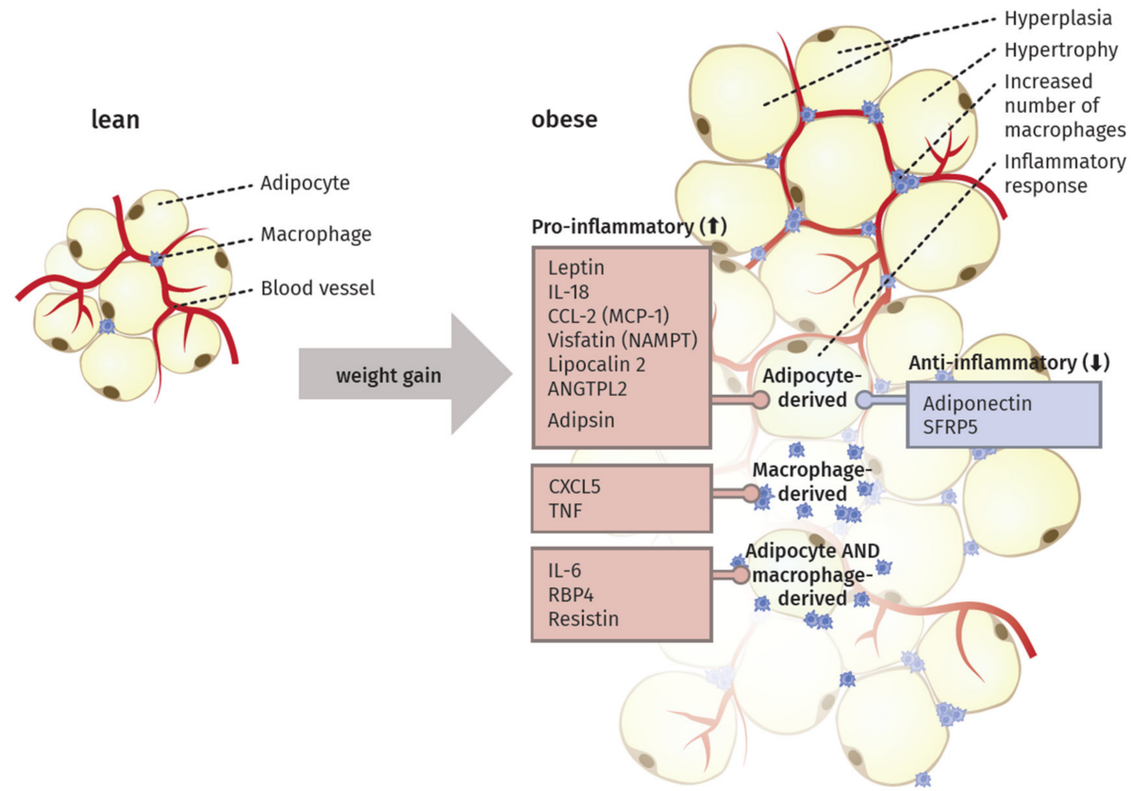
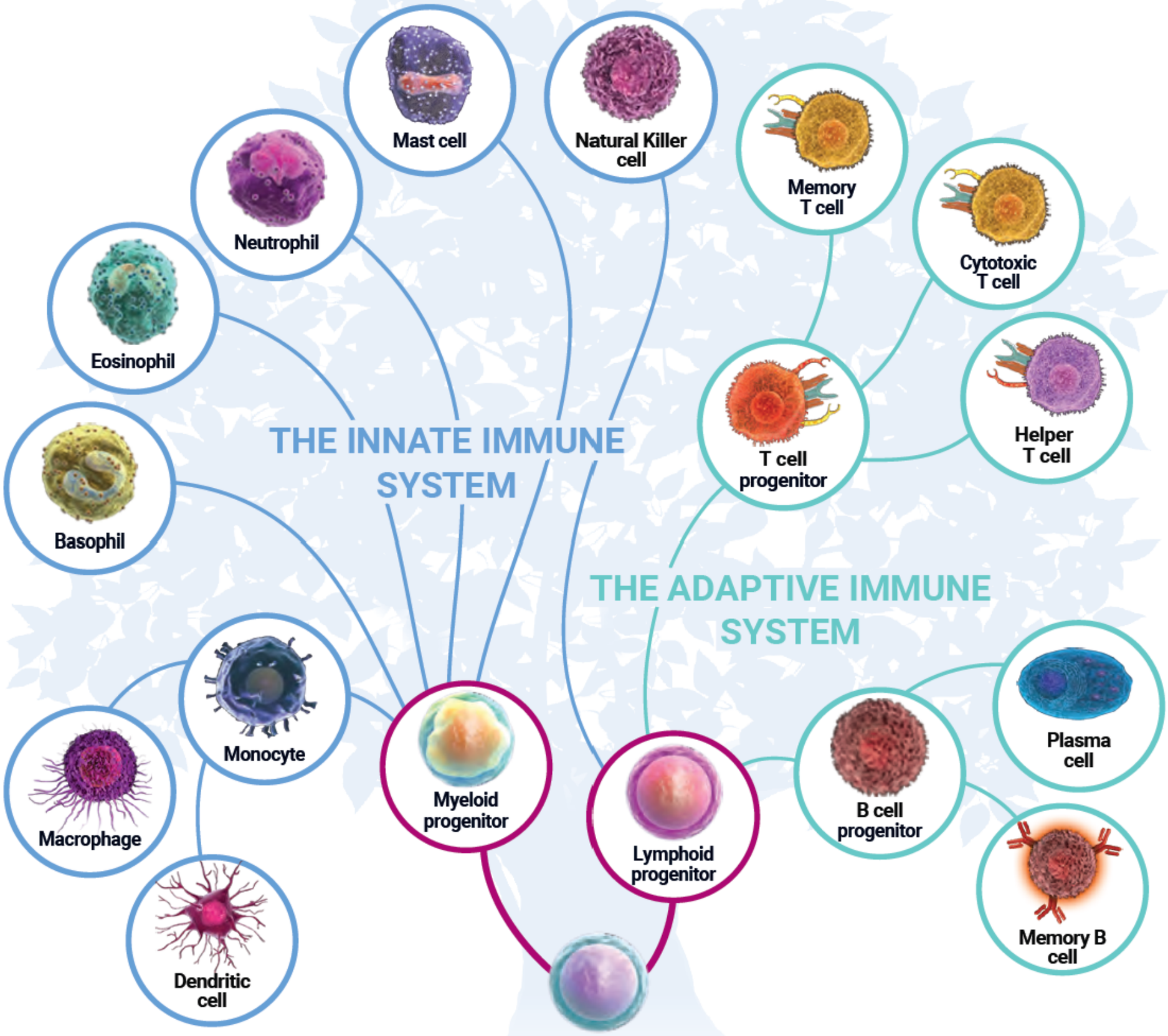
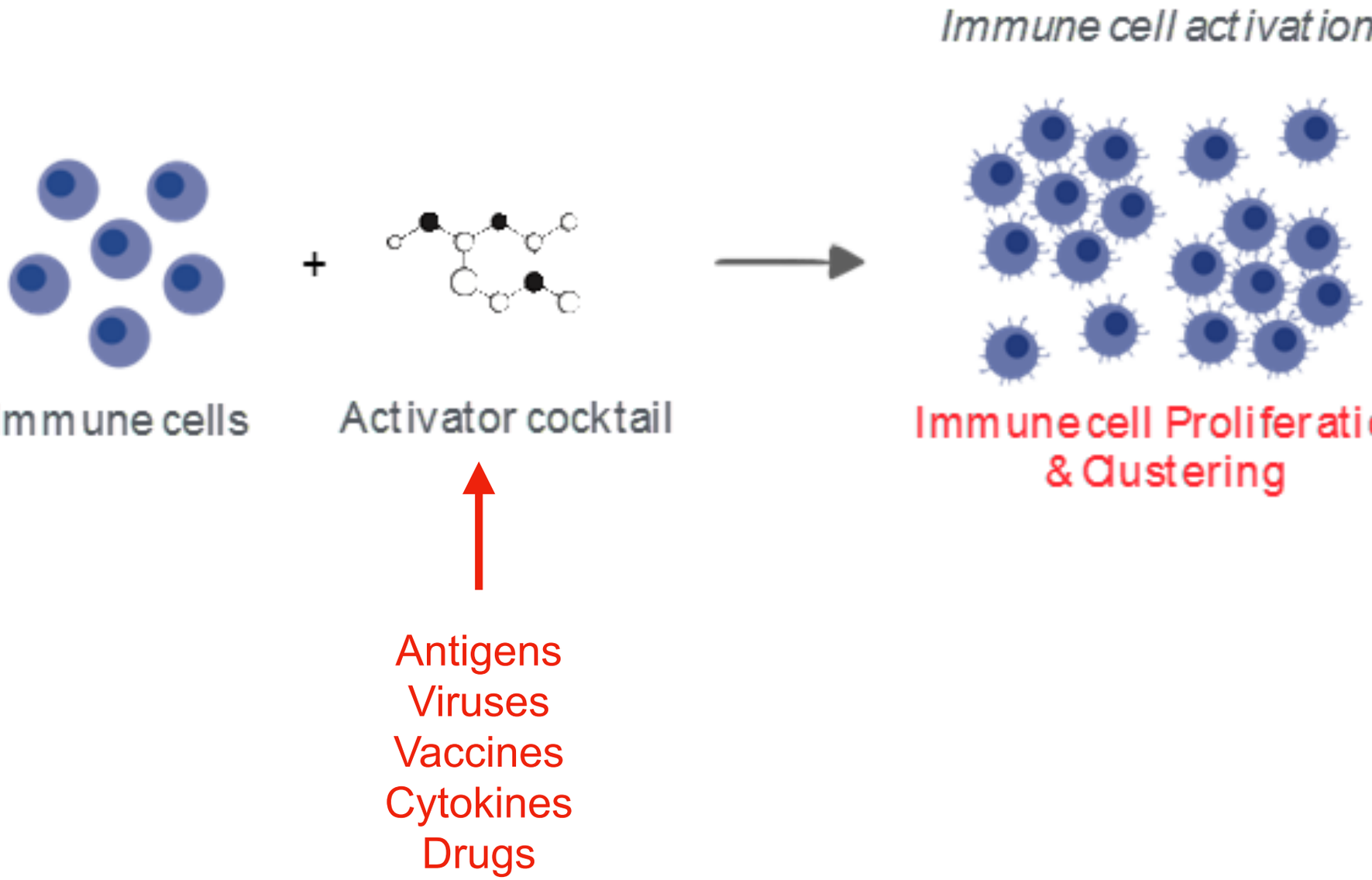


In addition to metabolic tissues regulating immune cells, the metabolism of immune cells themselves is highly regulated. Signaling pathways are activated to promote aerobic glycolysis in stimulated immune cells and play key roles to reprogram metabolism from catabolic oxidative pathways to anabolic pathways.

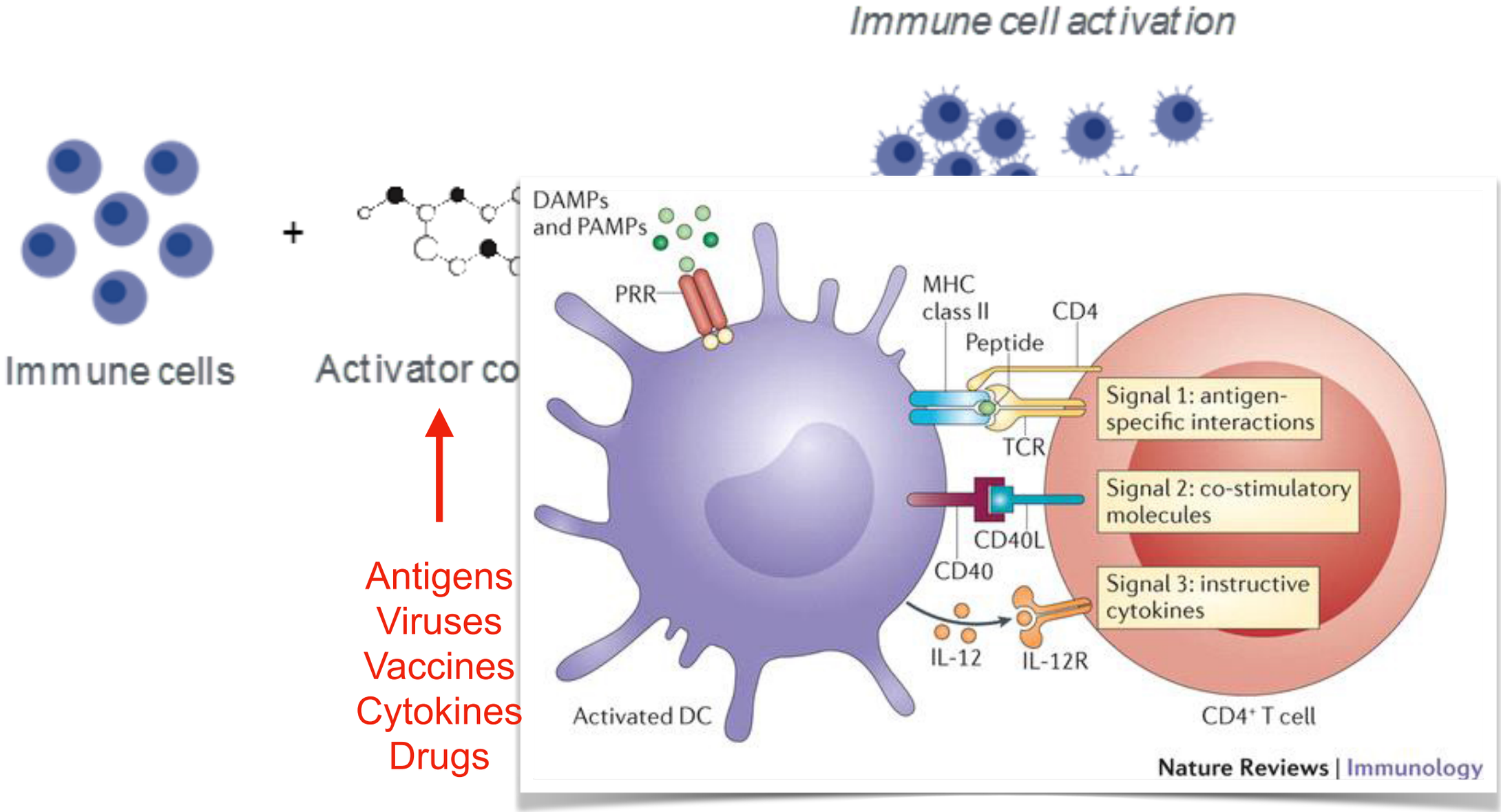

THE INNATE IMMUNE SYSTEM
THE ADAPTIVE IMMUNE SYSTEM
Mast cell
Natural Killer cell
Neutrophil
Eosinophil
Basophil
Memory T cell
Cytotoxic T cell
T cell progenitor
Helper T cell
Monocyte
Macrophage
Dendritic cell
Myeloid progenitor
Lymphoid progenitor
B cell progenitor
Plasma cell
Memory B cell
Hematopoietic stem cell

Activation stimulates proliferation



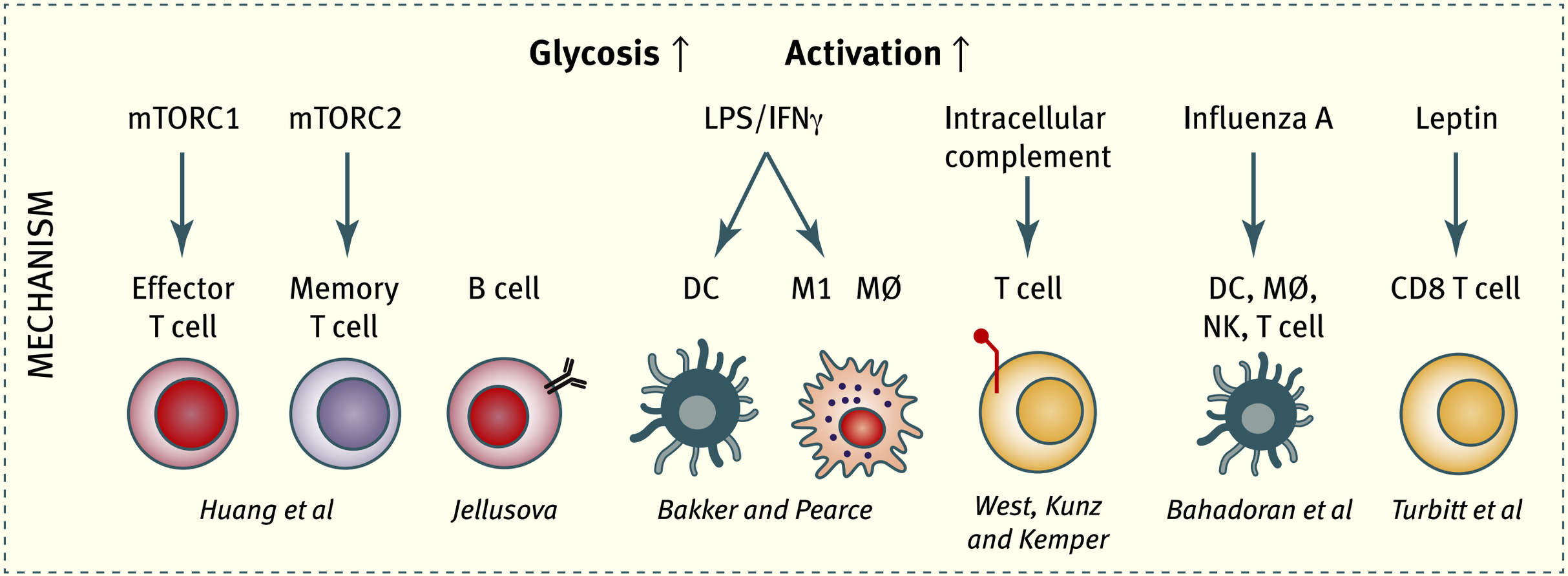
During an immune response, activated cells of the immune system, such as T lymphocytes, undergo rapid expansion in order to fight infection or disease. Many interactions also occur between activated immune cells (e.g., T cell interactions with antigen-presenting cells and interactions between T cells themselves).

Activation stimulates proliferation



During an immune response, activated cells of the immune system, such as T lymphocytes, undergo rapid expansion in order to fight infection or disease. Many interactions also occur between activated immune cells (e.g., T cell interactions with antigen-presenting cells and interactions between T cells themselves).

Activation stimulates glycolysis



Increased glycolysis can be considered a hallmark metabolic change in most immune cells undergoing rapid activation, for instance, in response to stimulation of PRRs, cytokine receptors or antigen receptors. Enhanced glycolysis enables the immune cell to generate sufficient ATP and biosynthetic intermediates to proliferate.

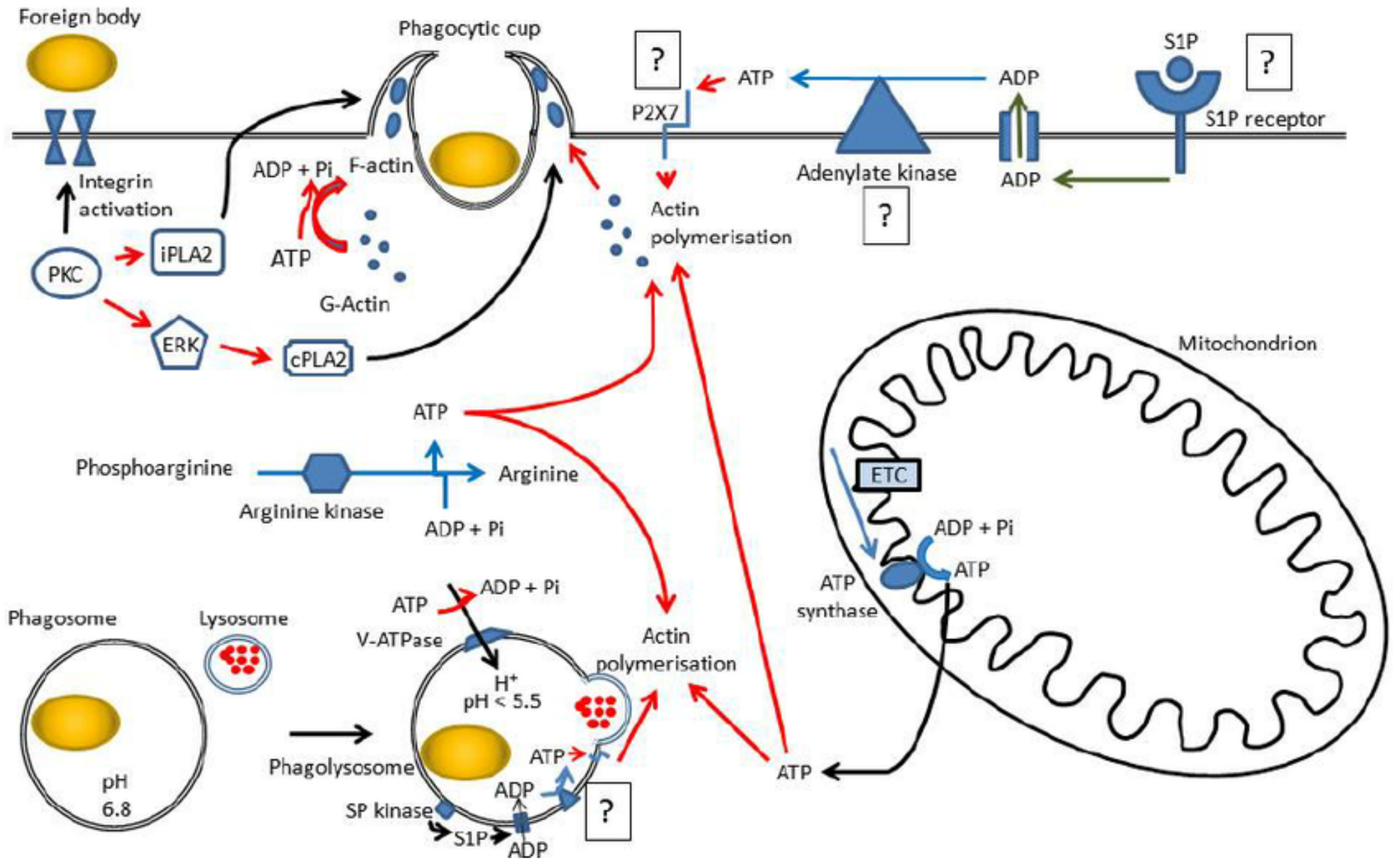
Makovski et al, ***Immunol Rev****, 2020*

There is abundant evidence that metabolic pathways are closely tied to cell signaling and differentiation which leads different subsets of immune cells to adopt unique metabolic programs specific to their state and environment. **In this way, metabolic signaling drives cell fate.**

It is also apparent that microenvironment greatly influences cell metabolism. Immune cells adopt programs specific for the tissues where they infiltrate and reside. **In this way, nutrient availability impacts effector function.**

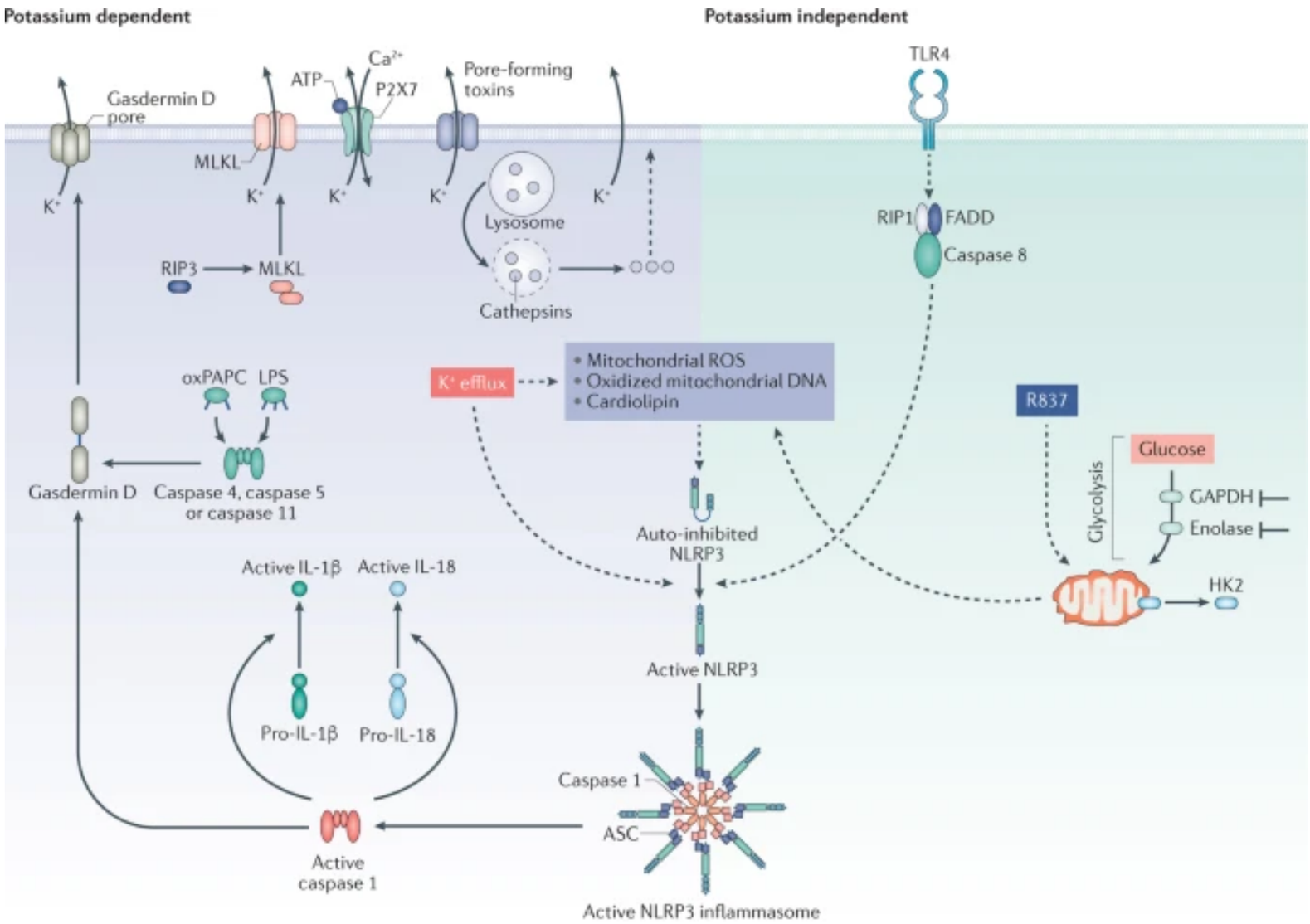
Metabolism in macrophage function

Enhanced glycolysis enables macrophages to generate sufficient ATP and biosynthetic intermediates to carry out its particular effector functions. For macrophages this includes phagocytosis and inflammatory cytokine production.



Metabolism in macrophage function

The NLRP3 inflammasome is a crucial regulator of caspase 1, which generates mature IL-1β, as well as active IL-18, and induces a type of cell death called pyroptosis.
The inflammasome is activated in response to mitochondrial (and glycolytic) activity.



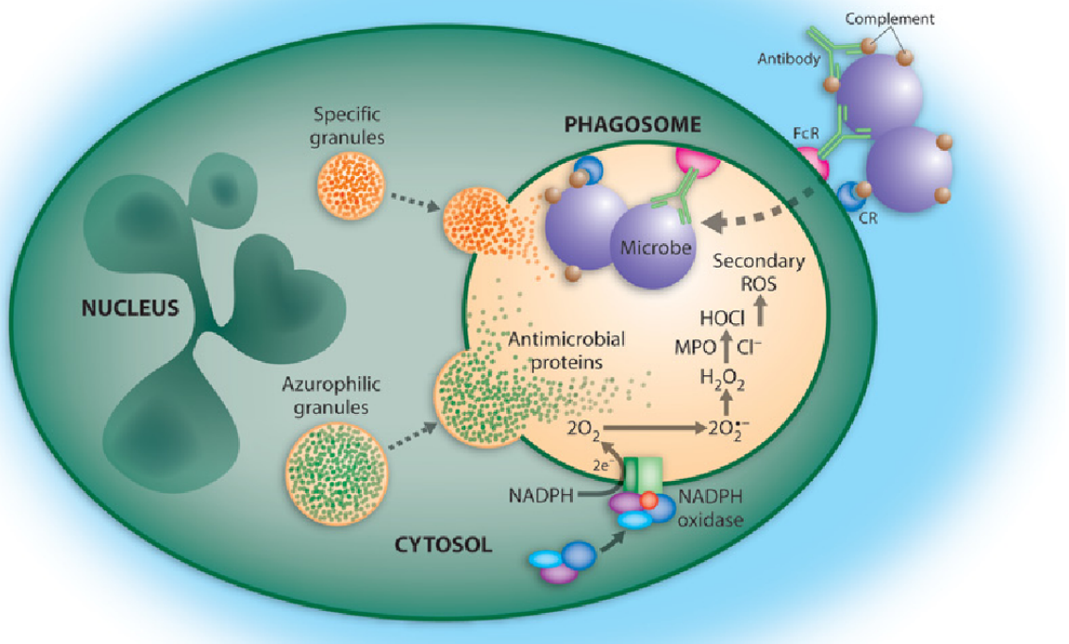
Mangan et al, ***Nat Rev Drug Discov****, 2018*

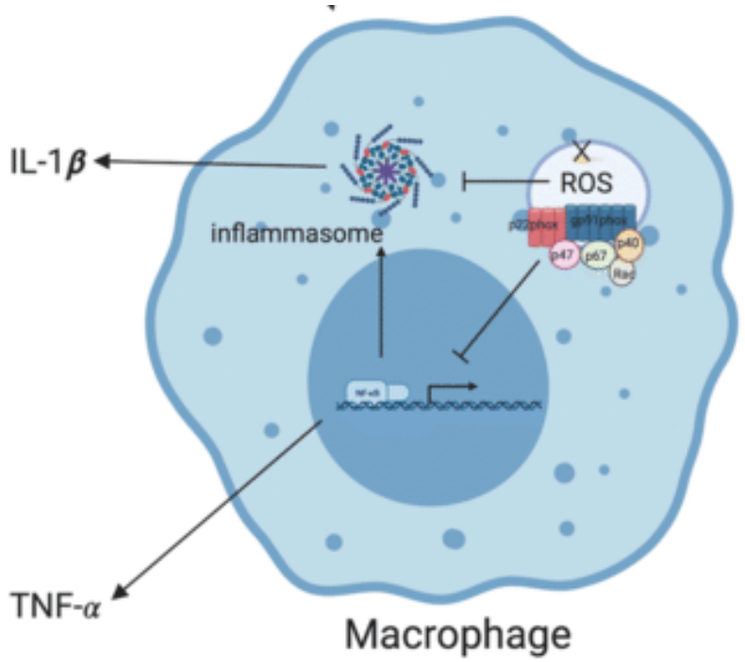
Macrophages adapt their redox status in response to infection

NADPH has multiple functions in immune cells.

It is used by the NADPH oxidase to generate reactive oxygen species (ROS) during the respiratory burst, but as a counter-balance it is also used to generate glutathione and other antioxidants.

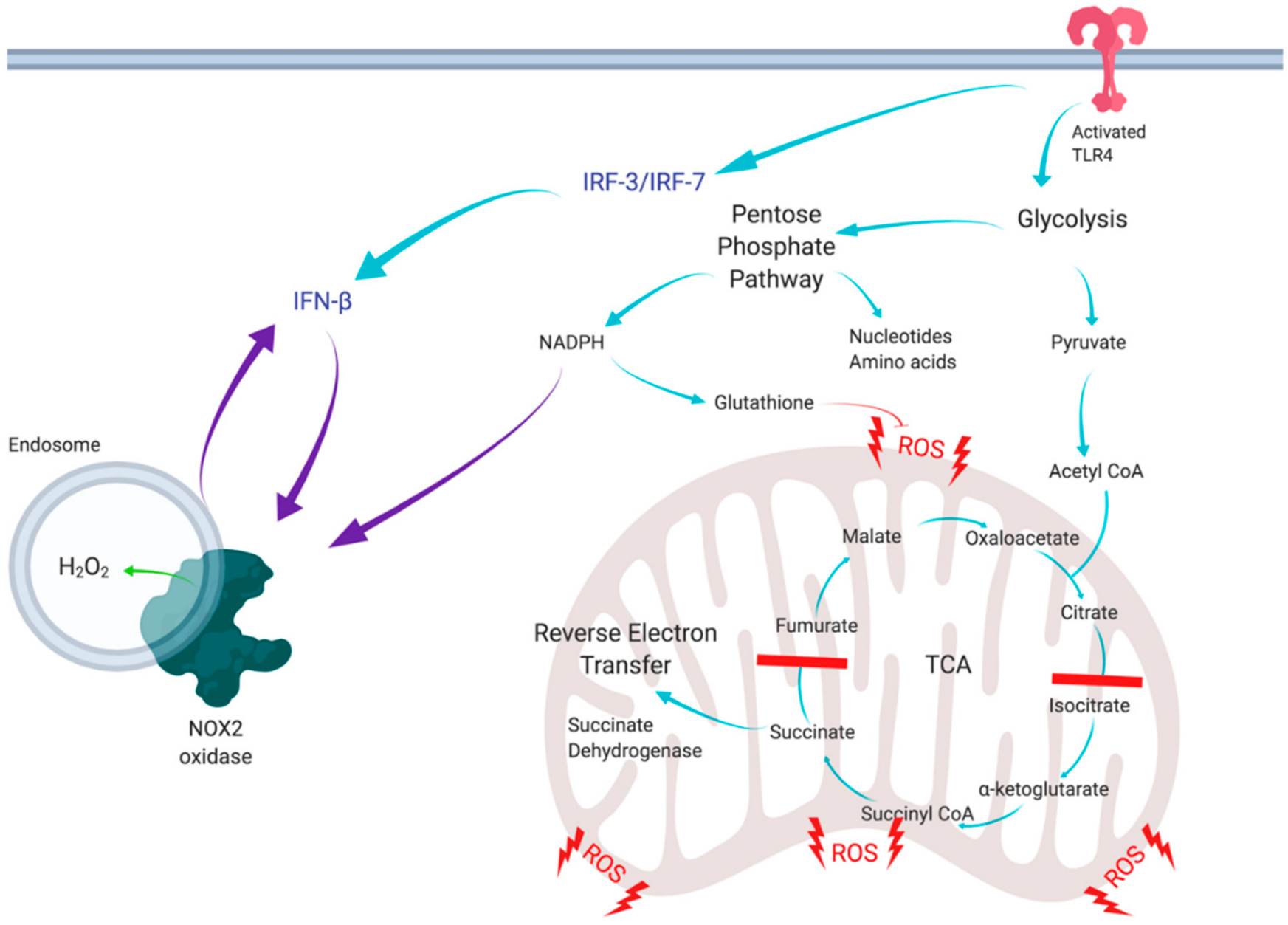
During an infection, macrophages and neutrophils probably require both of these NADPH-dependent functions — rapid ROS production to clear the infectious agent followed by induction of antioxidants to prevent excessive tissue damage.



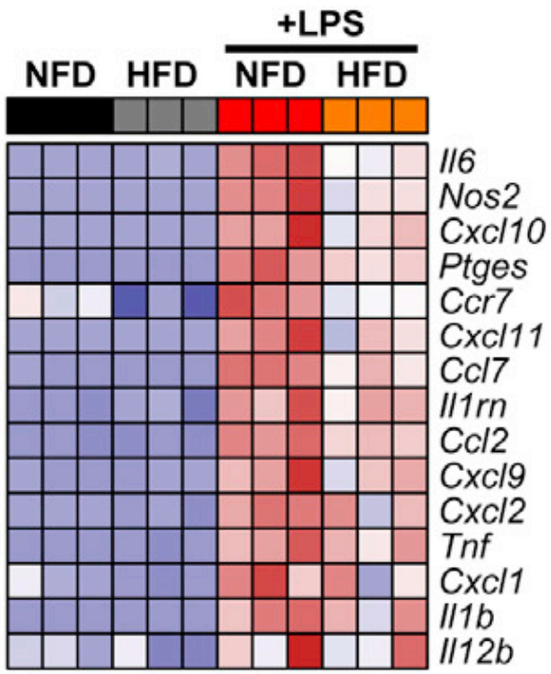


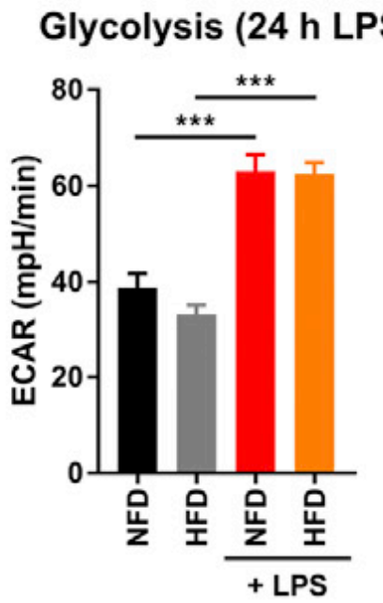
Macrophages adapt their redox status in response to infection

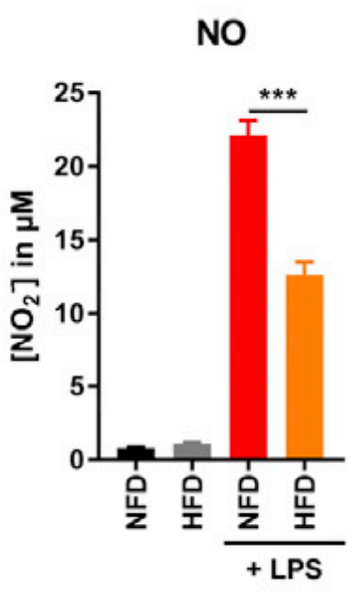
LPS-activated macrophages induce PPP to elevate NADPH availability



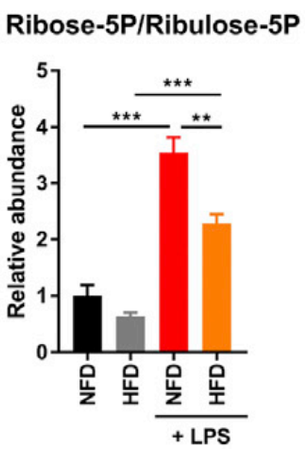
Hypercholesterolemia impairs macrophage redox status

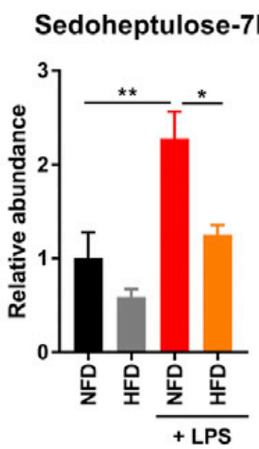


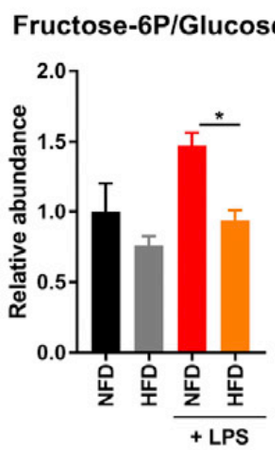




Hypercholesterolemia Attenuates Inflammatory Macrophage Responses without Major Changes in Glycolysis or the TCA Cycle







Hypercholesterolemia Reduces LPS-Mediated Induction of the PPP in Macrophages

Baardman et al, ***Cell Rep****, 2018*

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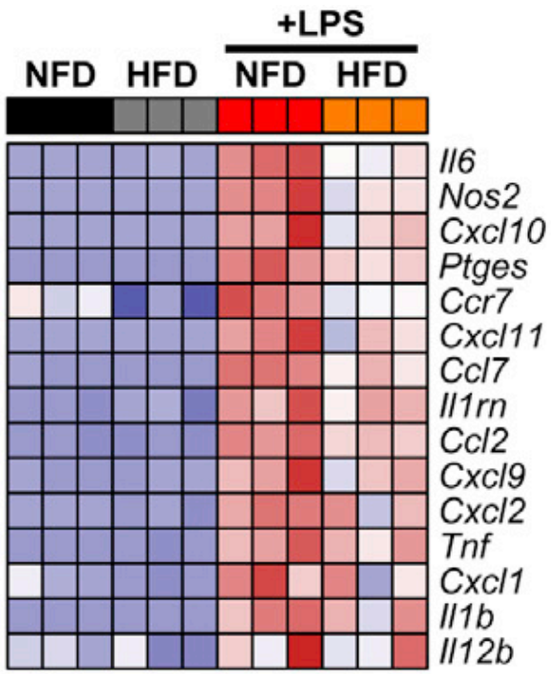

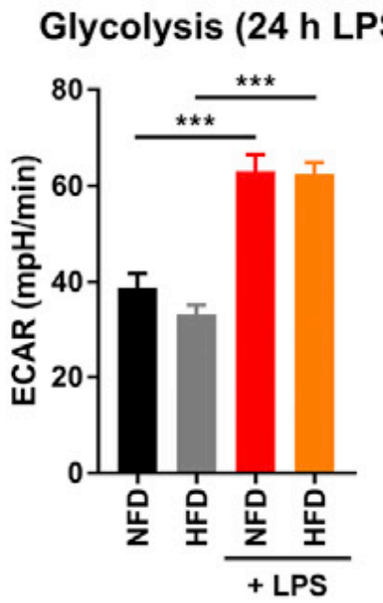

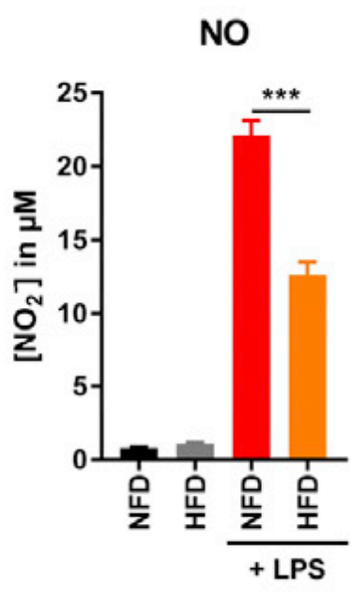

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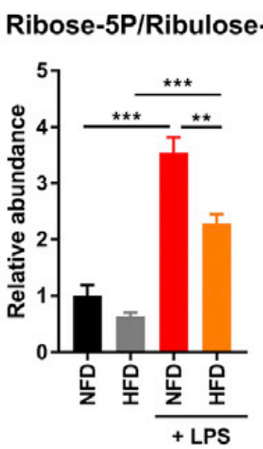
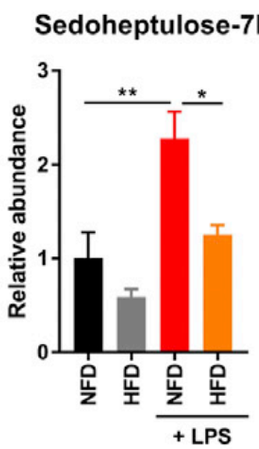
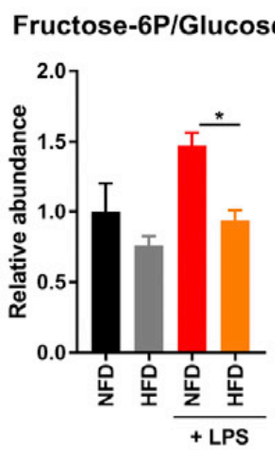
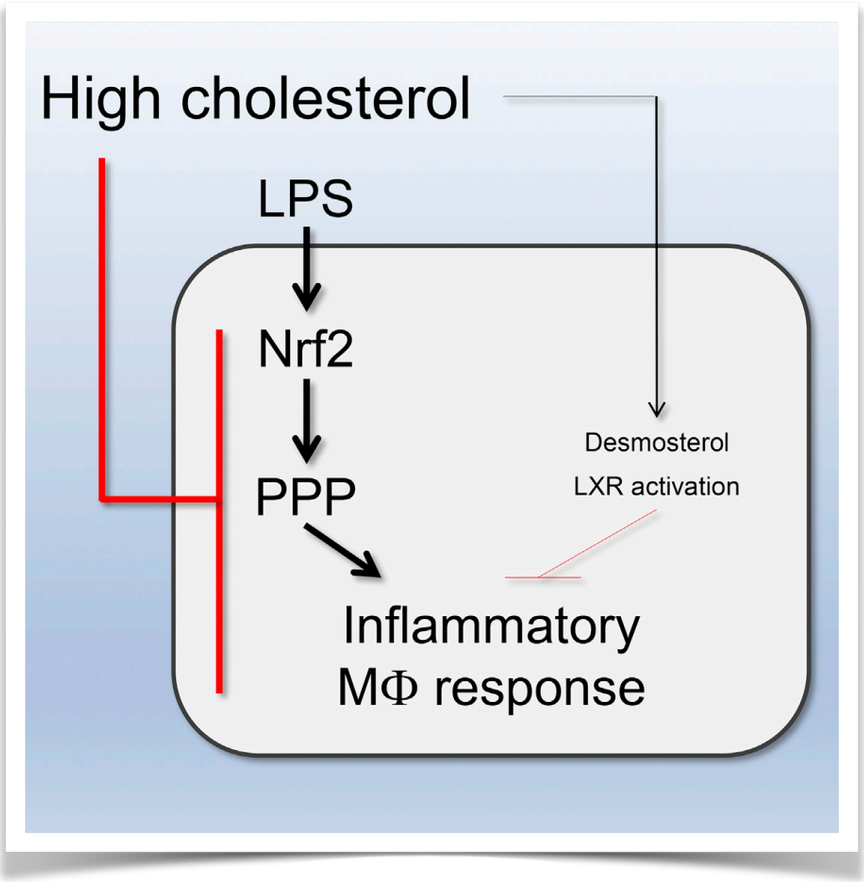








Hypercholesterolemia Reduces LPS-Mediated Induction of the PPP in Macrophages

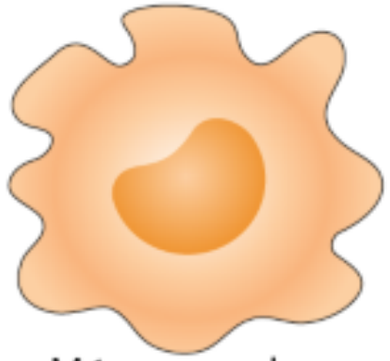
Baardman et al, ***Cell Rep****, 2018*

Metabolism in macrophage polarization

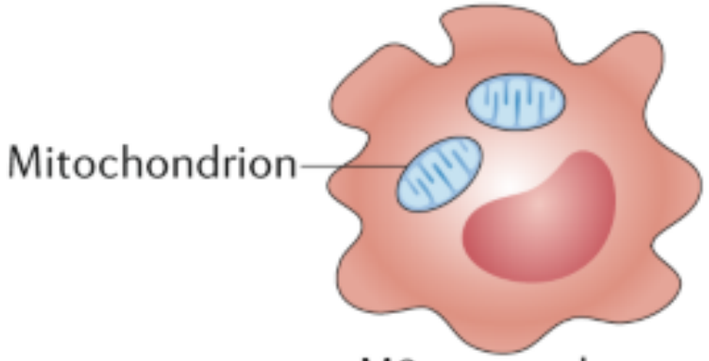
M0 macrophage

TNF and/or IFNγ

IL-4 and/or IL-13



M1 macrophage

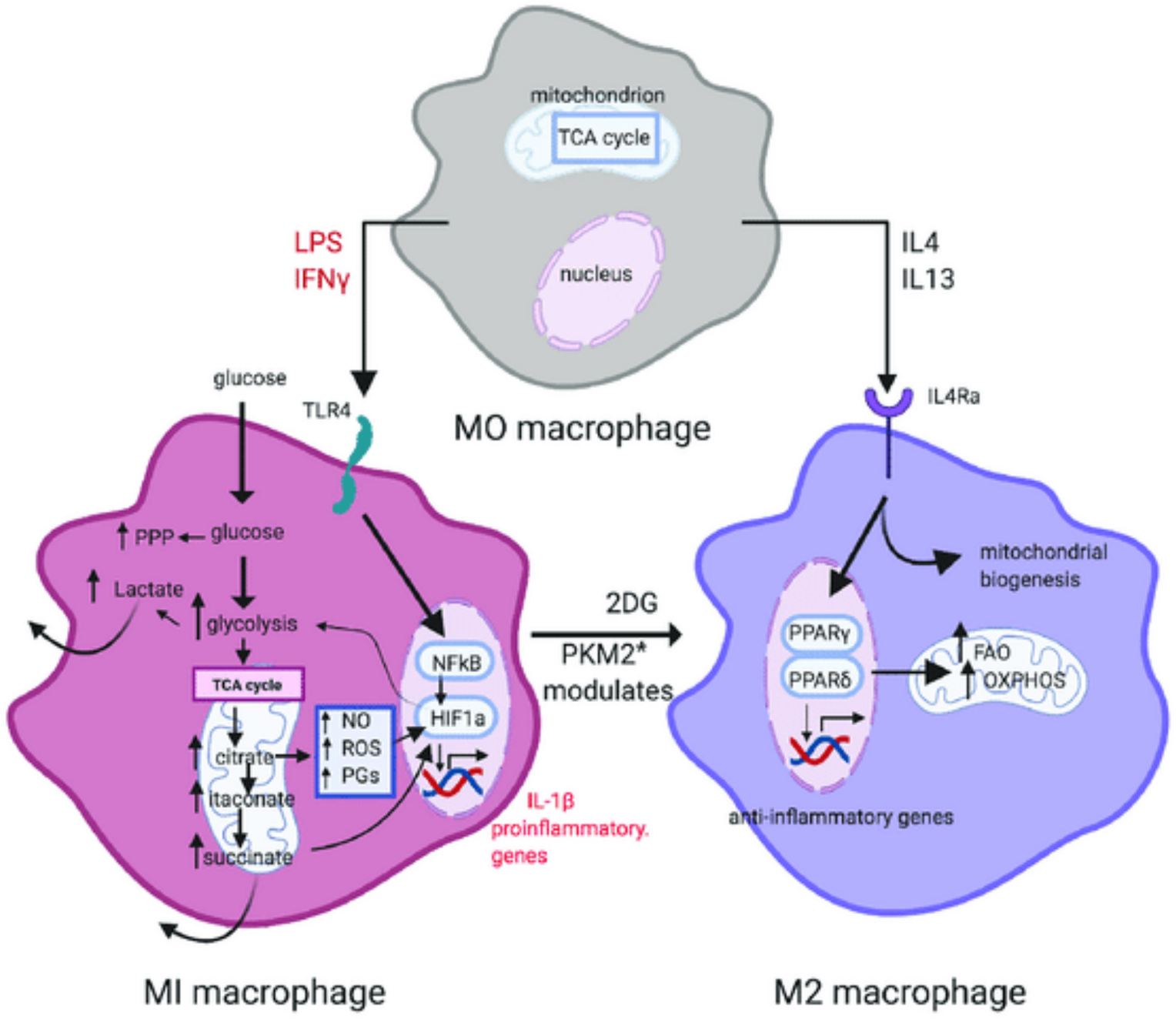


M2 macrophage

Antimicrobial properties
↑ Glycolysis
Blocked TCA cycle
↓ OXPHOS activity
↑ Production of inflammatory intermediates
↑ Antimicrobial responses
- ↑ NADPH oxidase activity
- Use of arginine to generate NO
- ↑ Antigen presentation
- ↑ Production of itaconate

Tissue repair properties
↑ Mitochondrial respiration
Intact TCA cycle
↑ Fatty acid utilization
↑ Production of anti-inflammatory cytokines
↑ Tissue remodelling responses
- ↓ Production of inflammatory lipids
- Promotion of angiogenesis
- ECM remodelling

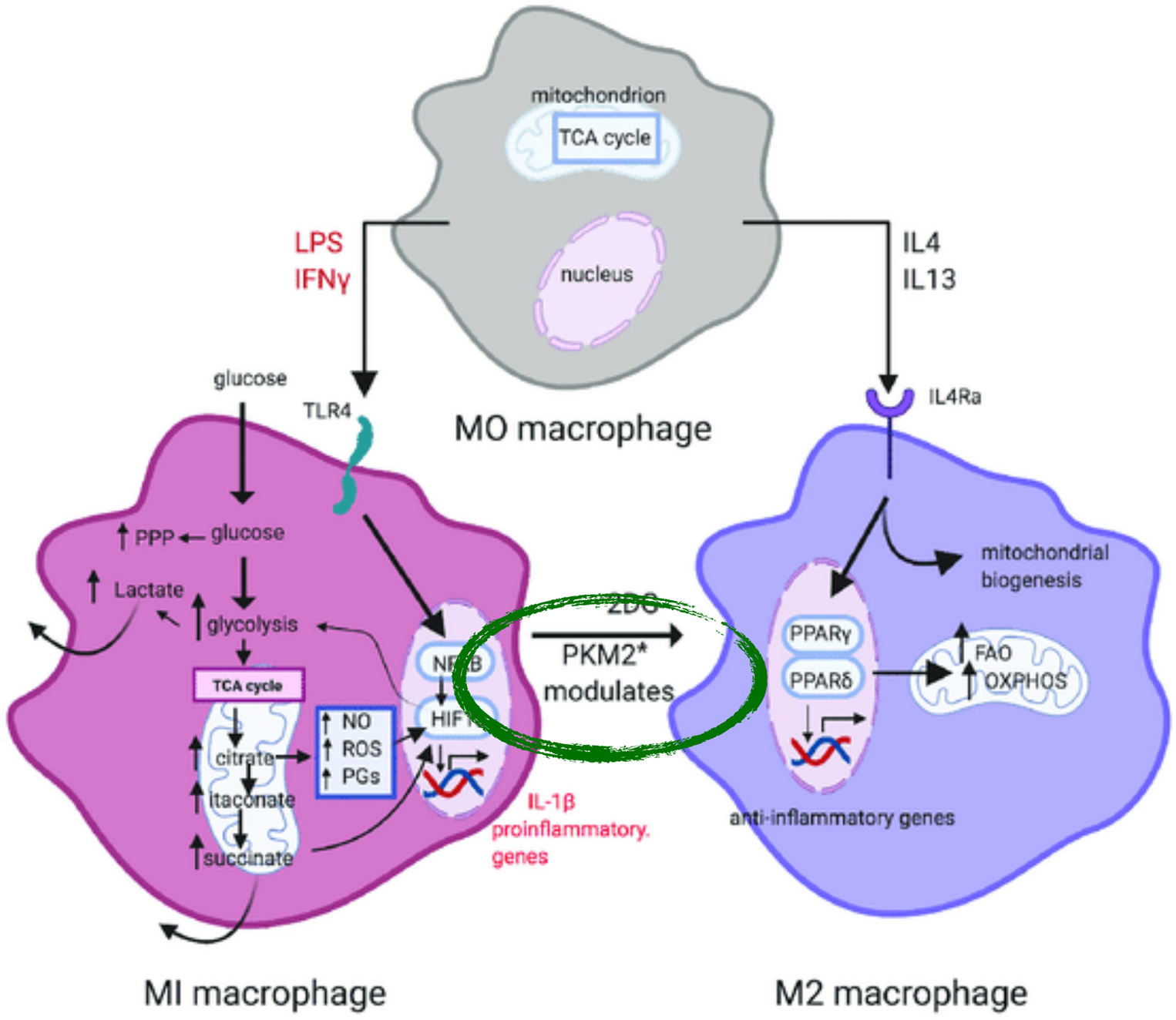
Metabolism in macrophage polarization



M1:
Glycolytic, broken TCA, elevated PPP

M2:
Oxidative metabolism, including FAO

Metabolism in macrophage polarization



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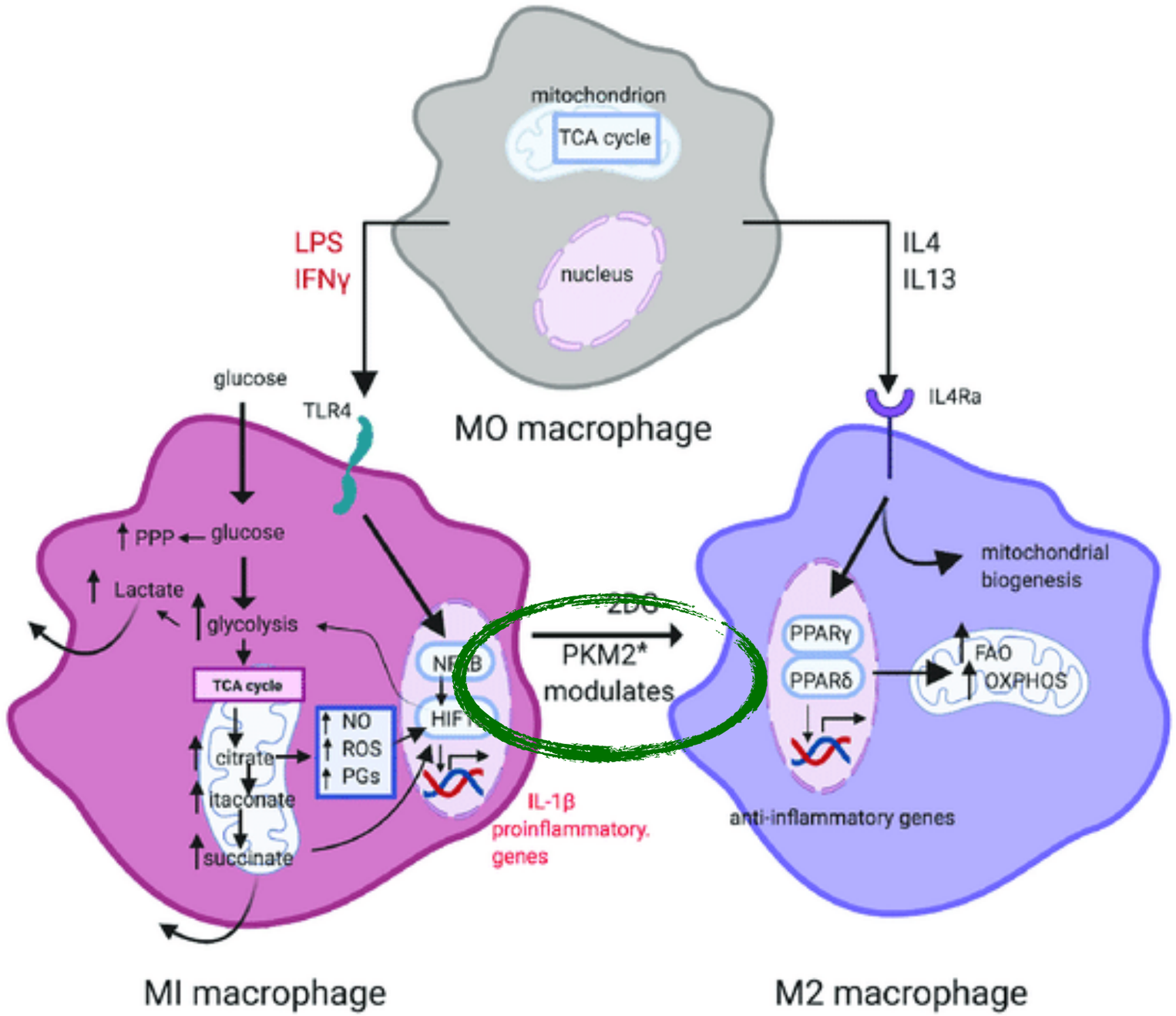
Metabolism in macrophage polarization

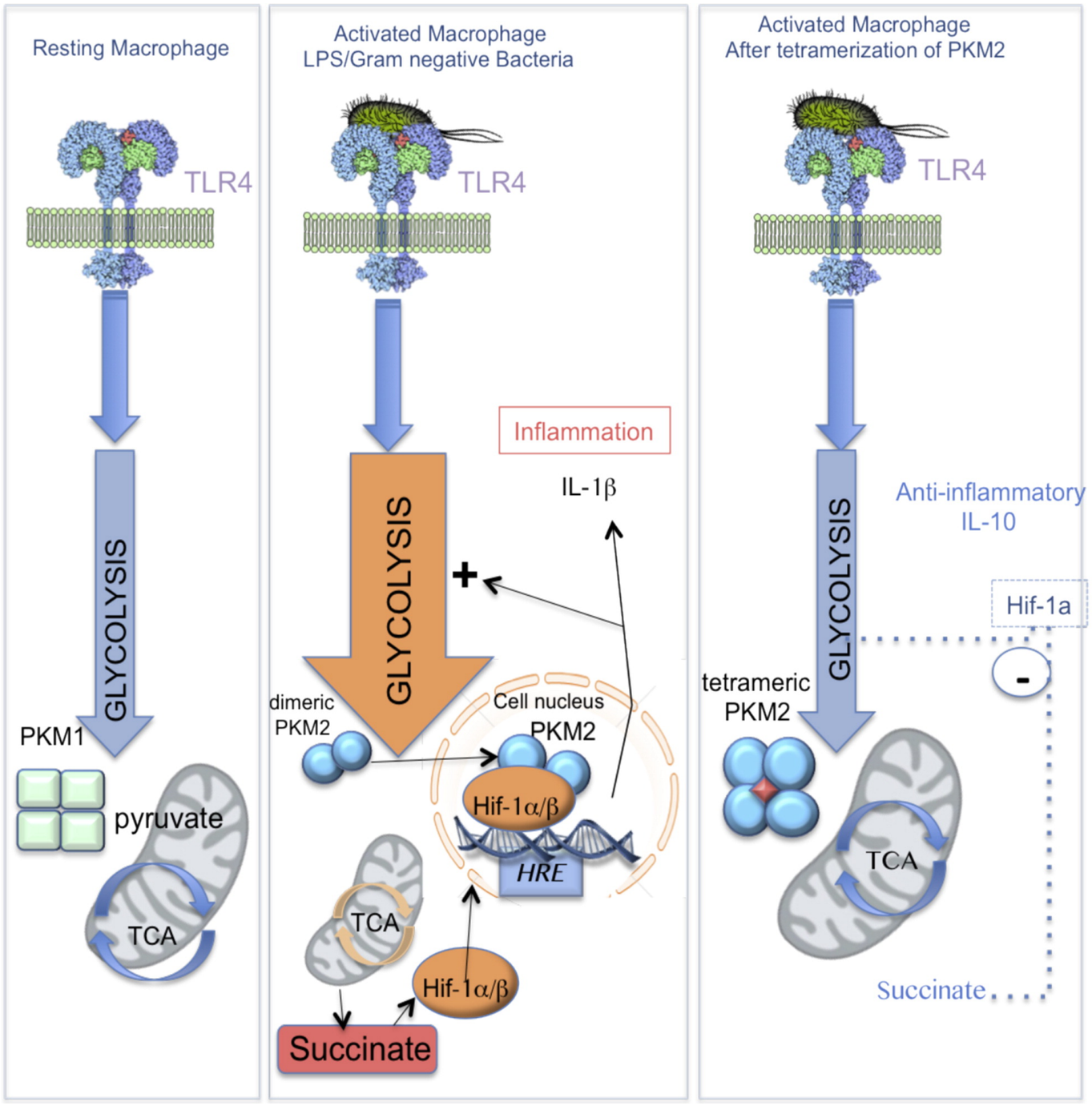


M1:
Glycolytic, broken TCA, elevated PPP

M2:
Oxidative metabolism, including FAO

PKM switch dictates macrophage polarization

PKM2 promotes M2 skewing

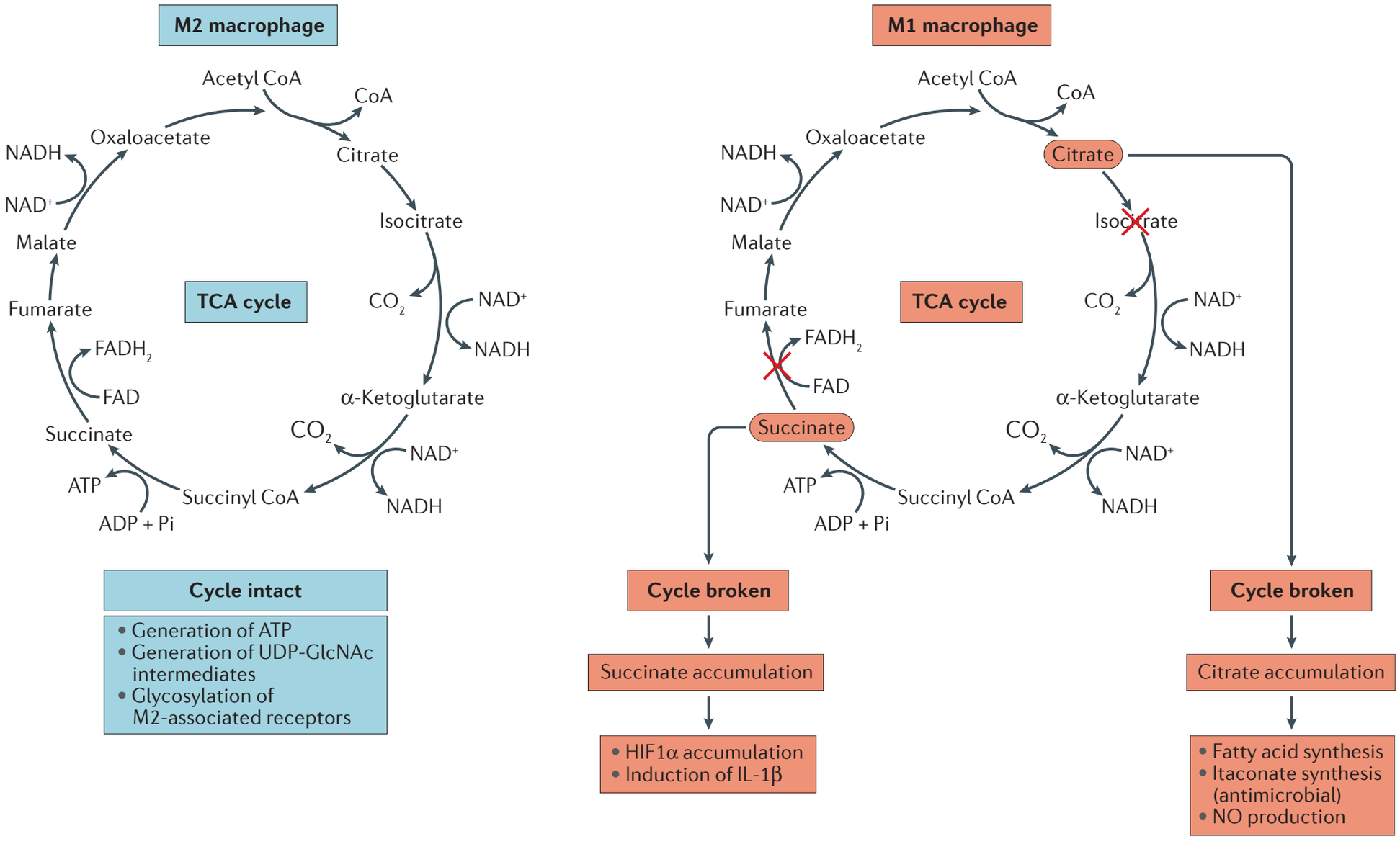


Highlights

- Tetramerization of PKM2 reverses the LPS-induced Warburg effect
- PKM2 plays a key role in stabilizing Hif-1α and regulates Hif-1α-dependent genes
- Tetramerization of PKM2 attenuates LPS-induced M1 macrophage traits
- PKM2 is a critical determinant of glycolytic reprogramming in macrophages

Palsson-McDermott et al, ***Cell Metab****, 2015*

TCA intermediates in macrophage polarization



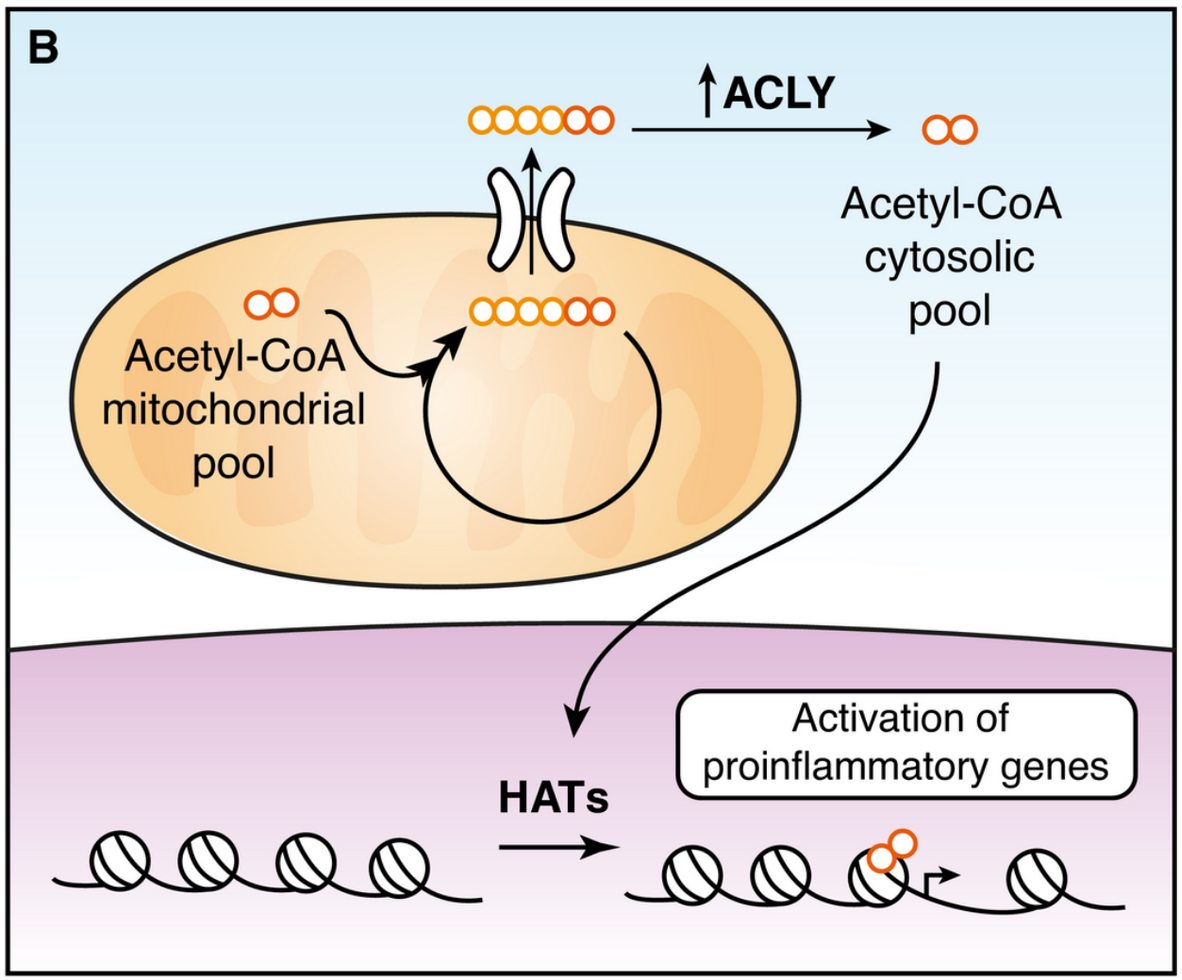
In M2 macrophages, there is an intact TCA cycle that is coupled to oxidative phosphorylation. This allows the generation of UDP-GlcNAc intermediates that are necessary for the glycosylation of M2-associated receptors, such as the mannose receptor.
However, in M1 macrophages the TCA cycle has been shown to be broken in two places — after citrate (owing to a decreasein expression of isocitrate lyase) and after succinate.

O'Neill et al, ***Nat Rev Immunol****, 2016*

Different acetyl-CoA utilization in M1 vs M2

The citrate that accumulates in M1 macrophages has been shown to be exported from the mitochondria via the citrate transporter. It is then utilized for the production of fatty acids, which in turn are used for membrane biogenesis.

Excess citrate can also feed into pathways that generate nitric oxide and prostaglandins, which are key effector molecules made by macrophages.



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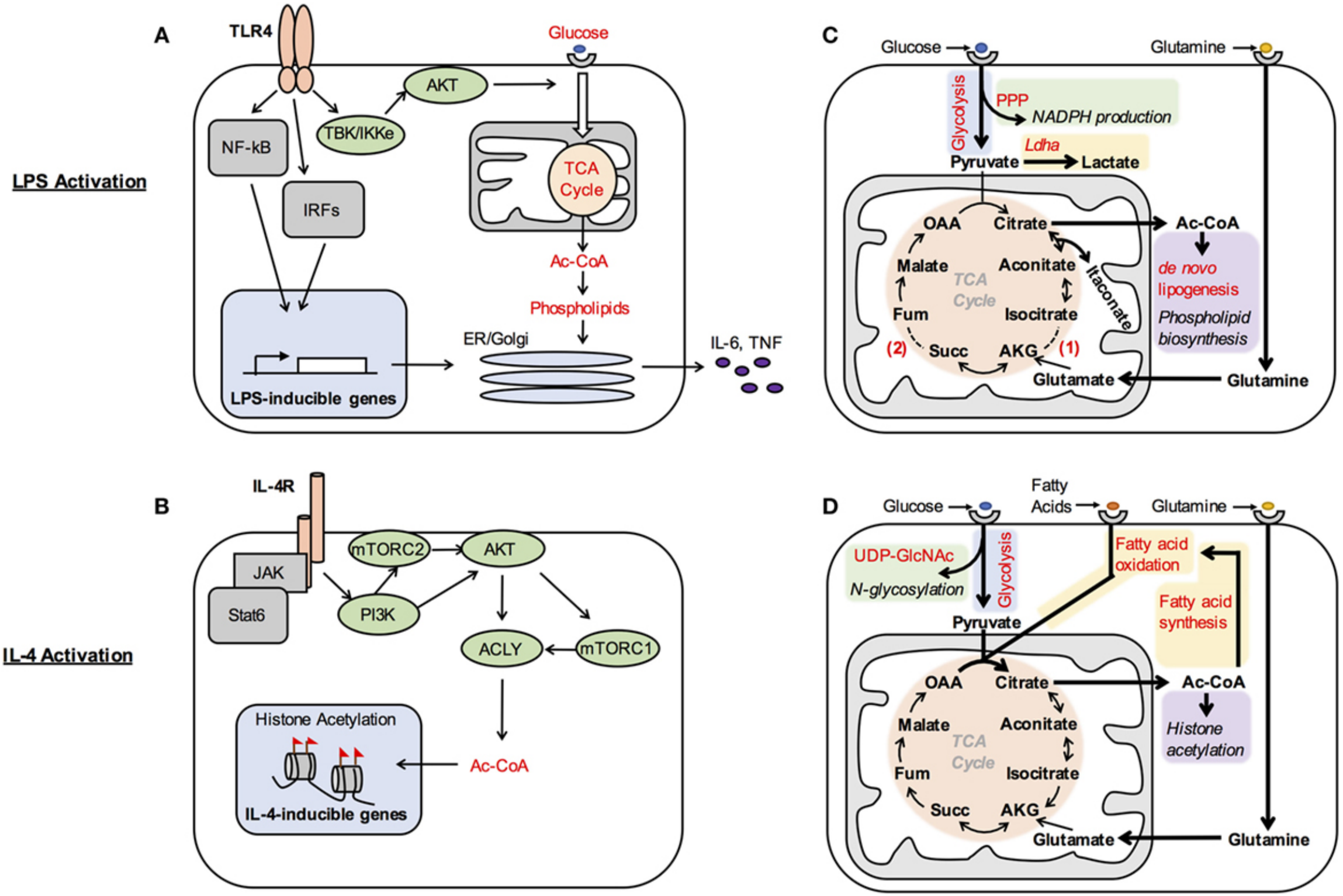
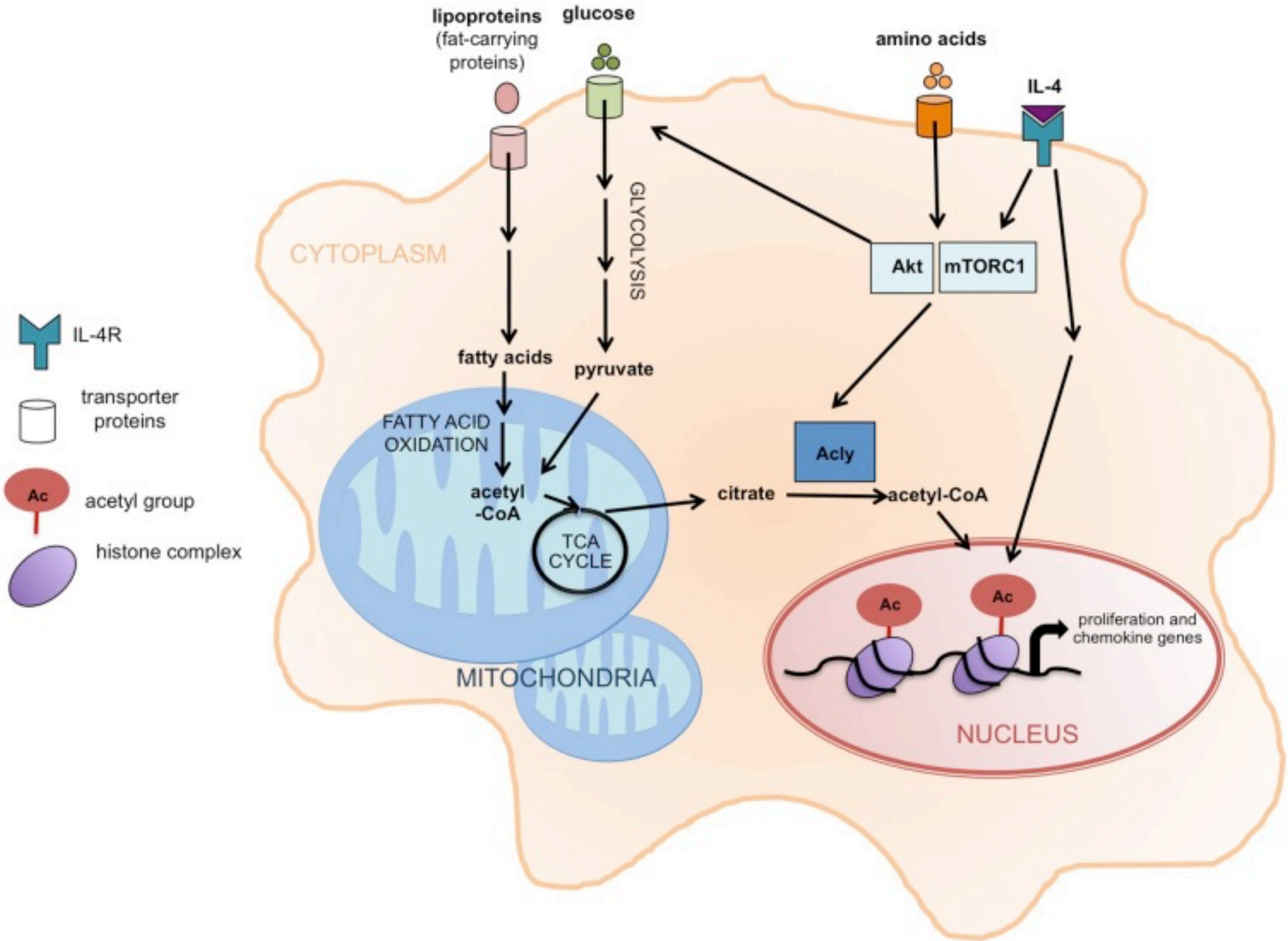
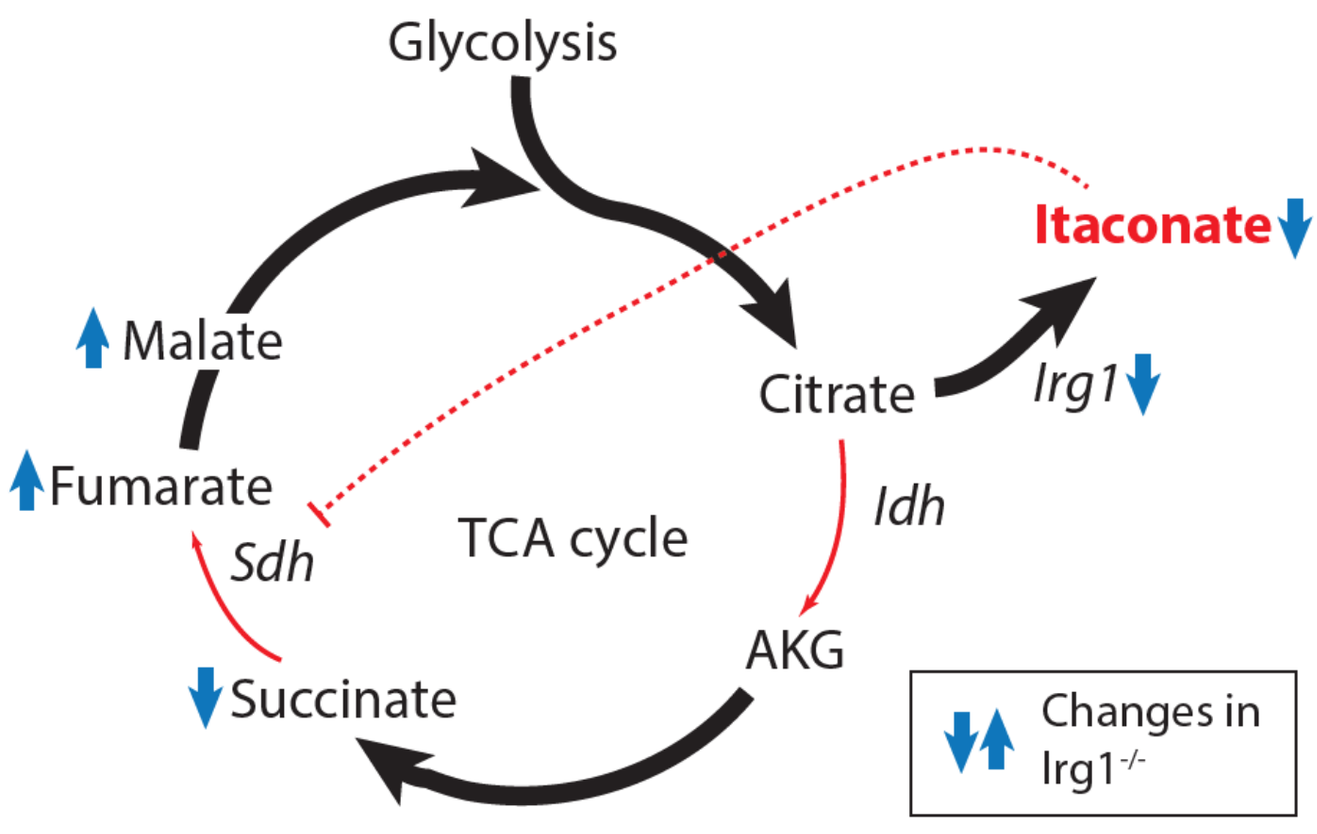




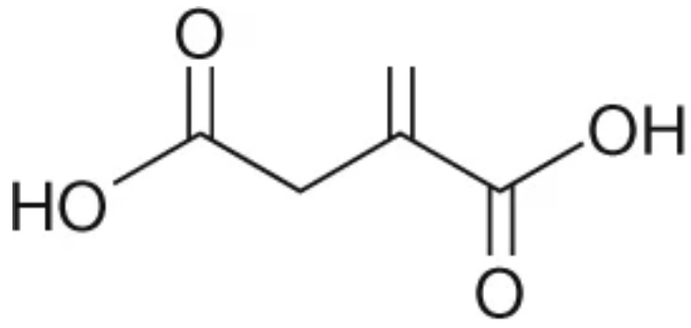
*Covarrubias et al, **eLife**, 2016*

A third metabolite generated from citrate is **<u>itaconic acid</u>**, which has been shown to have direct bactericidal effects on species such as *Salmonella enterica* and *Mycobacterium tuberculosis*. This particular example shows how a metabolic rewiring event can generate metabolites with direct antimicrobial activity.

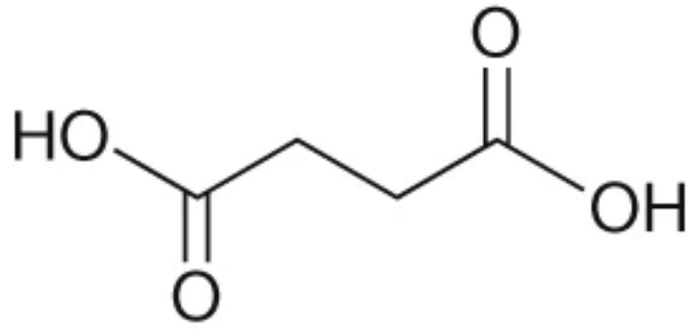


Itaconate is a competitive inhibitor

(endogenous)



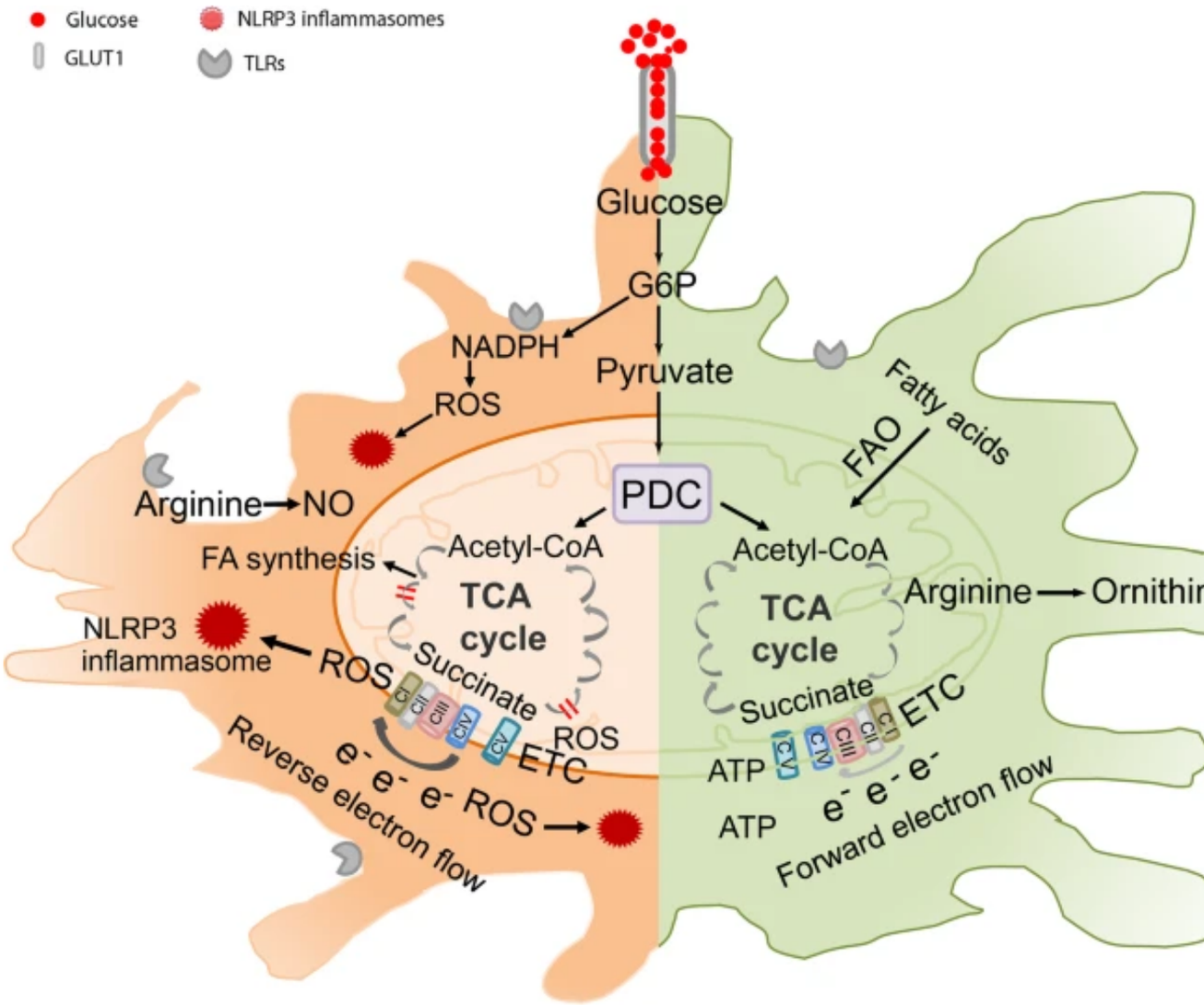
Itaconate

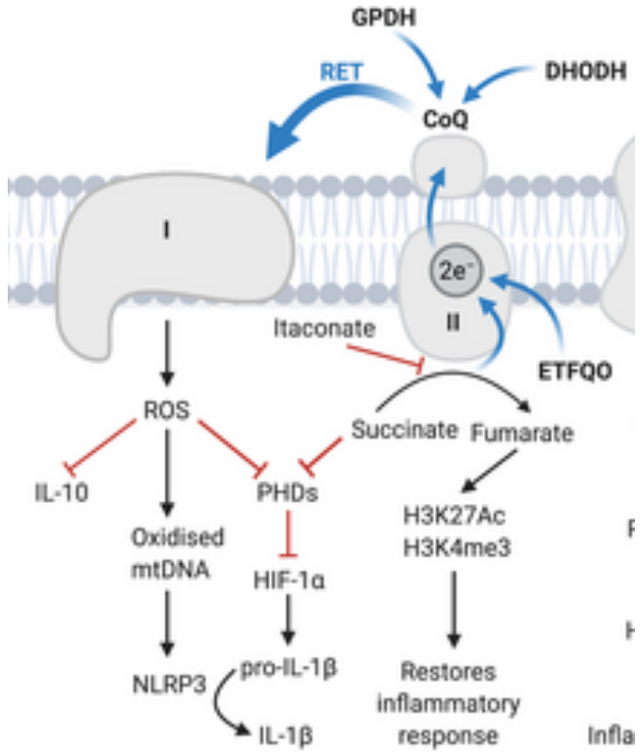


Succinate

Itaconate is an endogenous SDH inhibitor

Inhibiting SDH, Itaconate promotes reverse electron flow along the ETC and ROS generation (to support phagocytosis)

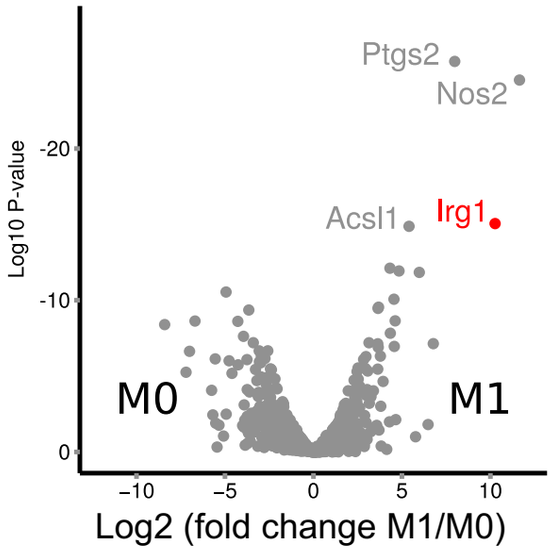


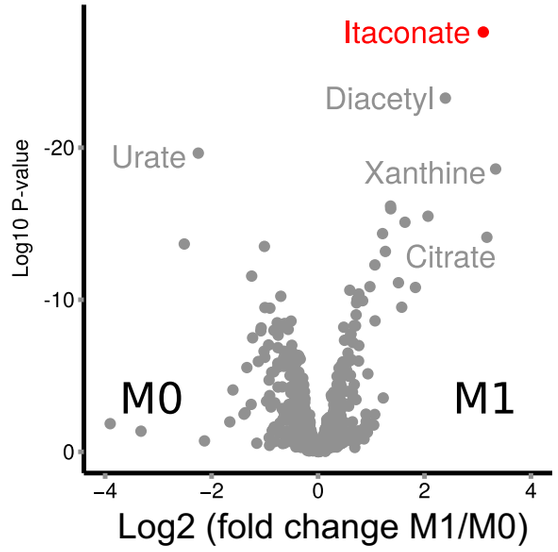


Complex II is the site of reverse electron transport (RET) in inflammatory macrophages (ROS, hence NRF2 activation) and is also responsible for regulating fumarate levels linking to epigenetic changes.

In trained immunity, fumarate-induced epigenetic changes (i.e., H3K27Ac and H3K4me3) can restore the inflammatory response to LPS, rescuing immune paralysis.

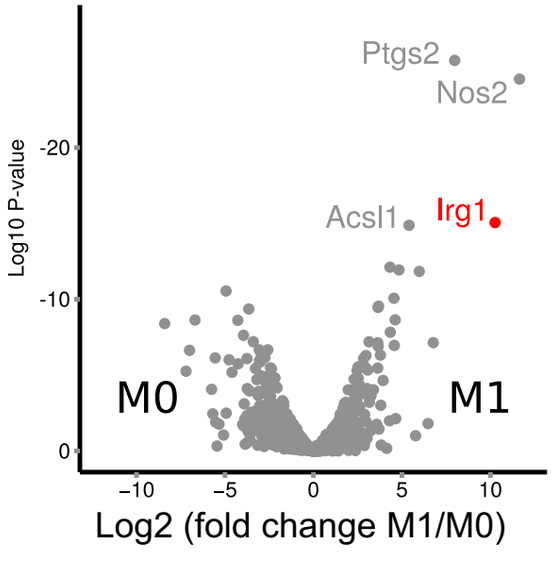
Itaconate is an endogenous PDH inhibitor

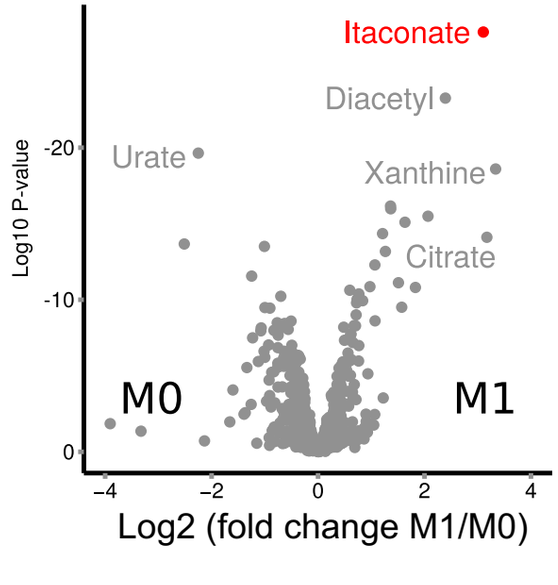


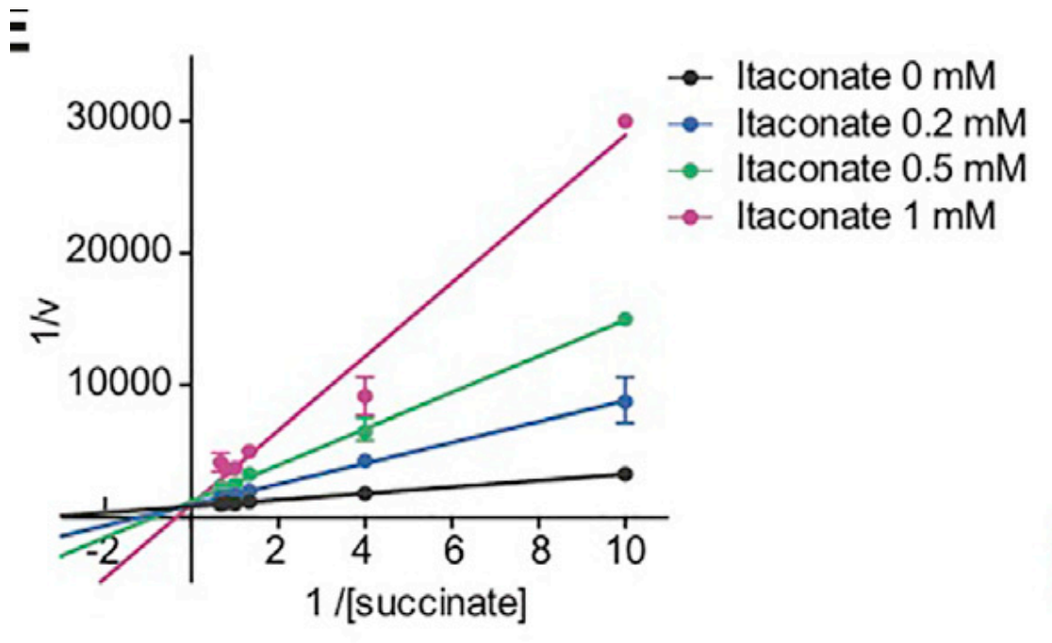


Lampropoulou et al, ***Cell Metab****, 2016*

Itaconate is an endogenous PDH inhibitor

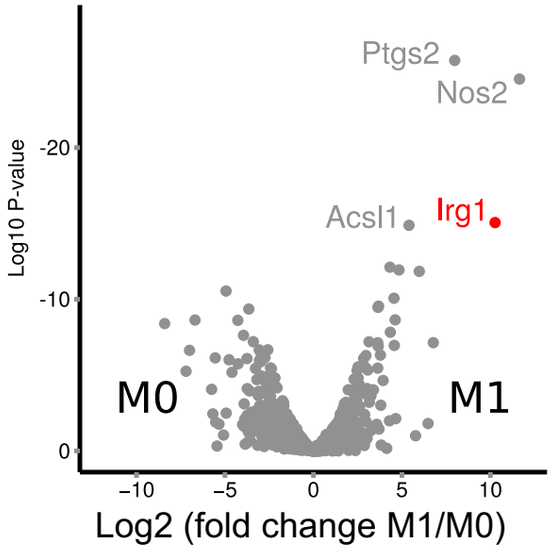


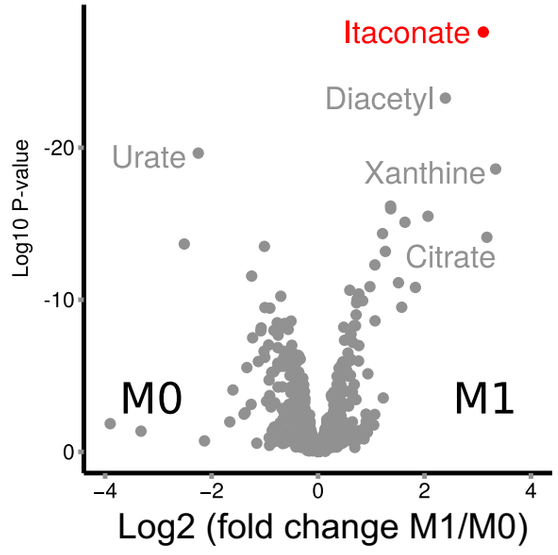


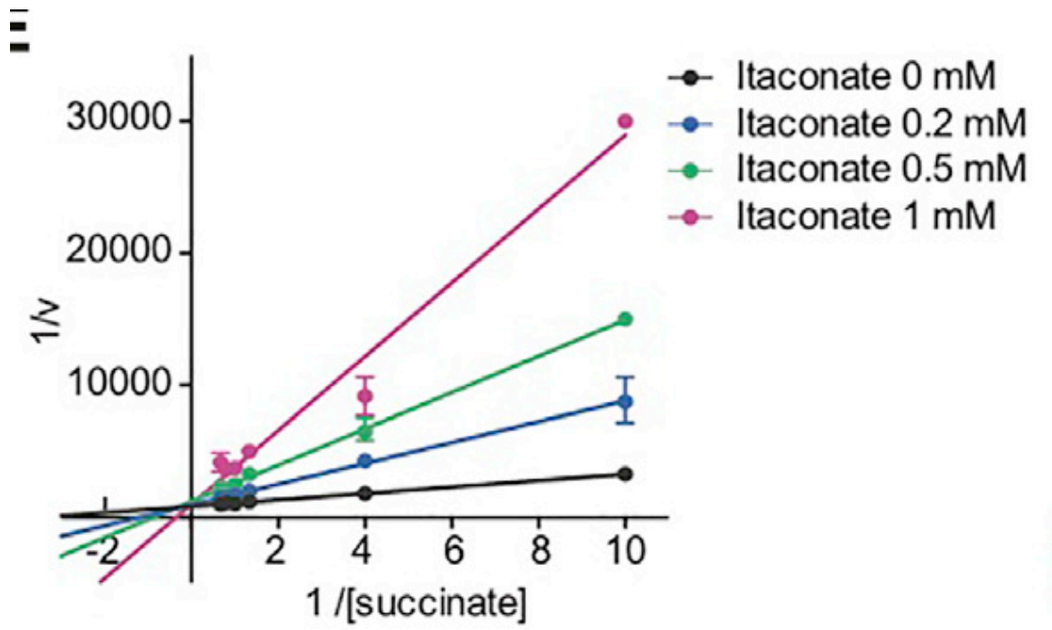


Lampropoulou et al, ***Cell Metab****, 2016*

Itaconate is an endogenous PDH inhibitor





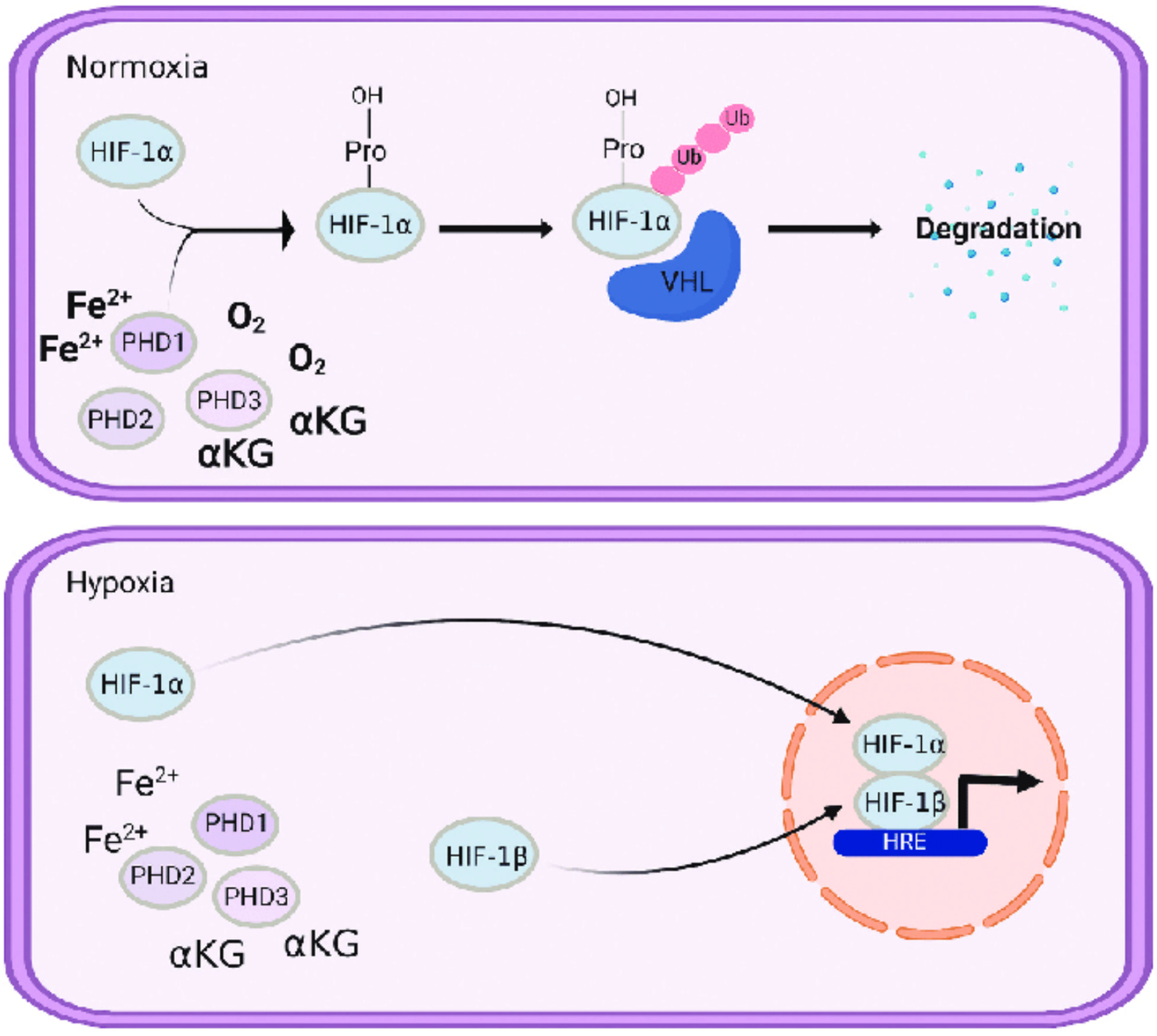


Succcinate that accumulates in M1 macrophages as a consequence of a broken TCA cycle has a direct impact on macrophage cytokine production. One mechanism involved is inhibition of prolyl-hydroxylases by succinate, leading to the stabilization of HIF1α and the sustained production of IL-1β. This pathway will operate under normoxia as well as in hypoxia, and is therefore a mechanism for HIF1α activation under aerobic conditions.

Lampropoulou et al, ***Cell Metab****, 2016*

Itaconate is an endogenous PDH inhibitor

aKG supports hypoxic response



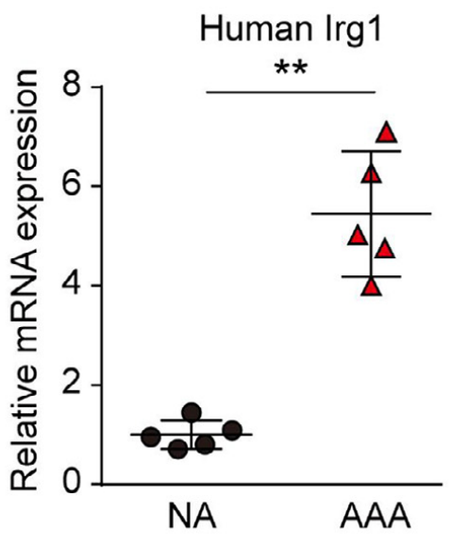
Succinate inhibits PDHs, leading to HIF stabilization

Itaconate prevents abdominal aortic aneurysm formation through inhibiting inflammation via activation of Nrf2

Haoyu Song[a,b], Tong Xu[a], Xiaofei Feng[a], Yanxian Lai[a], Yang Yang[a], Hao Zheng[a], Xiang He[a], Guoquan Wei[a], Wangjun Liao[d], Yulin Liao[a], Lintao Zhong[a,c,*], Jianping Bin[a,b,*]

Abdominal aortic aneurysm (AAA) is a chronic inflammatory disease.

An AAA is a swelling in the aorta, the artery that carries blood from the heart to the tummy (abdomen). Most aneurysms do not cause any problems, but they can be serious because there's a risk they could burst (rupture).



Song et al, ***EBioMedicine****, 2020*

Itaconate prevents abdominal aortic aneurysm formation through inhibiting inflammation via activation of Nrf2

Haoyu Song[a,b], Tong Xu[a], Xiaofei Feng[a], Yanxian Lai[a], Yang Yang[a], Hao Zheng[a], Xiang He[a], Guoquan Wei[a], Wangjun Liao[d], Yulin Liao[a], Lintao Zhong[a,c,*], Jianping Bin[a,b,*]

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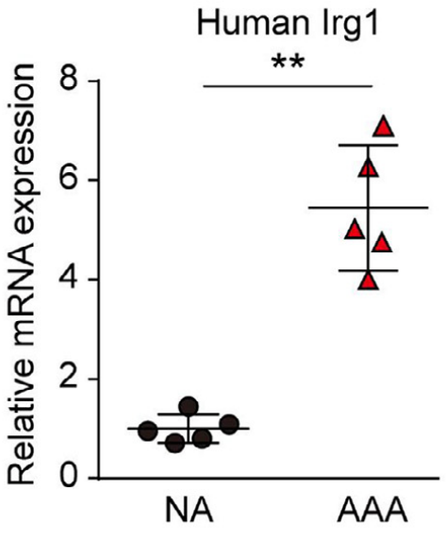
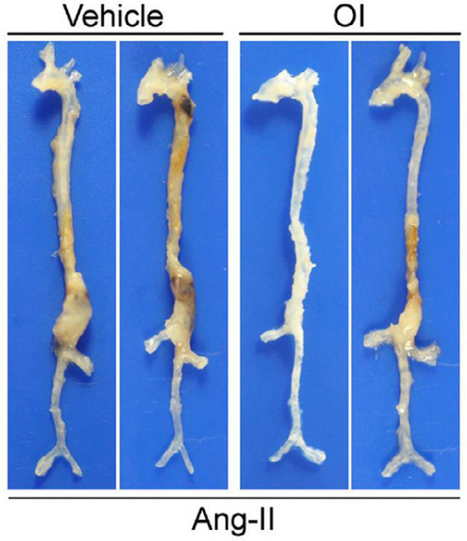
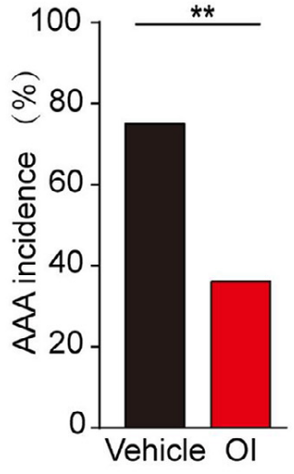
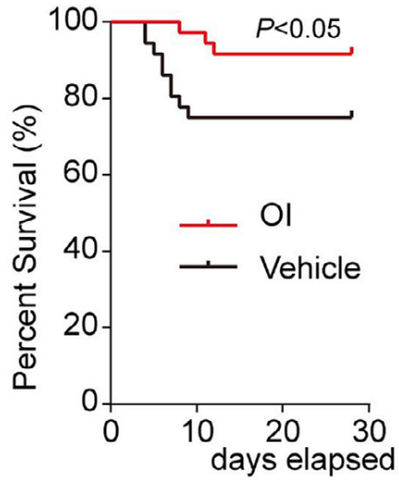
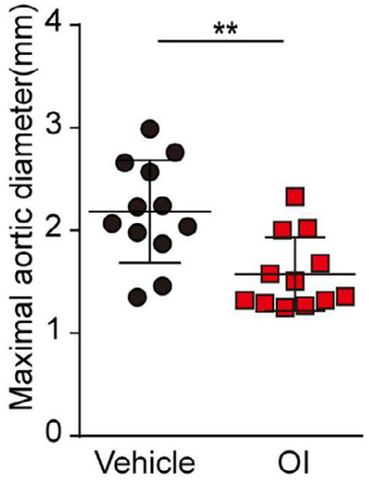








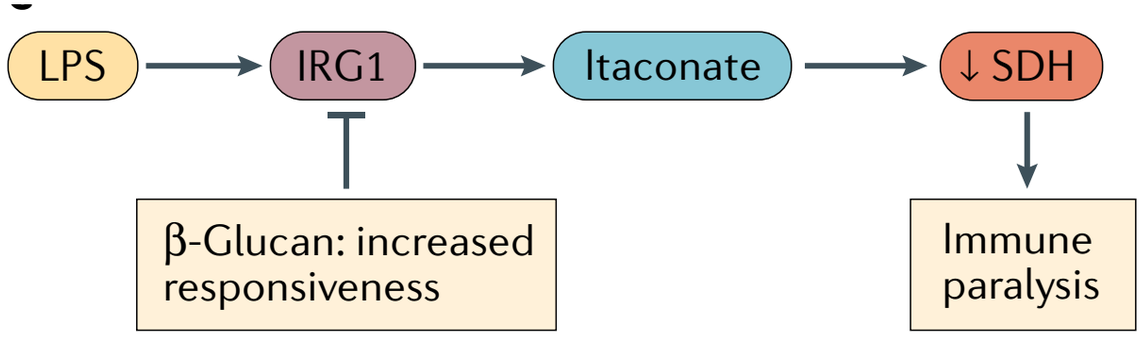


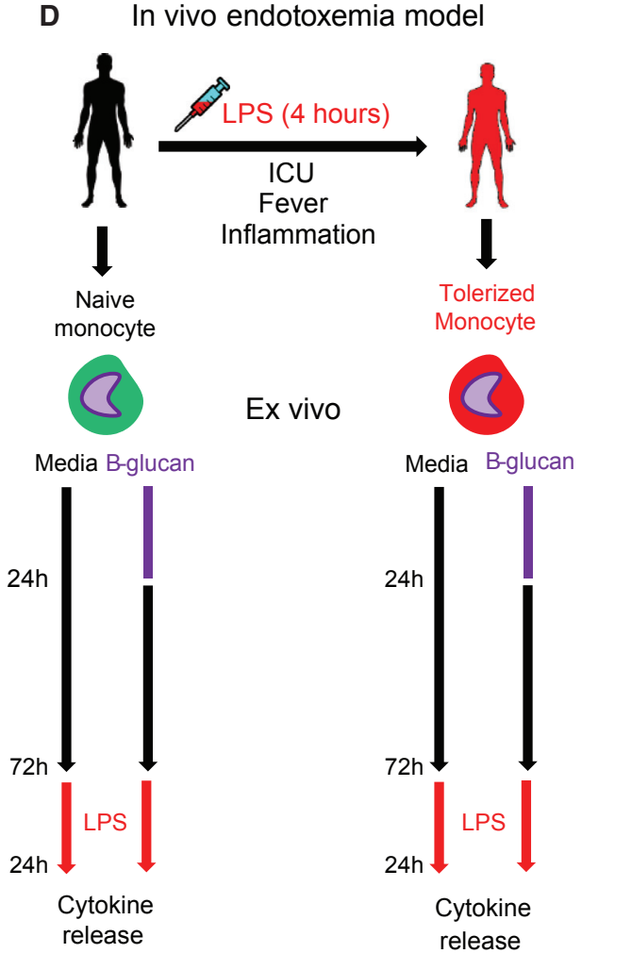
Exogenous addition of the itaconate analogue 4-octyl itaconate (OI) attenuates Ang II-induced AAA formation in ApoE-/- mice.

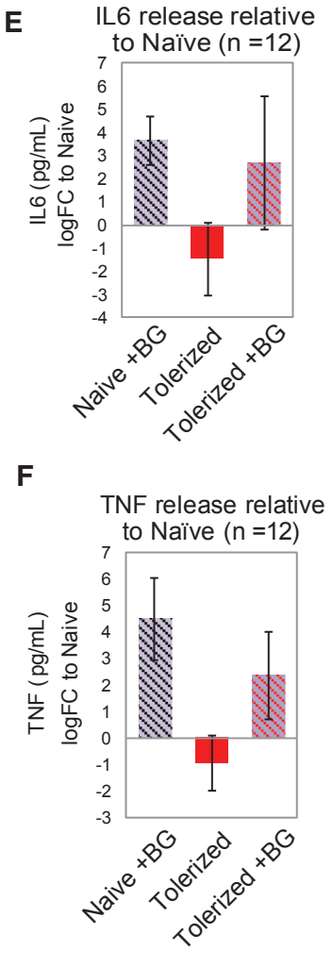
Song et al, ***EBioMedicine****, 2020*

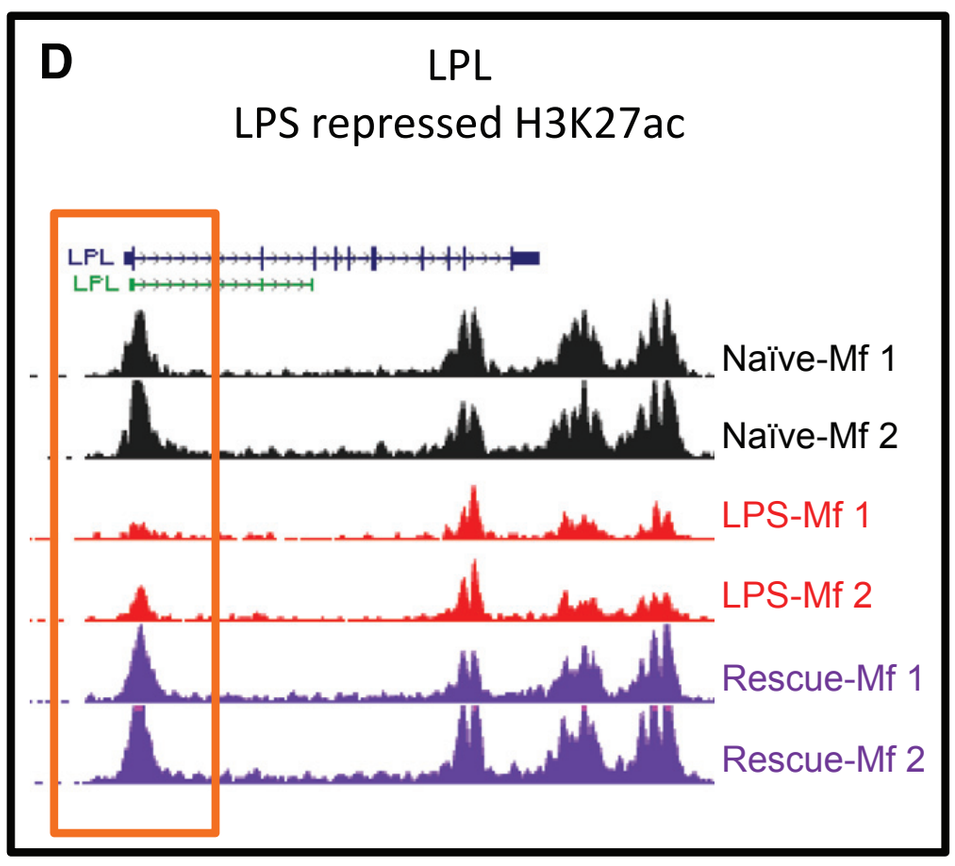
β-Glucan Reverses the Epigenetic State of LPS-Induced Immunological Tolerance

Boris Novakovic,[1,7] Ehsan Habibi,[1,7] Shuang-Yin Wang,[1,7] Rob J.W. Arts,[2] Robab Davar,[1] Wout Megchelenbrink,[1] Bowon Kim,[1] Tatyana Kuznetsova,[1] Matthijs Kox,[3] Jelle Zwaag,[3] Filomena Matarese,[1] Simon J. van Heeringen,[4] Eva M. Janssen-Megens,[1] Nilofar Sharifi,[1] Cheng Wang,[1] Farid Keramati,[1] Vivien Schoonenberg,[1] Paul Flicek,[5] Laura Clarke,[5] Peter Pickkers,[3] Simon Heath,[6] Ivo Gut,[6] Mihai G. Netea,[2] Joost H.A. Martens,[1] Colin Logie,[1] and Hendrik G. Stunnenberg[1,8,*]



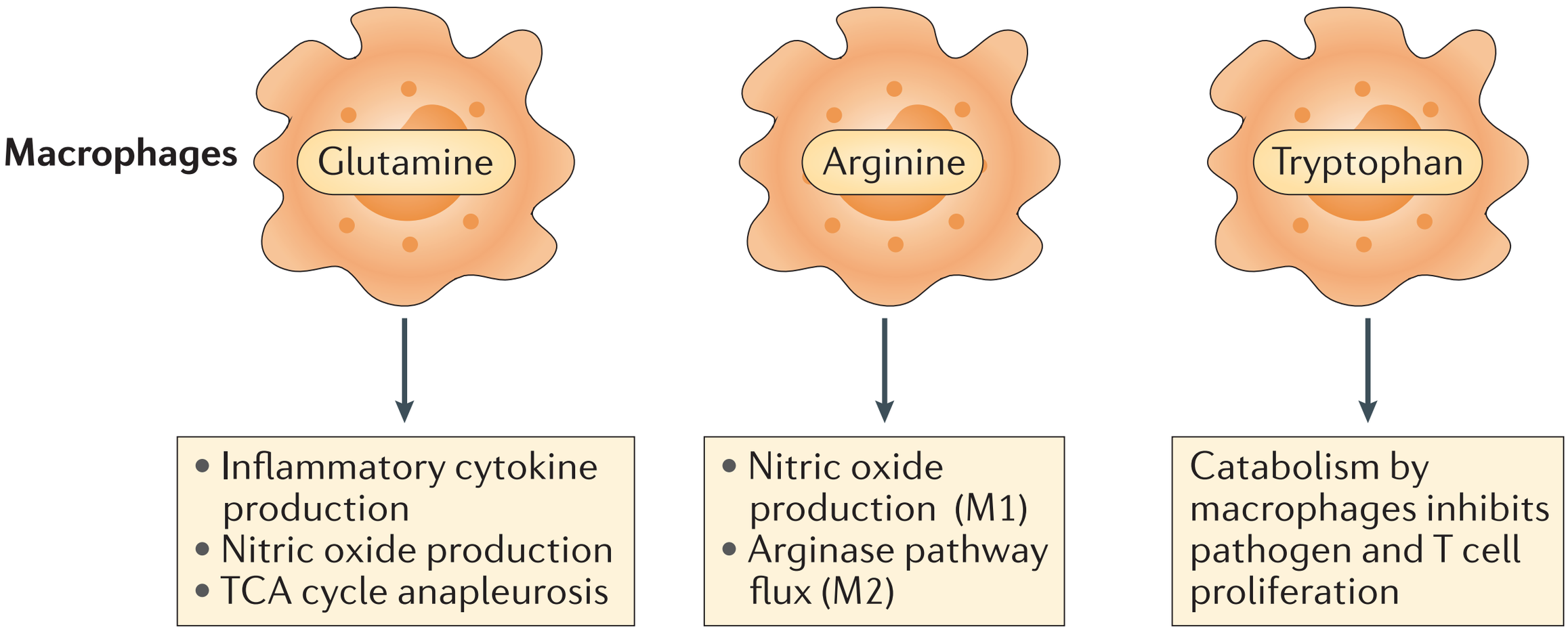






*Novakovic et al, **Cell**, 2016*

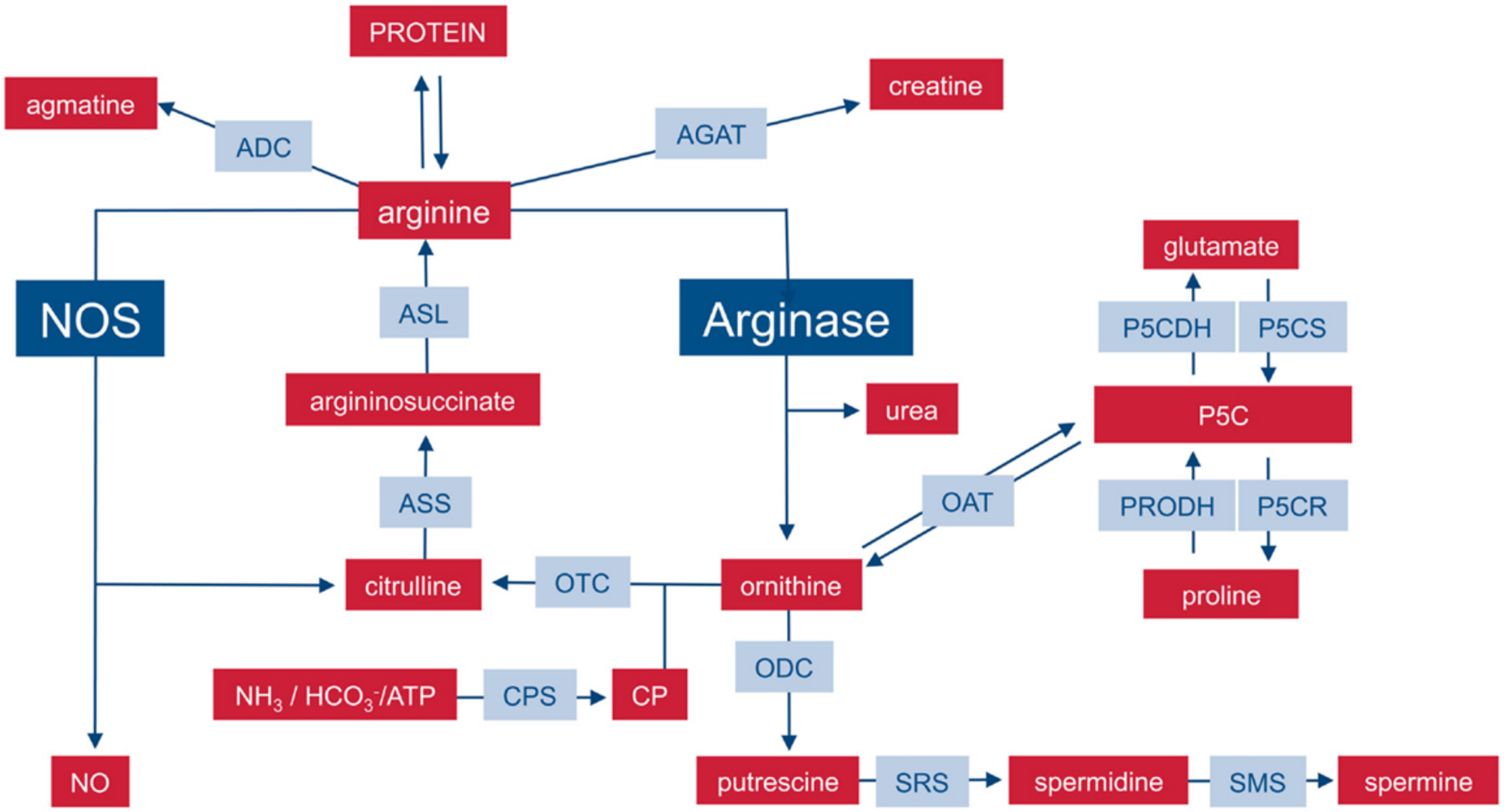
Amino acid (AA) metabolism supports macrophage functions



O'Neill et al, ***Nat Rev Immunol****, 2016*

Arginine metabolism for M1 and M2

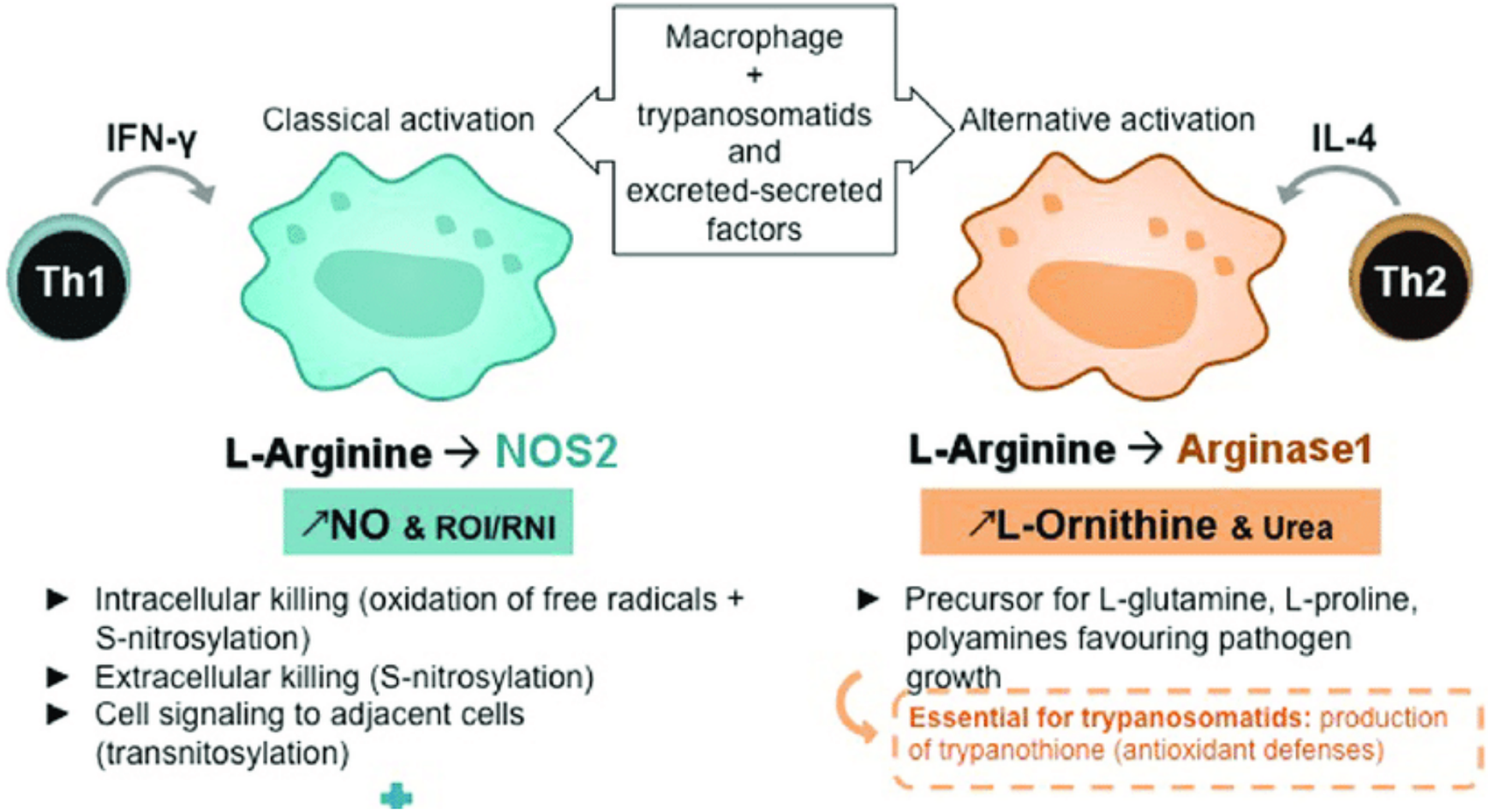
Arginine metabolism has been found to have a key role in the inflammatory function of macrophages. **Macrophages use arginine in two distinct metabolic pathways, the nitric oxide synthesis pathway and the arginase pathway.**



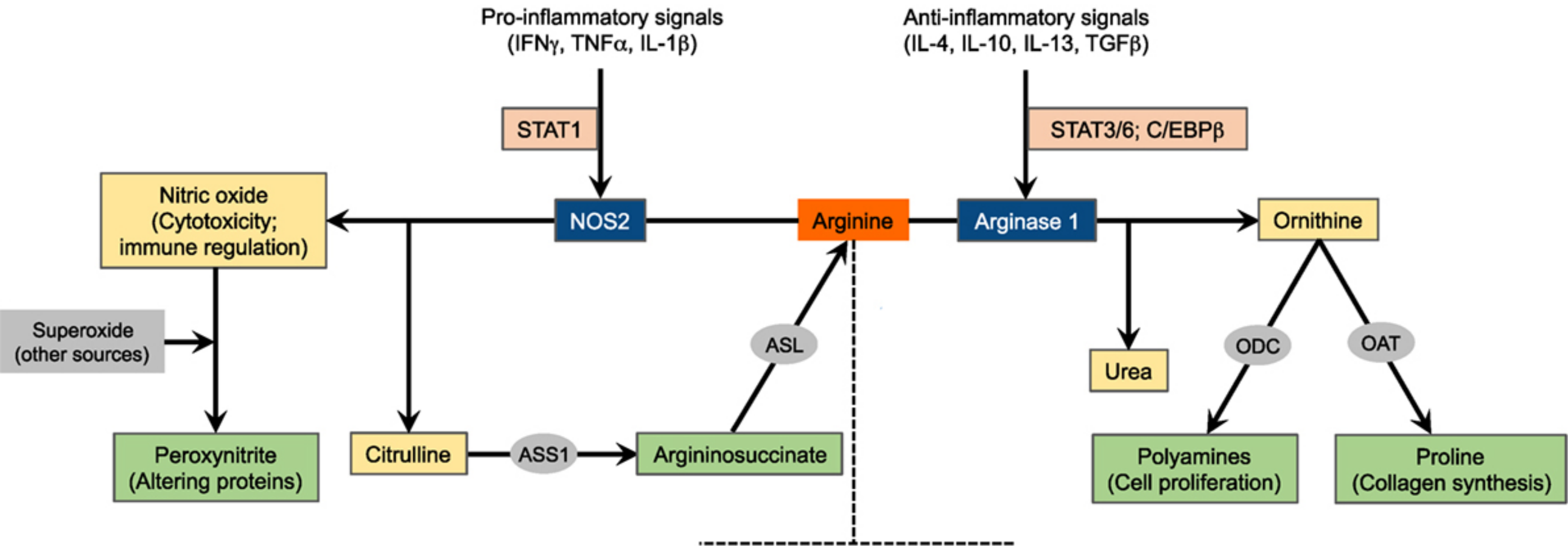
The pathway used for arginine metabolism in macrophages has profound effects on the immune function of the cell.

Arginine metabolism for M1 and M2

Macrophage flux of arginine into the nitric oxide synthesis pathway is associated with an inflammatory M1 phenotype. When macrophages direct arginine into this pathway, arginine (via citrulline) is converted into nitric oxide, a process mediated by inducible nitric oxide synthase (iNOS). It has been known for some time that iNOS expression is itself required for inflammatory macrophage function.
In contrast to the inflammatory involvement of arginine metabolism in the nitric oxide synthesis pathway, arginine flux through the arginase pathway is associated with a more tolerant immune response, often associated with wound healing.

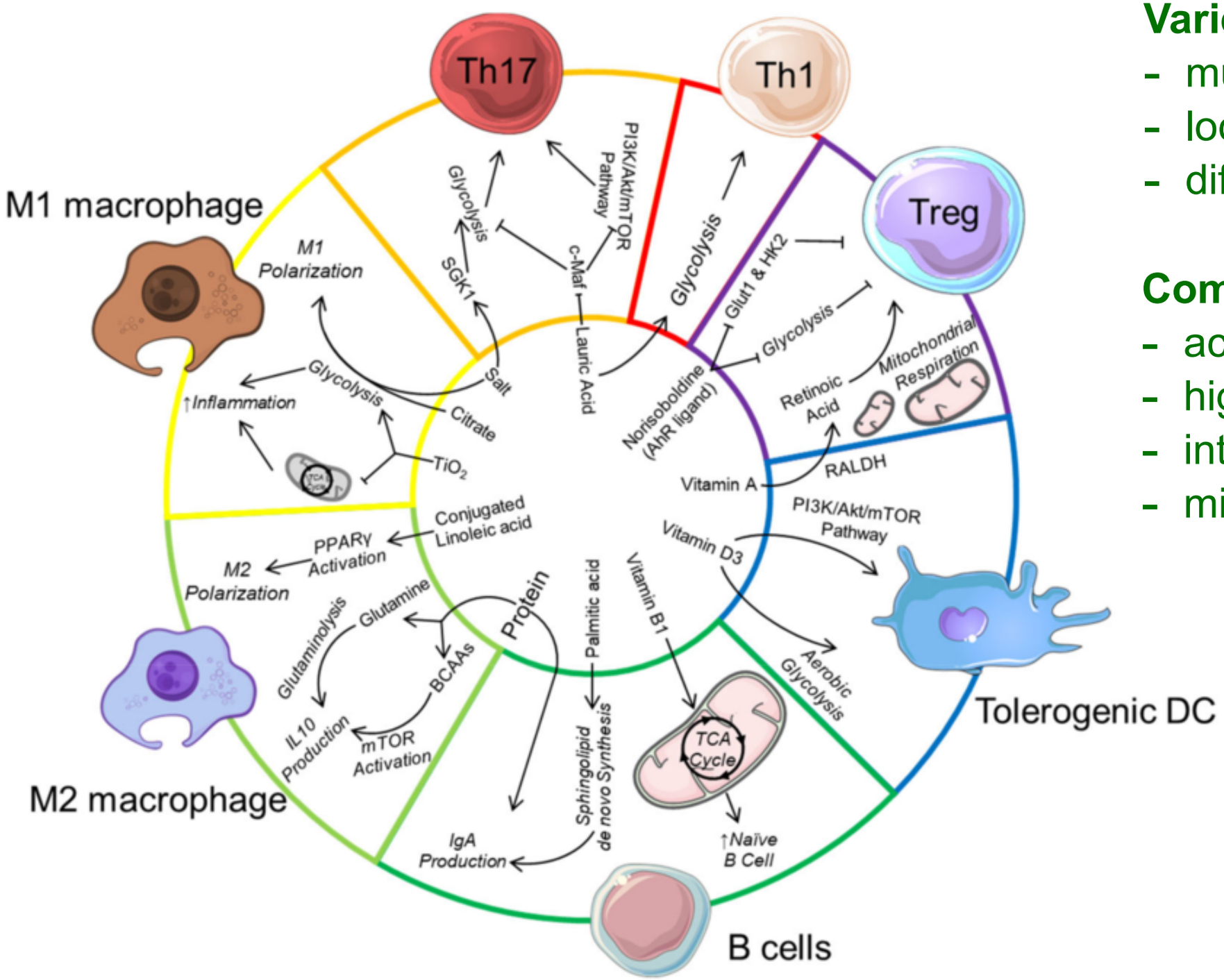


Arginine metabolism for M1 and M2



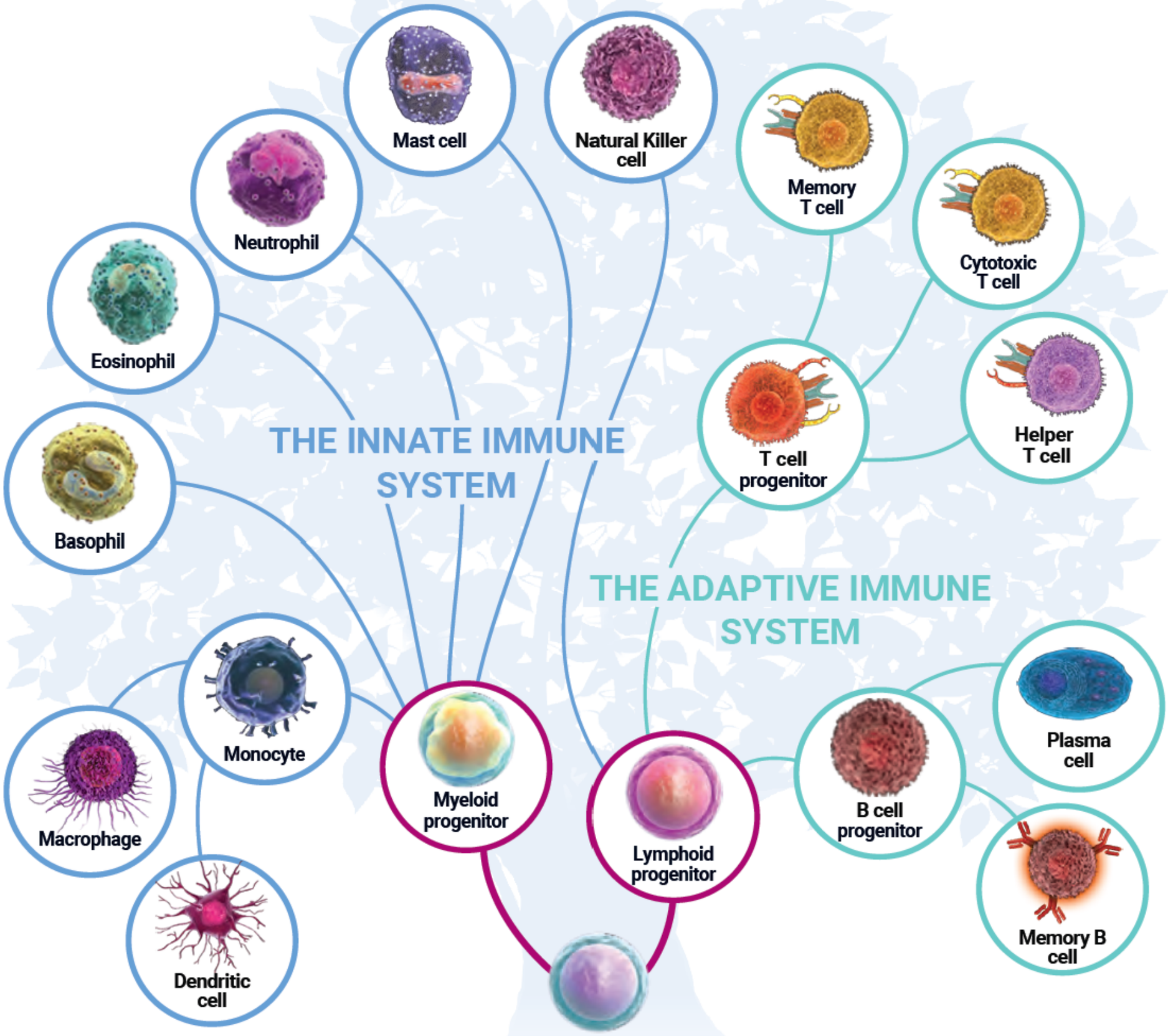
Note: forcing one pathway (ex: NOS2 KO) dictates macrophage polarization
(*Palmieri et al,* ***Nat Comm****, 2020*)

Immunometabolism across the immune system



Variety of cell types
- multiple phenotypes
- local microenvironments
- different functions

Common denominators
- actionable
- highly plastic
- interactive
- migrate and adapt


THE INNATE IMMUNE SYSTEM
THE ADAPTIVE IMMUNE SYSTEM
Mast cell
Natural Killer cell
Neutrophil
Eosinophil
Basophil
Memory T cell
Cytotoxic T cell
T cell progenitor
Helper T cell
Monocyte
Macrophage
Dendritic cell
Myeloid progenitor
Lymphoid progenitor
B cell progenitor
Plasma cell
Memory B cell
Hematopoietic stem cell

Lymphocytes face major metabolic challenges upon activation. They must meet the bioenergetic and biosynthetic demands of increased cell proliferation and also adapt to changing environmental conditions, in which nutrients and oxygen may be limiting.

Why T cells adopt specific metabolic programs and the impact that these programs have on T cell function and, ultimately, immunological outcome remain unclear.

- Improve response to infections (lower morbidity)
- Tune subtype differentiation
- Improve efficiency of vaccination
- Ameliorate (cure or prevent) auto-immune diseases
- Curtail exhaustion (*i.e.: immune evasion by cancer*)
- Improve immunotherapy (*adaptive: CAR T cells*)

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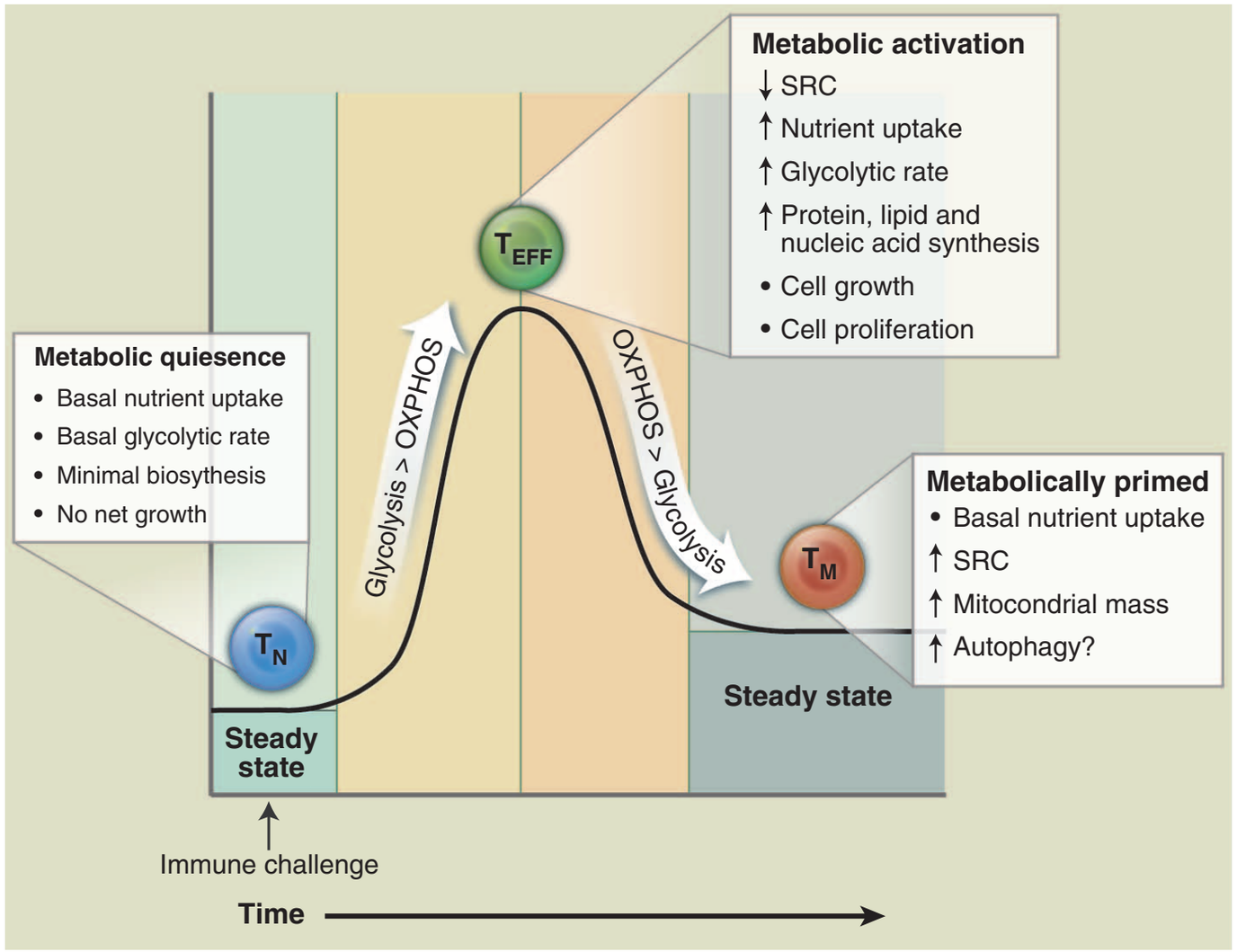
…hinge on the ability to activate immunogenic programs (gene expression) and generate effector/memory cells (epigenetic rearrangements).

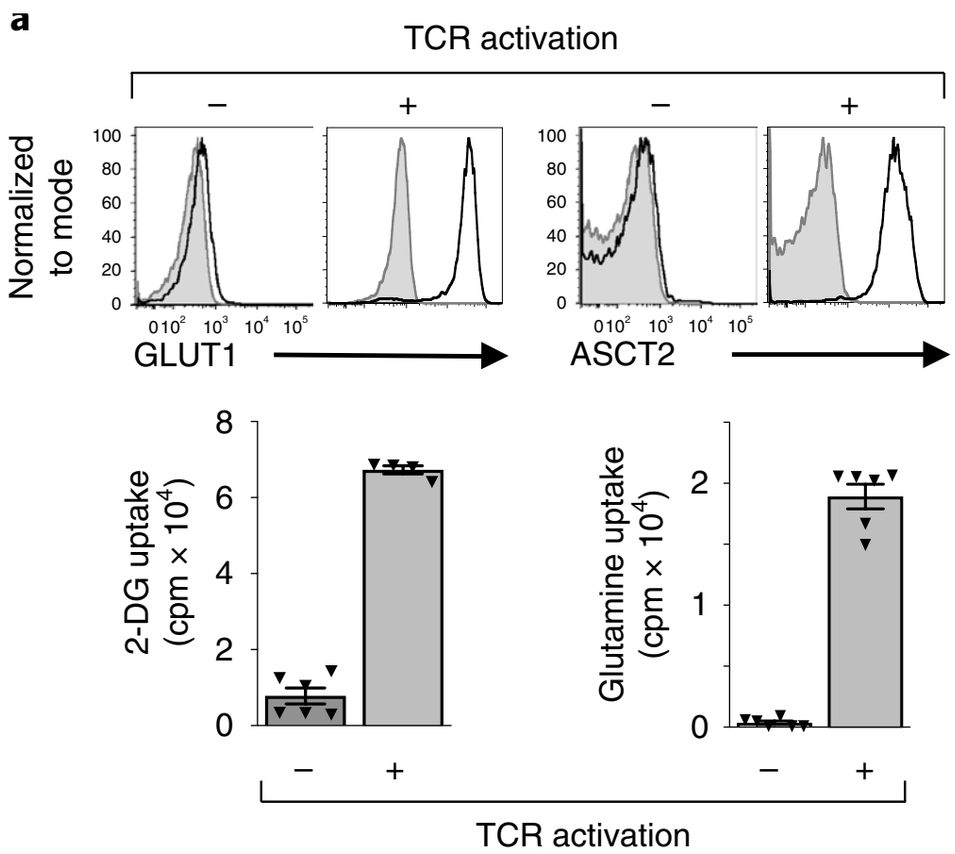
Metabolic rewiring of activated T cells

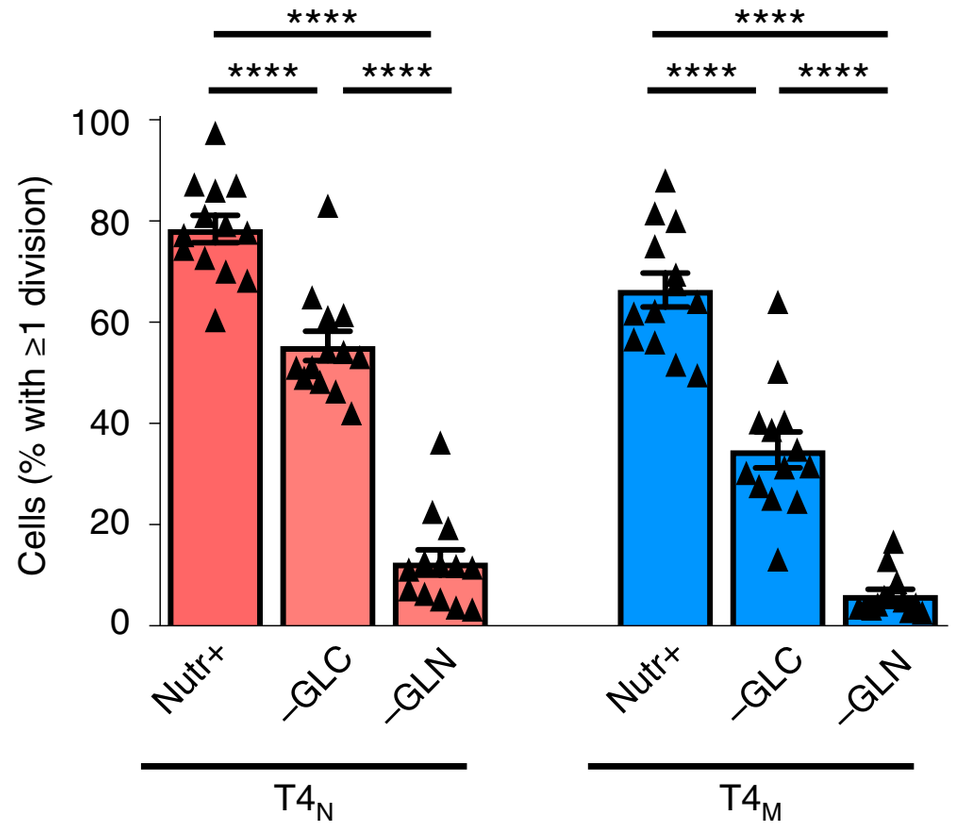


Bioenergetic profiling of T cells has revealed that T cell metabolism changes dynamically with activation state. Upon antigen encounter, T cells become activated, undergo extensive proliferation, and differentiate into effector T cells (T_{EFF}); upon pathogen clearance, most T_{EFF} cells die, leaving behind a small population of long-lived antigen-specific memory T cells (T_M). Resting naïve T cells maintain low rates of glycolysis and predominantly oxidize glucose-derived pyruvate. Upon activation, T cells switch to a program of anabolic growth and biomass accumulation to generate daughter cells, which by definition dictates increased demand for ATP and metabolic resources. In this state, T cells are considered to be metabolically activated. **T cell receptor (TCR) signaling directs the metabolic reprogramming of naïve T cells.**

Entry of glucose- and glutamine-derived carbons into the citric acid cycle supports early steps of HIV-1 infection in CD4 T cells

Isabelle Clerc[1,6], Daouda Abba Moussa[1,6], Zoi Vahlas[1,6], Saverio Tardito[2,3], Leal Oburoglu[1], Thomas J. Hope[4], Marc Sitbon[1], Valérie Dardalhon[1], Cédric Mongellaz[1,7*] and Naomi Taylor[1,5,7*]

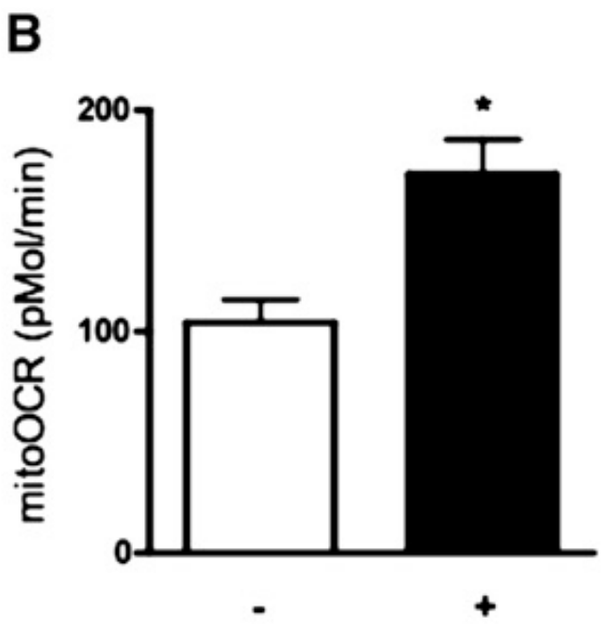


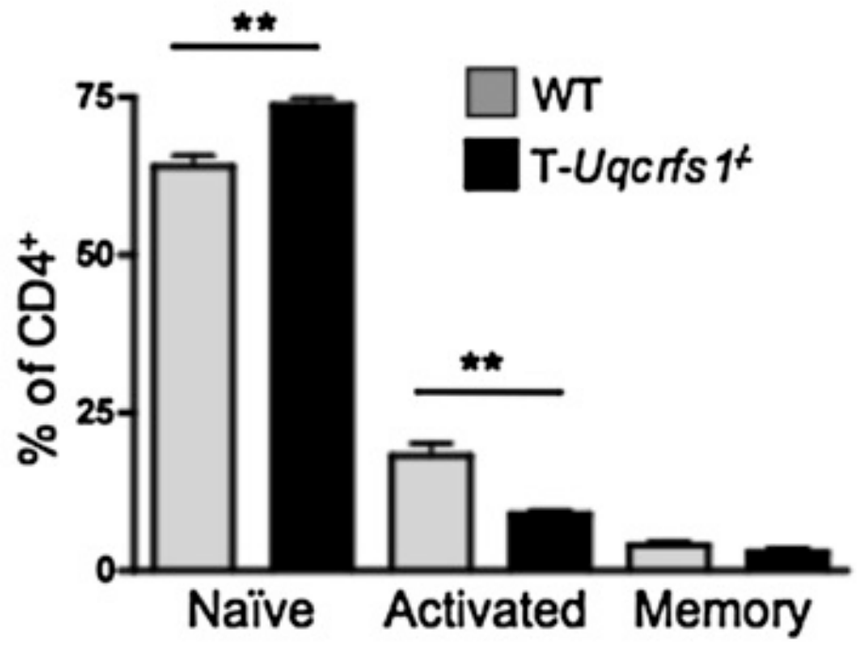


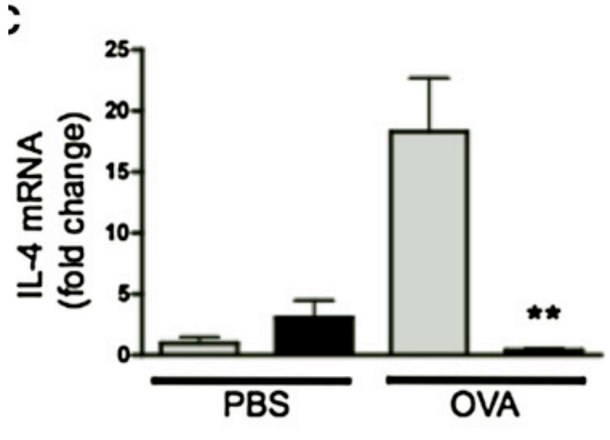
Clerc et al, ***Nat Metab****, 2019*

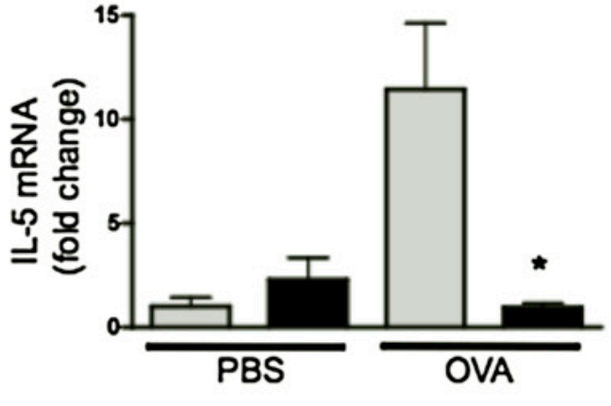
Mitochondria Are Required for Antigen-Specific T Cell Activation through Reactive Oxygen Species Signaling

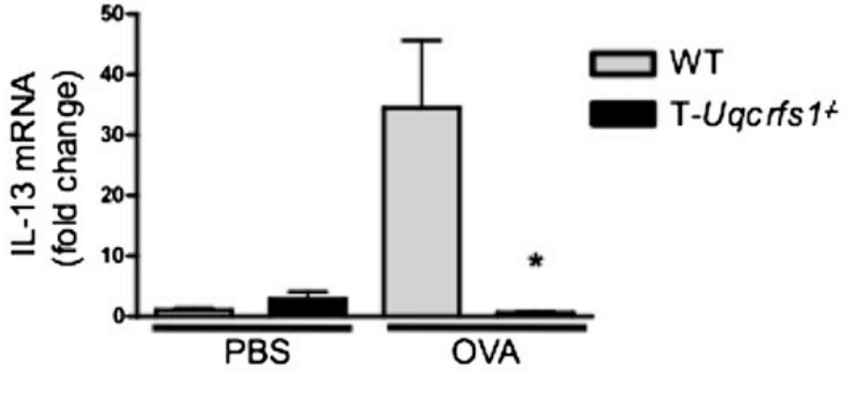
Laura A. Sena,[1] Sha Li,[2] Amit Jairaman,[3] Murali Prakriya,[3] Teresa Ezponda,[1] David A. Hildeman,[5] Chyung-Ru Wang,[2] Paul T. Schumacker,[4] Jonathan D. Licht,[1] Harris Perlman,[1] Paul J. Bryce,[1] and Navdeep S. Chandel[1,*]





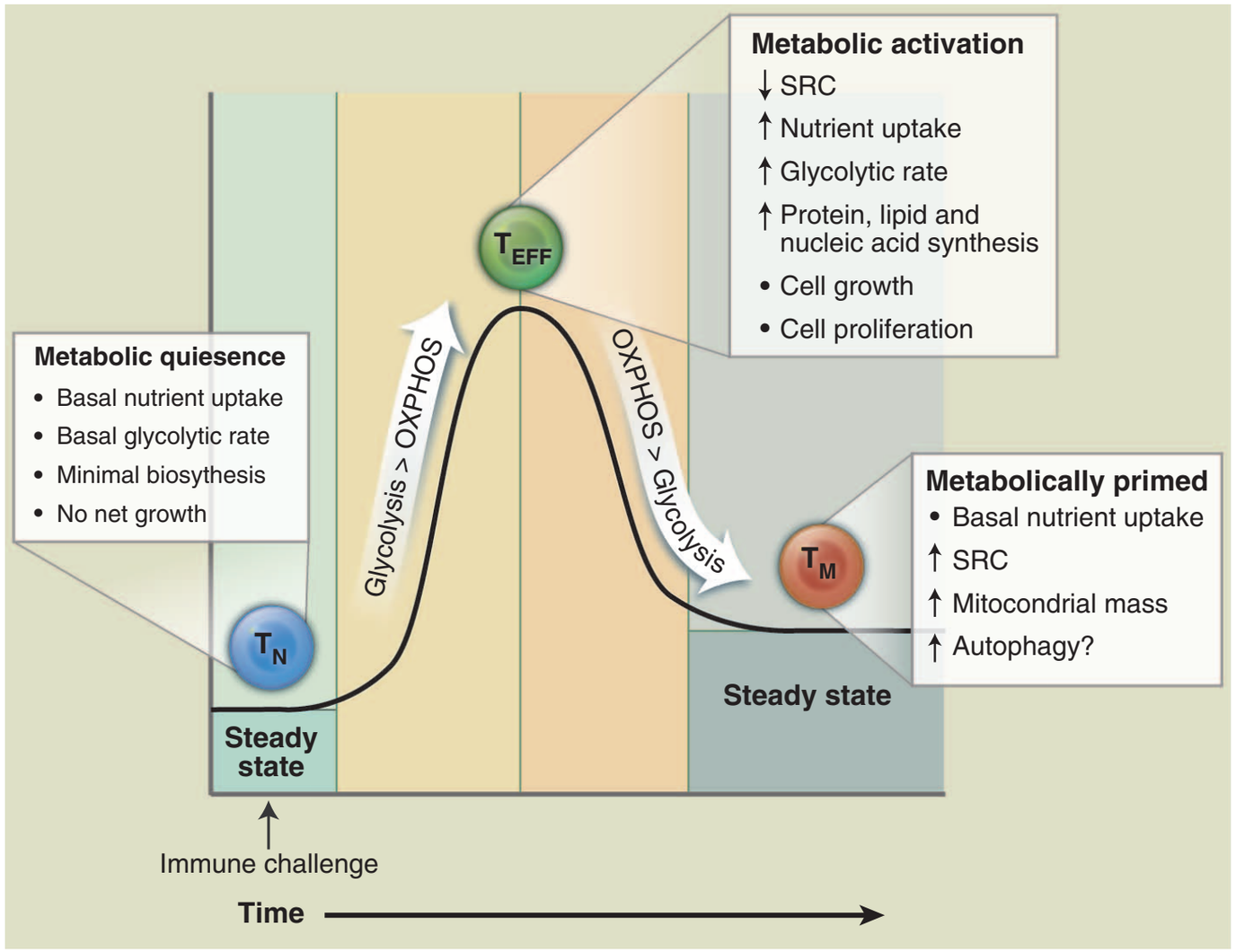






*Sena et al, **Immunity**, 2013*

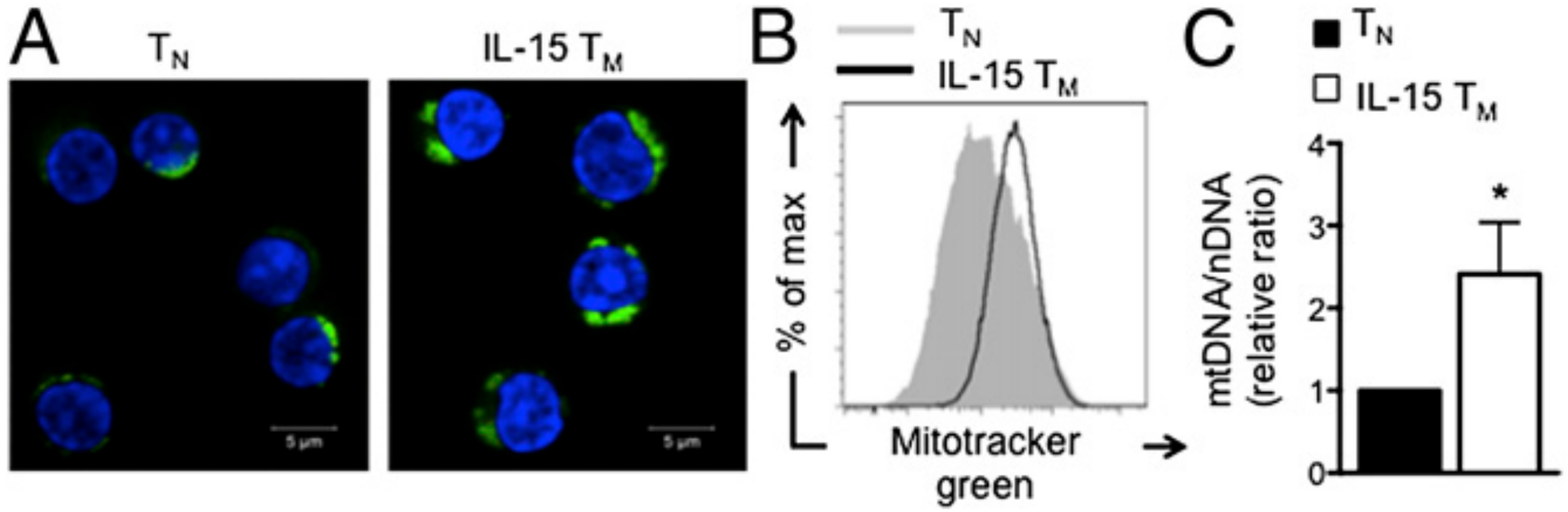
Metabolic rewiring of activated T cells

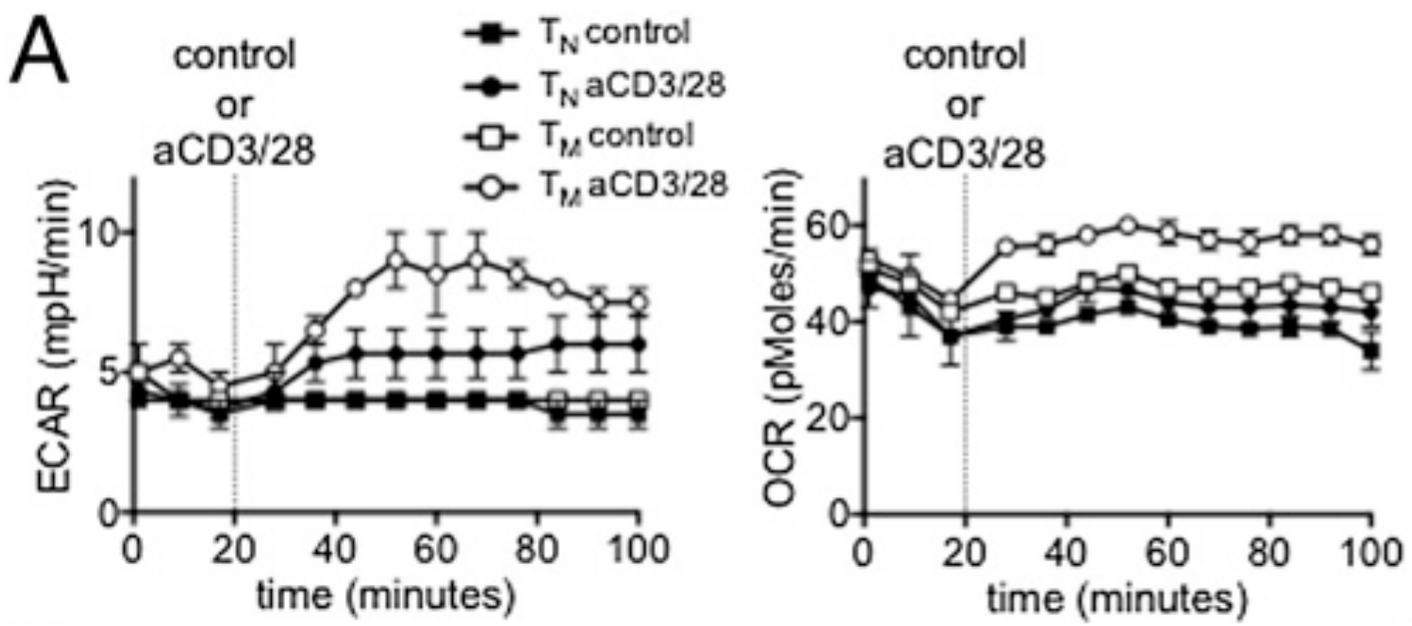


As a quiescent T cell population, T_M cells adopt a metabolic profile similar to that of naïve T cells — a catabolic metabolism characterized by increased reliance on OXPHOS and lower rates of nutrient uptake and biosynthesis relative to T_{EFF} cells. However, T_M cells also display a characteristic increase in mitochondrial mass, which translates into greater mitochondrial spare respiratory capacity (SRC) relative to naïve or TEFF populations. SRC can be viewed as the maximal respiratory capacity available to a cell, much like the maximum speed that can be achieved by a car engine. Under increased workload, stress, or nutrient limitation, cells en- gage this reserve capacity to generate more energy and promote cell viability

CD8 memory T cells have a bioenergetic advantage that underlies their rapid recall ability

Gerritje J. W. van der Windt[a], David O'Sullivan[a], Bart Everts[a], Stanley Ching-Cheng Huang[a], Michael D. Buck[a], Jonathan D. Curtis[a], Chih-Hao Chang[a], Amber M. Smith[a], Teresa Ai[a], Brandon Faubert[b], Russell G. Jones[b], Edward J. Pearce[a], and Erika L. Pearce[a,1]



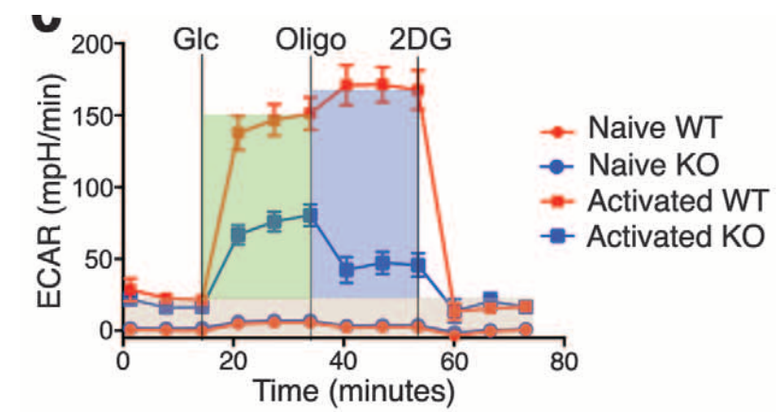


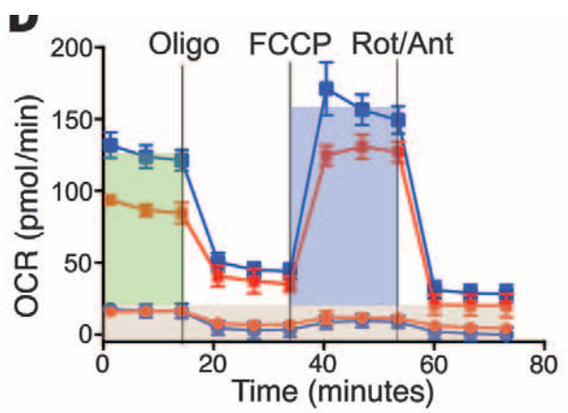
Van der Windt et al, ***PNAS****, 2013*

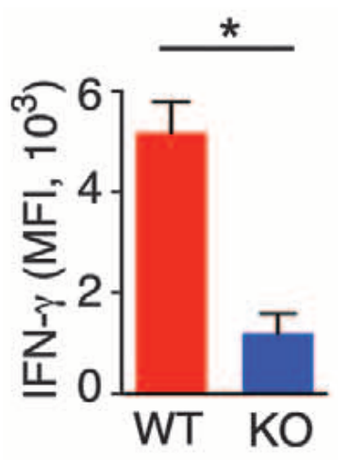
Mechanism??

Aerobic glycolysis promotes T helper 1 cell differentiation through an epigenetic mechanism

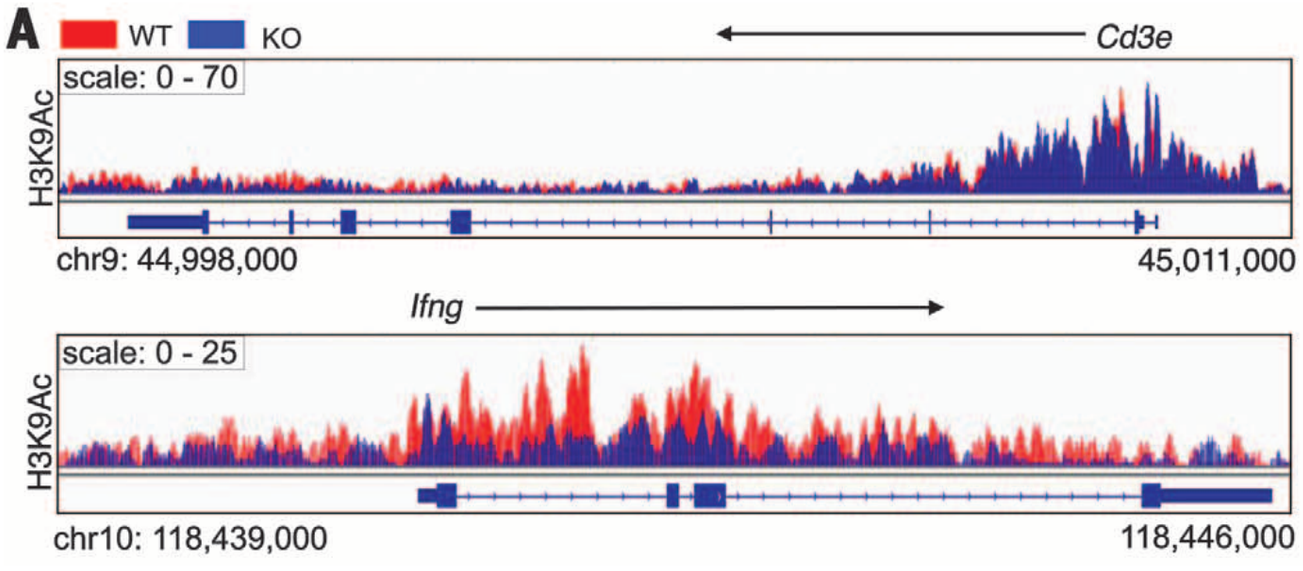
Min Peng,[1]* Na Yin,[1]* Sagar Chhangawala,[2,3] Ke Xu,[1,4] Christina S. Leslie,[2] Ming O. Li[1]†

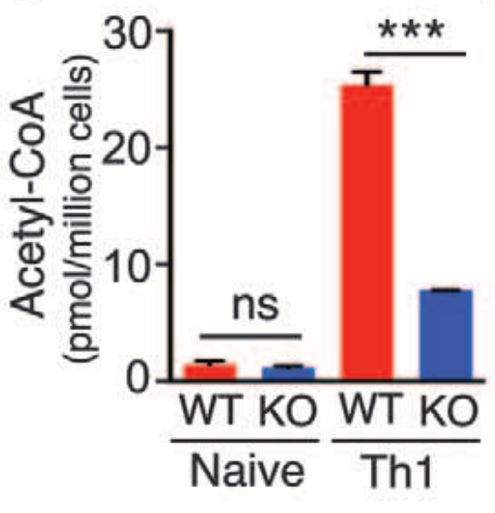






LDHA dictates aerobic glycolysis and supports INFg expression in activated $CD4^+$ T cells.



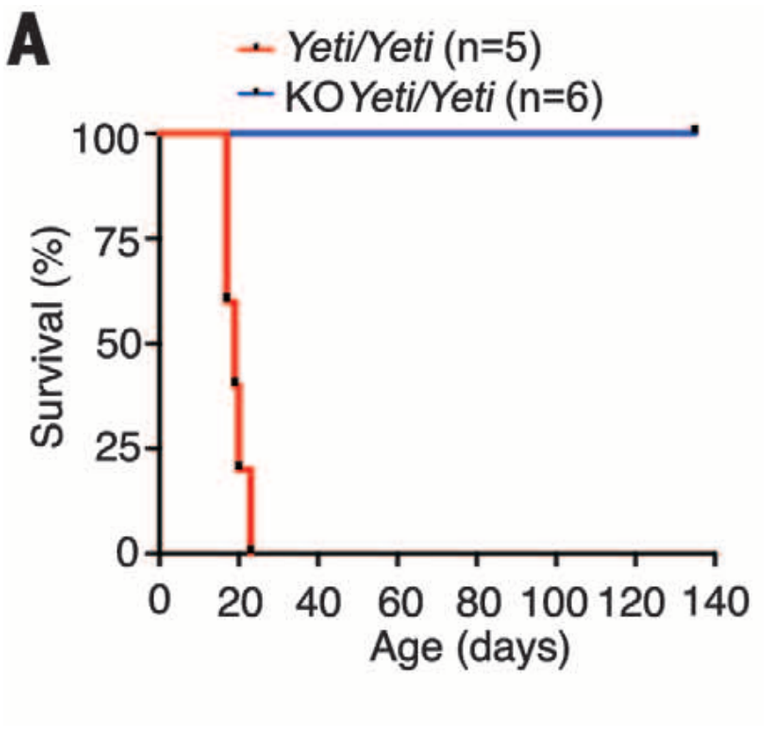


LDHA promotes INFg expression through acetyl-CoA dependent histone acetylation.

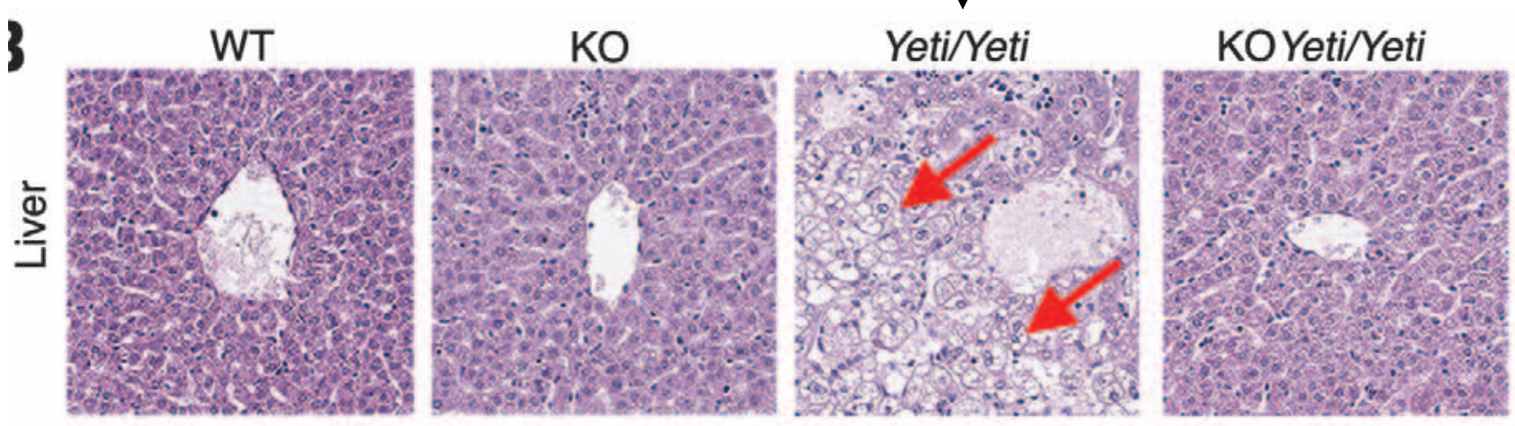
Peng et al, ***Science****, 2016*

Aerobic glycolysis promotes T helper 1 cell differentiation through an epigenetic mechanism

Min Peng,[1]* Na Yin,[1]* Sagar Chhangawala,[2,3] Ke Xu,[1,4] Christina S. Leslie,[2] Ming O. Li[1]†



Sustained INFg expression and auto-inflammatory phenotype

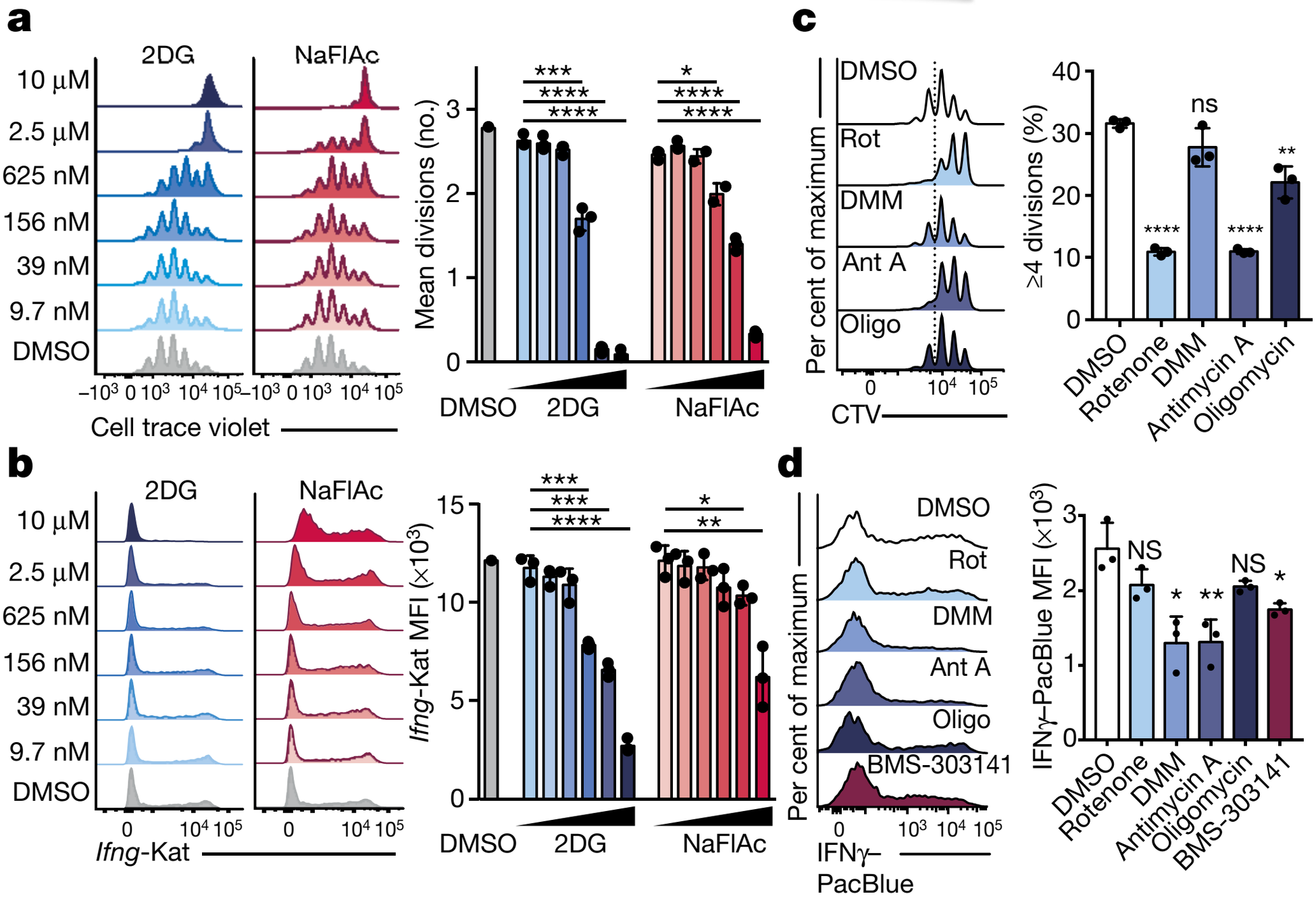


LDHA KO ameliorates Th-driven autoimmunity

*Peng et al, **Science**, 2016*

Distinct modes of mitochondrial metabolism uncouple T cell differentiation and function

Will Bailis[1,2,12], Justin A. Shyer[1,12], Jun Zhao[1,3,4], Juan Carlos Garcia Canaveras[5,6,7], Fatimah J. Al Khazal[8], Rihao Qu[1,3,4], Holly R. Steach[1], Piotr Bielecki[1], Omair Khan[1], Ruaidhri Jackson[1], Yuval Kluger[3,4,9], Louis J. Maher III[8], Joshua Rabinowitz[5,6,7], Joe Craft[1,10]* & Richard A. Flavell[1,11]*

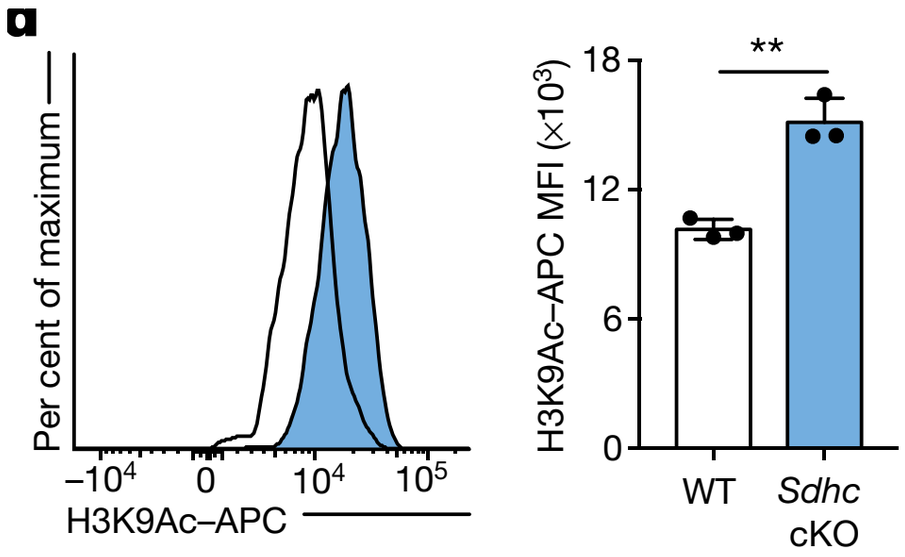


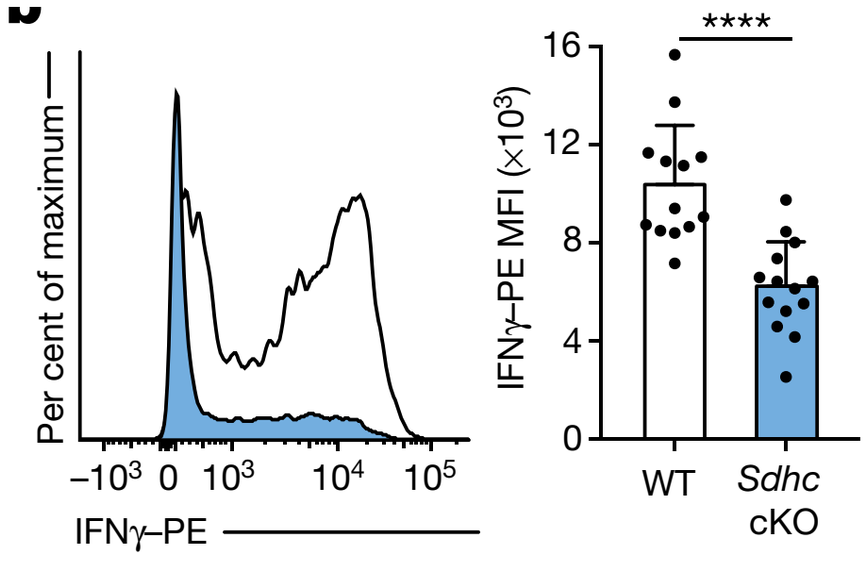
Mitochondria promote both cell proliferation and INFg expression

Bailis et al, ***Nature****, 2019*

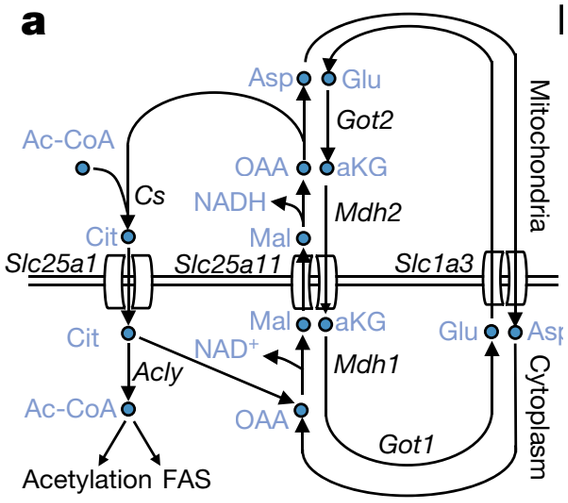
Distinct modes of mitochondrial metabolism uncouple T cell differentiation and function

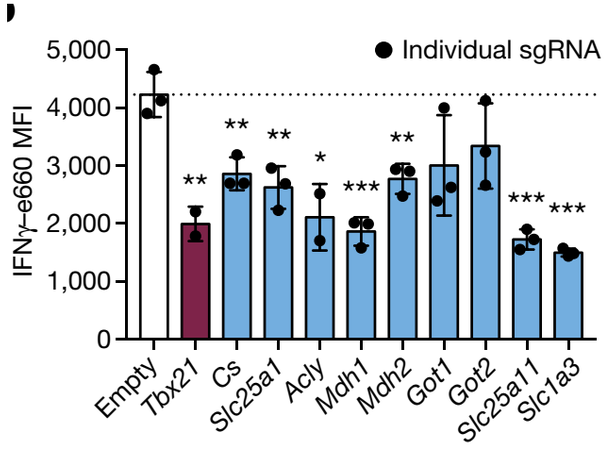
Will Bailis[1,2,12], Justin A. Shyer[1,12], Jun Zhao[1,3,4], Juan Carlos Garcia Canaveras[5,6,7], Fatimah J. Al Khazal[8], Rihao Qu[1,3,4], Holly R. Steach[1], Piotr Bielecki[1], Omair Khan[1], Ruaidhri Jackson[1], Yuval Kluger[3,4,9], Louis J. Maher III[8], Joshua Rabinowitz[5,6,7], Joe Craft[1,10]* & Richard A. Flavell[1,11]*





Complex II uncouples differentiation and effector function of Th1 cells



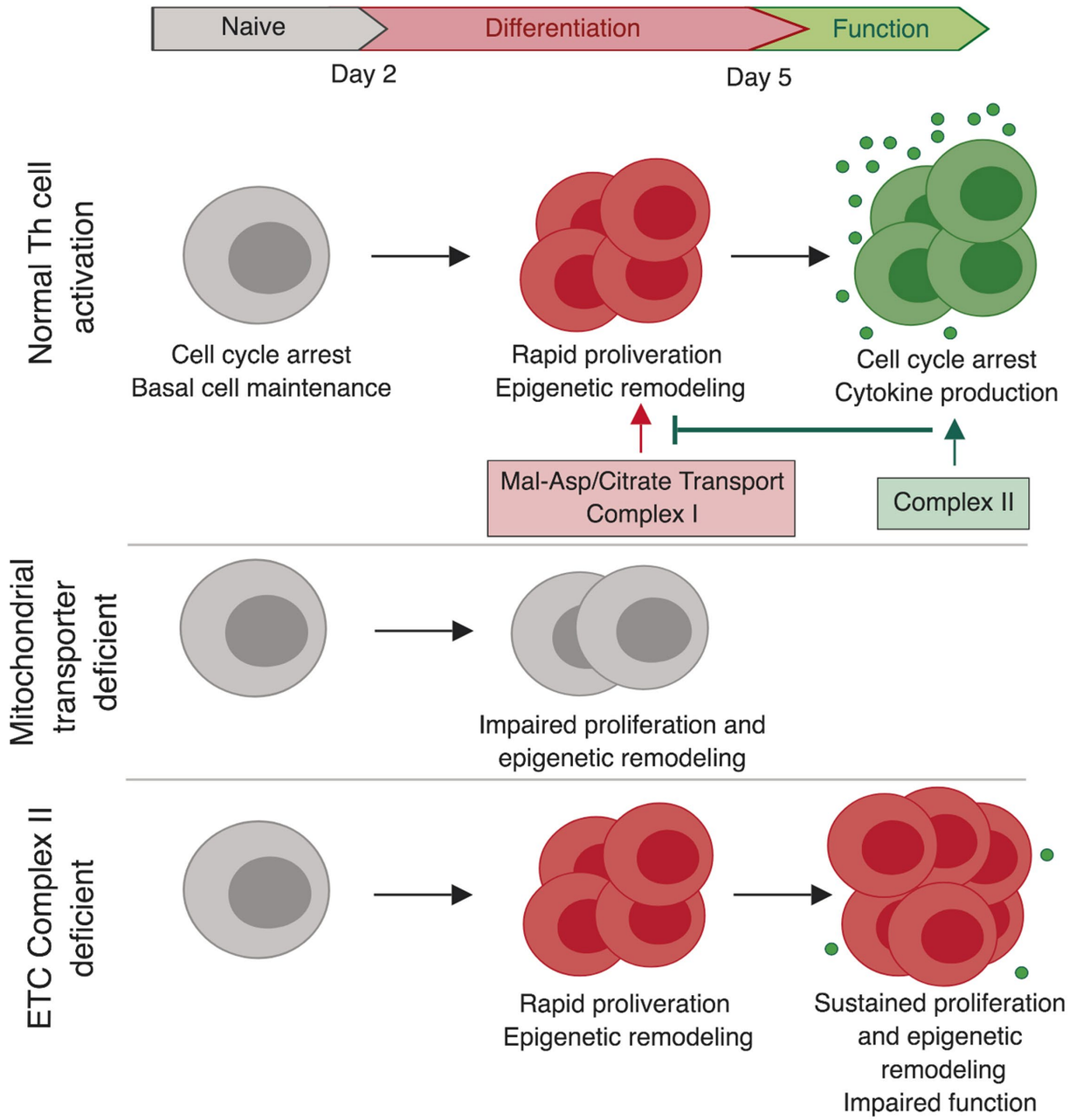


Citrate export (malate shuttle) supports histone acetylation and synthesis of effector genes

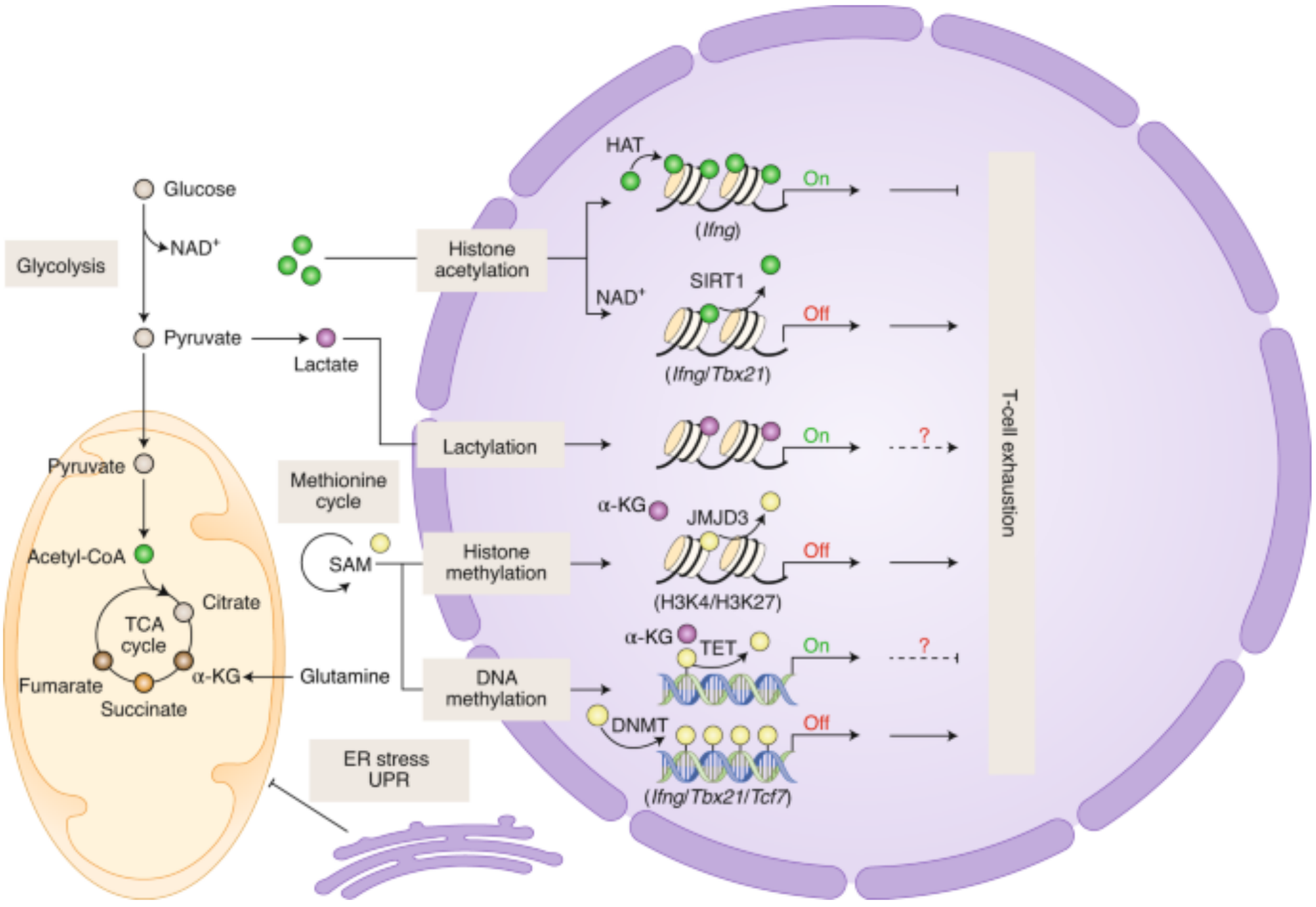
Bailis et al, ***Nature****, 2019*

Distinct modes of mitochondrial metabolism uncouple T cell differentiation and function

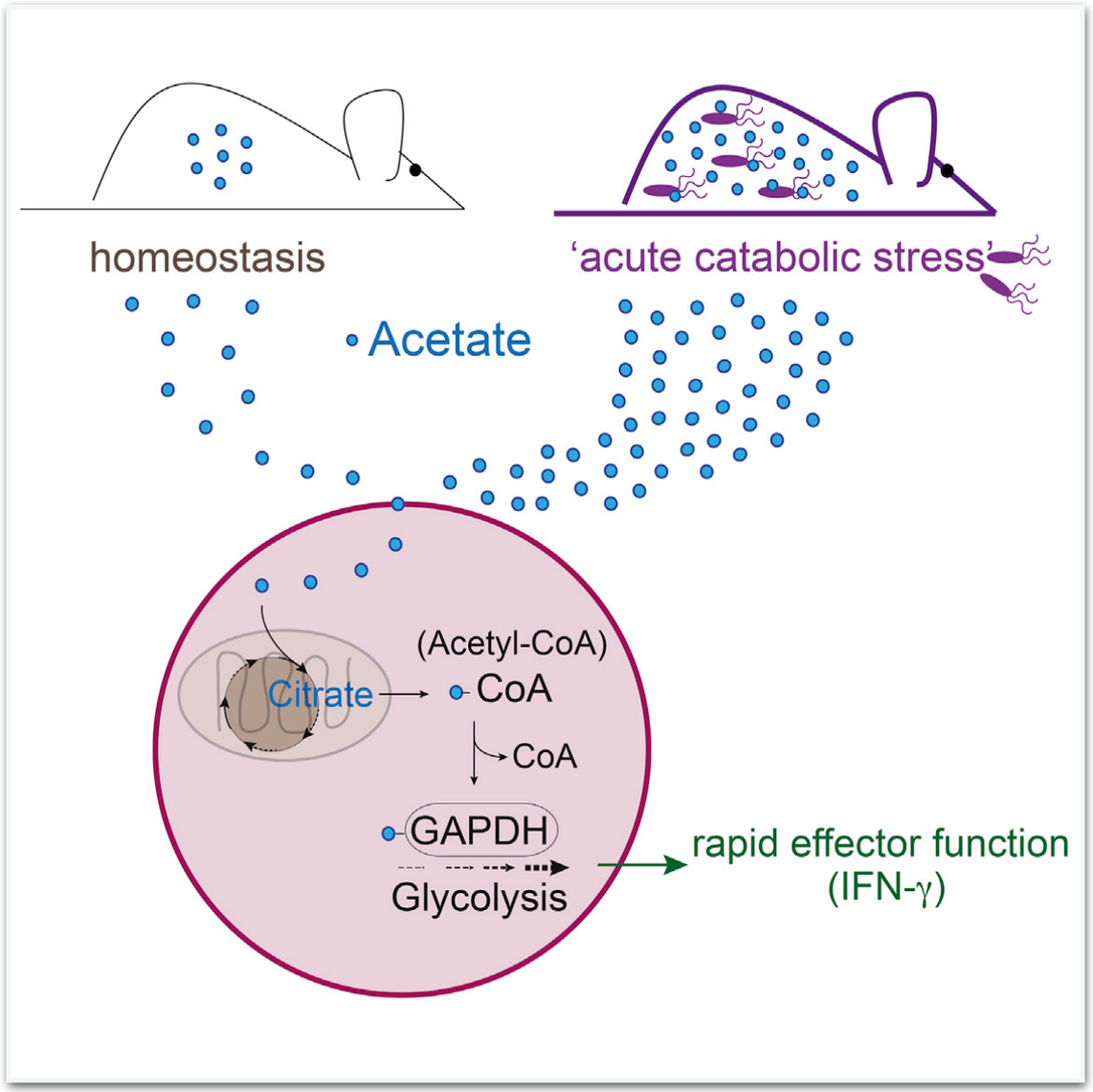
Will Bailis[1,2,12], Justin A. Shyer[1,12], Jun Zhao[1,3,4], Juan Carlos Garcia Canaveras[5,6,7], Fatimah J. Al Khazal[8], Rihao Qu[1,3,4], Holly R. Steach[1], Piotr Bielecki[1], Omair Khan[1], Ruaidhri Jackson[1], Yuval Kluger[3,4,9], Louis J. Maher III[8], Joshua Rabinowitz[5,6,7], Joe Craft[1,10]* & Richard A. Flavell[1,11]*



Bailis et al, ***Nature****, 2019*



Franco et al, ***Nat Metab****, 2020*



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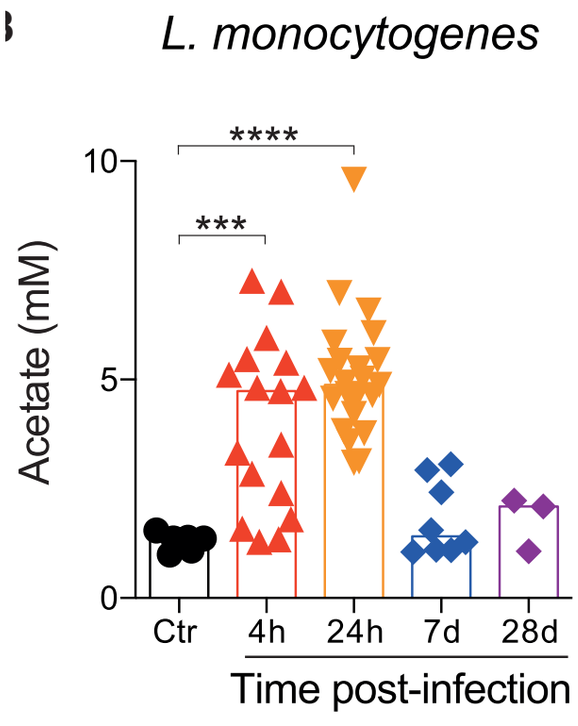
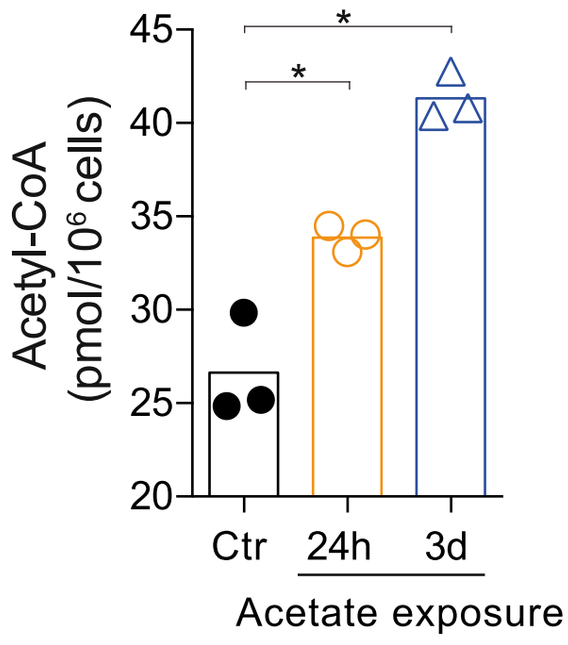
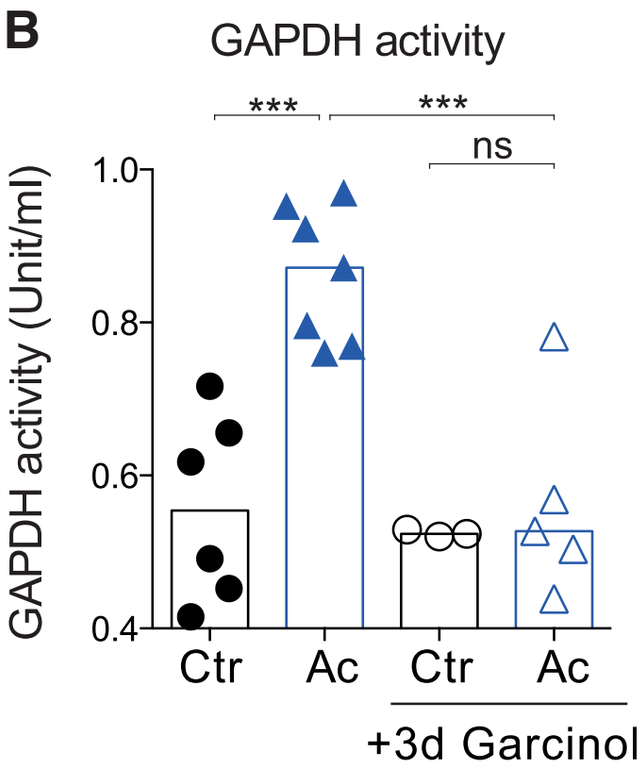
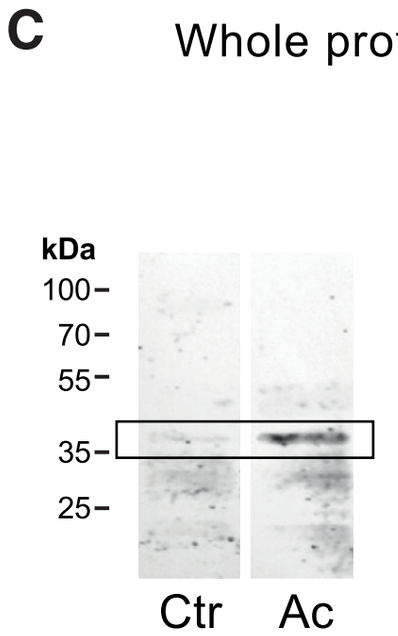
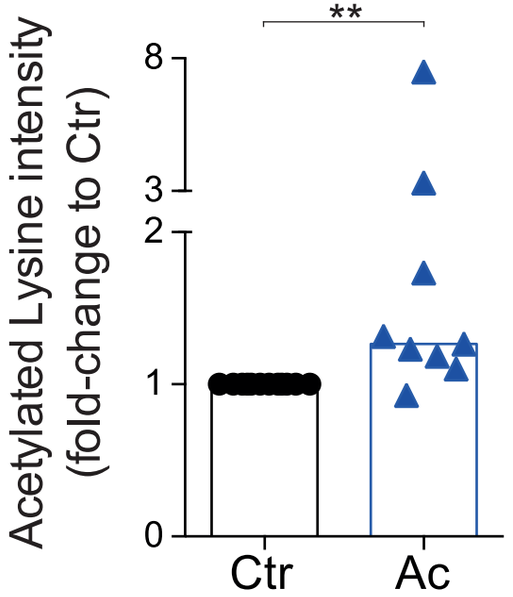




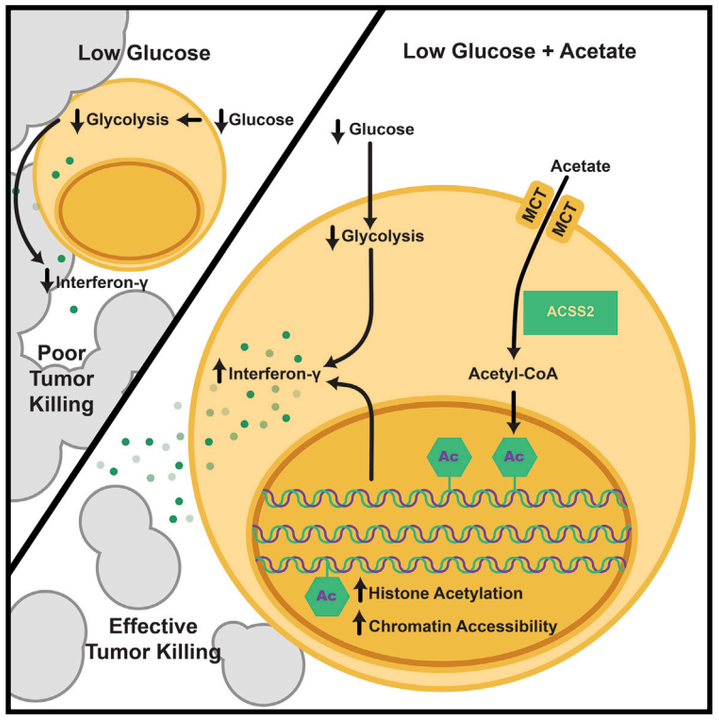
Balmer et al, ***Immunity****, 2016*
Qiu et al, ***Cell Rep****, 2019*

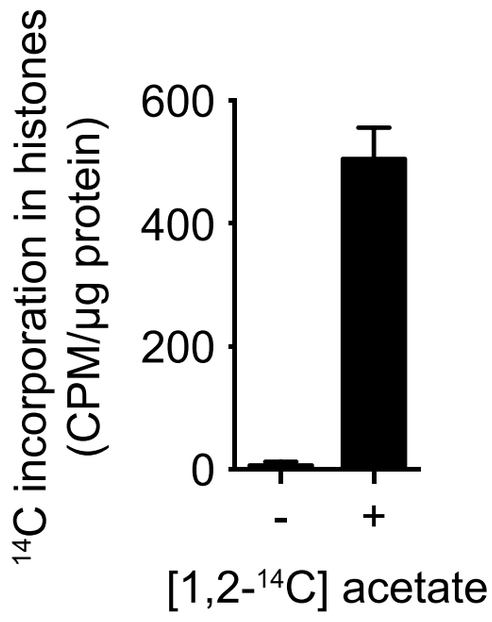


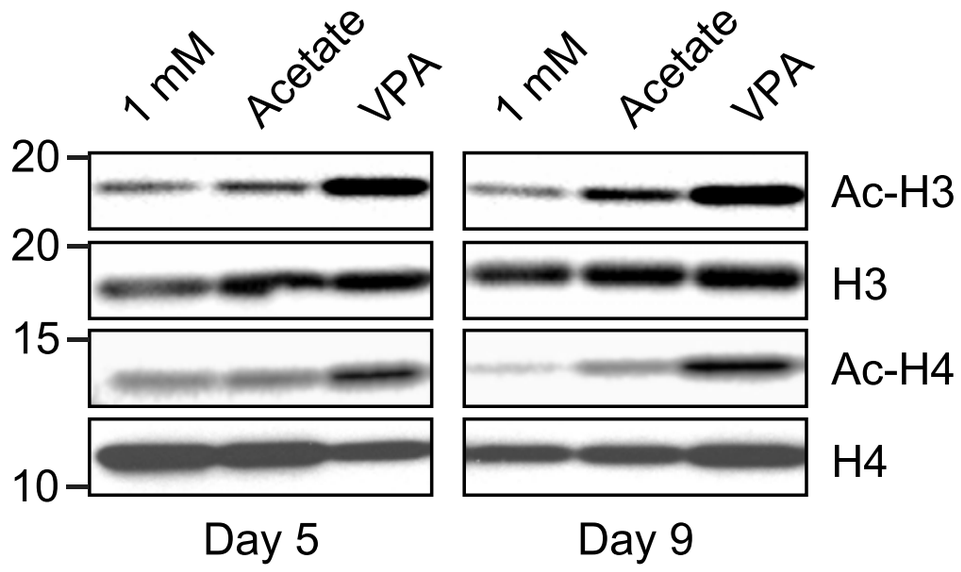




Balmer et al, ***Immunity****, 2016*
Qiu et al, ***Cell Rep****, 2019*







Balmer et al, ***Immunity****, 2016*
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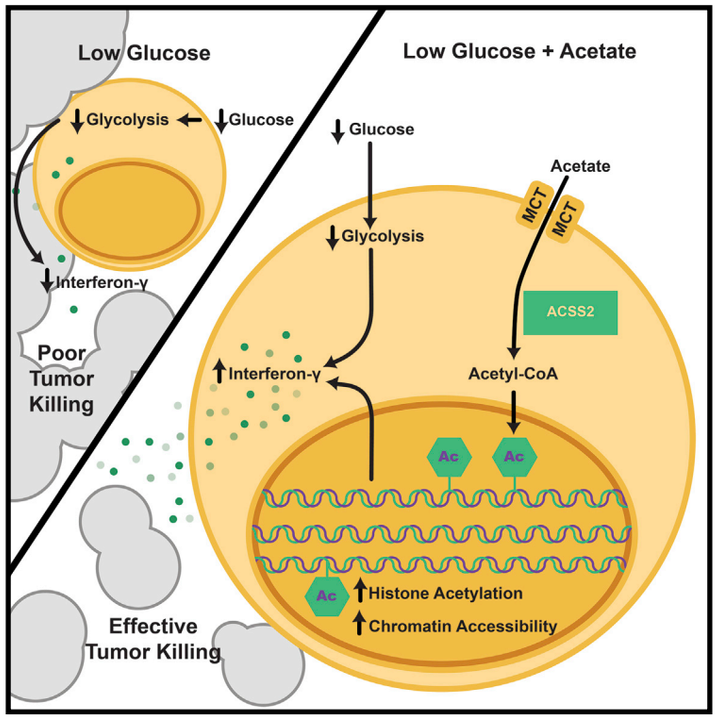
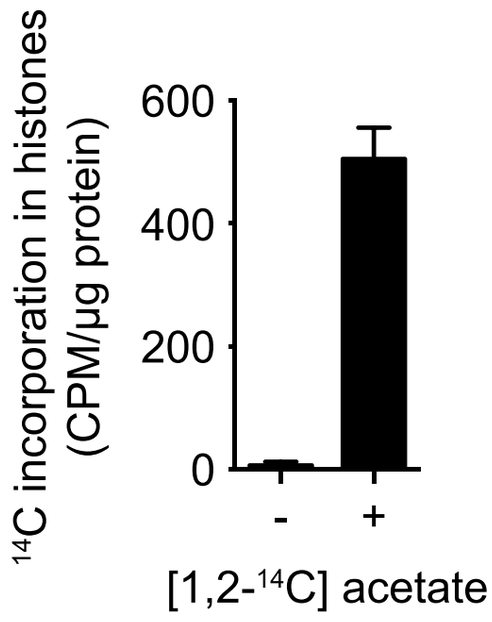
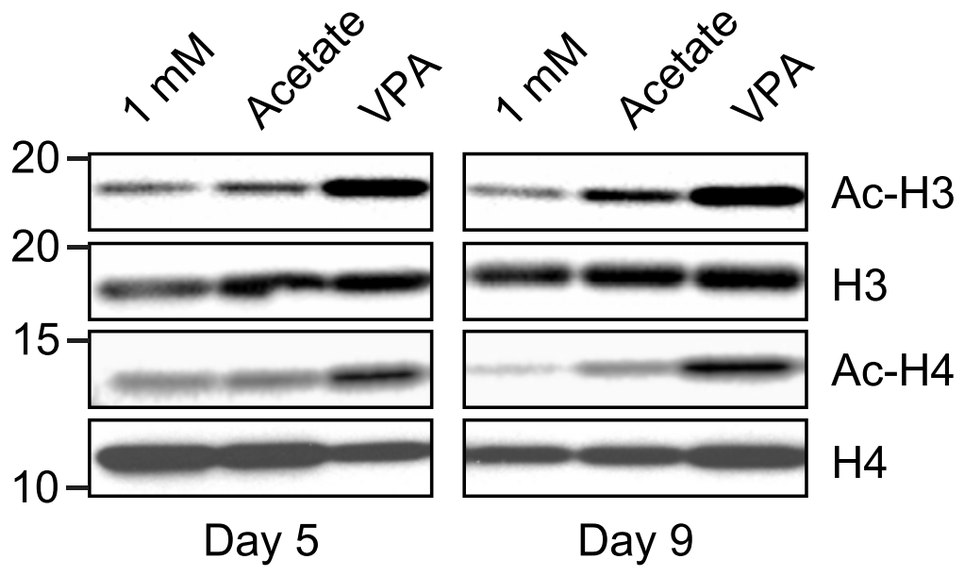
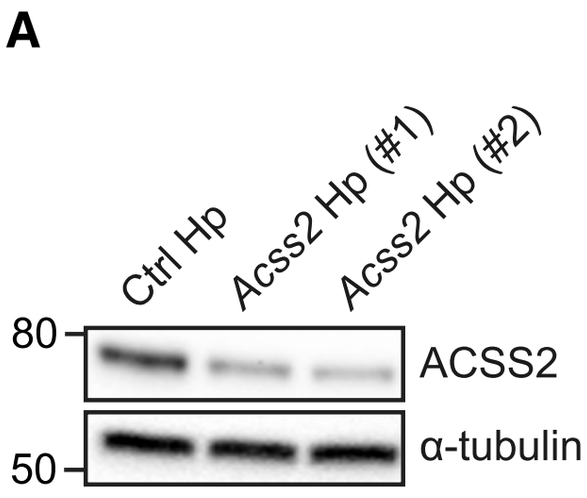
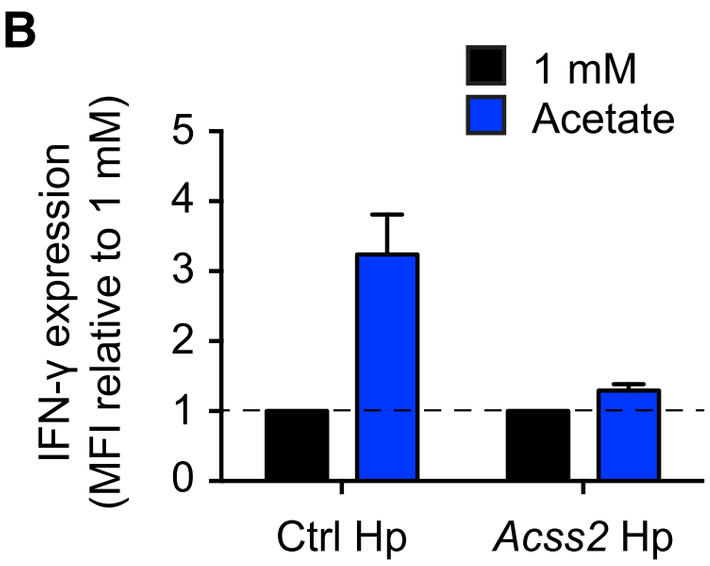
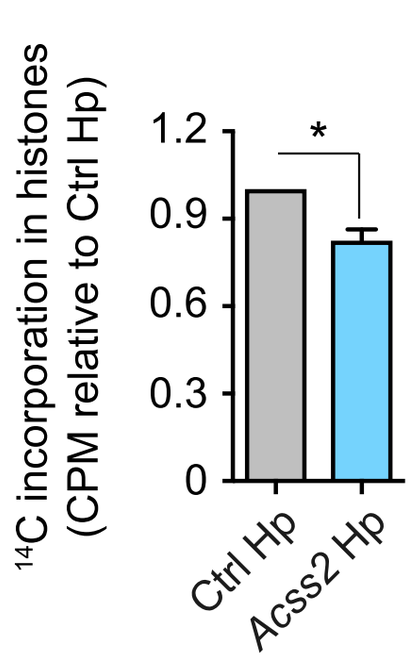


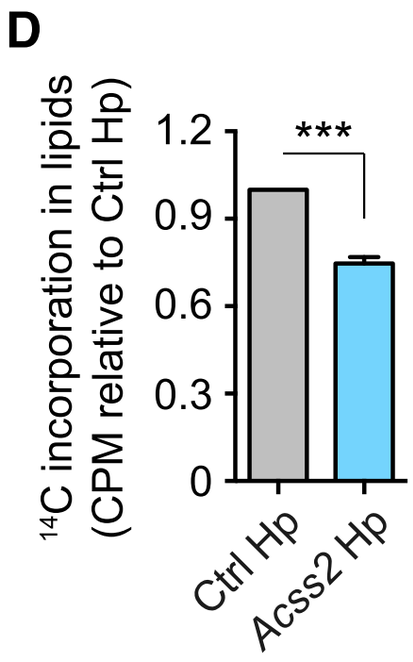












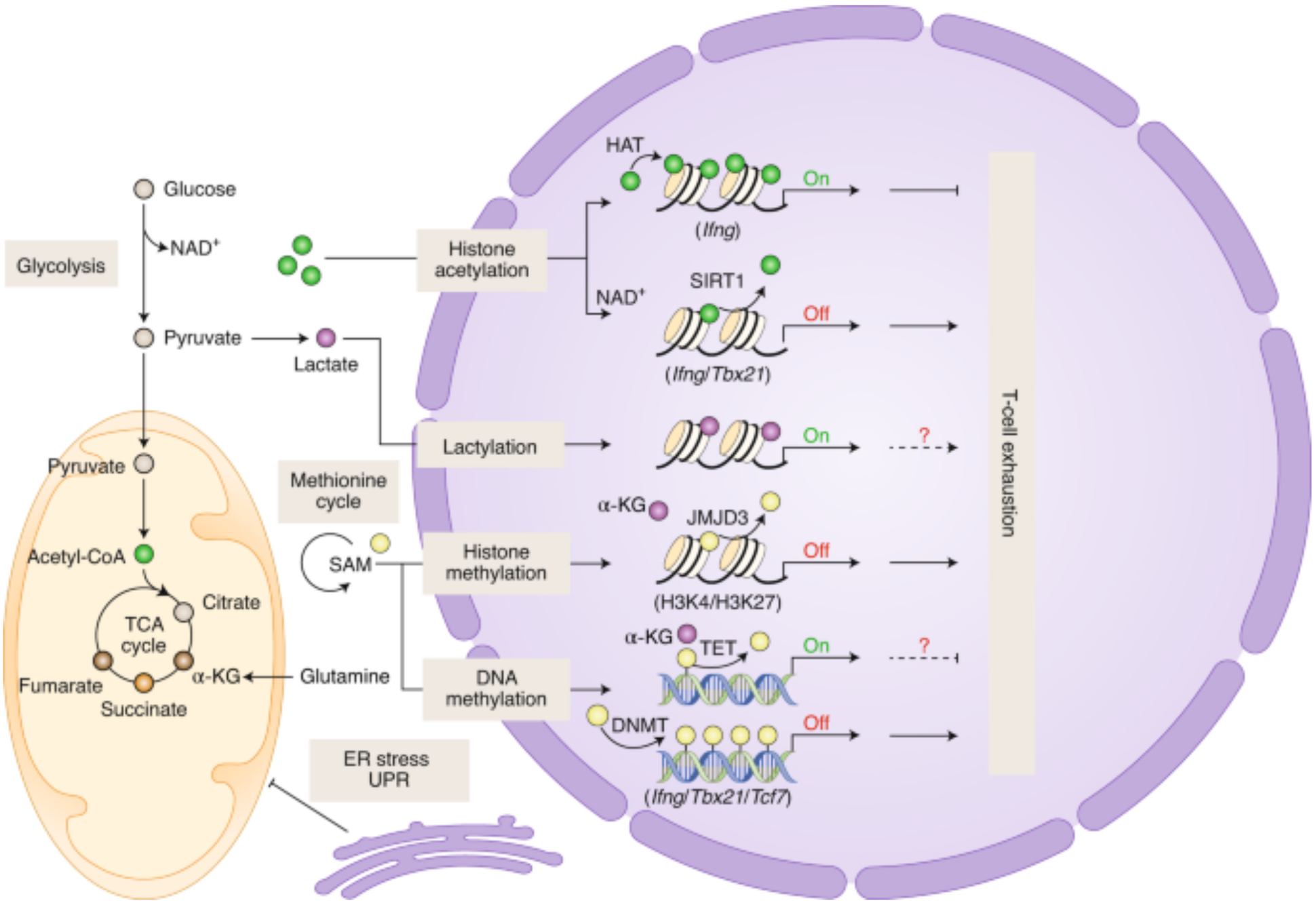
Balmer et al, ***Immunity****, 2016*
Qiu et al, ***Cell Rep****, 2019*

T cells need acetyl-CoA to mature

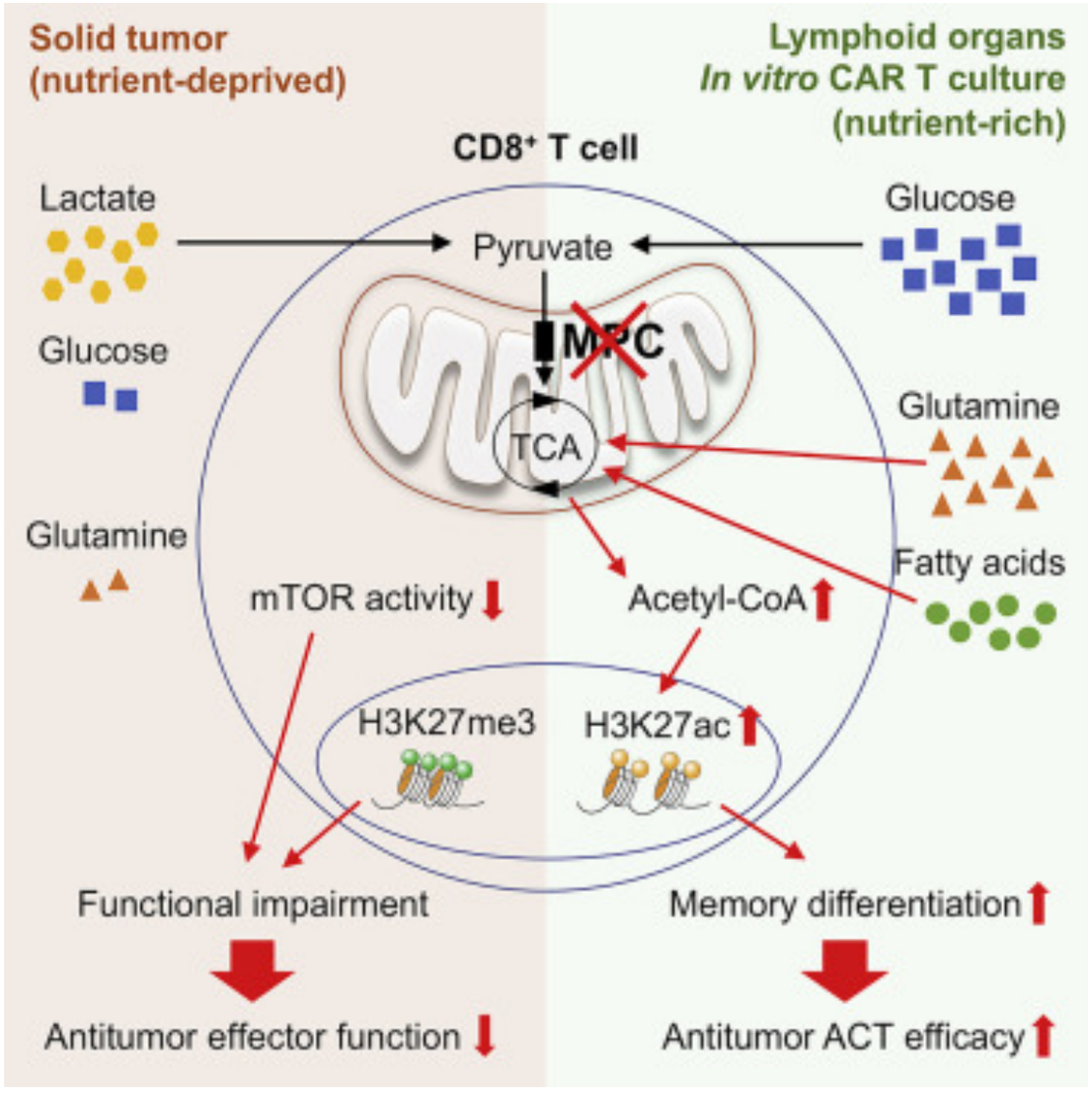
Anabolic substrate for macromolecule synthesis (proliferation)

Histone acetylation substrate for gene expression (effector function)

How is this impaired in disease??



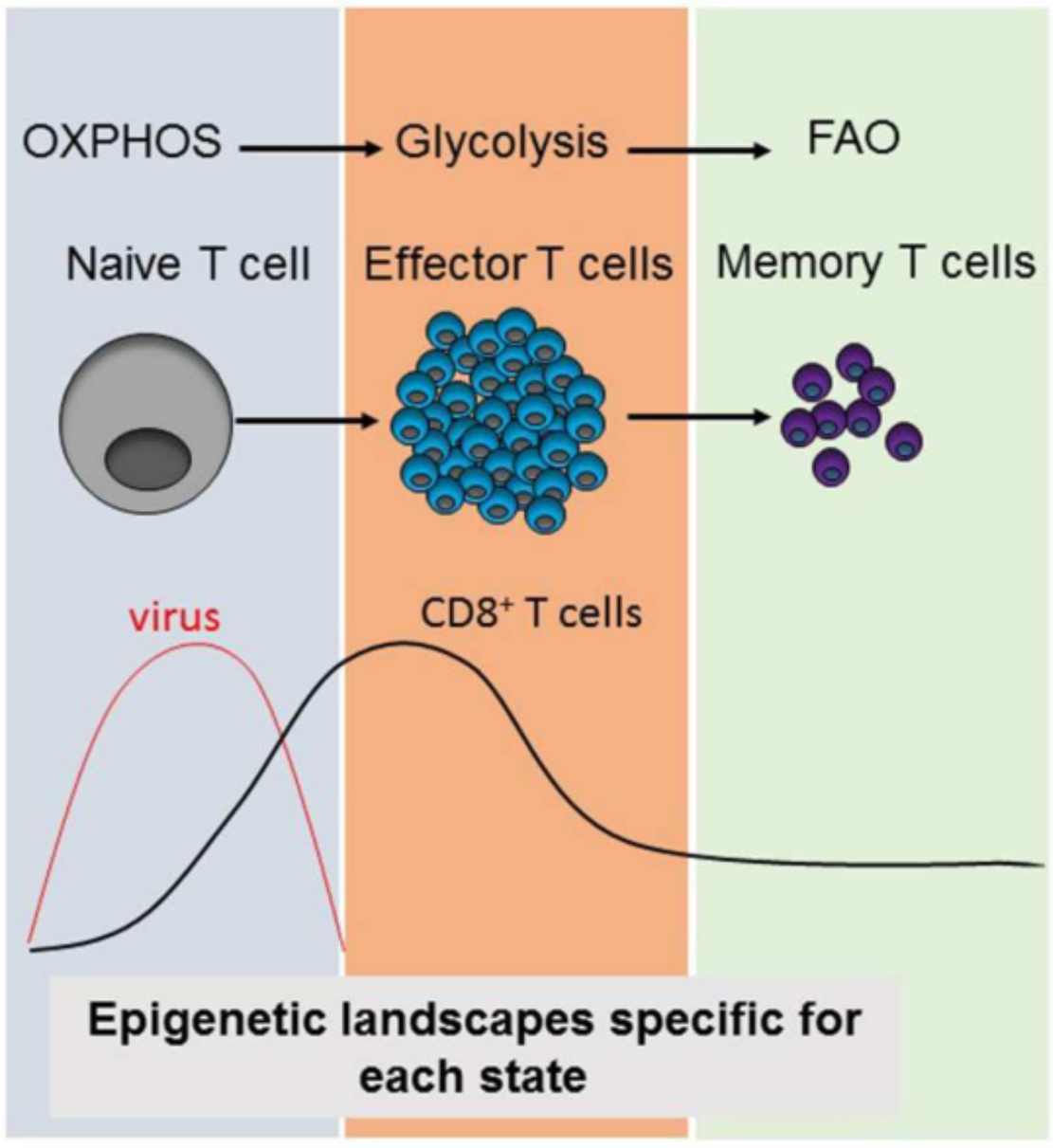
Franco et al, ***Nat Metab****, 2020*



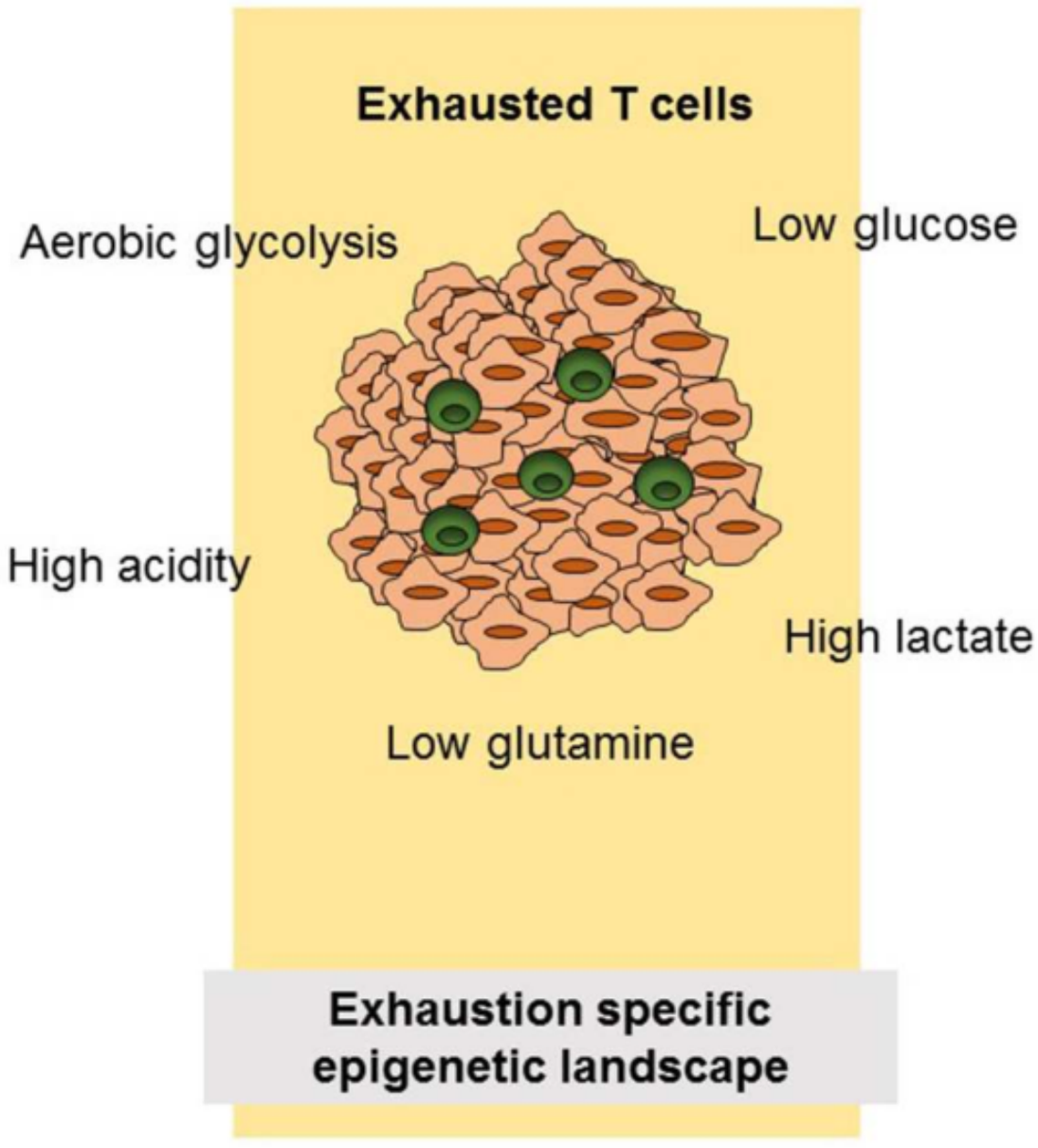
The composition of the microenvironment affects acetyl-CoA availability and global levels of histone acetylation/methylation

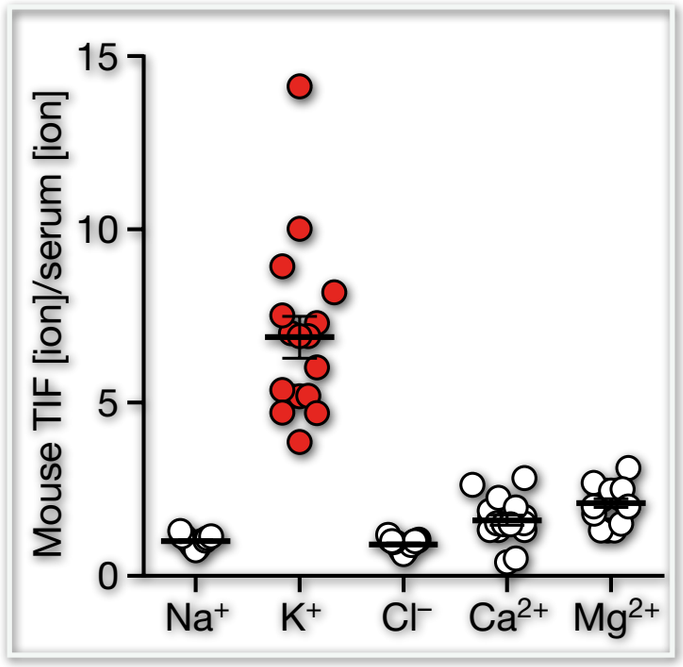
Wenes et al, ***Cell Metab****, 2022*

A

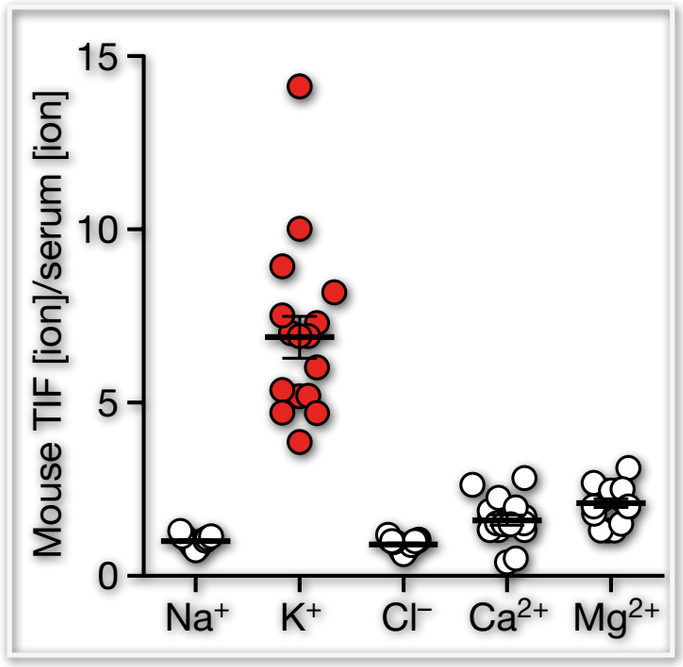

Infection
OXPHOS
Glycolysis
FAO
Naive T cell
Effector T cells
Memory T cells
virus
CD8+ T cells
Epigenetic landscapes specific for each state

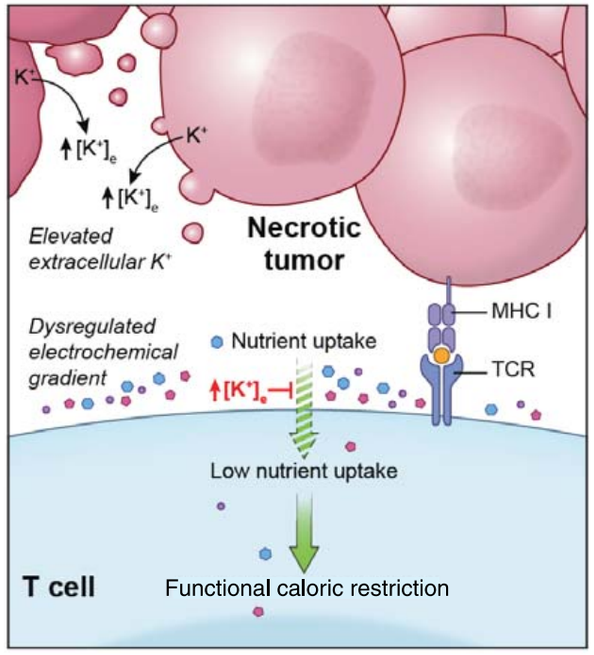
B


Tumor
Exhausted T cells
Aerobic glycolysis
Low glucose
High acidity
High lactate
Low glutamine
Exhaustion specific epigenetic landscape

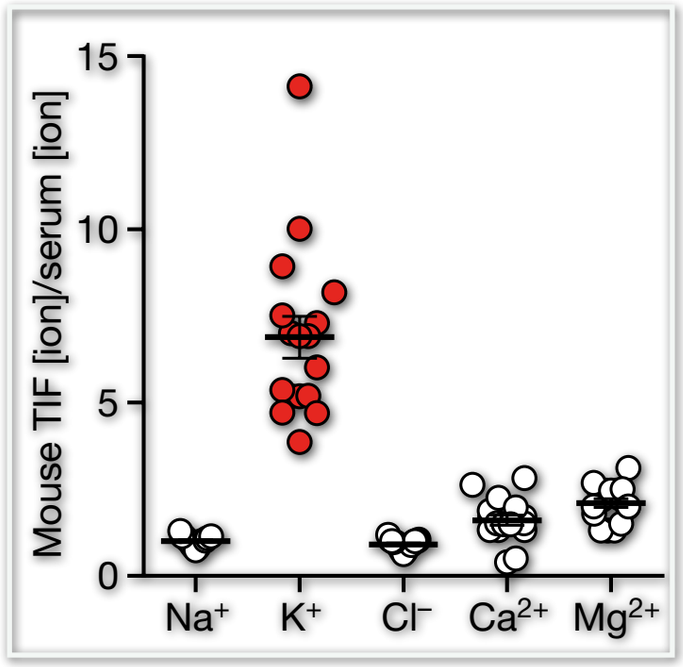


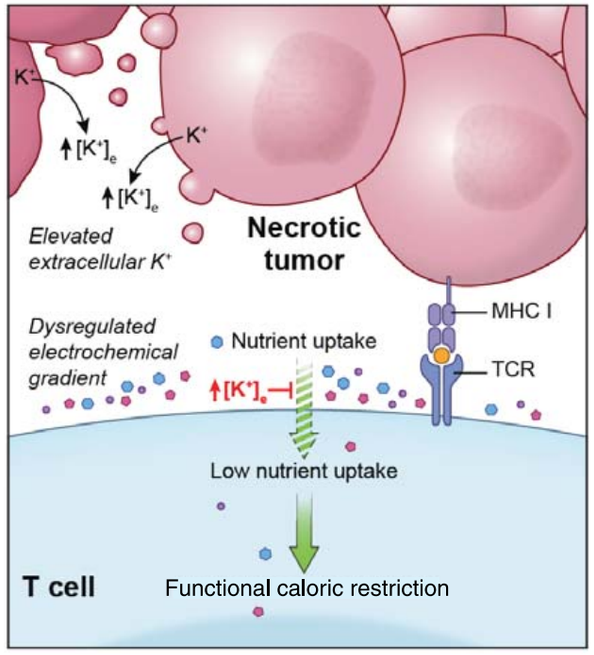
Eil et al, ***Nature****, 2016*
Vodnala et al, ***Science****, 2019*

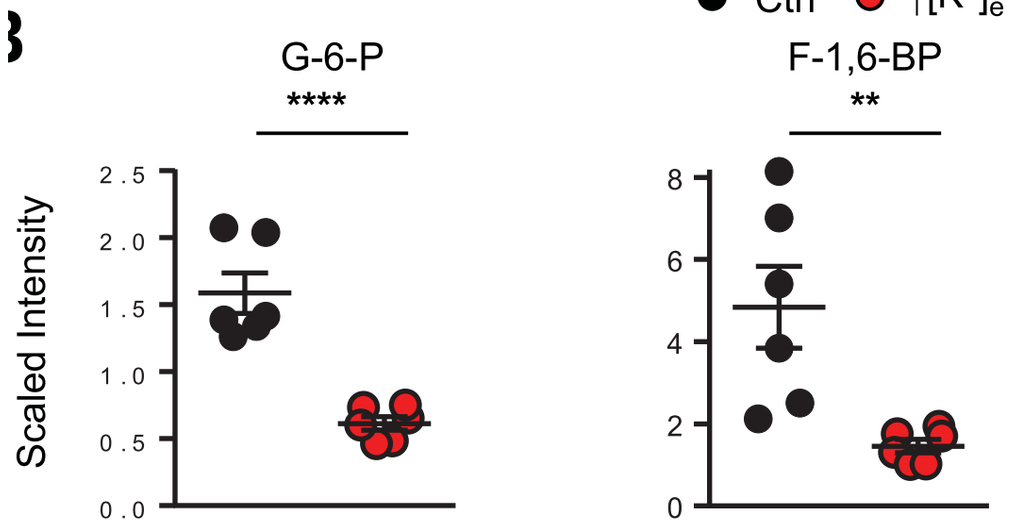




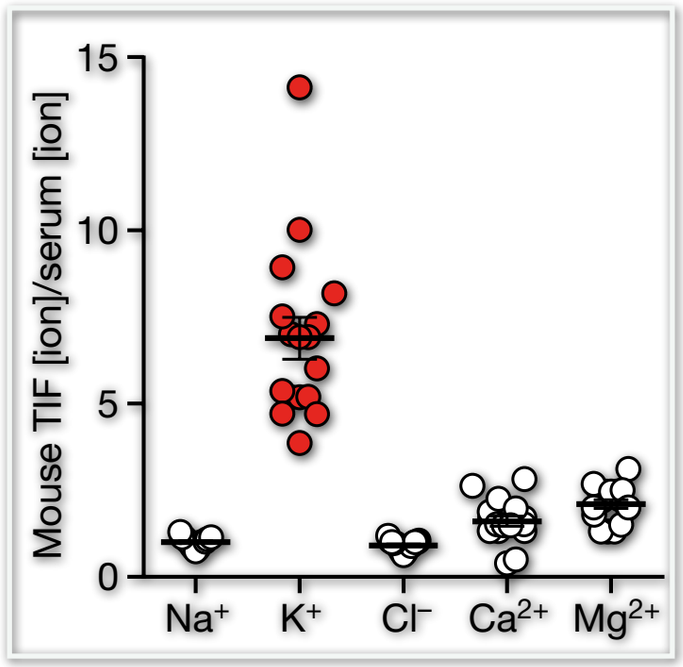
Eil et al, ***Nature****, 2016*
Vodnala et al, ***Science****, 2019*

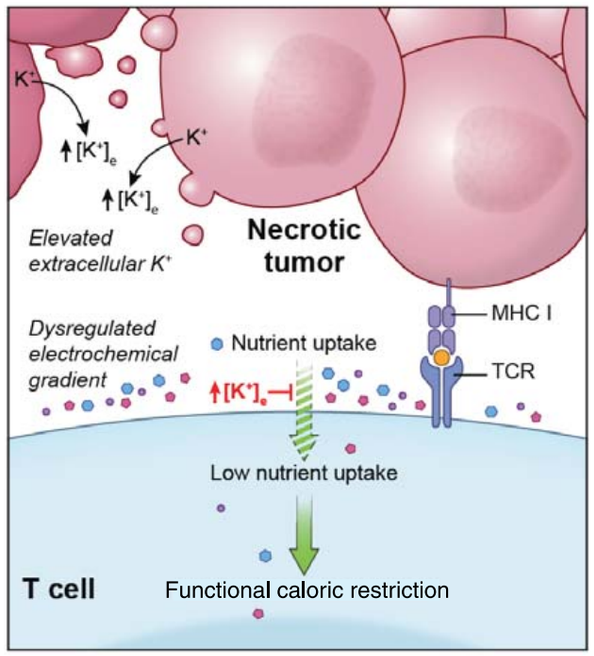


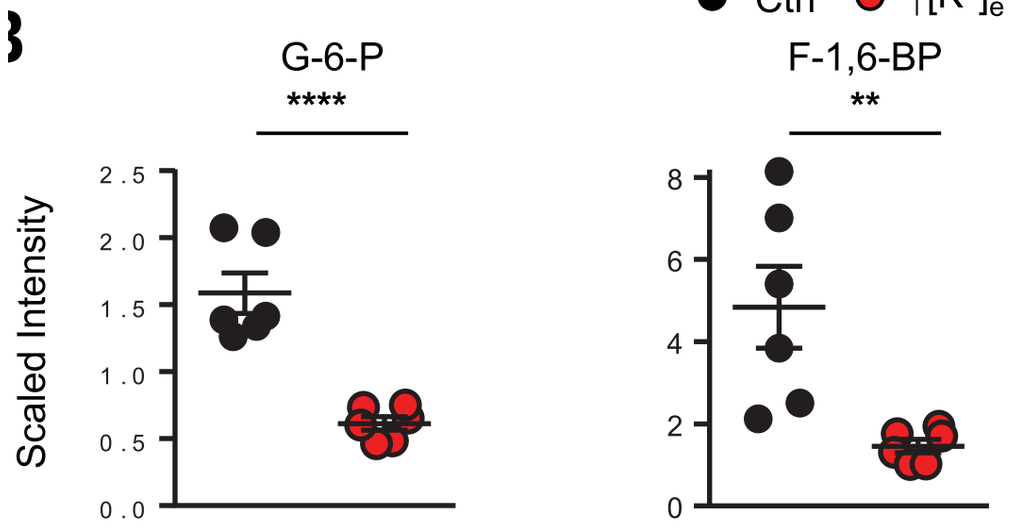


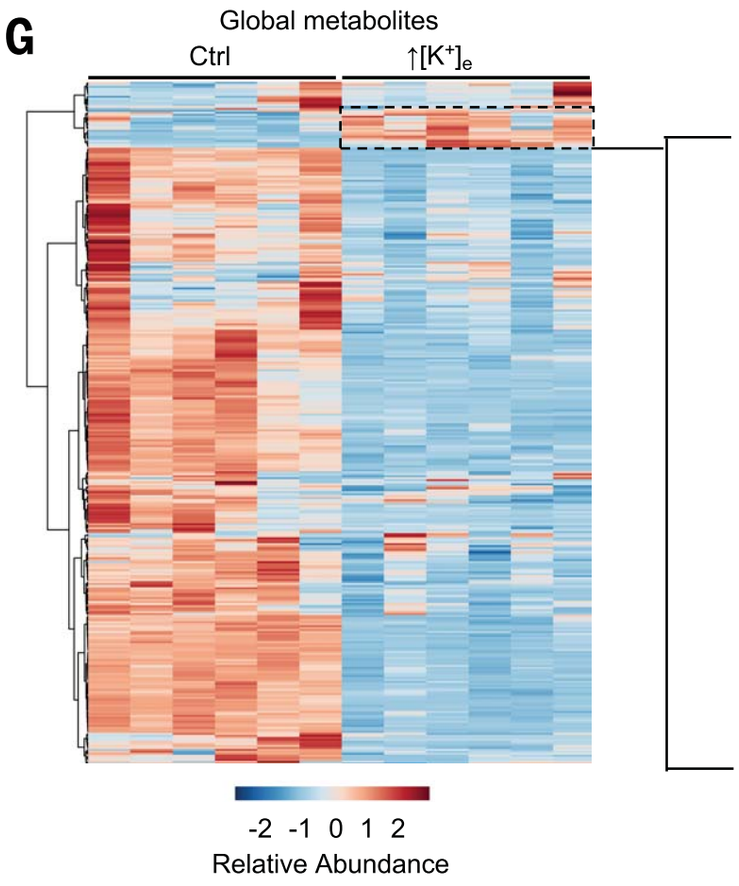


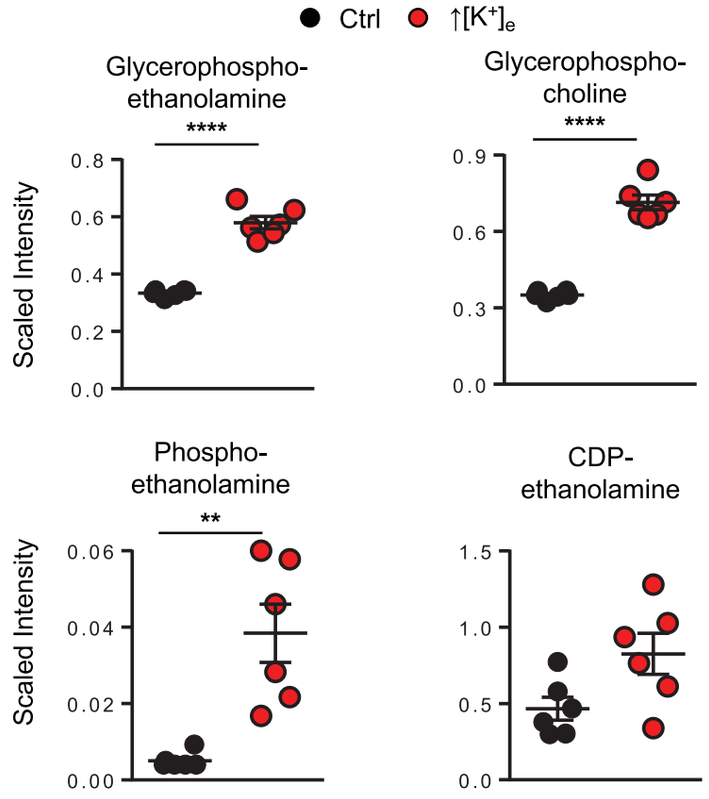
Eil et al, ***Nature****, 2016*
Vodnala et al, ***Science****, 2019*

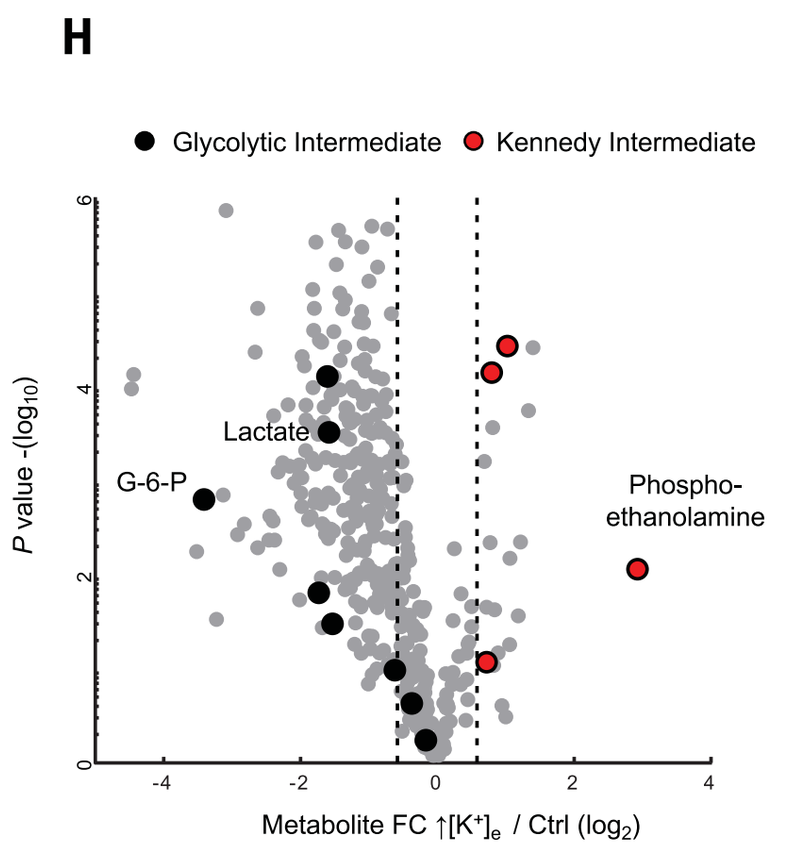




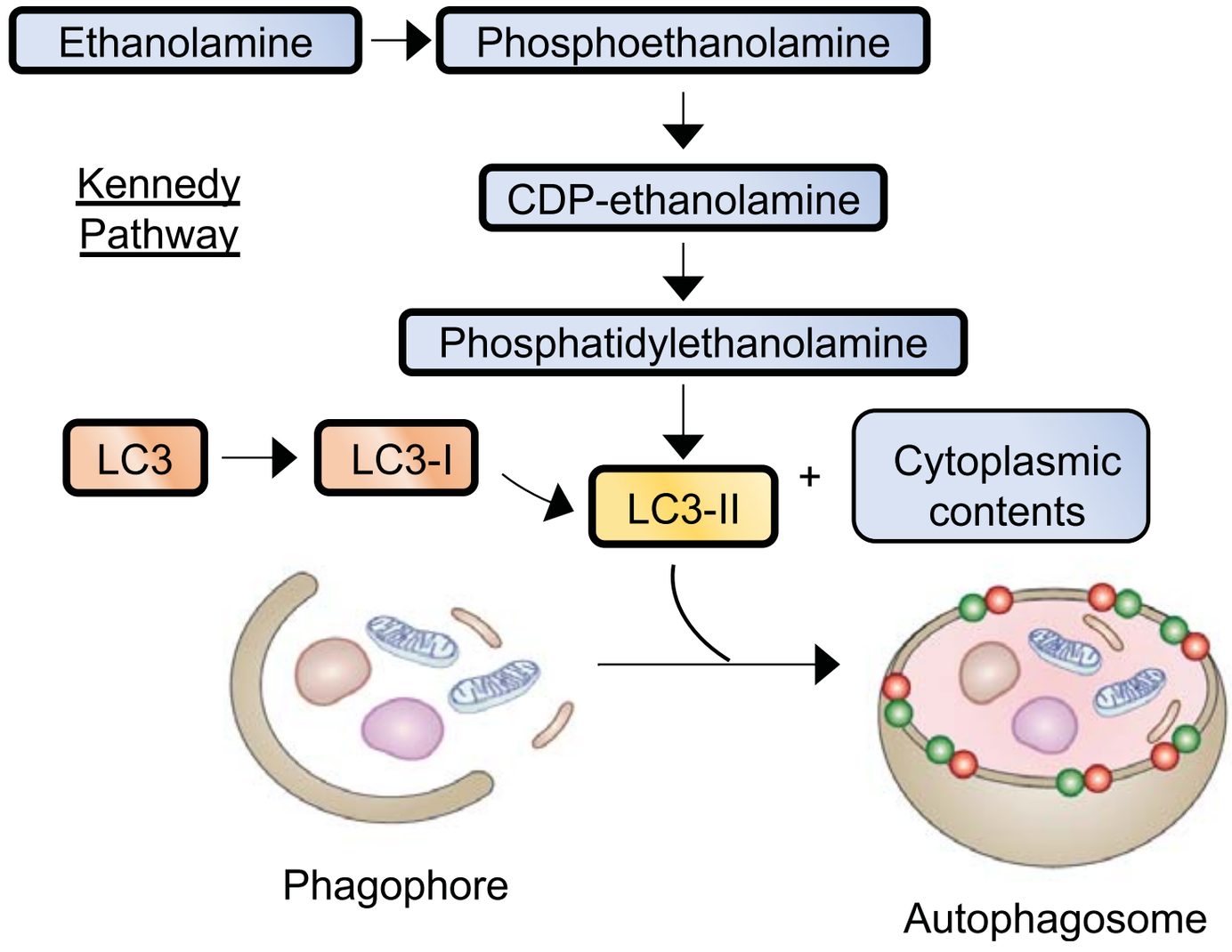




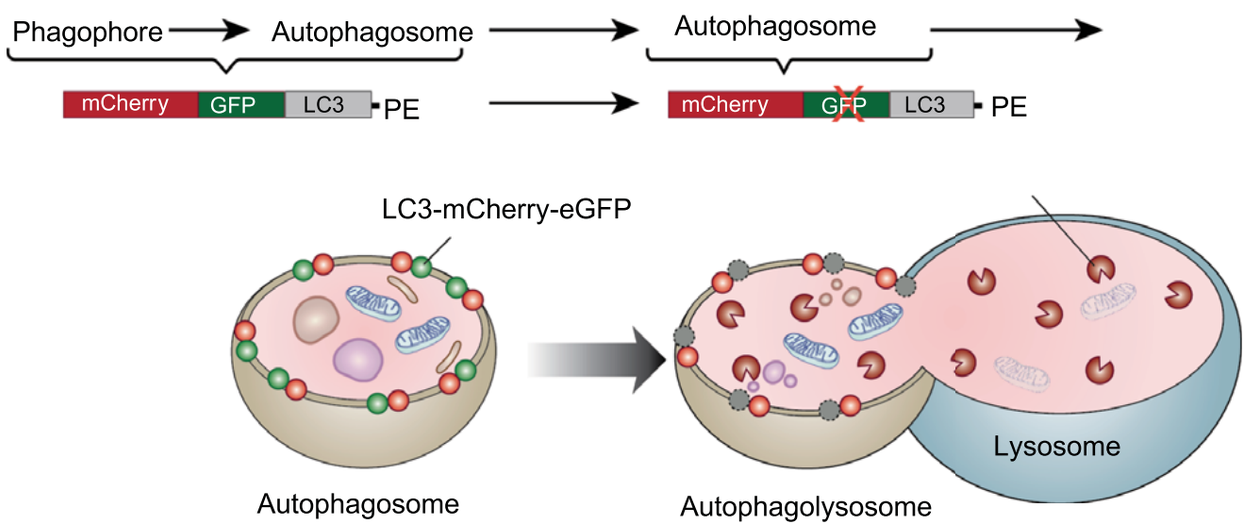


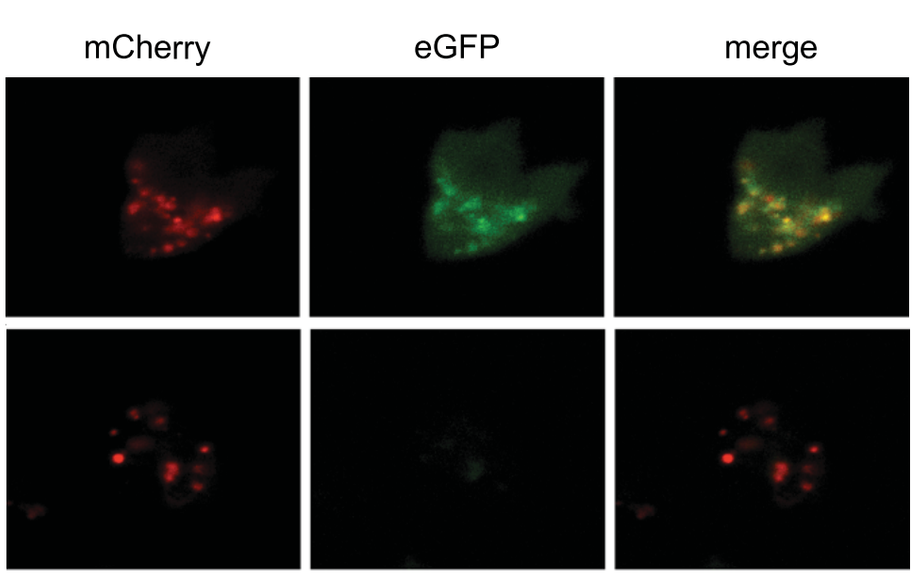


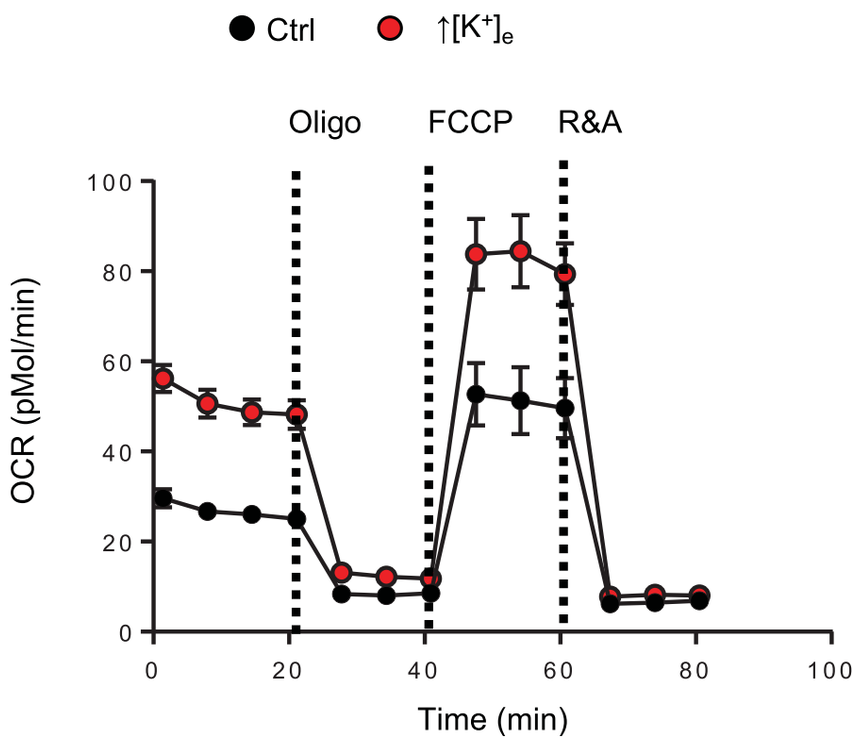
Eil et al, ***Nature****, 2016*
Vodnala et al, ***Science****, 2019*



Eil et al, ***Nature****, 2016*
Vodnala et al, ***Science****, 2019*

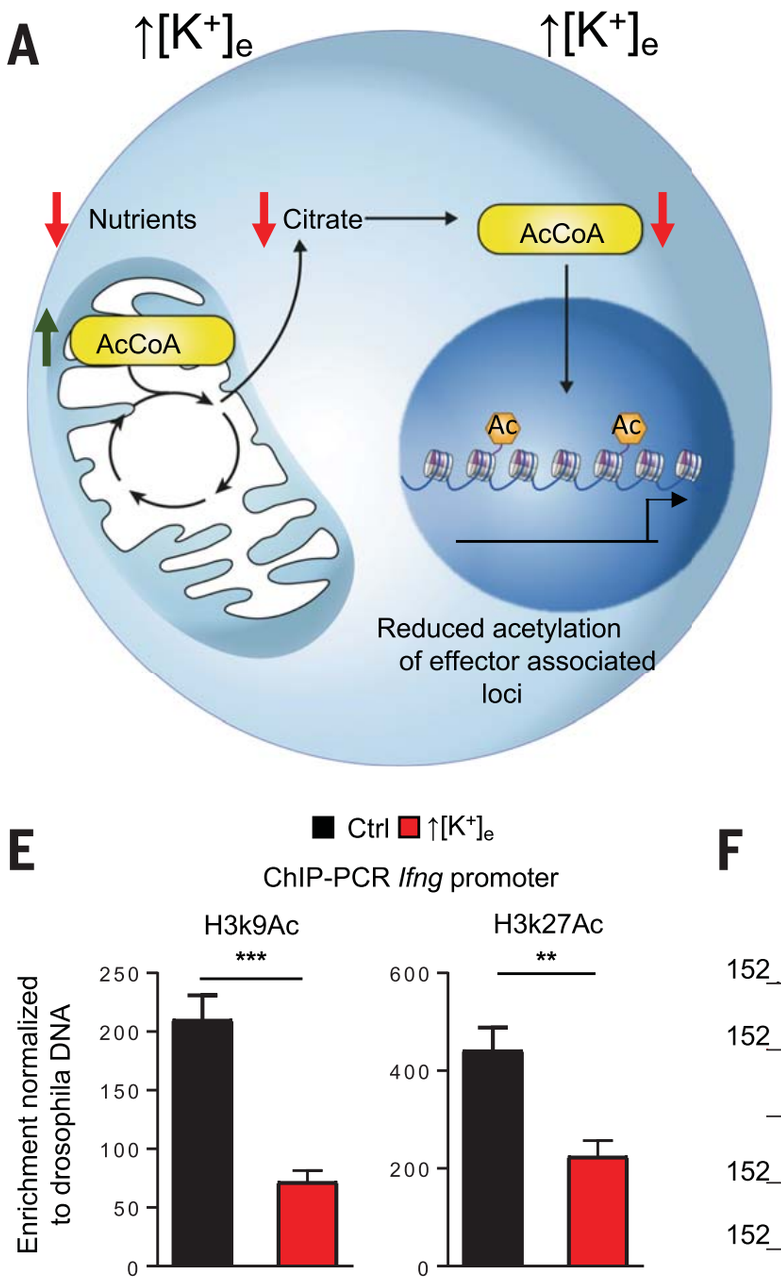


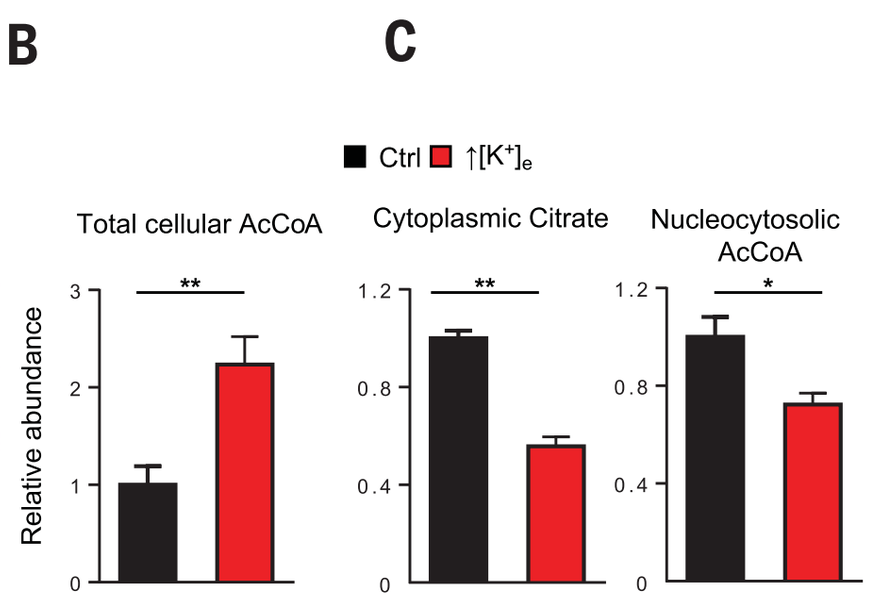


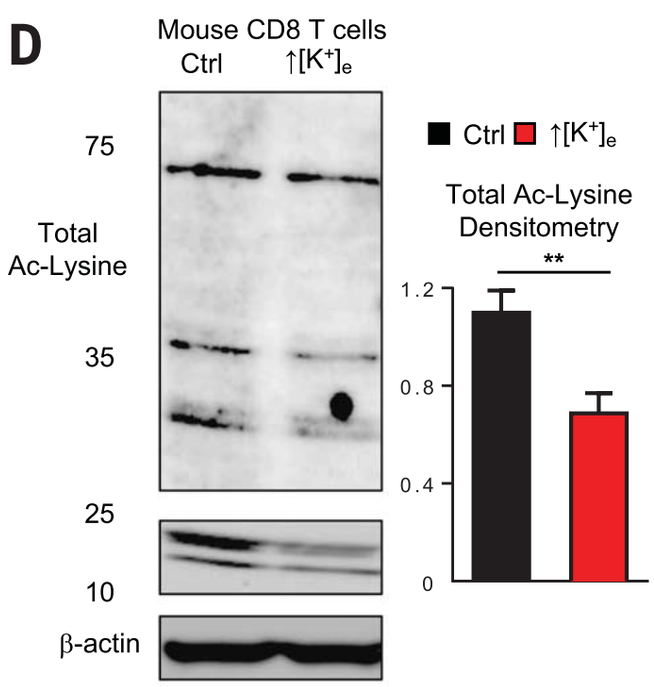


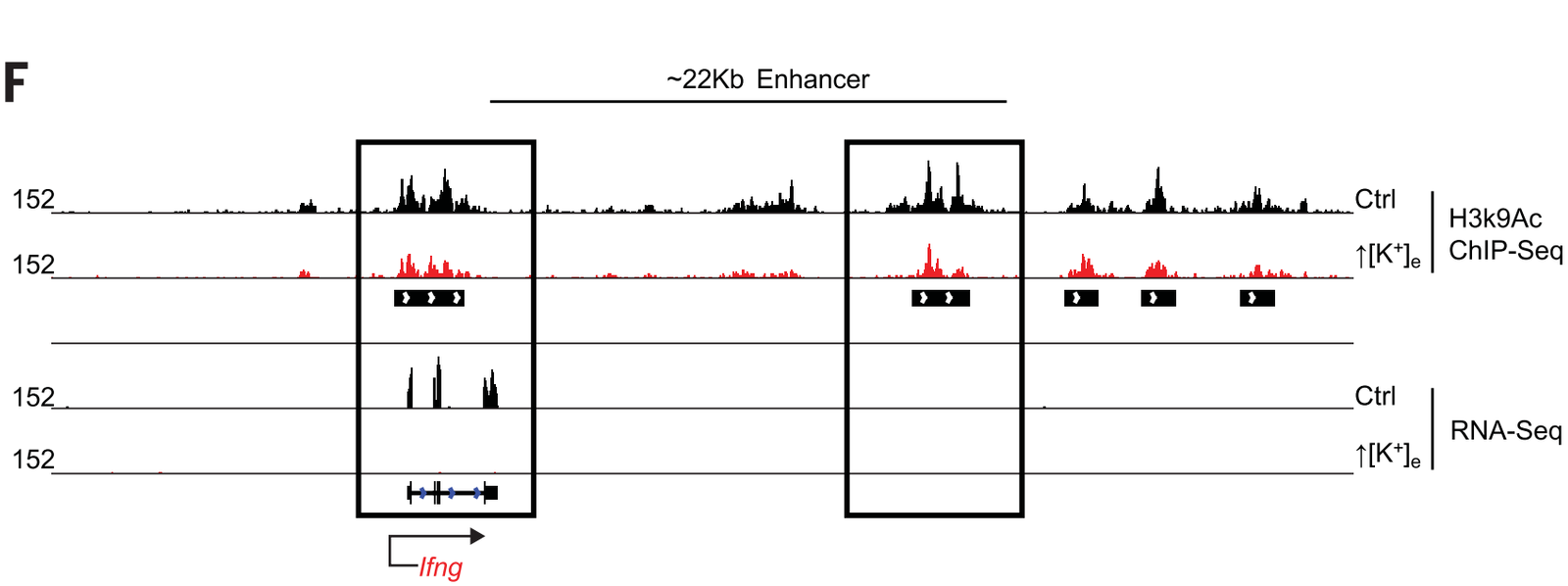
T cells exposed to increased $[K^+]_e$ recycle nutrients via autophagy during functional caloric restriction.

Eil et al, ***Nature****, 2016*
Vodnala et al, ***Science****, 2019*

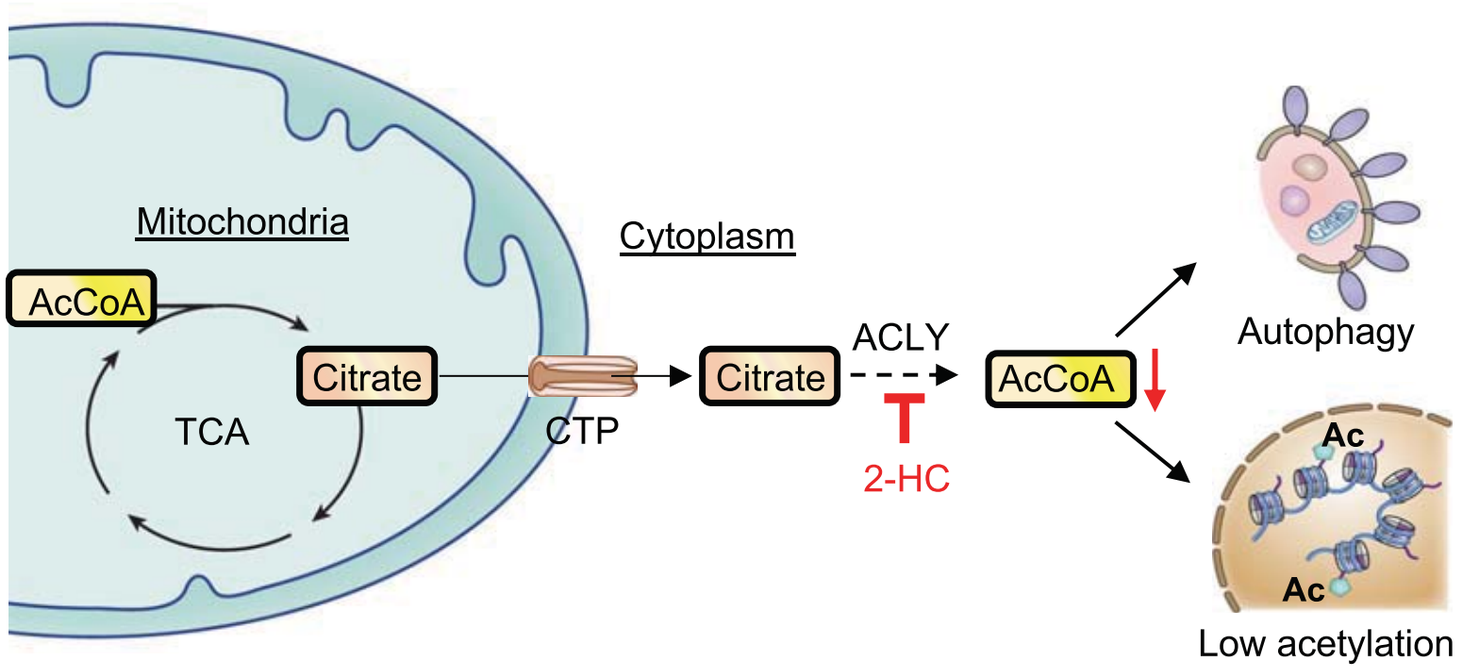


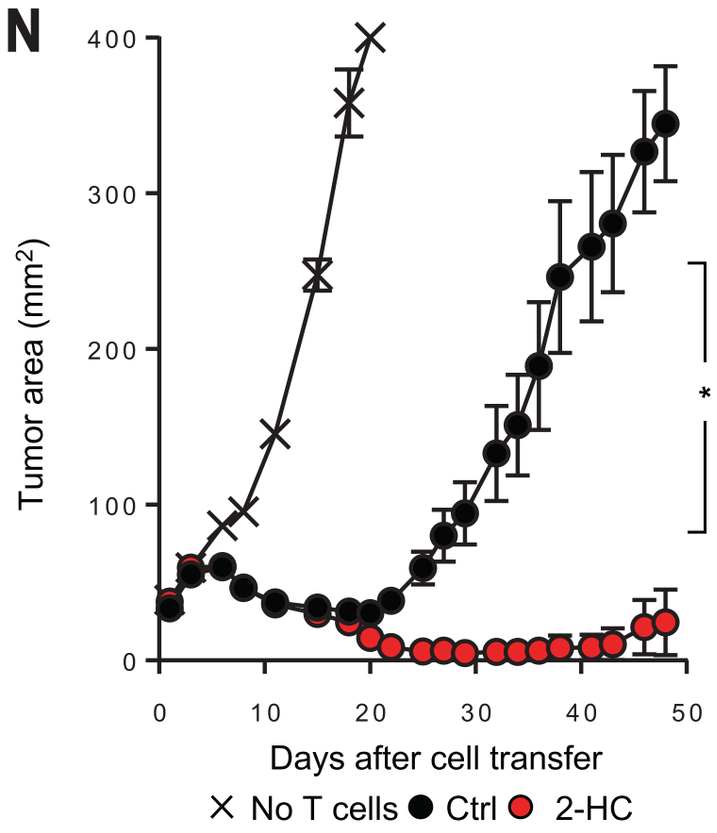


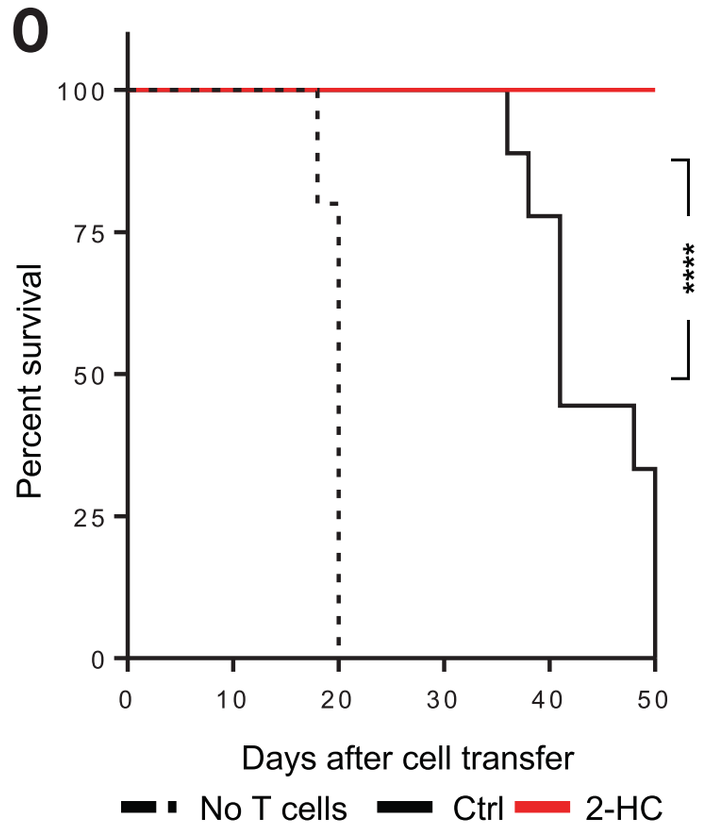




Eil et al, ***Nature****, 2016*
Vodnala et al, ***Science****, 2019*

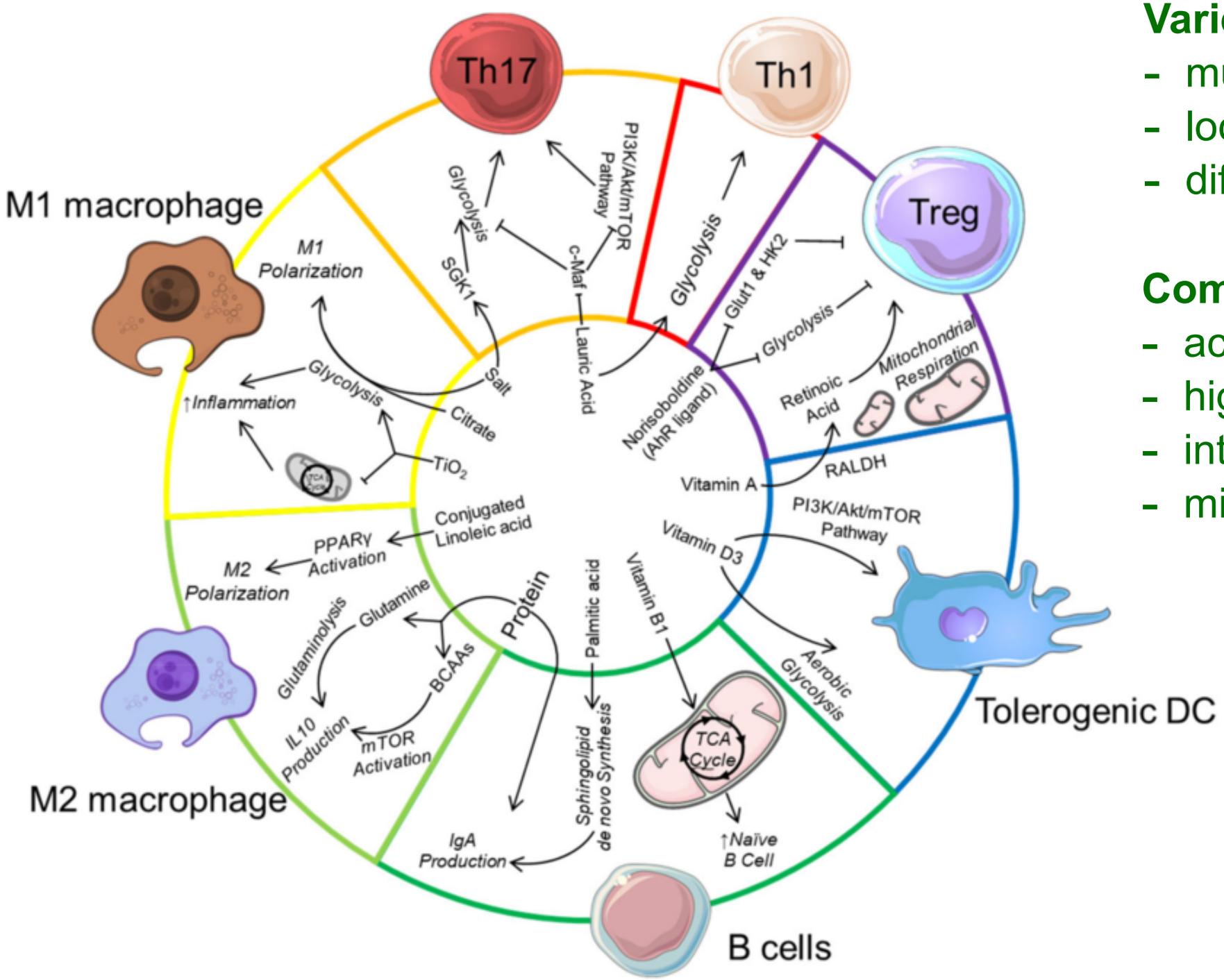






Eil et al, ***Nature****, 2016*
Vodnala et al, ***Science****, 2019*

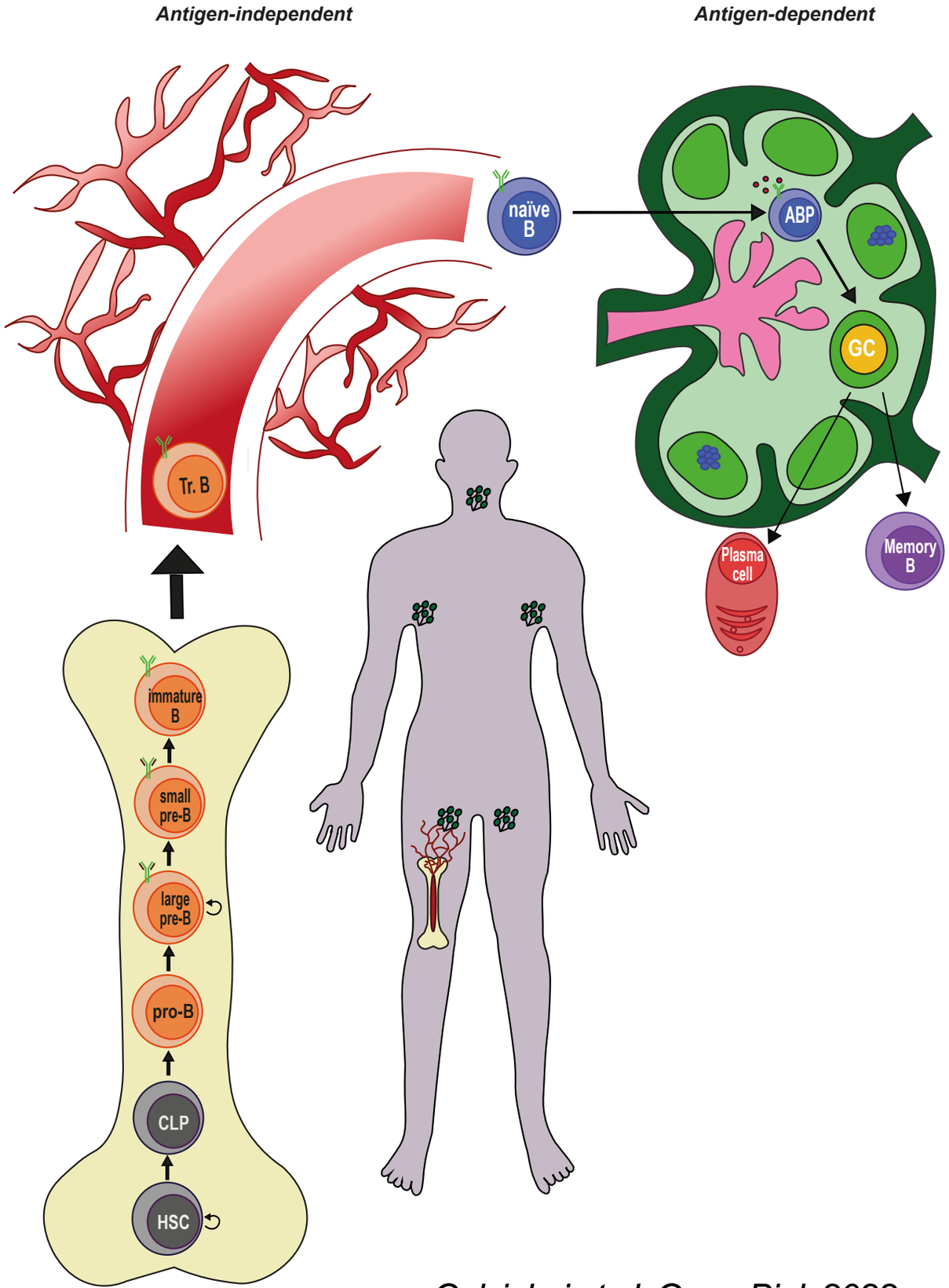
Immunometabolism across the immune system



Variety of cell types
- multiple phenotypes
- local microenvironments
- different functions

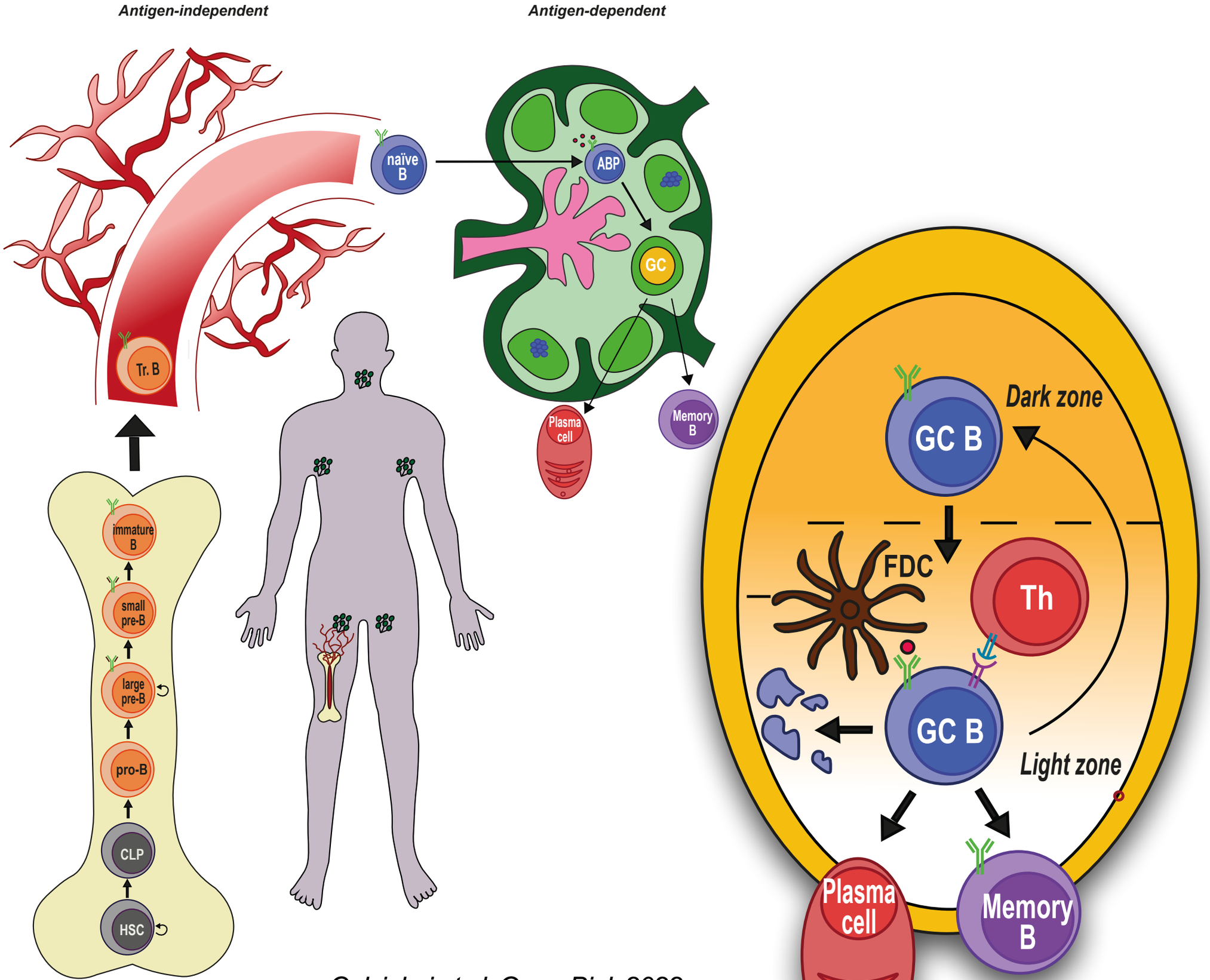
Common denominators
- actionable
- highly plastic
- interactive
- migrate and adapt

B cell maturation and Germinal Center (GC) reaction



Calciolari et al, Open Biol, 2022

B cell maturation and Germinal Center (GC) reaction



Calciolari et al, Open Biol, 2022

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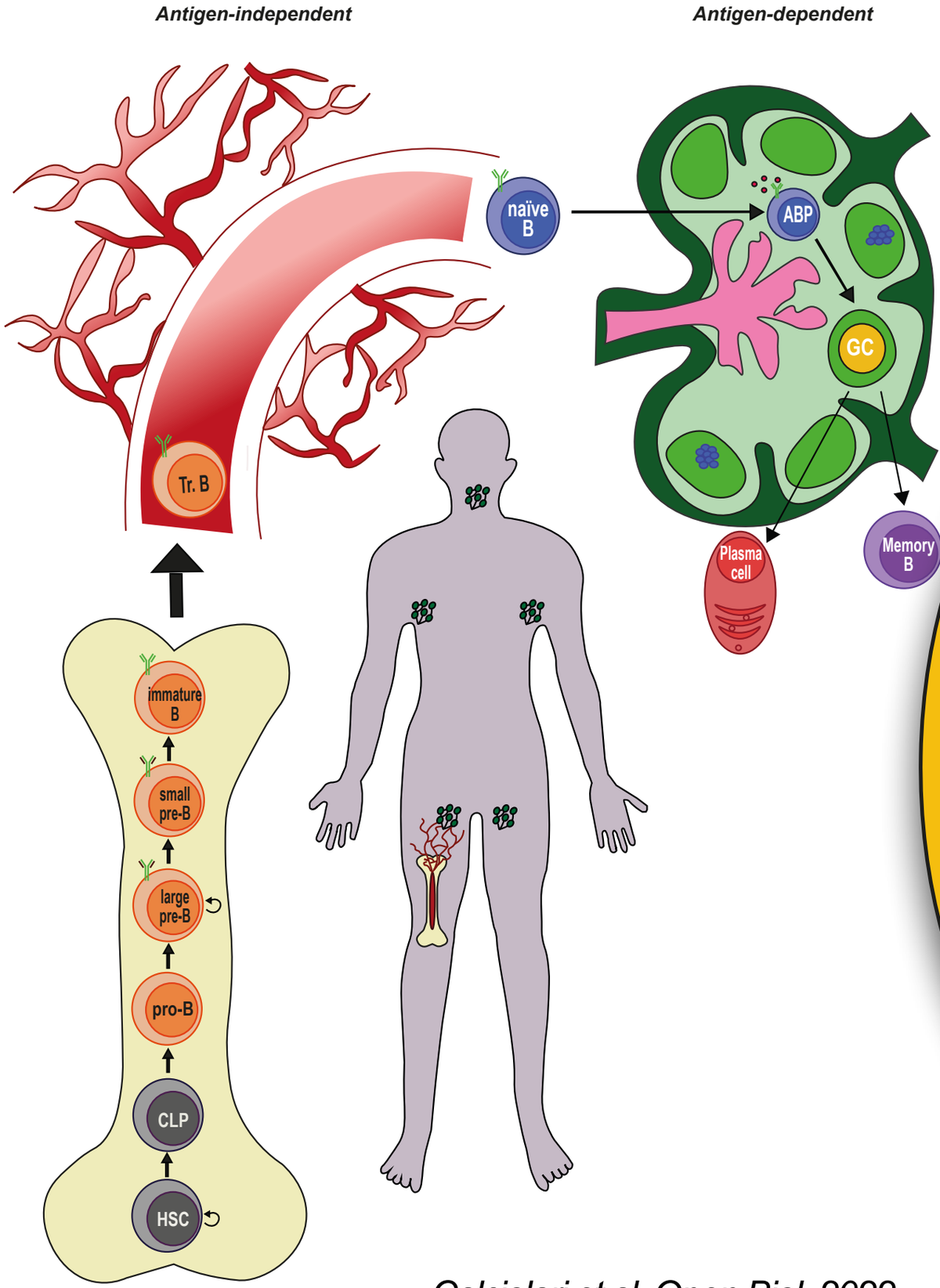
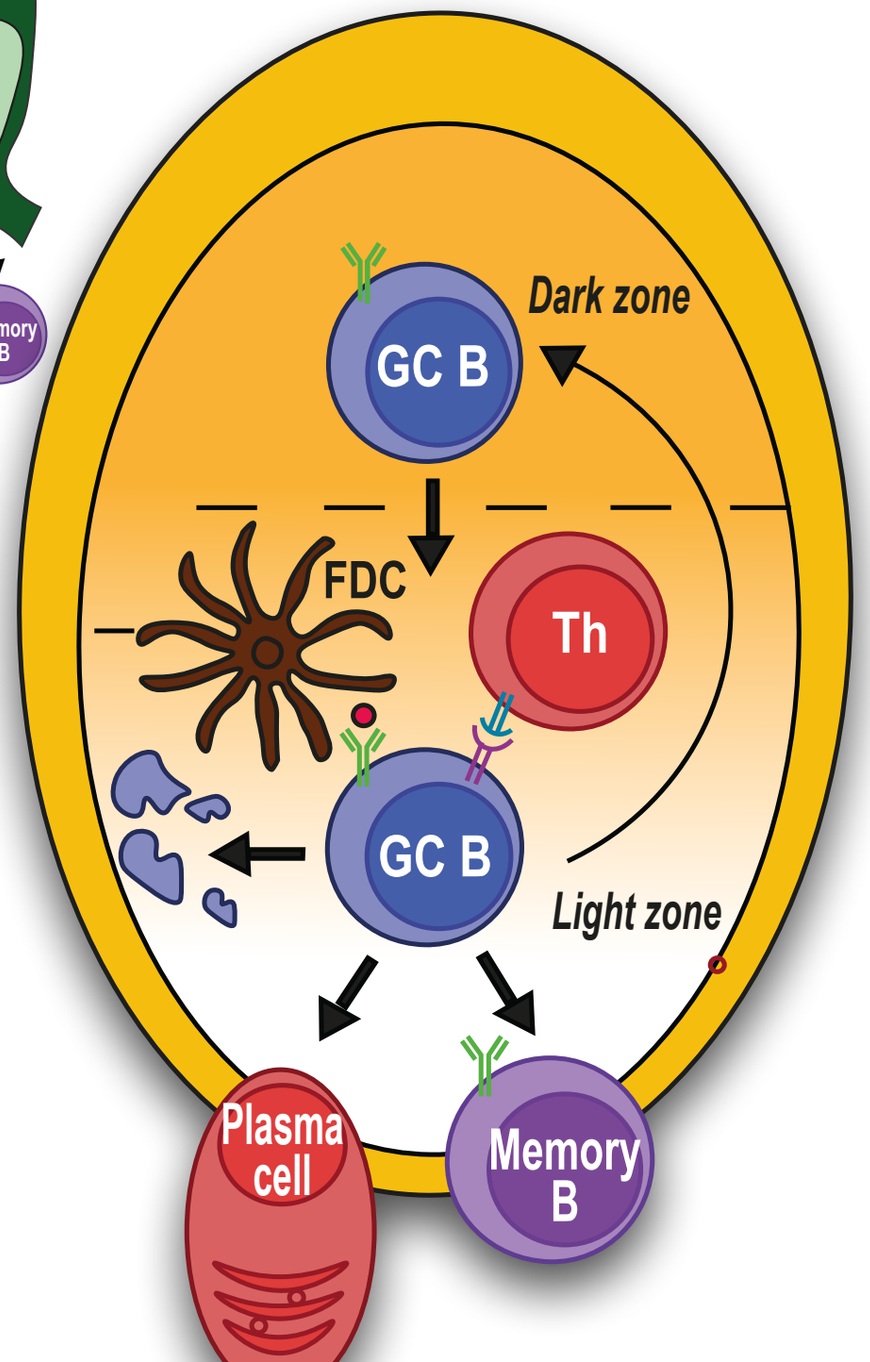
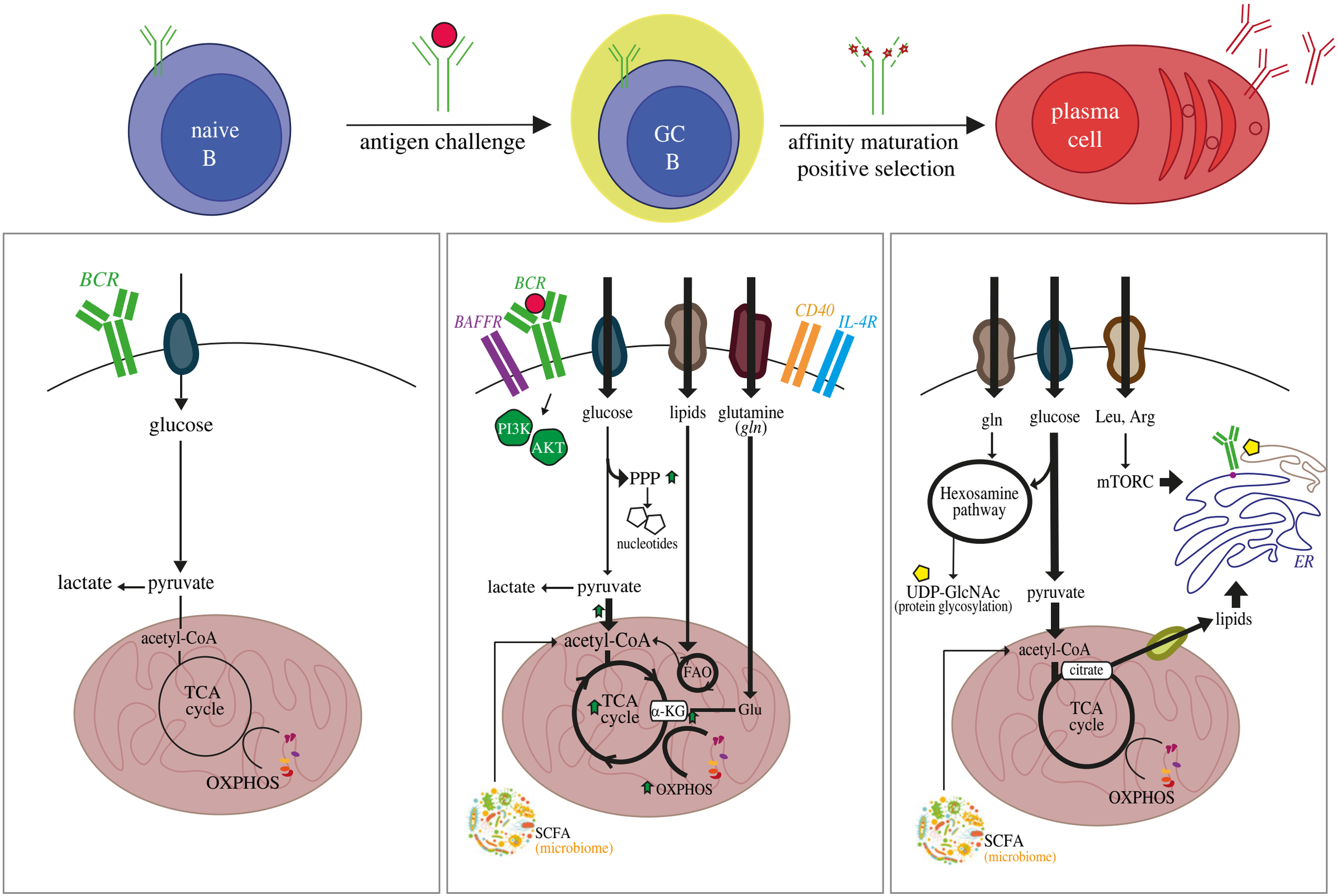


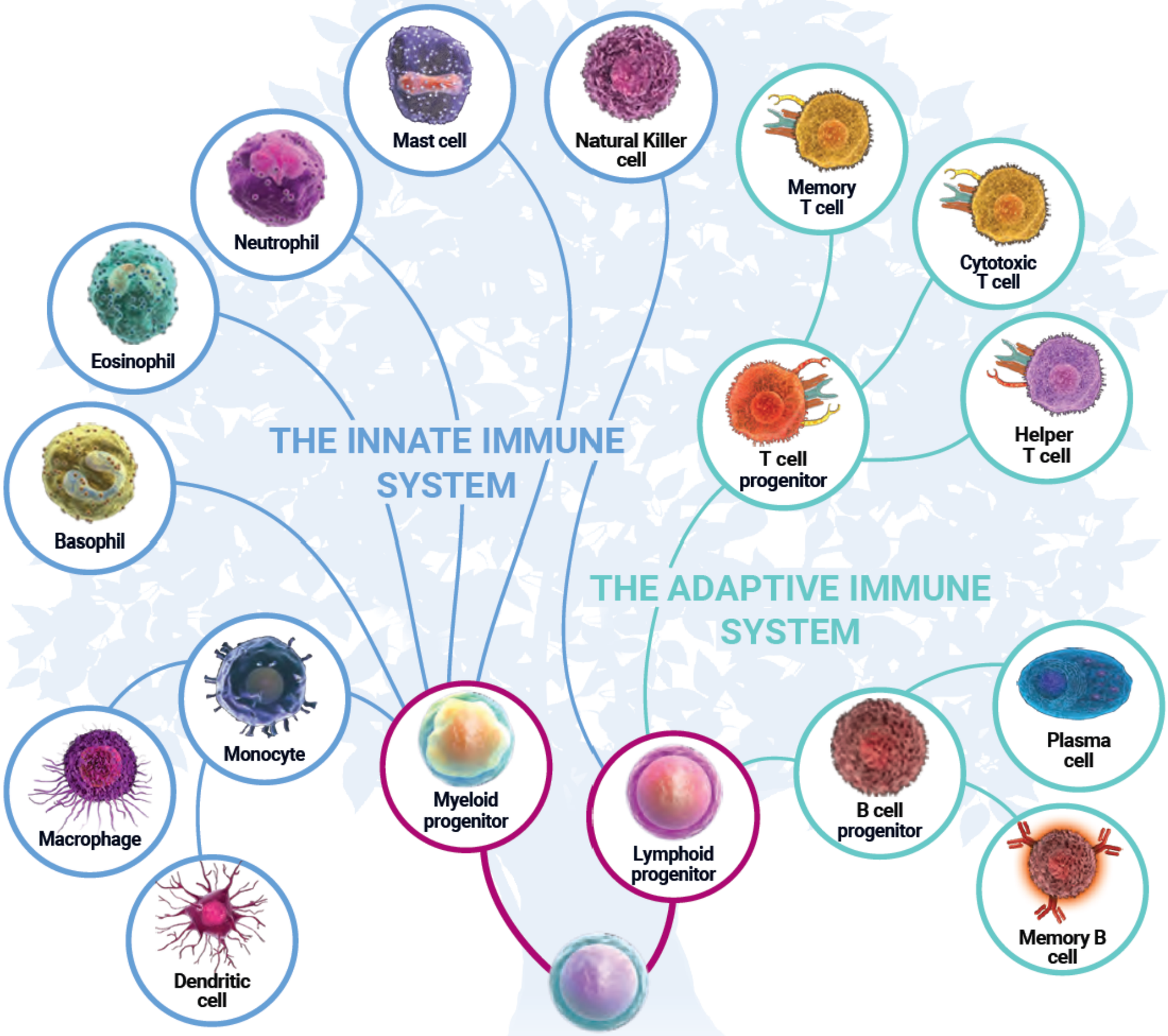
Role of metabolism not elucidated!!!!!



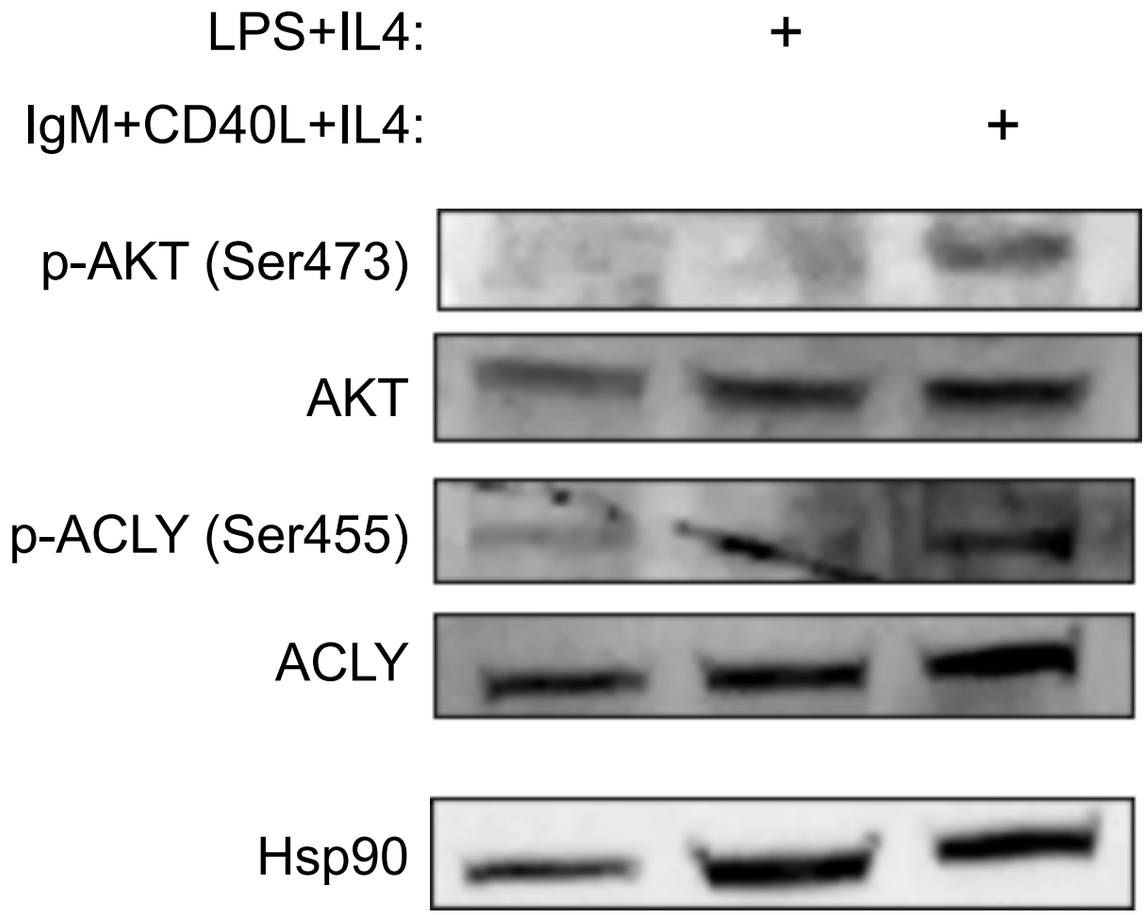
Calciolari et al, Open Biol, 2022



Calciolari et al, ***Open Biol****, 2021*


THE INNATE IMMUNE SYSTEM
THE ADAPTIVE IMMUNE SYSTEM
Mast cell
Natural Killer cell
Neutrophil
Eosinophil
Basophil
Memory T cell
Cytotoxic T cell
T cell progenitor
Helper T cell
Monocyte
Macrophage
Dendritic cell
Myeloid progenitor
Lymphoid progenitor
B cell progenitor
Plasma cell
Memory B cell
Hematopoietic stem cell

In vitro-activated B cells enhance acetyl-CoA metabolism



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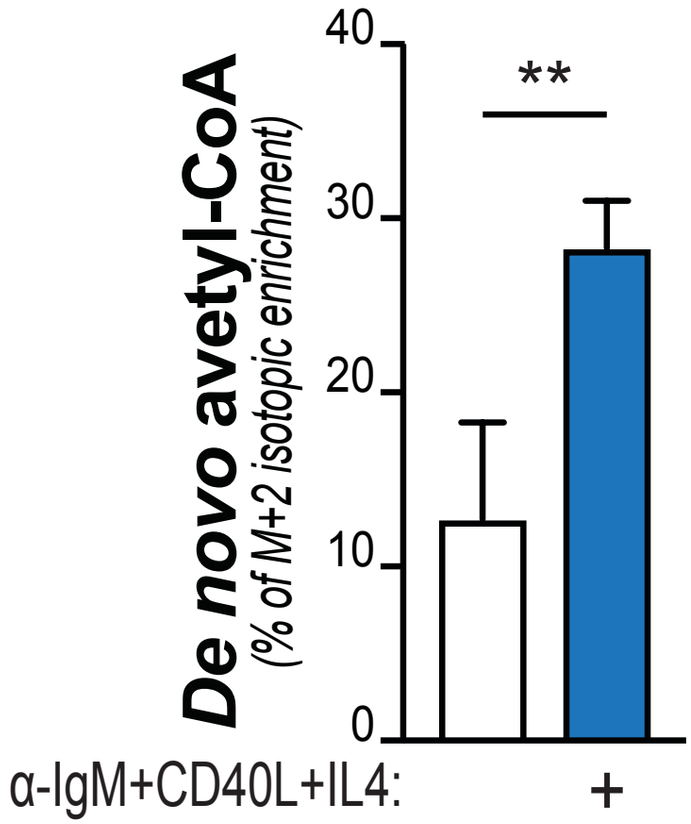
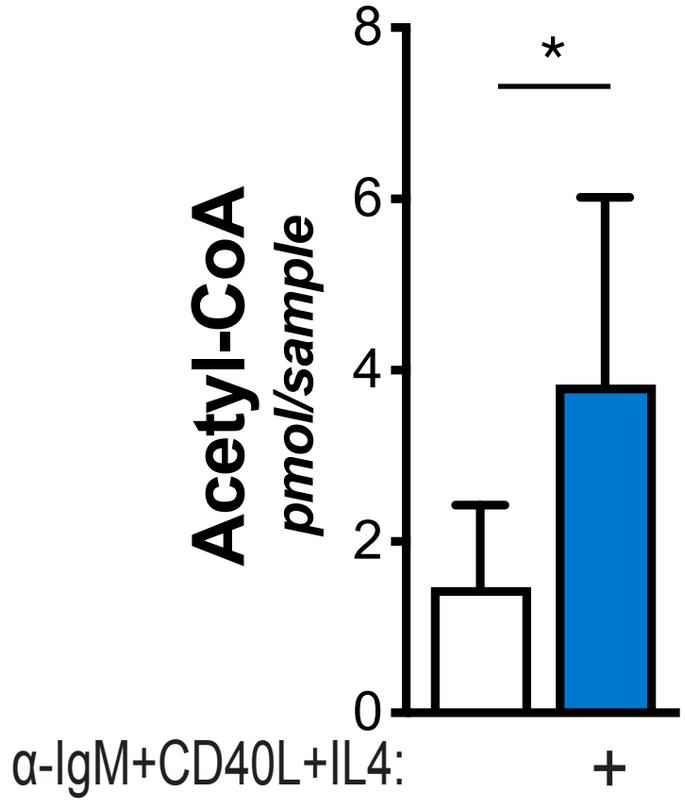
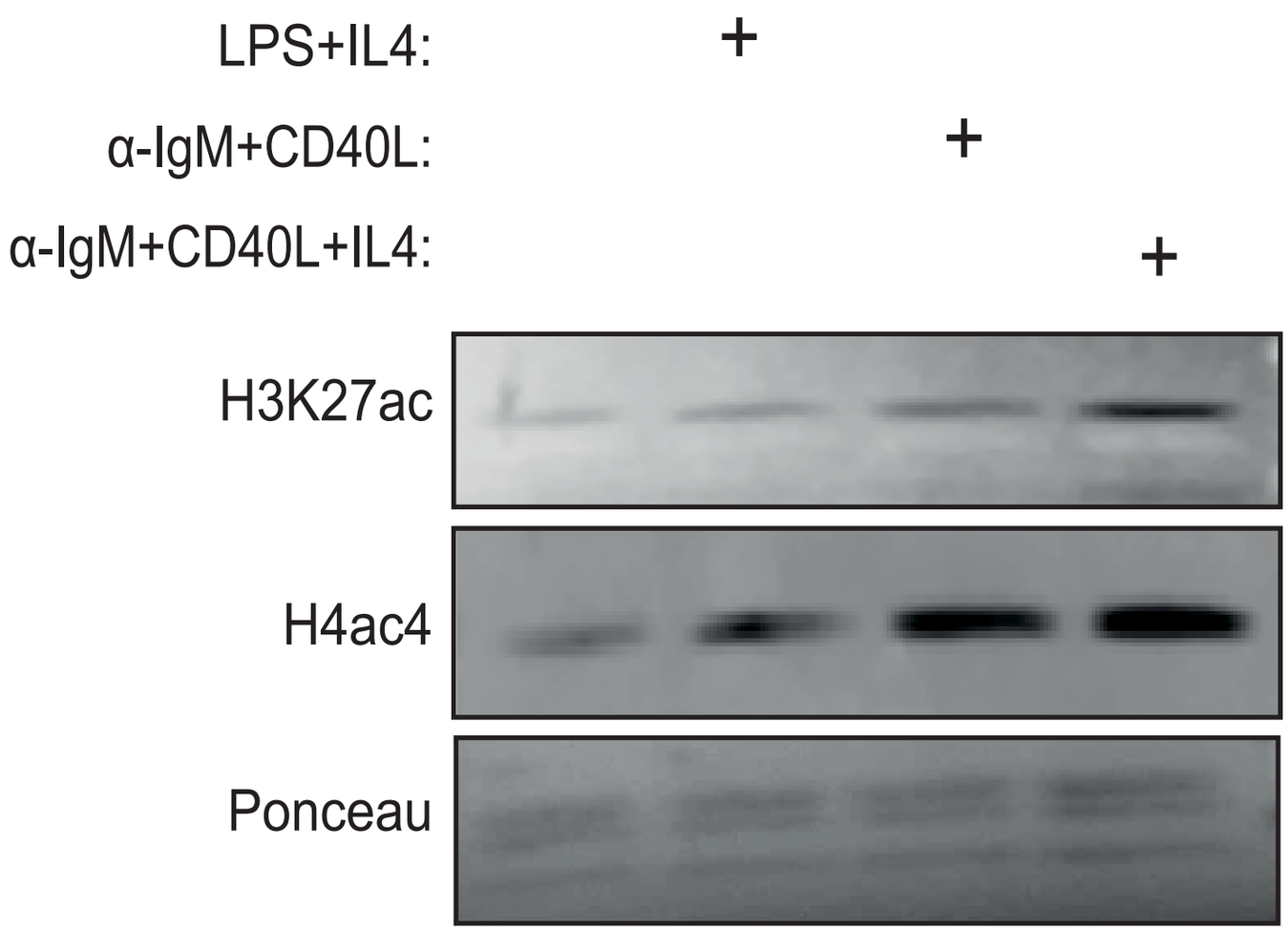




In vitro-activated B cells show increased histone acetylation



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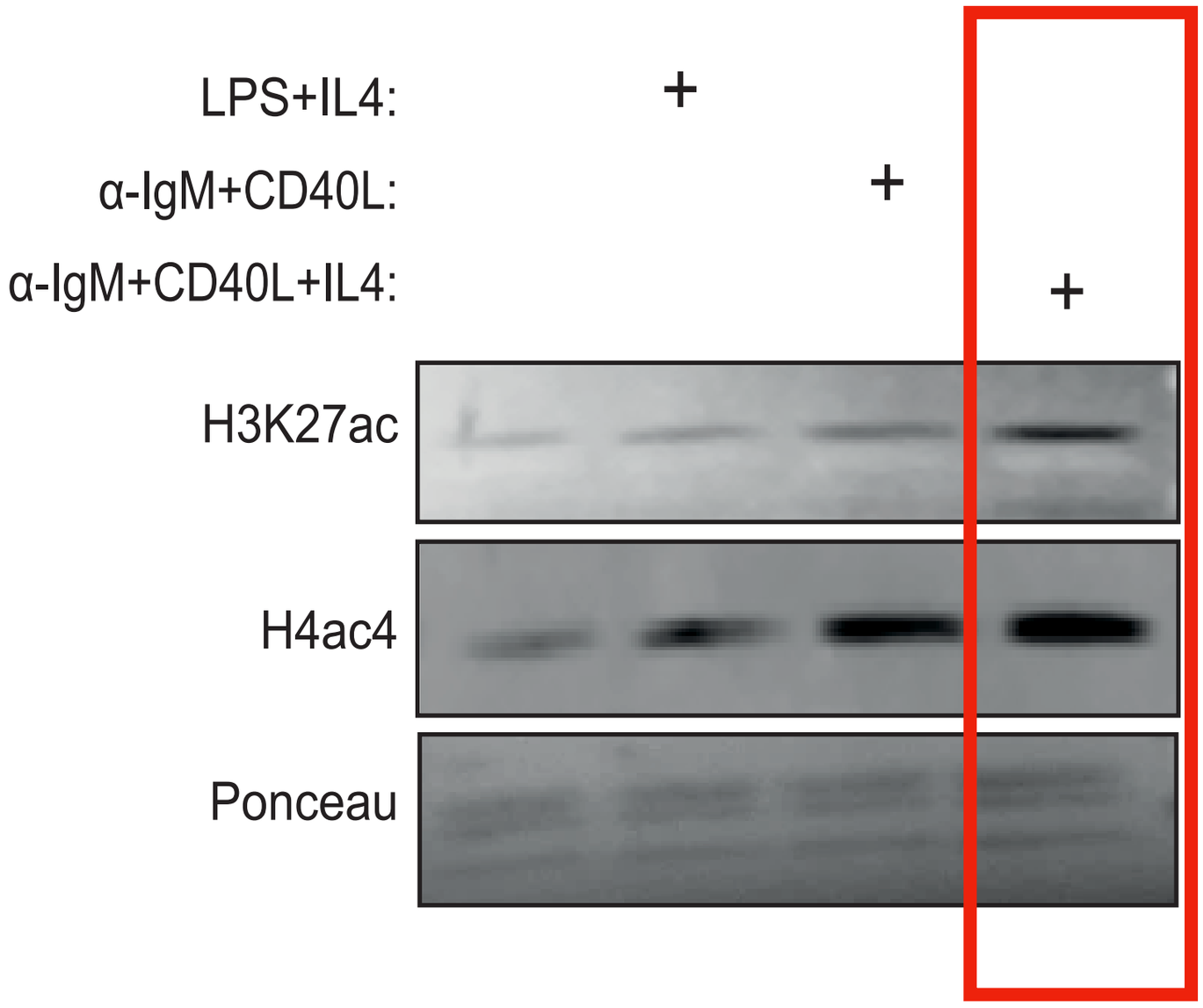

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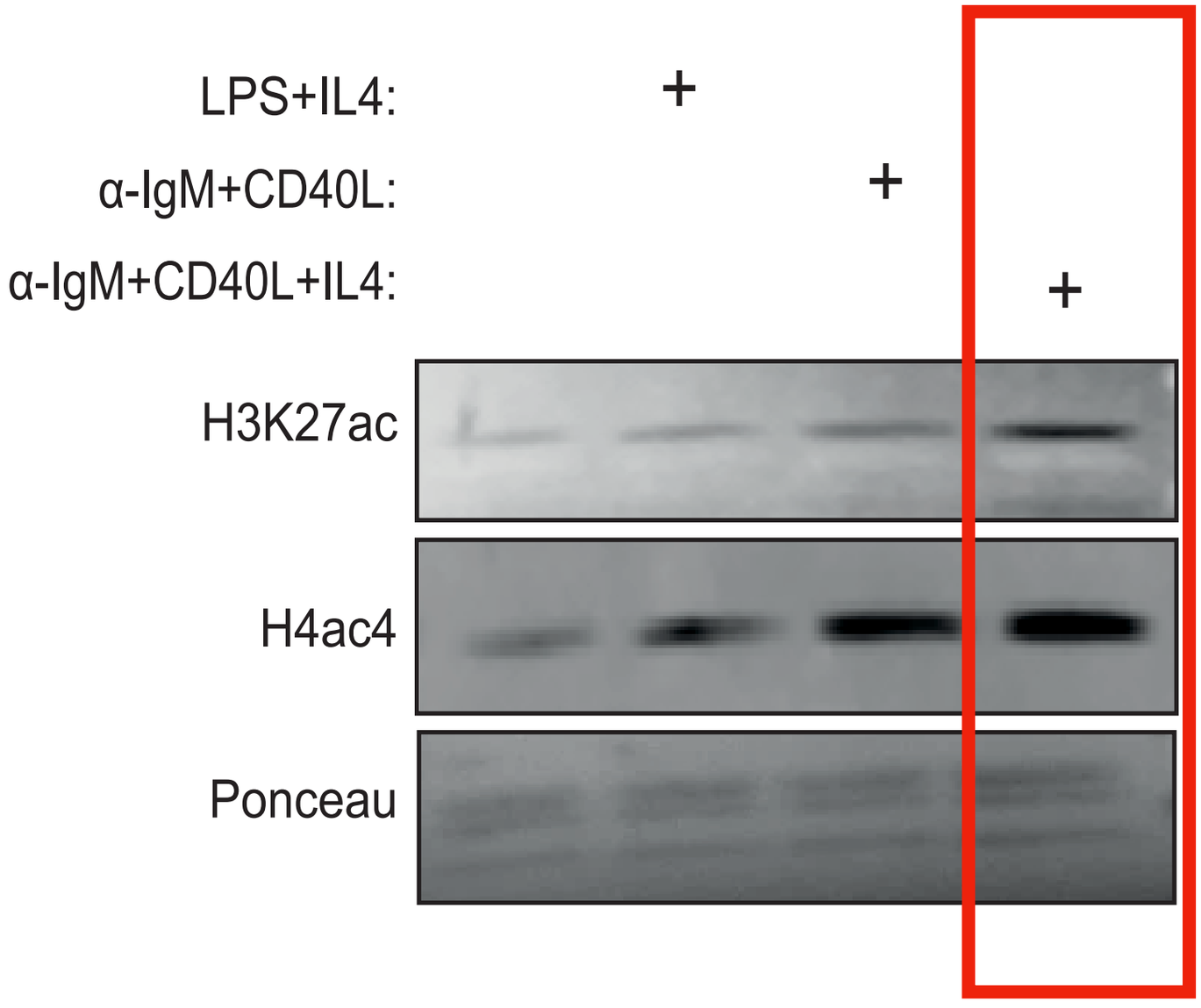
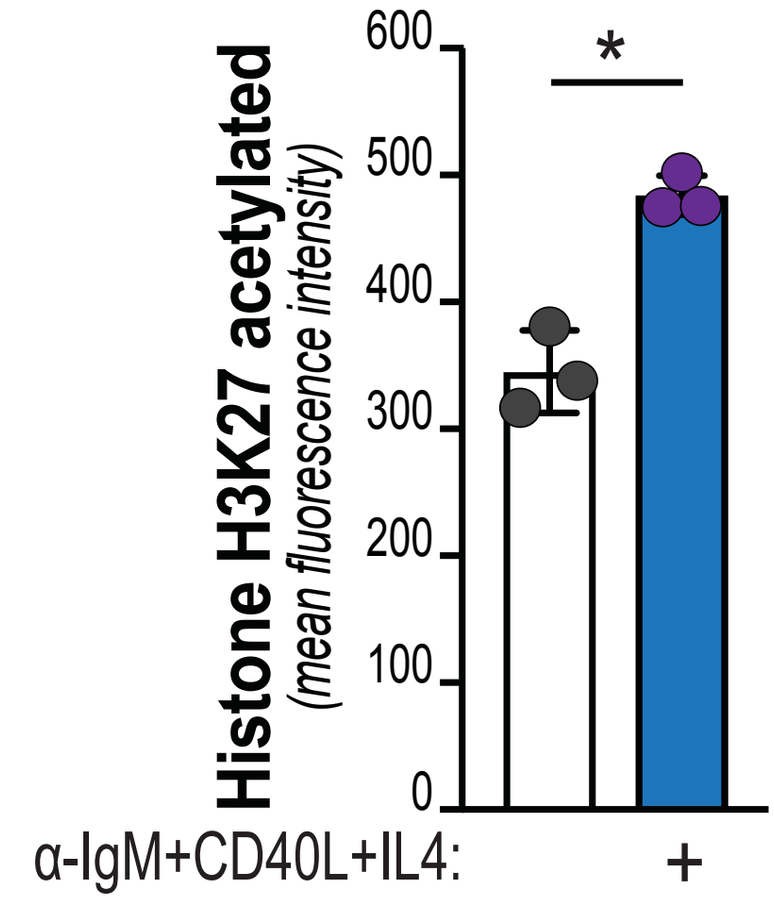
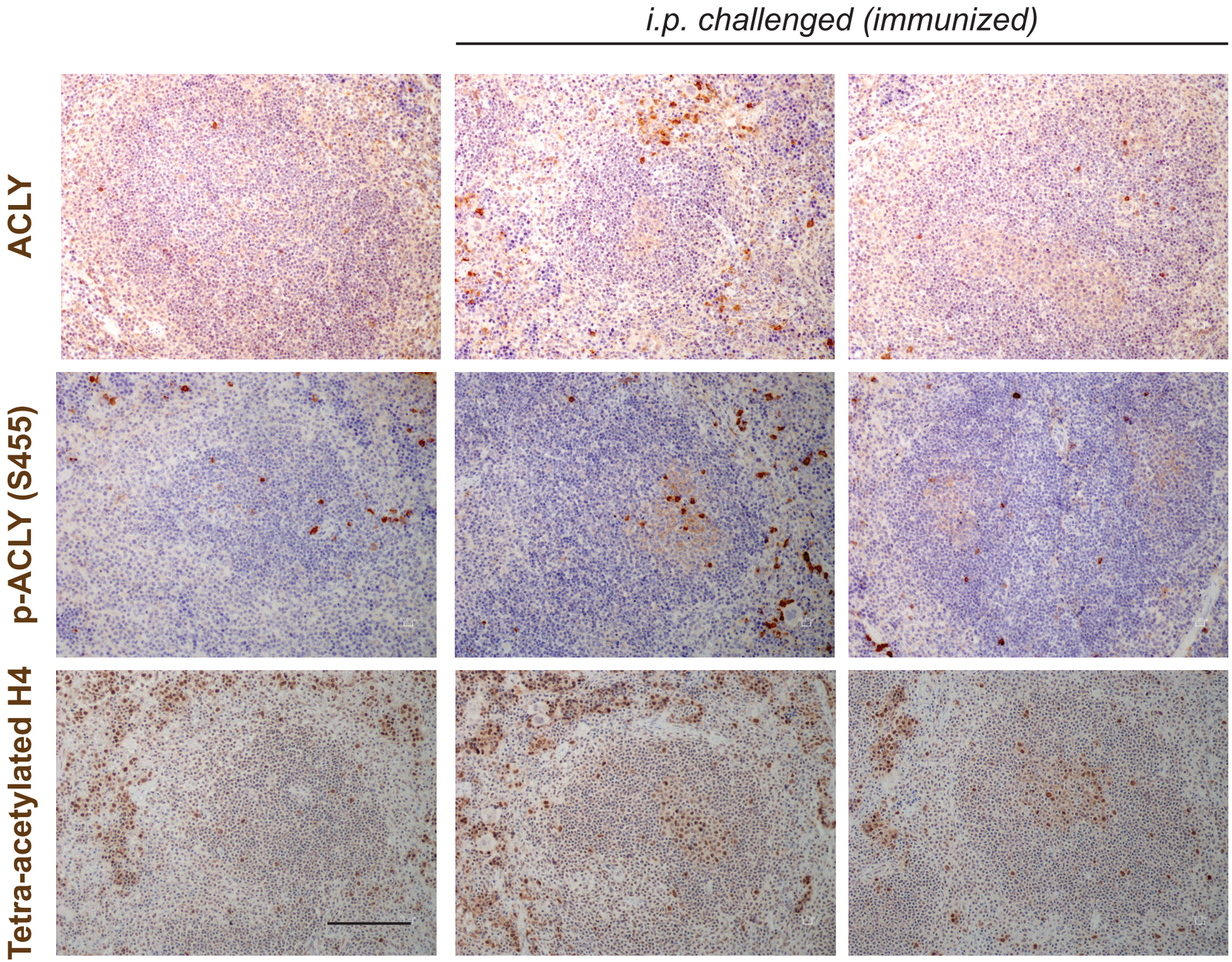


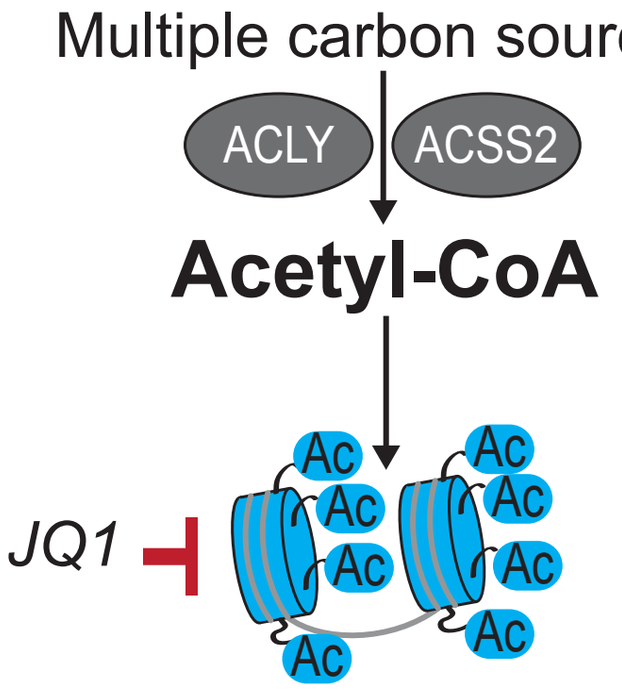


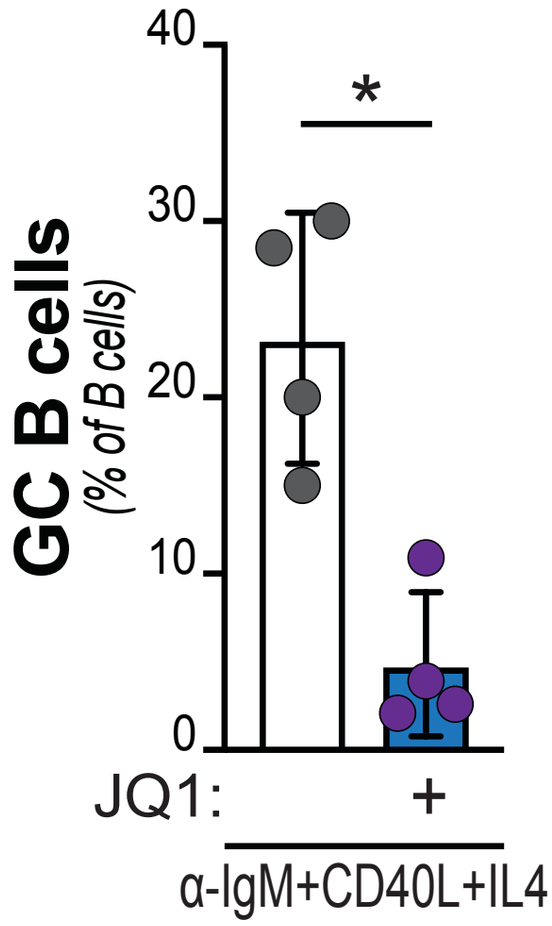
Murine GCs are hyperacetylated



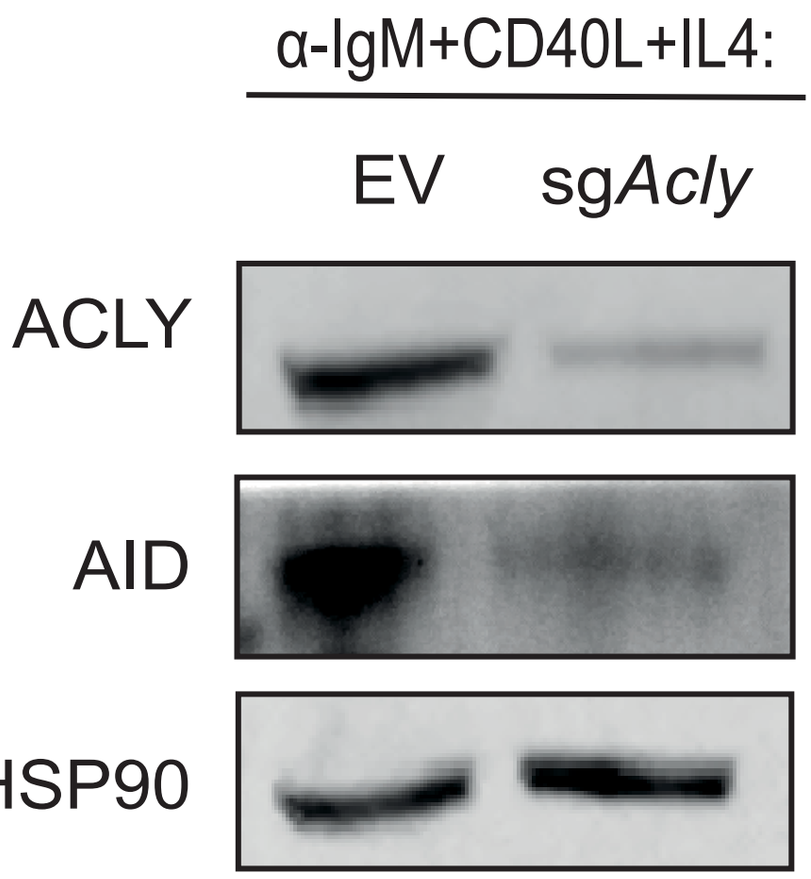
***also seen in FACS sorted cells*

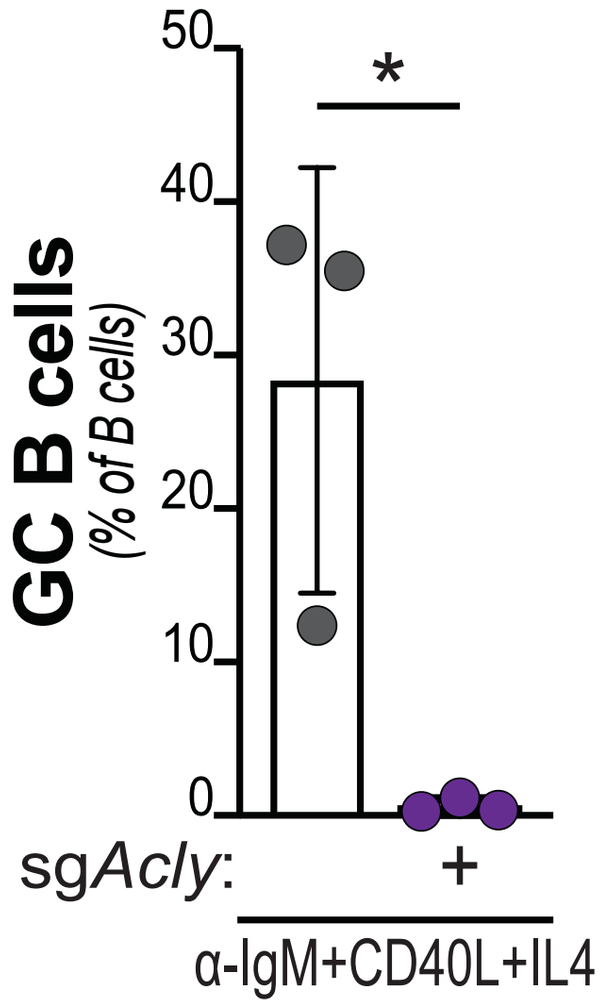
Bromodomain inhibition suppresses GC maturation in vitro



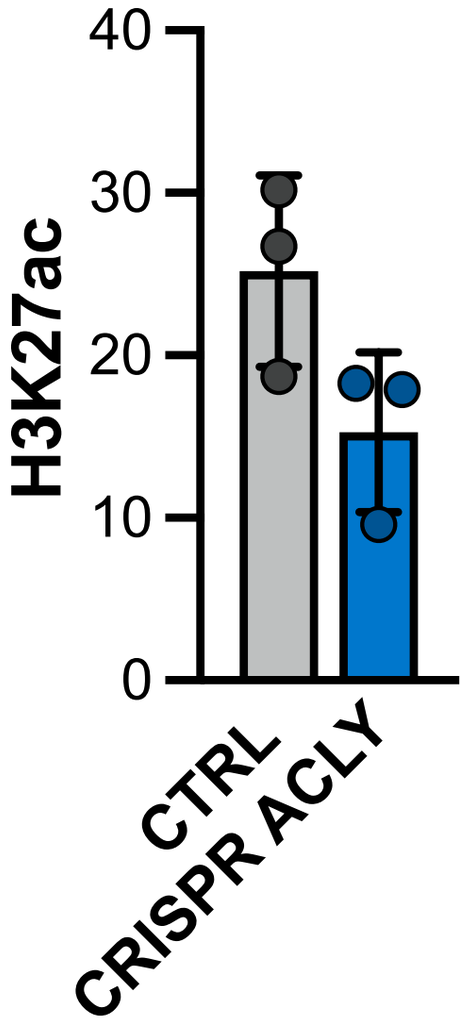


ACLY ablation suppresses GC maturation in vitro



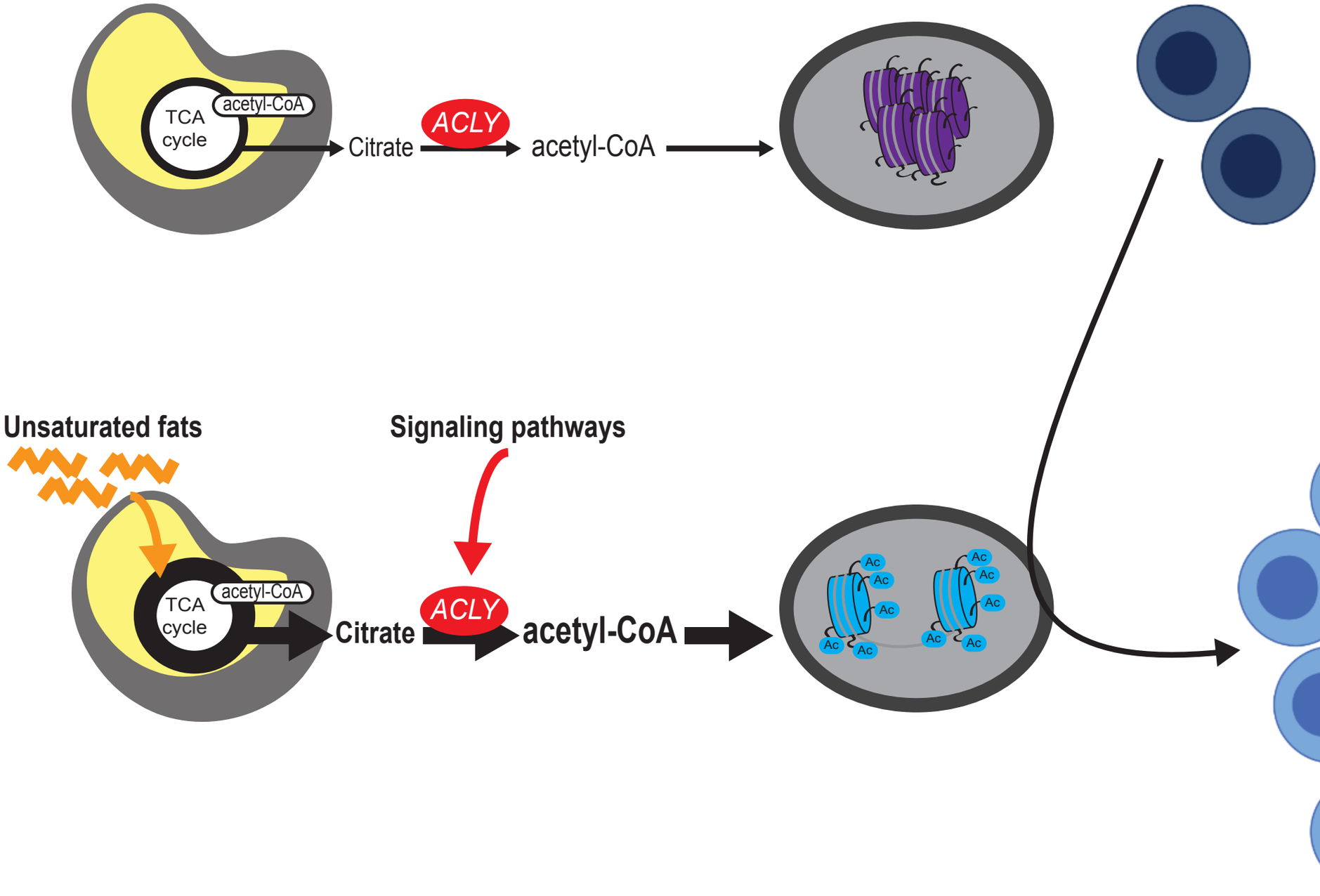


ACLY ablation hampers GC histone hyperacetylation in vitro



Working model:

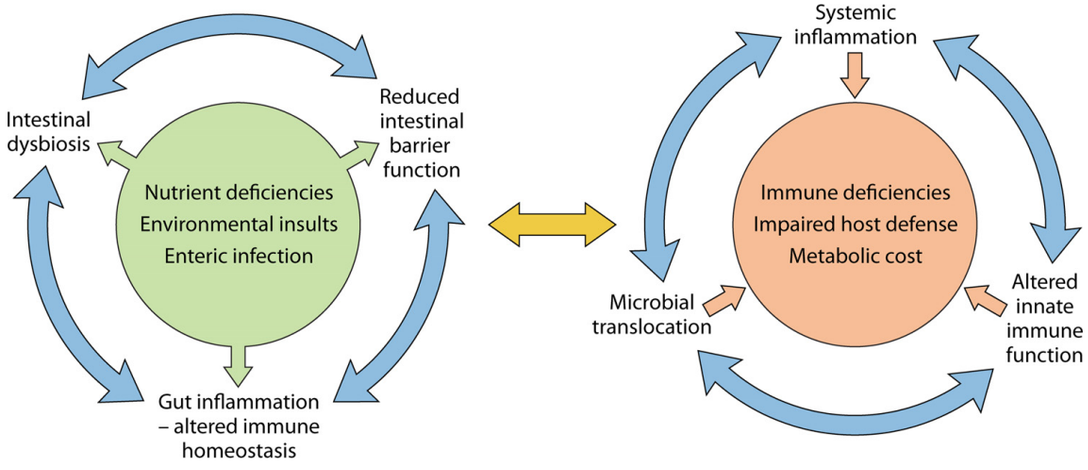
B cell maturation is promoted by metabolic-dependent histone acetylation

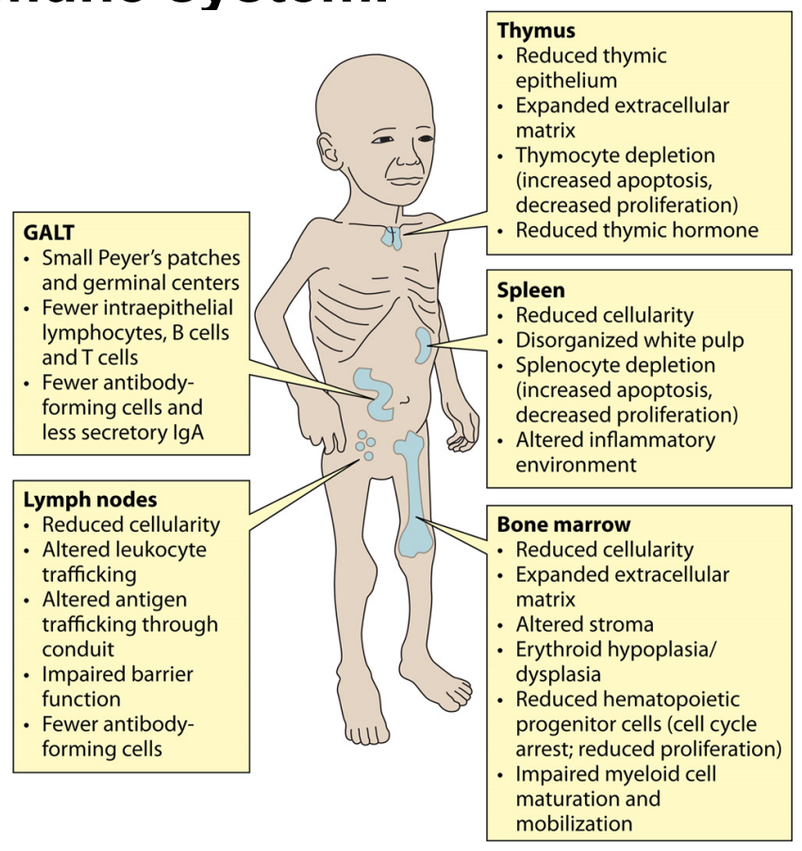


Diet and immune function

Is cell metabolism involved??

Adequate and appropriate nutrition is required for all cells to function optimally and this includes the cells in the immune system.





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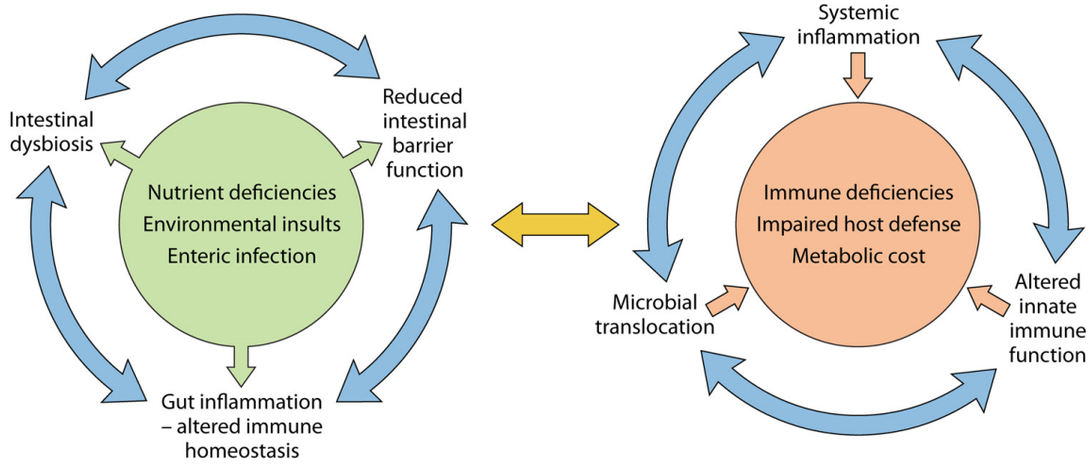
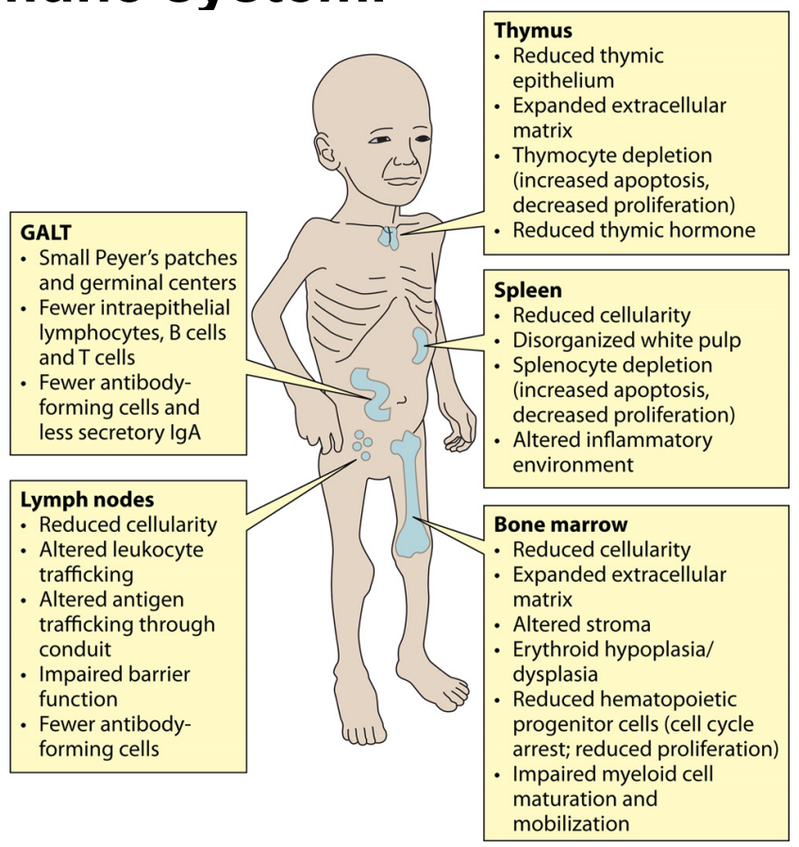


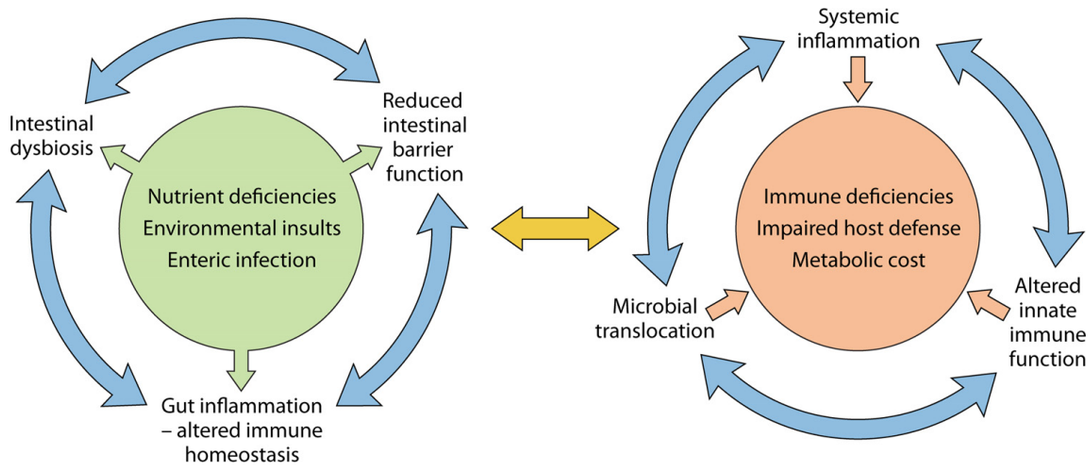


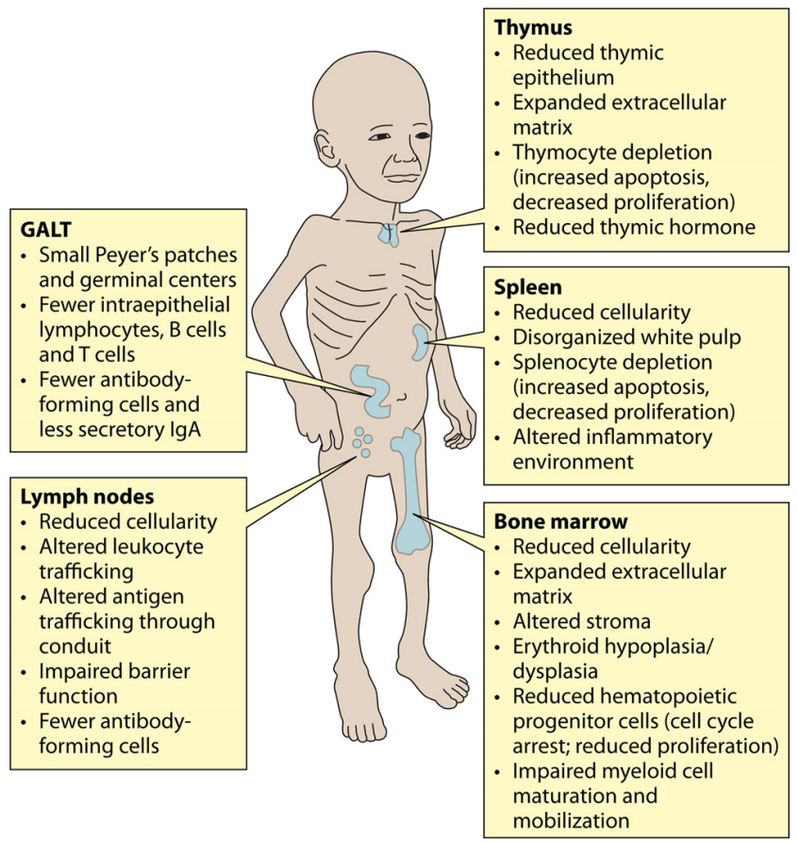
Energetically expensive vital functions such as immunological responses might have thus evolved to respond accordingly to dietary surplus and deficit of macronutrient intake.

An “activated” immune system further increases the demand for energy during periods of infection, with greater basal energy expenditure during fever for example. Thus, optimal nutrition for the best immunological outcomes would be nutrition, which supports the functions of immune cells allowing them to initiate effective responses against pathogens but also to resolve the response rapidly when necessary and to avoid any underlying chronic inflammation.

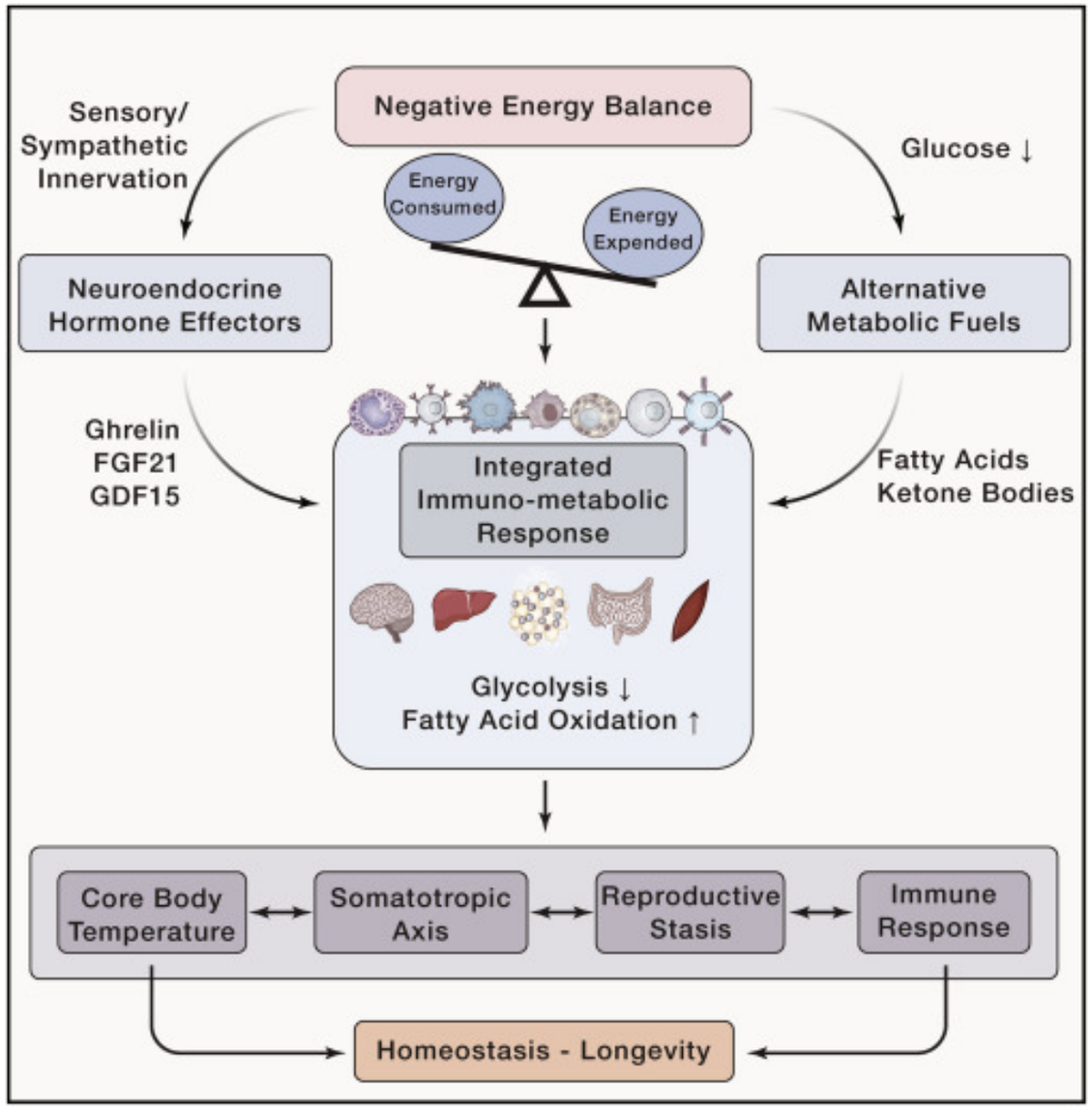
The immune system’s demands for energy and nutrients can be met from exogenous sources i.e., the diet, or if dietary sources are inadequate, from endogenous sources such as body stores. Some micronutrients and dietary components have very specific roles in the development and maintenance of an effective immune system throughout the life course or in reducing chronic inflammation.

For example, the amino acid arginine is essential for the generation of nitric oxide by macrophages, and the micronutrients vitamin A and zinc regulate cell division and so are essential for a successful proliferative response within the immune system.





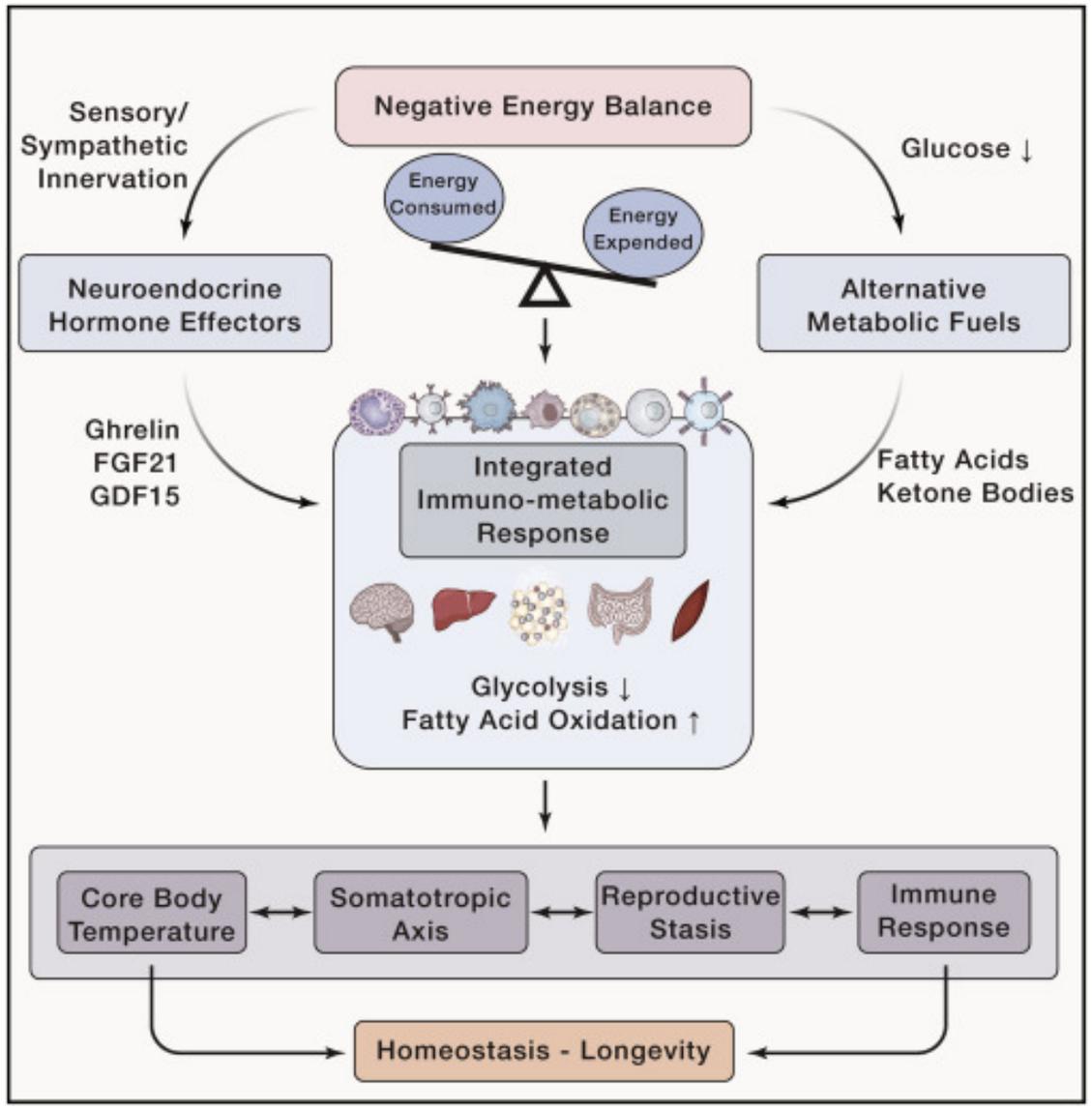
As well as nutrition having the potential to effectively treat immune deficiencies related to poor intake, there is a great deal of research interest in whether specific nutrient interventions can further enhance immune function in sub-clinical situations, and so prevent the onset of infections or chronic inflammatory diseases.



Humans evolved with larger and intensive energetic demands for brain function. Host survival thus required mechanisms that balance the energetic costs of essential functions such as successful immune response against infections and tissue repair. Accordingly, humans have developed an integrated immunometabolic response (IIMR) that involves sensing of nutrient balance by neuronal (sympathetic and sensory innervation) and humoral signals (e.g., hormones like insulin, FGF21, GDF15, ghrelin…) between the hypothalamus and peripheral tissues to allow the host to prioritize storage and/or utilize substrates for tissue growth, maintenance, and immune responses.

Hence, severe reduction in nutrient and energy intake might cause tradeoffs in non-essential functions.

Lee & Dixit, ***Immunity****, 2020*



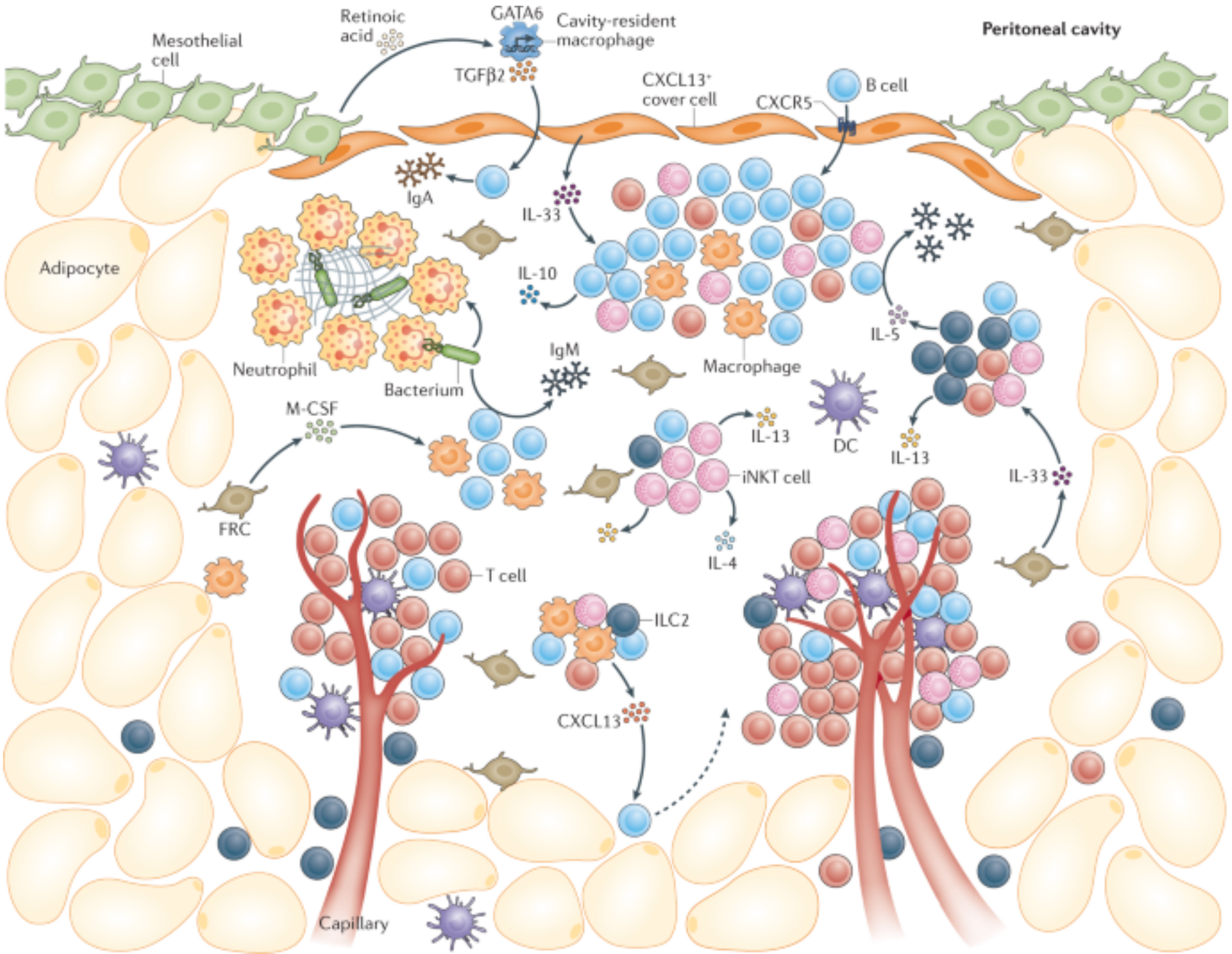
In an event of low glucose availability, such as food restriction, the limited glycogen reserves in the liver and muscle cannot sustain non-essential metabolic demand. Instead, triglycerides undergo fatty acid oxidation, ketogenesis, and ketolysis to support ATP production.

Calorie restriction (CR) has typically beneficial effects on the immune system (and longevity)

Lee & Dixit, ***Immunity****, 2020*

Modern diets are rich in saturated fats and processed carbohydrates, such as high fructose corn syrup, and are deficient in fiber, vitamins, and minerals, while containing high levels of salt. These diets are a leading cause of the emergence of obesity-associated chronic diseases, the majority of which are linked to chronic inflammation.

Adipose is an immunologic tissue



Trim & Lynch, ***Nat Rev Immunol****, 2022*

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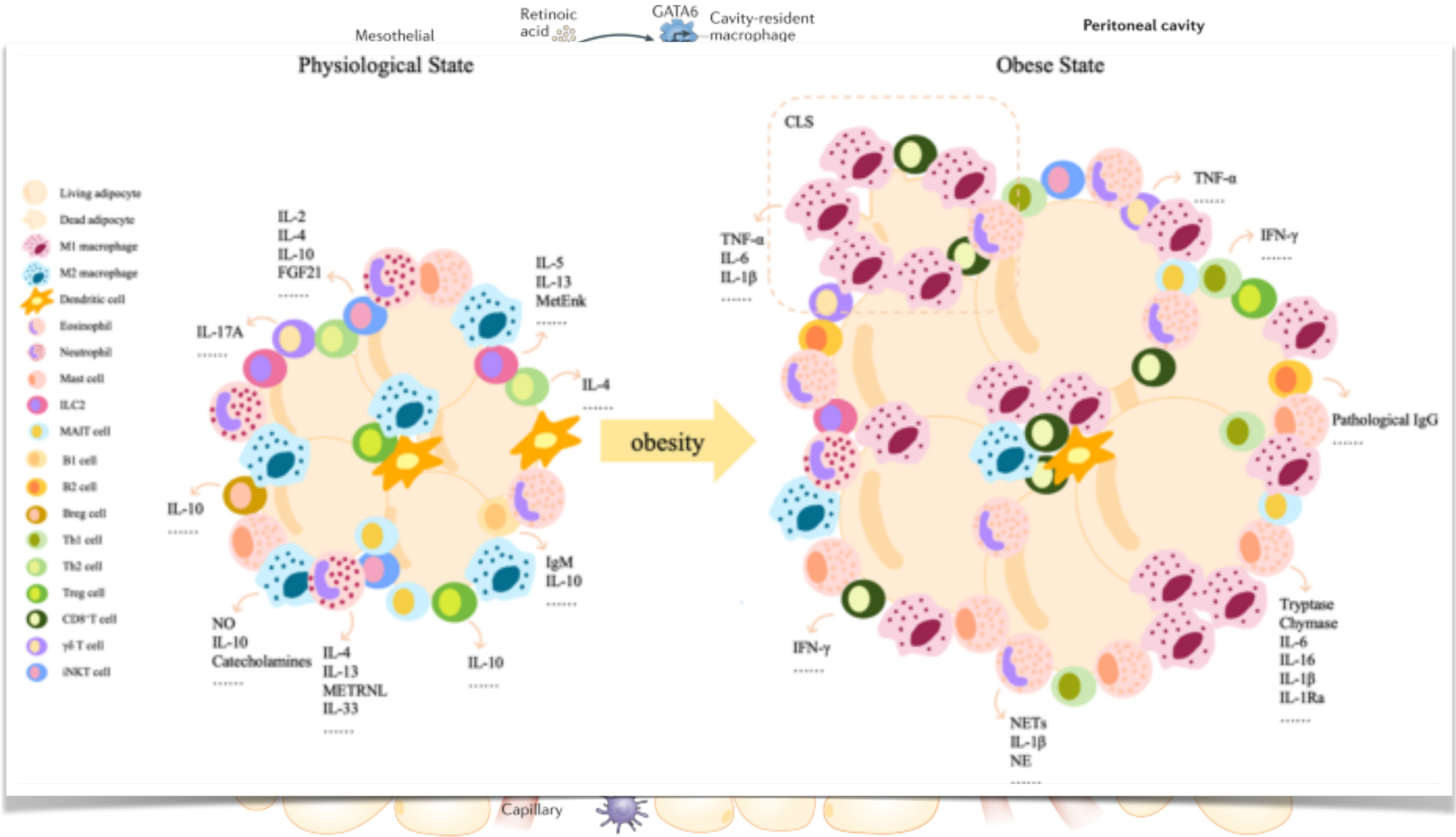

Trim & Lynch, ***Nat Rev Immunol****, 2022*

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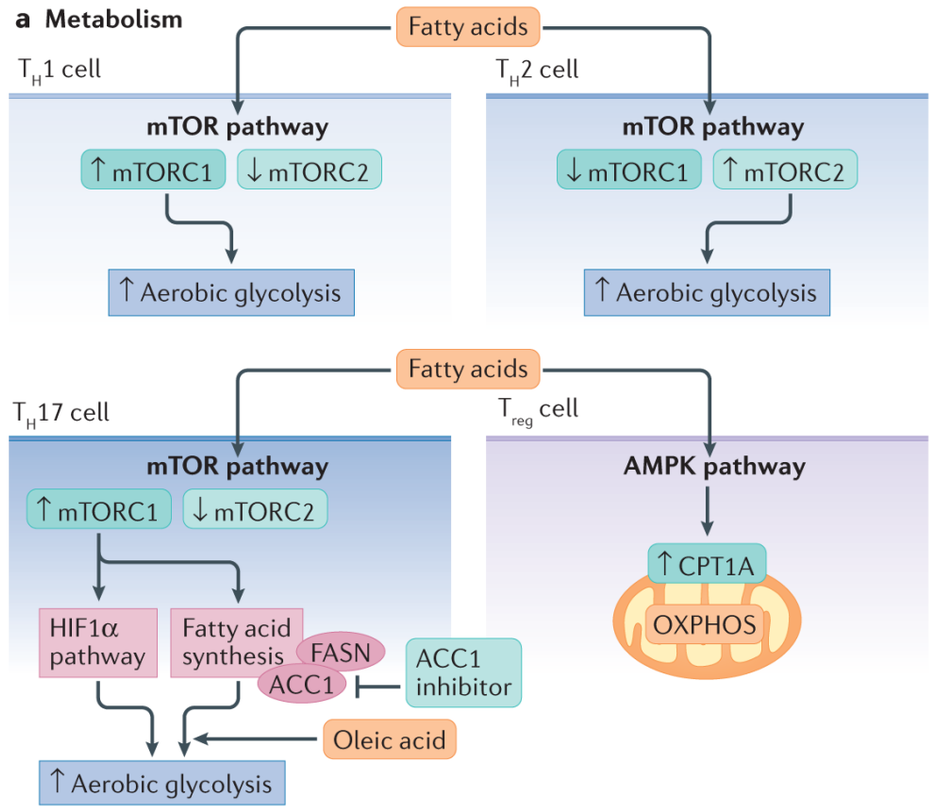
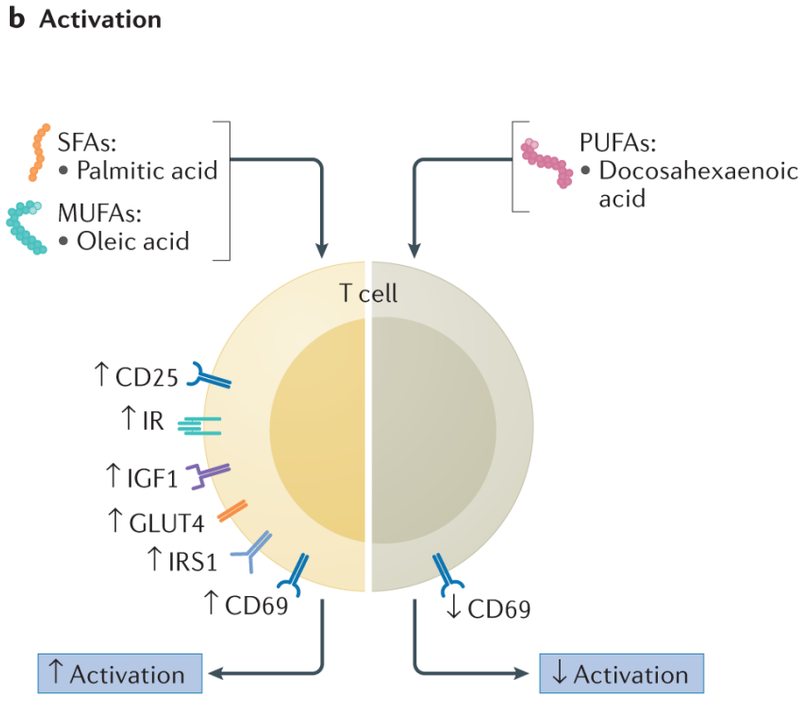
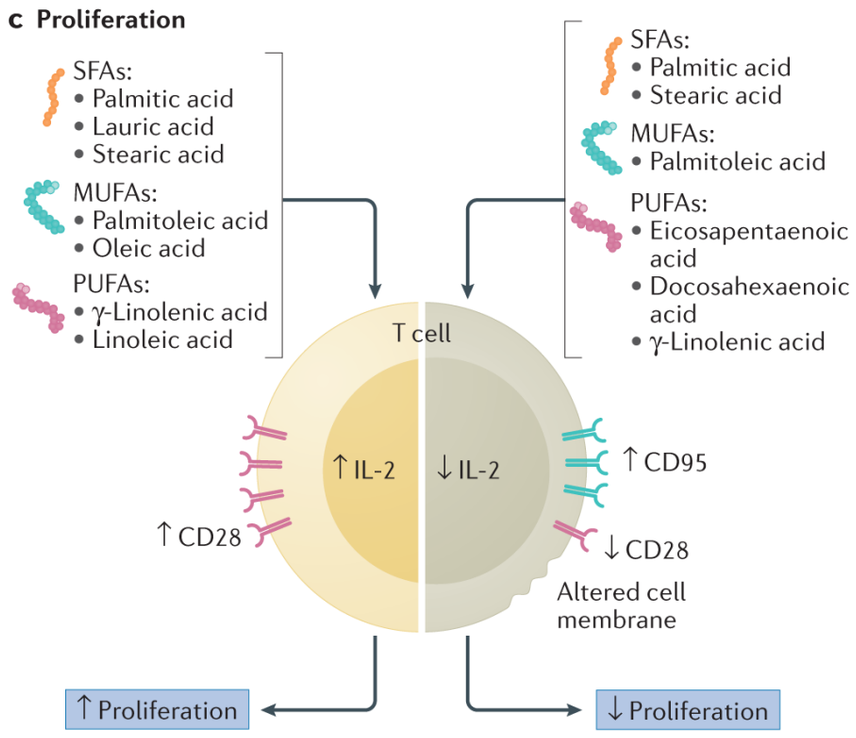
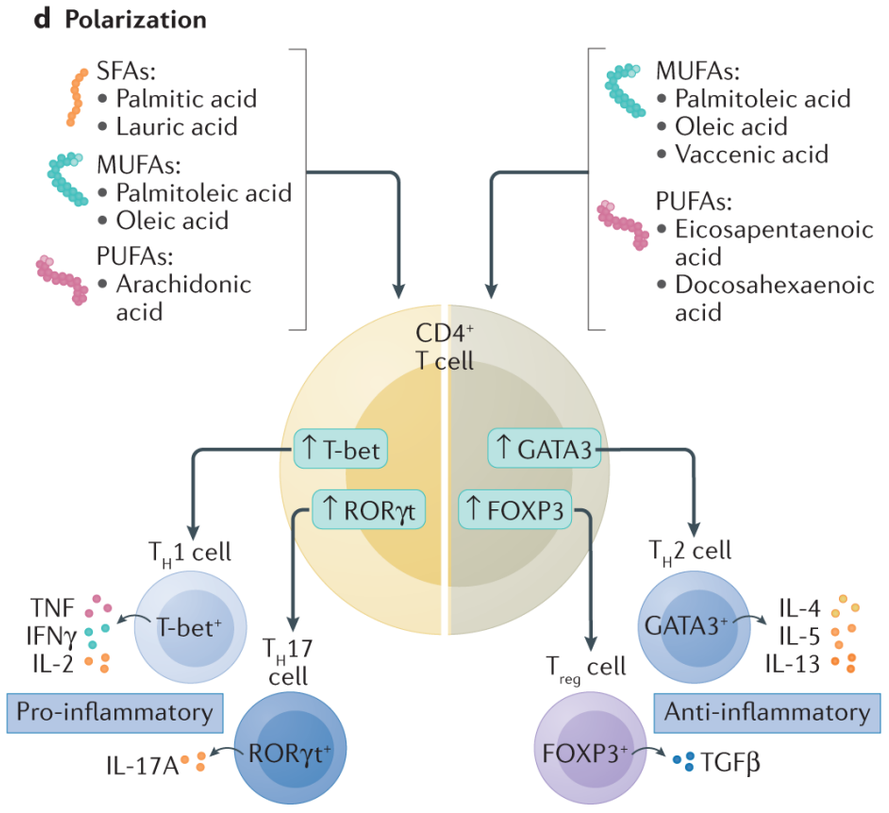
Obesity promotes hyperglycemia and hyperlipidemia



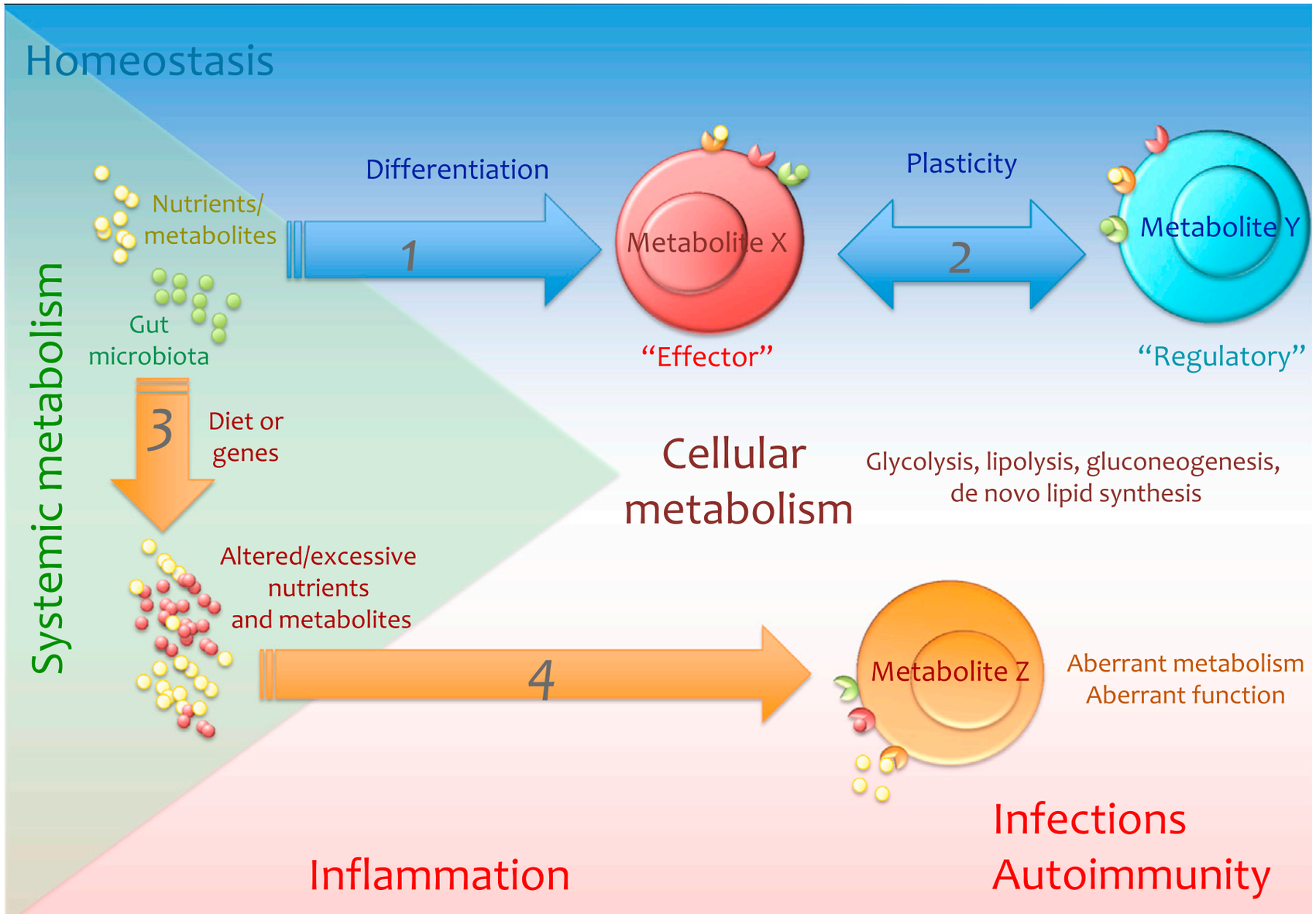






Reilly et al, ***Nat Rev Cardiol****, 2021*

Dietary components can affect immunity



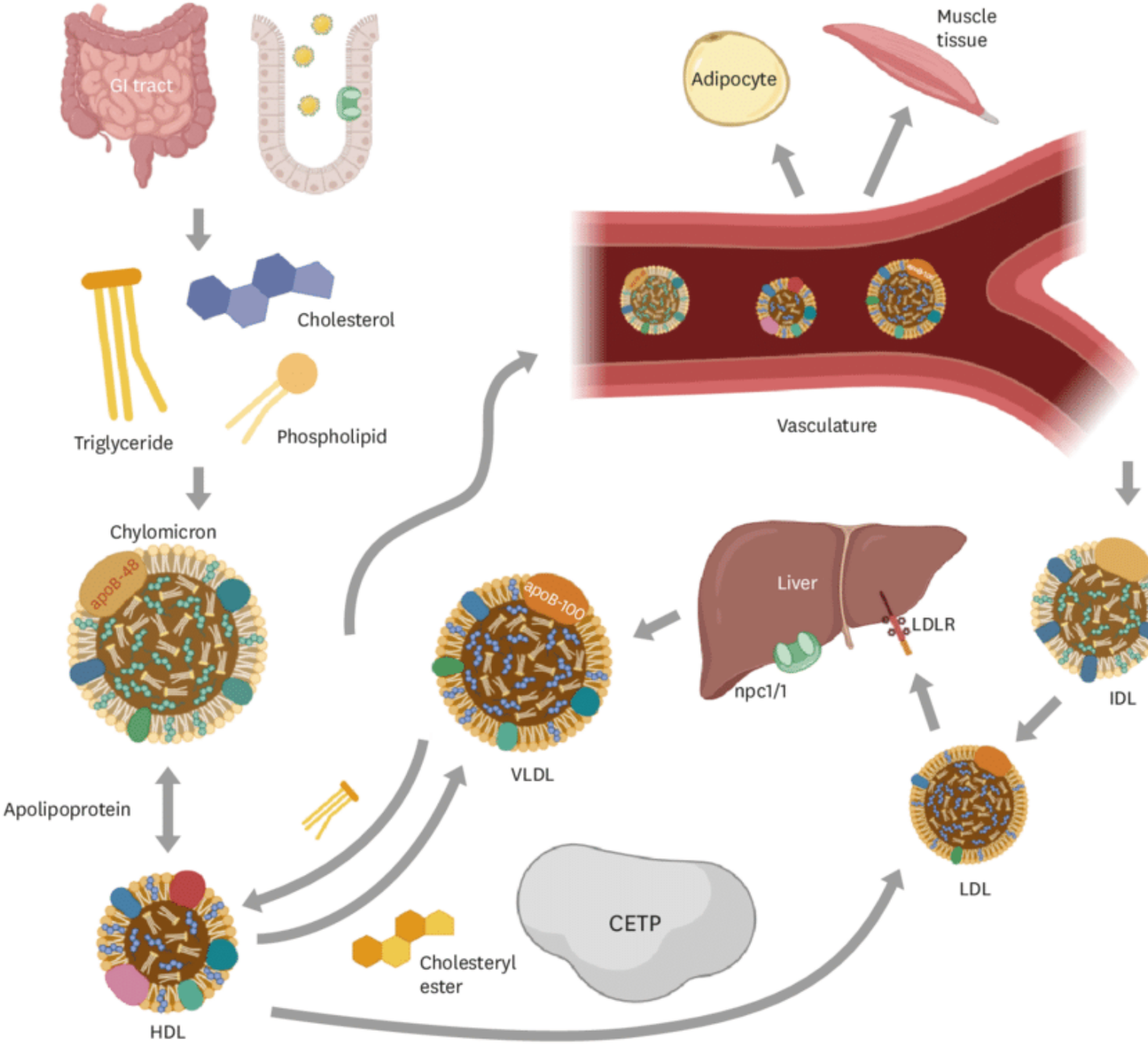
Some metabolite bypass homeostatic control at the systemic (or tissue) level and can impact immune cell differentiation and/or effector function

Mechanisms:

- Lack of feedback regulation
- Feedforward regulation
- Microbiome processing

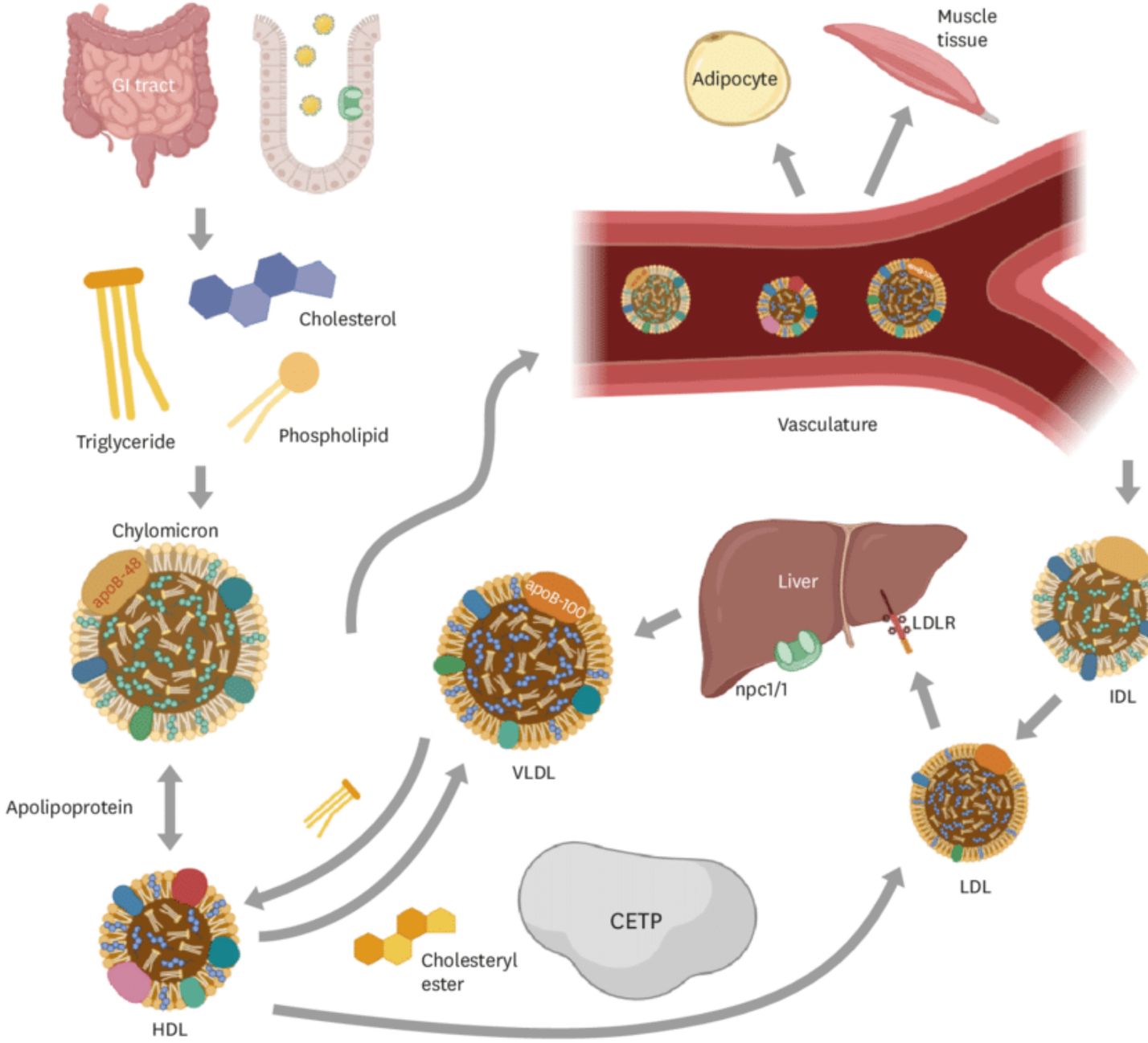
Norata et al, ***Immunity****, 2015*

Hypercholesterolaemia



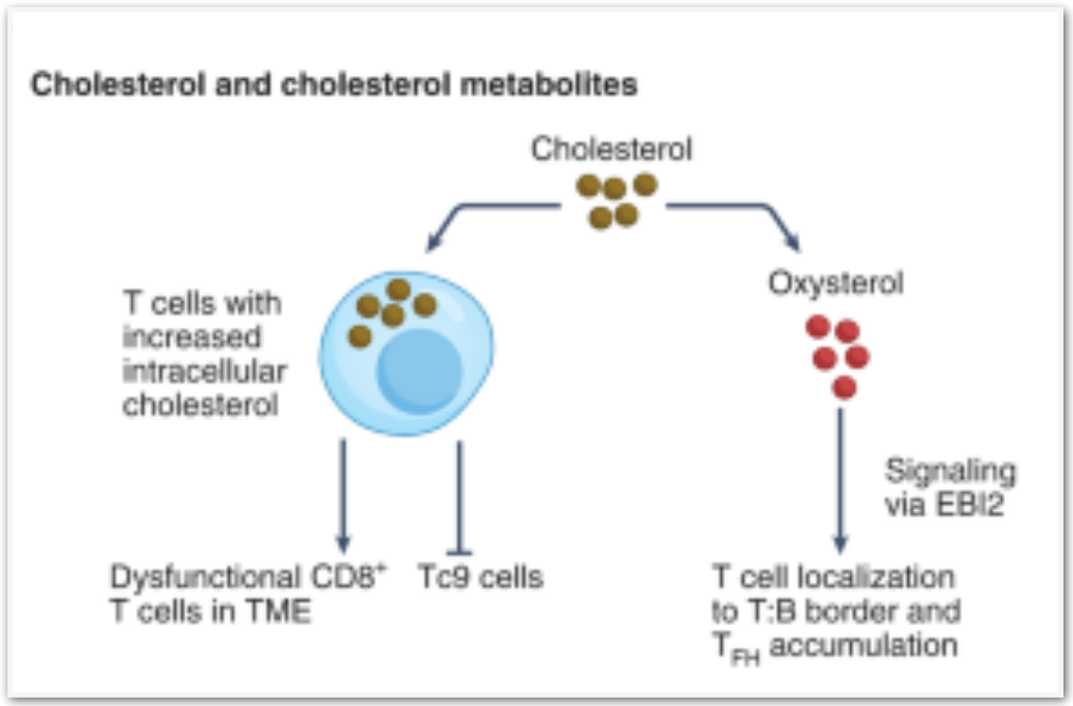
Excessive lipid intake leads to hypercholesterolemia (including elevated ox-LDL)

Hypercholesterolaemia

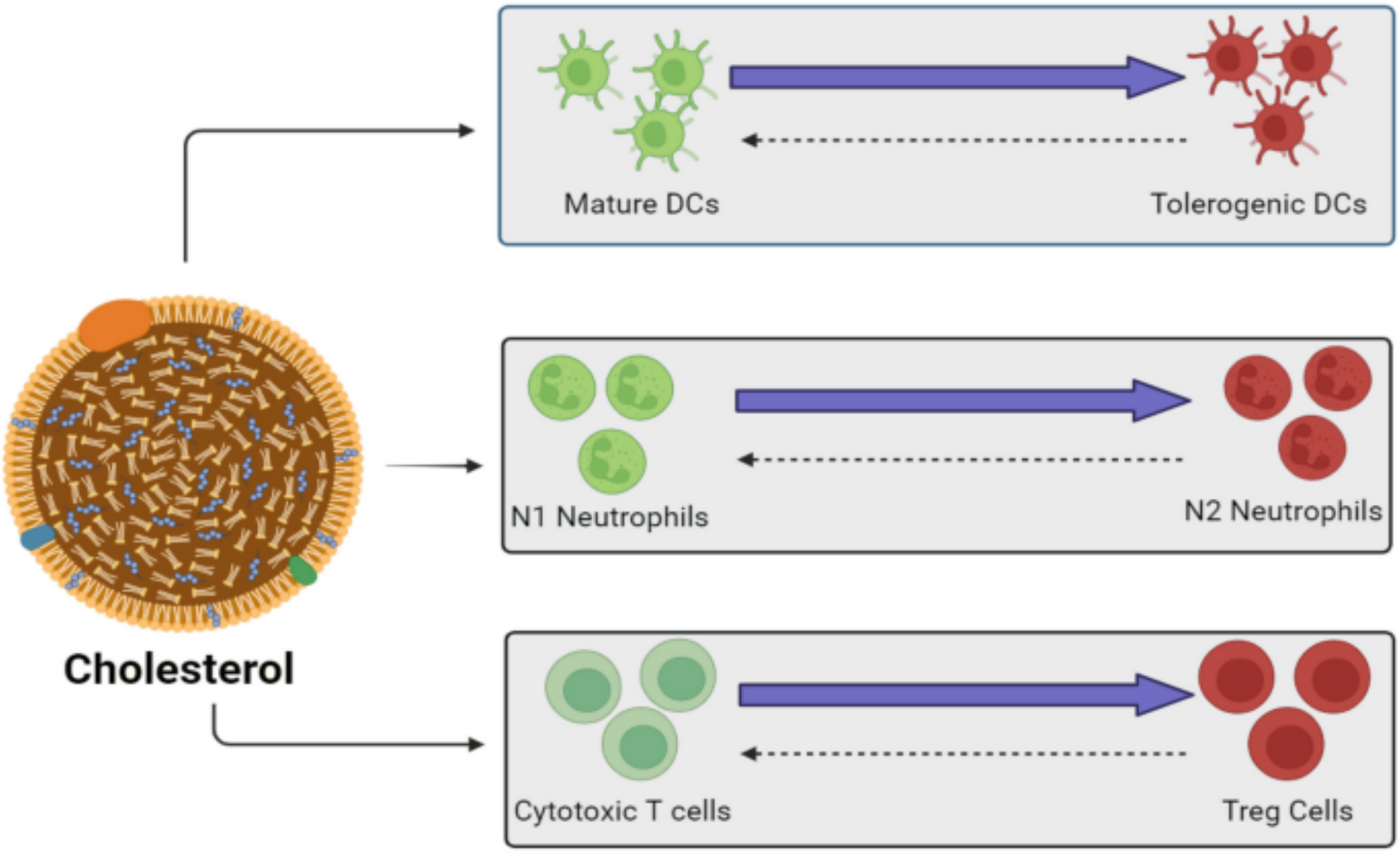


Excessive lipid intake leads to hypercholesterolemia (including elevated ox-LDL)

Hypercholesterolemia induces cholesterol accumulation within immune cells



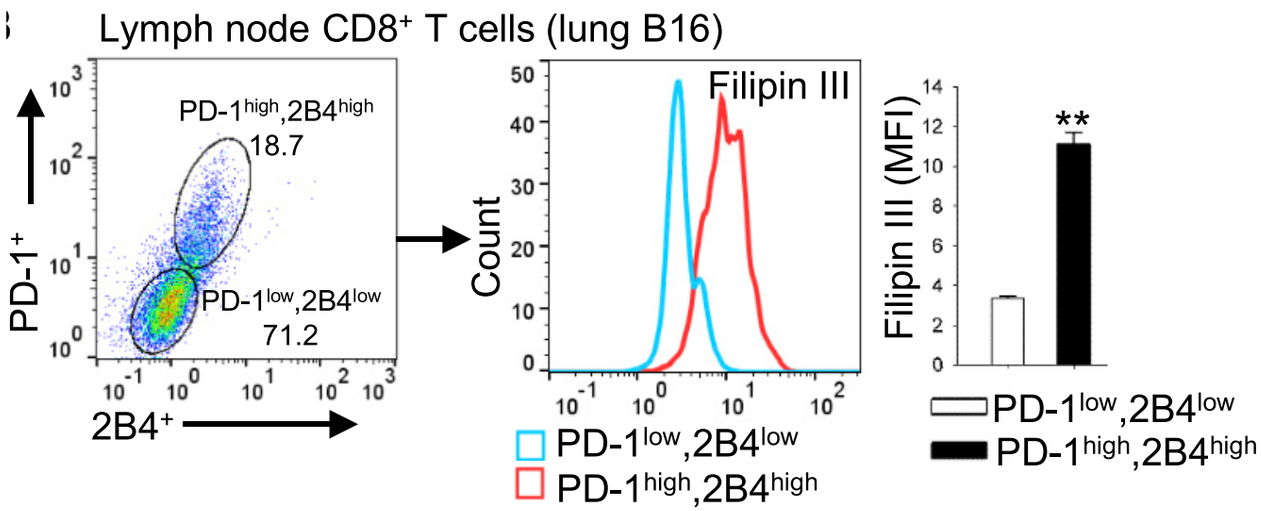
Exogenous cholesterol promotes immunosuppression (highly heterogeneous effects)



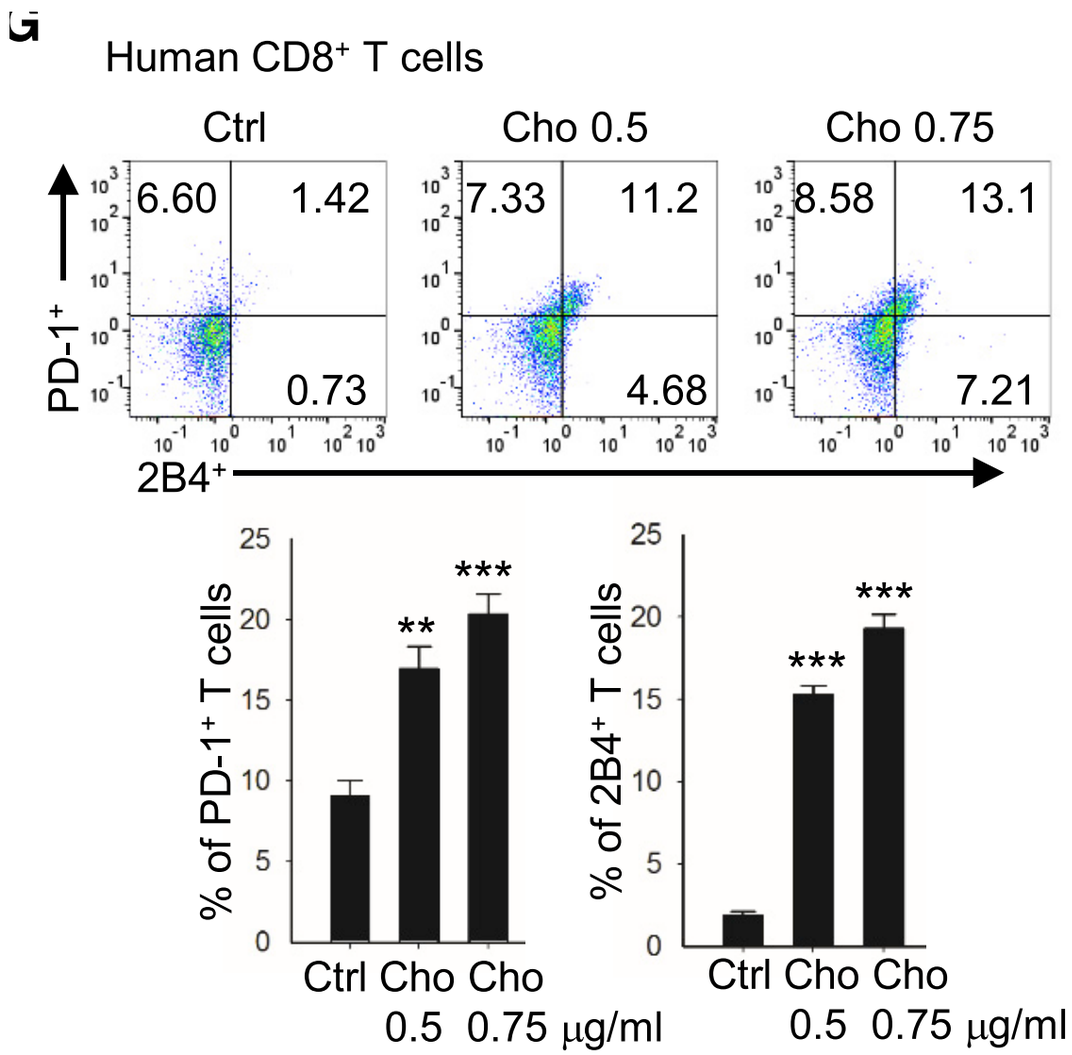
Saad et al, ***Curr Nutr Rep****, 2024*

Cholesterol Induces CD8$^+$ T Cell Exhaustion in the Tumor Microenvironment

Xingzhe Ma,[1,6] Enguang Bi,[1,6] Yong Lu,[2] Pan Su,[1] Chunjian Huang,[1] Lintao Liu,[1] Qiang Wang,[1] Maojie Yang,[1] Matthew F. Kalady,[3] Jianfei Qian,[1] Aijun Zhang,[4] Anisha A. Gupte,[4] Dale J. Hamilton,[4] Chengyun Zheng,[5] and Qing Yi[1,7,*]



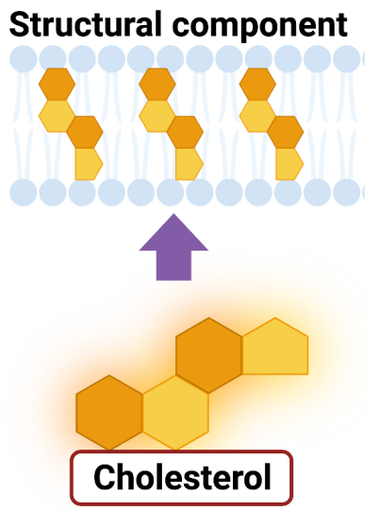
Elevated cholesterol at immunosuppressed T cells



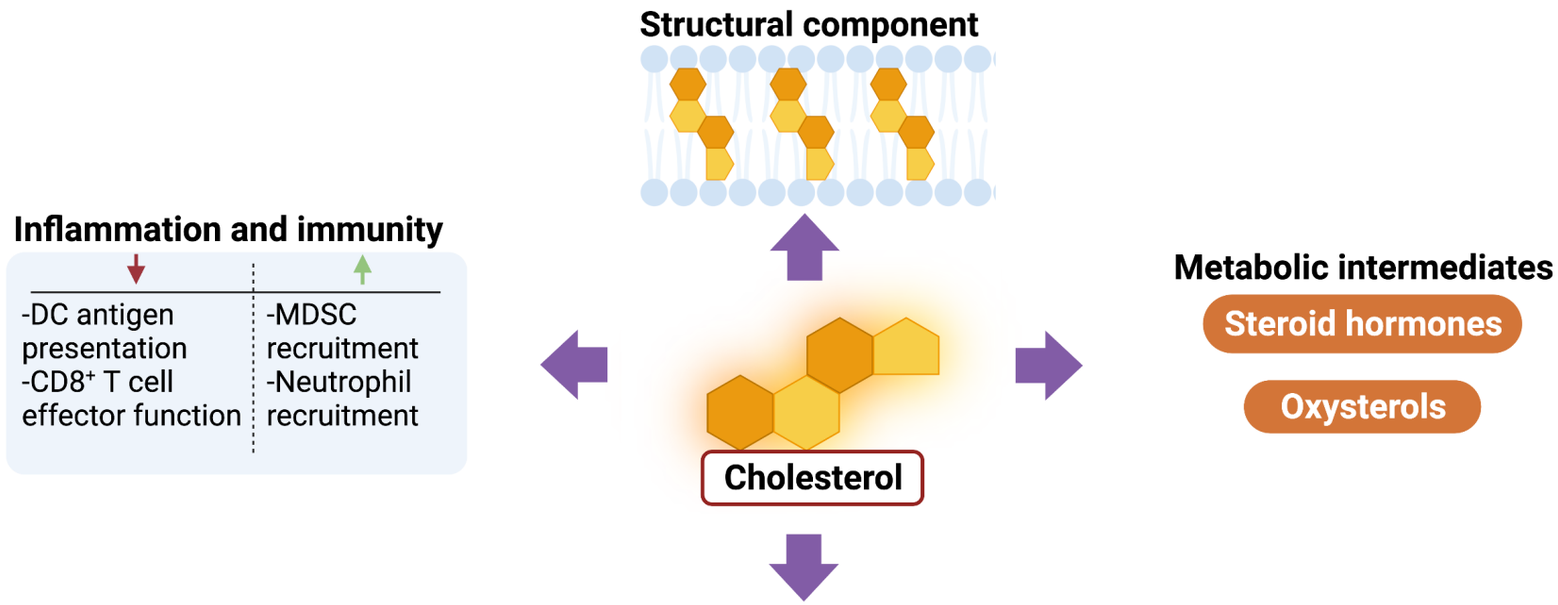
Cholesterol supplementation induces immune checkpoints

Ma et al, ***Cell Metab****, 2019*

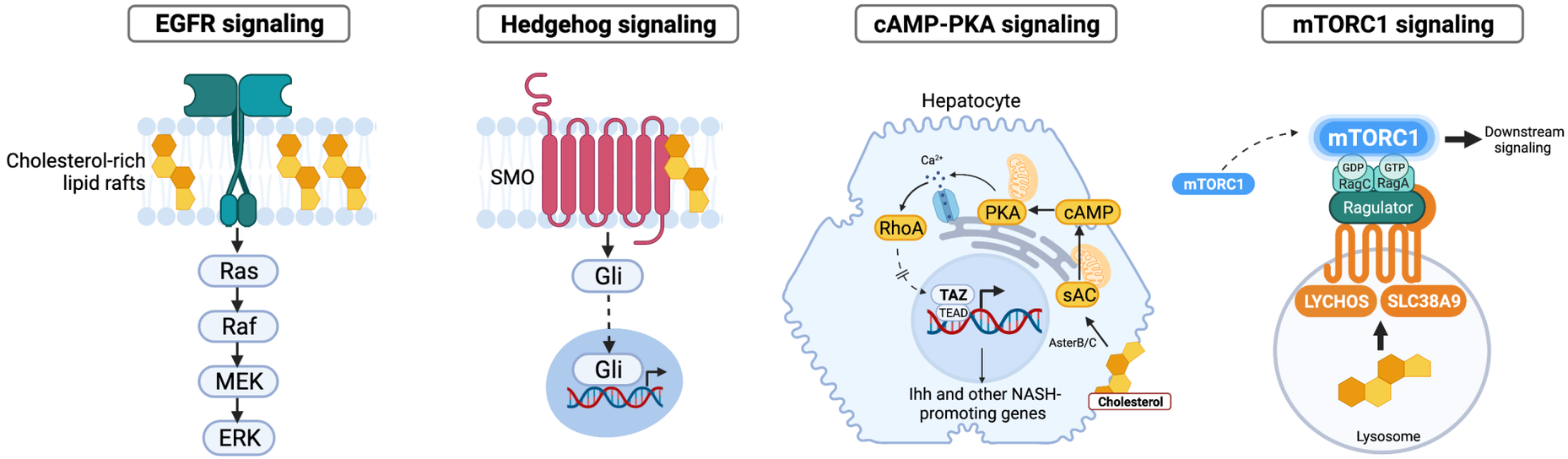
Cholesterol supports signaling

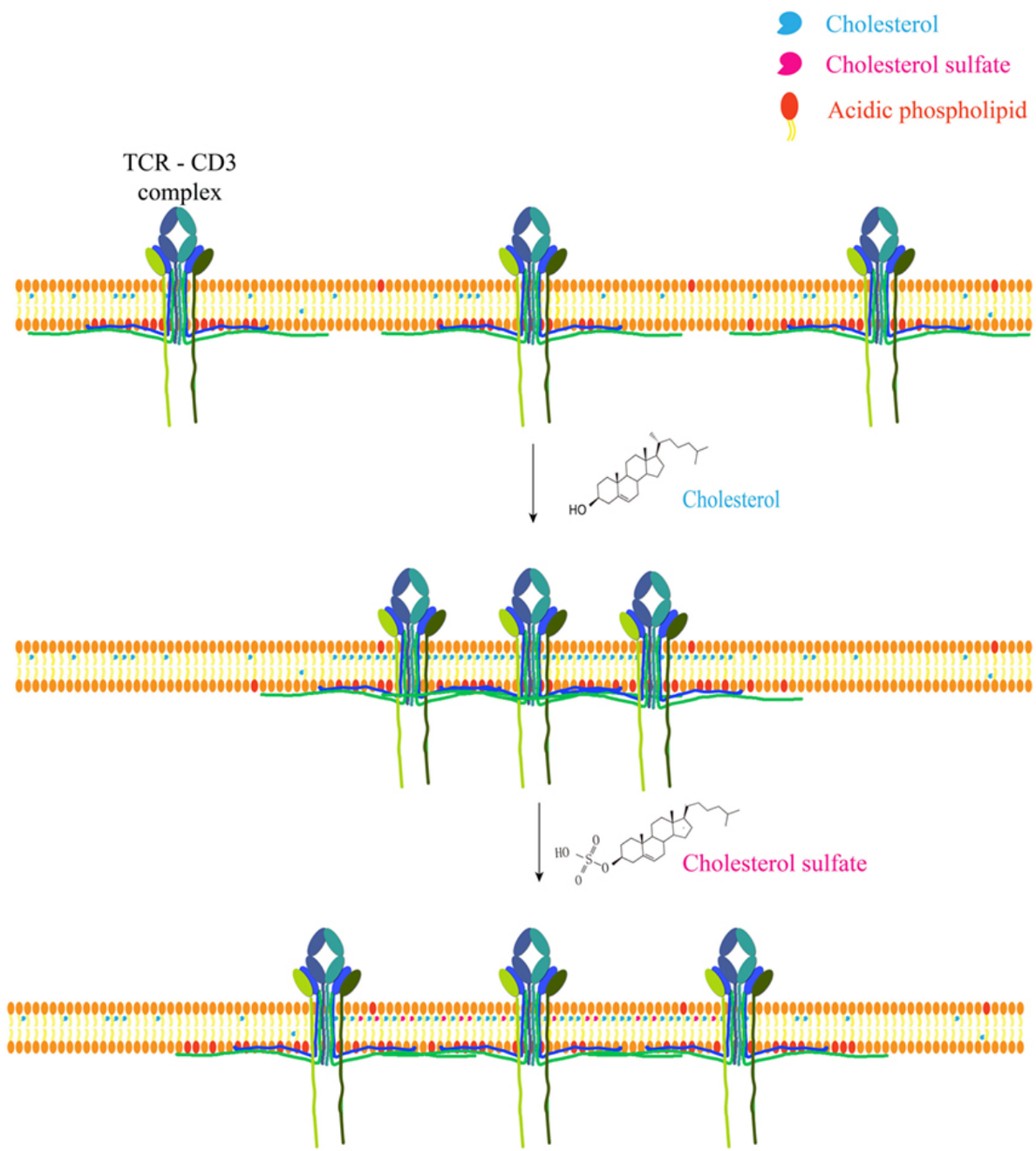


Cholesterol supports signaling



Signaling functions

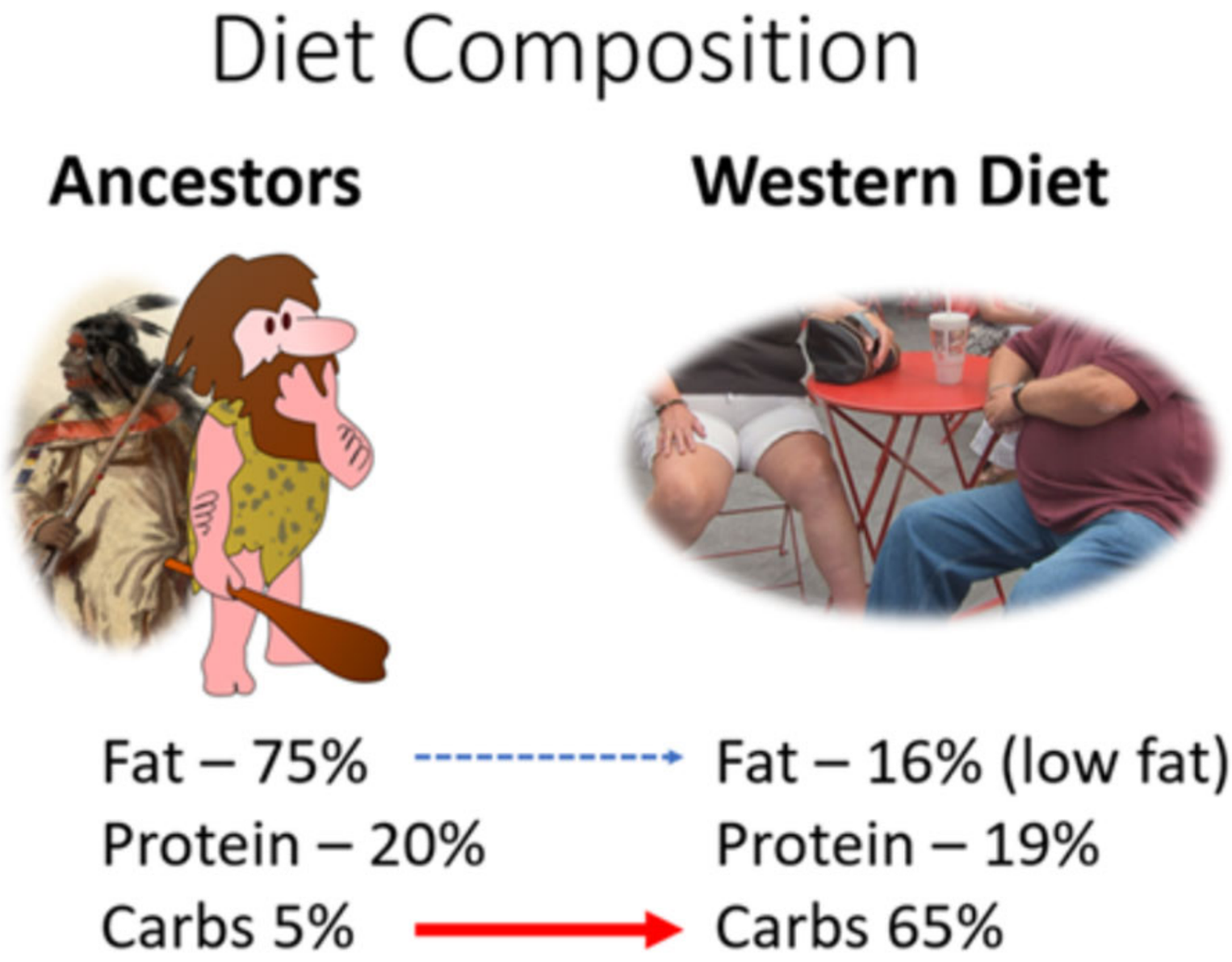




Cholesterol and metabolite regulate T cell receptor clustering. Cholesterol can directly bind to the transmembrane domain of TCR-β chain to mediate TCR clustering on T cell surface, which can increase the avidity of TCR to foreign antigens and therefore augment TCR signaling.

Bietz et al, ***Front Immunol****, 2017*

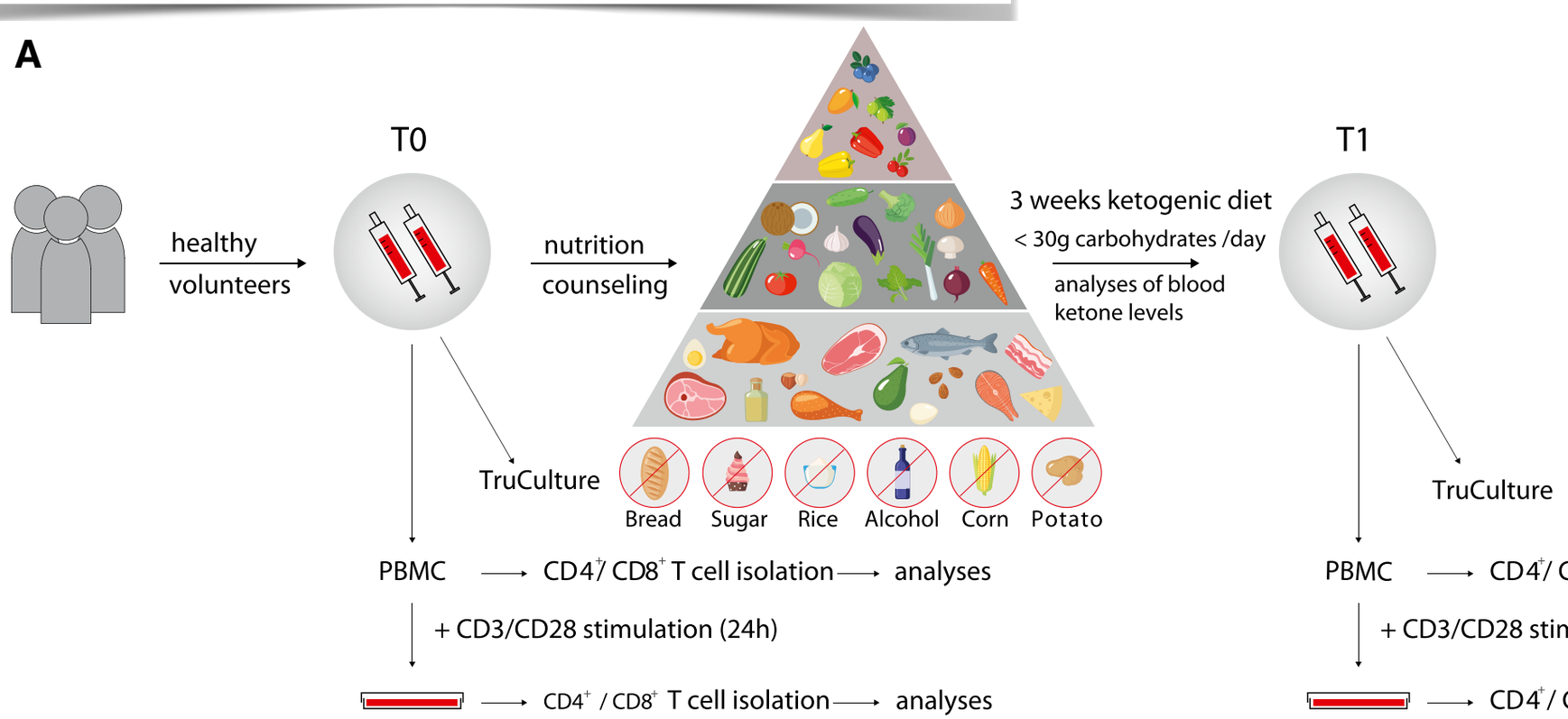
Intake of carbohydrates is elevated in WD

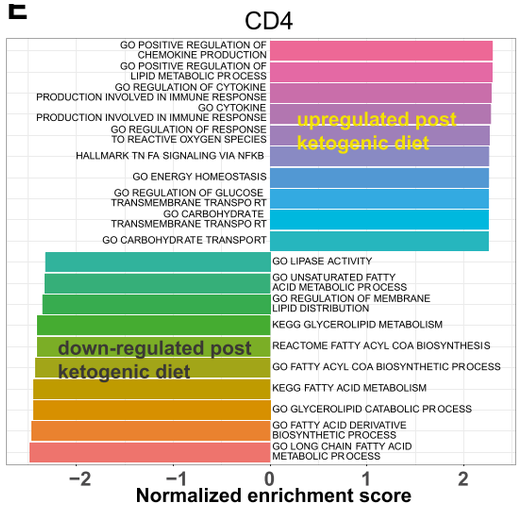


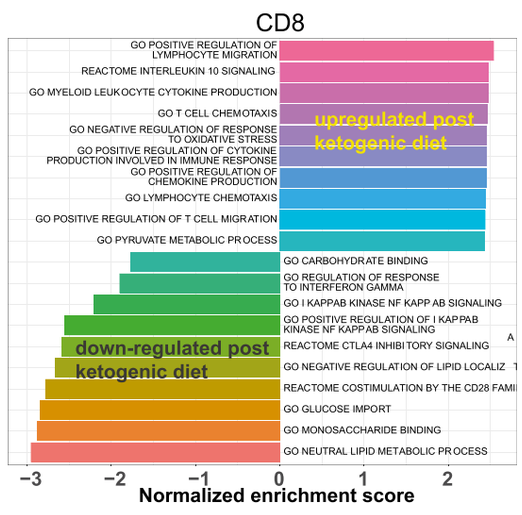
Novel nutritional concepts promote a restriction of carbohydrates in favor of fat to ameliorate detrimental low-grade inflammation *(Paoli et al, 2015; Bosco et al, 2018; Myette-Coté et al, 2018)*

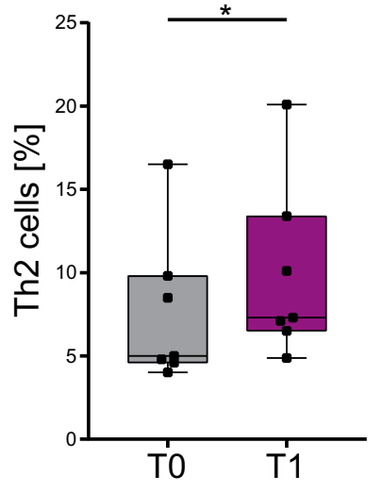
Very-low-carbohydrate diet enhances human T-cell immunity through immunometabolic reprogramming

Simon Hirschberger[1,2,†], Gabriele Strauß[1,2,†], David Effinger[1,2], Xaver Marstaller[1], Alicia Ferstl[1], Martin B Müller[1,2], Tingting Wu[1], Max Hübner[1,2], Tim Rahmel[3], Hannah Mascolo[1], Nicole Exner[4], Julia Heß[5,6], Friedrich W Kreth[1], Kristian Unger[5,6] & Simone Kreth[1,2,*]









Hirschberger et al, ***EMBO Mol Med****, 2021*

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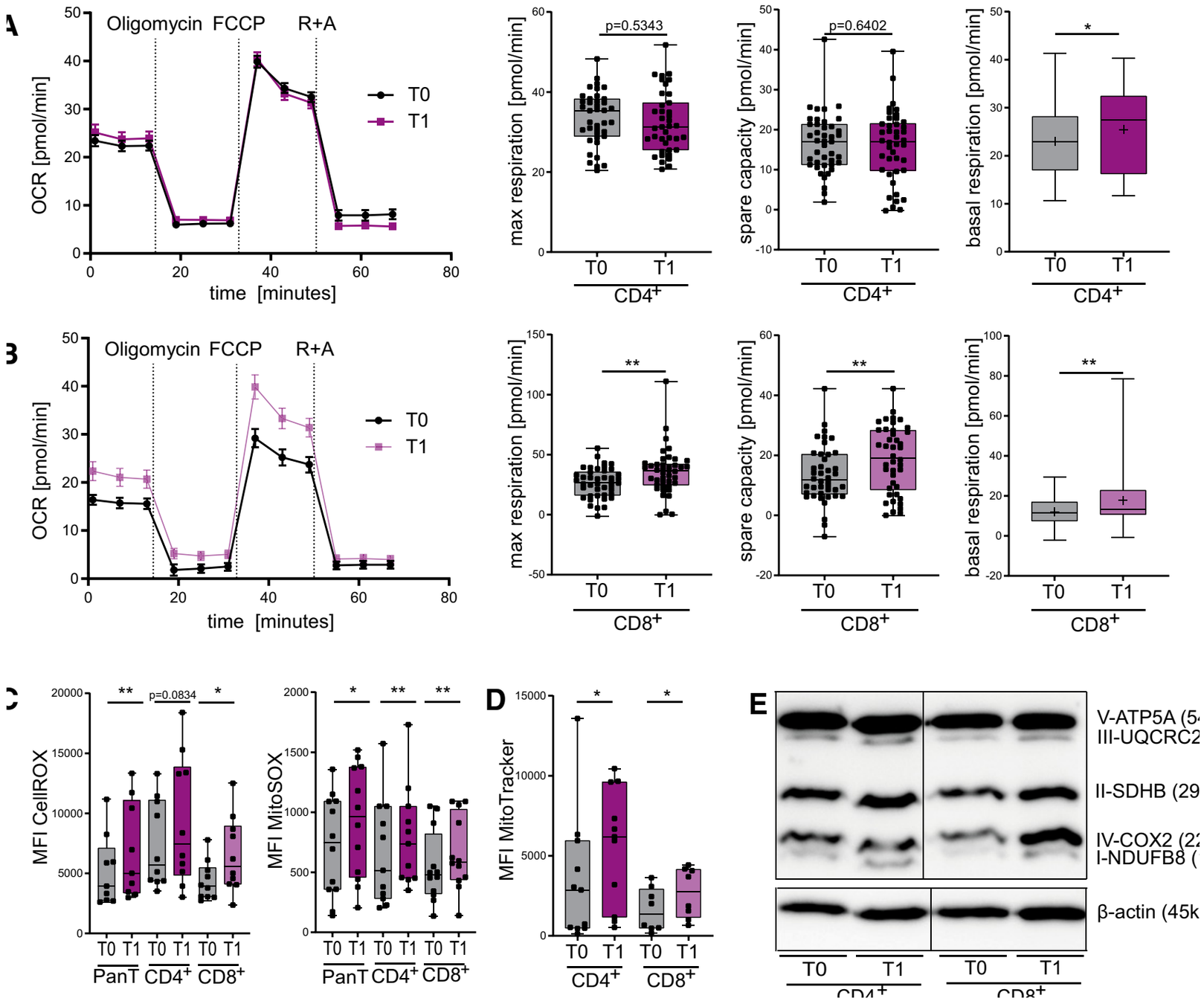

Hirschberger et al, ***EMBO Mol Med****, 2021*

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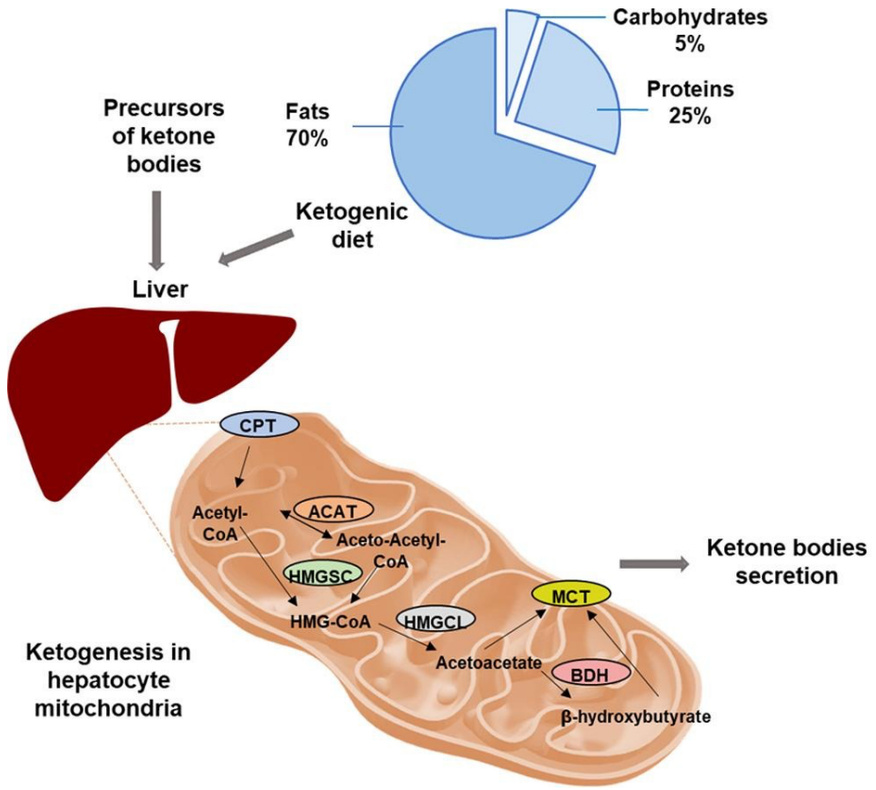
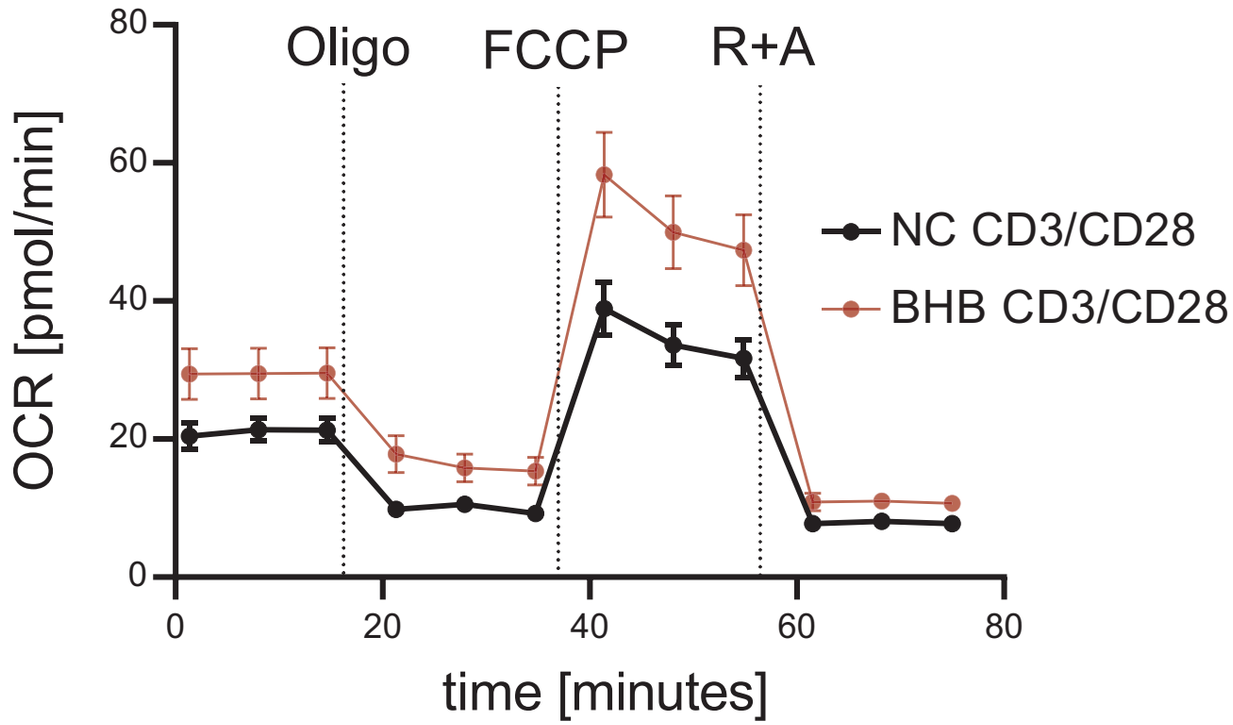
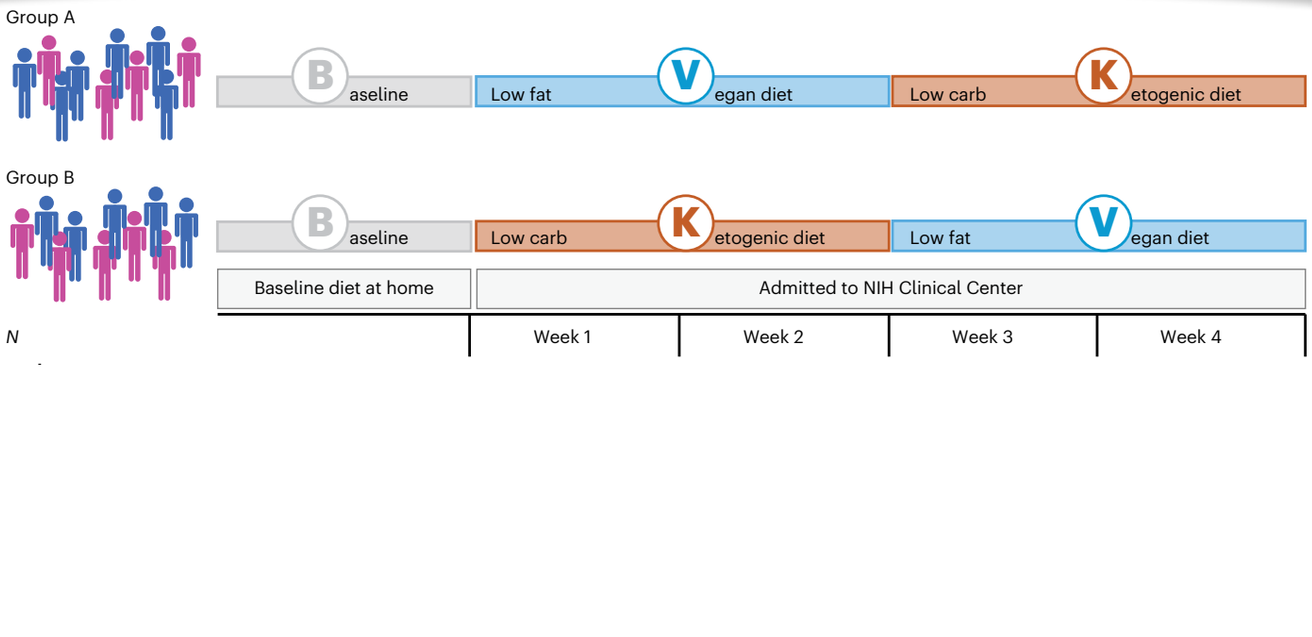




Hirschberger et al, ***EMBO Mol Med****, 2021*

Article https://doi.org/10.1038/s41591-023-02761-2

Differential peripheral immune signatures elicited by vegan versus ketogenic diets in humans



Link et al, ***Nat Med****, 2024*

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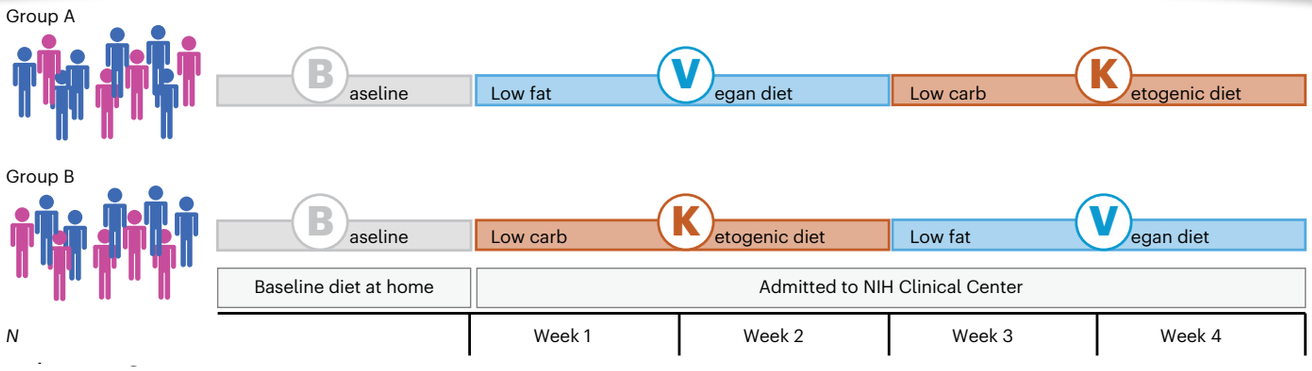
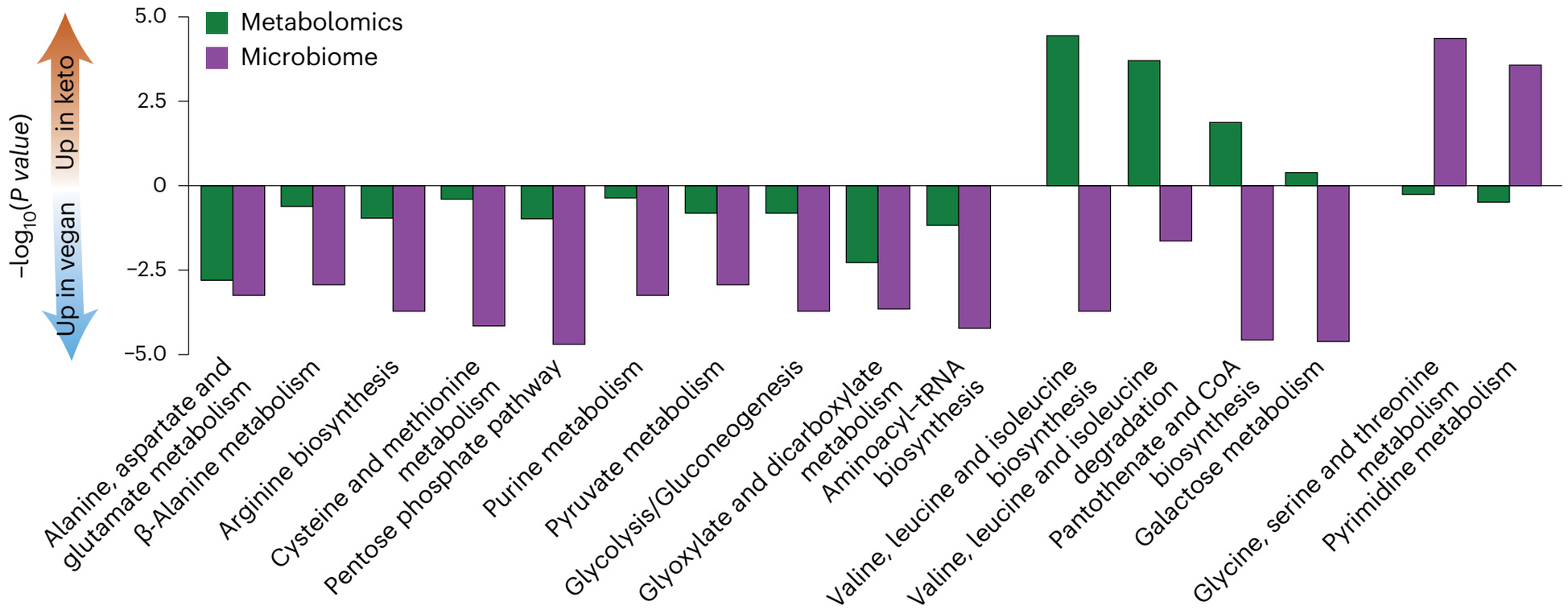
Differential peripheral immune signatures elicited by vegan versus ketogenic diets in humans



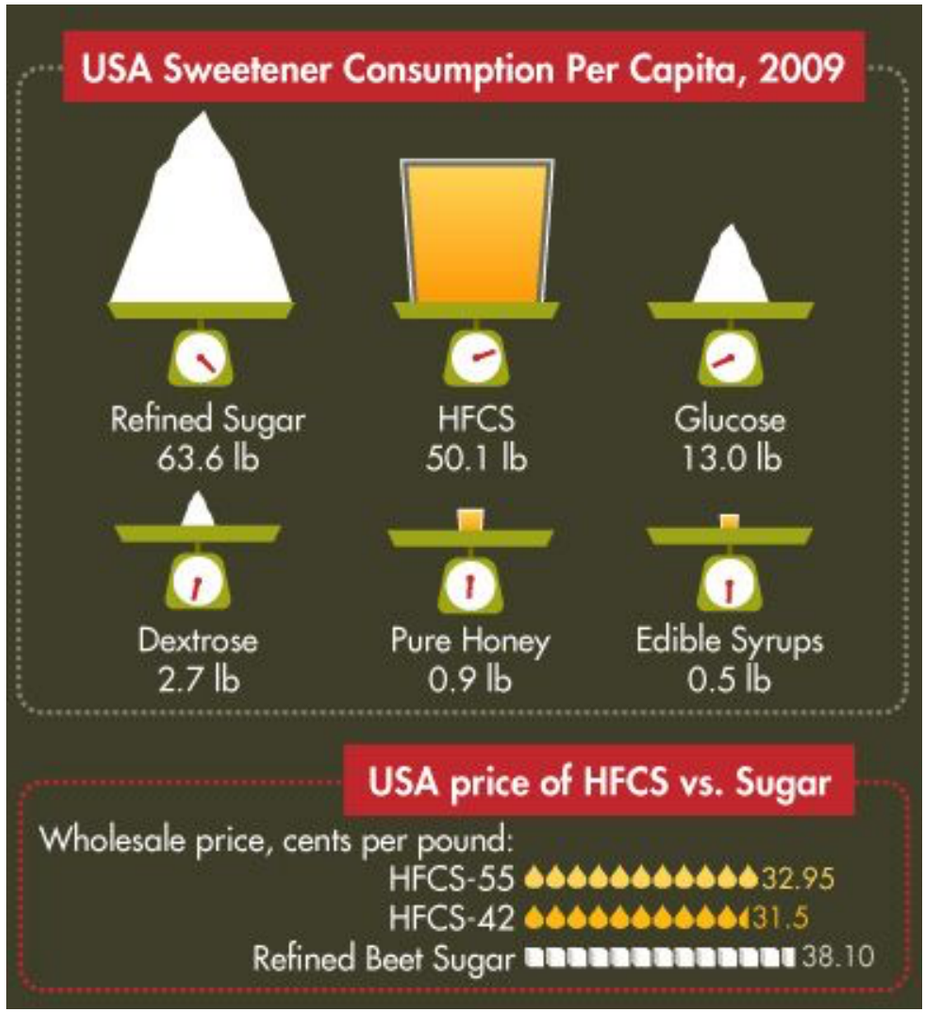


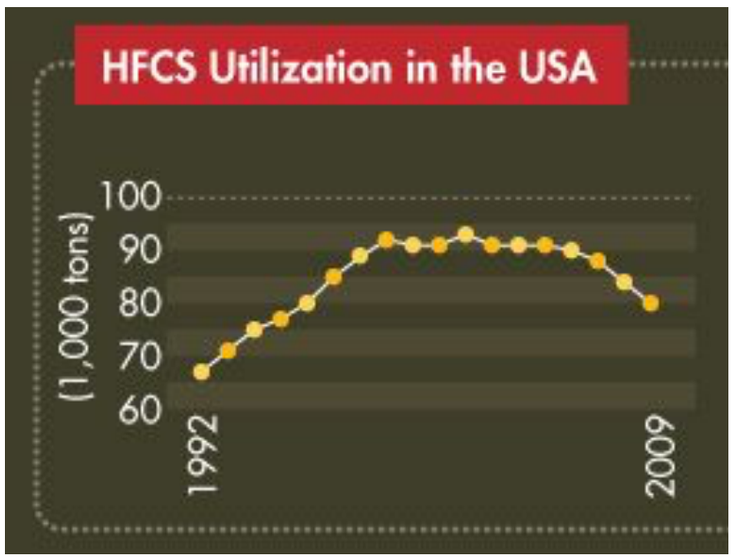
A ketogenic diet was associated with a significant upregulation of pathways and enrichment in cells associated with the adaptive immune system.

In contrast, a vegan diet had a significant impact on the innate immune system, including upregulation of pathways associated with antiviral immunity.

Link et al, ***Nat Med****, 2024*

Fructose utilization has increased dramatically

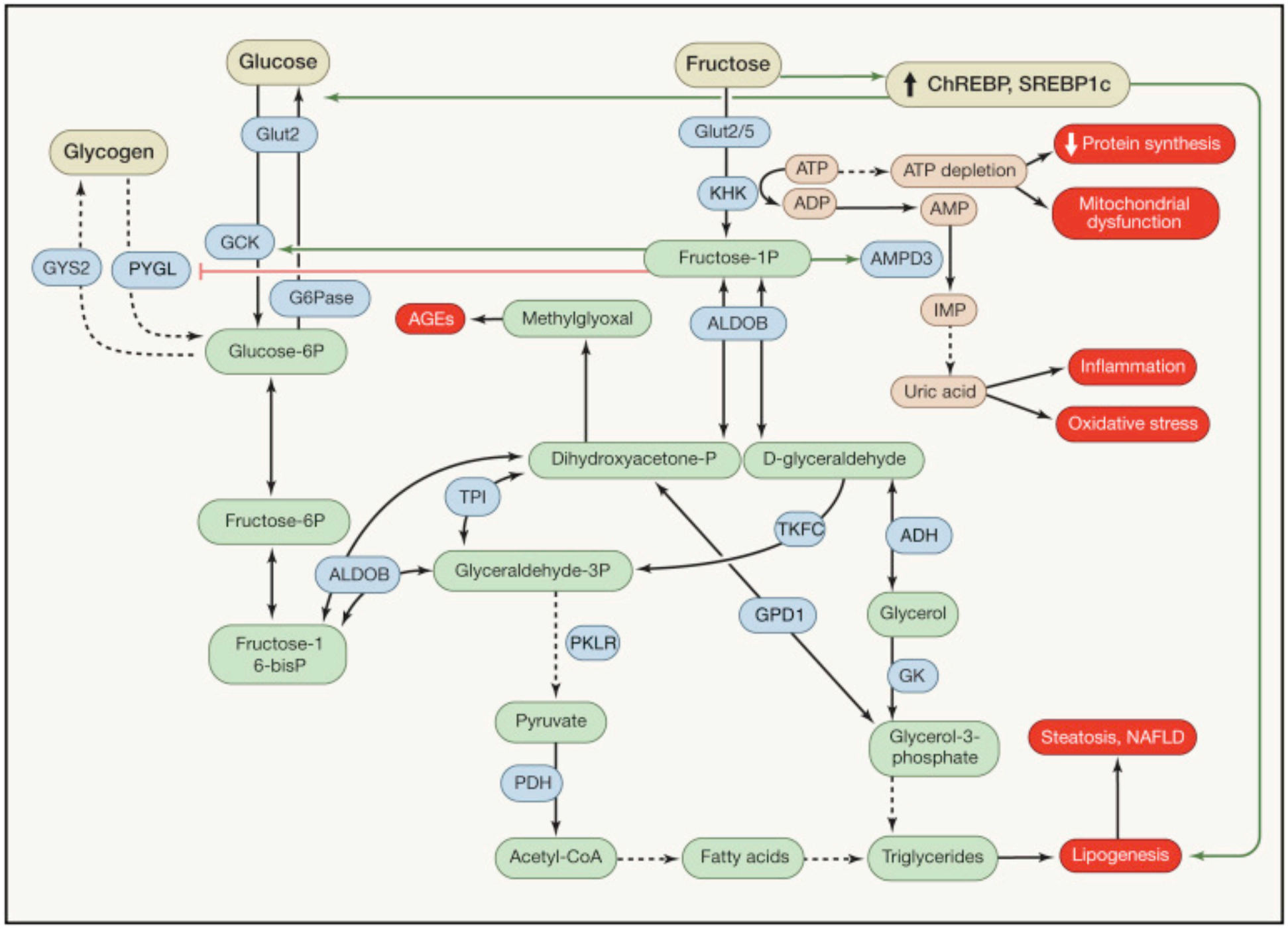




Contributes to obesity pandemic

Source: ***USDA reports***

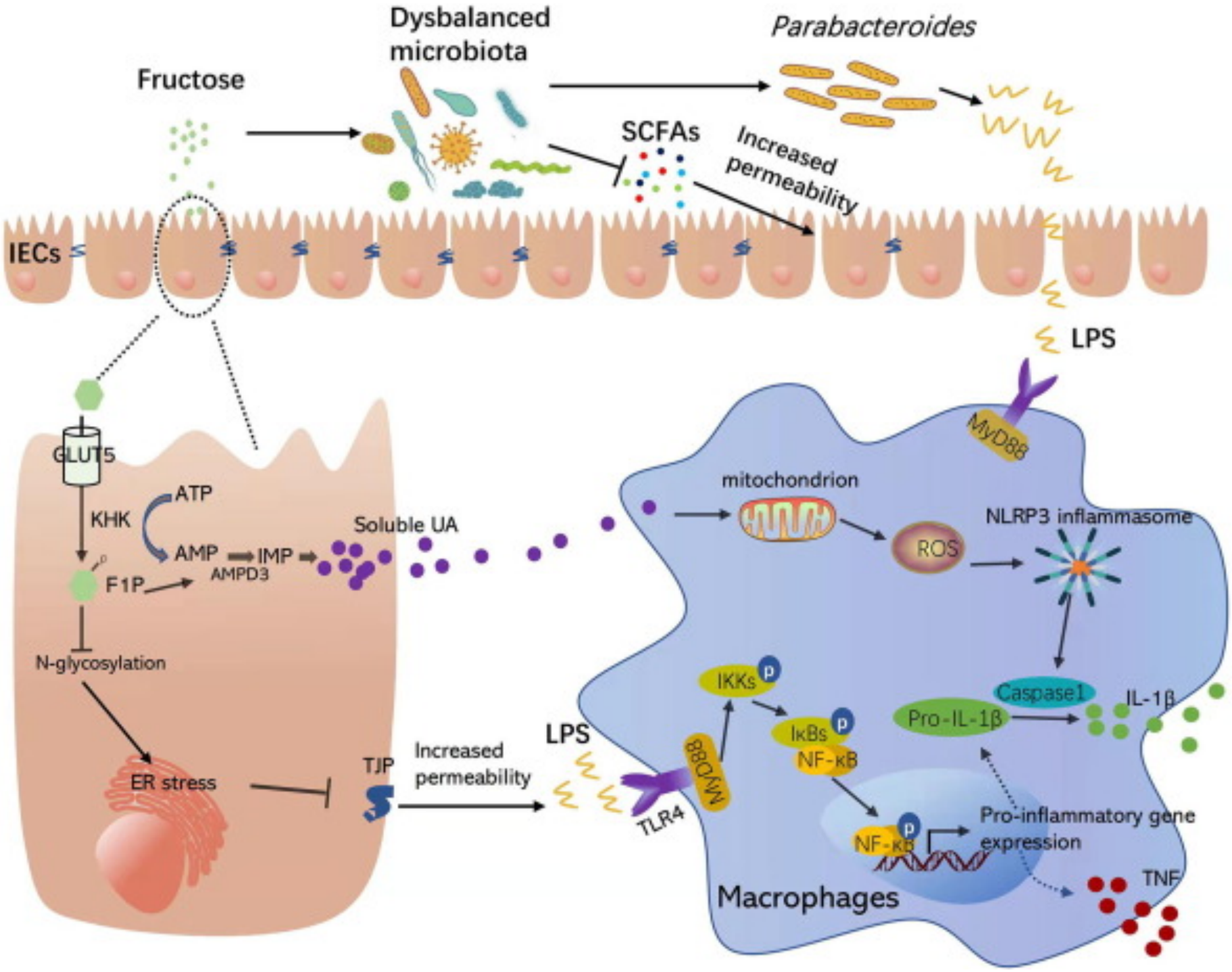
Fructose metabolism alters nucleotide, UA and lipid abundance



Note: only in cells that express SLC25A2 (GLUT5) and KHK-C (hepatocytes and colonocytes)

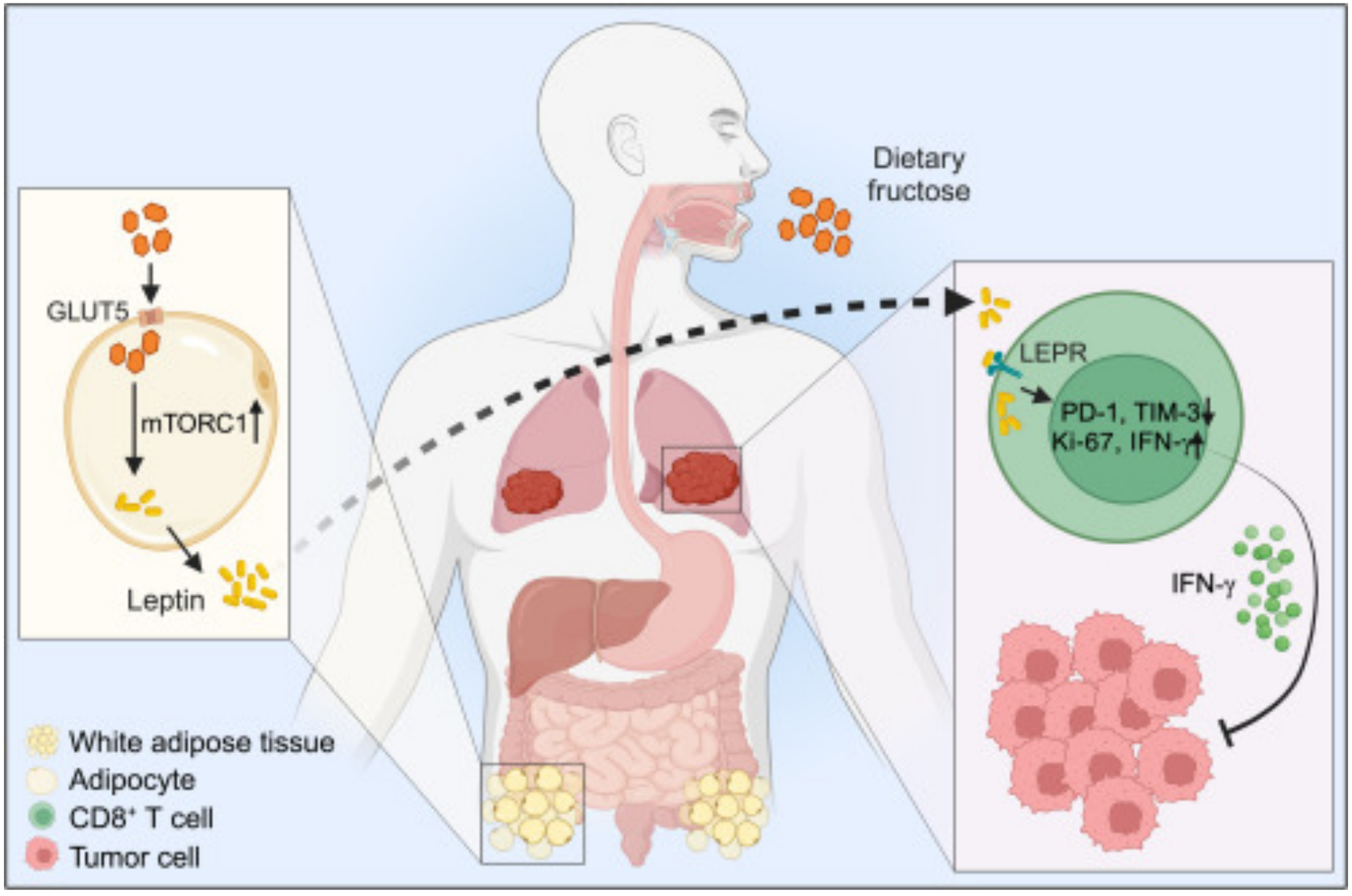
Kroemer et al, ***Cell****, 2018*

UA release impacts pro-inflammatory phenotypes in macrophages



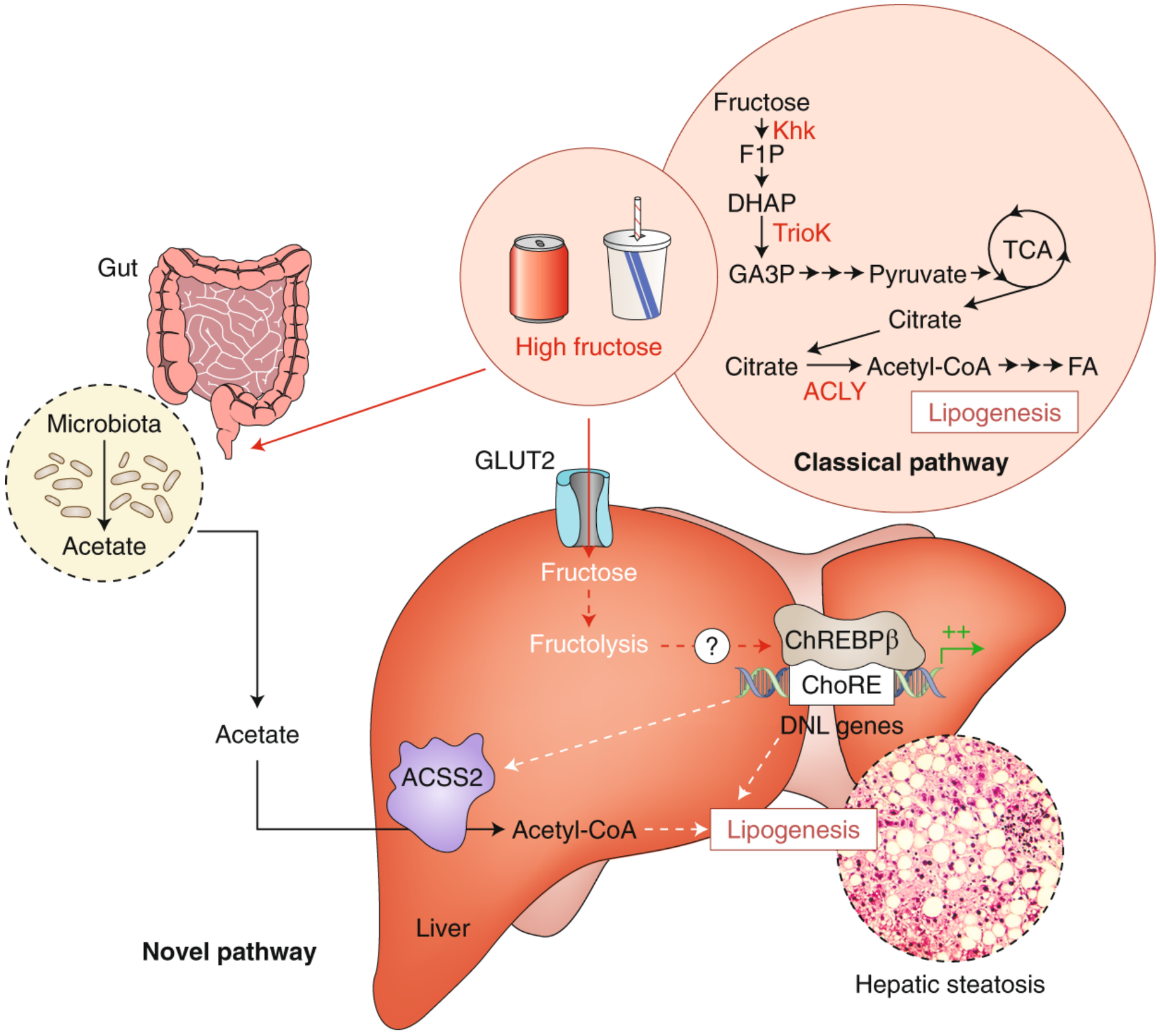
Cheng et al, ***Hum Immunol****, 2022*

Fructose is sensed by mTORC1 in adipocytes



Zhou & Chi, ***Cell Metab****, 2023*
Zhang et al, ***Cell Metab****, 2023*

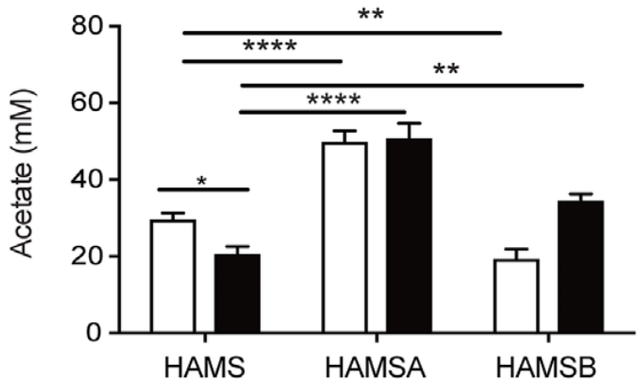
Excessive fructose is converted into acetate

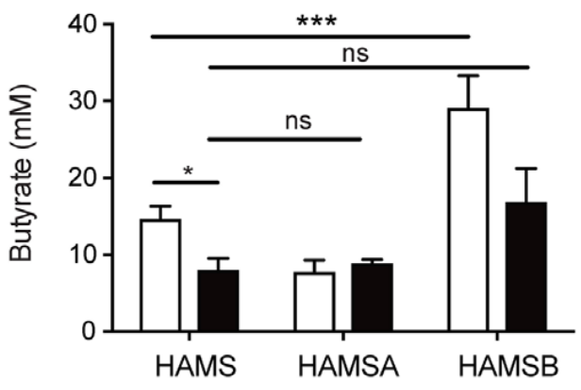


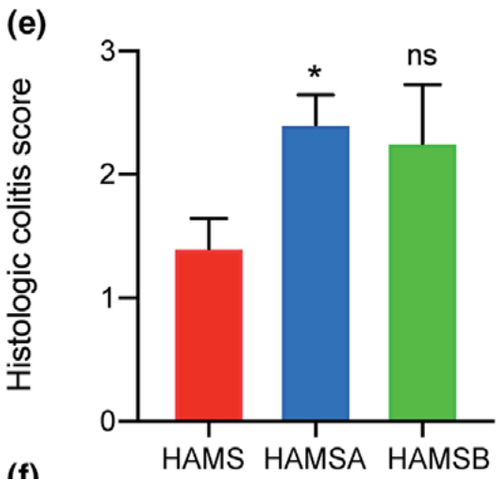
Zhao et al, ***Nature****, 2020*

An acetate-yielding diet imprints an immune and anti-microbial programme against enteric infection

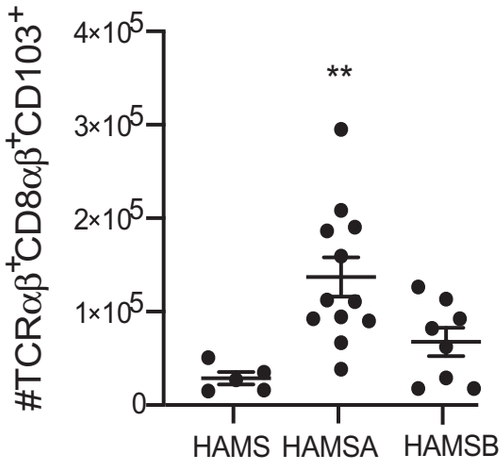
Yu Anne Yap[1†], Keiran H McLeod[1†], Craig I McKenzie[1†], Patrick G Gavin[2], Mercedes Davalos-Salas[1], James L Richards[1], Robert J Moore[3,4], Trevor J Lockett[5], Julie M Clarke[6], Vik Ven Eng[3,7], Jaclyn S Pearson[3,7,8], Emma E Hamilton-Williams[2], Charles R Mackay[3] & Eliana Mariño[1]







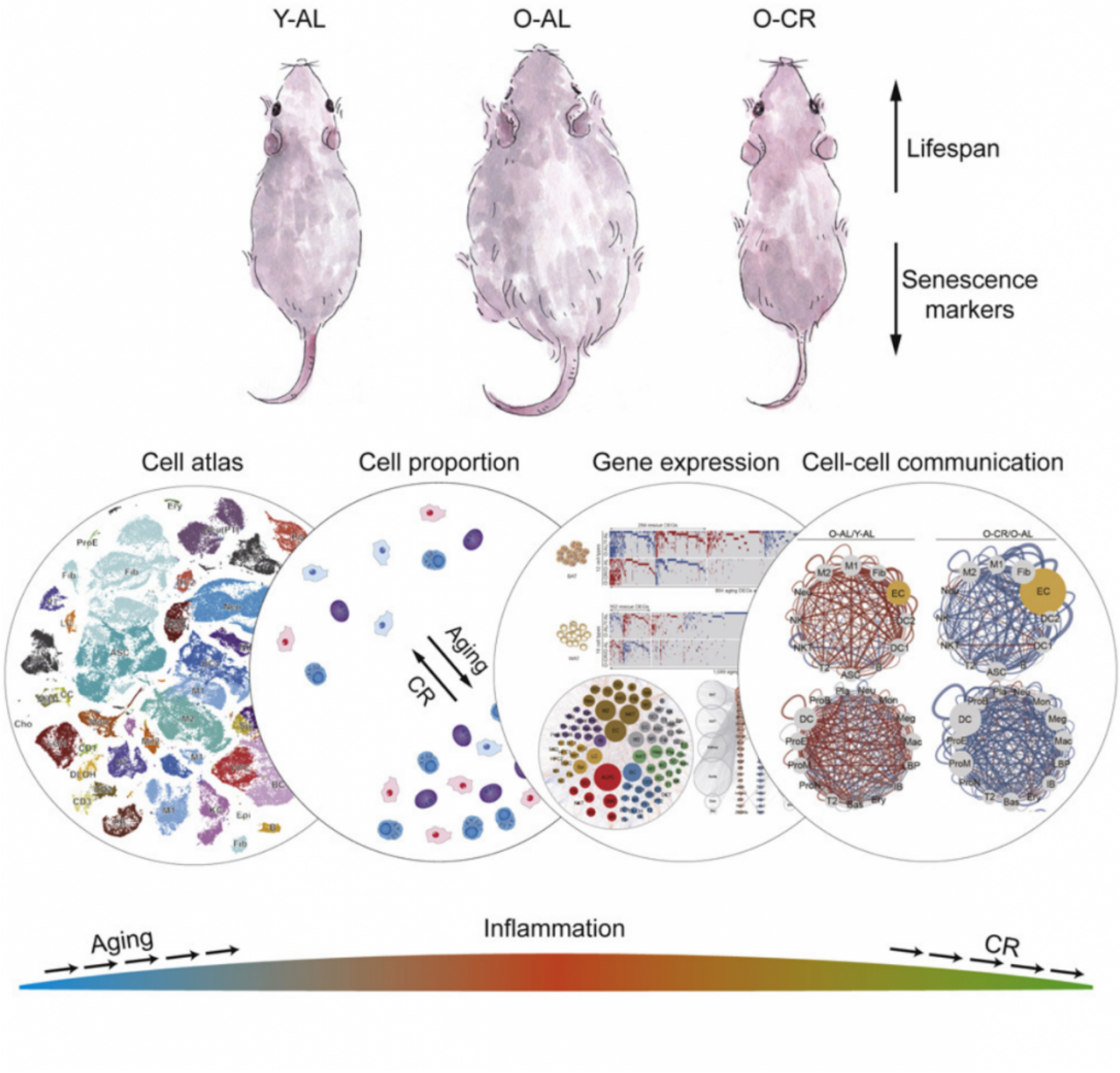
Restored concentrations of SCFA acetate by HAMSA diet is associated with reduced susceptibility to *C. rodentium* infection (colitis).



Increased regulatory intraepithelial lymphocytes (IELs) induced by HAMSA are associated with protection against *C. rodentium*.

Yap et al, ***Clin Transl Immunol****, 2021*

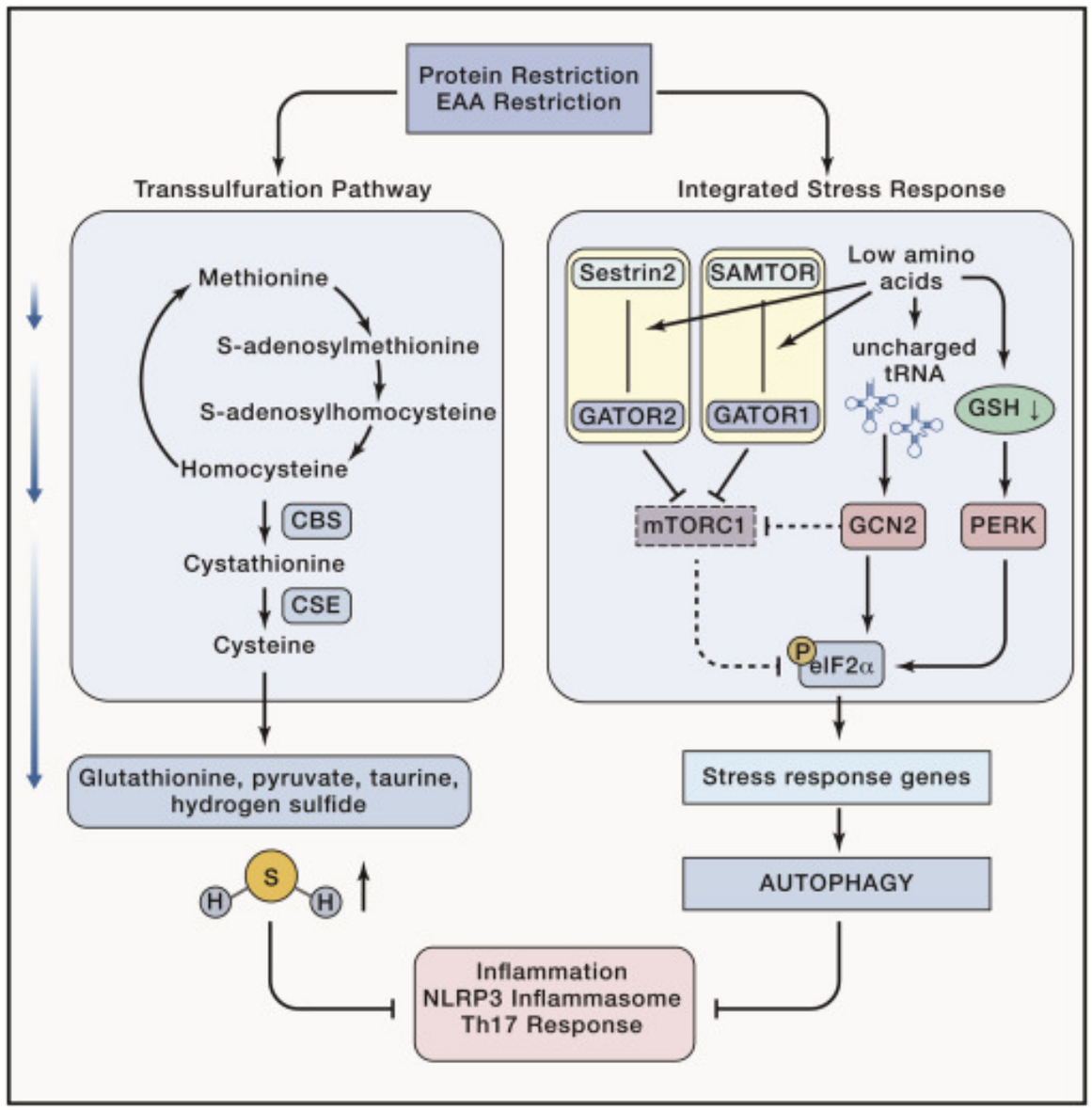
Calorie restriction is beneficial for health



Ma et al, ***Cell****, 2020*

Calorie restriction is beneficial for health

Although the mechanisms of CR are not completely understood, protein quality and amino acid composition of diet have been more strongly associated with metabolic and age-associated health.



One of the pathways that are induced with protein and amino acid restriction, is the transsulfuration pathway (TSP). The TSP involves the catabolism of methionine to generate intermediates such as the methyl donor S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), homocysteine, and cystathionine. The TSP also allows for the generation of cysteine through the action of cystathionine-γ lyase (CSE), which can further provide important metabolites and byproducts such as glutathione, pyruvate, and hydrogen sulfide (H2S).
Some TSP metabolites such as SAM and homocysteine are increased with obesity and aging and have been implicated with inflammation and disease risk.

Lee & Dixit, ***Immunity****, 2020*