Ruolo della dieta chetogenica nella gestione delle flogosi sistemiche: dalle malattie reumatiche alle complicanze della malattia da Covid19

OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria

Samir Giuseppe Sukkar
U.O.D. Dietetica e Nutrizione Clinica
IRCCS Ospedale Policlinico San Martino di Genova

Il sottoscritto …Sukkar Samir …….
ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

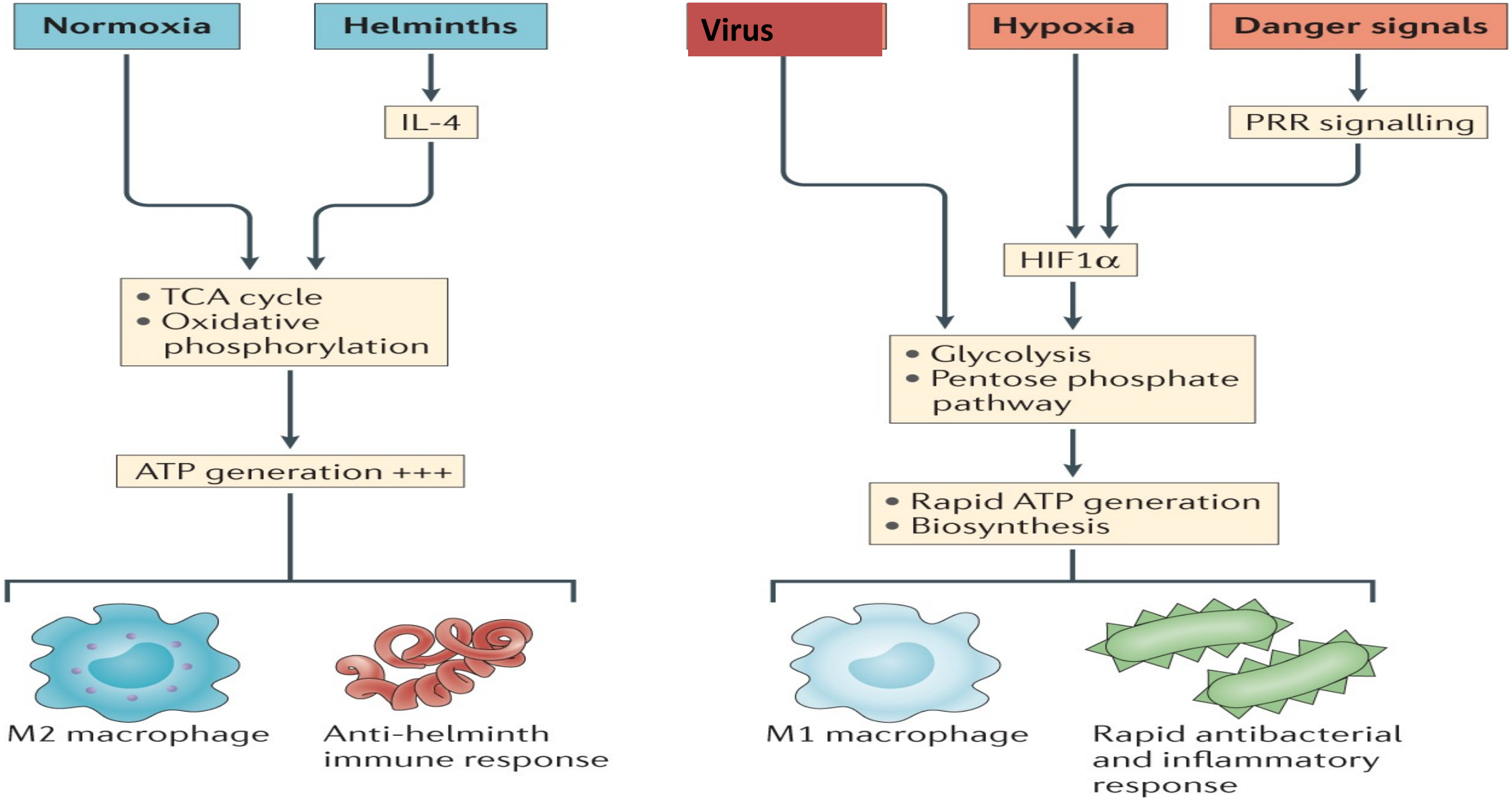
- ❑ *X che negli ultimi due anni NON ha avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario*

RIPROGRAMMAZIONE METABOLICA DEL SISTEMA IMMUNITARIO

- Negli ultimi anni si è avuto un sostanziale incremento delle conoscenze nell'area dell'immuno metabolismo ovvero nelle modifiche delle vie fisio patologiche metaboliche intra cellulari nelle cellule immunitarie correlate con la funzione.
- Quello che emerge è una complessa interconnessione tra riprogrammazione metabolica e immunità che unisce fortemente il ruolo della nutrizione, del metabolismo e dell'immunità nella corretta gestione delle malattie autoimmuni e delle malattie infettive

La riprogrammazione metabolica immunitaria

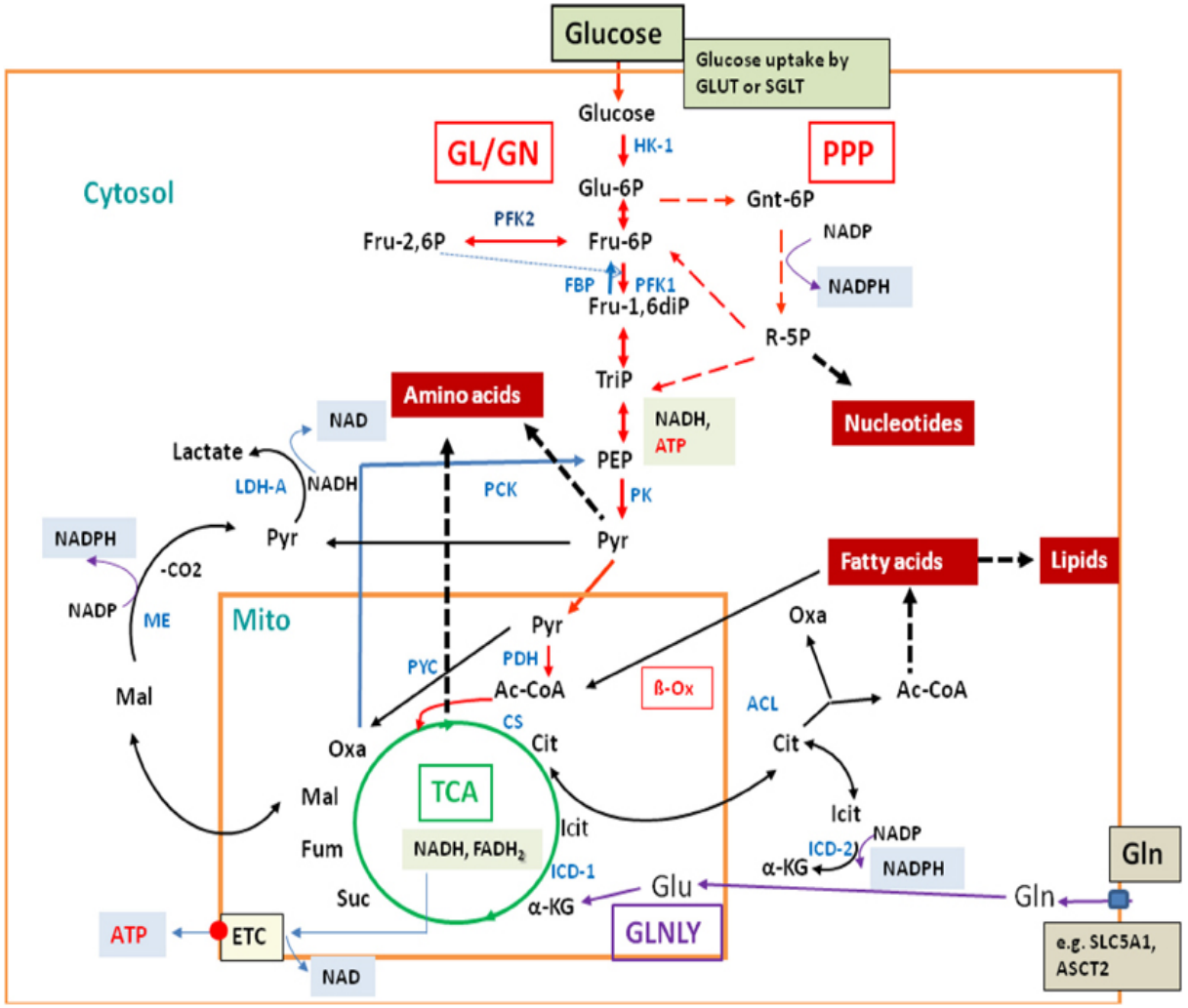
- Glicolisi
- Via del pentoso fosfato (PPP)
- Il ciclo di Krebs (TCA)
- Vie metaboliche degli acidi grassi
- Vie metaboliche degli AA



Lee, P., Chandel, N.S. & Simon, M.C*. Cellular adaptation to hypoxia through hypoxia inducible factors and beyond. Nat Rev Mol Cell Biol* ***21,*** *268–283 (2020). https://doi.org/10.1038/s41580-020-0227-y*

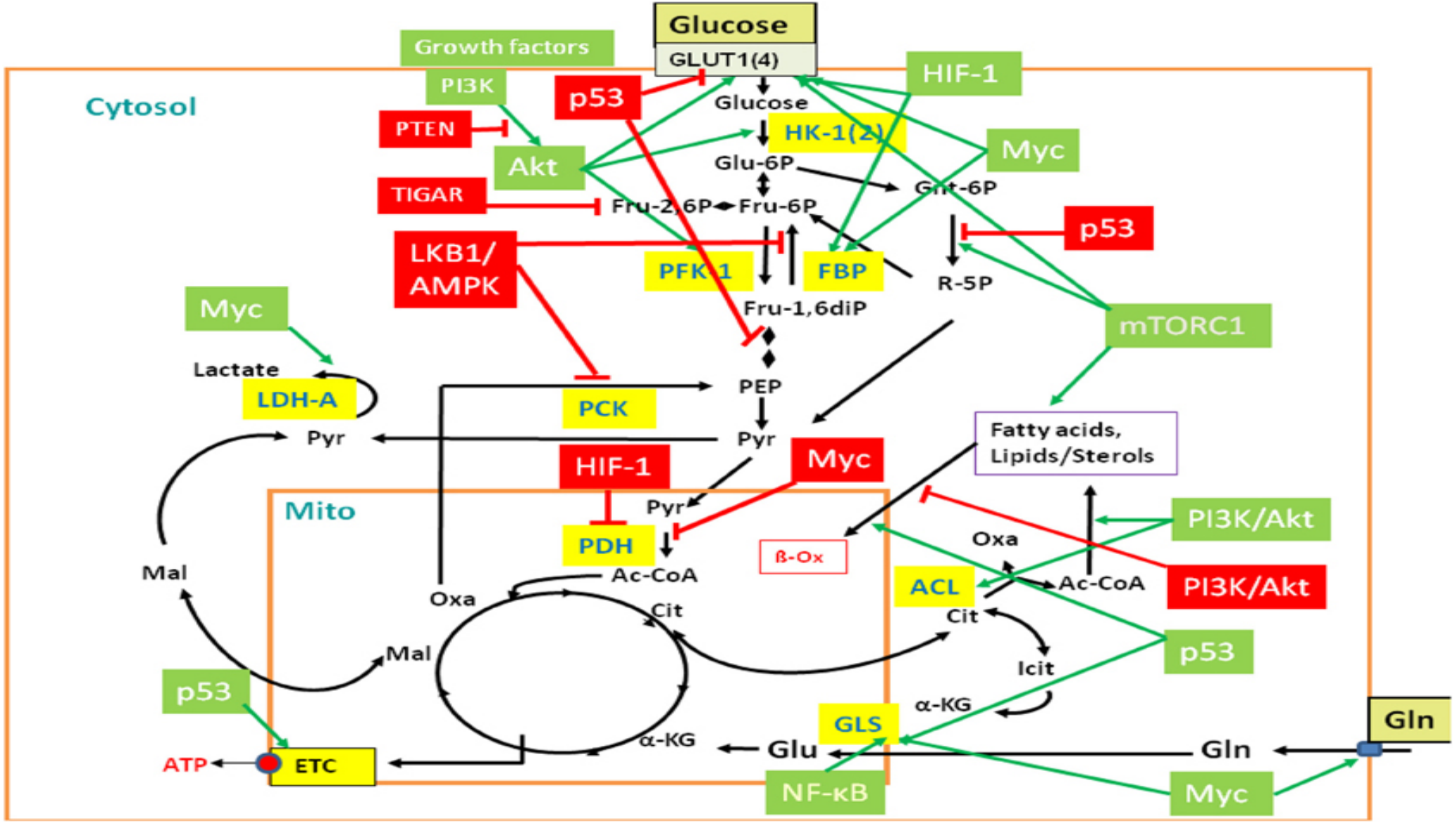
Principali vie cataboliche e anaboliche coinvolte nella riprogrammazione immunitaria

- I macrofagi e le cellule T hanno un'elevata voracità per il glucosio quindi la glicolisi è cruciale per la funzione immunitaria cellulare.
- Il problema è che l'incremento della fosforilazione ossidativa implica la biogenesi mitocondriale che è complesso e lento.
- La necessità di avere rapida produzione di ATP è correlata con la necessità di biosintesi di intermedi che supportino una rapida crescita cellulare , in particolare il ciclo di Krebs, intermedi della via del pentoso fosfato PPP.
- I fattori di crescita promuovono fortemente l'aumento dell'assorbimento di glucosio e la glicolisi, che fornisce ATP, supporta il ciclo TCA e dona intermedi per PPP, le reazioni di glicosilazione e la sintesi dei principali costituenti della biomassa, tra cui serina, glicina, alanina e acetil-Coa per la sintesi lipidica.



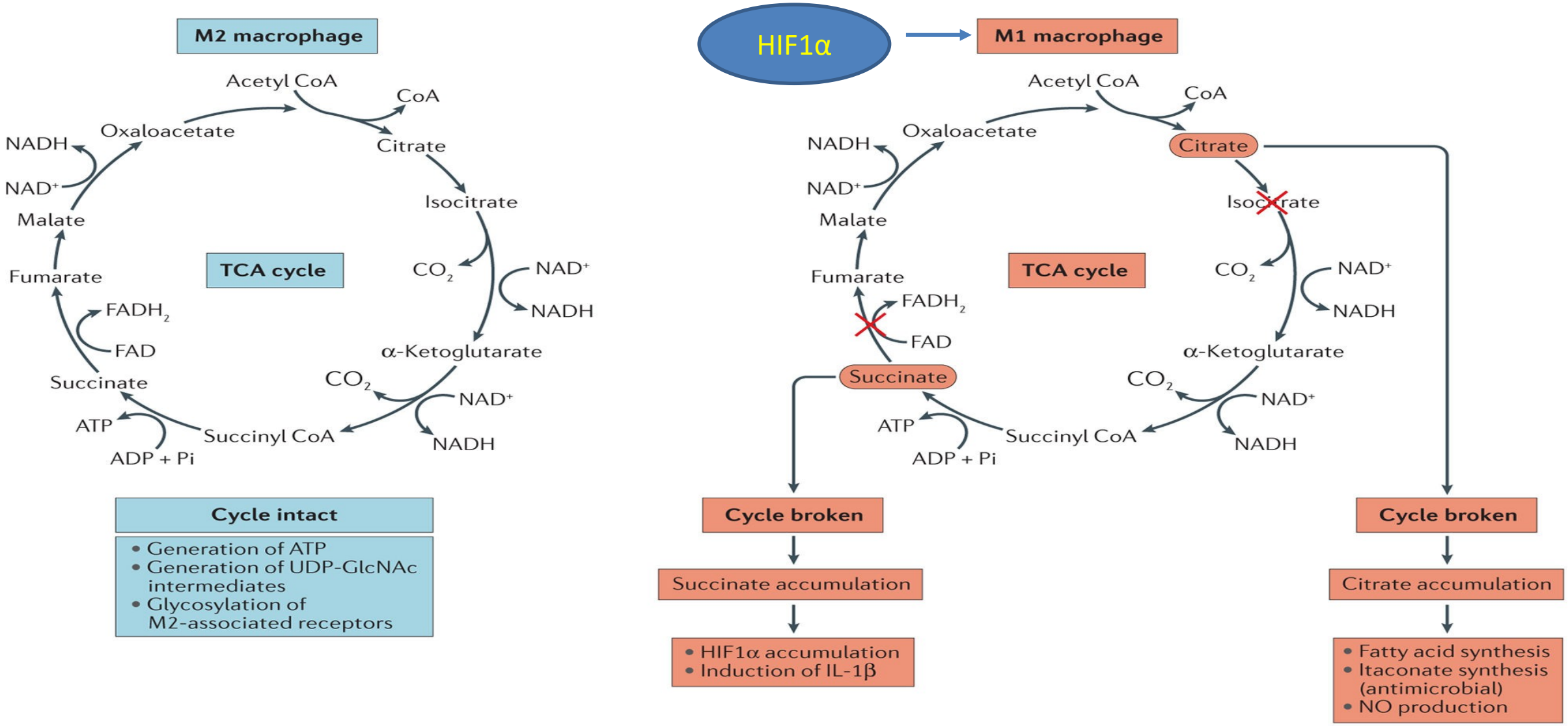
Eisenreich W et al Front. Cell. Infect. Microbiol., 09 July 2013

Regolazione delle vie cataboliche e anaboliche



Eisenreich W et al Front. Cell. Infect. Microbiol., 09 July 2013

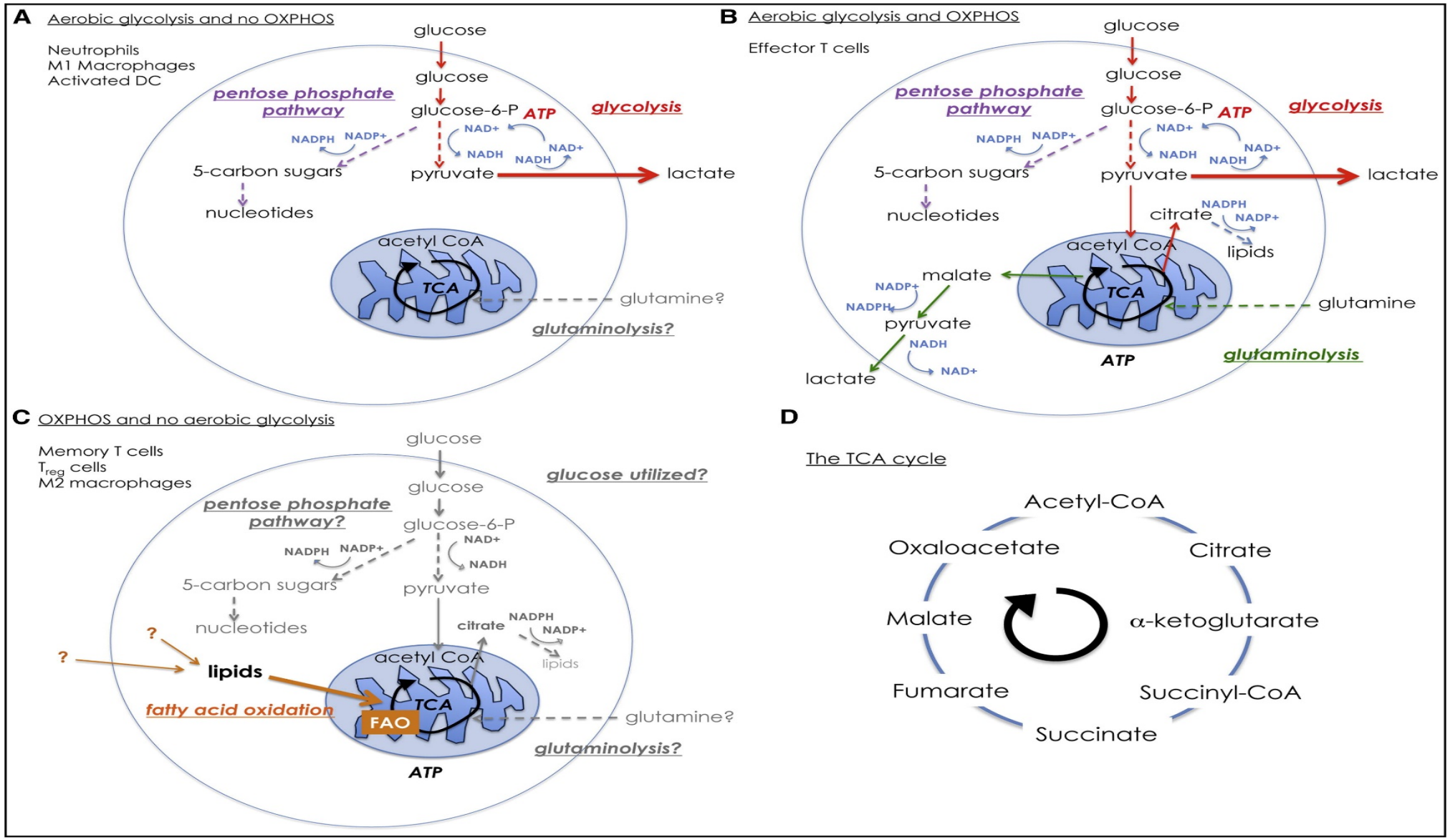
Il ciclo degli acidi tricarbossilici (TCA) nei macrofagi



Hif1α, fattore ipossia-inducibile 1α.

O'Neill, L., Kishton, R. & Rathmell, J. Nat Rev Immunol 16, 553–565 (2016).

Sintesi delle vie metaboliche nelle cellule immunitarie



E.L. Pearce & E.J. Pearce, Immunity,2013

Le cellule dentritiche shiftano dalla glicolisi alla OXPHOS nel momenti in cui assumono un fenotipo tollerante

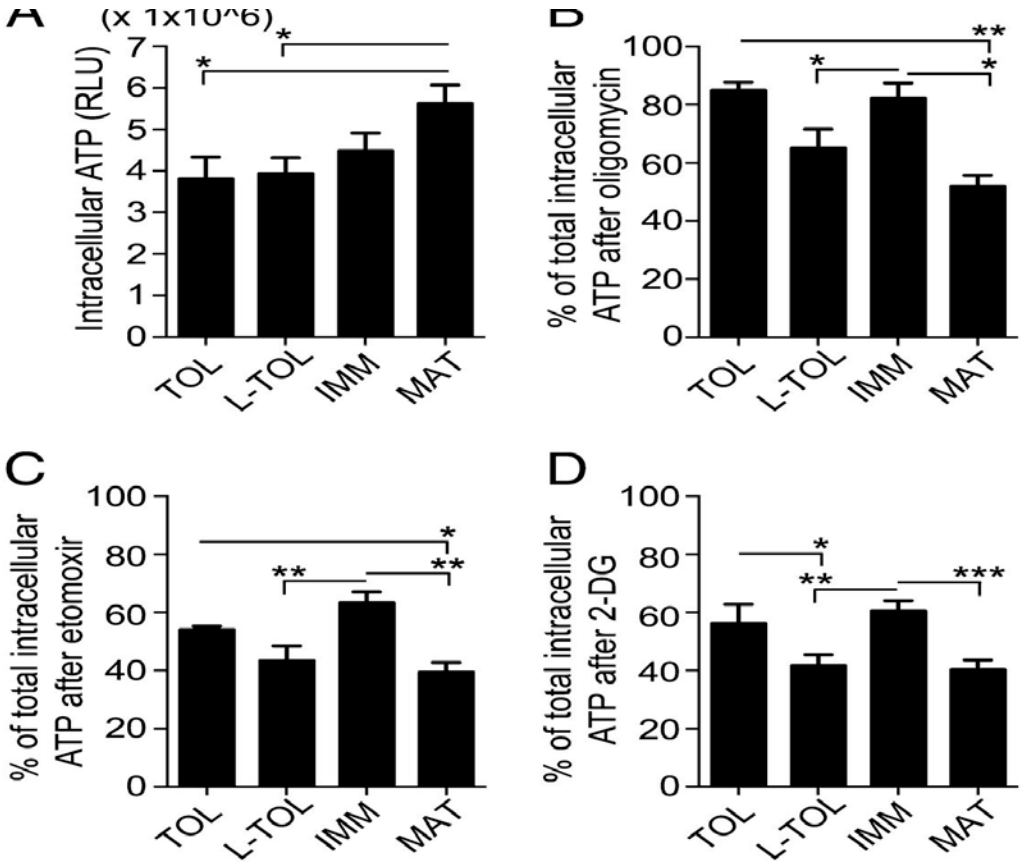
The Journal of Immunology

This information is current as of September 2, 2021.

High Mitochondrial Respiration and Glycolytic Capacity Represent a Metabolic Phenotype of Human Tolerogenic Dendritic Cells

Frano Malinarich, Kaibo Duan, Raudhah Abdull Hamid, Au Bijin, Wu Xue Lin, Michael Poidinger, Anna-Marie Fairhurst and John E. Connolly

J Immunol 2015; 194:5174-5186; Prepublished online 27 April 2015;
doi: 10.4049/jimmunol.1303316
http://www.jimmunol.org/content/194/11/5174



Bioenergetic adaptation of moDCs after inhibition of catabolic pathways. (**A**) Total intracellular ATP content in moDCs (IMM, immature; L-TOL, LPS-tolerogenic; MAT, mature; TOL, tolerogenic). ATP percentage of total after moDCs treatment with oligomycin (**B**), etomoxir (**C**), and 2-DG (**D**).. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

IN VIVO È ANCORA PIÙ COMPLESSO

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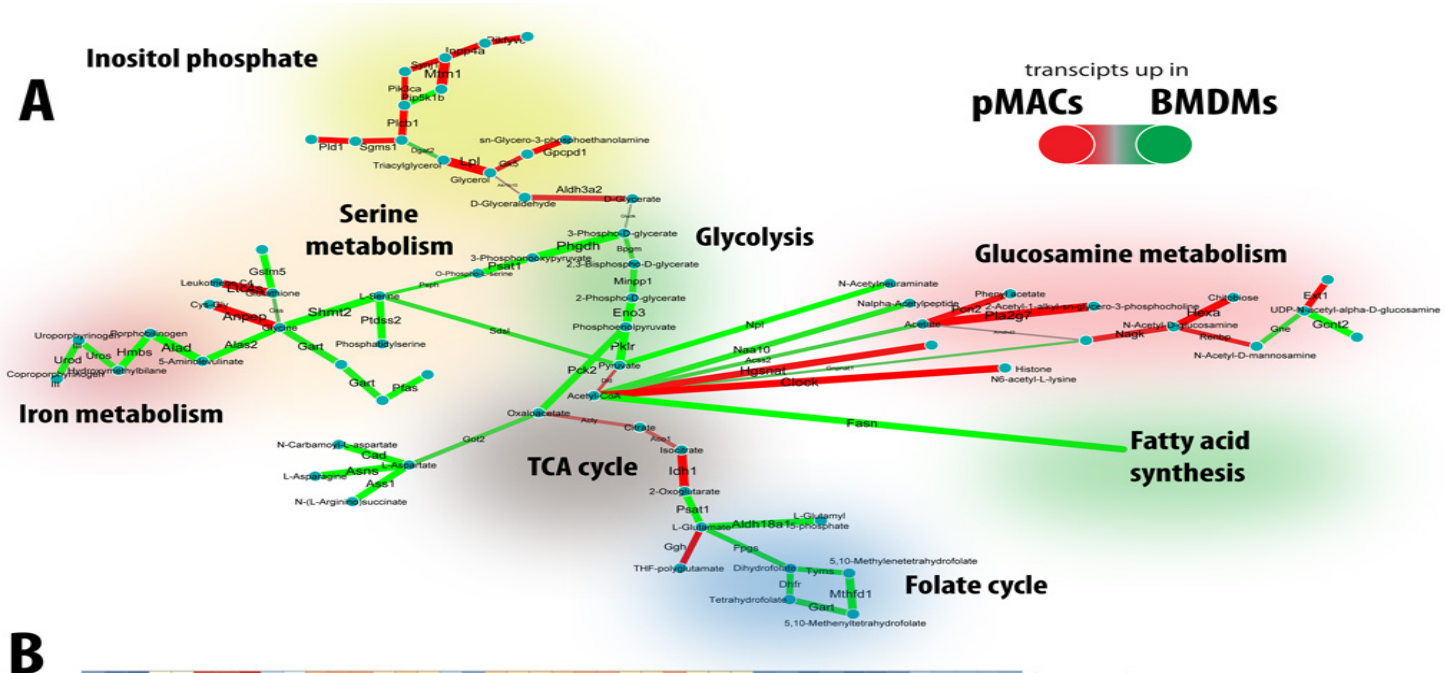
journal homepage: www.elsevier.com/locate/ysmim

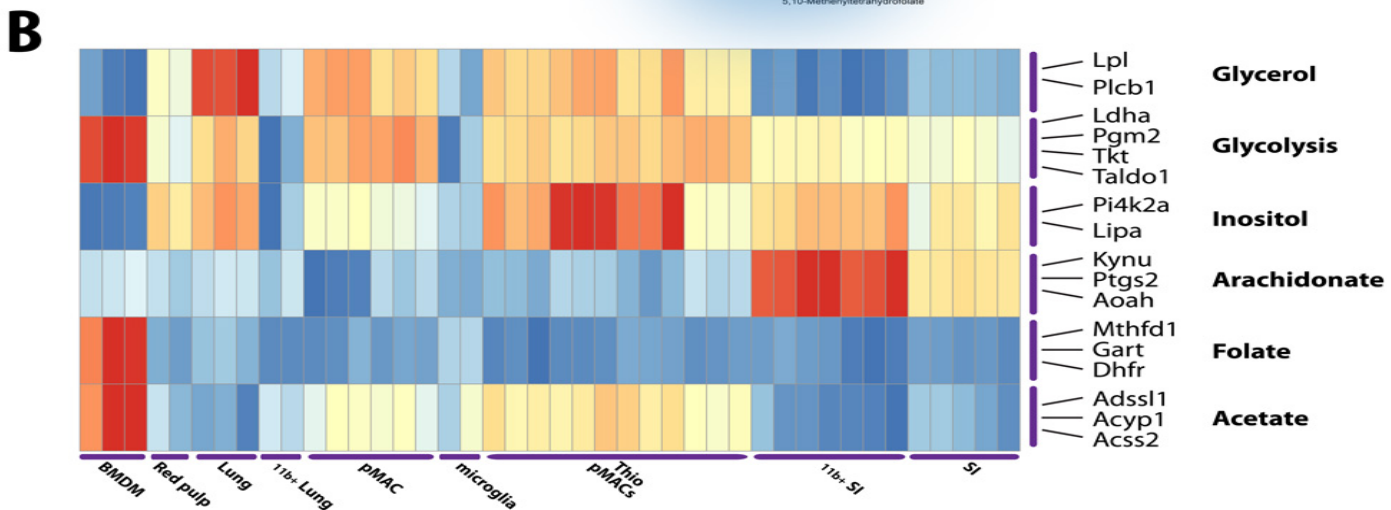
Review

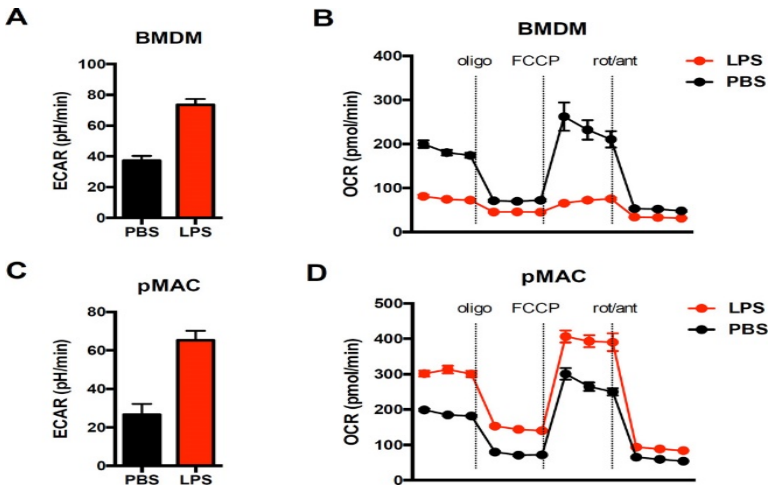
Integrating immunometabolism and macrophage diversity

Maxim N. Artyomov[a], Alexey Sergushichev[a,b], Joel D. Schilling (M.D., Ph.D.)[a,c,d,*]

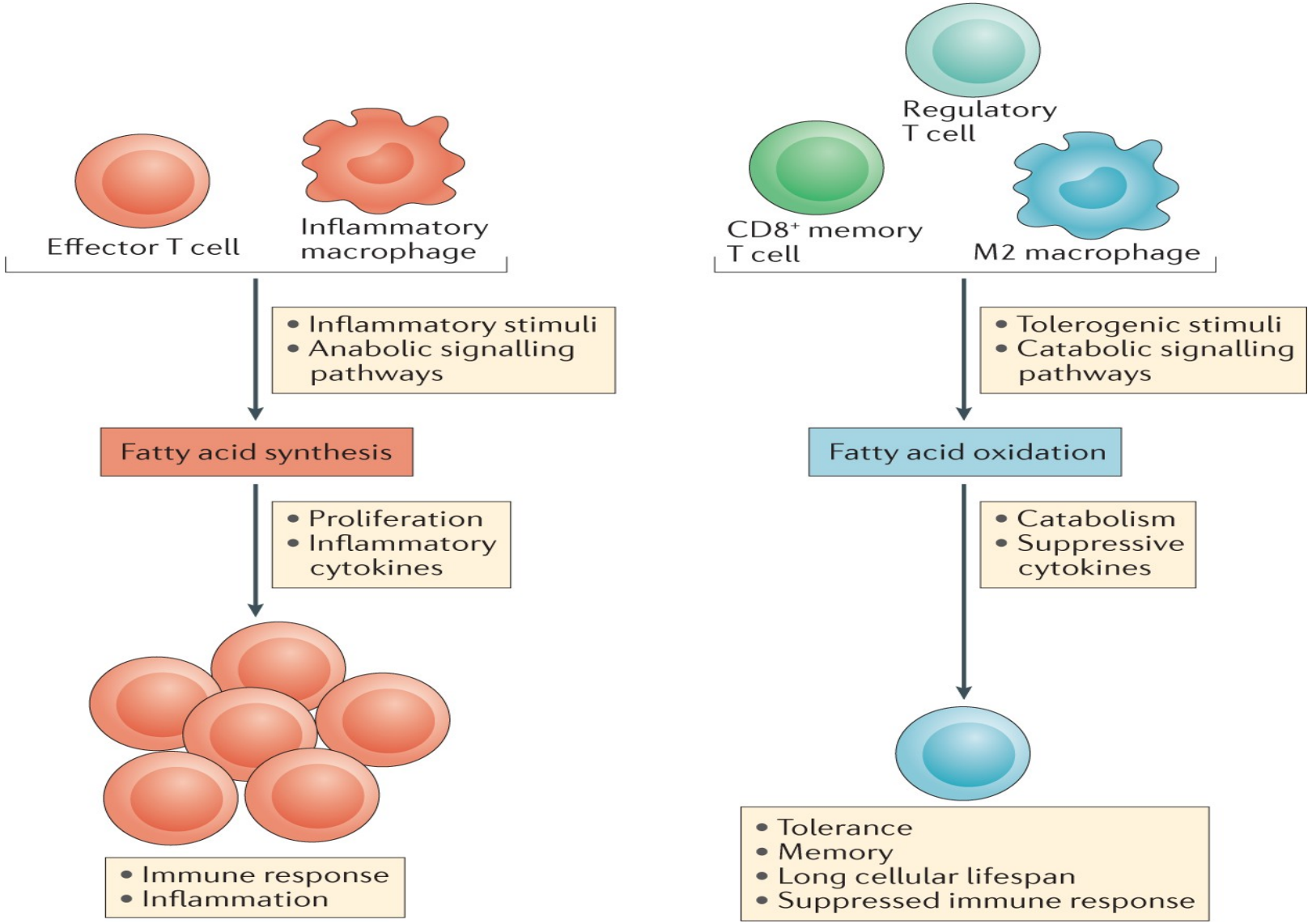
athology & Immunology, Washington University School of Medicine, St. Louis, MO 63110, USA
ologies Department, ITMO University, Saint Petersburg 197101, Russia
ascular Disease Center, Washington University School of Medicine, St. Louis, MO, USA
Medicine, Washington University School of Medicine, St. Louis, MO, USA





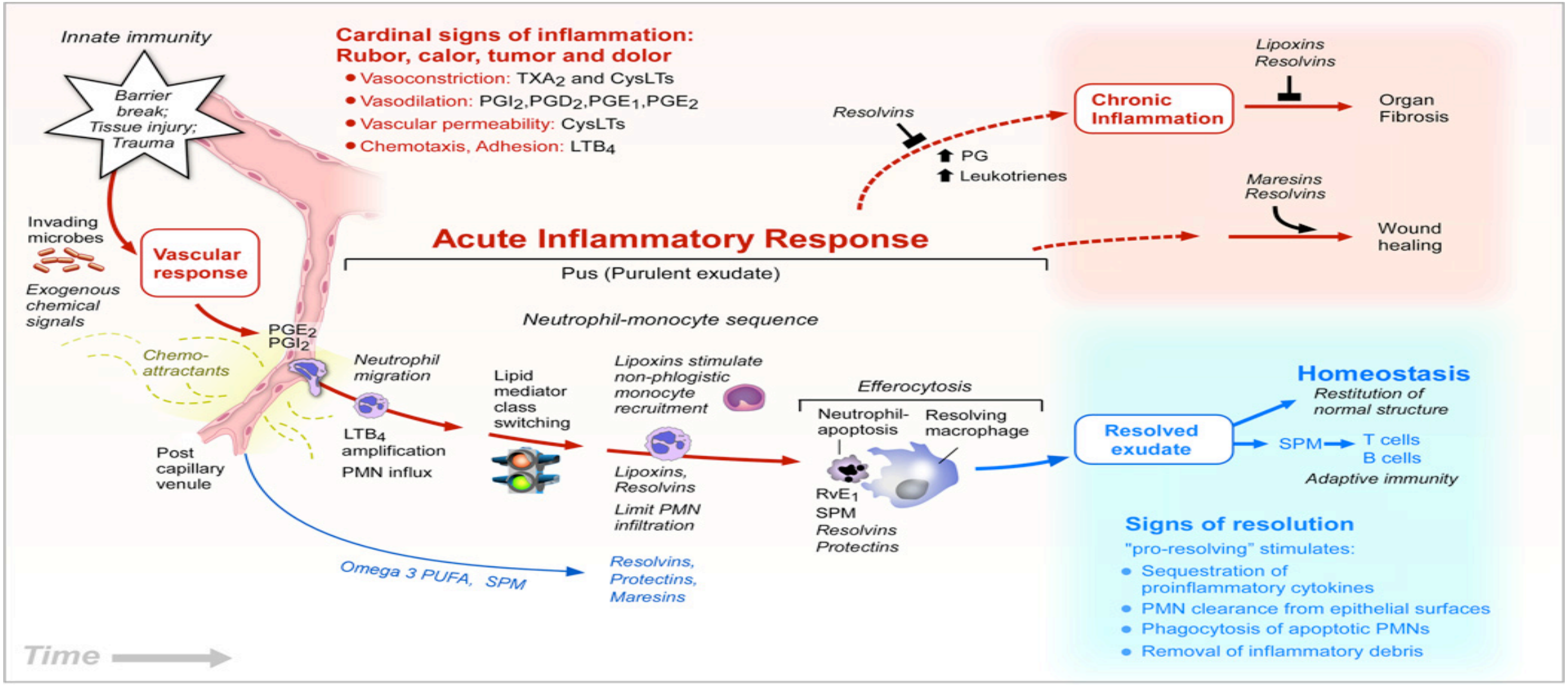


Sintesi degli acidi grassi e ossidazione nel l'immunità



O'Neill, L., Kishton, R. & Rathmell, J. Nat Rev Immunol 16, 553–565 (2016).

Lipid mediators in the acute inflammatory response, resolution and other outcomes



Serhans, Nature 2014

European Journal of Pharmacology ■ (■■■■) ■■■–■■■

Contents lists available at ScienceDirect

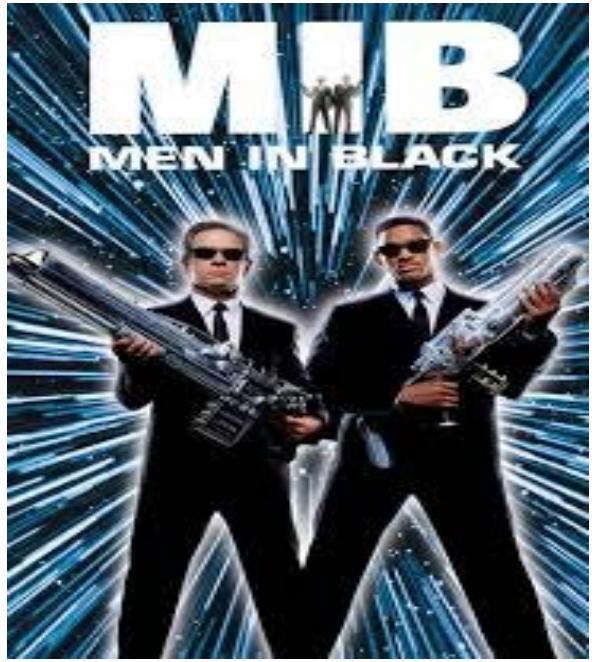
European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Full length article

- Docosapentaenoic acid derived metabolites and mediators – The new world of lipid mediator medicine in a nutshell

Karsten-H. Weylandt [a,b,*]

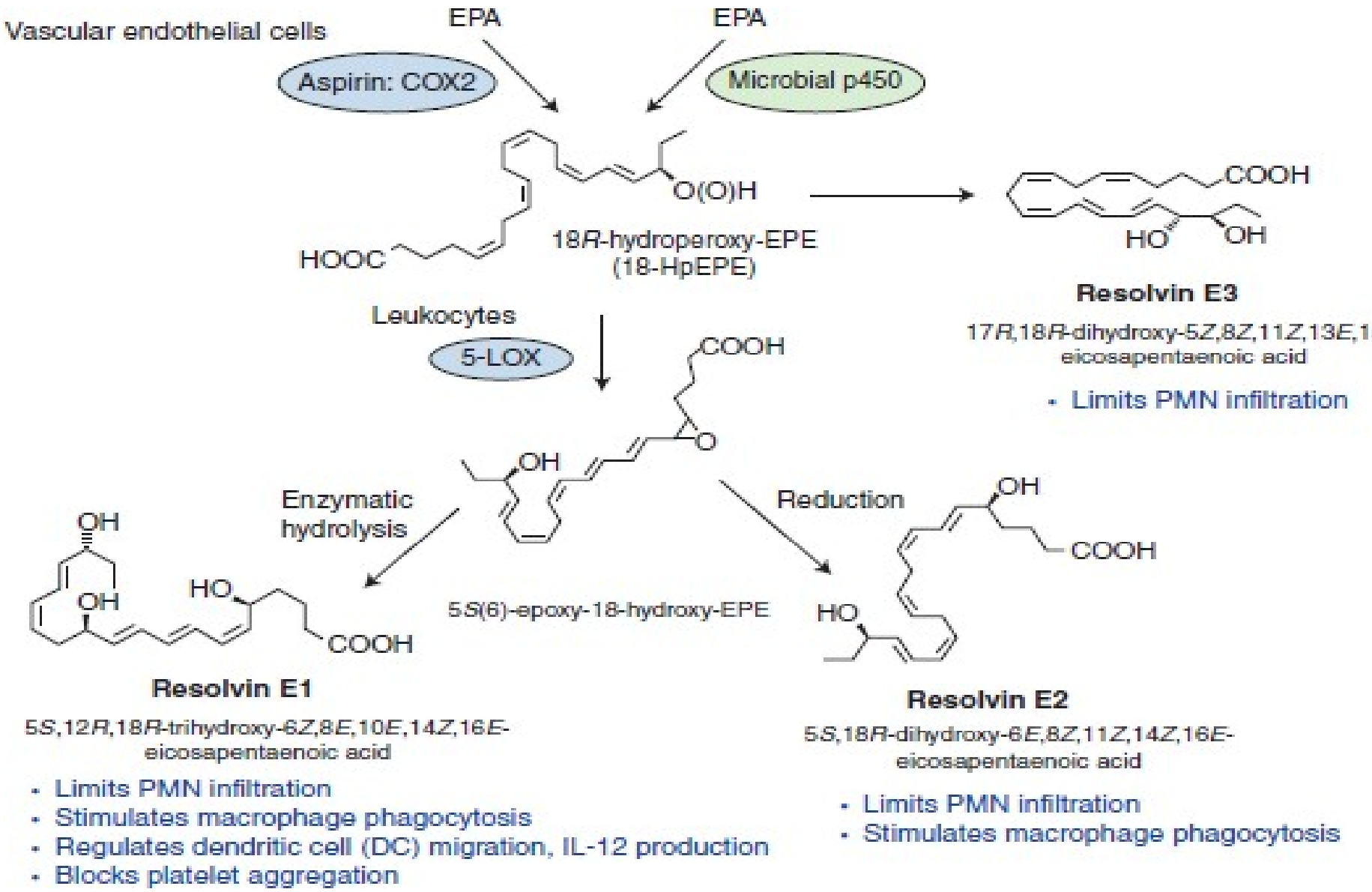


specialized pro-resolution mediators (SPMs)

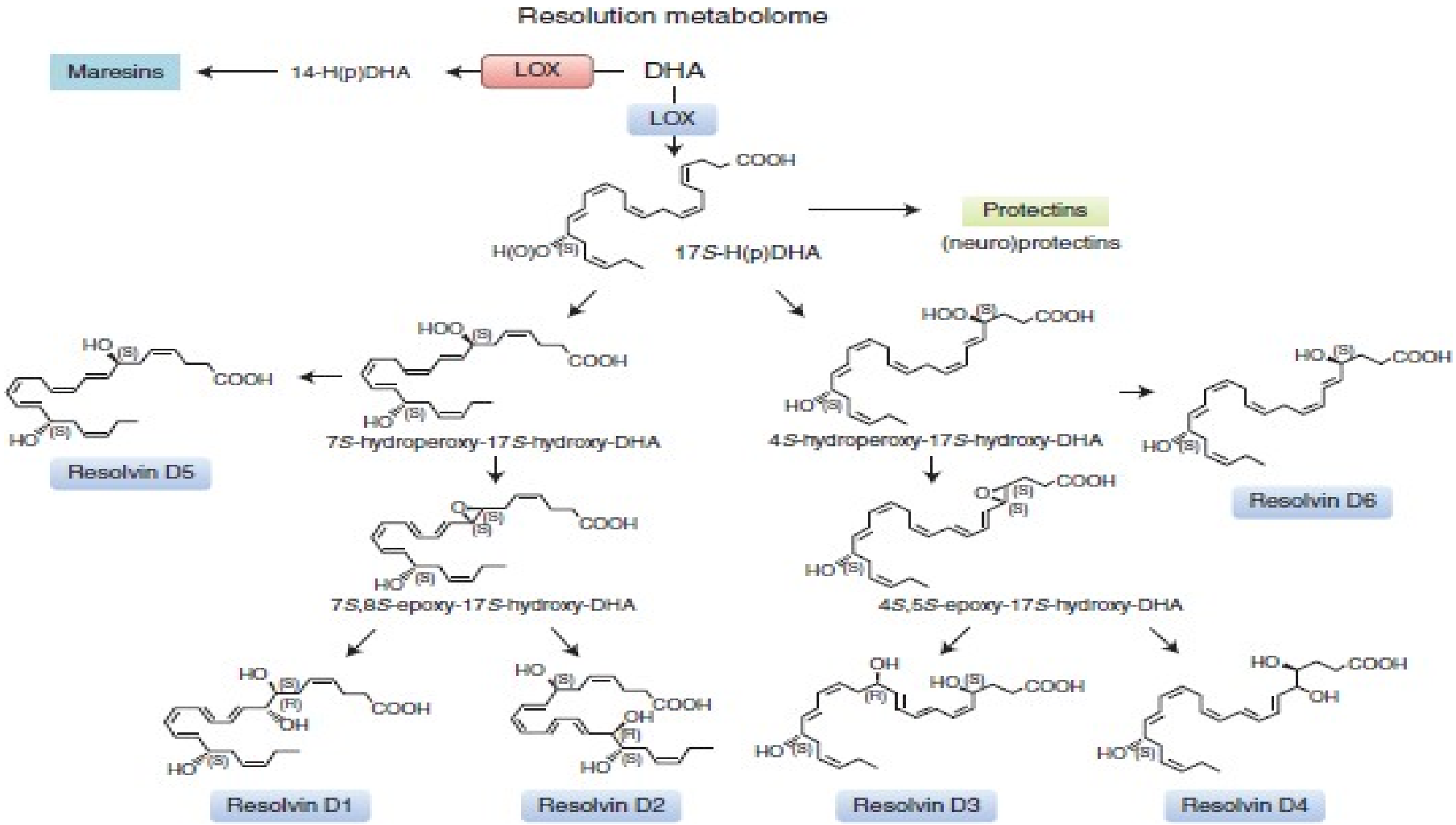
Lipid Mediators in the Resolution of Inflammation

SPM	Disease/tissues	Formation
Lipoxins and aspirin-triggered lipoxins (ATLs)	Asthma	Higher urinary ATL levels in aspirin-tolerant asthma than in aspirin-intolerant asthma (Sanak et al. 2000; Levy et al. 2005; Yamaguchi et al. 2011) and regulate natural killer (NK) cell and innate lymphoid cell activation (Barnig et al. 2013; Peebles 2013)
	Alzheimer's disease (AD)	LXA_4 levels are reduced in AD brain and CSF (Wang et al. 2014)
	Colitis	Elevated mucosal LXA_4 promotes remission in individuals with ulcerative colitis (Vong et al. 2012)
	Type 2 diabetes	Increased plasma ATL with intake of pioglitazone (Gutierrez et al. 2012)
	Rheumatoid arthritis	LXA_4 in synovial fluid from rheumatoid arthritis patients (Giera et al. 2012)
	Localized aggressive periodontitis (LAP)	Less LXA_4 in LAP whole blood compared with healthy individuals (Fredman et al. 2011)
	Peripheral artery disease	Plasma levels of ATL are lower in patients with symptomatic peripheral artery disease (Ho et al. 2010)
	Adipose tissues	LXA_4 identified in human adipocytes from obese patients (Clària et al. 2012)
	Milk	Lipoxins and resolvins at very high levels in the first month of lactation (Weiss et al. 2013)
Resolvins	Synovial fluid	RvD5 present in synovial fluid from rheumatoid arthritis patients (Giera et al. 2012)
	Blood (healthy volunteers)	Plasma RvD1 and RvD2 identified with oral omega-3 supplementation (Mas et al. 2012; Colas et al. 2014)
	Adipose tissues	RvD1 and RvD2 identified in human adipocytes from obese patients (Clària et al. 2012)
	Human plasma and milk	RvE1 identified in human plasma (Psychogios et al. 2011) and milk (Weiss et al. 2013)
	Multiple sclerosis	RvD1 was detected and up-regulated in serum and cerebrospinal fluid in the highly active group (Pruss et al. 2013)
	Human IgA nephropathy	RvE1 identified in patients supplemented with fish oil n-3 (Zivkovic et al. 2012)
Protectin	Asthma	PD1 in exhaled breath condensates in asthma exacerbation (Levy et al. 2007); decreased PD1 in eosinophils from patients with severe asthma compared with healthy individuals (Miyata et al. 2013)
	Embryonic stem cells	PD1 produced in embryonic stem cells (Yanes et al. 2010)
	Multiple sclerosis	NPD1 was detected in serum and cerebrospinal fluid in the highly active group (Pruss et al. 2013)
Maresins	Synovial fluid	MaR1 identified in synovial fluid from arthritis patients (Giera et al. 2012)

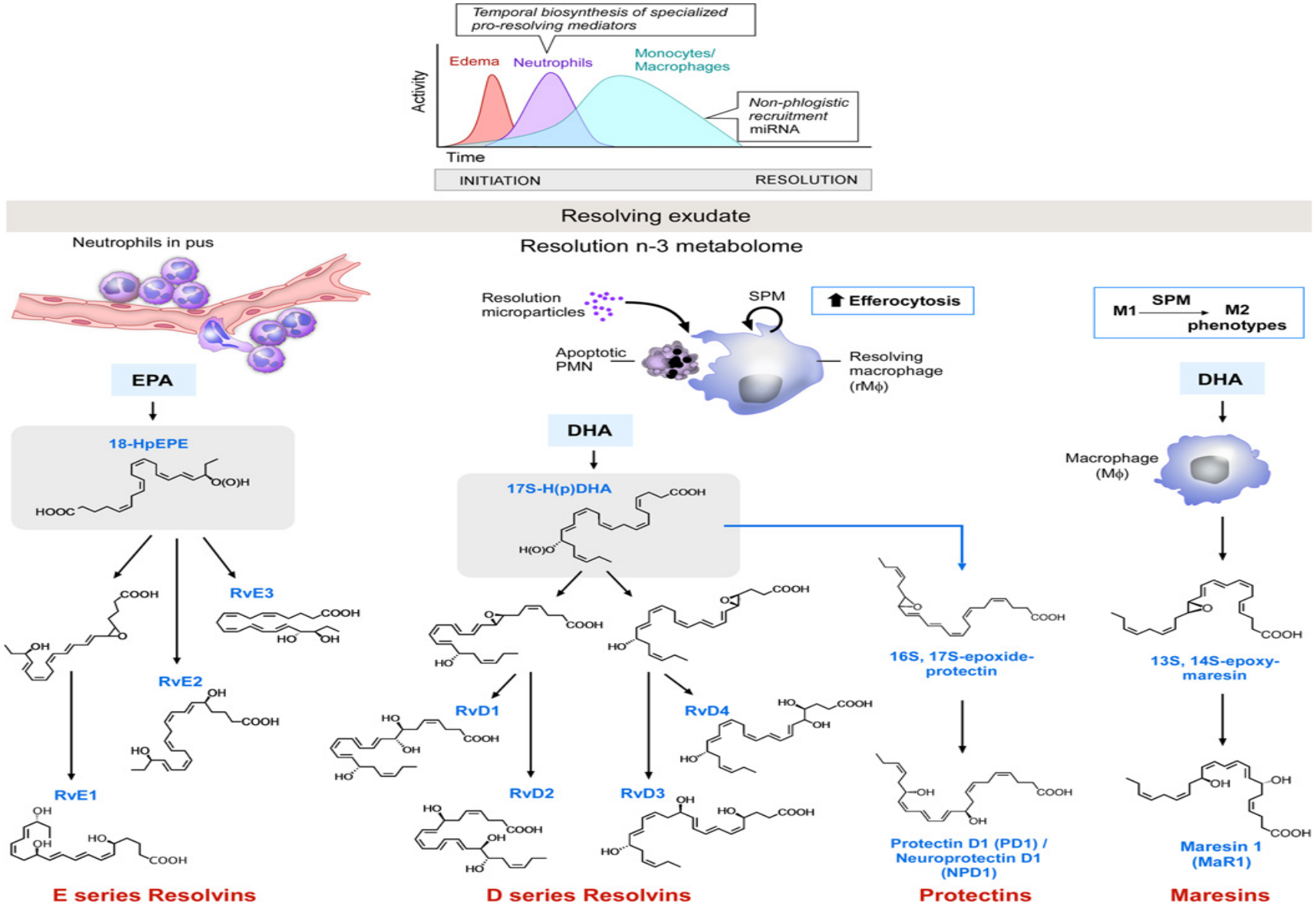
E-series (EPA) resolvin biosynthesis and major function



D-series (DHA) resolvin biosynthesis

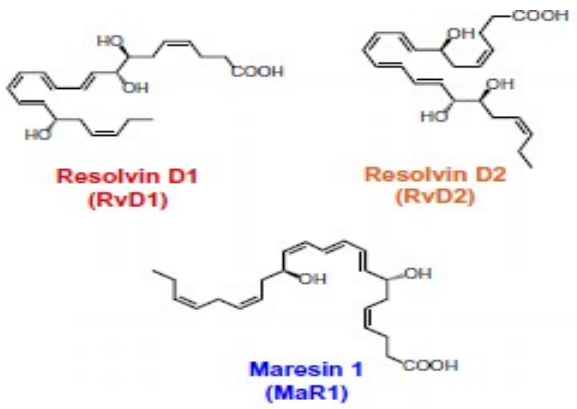


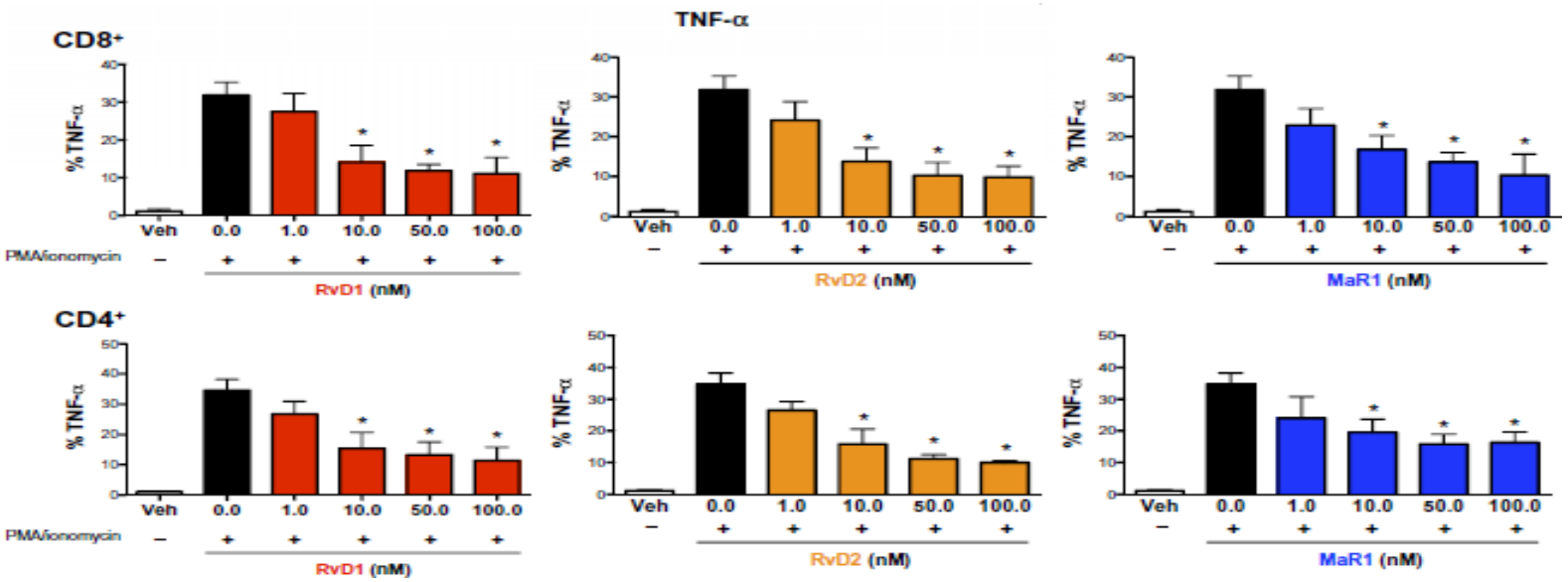
THE ORCHESTRA AND PLAYERS OF THE RESOLUTION PHASE



Serhans et al 2015

Resolvins inhibit immune responses

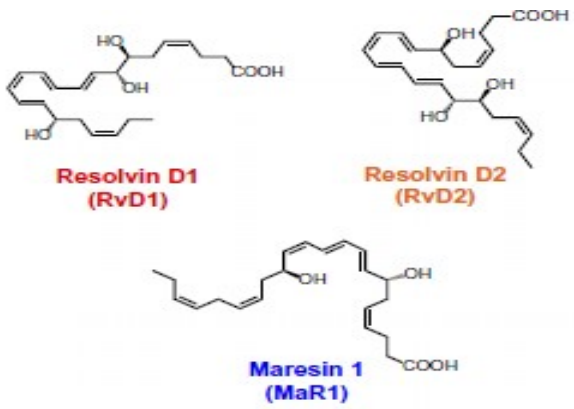


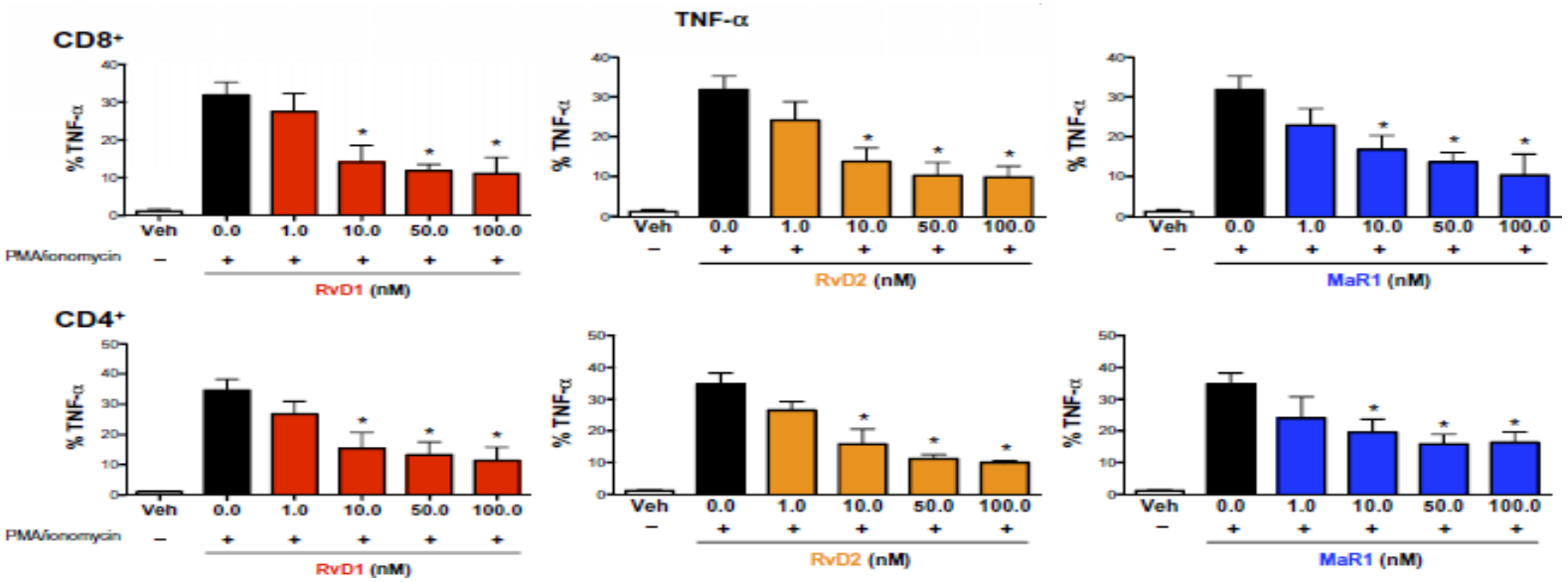


Chiurchiù V, et al. Sci Transl Med. 2016;

Resolvins inhibit immune responses

by inhibiting proinflammatory cytokine production

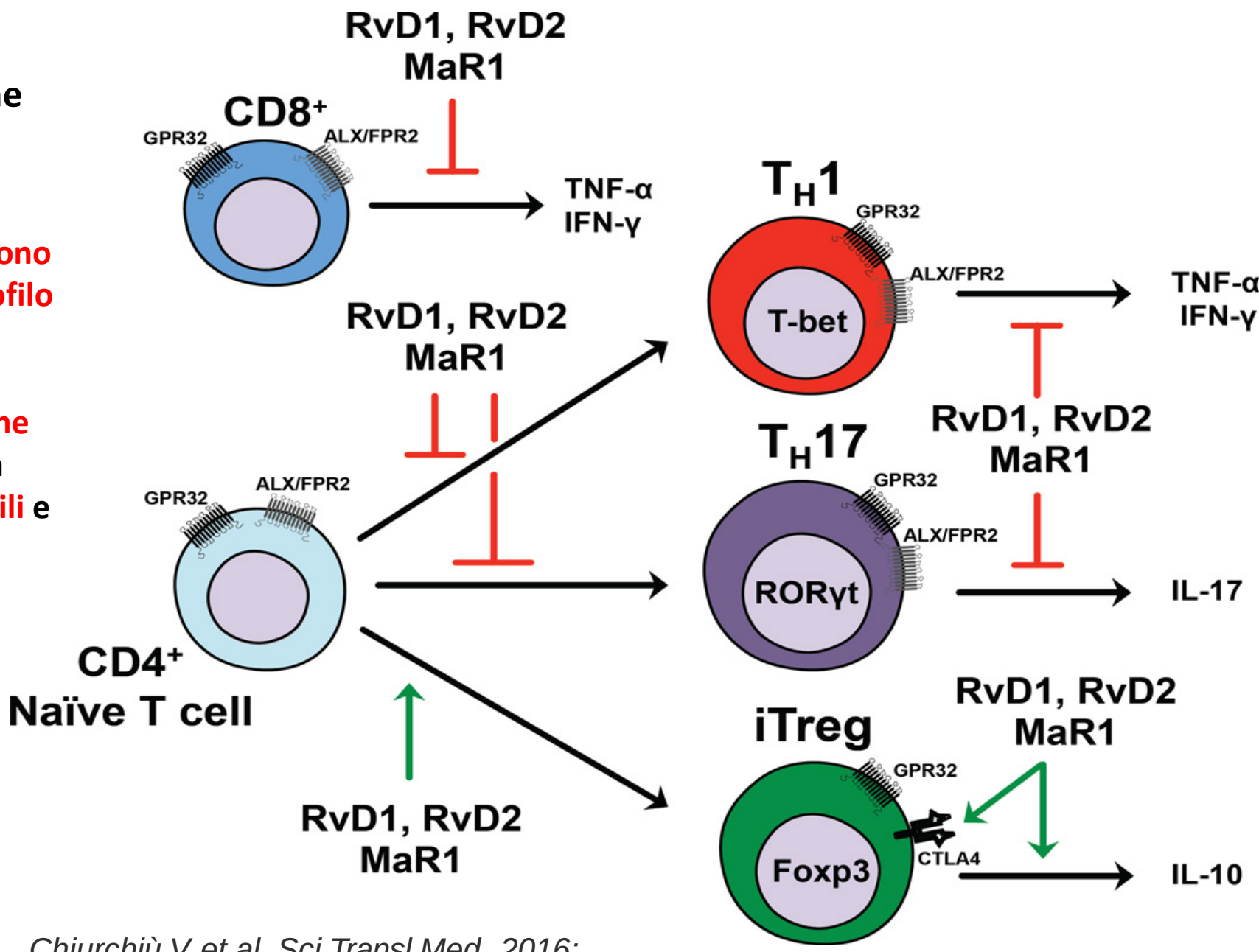




Chiurchiù V, et al. Sci Transl Med. 2016;

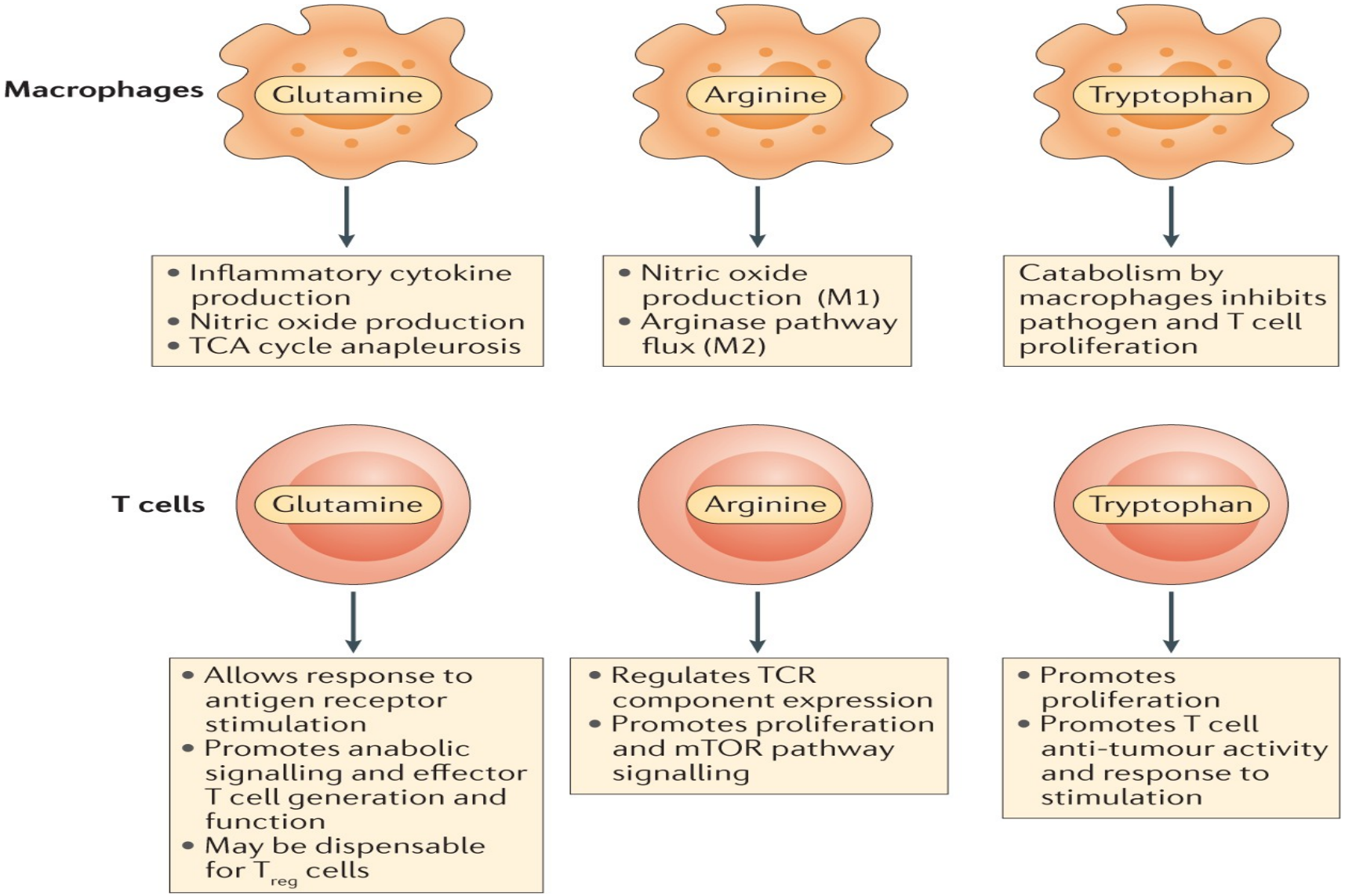
fase avanzate dell'infiammazione acuta,i

neutrofili e i macrofagi risolutori subiscono una riconfigurazione molecolare del profilo dei loro mediatori lipidici e iniziano a produrre SPM (compresi resolvine e maresine) che promuovono la risoluzione dell'infiammazione, che è caratterizzata dall'induzione dell'apoptosi nei neutrofili e dalla rimozione dei detriti cellulari.



Chiurchiù V, et al. Sci Transl Med. 2016;

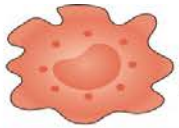
Metabolismo degli aminoacidi nell'immunità



O'Neill, L., Kishton, R. & Rathmell, J. Nat Rev Immunol 16, 553–565 (2016).

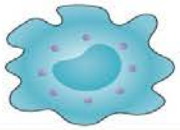
IN SINTESI

Metabolismo dei sottotipi delle cellule immunitarie



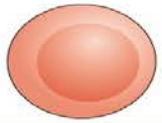
Inflammatory M1 macrophage

Pathways used:	
Glycolysis	Supports phagocytosis and inflammatory cytokine production
TCA cycle	Redirected to produce citrate to promote fatty acid synthesis
Pentose phosphate pathway	Supports nucleotide and ROS production
Fatty acid synthesis	Supports proliferation and inflammatory cytokine production
Amino acid metabolism	Supports proliferation and nitric oxide production



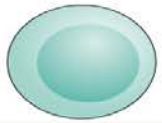
M2 macrophage

Pathways used:	
TCA cycle	Supports oxidative phosphorylation
Fatty acid oxidation	Promotes M2 phenotype by inhibiting inflammatory signals
Amino acid metabolism	Supports arginase pathway activity



Effector T cell

Pathways used:	
Glycolysis	Supports proliferation and inflammatory cytokine production
Fatty acid synthesis	Promotes proliferation and regulates cytokine production
Amino acid metabolism	Promotes proliferation and effector cell differentiation



Regulatory T cell

Pathways used:	
TCA cycle	Associated with suppressive function
Fatty acid oxidation	Promotes generation of T_{reg} cells and linked to tolerogenic stimuli

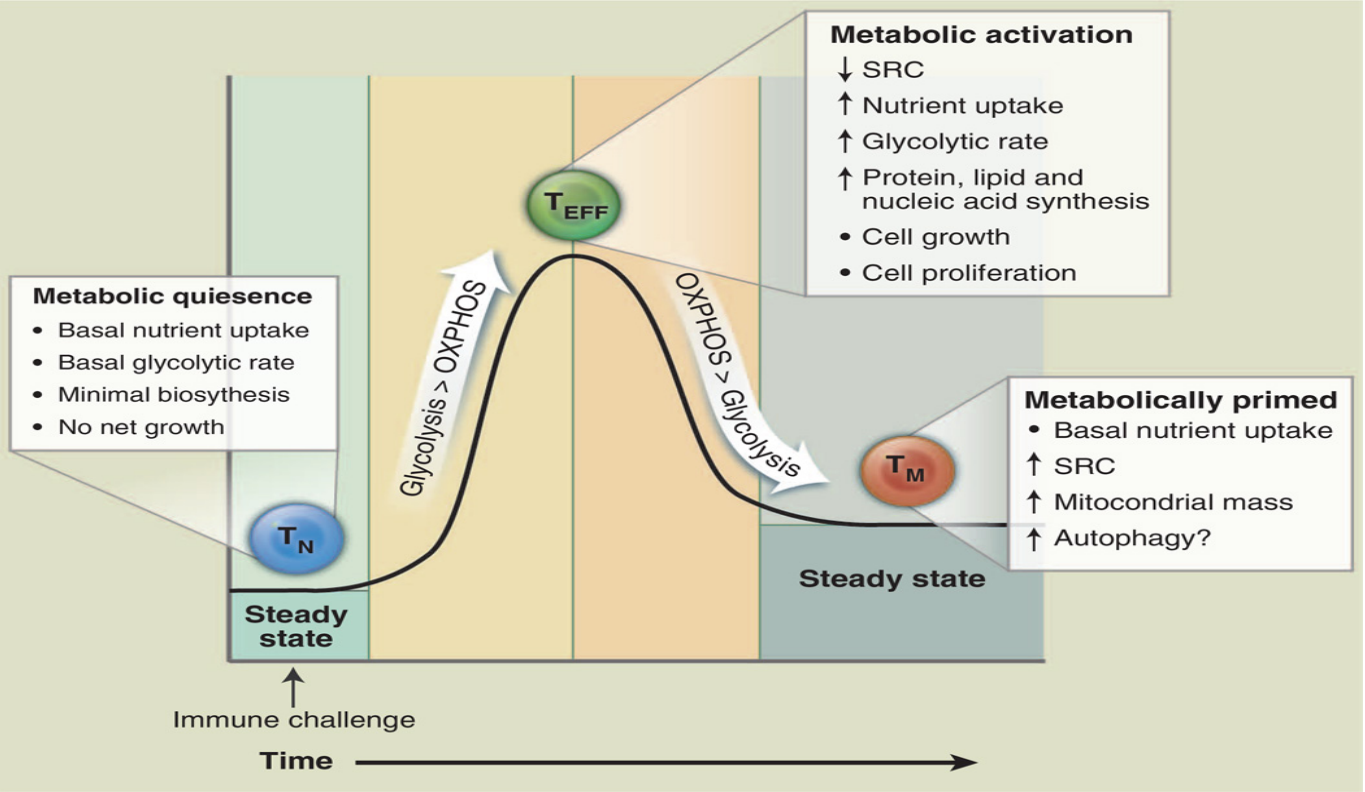
Memory $CD8^+$ T cell

Pathways used:	
TCA cycle	Associated with memory cell phenotype
Fatty acid oxidation	Promotes memory cell generation and survival

O'Neill, L., Kishton, R. & Rathmell, J. Nat Rev Immunol 16, 553–565 (2016).

KD MALATTIE AUTOIMMUNI E INFETTIVE

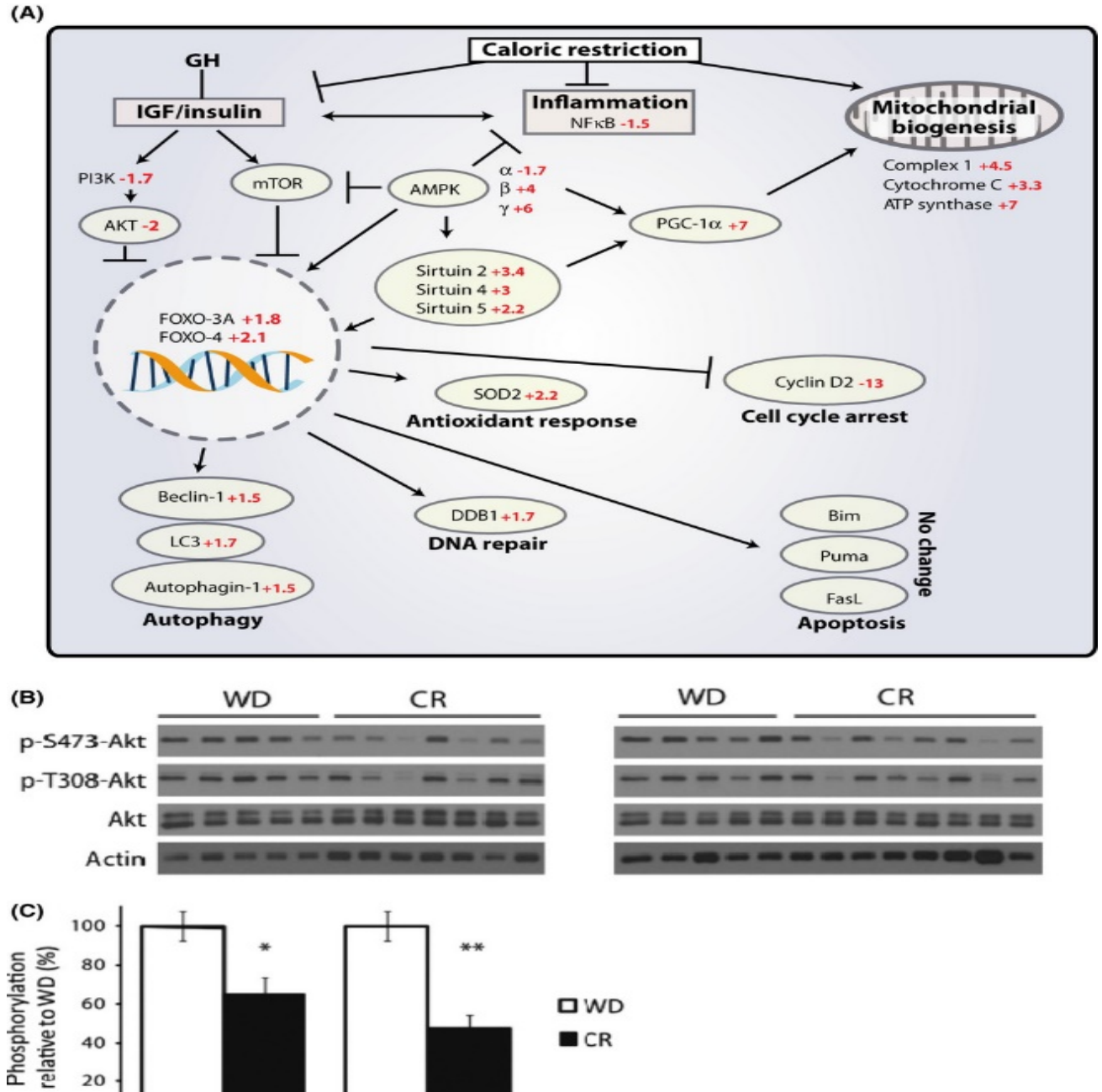
THE IMMUNOLOGIC WARBURG EFFECT REPRESENTS A POTENTIAL TARGET FOR TREATING AUTOIMMUNE DISEASES AND INFECTIOUS DISEASES THROUGH BOTH PHARMACOLOGIC AND DIETARY STRATEGIES.



- promuovere una restrizione dei carboidrati a favore dei grassi per migliorare
l’infiammazione di basso grado (Paoli et al, 2015; Bosco et al,2018)

Very-low-carbohydrate diet enhances human
T-cell immunity through immunometabolic
Reprogramming 10.15252/emmm.202114323
Simon Hirschberger[1,2,]

Calorie restriction in humans inhibits the PI3K/AKT pathway

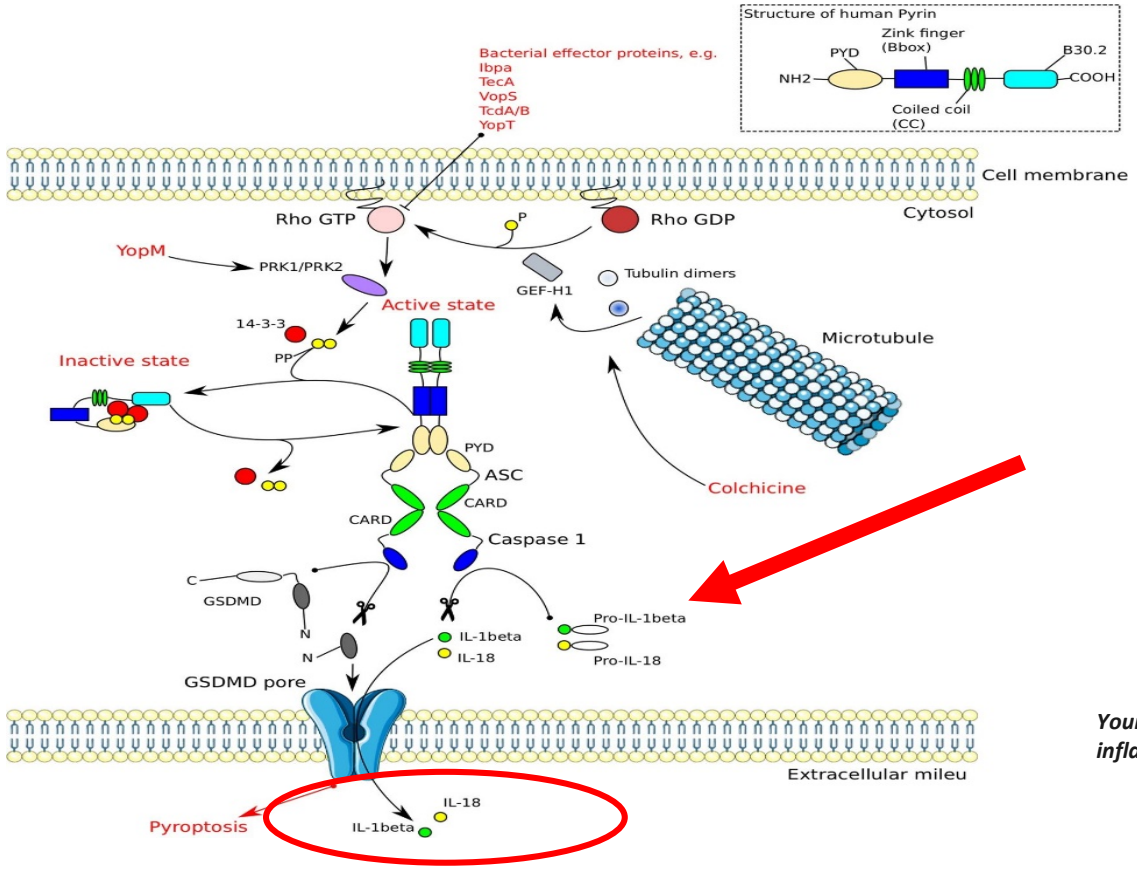


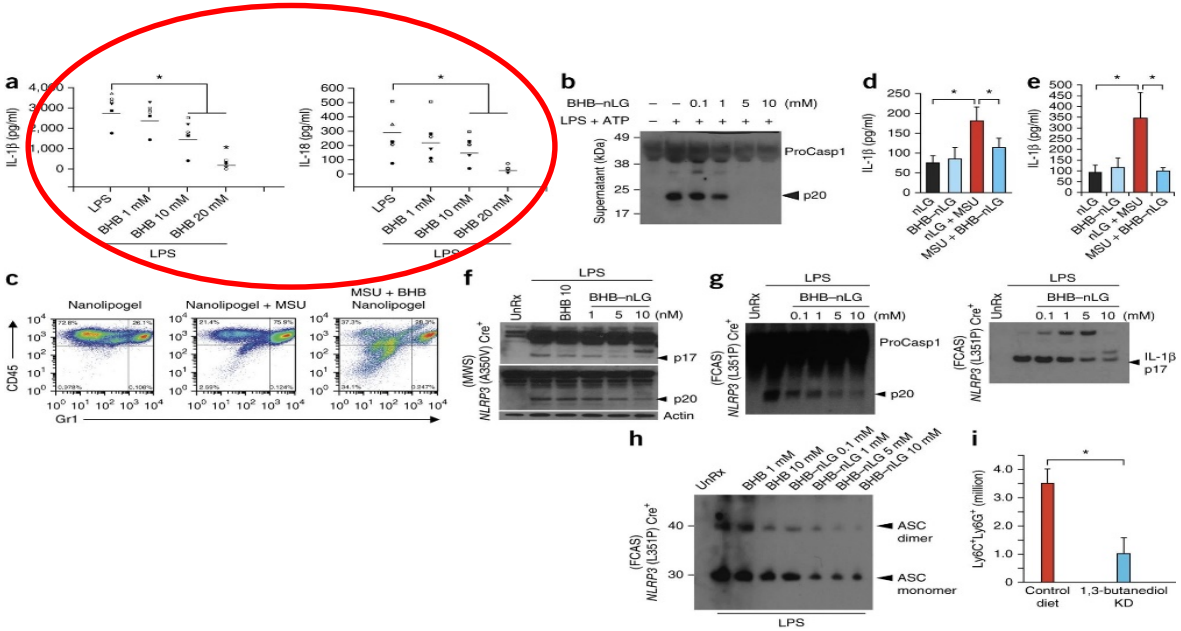
Aging Cell, Volume: 12, Issue: 4, Pages: 645-651, F
irst published: 20 April 2013, DOI: (10.1111/acel.12088)

- Nel modello animale il BHB ha un effetto inibitorio sulla risposta immune inappropriata mediante la soppressione del NLRP3 infiammasoma, migliorando la infiammazione a basso grado (Youm et al, 2015; Johnson 2007).

EFFETTI DELLA KD E DEL B-OH BUTIRRATO SULL’IMMUNITÀ E INFIAMMAZIONE

Beta –OH butrirrato :Effetti su inflammasoma





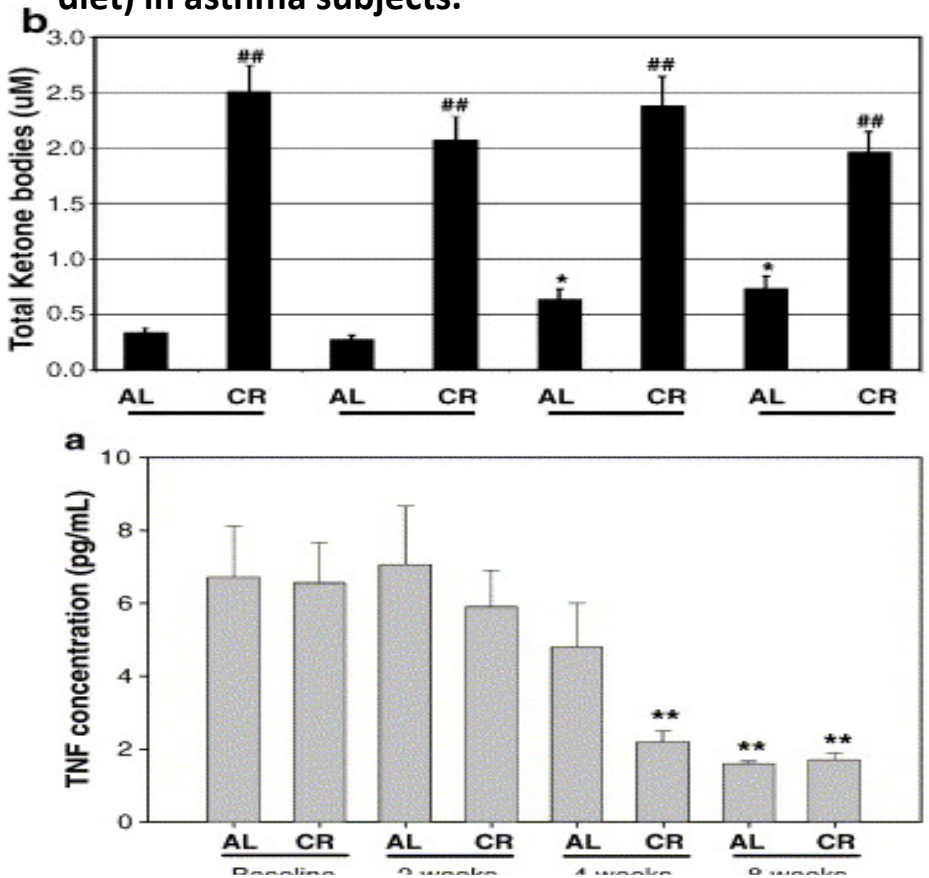
Youm, YH., Nguyen, K., Grant, R. et al. The ketone metabolite β-hydroxybutyrate blocks NLRP3 inflammasome–mediated inflammatory disease. Nat Med 21, 263–269 (2015). https://doi.org/10.1038/nm.3804

Effetto della restrizione calorica alternante e del B-OH butirrato sul'infiammazione

Markers of inflammation are reduced in asthma subjects in response to the Alternate day calorie restriction (ADCR diet) in asthma subjects.

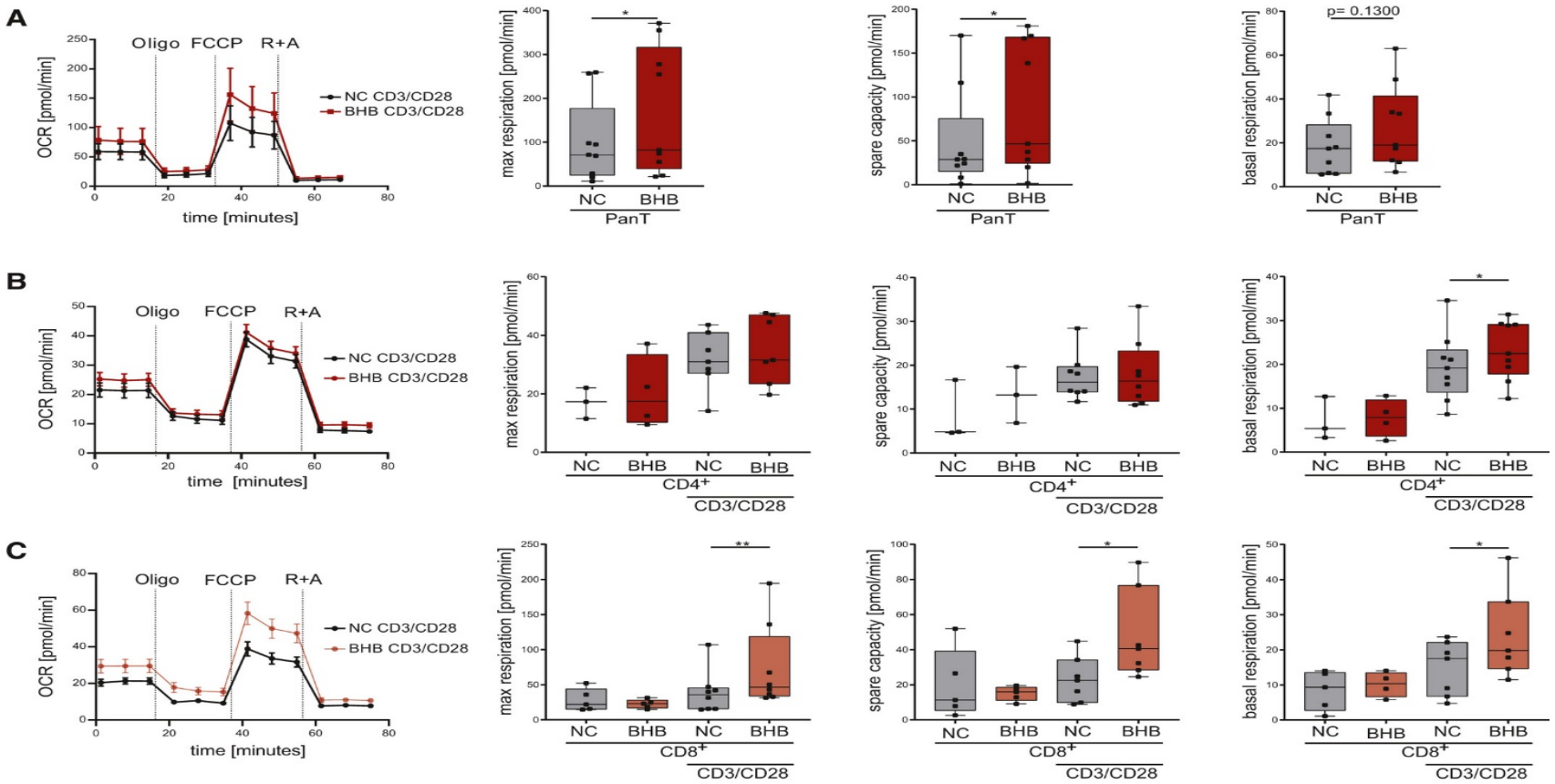
Levels 3-hydroxybutyrate (b) were measured in serum samples from asthma subjects on successive ad libitum (AL) and CR days at baseline and at 2, 4, and 8 weeks of ADCR. $^{\#\#}P < 0.01$ compared the corresponding CR value.

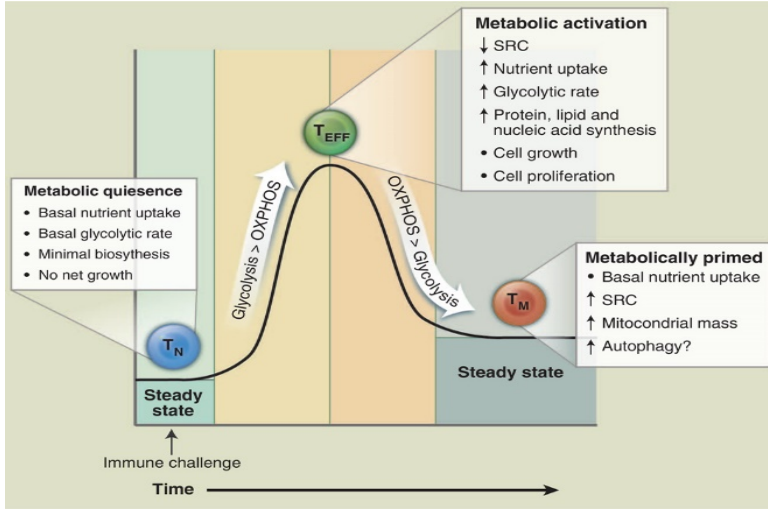
Markers of inflammation are reduced in asthma subjects in response to the ADCR diet**. Levels of TNF-α** (awere measured in serum samples from asthma subjects on successive ad libitum (AL) and CR days at baseline and at 2, 4, and 8 weeks of ADCR. $^{**}P < 0.01$, compared to the baseline value.



Johnson J et al
Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma,
Free Radical Biology and Medicine, Volume 42, Issue 5, 2007, 665-674,

Ketone bodies shift T-cell metabolism to oxidative phosphorylation

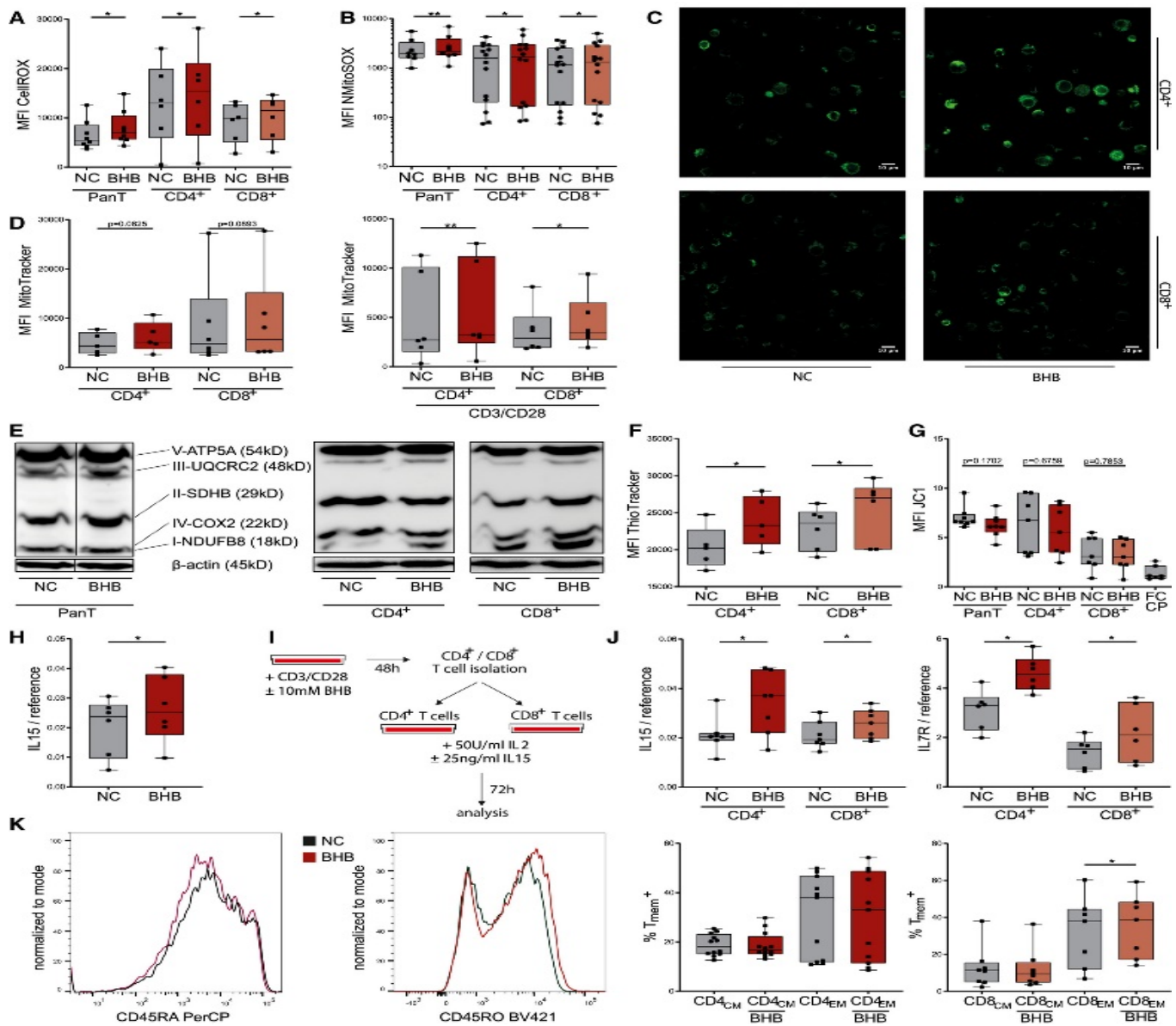




EMBO Mol Med, Volume: 13, Issue: 8, First published: 21 June 2021, DOI: (10.15252/emmm.202114323)

BHB amplifies ROS production and directs T cells toward memory cell formation

Beta-hydroxybutyrate increases ROS formation in human T cells and directs them to memory cell formation *in vitro*



EMBO Mol Med, Volume: 13, Issue: 8, First published: 21 June 2021, DOI: (10.15252/emmm.202114323)

Ketogenic diet *in vivo*

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,*]

La VLKD :

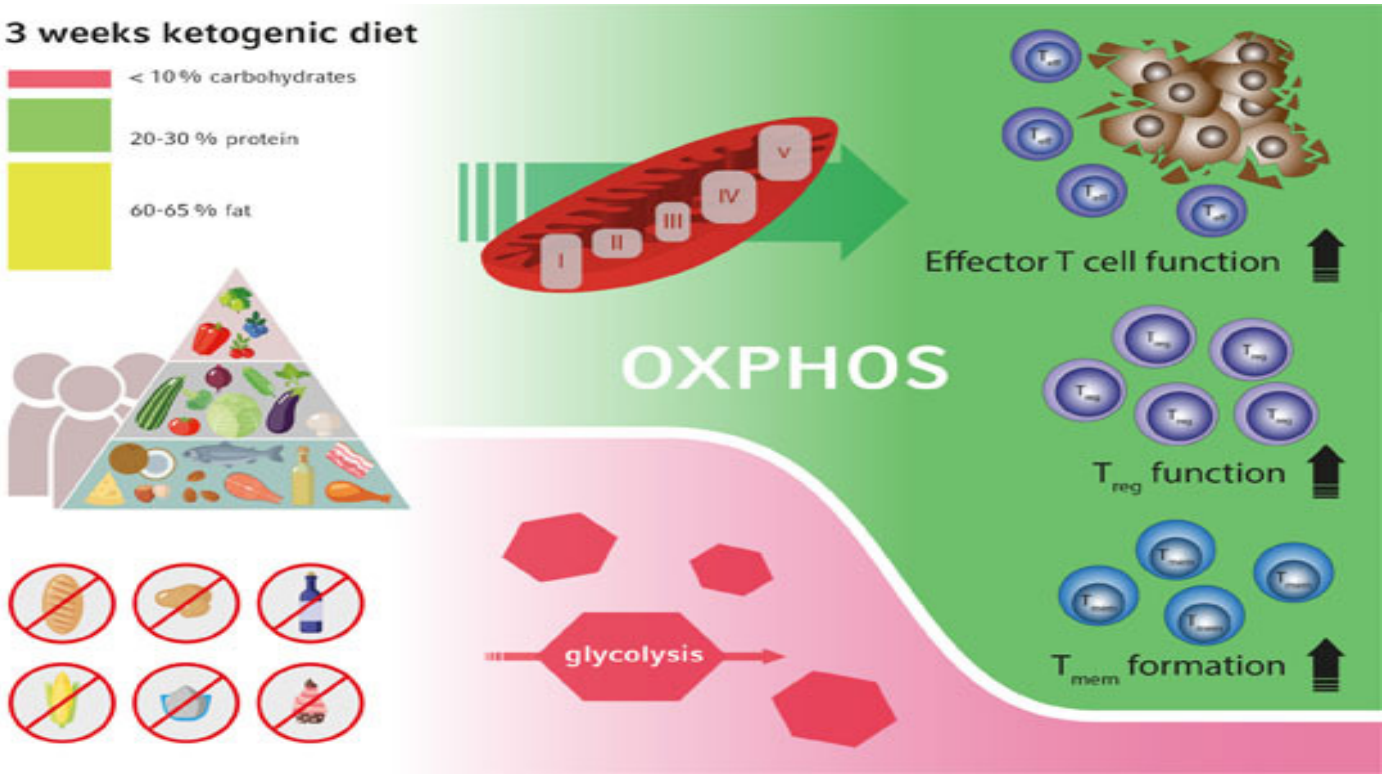
1. **aumenta della produzione di citochine umane CD4+ e CD8+ e la capacità di lisi cellulare in vitro e in vivo.**

2. **aumenta e migliora la funzione delle cellule T regolatrici e attiva la formazione di cellule T di memoria.**

3. **aumenta i mitocondri, la fosforilazione ossidativa e la produzione di ROS**

L'analisi trascrittomica rivela una riprogrammazione immunometabolica fondamentale delle cellule T umane CD4+ e CD8+ dopo 3 settimane di KD.

Sia la elevata capacità bioenergetica che i ROS - servono come molecole secondo messaggero dei T linfociti forniscono la base immunometabolica per una maggiore immunità delle cellule T .



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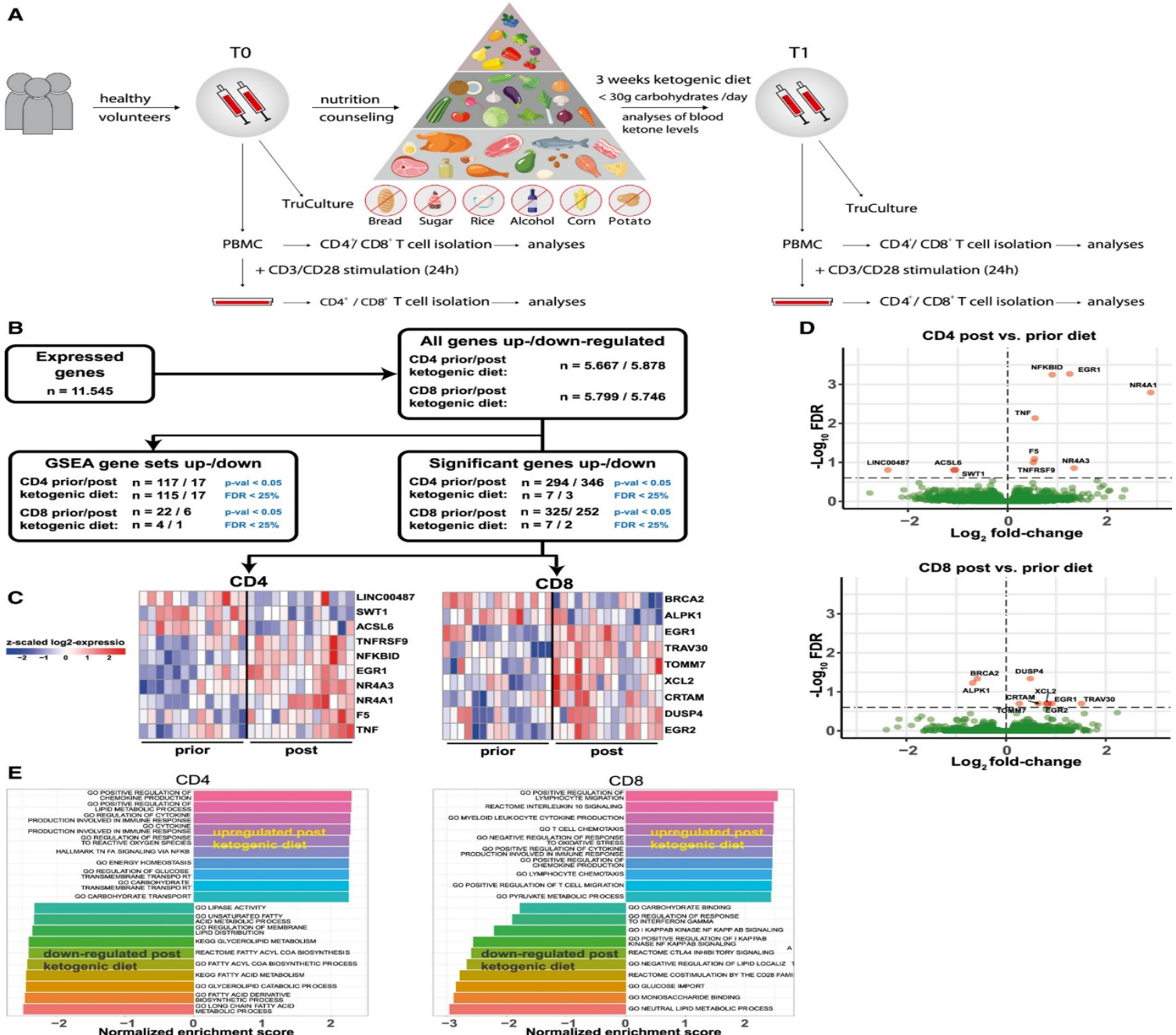
Next-generation sequencing reveals immunometabolic reprogramming in human T cells on KD



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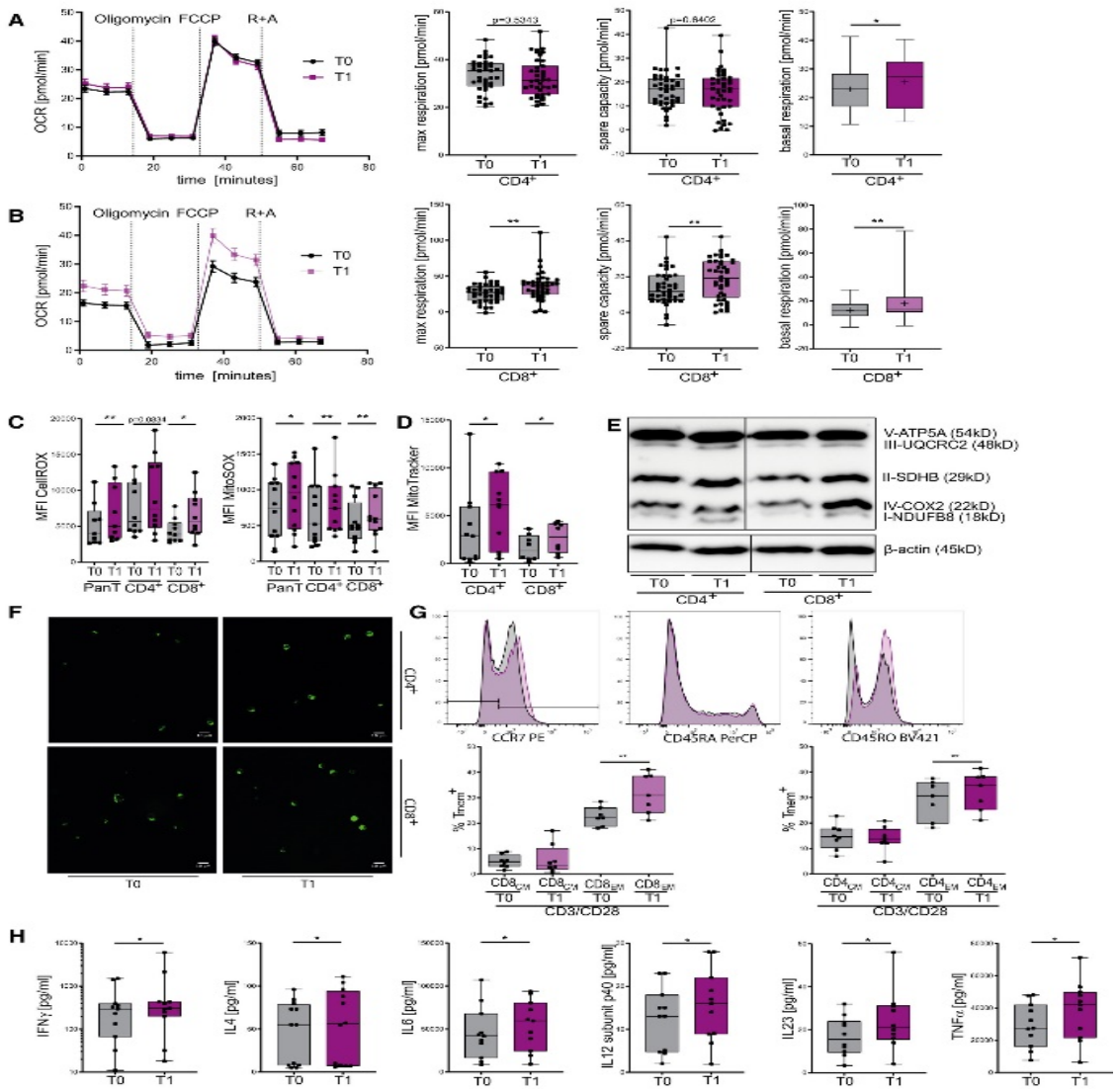
KD strengthens mitochondrial metabolism and memory cell development

Ketogenic diet primes human T cells to mitochondrial metabolism and memory cell development *in vivo*



EMBO Mol Med, Volume: 13, Issue: 8, First published: 21 J

KD NELLA MALATTIE AUTOIMMUNI

MALATTIE AUTOIMMUNI

Risposte immuni che si generano contro autoantigeni
o antigeni self.
Colpiscono 3-5% della popolazione

- **PROGRESSIVE E CRONICHE**
- **ORGANO SPECIFICHE (tiroiditi)**
- **SISTEMICHE (AR, LES)**
- **ETA' (età adulta, >50 anni)**
- **SESSO (femminile> maschile)**

MALATTIE AUTOIMMUNI

Ipotesi ezio-patogenetiche: errori nell'induzione o nel mantenimento della

tolleranza immunologica

=

Meccanismi immunologici che consentono di distinguere *self - non self*

Malattie autoimmuni
meccanismi patogenetici

- Anticorpi verso recettori
  - Morbo di Graves-Basedow
  - Miastenia gravis
- Anticorpi contro antigeni di superficie o della matrice:
  - anemia emolitica autoimmune
  - febbre reumatica acuta
  - Malattia celiaca
- Malattie da immunocomplessi
  - Lupus eritematoso sistemico
- Linfociti T citotossici
  - Artrite reumatoide
  - Diabete insulino-dipendente

Malattie autoimmuni
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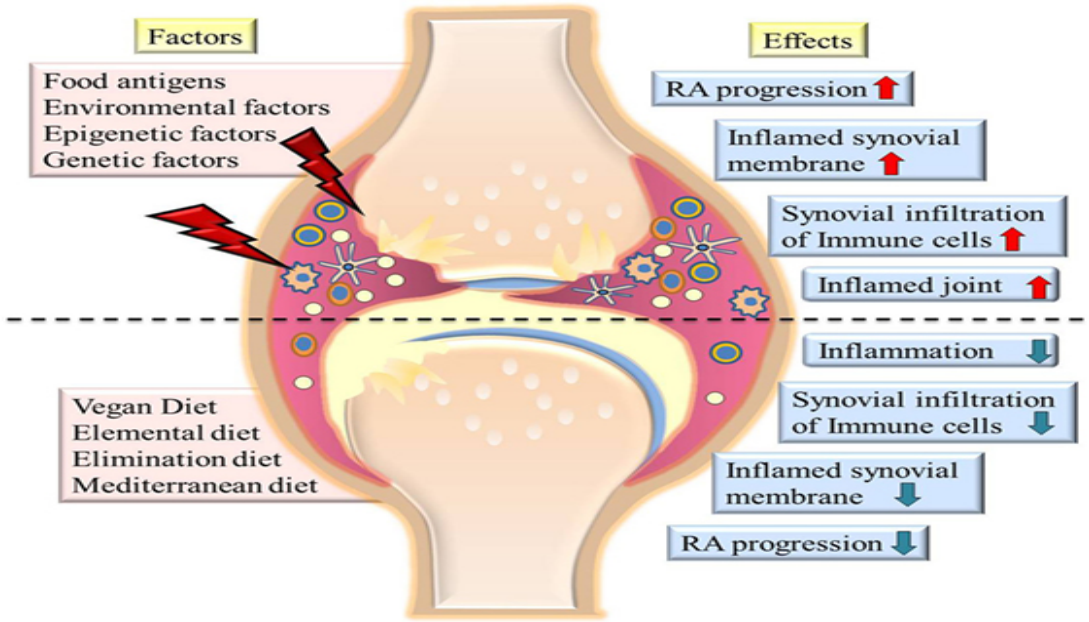
- Linfociti T citotossici
  - Artrite reumatoide
  - Diabete insulino-dipendente

Artrite reumatode: patogenesi

1. Edema sinoviale e proliferazione di piccoli vasi.
2. Infiltrato sinoviale di leucociti mononucleati:

- **Plasmacellule** → produzione di autoanticorpi contro collagene di tipo II e fattore reumatoide
→ formazione di immunocomplessi
- **Linfociti T CD4+**
- **Macrofagi**



Artrite reumatoide: patogenesi

3. Produzione locale di **citochine** infiammatorie (IL-2, IL-6, GM-CSF, IL-1, TNFα etc.)
4. Induzione del **panno sinoviale** → produzione di enzimi litici
5. Erosione osso e distruzione della cartilagine

→dolore e deformazione dell'articolazione colpita

6. Evoluzione in fibrosi del panno sinoviale → formazione di sinfisi ossea e perdita della mobilità articolare

- L'attivazione della cellula CD4+ T e l'ulteriore differenziazione nelle linee Th1 e Th17 sono responsabili della progressione di AR
- (Tripathy, A et al *et al.* Direct recognition of LPS drive TLR4 expressing $CD8^+$ T cell activation in patients with rheumatoid arthritis. *Sci Rep* **7,** 933 (2017). https://doi.org/10.1038/s41598-017-01033-).

- 7 days Fasting (<50 CHO ; 215 Kcal/die ; vitamins, minerals) followed by lacto vegetarian diet decreased $CD4^+$ lymphocyte activation and numbers.
- Fraser D, Thoen J, Reseland J, Førre Ø, Kjeldsen-Kragh J. Decreased CD4+ lymphocyte activation and increased interleukin-4 production in peripheral blood of rheumatoid arthritis patients after acute starvation. *Clin Rheumatol* (1999) 18(5):394–401. doi:10.1007/s100670050125
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changes in the percentage of CD4+ and CD8+ cells expressing CD69 in response to fasting

Clin Rheumatol (1999) 18:394–401
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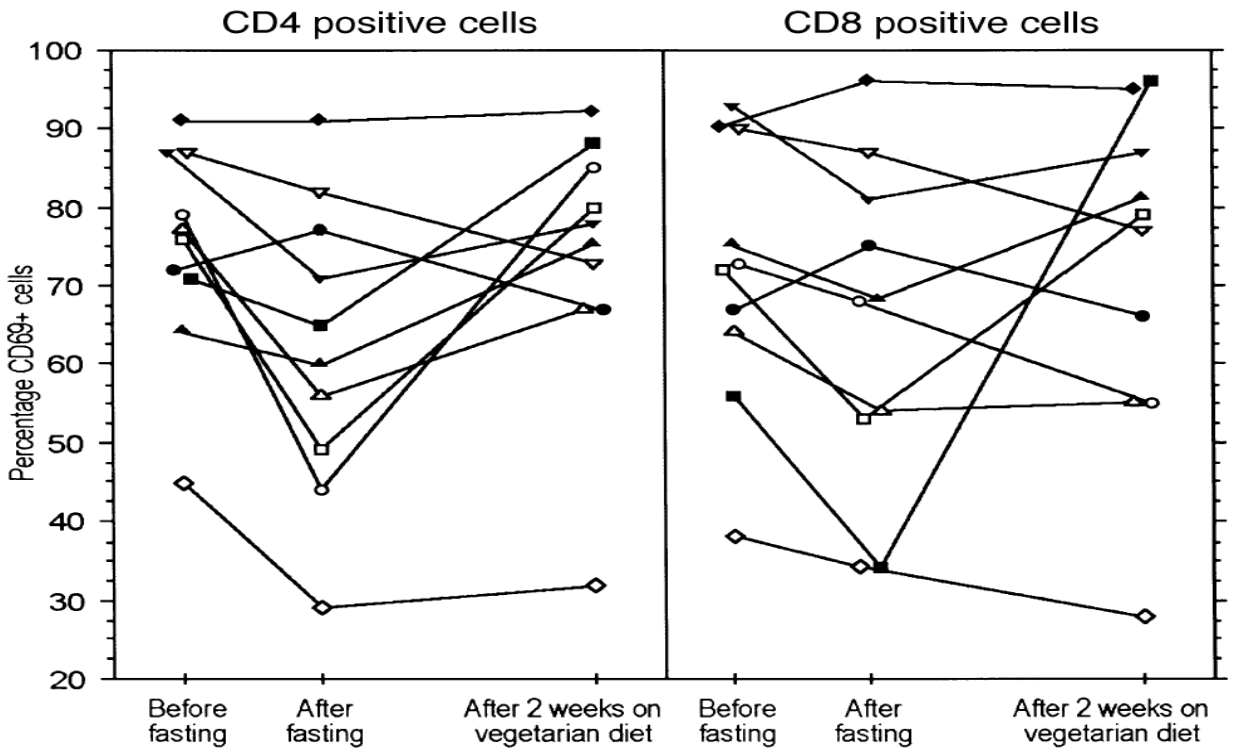
Clinical Rheumatology

Original Article

Decreased CD4+ Lymphocyte Activation and Increased Interleukin-4 Production in Peripheral Blood of Rheumatoid Arthritis Patients After Acute Starvation

D. A. Fraser[1,2], J. Thoen[1], J. E. Reseland[3], Ø. Forre[1] and J. Kjeldsen-Kragh[2]
[1]Centre for Rheumatic Diseases, National Hospital, Oslo, [2]Department of Immunology and Transfusion Medicine, Ullevaal University Hospital, Oslo and [3]Institute for Nutrition Research, University of Oslo, Oslo, Norway



	Before fasting	After fasting	After 2 weeks refeeding
Lymphocyte count (10^9/l)	1.65 (1.18–1.90)	1.15 (0.92–1.53)*	1.38 (1.12–1.74)
CD4+ (cells/μl)	750 (480–1010)	420 (310–860)*	610 (470–780)*
CD8+ (cells/μl)	270 (150–450)	230 (110–360)*	310 (130–410)
CD4+ cells (% of total lymphocytes)	46 (35–51)	45 (33–50)	46 (32–54)
CD8+ cells (% of total lymphocytes)	19 (14–23)	18 (14–21)	19 (13–25)
IL-4 (pg/million T-lymphocytes)	64 (48–116)	157 (46–464)**	99 (52–142)
IFN-γ (pg/million T-lymphocytes)	2034 (734–2222)	2702 (250–5760)	2364 (1483–2407)

Data expressed as median (95% confidence interval); n=10 except for cytokine data where n=8.
Significantly different from pre-fasting (Wilcoxon signed rank): *p<0.05, **p<0.03.

Fraser D et al Decreased CD4+ lymphocyte activation and increased interleukin-4 production in peripheral blood of rheumatoid arthritis patients after acute starvation. Clin Rheumatol (1999) 18(5):394–401.

TABLE 1 | Summary of clinical trials of various dietary interventions in rheumatoid arthritis (RA).

Reference	Subjects, duration, and diet	Outcome
Kjeldsen-Kragh et al. (42)	*Diet group*—27 patients 7–10 days *subtotal fasting* (limited amount of nutritional supplements) 3.5 months on individually adjusted gluten-free vegan diet followed by lactovegetarian diet *Control group*—26 patients Ordinary diet throughout the study	After 1 month of diet Reduction in number of tender ($p < 0.0002$) and swollen joints ($p < 0.04$), Ritchie articular index (RAI) ($p < 0.0004$), pain ($p < 0.0001$), morning stiffness duration ($p < 0.0002$), grip strength, HAQ score, erythrocyte sedimentation rate (ESR) ($p < 0.002$), C-reactive protein (CRP) ($p < 0.005$), and WBC count ($p < 0.0001$) which were maintained even after 1 year of administration of diet *Key note:* Improvement can be maintained by continuing with individually adjusted diet
Kjeldsen-Kragh et al. (49)	*Diet group*—27 patients 7–10 days *subtotal fasting* 3.5 months on individually adjusted gluten-free vegan diet followed by lactovegetarian diet *Control group*—26 patients Ordinary diet throughout the study	After 1 month of treatment Significant decrease in leukocyte and platelet count ($p < 0.003$), IgM rheumatoid factors ($p < 0.02$), IgG, C3 ($p < 0.04$) and C4 complement components ($p < 0.01$), calprotectin ($p < 0.03$) and C3 activation products in diet responders in vegetarian diet group *Key note:* Dietary interventions can help in improvement of disease in some RA patients
Peltonen et al. (50)	*Diet group*—27 patients 7–10 days *subtotal fasting* 3.5 months on individually adjusted gluten-free vegan diet followed by 9 months lactovegetarian diet administration *Control group*—26 patients Ordinary diet throughout the study	Significant difference in fecal fatty acid profile at different times during the dietary intervention as compared to baseline in diet group was observed ($p < 0.005$). Fecal flora was significantly different between vegan diet (post 1 month treatment) and lactovegetarian diet period ($p < 0.001$). Significant difference in fecal flora was also observed between high improvement to low improvement groups ($p < 0.001$). This difference was also found at 1 month (vegan diet) and 13 months (lactovegetarian diet) *Key note:* Study finds association between disease activity and intestinal flora indicating impact of diet on disease progression
Haugen et al. (51)	*Diet group*—27 patients 7–10 days *subtotal fasting* 3.5 months on individually adjusted gluten-free vegan diet followed by lactovegetarian diet *Control group*—26 patients Ordinary diet throughout the study	Post 3.5 months of vegan diet Significant reduction in plasma fatty acid 20:3n-6 ($p < 0.0001$) and 20:4n-6 ($p < 0.01$) was observed which reversed to baseline concentration after lactovegetarian diet Significant reduction in 20:5n-3 post-vegan diet ($p < 0.0001$) and lactovegetarian diet ($p < 0.01$) No significant difference in fatty acid concentration between diet responders and non-responders after vegan or lactovegetarian *Key note:* Change in fatty acid profile could not explain disease improvement
Haugen et al. (47)	*Diet group*—17 patients 7–10 days *fasting* 3.5 months on gluten-free vegan diet followed by 9 months lactovegetarian diet administration *Control group*—17 patients Ordinary diet throughout the study	After 1 month Significant reduction in body mass index (BMI) and triceps skin fold thickness in diet group as compared with baseline (post 1 month) ($p < 0.001$) and controls (post study) ($p = 0.04$; $p < 0.01$) *Key note:* One year of dietary intervention had a minor impact on nutritional status of patients. No significant differences in other clinical variables studied were observed between the two groups
Kjeldsen-Kragh et al. (44)	Patients of above study were (42, 49) called for follow-up; 1 year post-trial. All responders and half non-responders were still on diet. Most of the patients eliminated those food which they thought aggravated their disease	Diet responders showed greatest change in clinical variables including HAQ ($p < 0.04$) and RAI ($p < 0.02$) from the baseline. Significant improvements were observed in all clinical variables including pain ($p < 0.005$), morning stiffness duration ($p < 0.005$), tender joint ($p < 0.0003$), RAI ($p < 0.0001$) and swollen joints ($p < 0.05$) except grip strength as compared to non-responders and controls *Key note:* Patients gained benefit from manipulation of diet which can be maintained for long term
Kjeldsen-Kragh et al. (52)	*Diet group*—26 RA patients 7–10 days *fasting* followed by 3.5 months of gluten-free vegetarian diet	Agalactosyl IgG antibodies reduced in RA patients and correlated significantly ($p = 0.04$) with clinical improvement post fasting which was not observed after administration of vegetarian diet *Key note:* IgG glycosylation may improve disease status during fasting
Fraser et al. (53)	*Diet group*—10 patients 7 days *subtotal fasting* 13 patients—ketogenic diet for 7 days All patients followed 2 weeks period of re-feeding on lactovegetarian diet	Post 7 days fasting Significant decrease in serum IL-6 levels in fasting group ($p < 0.03$) on seventh day as compared to baseline and after re-feeding. Improvement was observed in ESR, CRP, and tender joint counts post 7 days fasting *Key note:* Fasting improves disease activity in RA patients
Michalsen et al. (54)	16 RA patients and 35 fibromyalgia patients 21 patients—vegetarian Mediterranean diet (MD) 30 patients—intermittent modified 8 days fasting therapy	No difference in the fecal bacterial counts, concentration of secretory immunoglobulin or pH of the stool within or between the two diet groups. Post 2 weeks of study, fasting RA patients showed more clinical improvement as compared to non-fasting patients *Key note:* Clinical improvement is not related to intestinal flora

Necessità di studi RCT

Dieta Chetogenica nel COVID-19

- In prevenzione
- In corso di malattia
- Nella riabilitazione

Dieta Chetogenica nel COVID-19

- In prevenzione
- In corso di malattia
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Dieta Chetogenica nel COVID-19

ELSEVIER

Nutrition

Volumes 79–80, November–December 2020, 110967

Applied nutritional investigation

Induction of ketosis as a potential therapeutic option to limit hyperglycemia and prevent cytokine storm in COVID-19

Samir Giuseppe Sukkar M.D. [a], Matteo Bassetti M.D., Ph.D. [b]

Nutrition 89 (2021) 111236

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journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Clinical efficacy of eucaloric ketogenic nutrition in the COVID-19 cytokine storm: A retrospective analysis of mortality and intensive care unit admission

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[b] Infectious Disease Clinic Genoa University, IRCCS-Policlinic Hospital San Martino, Genoa, Italy
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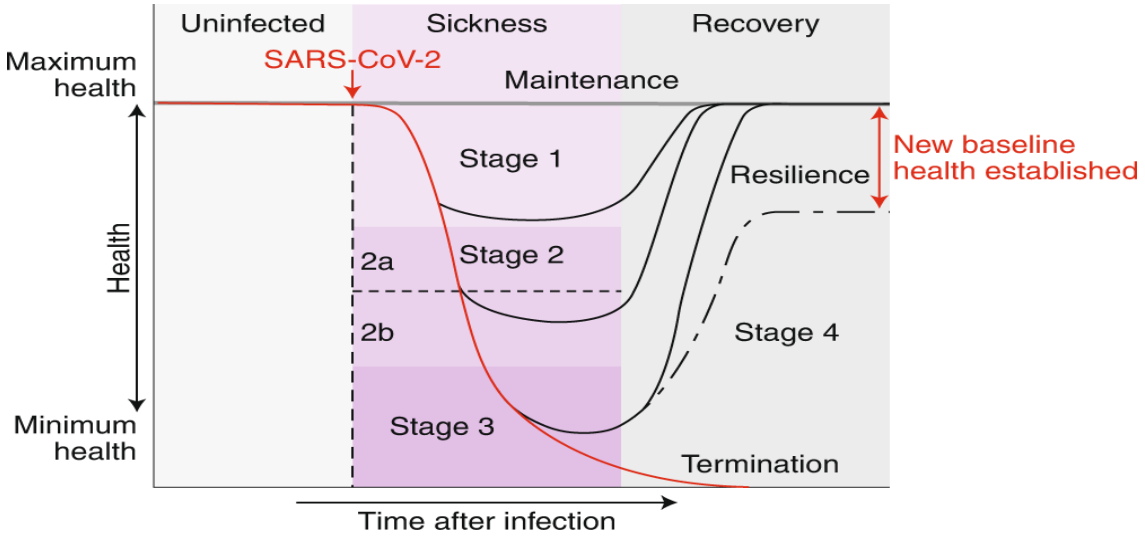
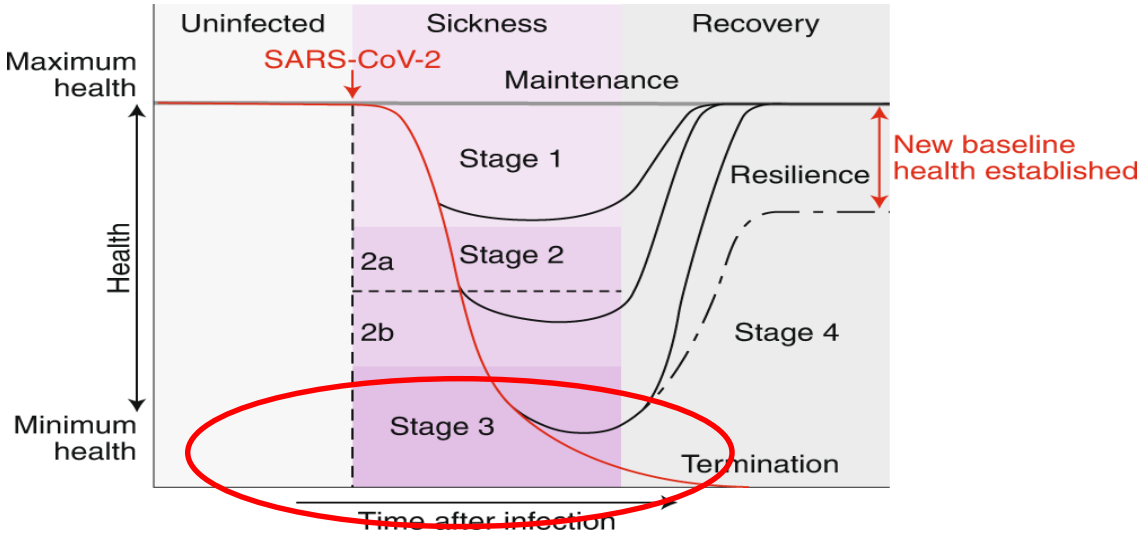
[e] Epidemiology and Biostatistics, University of Genoa, Italy

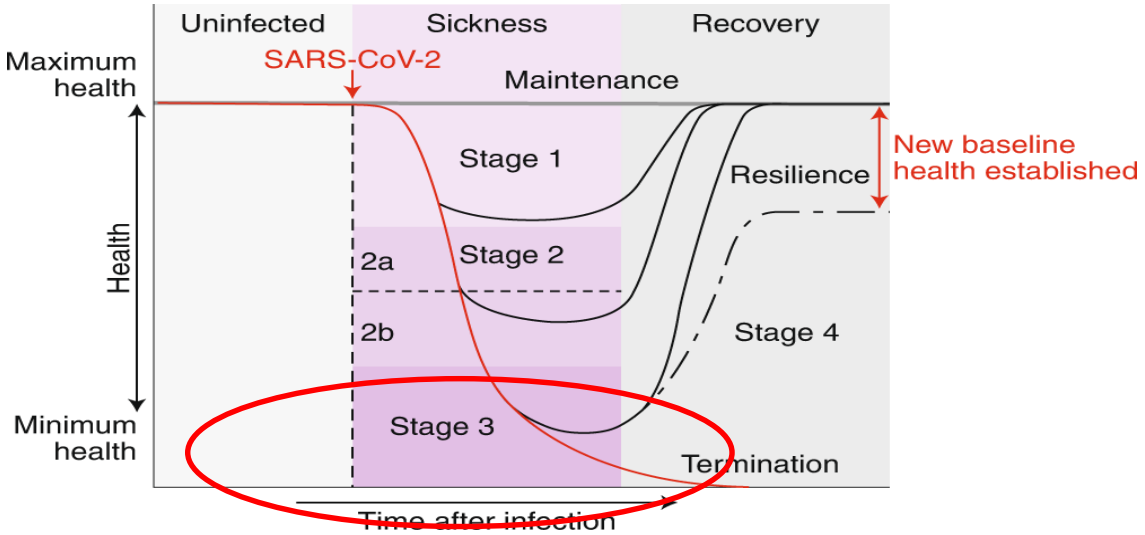
- COVID-19 is a predominantly respiratory viral infection due to coronavirus 2 (SARS-CoV-2).



- COVID-19 is a predominantly respiratory viral infection due to coronavirus 2 (SARS-CoV-2). **Recent evidence suggest that the subgroup of patients who have the most severe clinical picture of COVID-19 and require hospitalization in intensive care, may have a "cytokine storm syndrome"(CSS) (stage 3 III)**



- COVID-19 is a predominantly respiratory viral infection due to coronavirus 2 (SARS-CoV-2). Recent evidence suggest that the subgroup of patients who have the most severe clinical picture of COVID-19 and require hospitalization in intensive care, may have a "cytokine storm syndrome"(CSS). (Stage 3 III)
- **CSS is characterized by acute respiratory distress syndrome (ARDS), septic shock, followed by multi-organ failure, and disseminated intravascular coagulation (DIC) which represent the main cause of mortality.**



- CSS seems due to innate immune hyperactivation induced by SARS-COV-2 and hyper production of pro-inflammatory cytokines as well as chemokines in pts with more critical conditions .
- In particular, CSS is more frequently observed in presence of diabetes, hypertension, cardiovascular disease, and obesity.
-

Factors associated with hospitalization and critical illness among 4,103 patients with COVID-19 disease in New York City

Table 1: Characteristics of tested patients, by hospitalization status

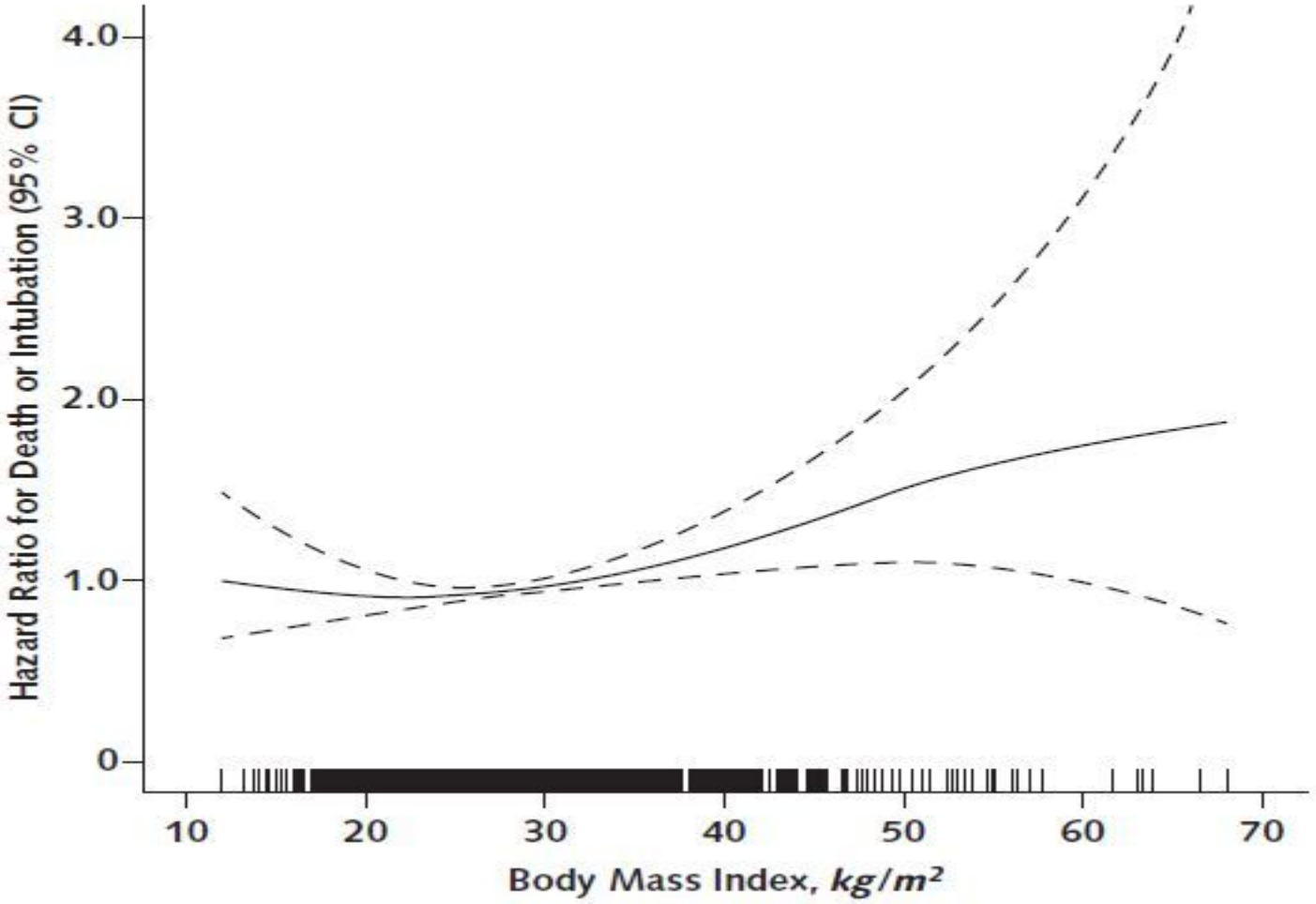
Characteristic	Not hospitalized, N=2,104 N (%) or median (IQR)	Hospitalized, N=1,999 N (%) or median (IQR)
Age	41 (31, 54)	62 (50, 74)
Male sex	821 (39.0)	1,251 (62.6)
Race		
White	887 (42.2)	925 (46.3)
African American	365 (17.3)	290 (14.5)
Asian	166 (7.9)	118 (5.9)
Other	391 (18.6)	536 (26.8)
Multiracial/Unknown	295 (14.0)	130 (6.5)
Tobacco use		
Never or unknown	1746 (83.0)	1479 (74.0)
Former	250 (11.9)	416 (20.8)
Current	108 (5.1)	104 (5.2)
Obesity	304 (14.4)	796 (39.8)
BMI 30-40 kg/m^2	256 (12.2)	659 (33.0)
BMI >40 kg/m^2	48 (2.3)	137 (6.9)
Any chronic condition*	629 (29.9)	1438 (71.9)
Any cardiovascular condition*	344 (16.3)	891 (44.6)
Hyperlipidemia	221 (10.5)	517 (25.9)
Hypertension	241 (11.5)	742 (37.1)
Coronary artery disease	38 (1.8)	197 (9.9)
Heart failure	7 (0.3)	124 (6.2)
Diabetes	111 (5.3)	503 (25.2)
Asthma or chronic obstructive pulmonary disorder	106 (5.0)	206 (10.3)
Chronic kidney disease	20 (1.0)	195 (9.8)
Malignancy	42 (2.0)	143 (7.2)
Temperature at presentation, degrees Celsius	37.3 (36.9 – 37.8)	37.5 (36.9 – 38.3)
Temperature ≥ 38 at presentation	106 (5.0)**	669 (33.5)
Oxygen saturation at presentation	97 (96-99) **†	94 (91-97) ‡

*Not included in multivariable model
**Missing for 76% of non-hospitalized patients
†Measured on supplemental oxygen for 0.3% of patients
‡Measured on supplemental oxygen for 78.9% of patients

Table 2: Characteristics of admitted patients, by complication status

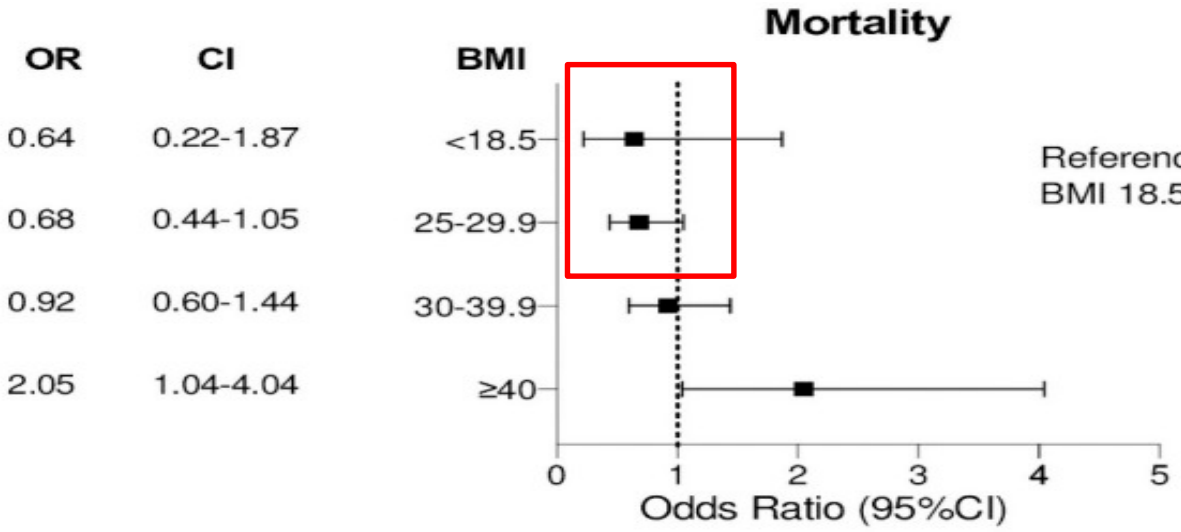
Christopher M. Petrilli, published in *BMJ* doi: 10.1136/bmj.m1966

Associazione BMI mortalità COVID

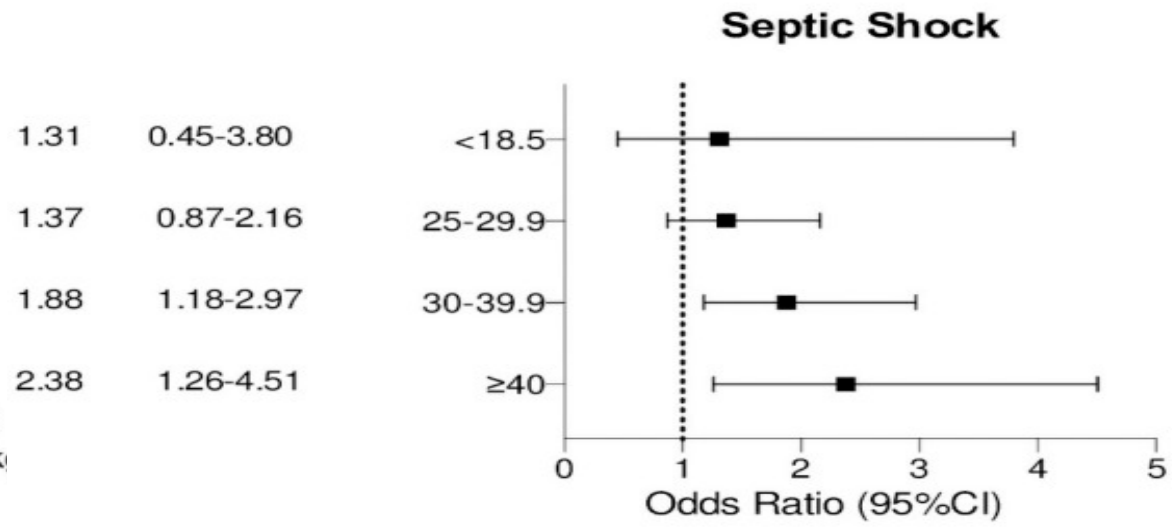


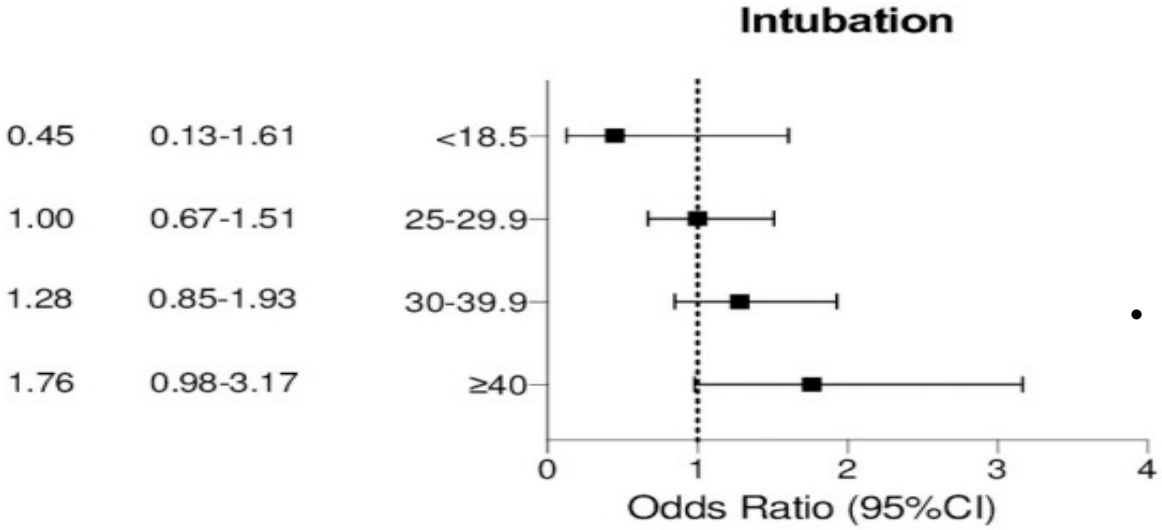
Anderson MR, et al. Body Mass Index and Risk for Intubation or Death in SARS-CoV-2 Infection : A Retrospective Cohort Study. Ann Intern Med. 2020;173(10):782-790. doi:10.7326/M20-3214

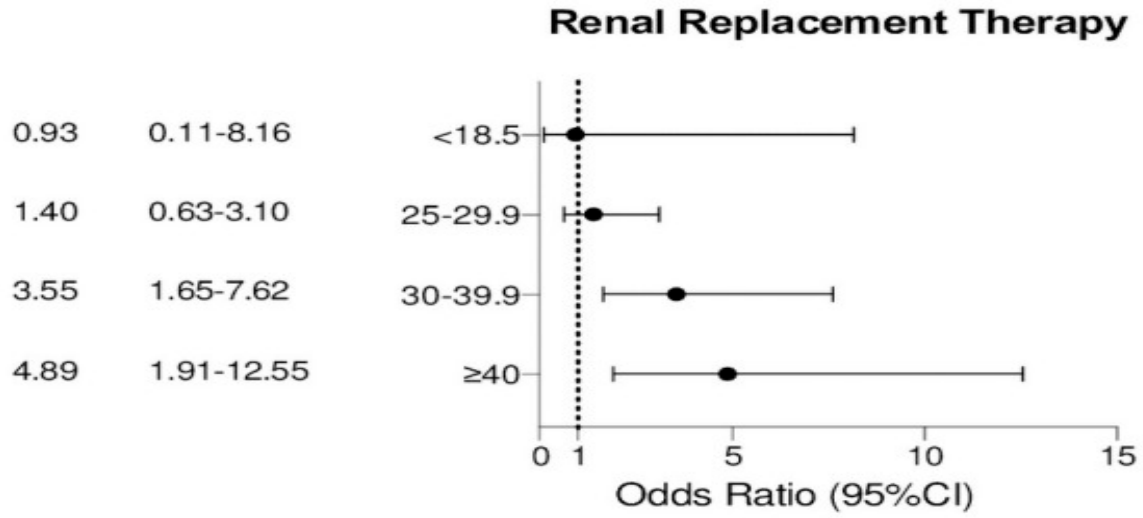
Obesity and COVID



Reference OR=1
BMI 18.5 - 24.9 k





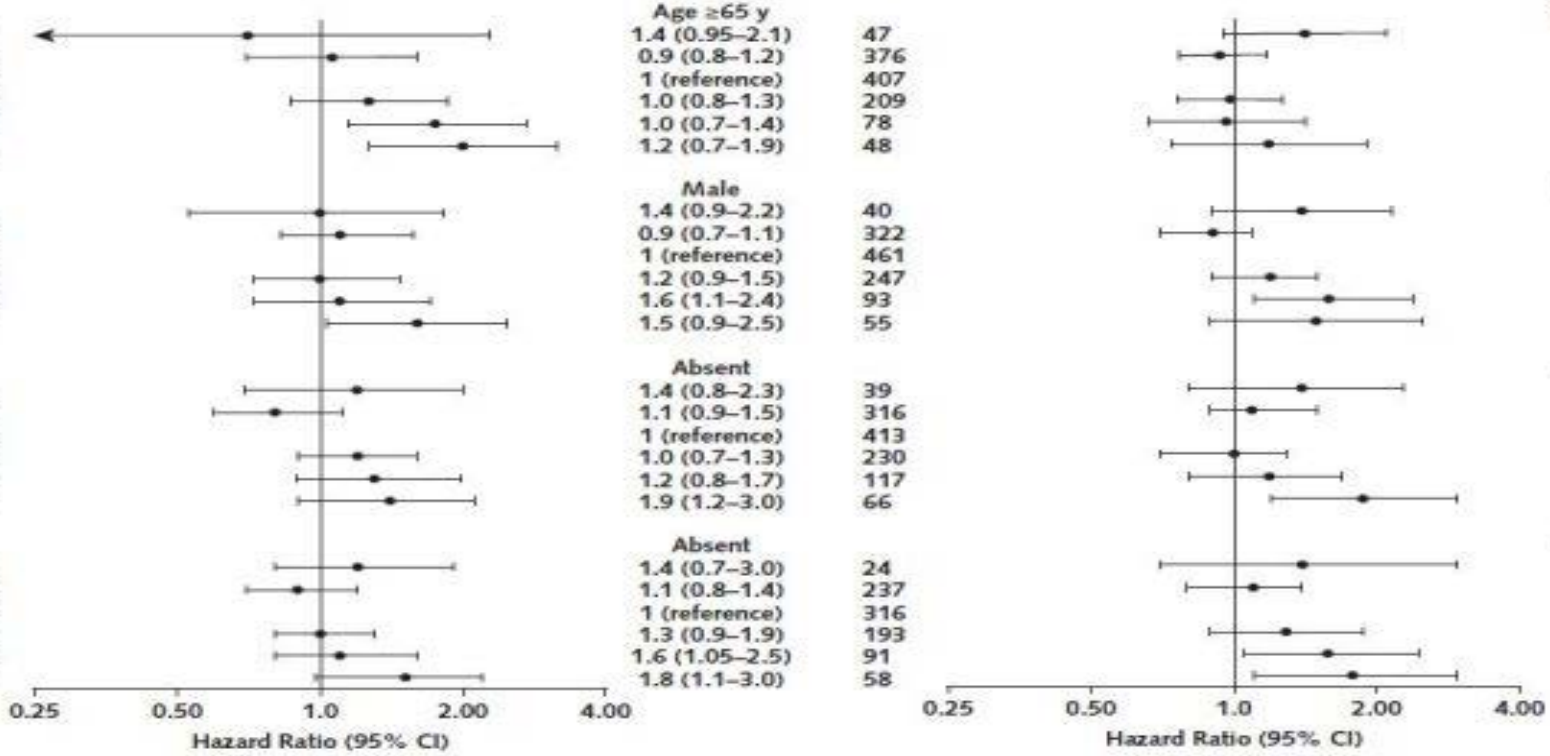


- *Page-Wilson G et al Obesity is independently associated with septic shock, renal complications, and mortality in a multiracial patient cohort hospitalized with COVID-19. PLoS One. 2021 Aug 12;16(8):e0255811.*

- Obese patients with COVID 19 have a higher incidence of: hospitalization (OR = 1.54, 95% CI: 1.33-1.78,I2 = 60.9%); hospitalization in intensive care (OR = 1.48, 95% CI: 1.24-1.77,I2 = 67.5%), invasive mechanical ventilation (OR = 1.47, 95% CI: 1.31-1.65,I2= 18.8%) and hospital mortality (OR = 1,14, 95% CI: 1,04-1,26,I2= 74,4%) [6] The breakdown of BMI classes clearly demonstrates that BMI plays an extremely important role in ongoing ICU morbidity and mortality. [9]
- Paradoxically, it almost appears that normal BMI or below 18.5 is a protective factor against obesity related to mortality (BMI 18.5 OR:0.64; BMI25-29.9: OR 0.68; BMI 30-39.9: OR 0.92 BMI>4: OR 2.05) and intubation (BMI 18.5 OR:0.45; BMI25-29.9: OR 1; BMI 30-39.9: OR 1.28; BMI>4: OR 1.76) [9]

Associazione BMI mortalità COVID

Variable	HR (95% CI)	Admissions, n	HR (95% CI)	Admissions, n	P Value for Interaction
Age	Age <65 y		Age ≥65 y		0.042
Underweight	0.7 (0.2–2.3)	21	1.4 (0.95–2.1)	47	
Normal weight	1.1 (0.7–1.6)	166	0.9 (0.8–1.2)	376	
Overweight	1 (reference)	310	1 (reference)	407	
Class 1 obesity	1.3 (0.9–1.9)	235	1.0 (0.8–1.3)	209	
Class 2 obesity	1.8 (1.1–2.7)	121	1.0 (0.7–1.4)	78	
Class 3 obesity	2.0 (1.3–3.1)	94	1.2 (0.7–1.9)	48	
Sex	Female		Male		0.29
Underweight	1.0 (0.5–1.8)	28	1.4 (0.9–2.2)	40	
Normal weight	1.1 (0.8–1.6)	220	0.9 (0.7–1.1)	322	
Overweight	1 (reference)	256	1 (reference)	461	
Class 1 obesity	1.0 (0.7–1.5)	197	1.2 (0.9–1.5)	247	
Class 2 obesity	1.1 (0.7–1.7)	106	1.6 (1.1–2.4)	93	
Class 3 obesity	1.6 (1.03–2.5)	87	1.5 (0.9–2.5)	55	
Diabetes	Present		Absent		0.97
Underweight	1.2 (0.7–2.0)	29	1.4 (0.8–2.3)	39	
Normal weight	0.8 (0.6–1.1)	226	1.1 (0.9–1.5)	316	
Overweight	1 (reference)	304	1 (reference)	413	
Class 1 obesity	1.2 (0.9–1.6)	214	1.0 (0.7–1.3)	230	
Class 2 obesity	1.3 (0.9–2.0)	82	1.2 (0.8–1.7)	117	
Class 3 obesity	1.4 (0.9–2.1)	76	1.9 (1.2–3.0)	66	
Hypertension	Present		Absent		0.41
Underweight	1.2 (0.8–1.9)	44	1.4 (0.7–3.0)	24	
Normal weight	0.9 (0.7–1.2)	305	1.1 (0.8–1.4)	237	
Overweight	1 (reference)	401	1 (reference)	316	
Class 1 obesity	1.0 (0.8–1.3)	251	1.3 (0.9–1.9)	193	
Class 2 obesity	1.1 (0.8–1.6)	108	1.6 (1.05–2.5)	91	
Class 3 obesity	1.4 (0.98–2.2)	94	1.8 (1.1–3.0)	58	



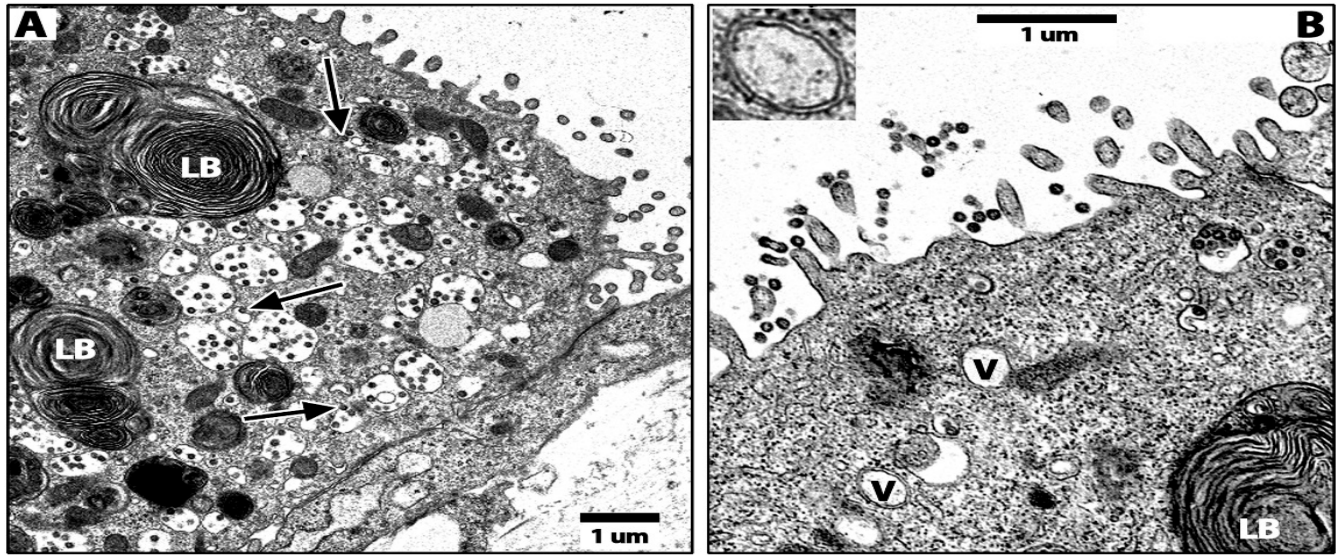
Anderson MR, et al. Body Mass Index and Risk for Intubation or Death in SARS-CoV-2 Infection : A Retrospective Cohort Study. Ann Intern Med. 2020;173(10):782-790. doi:10.7326/M20-3214

Fattore età

- Nei giovani in BMI è correlato negativamente mentre negli anziani è correlato positivamente con la mortalità
- Di fatto gli anziani con basso BMI sono sarcopenici, immunodepressi, con polipatologie

- Diabetes, obesity and hypertension have, as minor common denominator, chronic low-grade inflammation and high levels of plasma MPO that could be linked to pulmonary phagocytic hyper activation and CSS.
- MPO could amplify oxidative stress in hypertension in presence of hyperglycaemia.

- Currently, there is an increasing evidence to suggest that macrophages, including resident alveolar macrophages (AM) and macrophages recruited from blood, are crucial in ALI/ARDS pathogenesis



- Coronavirus, as observed in SARS, binds to the SARS receptor angiotensin-converting enzyme 2 to infect ATII cells, which represent the first line of innate alveolar immunity.
- ATII cells release cytokines and chemokines that activate alveolar macrophages and lead to the migration of neutrophils

Published in: Zhaohui Qian; Emily A. Travanty; Lauren Oko; Karen Edeen; Andrew Berglund; Jieru Wang; Yoko Ito; Kathryn V. Holmes; Robert J. Mason; *Am J Respir Cell Mol Biol* 48742-748.
DOI: 10.1165/rcmb.2012-0339OC
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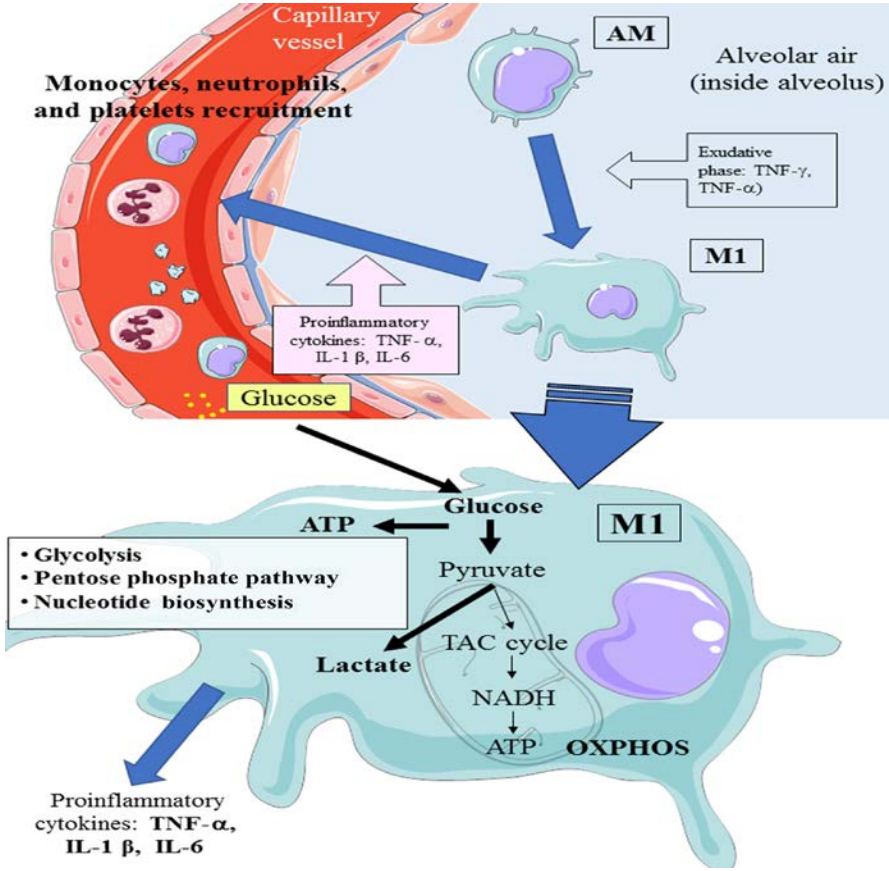
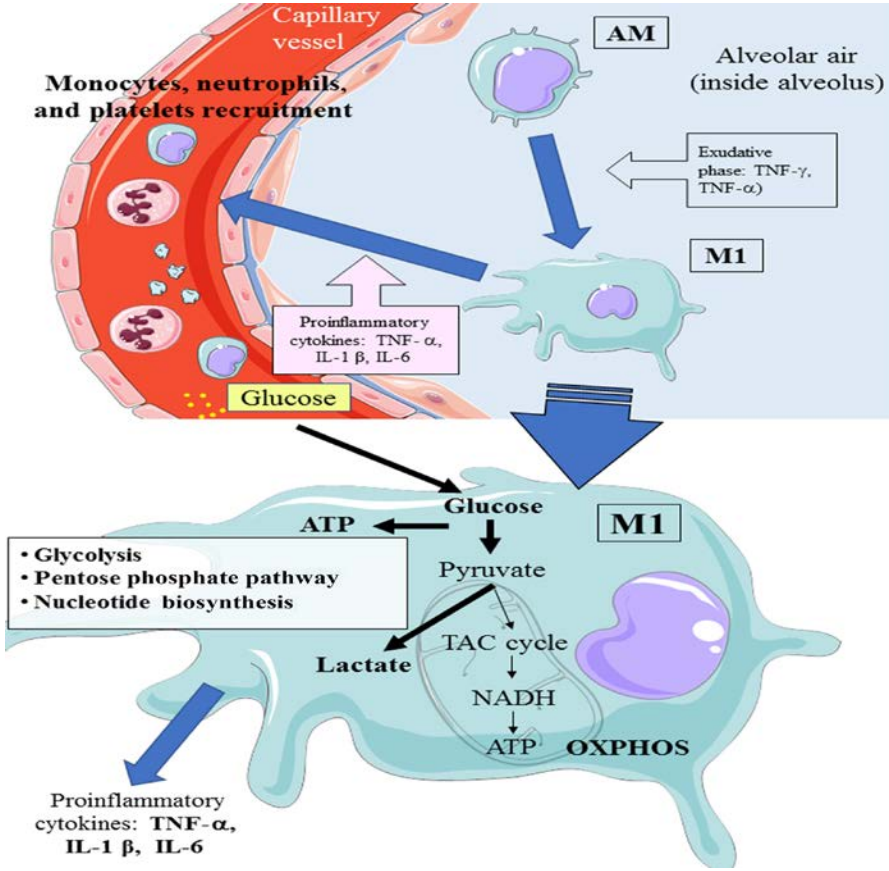
Supposed Metabolic pathway during activation of macrophage AM in M1 during COVID-19 infection



- During the exudative phase of ARDS, resident AM are activated and differentiate into the M1 phenotype.

Sukkar SG and Bassetti M. Nutrition 79–80 (2020)

Supposed Metabolic pathway during activation of macrophage AM in M1 during COVID-19 infection



- During the exudative phase of ARDS, resident AM are activated and differentiate into the M1 phenotype.

metabolically:

Pathways used:	
Glycolysis	Supports phagocytosis and inflammatory cytokine production
TCA cycle	Redirected to produce citrate to promote fatty acid synthesis
Pentose phosphate pathway	Supports nucleotide and ROS production
Fatty acid synthesis	Supports proliferation and inflammatory cytokine production
Amino acid metabolism	Supports proliferation and nitric oxide production

Sukkar SG and Bassetti M. Nutrition 79–80 (2020)

Pathways used:	

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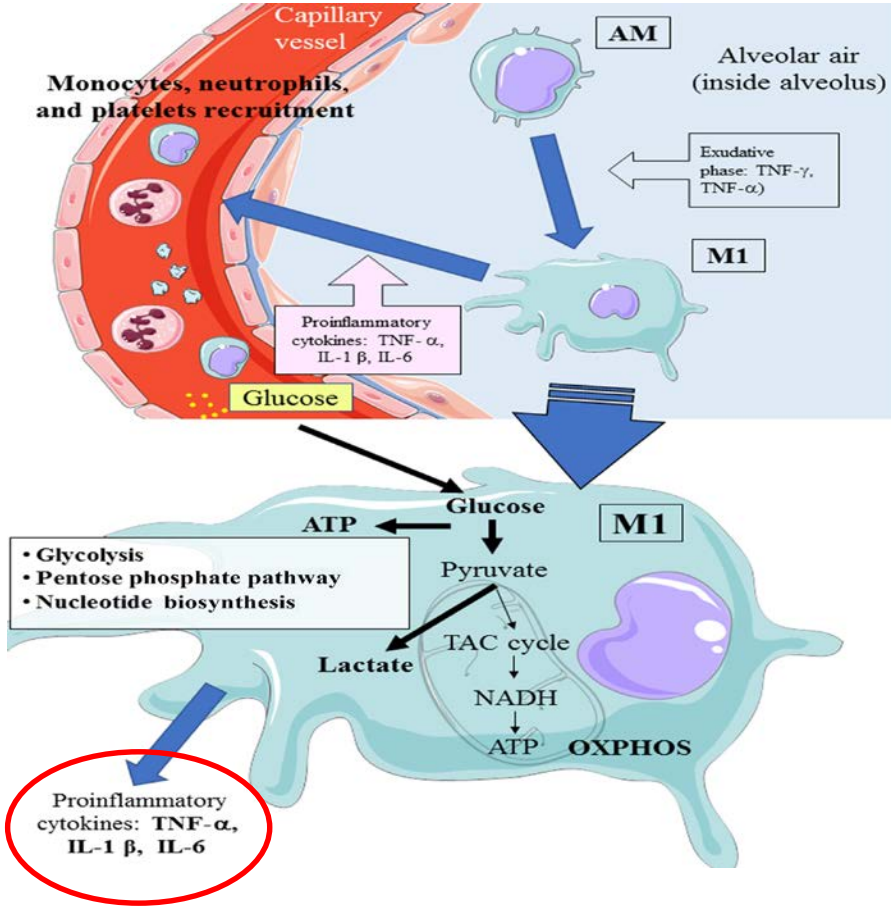

- During the exudative phase of ARDS, resident AM are activated and differentiate into the M1 phenotype.
- The activation of macrophages caused by infections induces a metabolic shift in M1 macrophages from OXPHOS to aerobic glycolysis (Warburg-like effect). [9-10] **The hyperactivation of M1 macrophages leads to the overproduction of proinflammatory cytokines (IFN-*γ*, TNF-*α*, and IL-1*β*).**
-
- *ARDS: acute respiratory distress syndrome; AM: alveolar quiescent macrophage; M1: activated macrophage; OXPHOS: oxidative phosphorylation; IFN-γ: interferon gamma; TNF-α: tumor necrosis factor-alpha; and IL-1β: interleukin 1-beta; MCP: monocyte chemoattractant protein; NETs: neutrophil extracellular traps.*

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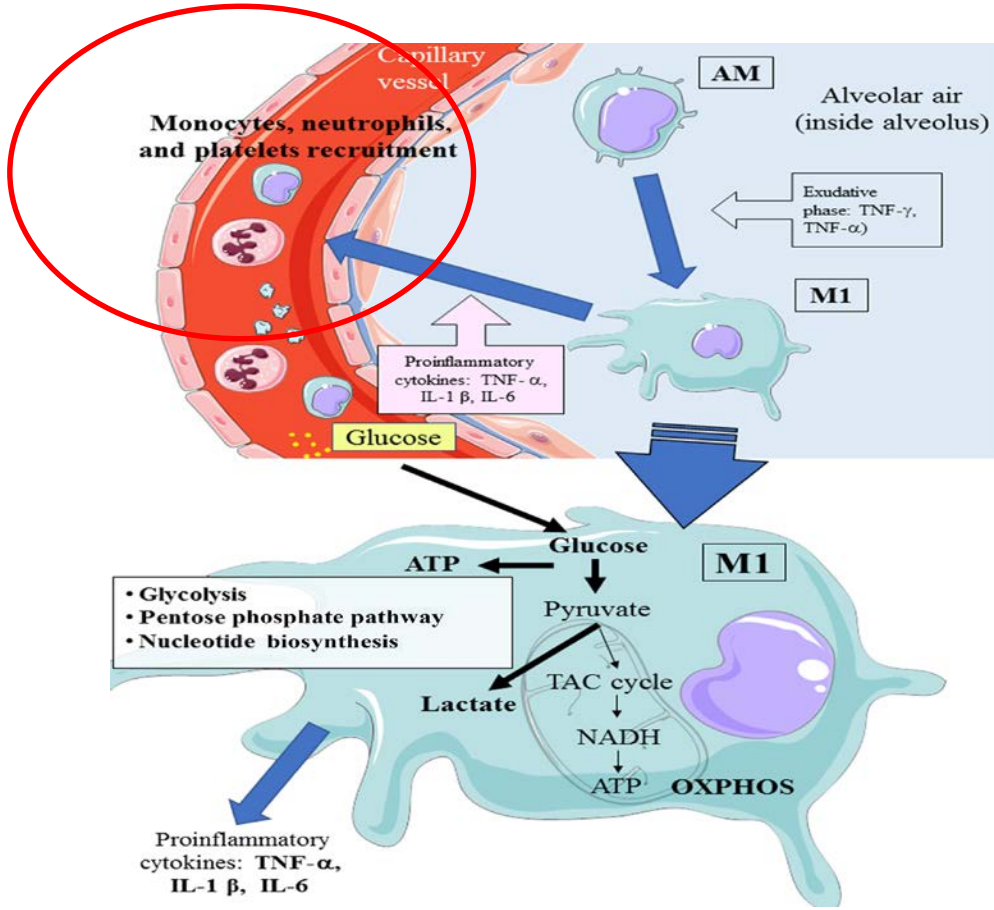
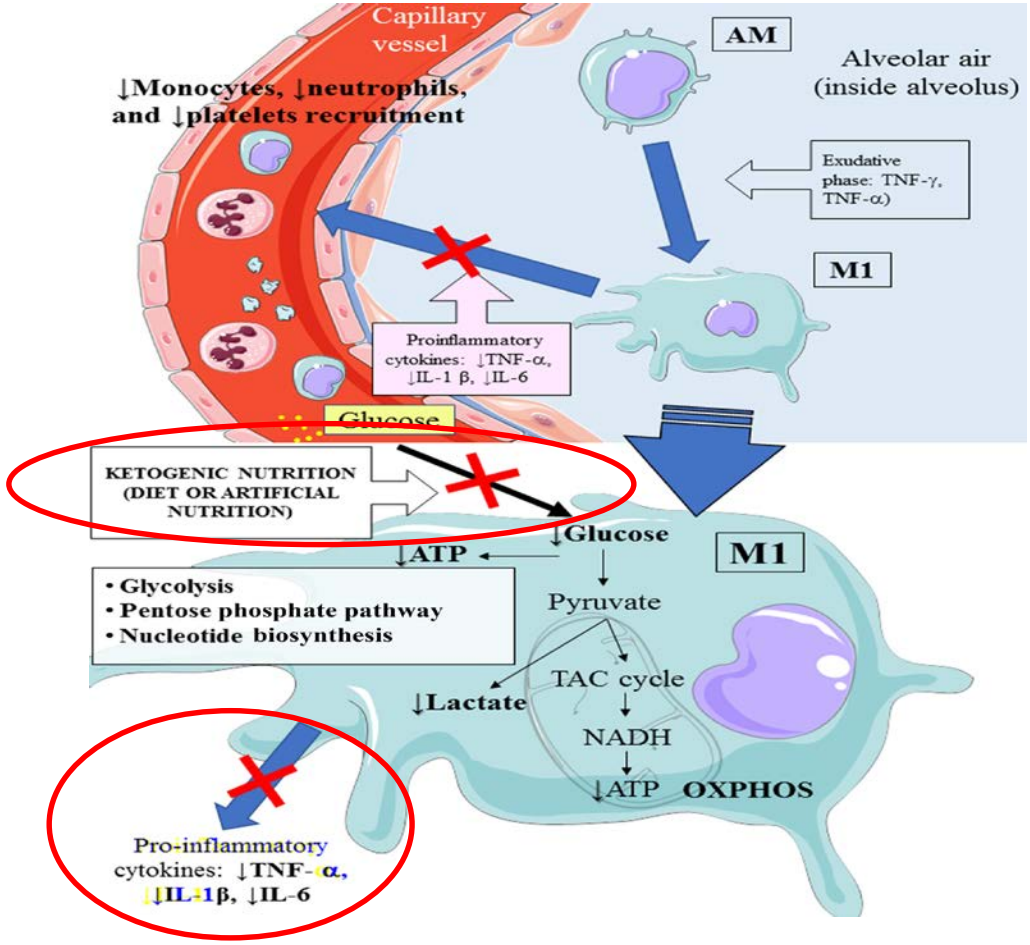
Supposed Metabolic pathway during activation of macrophage AM in M1 during COVID-19 infection

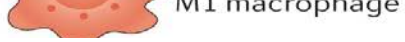


- During the exudative phase of ARDS, resident AM are activated and differentiate into the M1 phenotype.
- **The activation of macrophages caused by infections induces a metabolic shift in M1 macrophages from OXPHOS to aerobic glycolysis (Warburg-like effect). [9-10] The hyperactivation of M1 macrophages leads to the overproduction of proinflammatory cytokines (IFN-*γ*, TNF-*α*, and IL-1*β*).**
- **M1 macrophages secrete cytokines into the site of inflammation and recruit monocytes, which turn in, recruit M1 macrophages, by means of monocyte chemoattractant protein (MCP), neutrophils and platelets from circulating blood into the alveolar space, causing tissue damage and neutrophil extracellular traps (NETs), and monocyte–platelet aggregates, which could be responsible for DIC.**
- *ARDS: acute respiratory distress syndrome; AM: alveolar quiescent macrophage; M1: activated macrophage; OXPHOS: oxidative phosphorylation; IFN-γ: interferon gamma; TNF-α: tumor necrosis factor-alpha; and IL-1β: interleukin 1-beta; MCP: monocyte chemoattractant protein; NETs: neutrophil extracellular traps.*

Hypotetical attenuation of phagocyte hyperactivation by means of Ketogenic diet



- **A working hypothesis to decrease phagocyte hyperactivation** which provokes excessive monocyte and neutrophils accrual from blood, increasing the production of IFN type I and reducing viral replication **could be the "metabolic way", by means of the ketogenic diet** (or ketogenic artificial nutrition) with the depletion of glucose availability for the aerobic glycolysis (Warburg effect) in M1.
- AM : alveolar quiescent macrophage; M1 : activated macrophage



Hypothetical effects of eucaloric ketogenic diets in COVID-19

a) Inhibition of Warburg-like effect
modulation of CSS by reducing metabolism of M1 macrophage phenotype by reducing glucose availability

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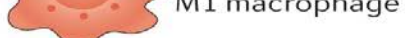

Hypothetical effects of eucaloric ketogenic diets in COVID-19

a) Inhibition of Warburg-like effect
modulation of CSS by reducing metabolism of M1 macrophage phenotype by reducing glucose availability
metabolic promotion of the anti-inflammatory M2 macrophage phenotype fueled by fatty acids

Pathways used:	
TCA cycle	Supports oxidative phosphorylation
Fatty acid oxidation	Promotes M2 phenotype by inhibiting inflammatory signals
Amino acid metabolism	Supports arginase pathway activity

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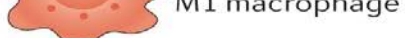

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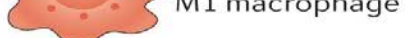

Hypothetical effects of eucaloric ketogenic diets in COVID-19

a) Inhibition of Warburg-like effect
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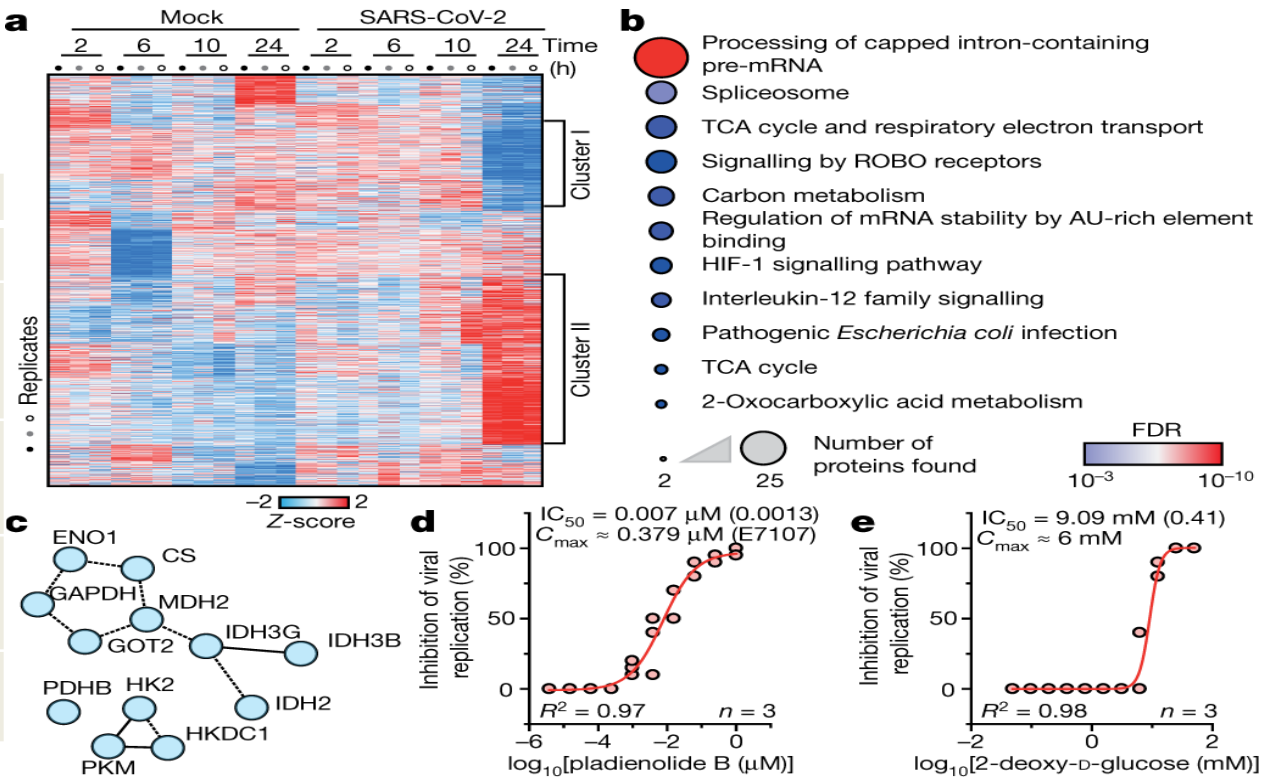
reduced production of lactate associated with disinhibition of IFN I production
b) Antiglycolytic effects in infected cells leading to inhibition of virus replication



Effects of KD

- ketosis protects healthy tissues against oxidative stress by simultaneously decreasing ROS production and increasing endogenous antioxidant capacity even if hypoxia has similar metabolic effects to hyperglycemia so that reduction of hyperglycemia might not cause substantial metabolic shift.
- KD reduces circulating inflammatory markers in humans.
- KD, via hydroxybutyrate (HB), inhibits NF-kB in macrophages, dendritic cells and reduces inflammation.
- Ketogenic diet is able to provoke, in preclinical studies in mice, an expansion of $\gamma\delta$ T cells in the lung improving barrier functions and antiviral resistance against Influenza A virus (IAV) .
- KD show a clinical improvement in respiratory function.

KD contraindications

- *Type I diabetes mellitus*
- *Type II diabetes treated with* insulin , derivatives of sulfonylurea, secretagogues non sulfonylurea (i.e. repaglinide), analogues of GLP-1 = (i.e. Exenatide, Liraglutide, lixisenatide), SGLT2 inhibitors (risk of euglycemic diabetic ketoacidosis) (i.e.Dapagliflozin, Canagliflozin , Empagliflozin)
- *Recent acute cardiovascular event (within one month)*
- *Food allergies to diet components*
- *Any metabolic disorder that may affect gluconeogenesis or the ability to adaptation to periods of hypoglucidic diet (i.e pyruvate kinase deficiency)*
- *Pregnancy and breastfeeding*
- *Pancreatitis*
- *Liver failure*
- *Disorders of fat metabolism (primary carnitine deficiency, carnitine palmitoyltransferase, deficiency carnitine, translocase deficiency etc)*
- *Porphyrias*

With the purpose to confirm these preliminary potentially encouraging results on the efficacy of EKD in COVID-19-CS , a randomized protocol was approved by the Liguria region Ethical Committee in June 2020 (KETOCOV-1 protocol 10517; *ClinicalTrials.gov identifier (NCT n. NCT04492228*).

The trial officially started in September 2020, with the recrudescence of the Covid-19 infection in Italy.

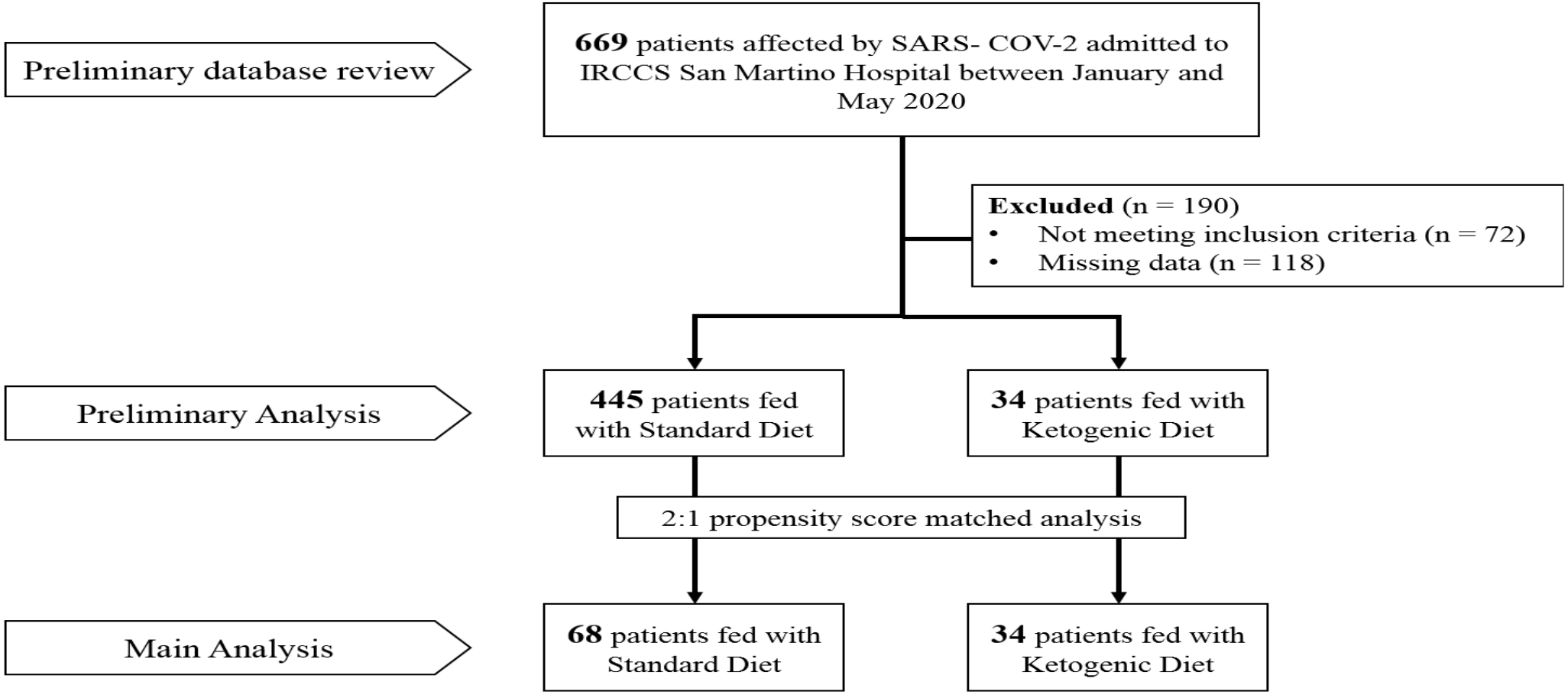
Pending the approval, in the absence of indications or contraindications for a specific diet in COVID-19, a EKD with natural foods was proposed to hospitalized patients, with the exception of those who had a possible contraindication

2 studies

1. Retrospective RT post with propensity score
2. Prospective RCT

Our experience

- retrospective analysis of 34 pts EKD vs 68 pts in standard diet during hospitalization for COVID-19
- selected and matched using propensity score one-to-two to avoid the confounding effect of interfering variables.


Preliminary database review
669 patients affected by SARS- COV-2 admitted to IRCCS San Martino Hospital between January and May 2020
Excluded (n = 190)
• Not meeting inclusion criteria (n = 72)
• Missing data (n = 118)
Preliminary Analysis
445 patients fed with Standard Diet
34 patients fed with Ketogenic Diet
2:1 propensity score matched analysis
Main Analysis
68 patients fed with Standard Diet
34 patients fed with Ketogenic Diet

Demographic variables

Variables	Standard Diet (N = 68)	Ketogenic Diet (N = 34)	All Patients (N = 102)	P-value
Demographics				
Age [years: median; IQ range]	67 (54-77)	67 (52-76)	67 (53-77)	0.943
Sex [M/F: n; %]	40 (58.8%) / 28 (41.2%)	23 (67.6%) / 11 (32.4%)	63 (61.8%) / 39 (38.2%)	0.387

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Comorbidities

Diabetes mellitus	7/68 (10.3%)	1/34 (2.9%)	8/102 (7.8%)	0.193
Hypertension	32/68 (47.1%)	15/34 (44.1%)	47/102 (46.1%)	0.779
ASCVD	27/68 (39.7%)	13/34 (38.2%)	40/102 (39.2%)	0.886
Heart failure	3/68 (4.4%)	2/34 (5.9%)	5/102 (4.9%)	0.746
Pulmonary disease	4/68 (5.9%)	0/34 (0.0%)	4/102 (3.9%)	0.149
Solid neoplasia	7/68 (10.3%)	1/34 (2.9%)	8/102 (7.8%)	0.193
Hematological neoplasia	4/68 (5.9%)	5/34 (14.7%)	9/102 (8.8%)	0.139
Ulcerative disease	3/68 (4.4%)	0/34 (0.0%)	3/102 (2.9%)	0.214
Moderate-severe liver disease	2/68 (2.9%)	1/34 (2.9%)	3/102 (2.9%)	1.000
Dementia	3/68 (4.4%)	1/34 (2.9%)	4/102 (3.9%)	0.718
Collagenopathy	1/68 (1.5%)	0/34 (0.0%)	1/102 (1.0%)	0.477
Metastatic Neoplasia	0/68 (0.0%)	0/34 (0.0%)	0/102 (0.0%)	1.000
Hemiplegia	1/68 (1.5%)	1/34 (2.9%)	2/102 (2.0%)	0.614
Charlson score [point: mean±SD; median; IQ range]	3 (1-5)	3 (2-5)	3 (1-5)	0.838

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Clinical features

PaO2/Fi02 >100	281 (205-323)	312 (166-384)	286 (188-348)	0.312
Laboratory values				
WBC [mil/m³]	7.26 (5-10.58)	6.78 (5.3-8.96)	7.02 (5.09-10.06)	0.531
Limph [x100/m³]	0.9 (0.6-1.3)	1.05 (0.74-1.32)	1.00 (0.69-1.32)	0.514
PLT [x100/m³]	213 (151-274)	233 (144-305)	221 (149-293)	0.616
AST [UI/L]	31 (23-58)	47 (24-73)	36 (23-66)	0.118
ALT [UI/L]	38 (23-47)	34 (24-46.5)	34 (23-47)	0.650
Ferritin [µg/L]	737 (329-1204.5)	773 (326-1257)	771 (326-1207)	0.646
IL-6 [ρg/mL]	46.2 (27.85-94.35)	36.2 (18.3-108)	45.4 (21.5-101)	0.647
Albumin [g/L]	27.05 (23.5-30)	30.75 (28.9-34.1)	28.95 (24.85-34.05)	0.065
Concomitant Pharmacotherapy (n, %)				
Corticosteroid	51/68 (75,0%)	29/34 (85,3%)	80/102 (78,4%)	0.233
Antibiotic	37/68 (54,4%)	22/34 (64,7%)	59/102 (57,8%)	0.321
Hydroxychloroquine	42/68 (61,8%)	19/34 (55,9%)	61/102 (59,8%)	0.568
Remdesivir	2/68 (2,9%)	3/34 (8,8%)	5/102 (4,9%)	0.195
Tocilizumab	37/68 (54,4%)	23/34 (67,6%)	60/102 (58,8%)	0.200

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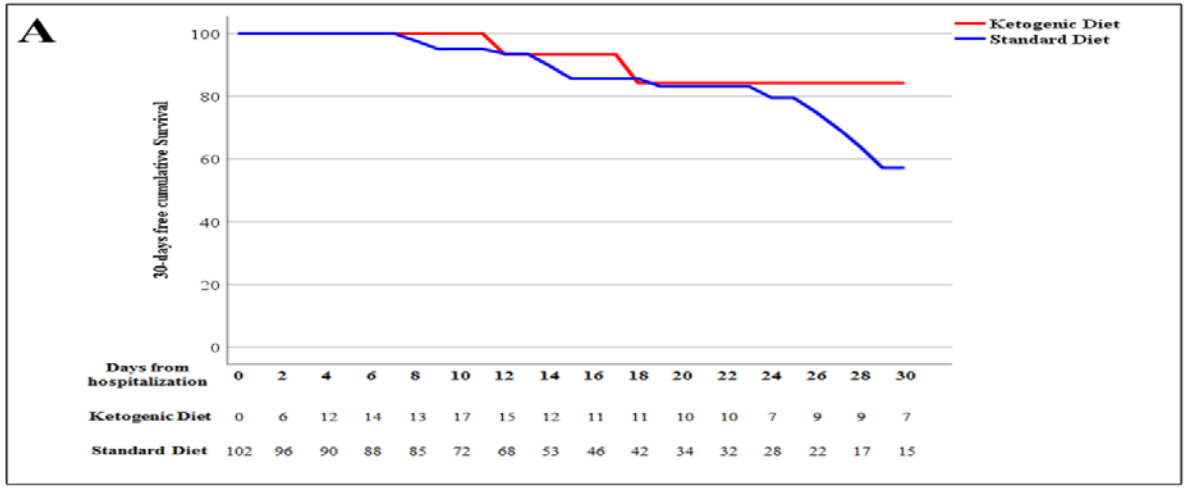
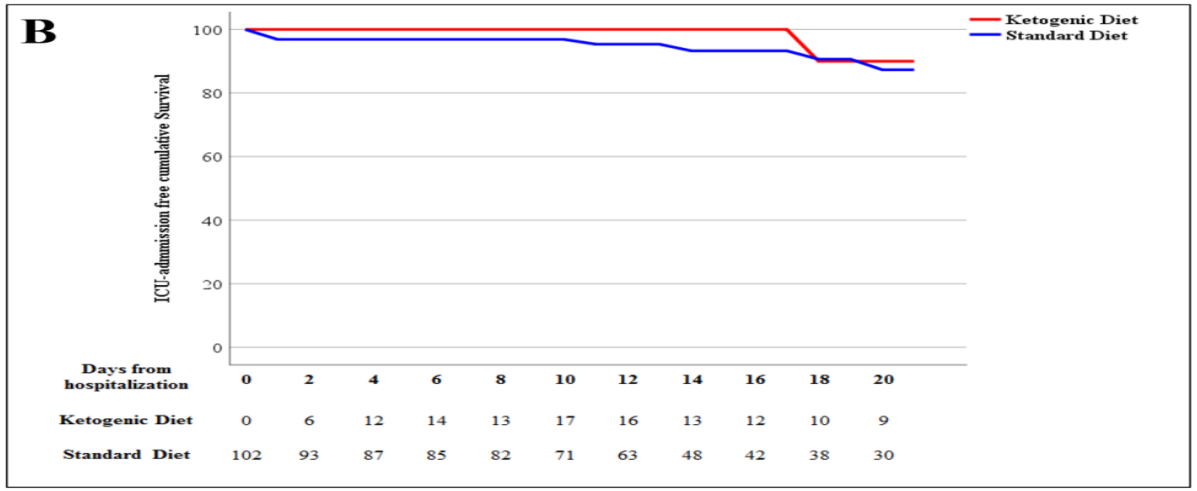
Hospitalization outcomes and complications in hospital of the patients after propensity score matched main analysis

30-day mortality (HR 0.416, 95% CI 0.122 – 1.413) (P = 0.160)

Admission in ICU (HR 0.357, 95% CI 0.045 – 2.847, P = 0.331)

Figure 2





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Variation of IL-6 before and after EKD

Delta IL-6 between t0 and t7	Controls, N (%)	Treated, N (%)
Increase	14 (58.3)	7 (30.4)
Decrease	10 (41.7)	16 (69.6)

Chisq = 3.698, df = 1, p-value = 0.05447
Data are median and IQR.
*p-value at Mann-Whitney U-Test

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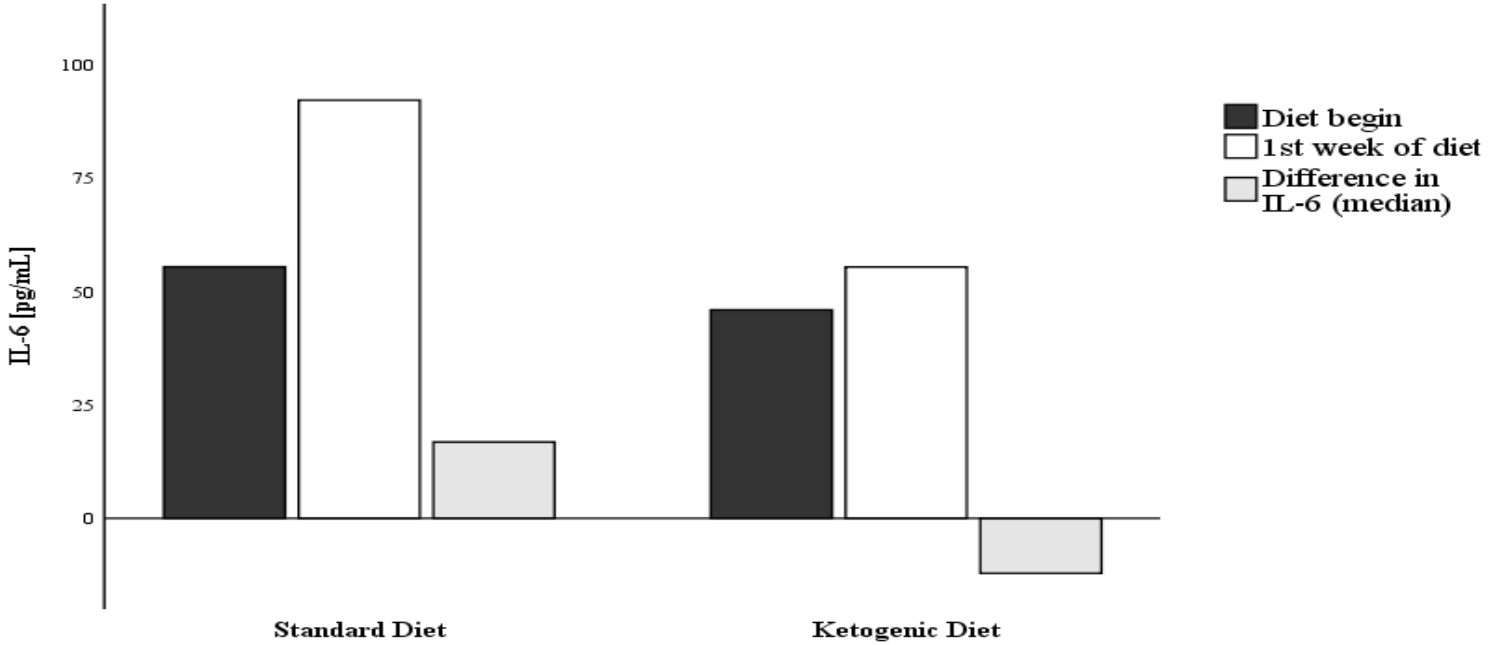
IL-6 values on time 0-7.



No statistically significant differences have been detected but a trend towards the significativity is observed.

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Covid e KD: preliminar conclusion

- EKD is possible alternative treatment to the disease, in the absence of side effects, additional costs or risks for the patient. Differently from other studies in which nutrition is considered a support to drug therapy, this study, firstly, underlines the role of clinical nutrition therapy as a pathophysiological support to drug therapy in improving the prognosis of COVID-19

KD in malattie autoimmuni e infettive: take home message

- L’effetto warburg rappresenta una risposta metabolica tipica di cellule immunitarie (Macrofagi, linf T, Cellule dendritiche) a stimoli diversi
- La dieta chetogenica e il B-OH-butirrato possono svolgere azione antiinfiammatoria mediante una immunomodulazione metabolica sul target della riprogrammazione immunitaria nelle patologie autoimmuni da linfociti citotossici (ad es. AR)
- in corso di COVID in particolare nei pazienti con infiammazione cronica (obesità, diabete, ipertensione) tale immunomodulazione può prevenire lo storm citochinico e migliorare la prognosi

KD in malattie autoimmuni e infettive: take home message

- La dieta chetogenica mediante una immunomodulazione metabolica sul target della riprogrammazione immunitaria a seguito di eventi patologici può rappresentare una terapia nella patologie autoimmuni e infettive oltre a rappresentare un modello preventivo o terapeutico alimentare

Grazie

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KDA
Ketogenic Diet
ACADEMY

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