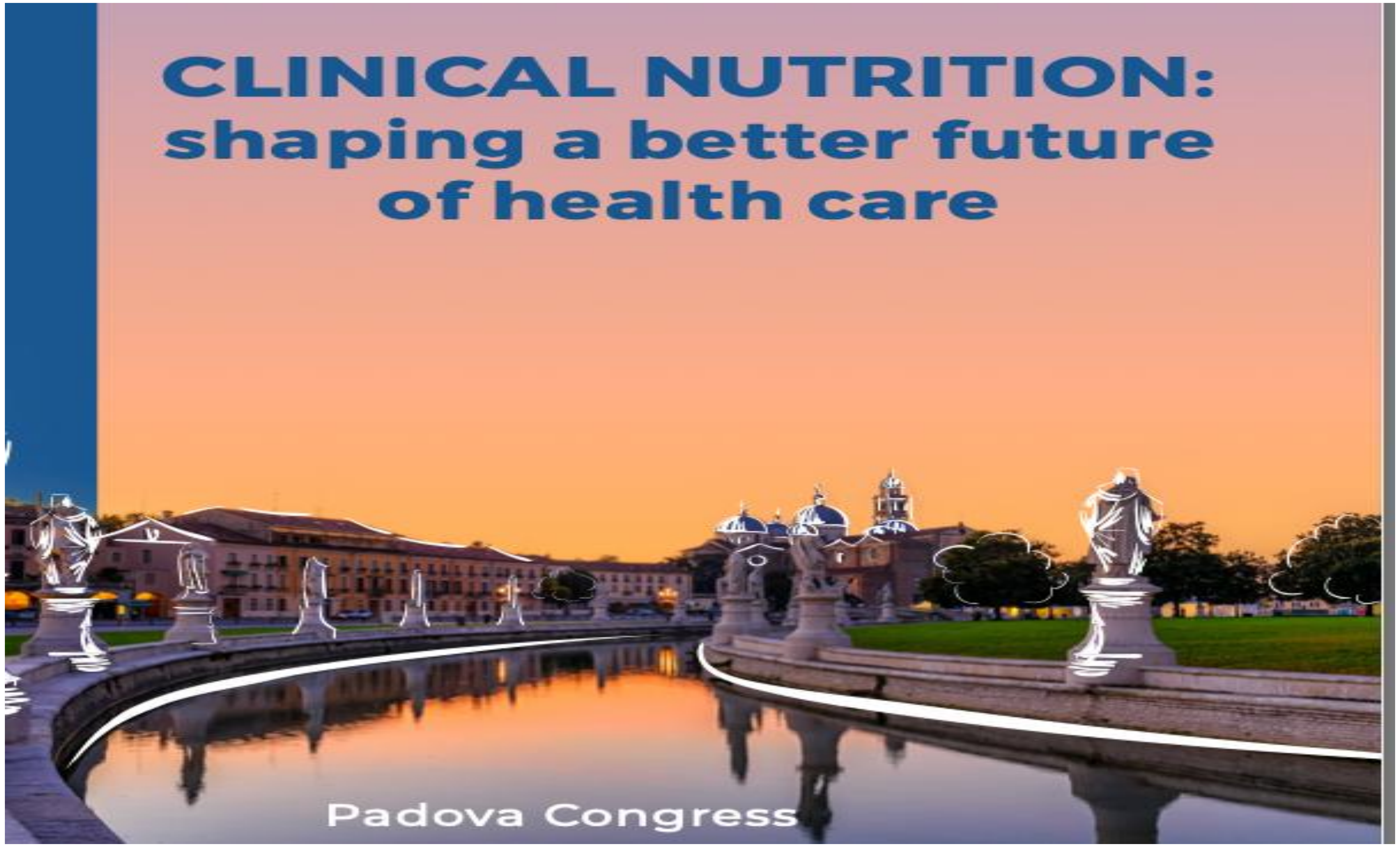
IL RUOLO DELLE RESOLVINE NELLA NUTRIZIONE ARTIFICIALE IN ICU



- *DR M.SCARCELLA. MD aPhD*
- *Intensive care Medicine*
- *Clinical Nutrition*
- *Researcher University Study of Perugia*

FAMILIES OF SPECIALIZED PRO RESOLVINE MEDIATORS –SPM

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Chem Rev. Author manuscript; available in PMC 2012 October 12.

Published in final edited form as:
Chem Rev. 2011 October 12; 111(10): 5922–5943. doi:10.1021/cr100396c.

Resolvins and Protectins in Inflammation-Resolution

Charles N. Serhan[†] and **Nicos A. Petasis**[‡]
Center for Experimental Therapeutics and Reperfusion Injury, Department of Anesthesiology, Perioperative and Pain Medicine, Harvard Institutes of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115, and Department of Chemistry and Loker Hydrocarbon Research Institute, LHI 219, University of Southern California, Los Angeles, CA 90089-1661

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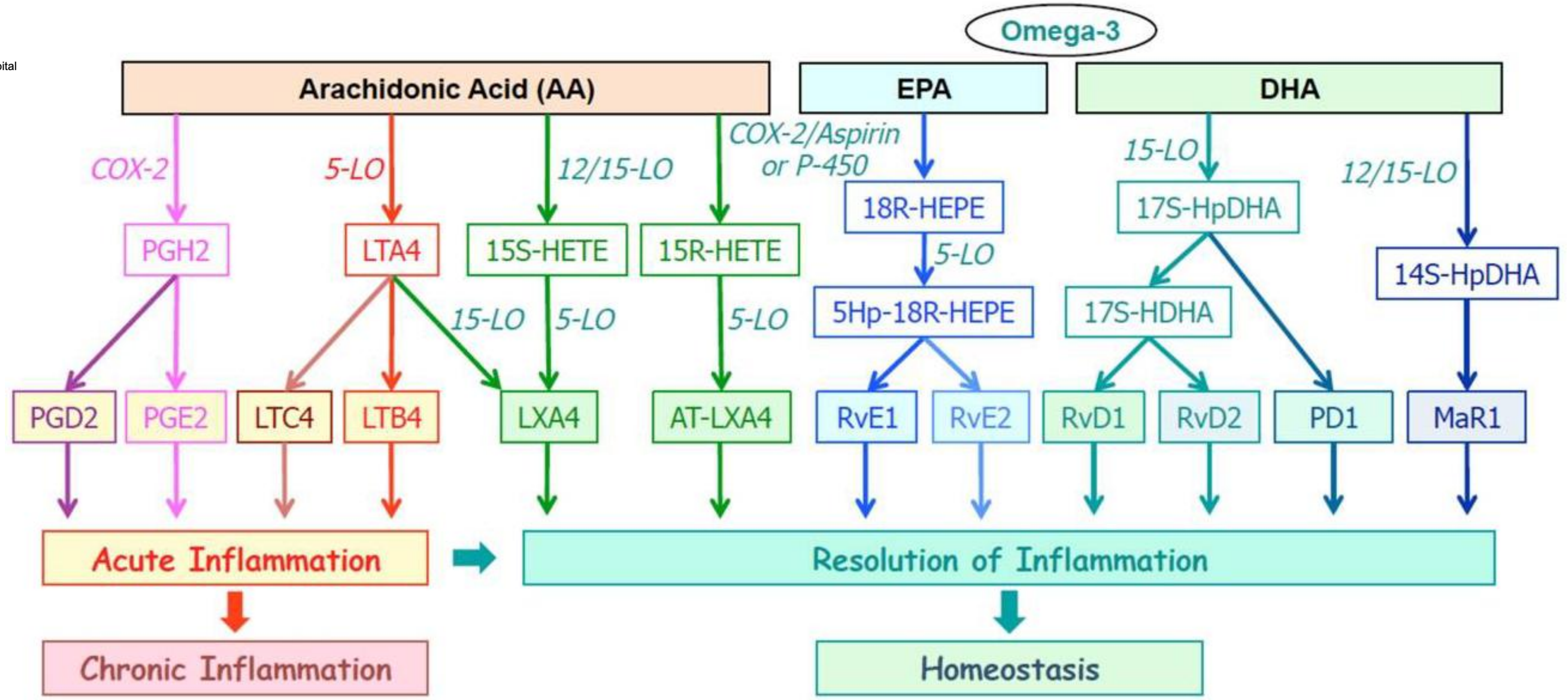
Biosynthetic cascades and actions of selected lipid mediators derived from arachidonic acid (AA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

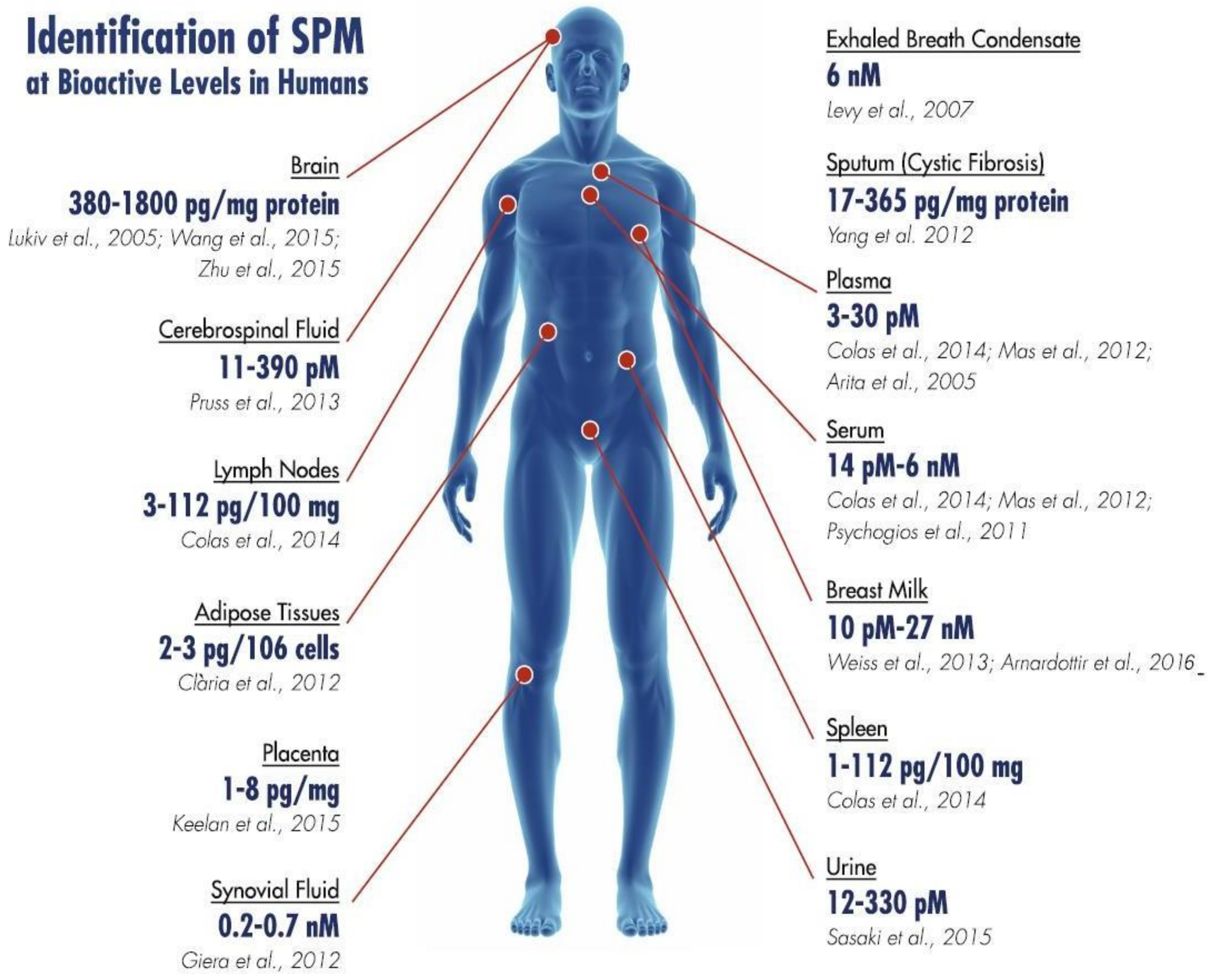


New classes of lipid mediators for regulating the resolution of inflammation derived from polyunsaturated fatty acids (PUFA)

Endogenously generated during inflammation

Potent anti-inflammatory actions and serve as *specialized pro-resolving lipid mediators (SPM)*

Promote the **resolution of inflammation.**



SPMs are *not* in diet, they are produced in-vivo from substrates primarily DHA and EPA

SPM = specialized pro-resolving mediator; EPA = eicosapentaeoic acid, DHA = docosahexaenoic acid

Serhan CN Molecular Aspects of Medicine 2017
Chiang N et al Essays in Biochemistry 2020
Serhan CN et al Seminars in Immunology 2022

A change in focus on inflammation: Inflammation's Stop Signals

Players in the endgame

An assortment of molecules shut down inflammation and promote tissue healing by targeting different cells.

Lipoxins
Lipids whose jobs include stimulating macrophages and preventing neutrophils from slipping between endothelial cells to enter damaged tissue.

Resolvins
Family of lipids that block neutrophils' exit from the bloodstream and prod macrophages to eat cellular debris.

Maresins
Made by macrophages, lipids that spur tissue repair and act on nerves to ease pain.

Protectins
Lipids that curtail release of inflammation-promoting molecules and are protective in the nervous system.

Annexin A1
A protein released by dying neutrophils, its functions include preventing other neutrophils from entering the injured site.

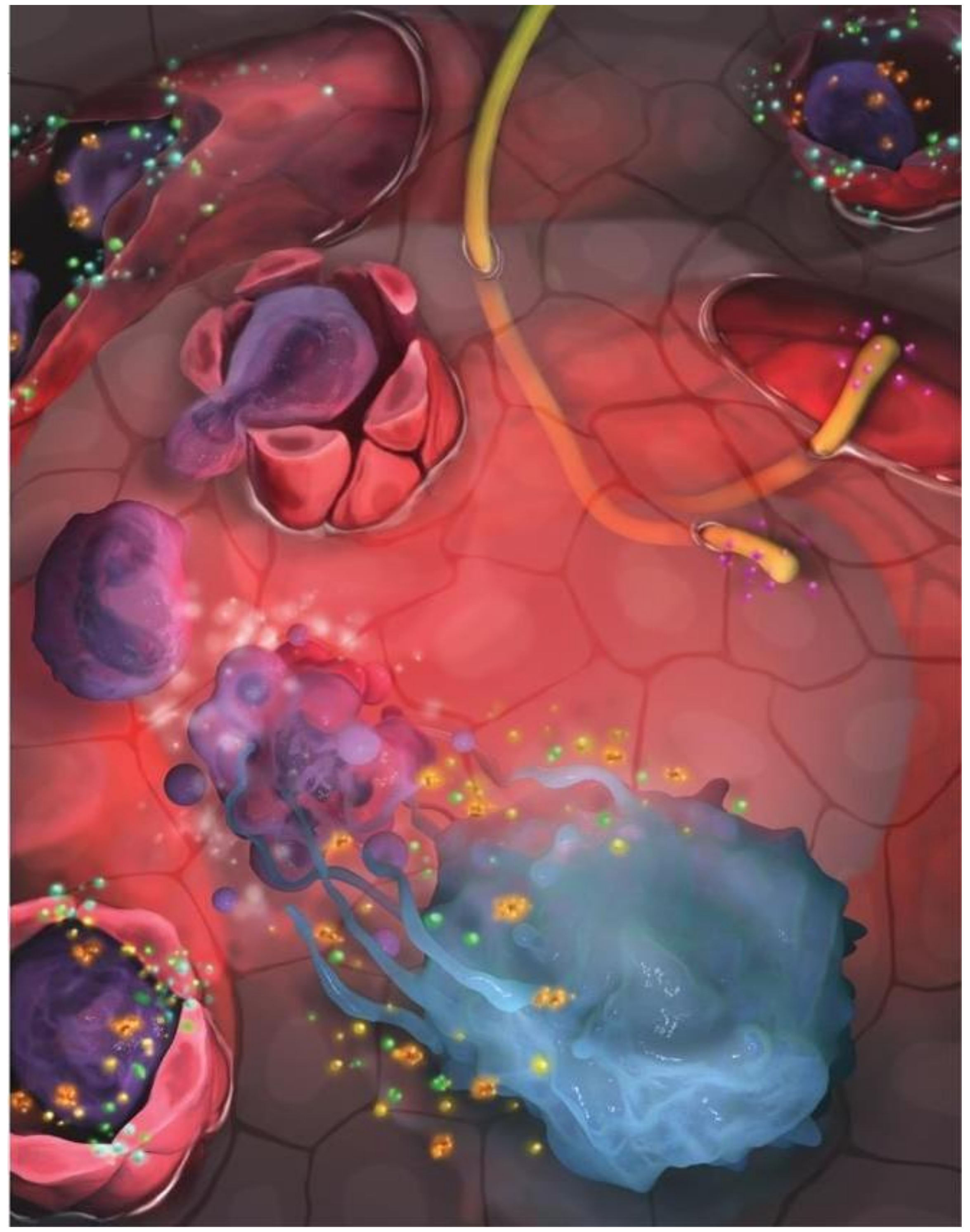
Hydrogen sulfide
Message-carrying gas that reduces pain and stimulates neutrophils to commit suicide.

Macrophages
After clearing an infection, these immune cells consume proinflammatory cellular remains.

Neutrophils
First responders to wounds and infections, they release inflammatory cytokines.

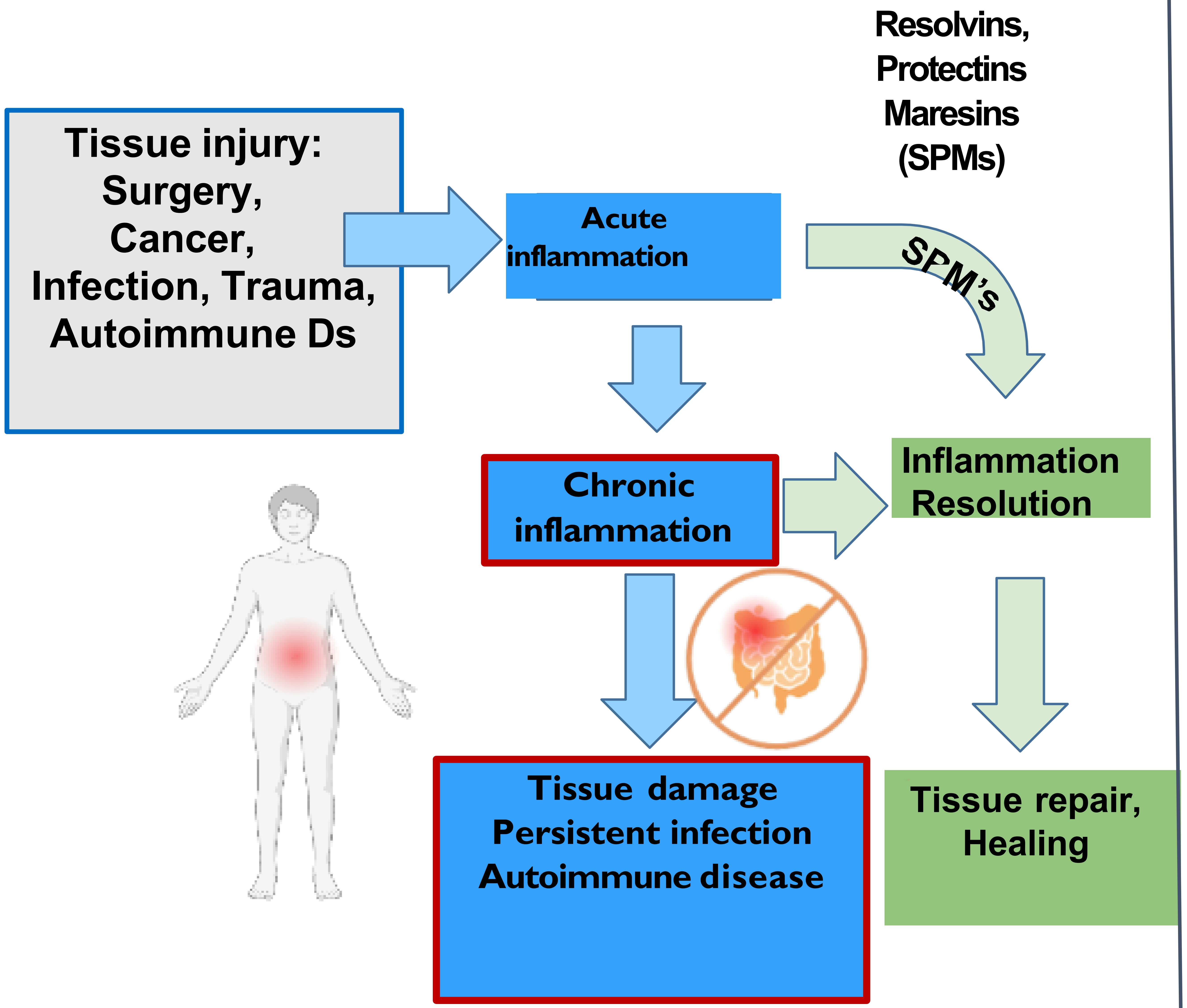
Endothelial cells
These cells form the walls of blood vessels and make H_2S.

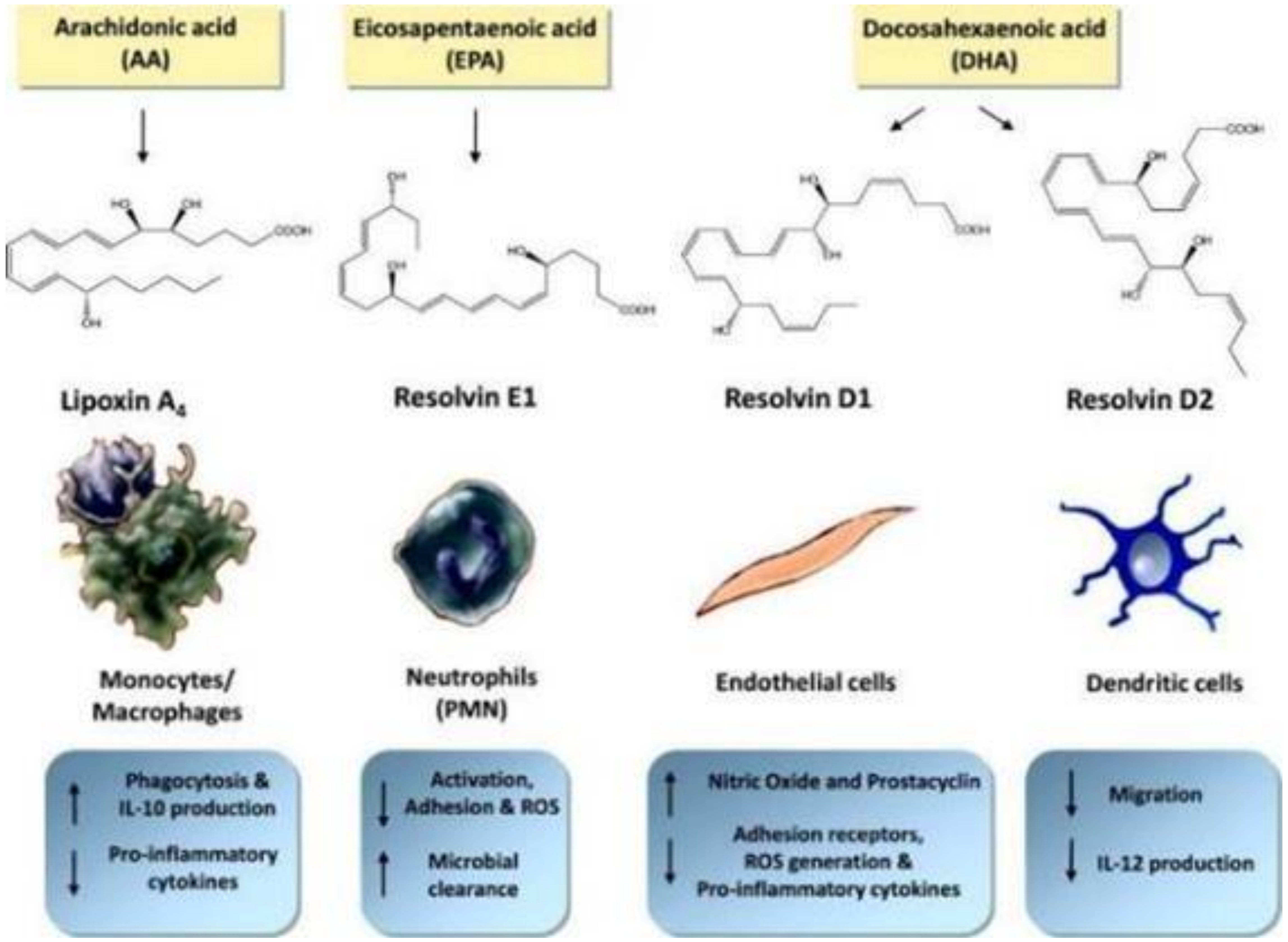
Nerves
Inflammatory molecules trigger nerve cells, creating pain and itchiness.



ILLUSTRATIONS: V. ALTOUNIAN/*SCIENCE*

Science 2015 – Charlie Serhan





Serhan CN, Levy BD. J Clinical Investigations 2018
Chiang N et al Essays in Biochem 2020

SPM = specialized pro-resolving mediator; IL-10 = interleukin 10; ROS = reactive oxygen species;
PMN = polymorphonuclear

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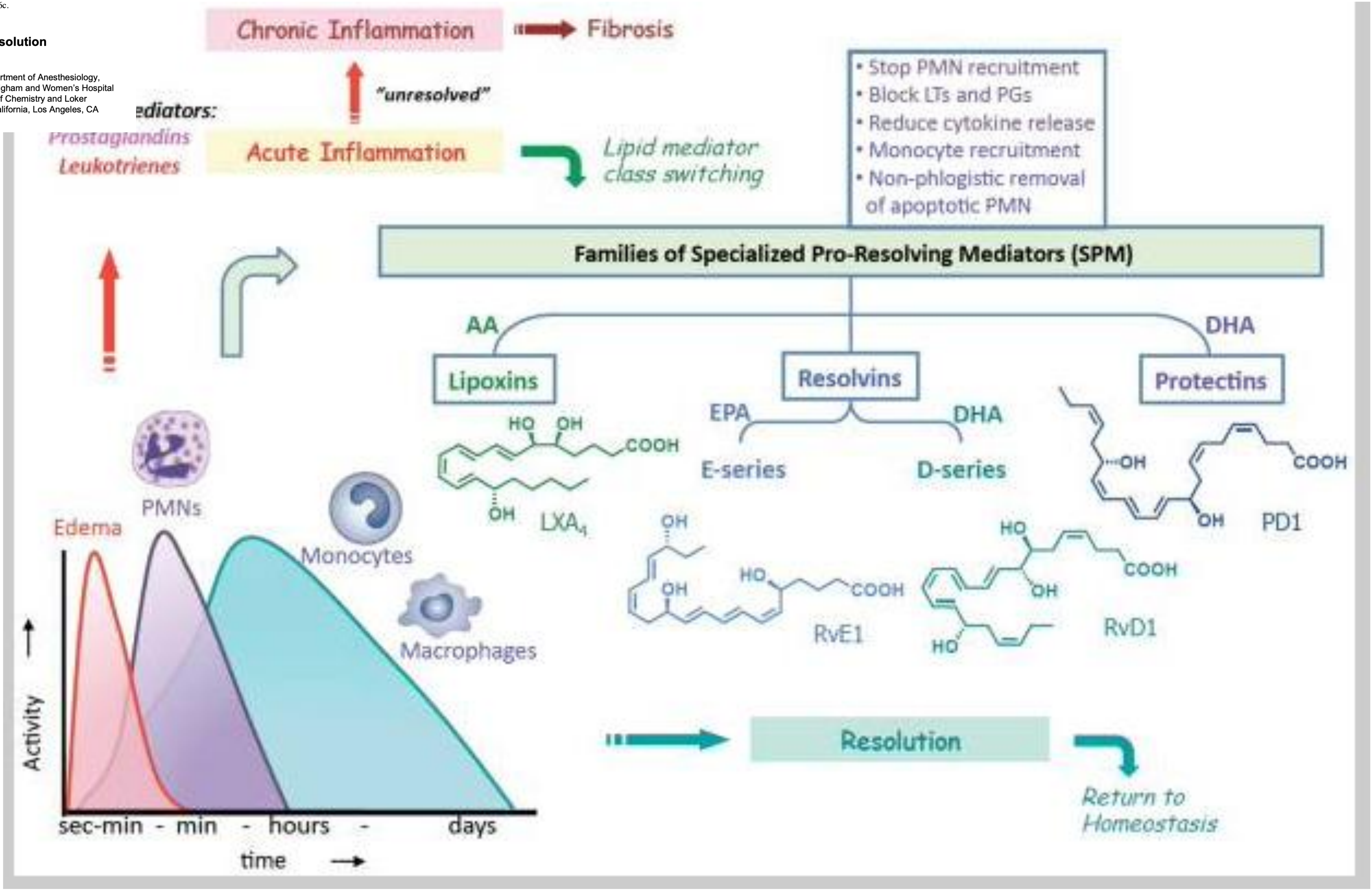
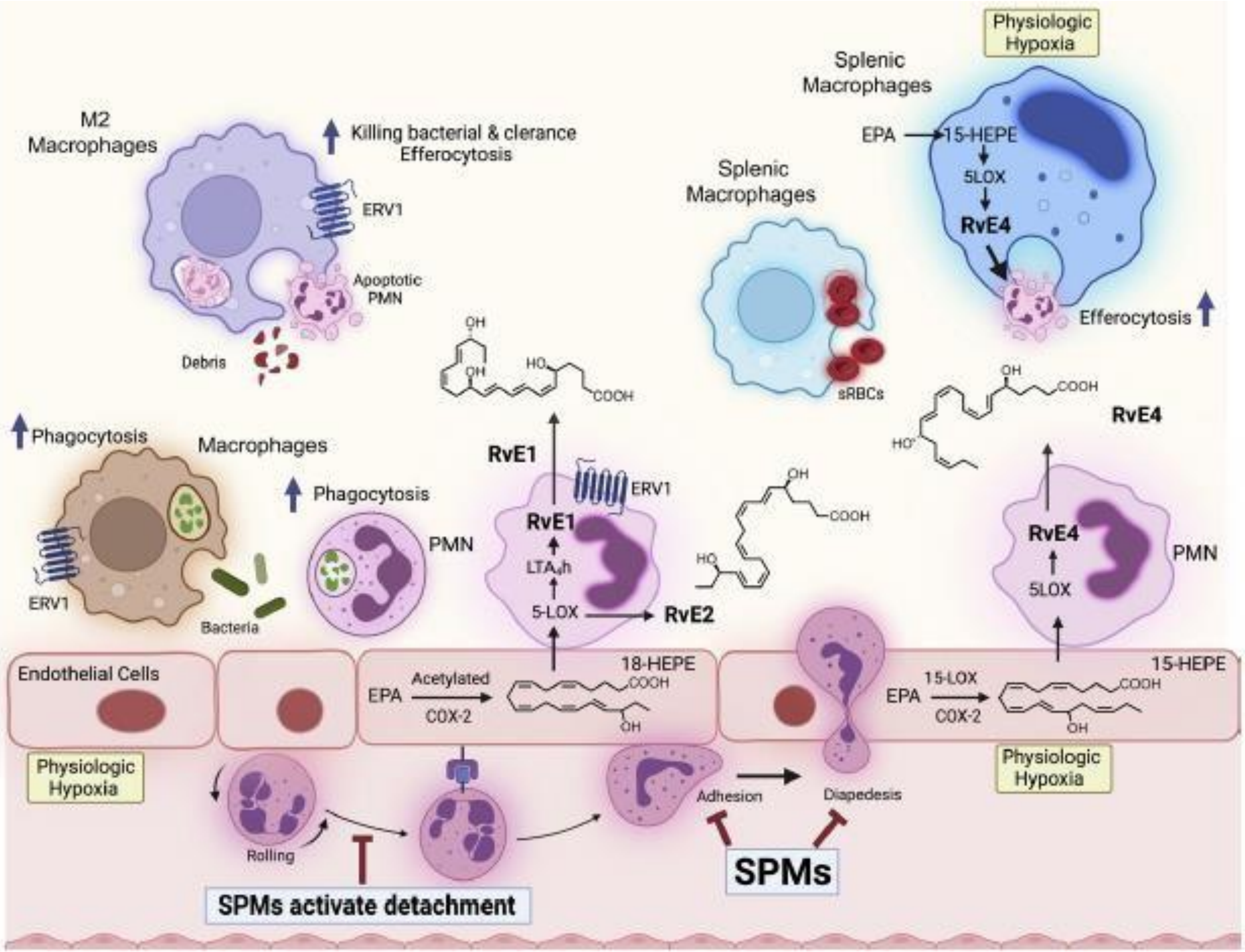


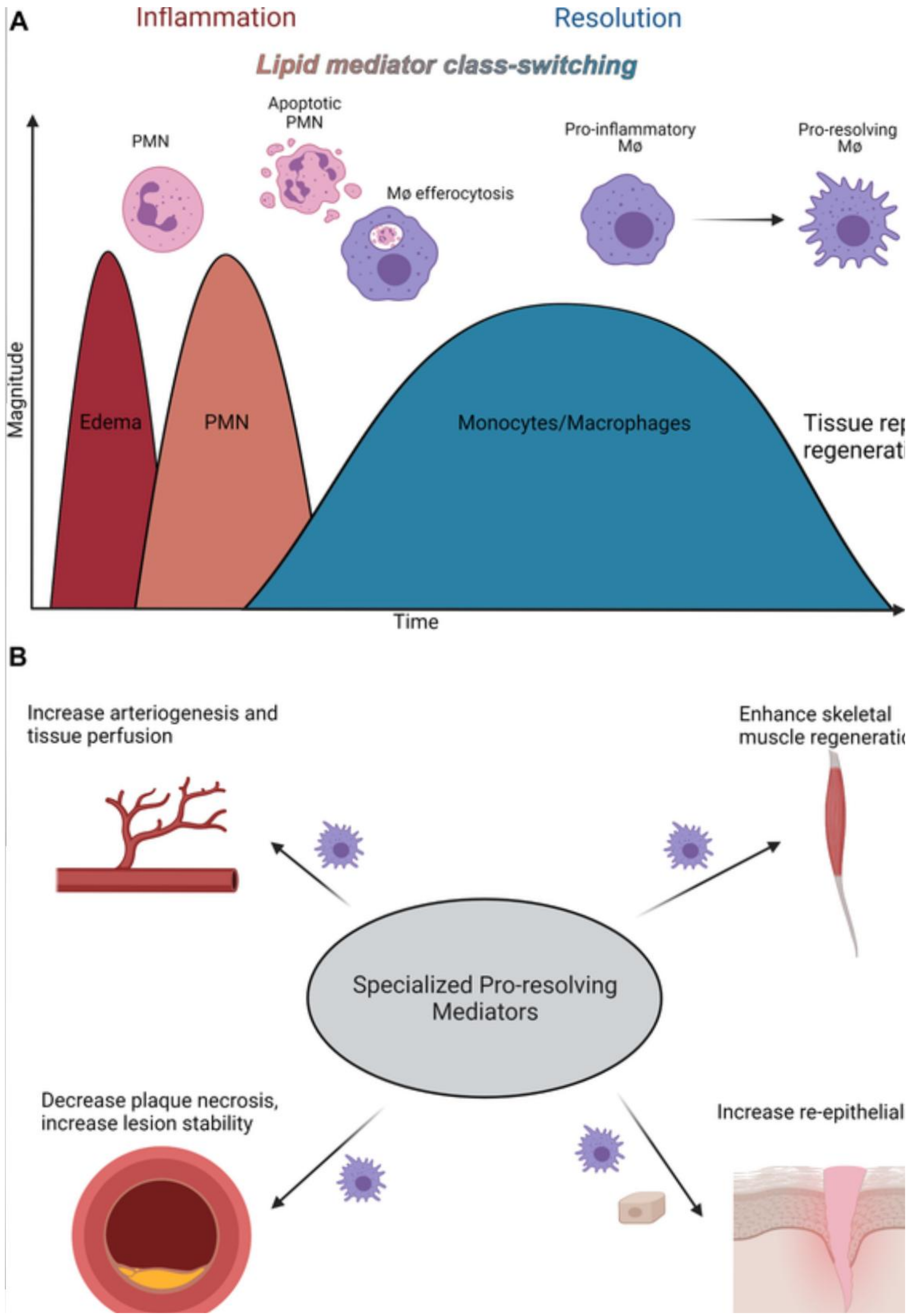
Multiple Mechanisms:
Actions on multiple cell types, at multiple levels of inflammatory cascade which initiate resolution

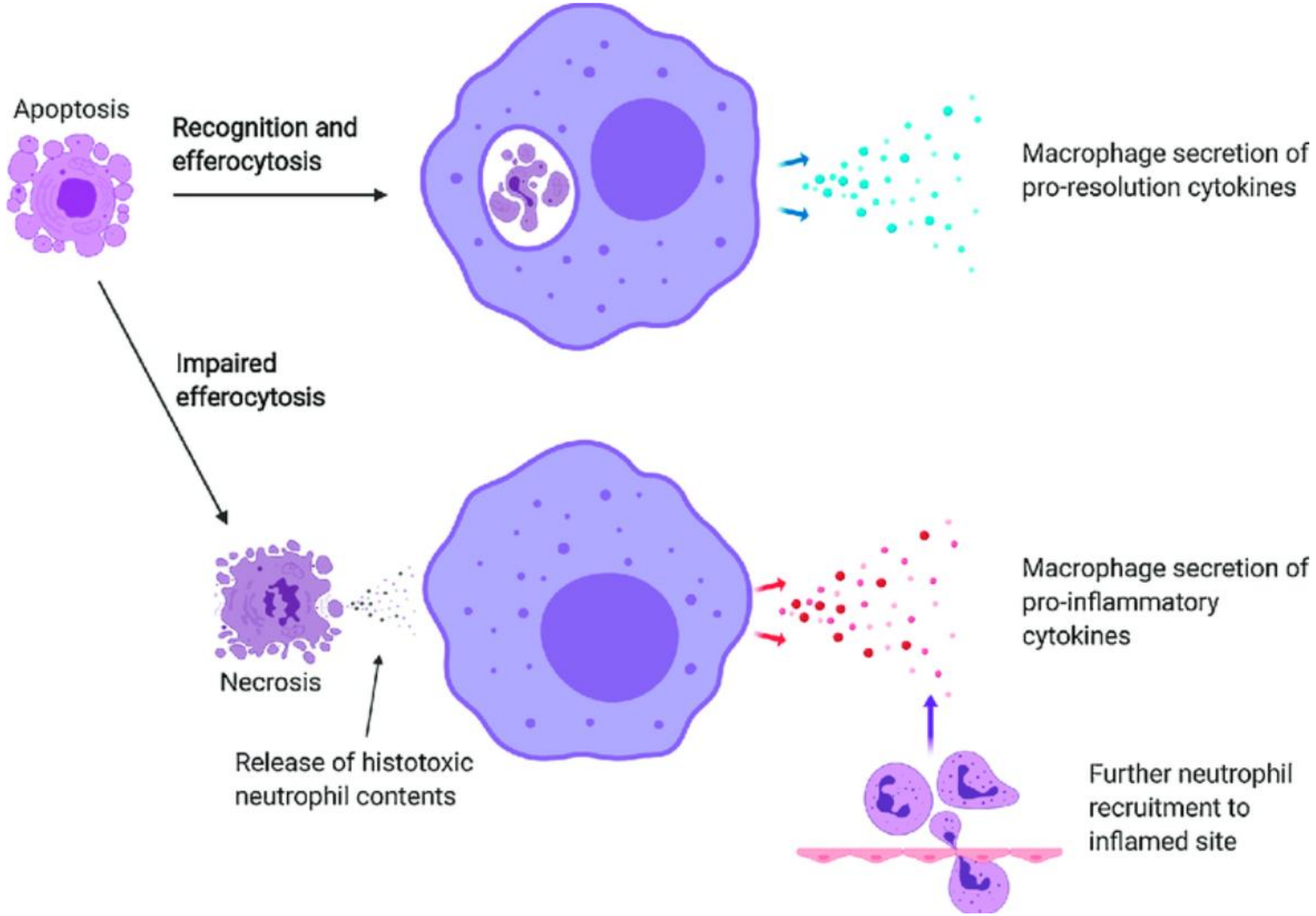


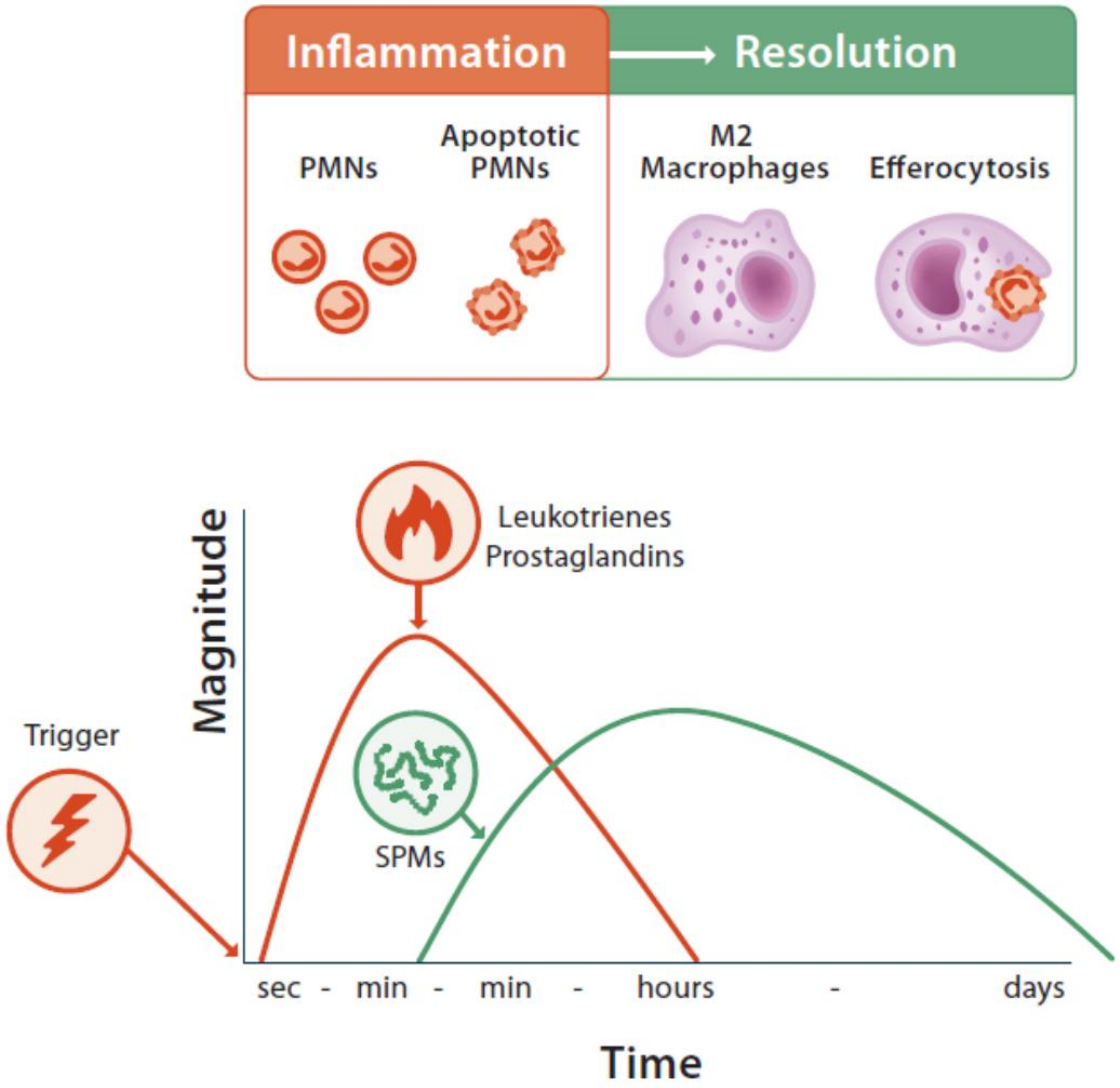
Efferocytosis is the process by which apoptotic cells are removed by phagocytic cells. It can be regarded as the 'burying of dead cells'

Serhan CN et al Seminars in Immunology 2022

SPM = specialized pro-resolving mediator; EPA = eicosapentaenoic acid; PMN = polymorphonuclear; Rv = resolvin; HEPE = hydroyeicosapentaenoic acid; ERV = endogeneous retrovirus, COX-2 = cacyloxygenase-2


A
Inflammation
Resolution
Lipid mediator class-switching
PMN
Apoptotic PMN
Mø efferocytosis
Pro-inflammatory Mø
Pro-resolving Mø
Magnitude
Edema
PMN
Monocytes/Macrophages
Time
B
Increase arteriogenesis and tissue perfusion
Specialized Pro-resolving Mediators
Decrease plaque necrosis, increase lesion stability


Apoptosis
Recognition and efferocytosis
Macrophage secretion of pro-resolution cytokines
Impaired efferocytosis
Necrosis
Release of histotoxic neutrophil contents
Macrophage secretion of pro-inflammatory cytokines
Further neutrophil recruitment to inflamed site



▸ Nature. Author manuscript; available in PMC: 2014 Dec 11.

Published in final edited form as: Nature. 2014 Jun 5;510(7503):92–101. doi: 10.1038/nature13479

Novel Pro-Resolving Lipid Mediators in Inflammation Are Leads for Resolution Physiology

Charles N Serhan [1]

▸ Author information

▸ Copyright and License information

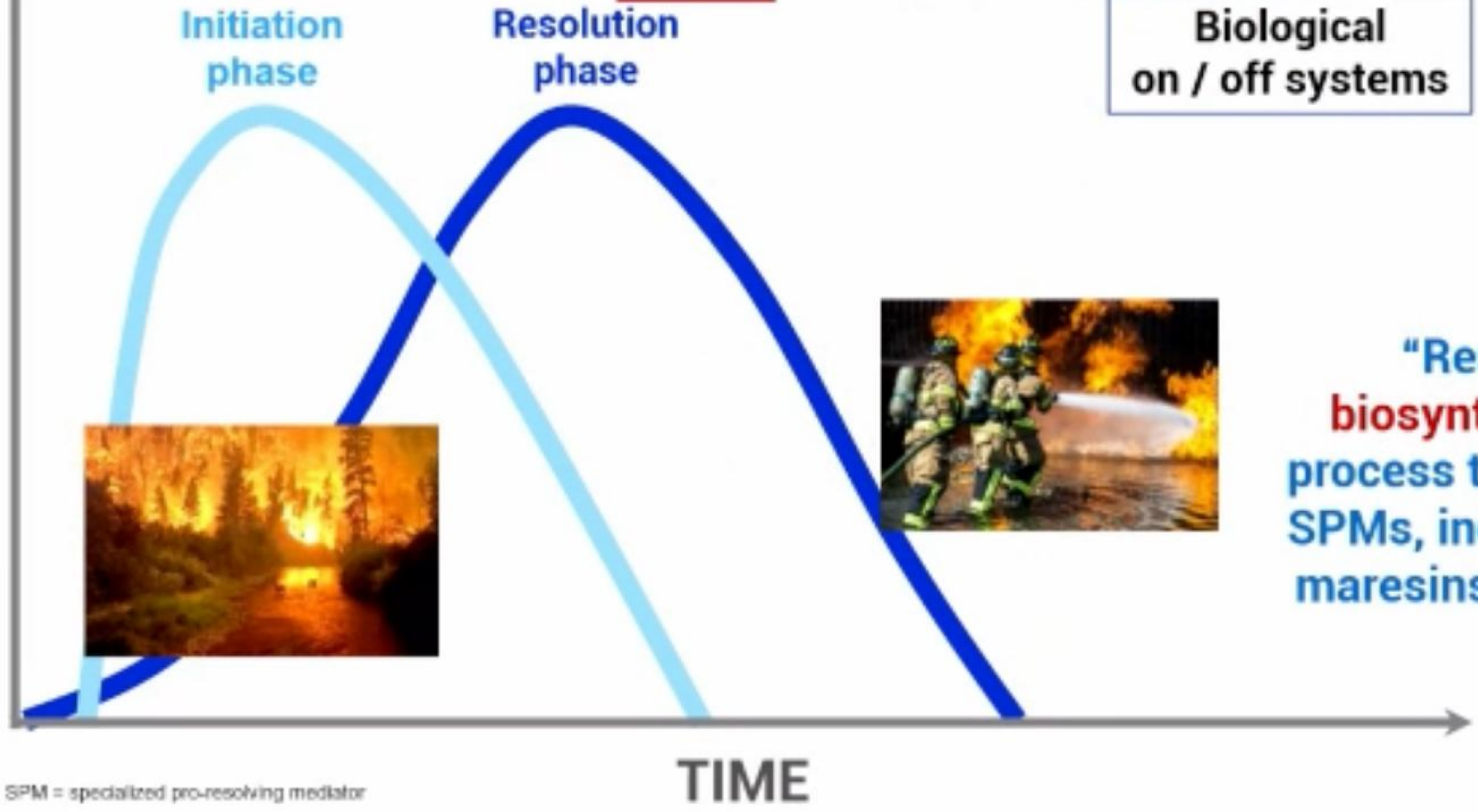
PMCID: PMC4263681 NIHMSID: NIHMS646633 PMID: 24899309

Acute Chronic inflammation

ARDS
Chronic Critical Illness
Cirrhosis
Valvular heart disease
Atherosclerosis
Rheumatoid arthritis
Periodontal disease
PICS

INFLAMMATION HAS TWO PHASES:

INITIATION AND RESOLUTION



Charlie Serhan

"Resolution is a biosynthetically active process that is initiated by SPMs, including resolvins, maresins, and protectins"

SPM = specialized pro-resolving mediator

Adapted with permission from Dr. Martindale

Progress in Lipid Research 64 (2016) 30–56

Contents lists available at ScienceDirect

Progress in Lipid Research

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

Metabolism and functional effects of plant-derived omega-3 fatty acids in humans

Ella J. Baker [a], Elizabeth A. Miles [a], Graham C. Burdge [a], Parveen Yaqoob [b], Philip C. Calder [a,c,*]

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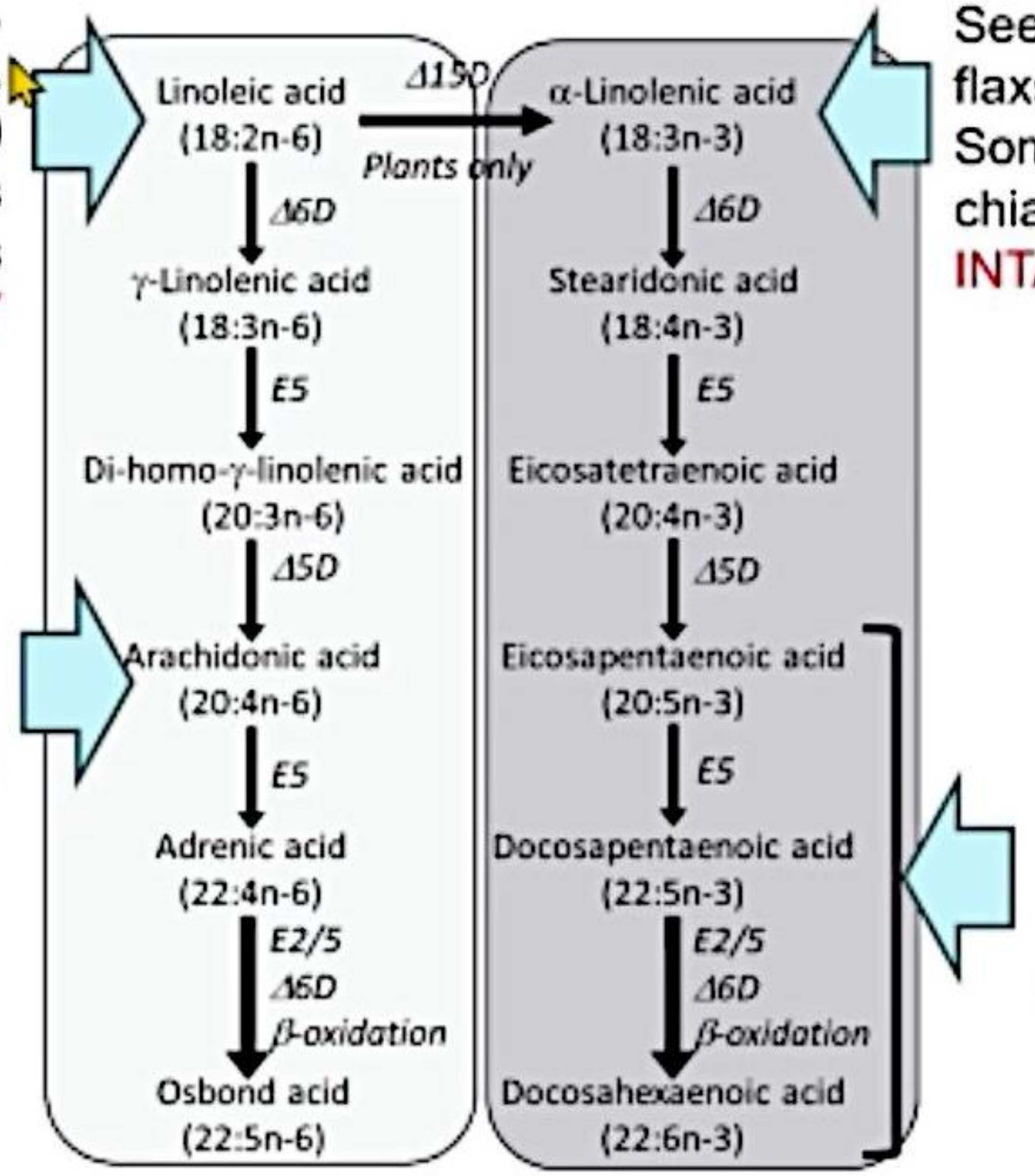
Polyunsaturated fatty acids: Dietary sources & intakes

Seed oils (Corn, sunflower, safflower, soybean)
Margarines
Grains
INTAKE 10 TO 20 G/DAY

Meat (esp. Red meat)
Eggs
Organ meats (Liver, kidney)
INTAKE: 250 to 500 MG/DAY



Seed oils (Soybean, flaxseed)
Some seeds (Flaxseed, chia) and nuts (Walnuts)
INTAKE 1 to 2 G/DAY

Fish (esp. Fatty fish)
"Fish oil" supplements
Algae and algal oils
INTAKE < 200 MG/DAY

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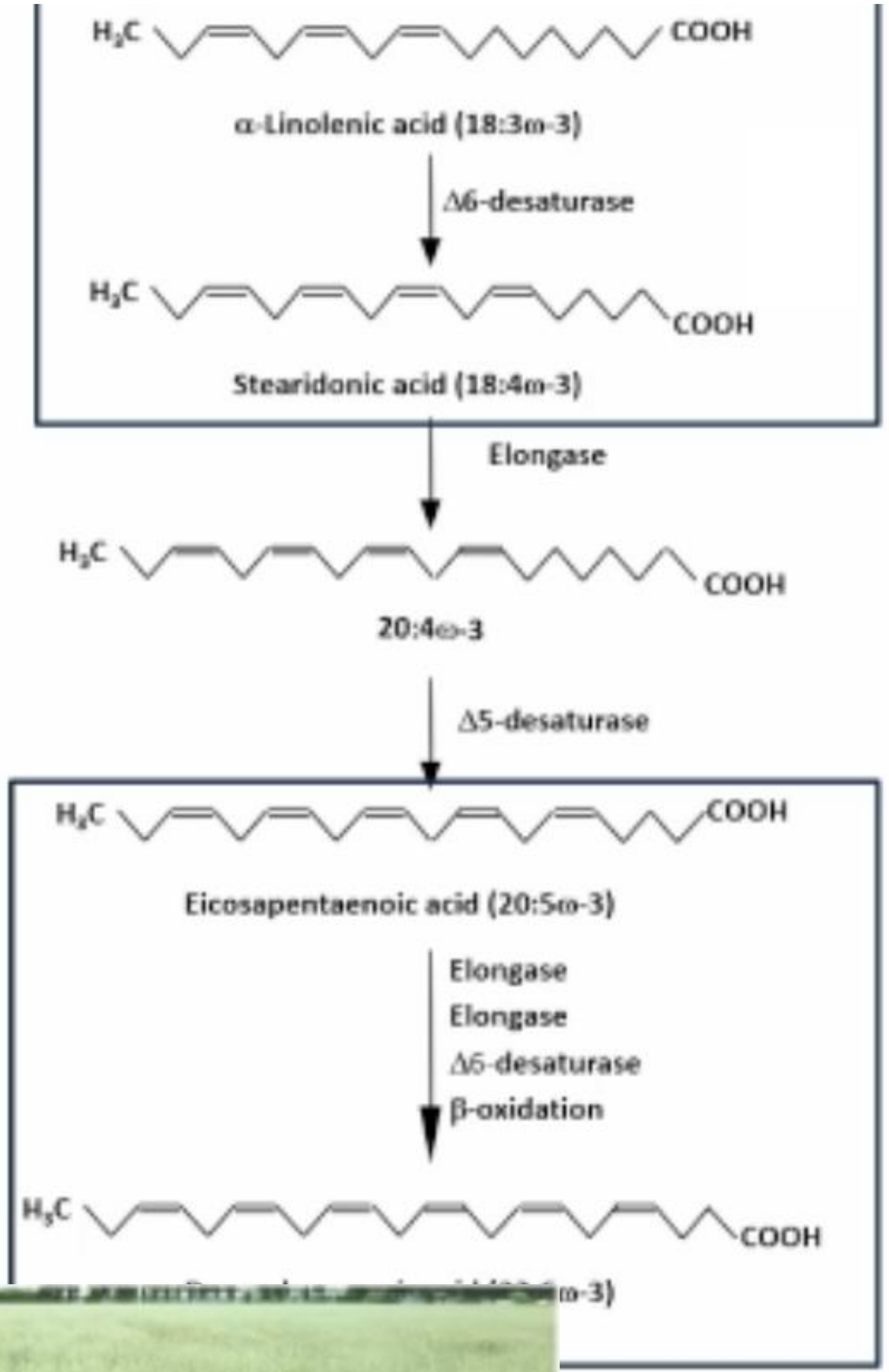

From plants

From fish and other seafood, "fish oils", other marine sources

Non-fish: Algae and algal oils, GM Camelina

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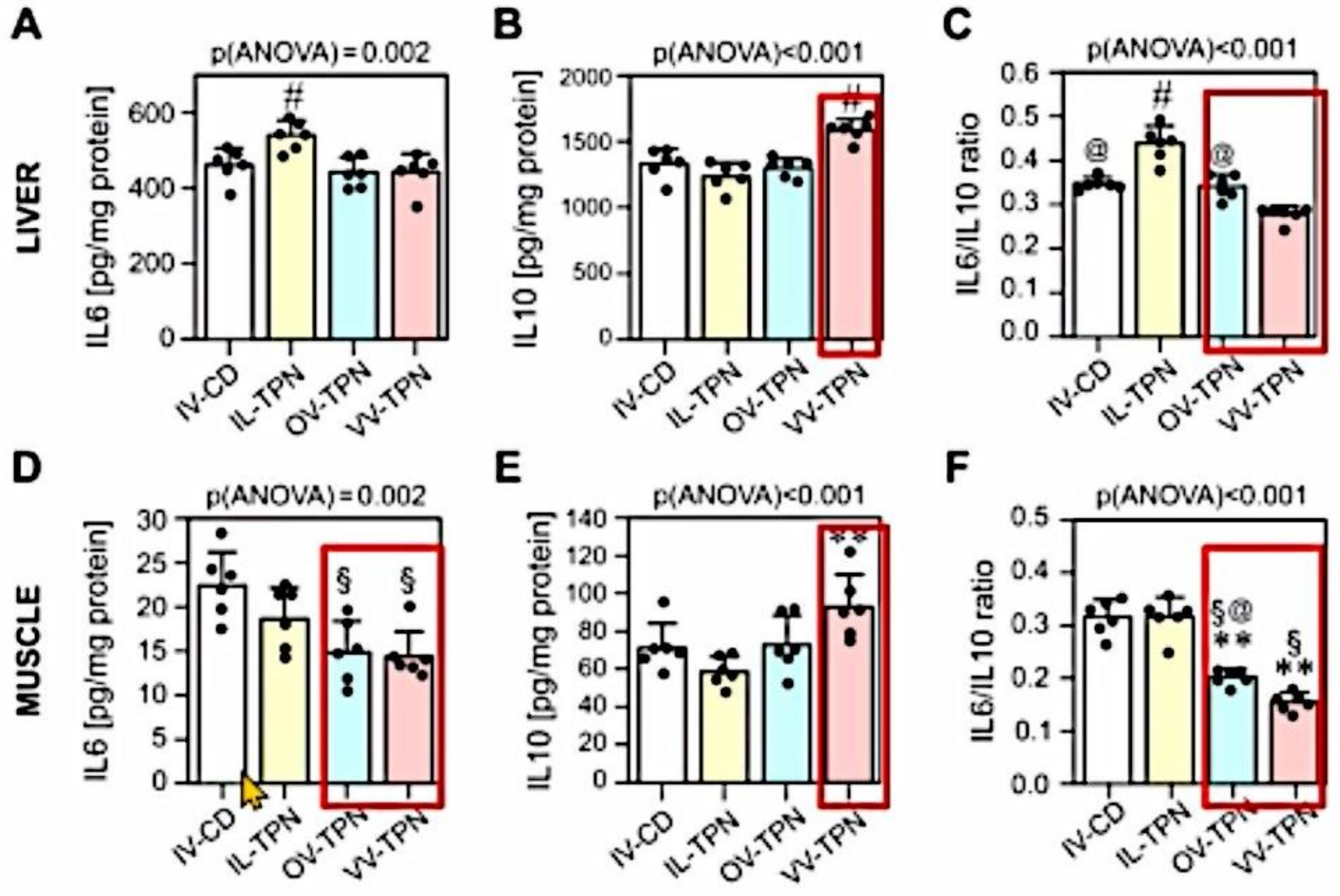
Ella J. Baker [a], Elizabeth A. Miles [a], Graham C. Burdge [a], Parveen Yaqoob [b], Philip C. Calder [a,c,*]

Fish oil and Ahiflower oil both promote a less inflammatory cytokine profile than Soybean oil



Ahiflower oil supplements increase EPA in human red blood cells and plasma

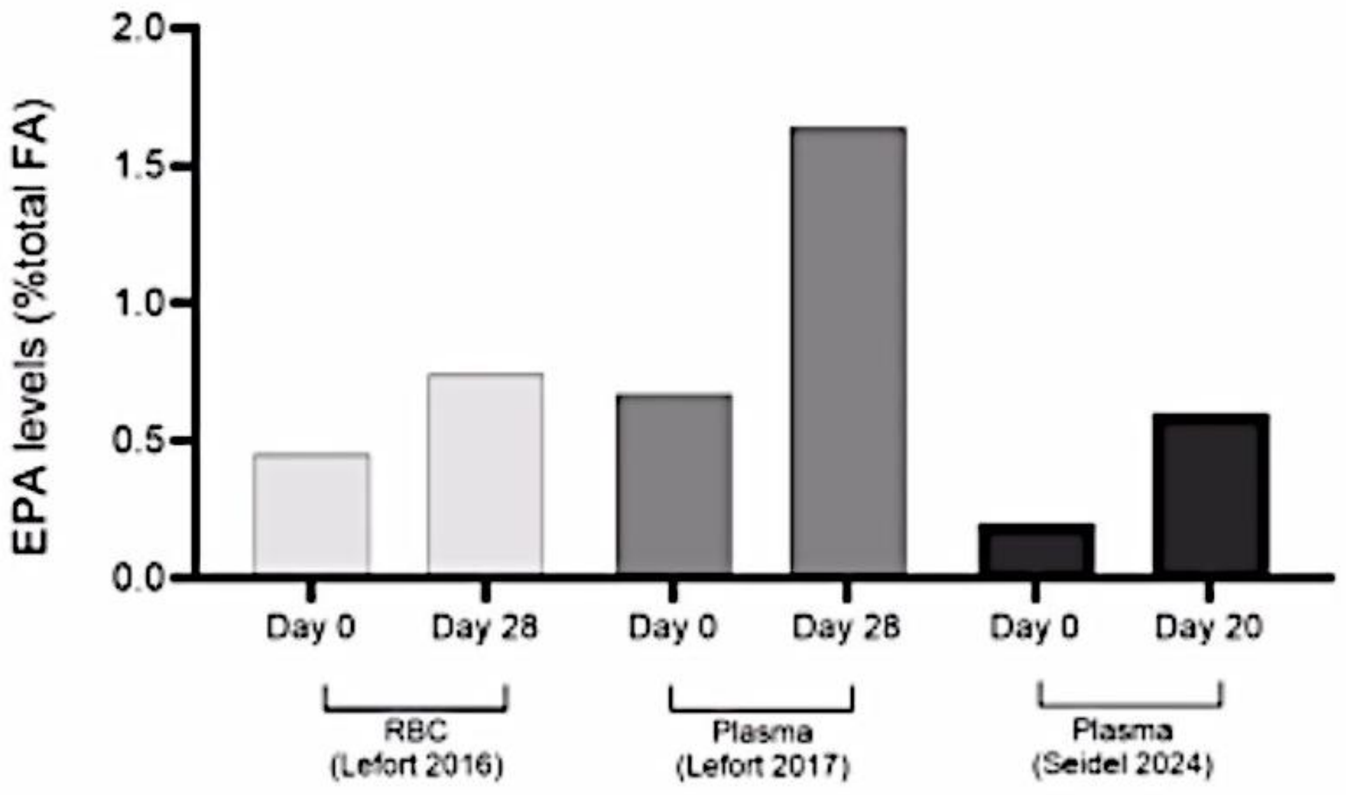
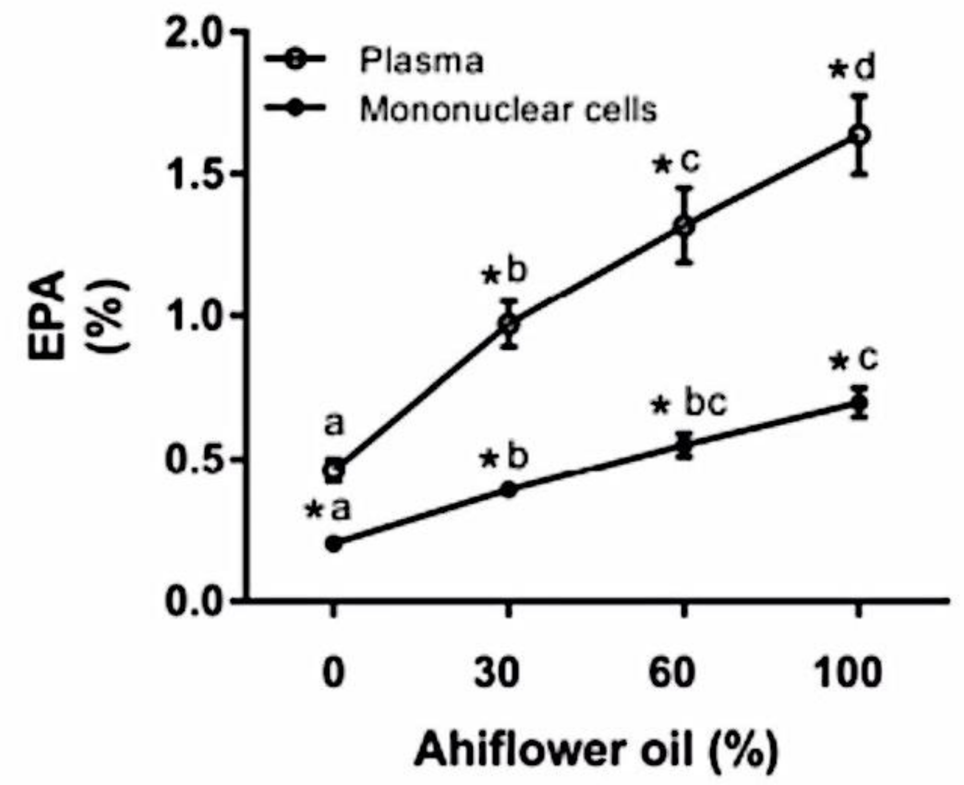


FIGURE 2 | Circulating EPA accrual from *Buglossoides arvensis* oil consumption in humans. Data taken from (Seidel et al. 2024; Lefort et al. 2016, 2017).

Baker et al. (2025) Lipids, in press

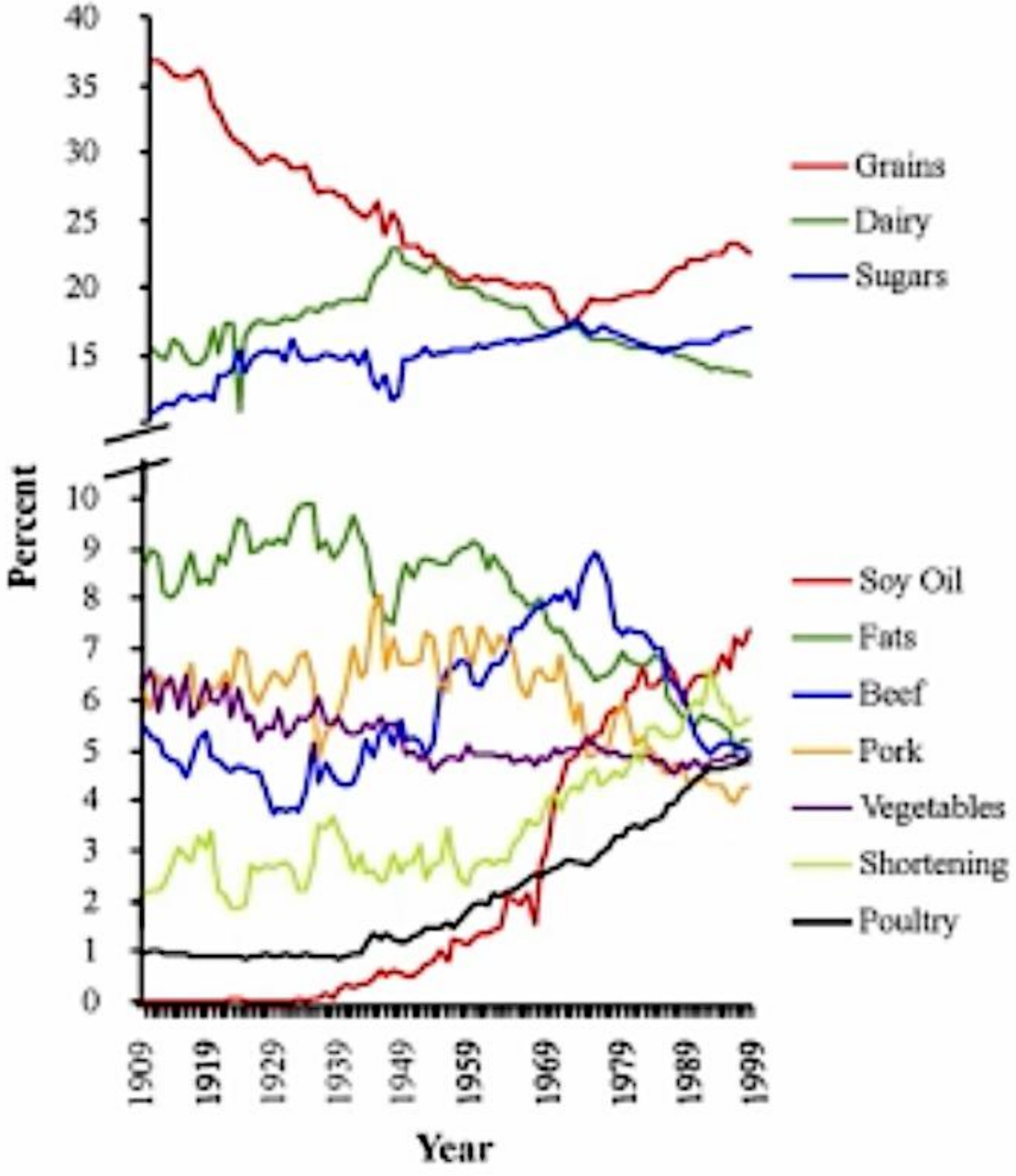
Increment in EPA in human plasma, white cells (and red cells) is dose dependent

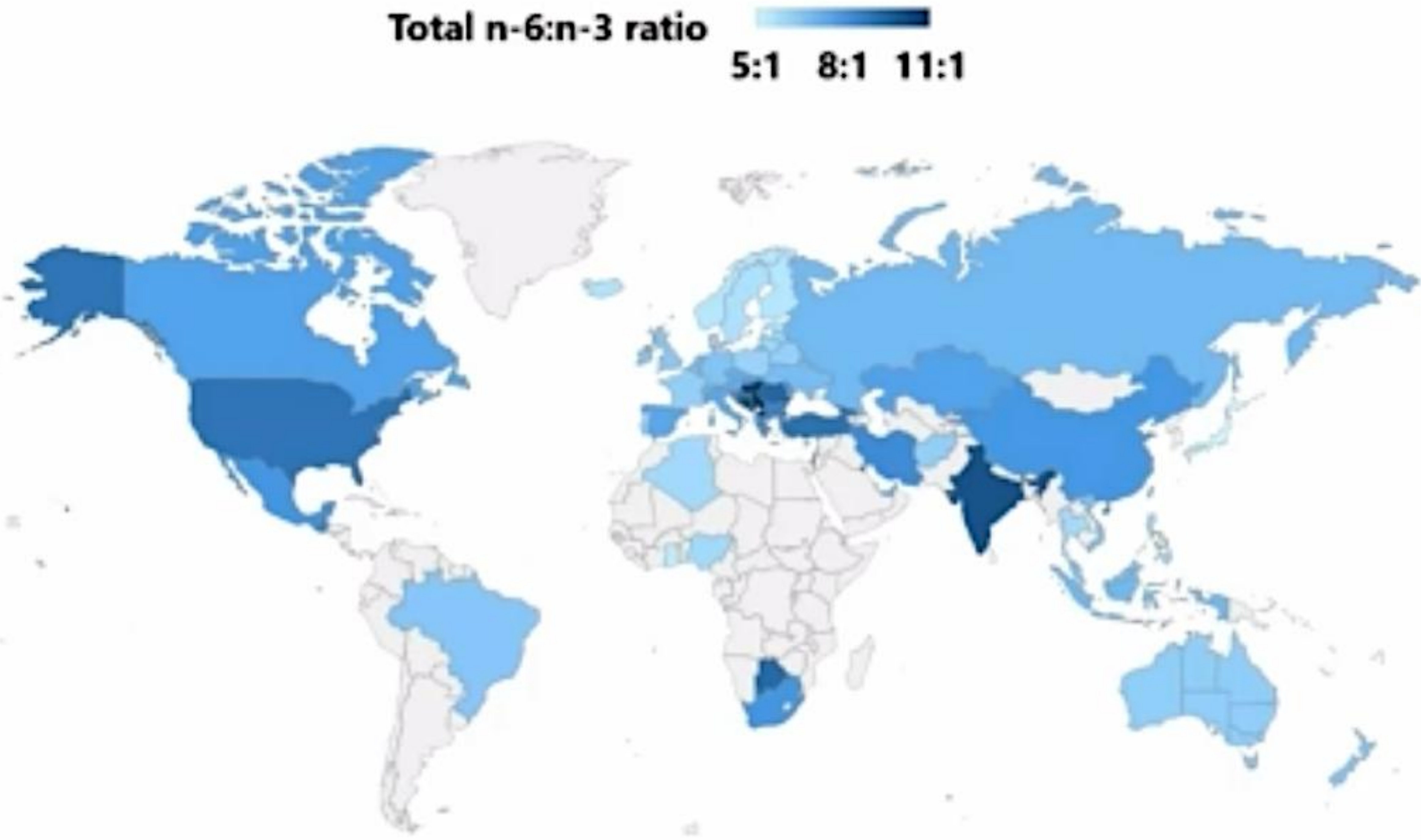


Lefort et al. (2017) Nutrients 9, 261

BACKGROUND
CURRENT DIET

- Significant increase in omega-6 to omega-3 ratio





Blasbalg TL et. al. The American Journal of Clinical Nutrition. 2011;93(5):950-962.
Torrissen M, et al. *Lipids Health Dis.* 2025;24:260.
Simopoulos AP. Biomed Pharmacotherapy 2002

BACKGROUND
CURRENT ENTERAL FORMULAS

- Current formulas with omega-6 to omega-3 ratio of 10:1 to 20:1
- Examined serum from 50 home enteral nutrition patients for at least 1 yr.

	High n-6/n-3	Intermediate n-6/n-3	Low n-6/n-3	EPA + DHA-containing
	Receiving formula with high n-6/n-3 ratio	Receiving formula with moderate n-6/n-3 ratio	Receiving formula with low n-6/n-3 ratio	Receiving formula containing EPA and DHA with low n-6/n-3 ratio
Summary of patient profile				
n	12	8	13	17
Male/female	7/5	4/4	8/5	11/6
Age (years)	30 ± 11	18 ± 14	22 ± 19	31 ± 16
Caloric intake (kcal/kg)	33 ± 8	38 ± 26	39 ± 29	32 ± 11
Composition of enteral nutrition				
**n*	4/8	3/5	7/6	17
Energy composition (% of energy)				
Protein	16/14.1	12/19	18/18	20
Total fat	28/31.5	39/27	20/23.4	25
Carbonhydrate	56/54.5	49/54	62/58.8	55
Fatty acid composition (mg/100 kcal)				
LA (18 : 2n-6)	956/1992.3	1458/1533	450/616	690
ALA (18 : 3n-3)	28/45.8	166/171	150/156	154
EPA (20 : 5n-3)	—	—	—	8
DHA (22 : 6n-3)	—	—	—	28
n-6/n-3 ratio	34/44	8.79/8.96	3.0/3.94	3.6

Munakata M, Nishikawa M, Togashi N, et al. The Nutrient Formula Containing Eicosapentaenoic Acid and Docosahexaenoic Acid Benefits the Fatty Acid Status of Patients Receiving Long-Term Enteral Nutrition. *Tohoku J Exp Med.* 2009;217(1):23-28

Journal of Inflammation Research

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REVIEW

Inflammatory Response and Anti-Inflammatory Treatment in Persistent Inflammation-Immunosuppression-Catabolism Syndrome (PICS)

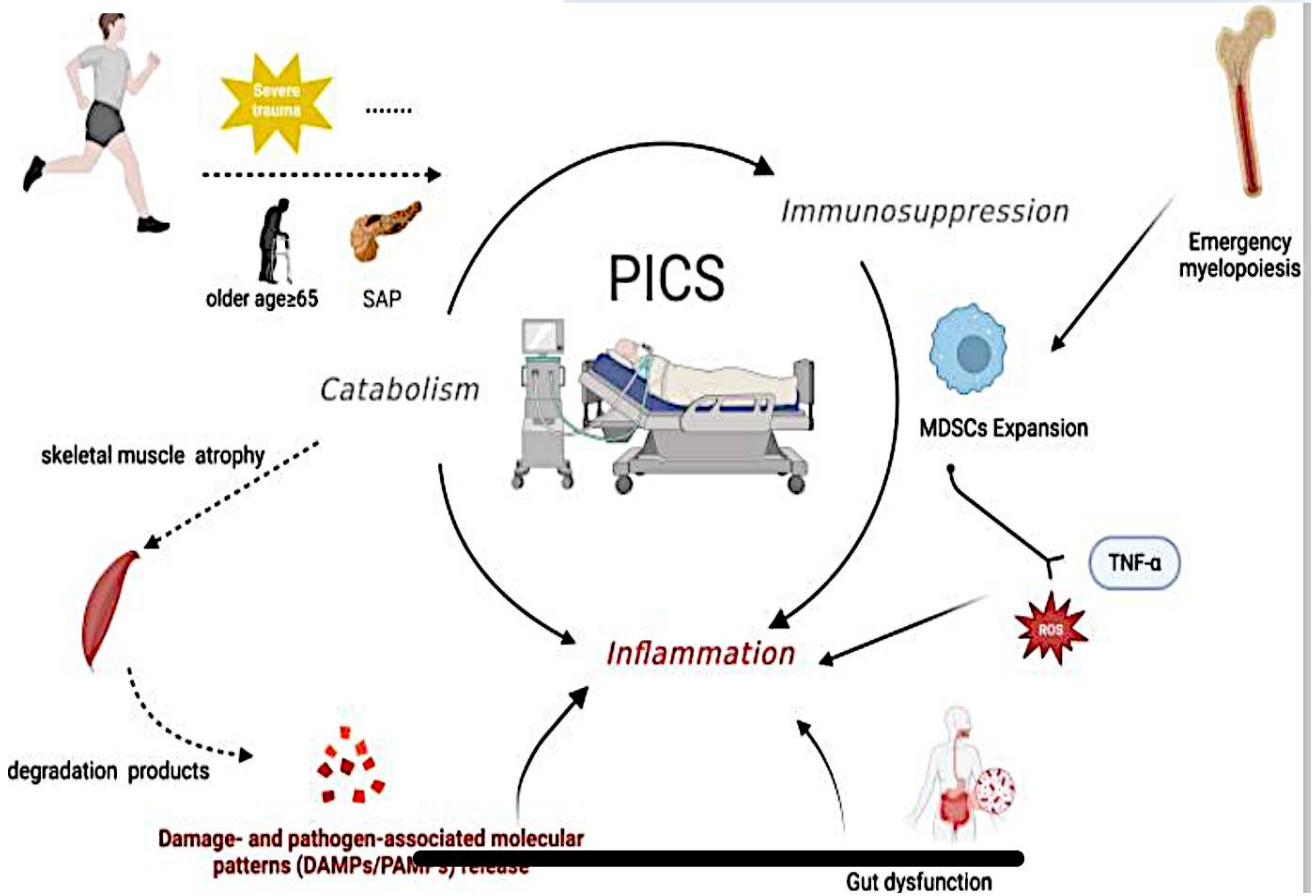
Dacheng Xiong[1,2], Huixian Geng[1,2], Xuechun Lv[1,2], Shuqi Wang[1,2], Lijing Jia[1,2]

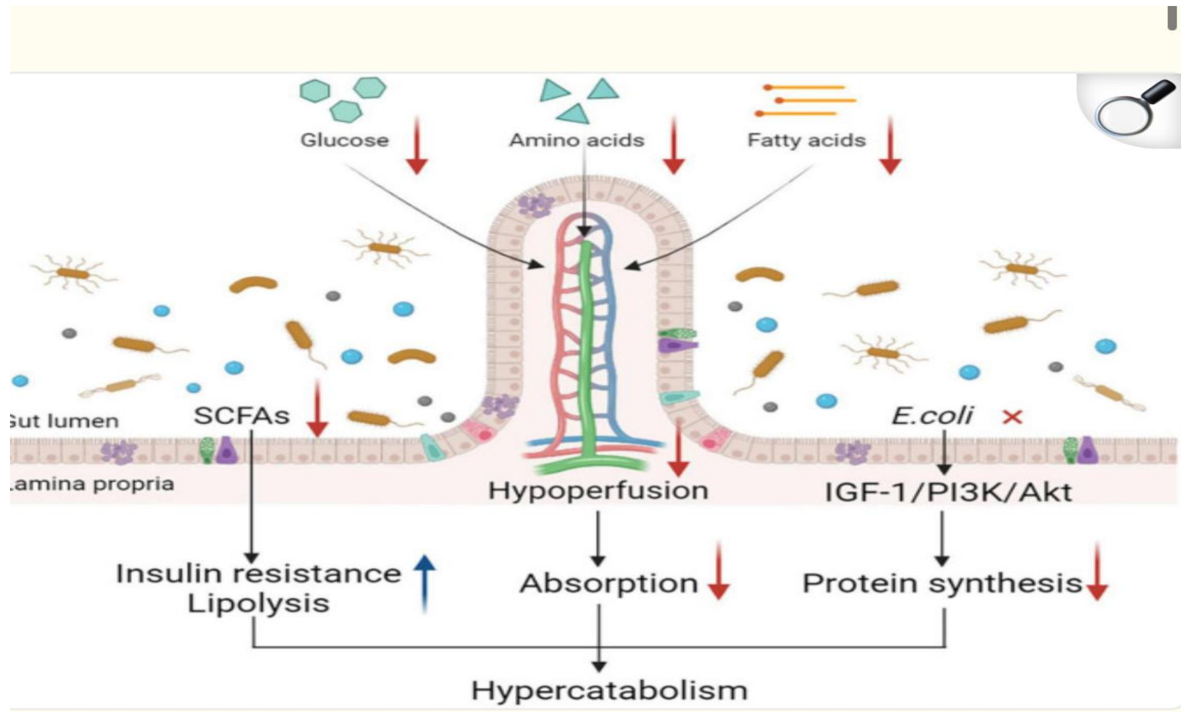
[1]Department of Intensive Care Medicine, Hebei Medical University, Shijiazhuang, People's Republic of China; [2]Department of Intensive Care Medicine, Hebei General Hospital, Shijiazhuang, People's Republic of China

Correspondence: Lijing Jia, Department of Intensive Care Medicine, Hebei General Hospital, Shijiazhuang, Hebei Province, People's Republic of China, Tel +86 31185989925, Fax +86 31185989925, Email 90030200@hebmu.edu.cn

Diagnostic Criteria for PICS

Authors	ICU Stay (Days)	C-reactive Protein (mg/L)	Total Lymphocyte Count (× 10^9/L)	Serum Albumin (g/dL)	Prealbumin (mg/dL)	Weight Loss (%)	BMI (kg/m²)
Gentile et al[5]	>10	>1.5	<0.8	<3.0	<10	>10	<18
Mira et al[11]	>14	>0.5	<0.8	<3.0	<10	>10	<18

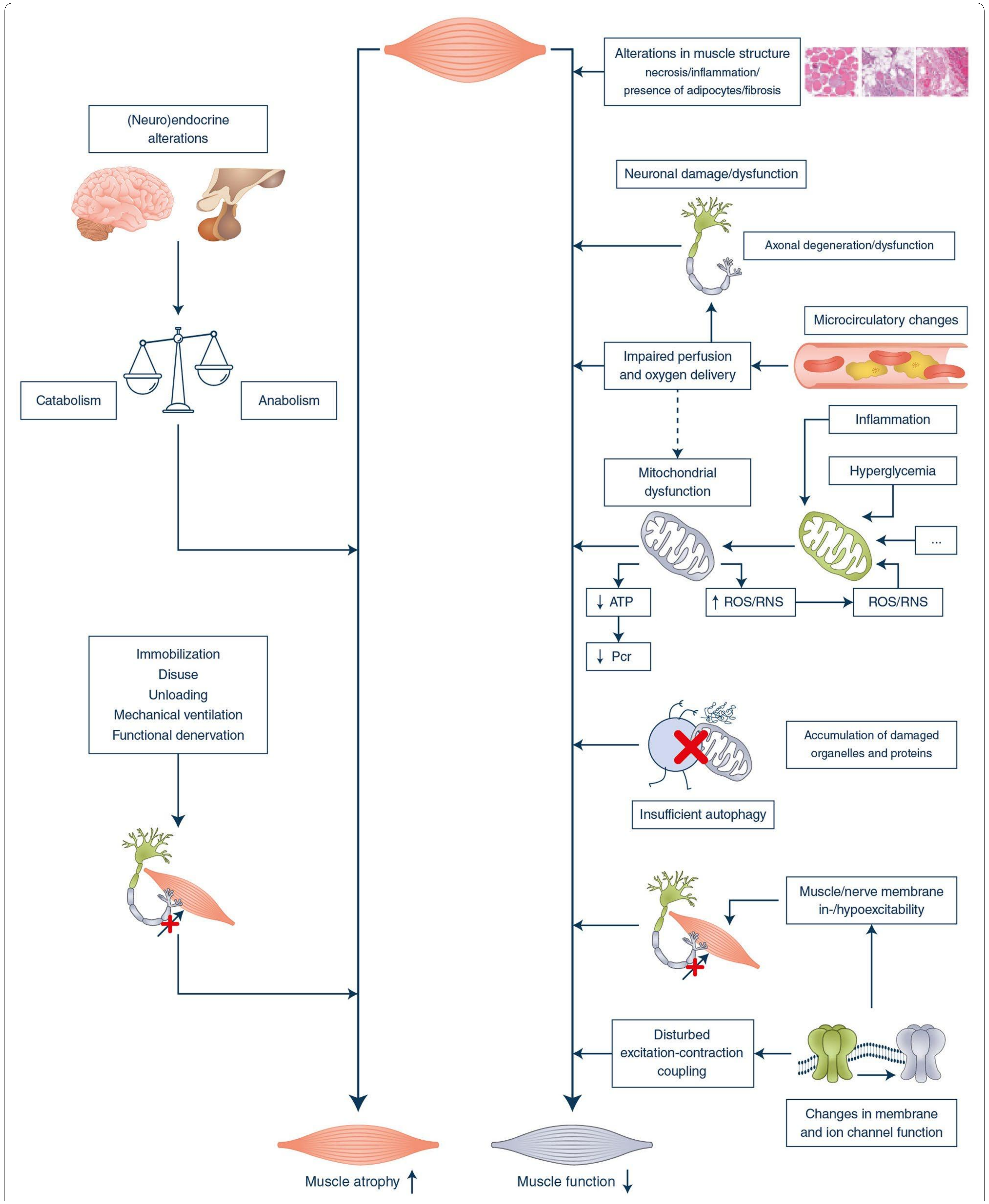




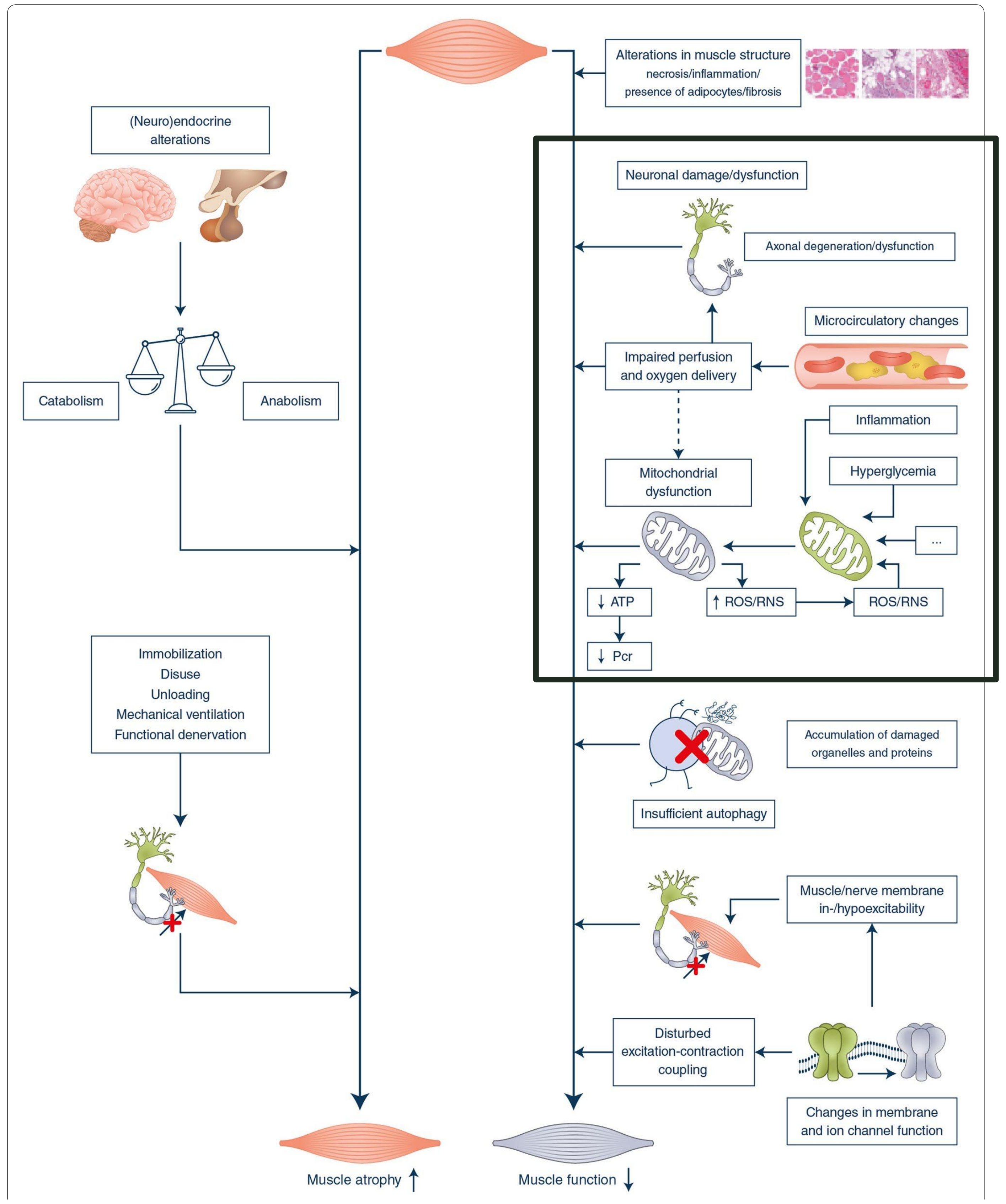
Open in a new tab

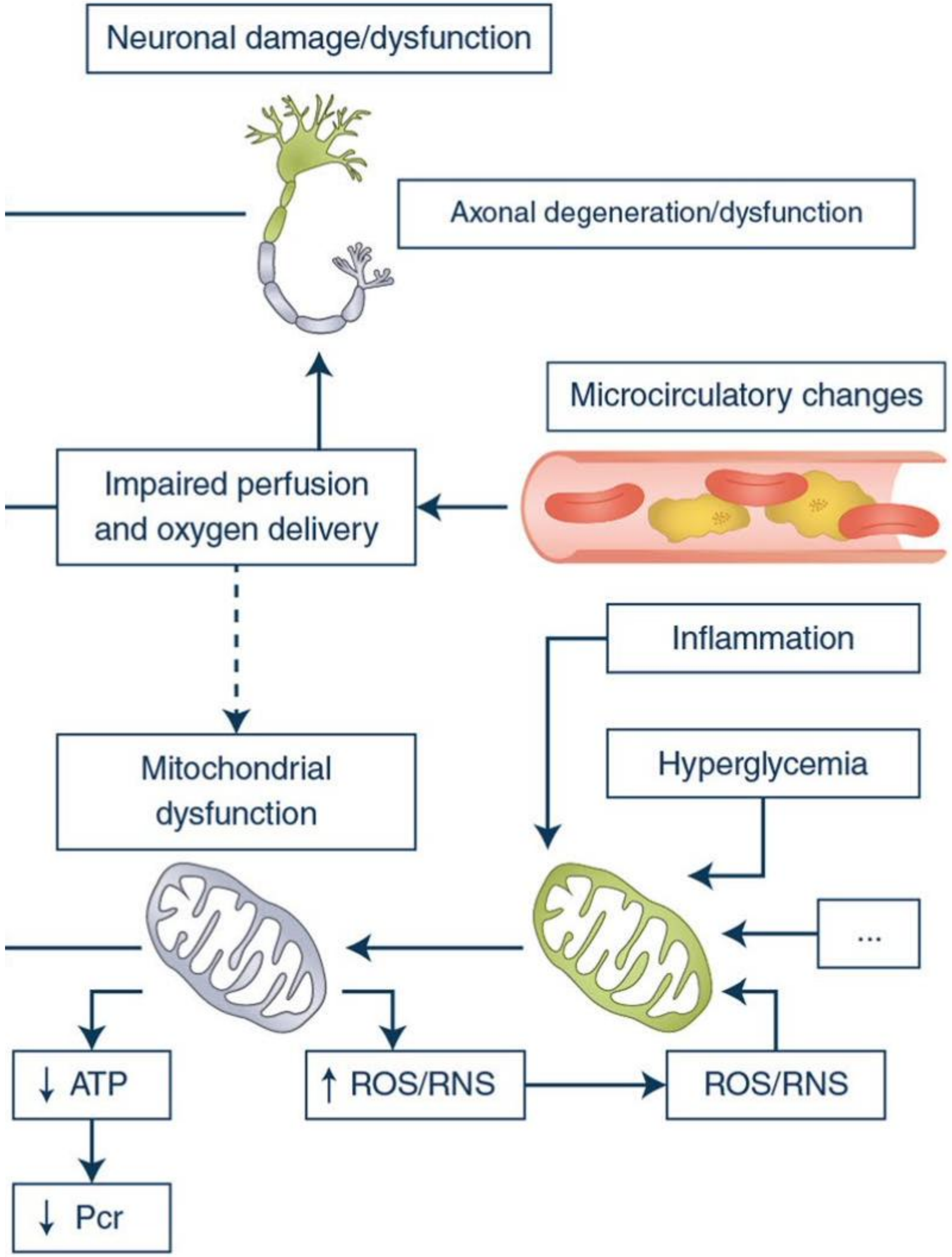
Gut dysfunction and its impact on catabolism. Gut dysfunction contributes to a hypercatabolic state in many ways. Gut hypoperfusion and

PICS Development: A conceptual framework



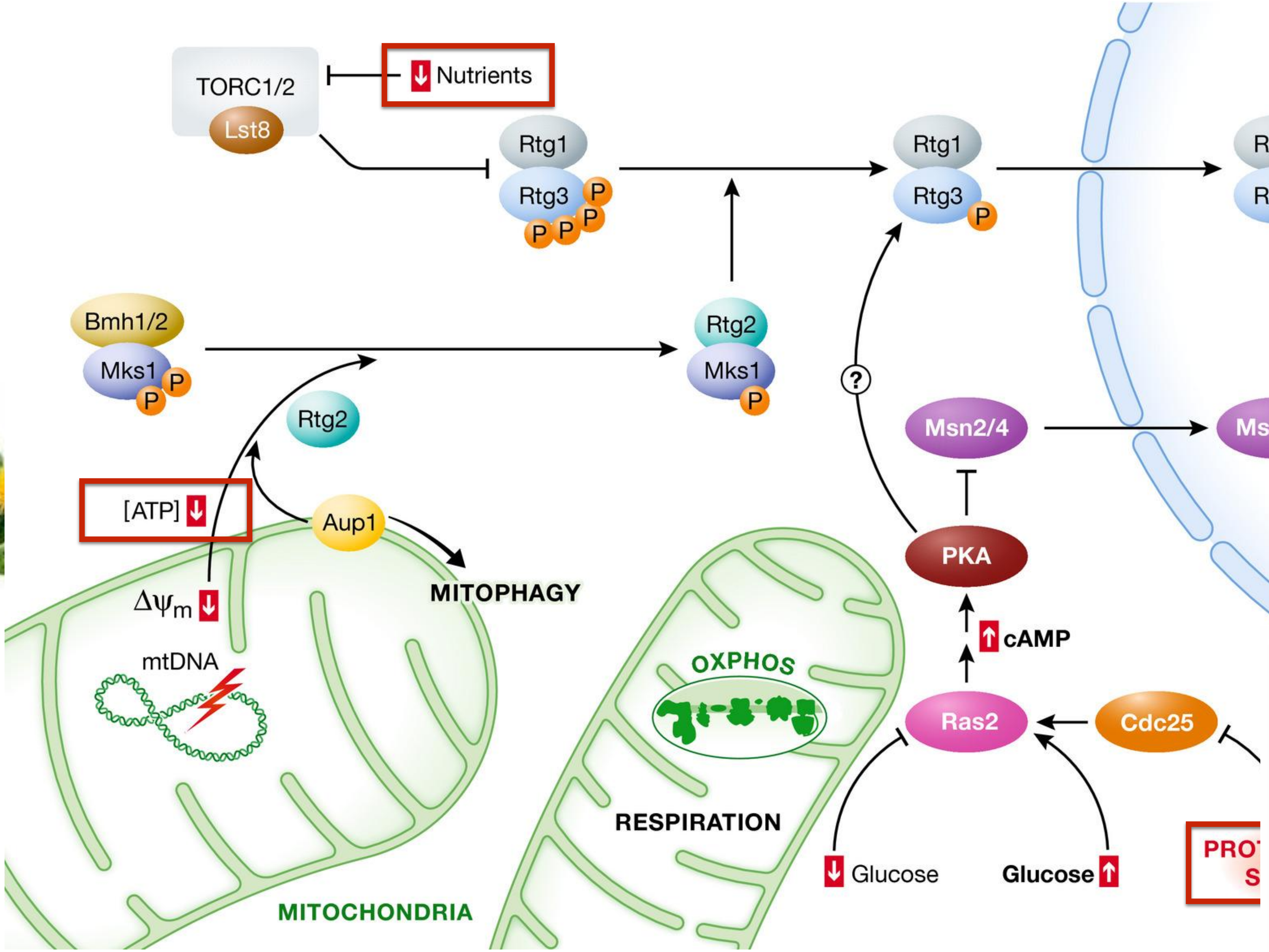
Vanhorebeek I, Latronico N, Van den Berghe G. ICU-acquired weakness. Intensive Care Med. 2020 Apr;46(4):637-653.

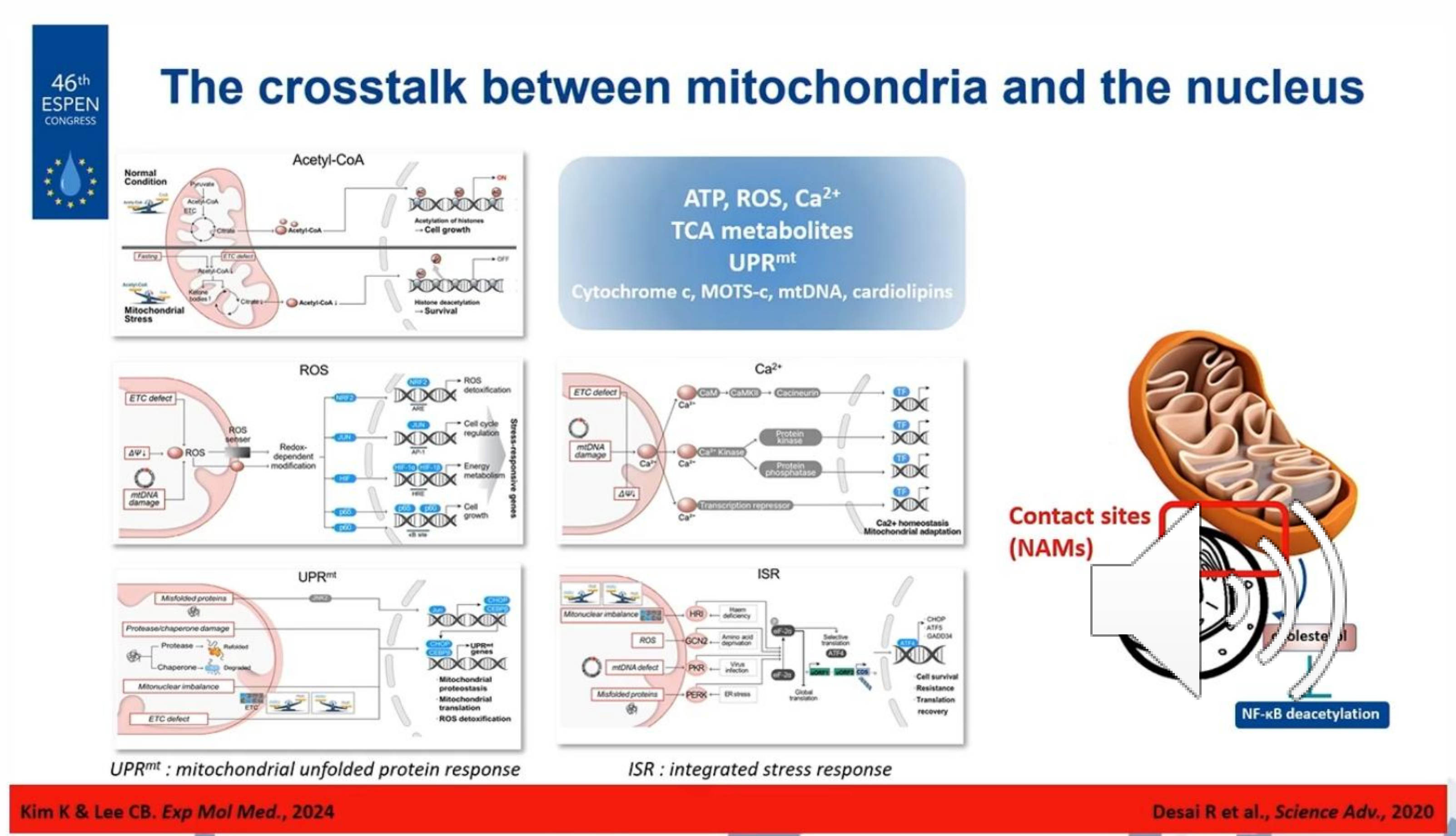


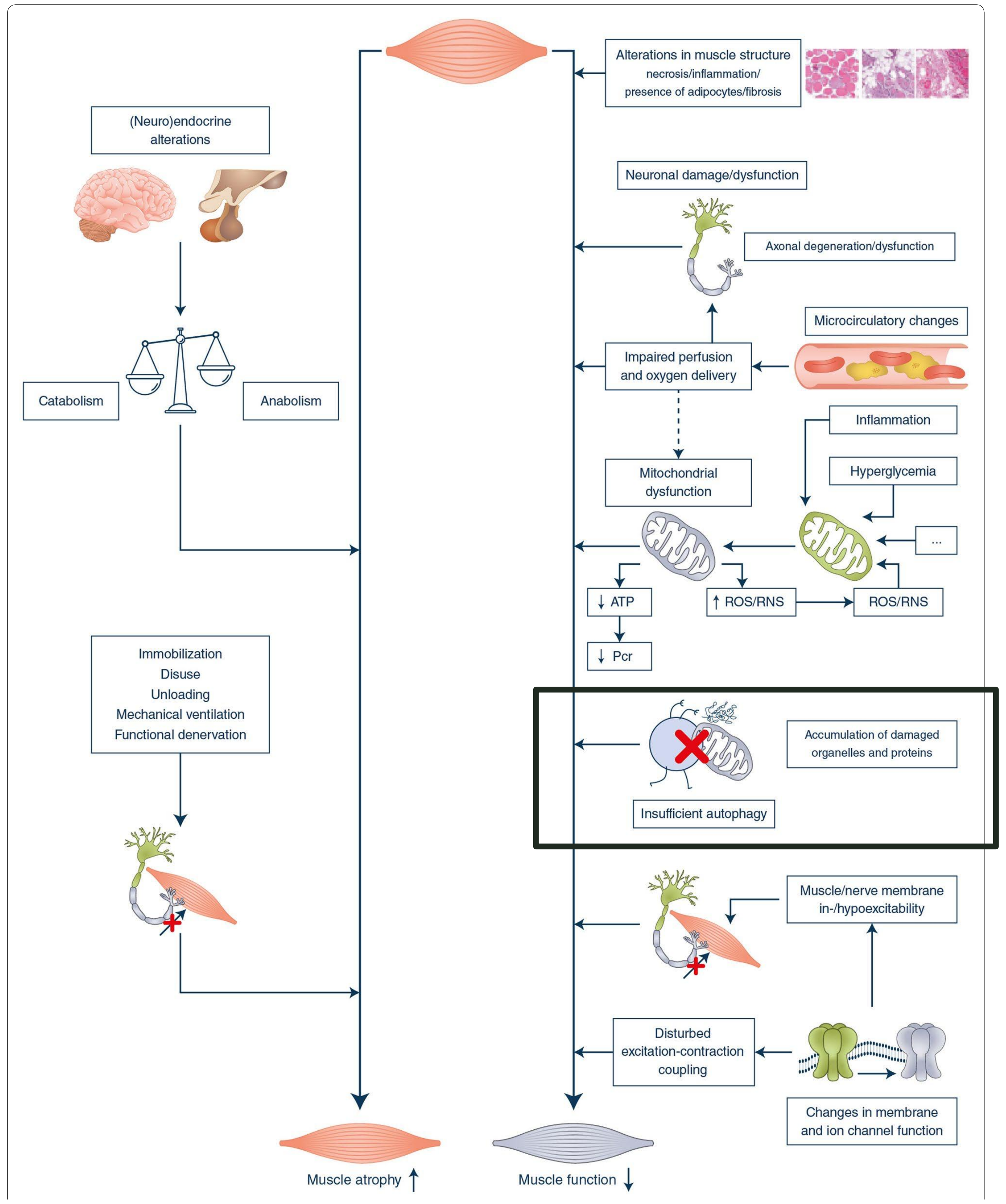


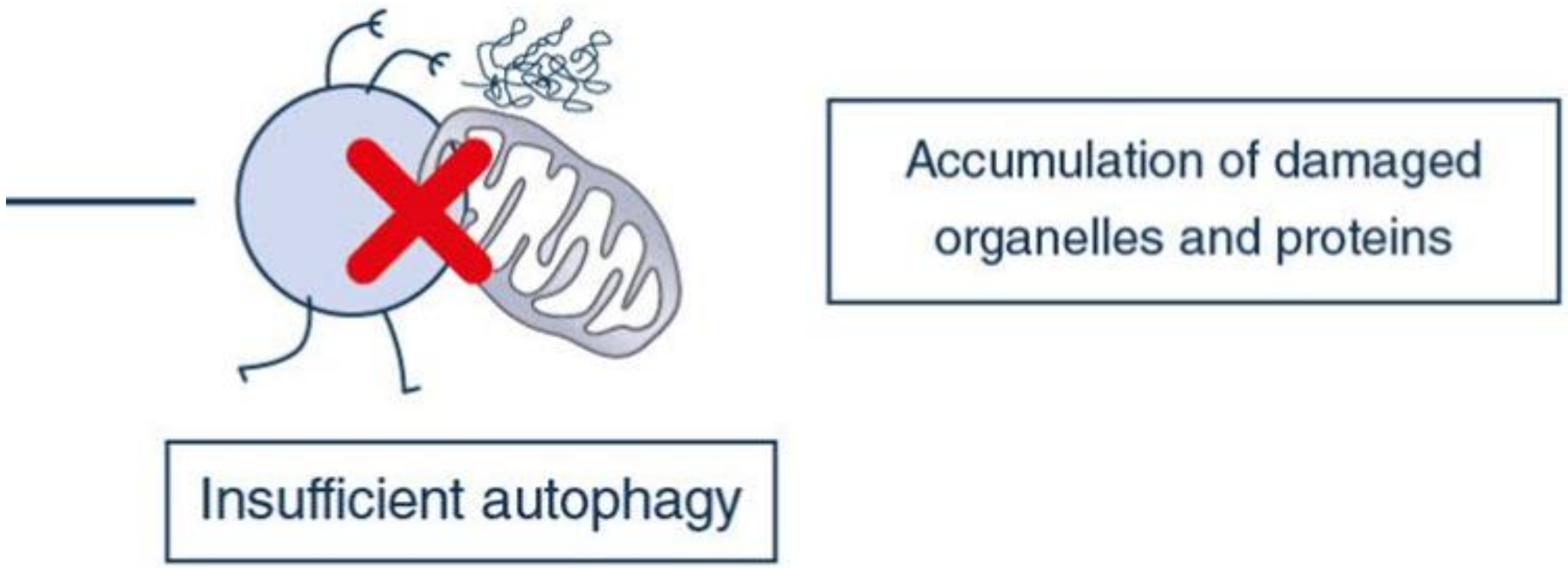
Vanhorebeek I, Latronico N, Van den Berghe G. ICU-acquired weakness. Intensive Care Med. 2020 Apr;46(4):637-653.

Mitochondria: hubs that integrate metabolic & proteostatic fluxes to modulate stress responses to various insults









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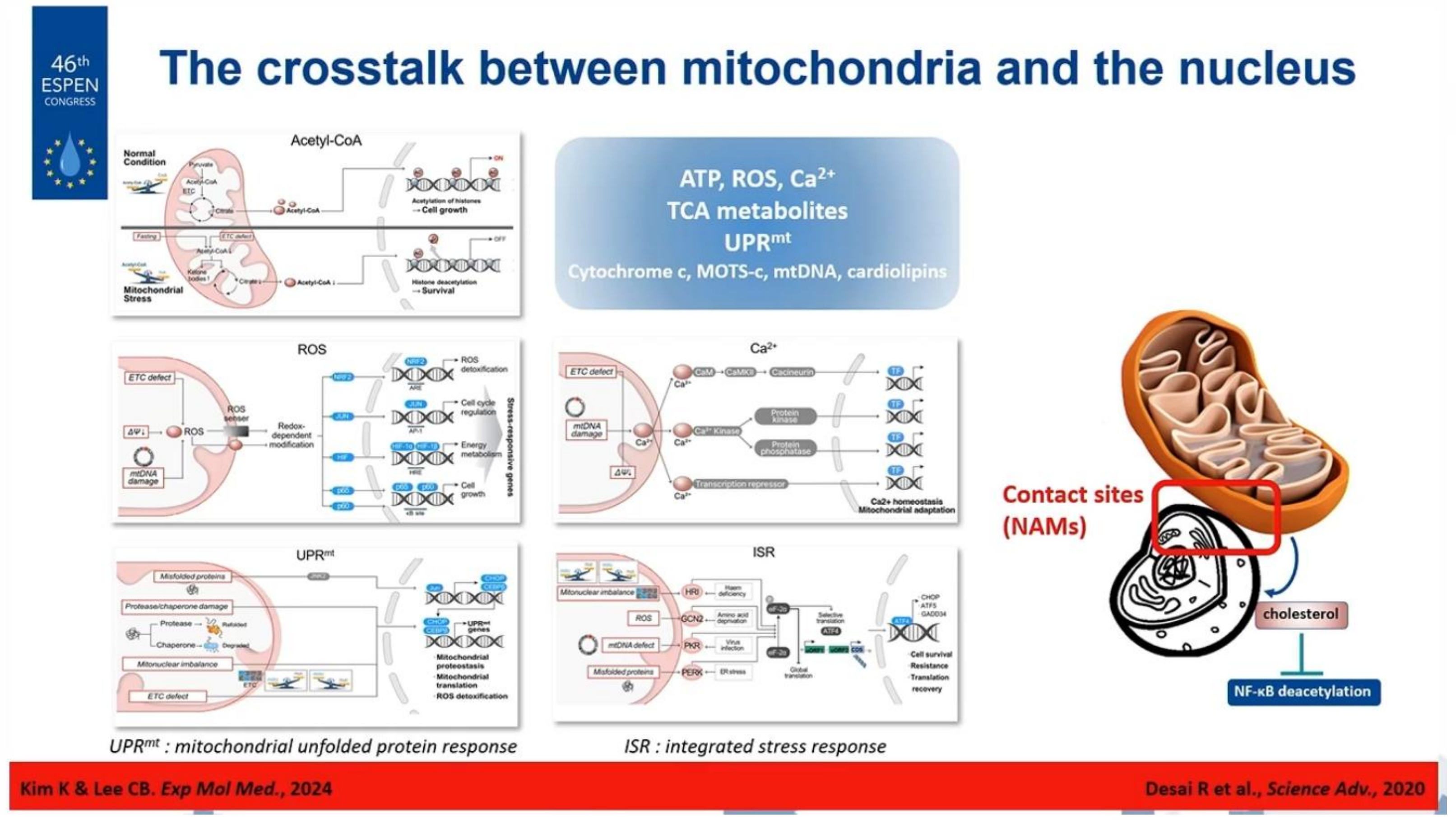
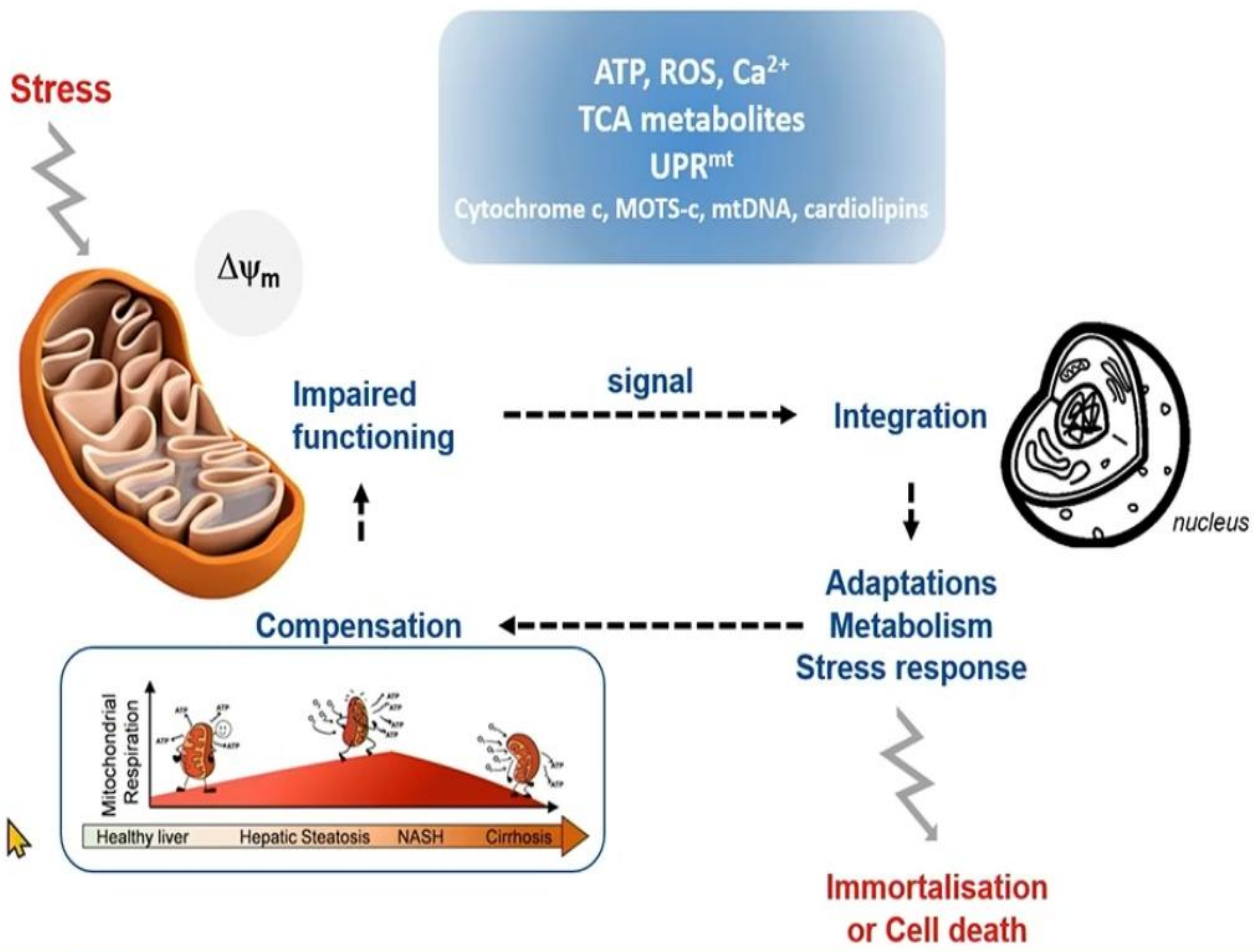
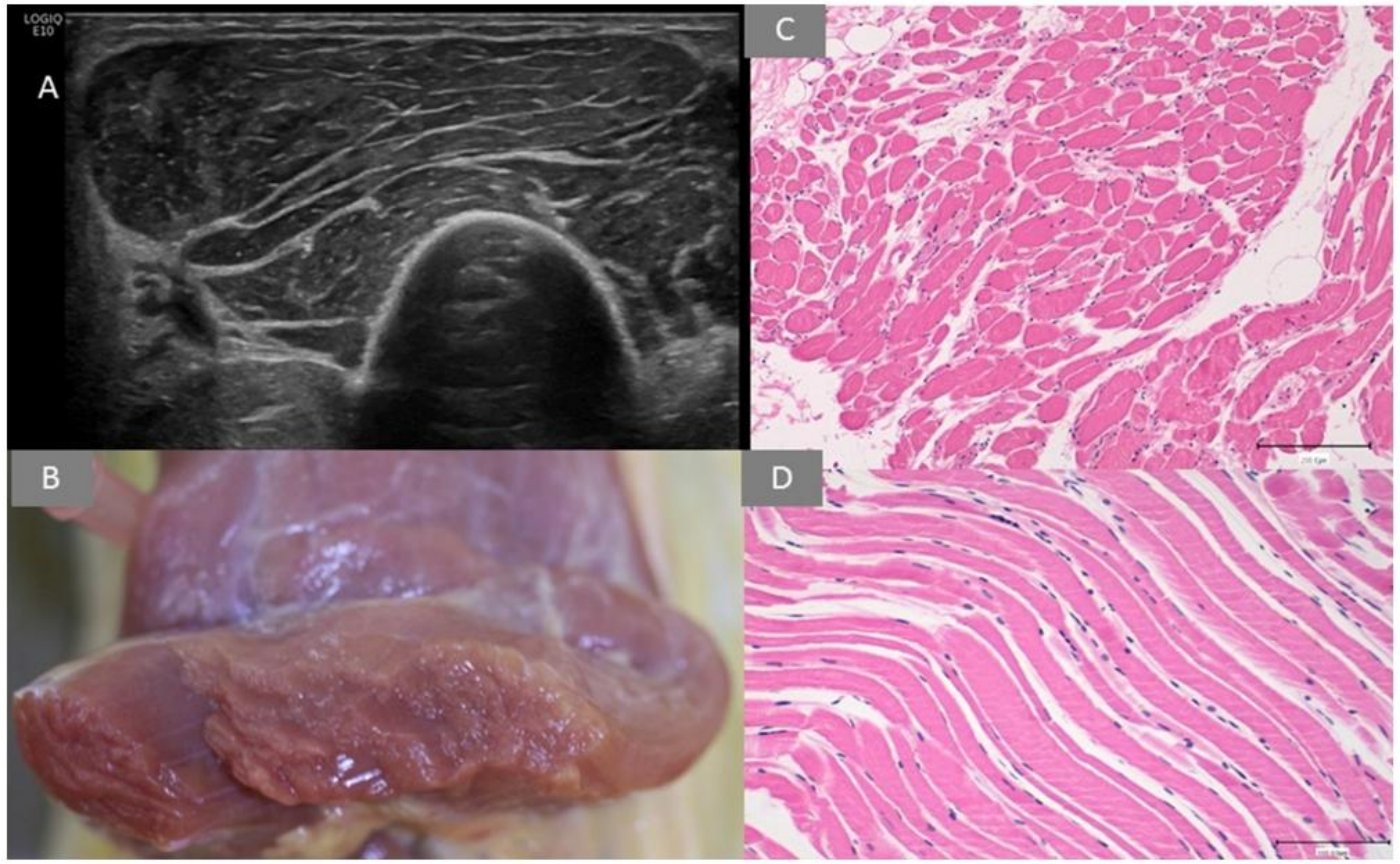


The crosstalk between mitochondria and the nucleus

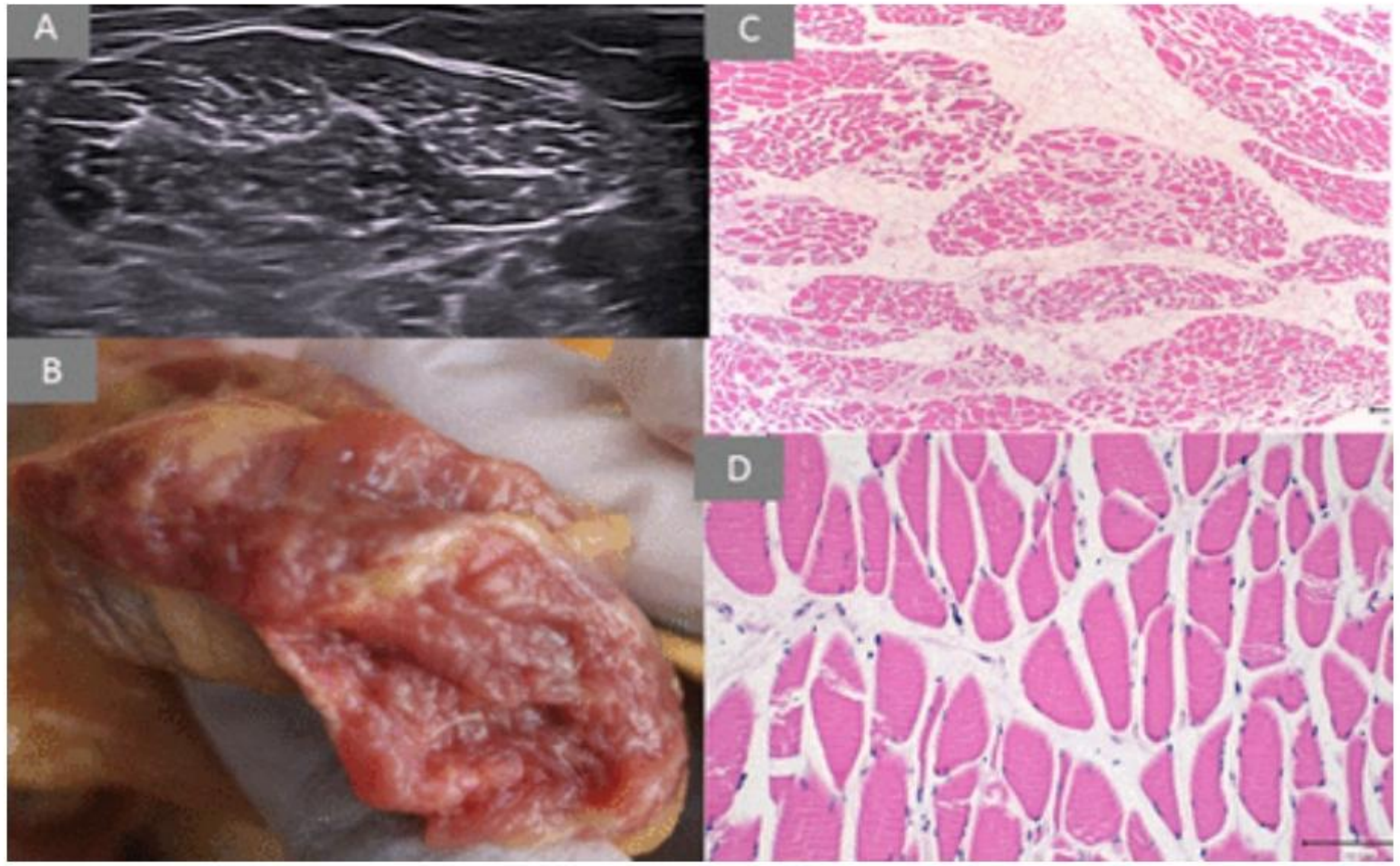


SARCOPENIC GRADES

Grade 1 (normal muscle) biceps brachii.



Ingrid Möller Parera et al. RMD Open 2023;9:e002779



Grade 2 (moderate sarcopenia) biceps brachii. (A) MSUS short axis view, (B) anatomical image, (C, D) histology. MSUS, musculoskeletal ultrasound.

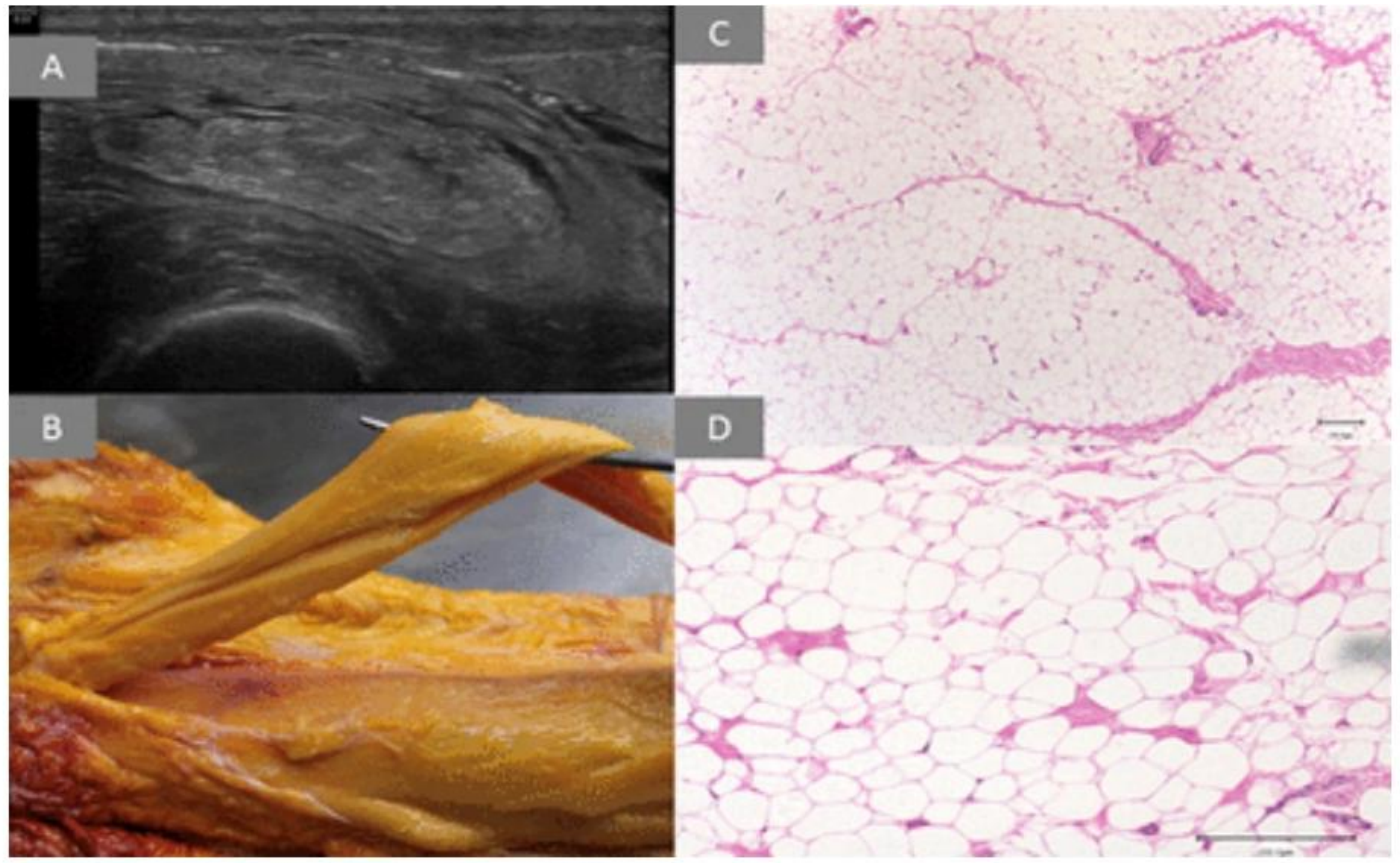
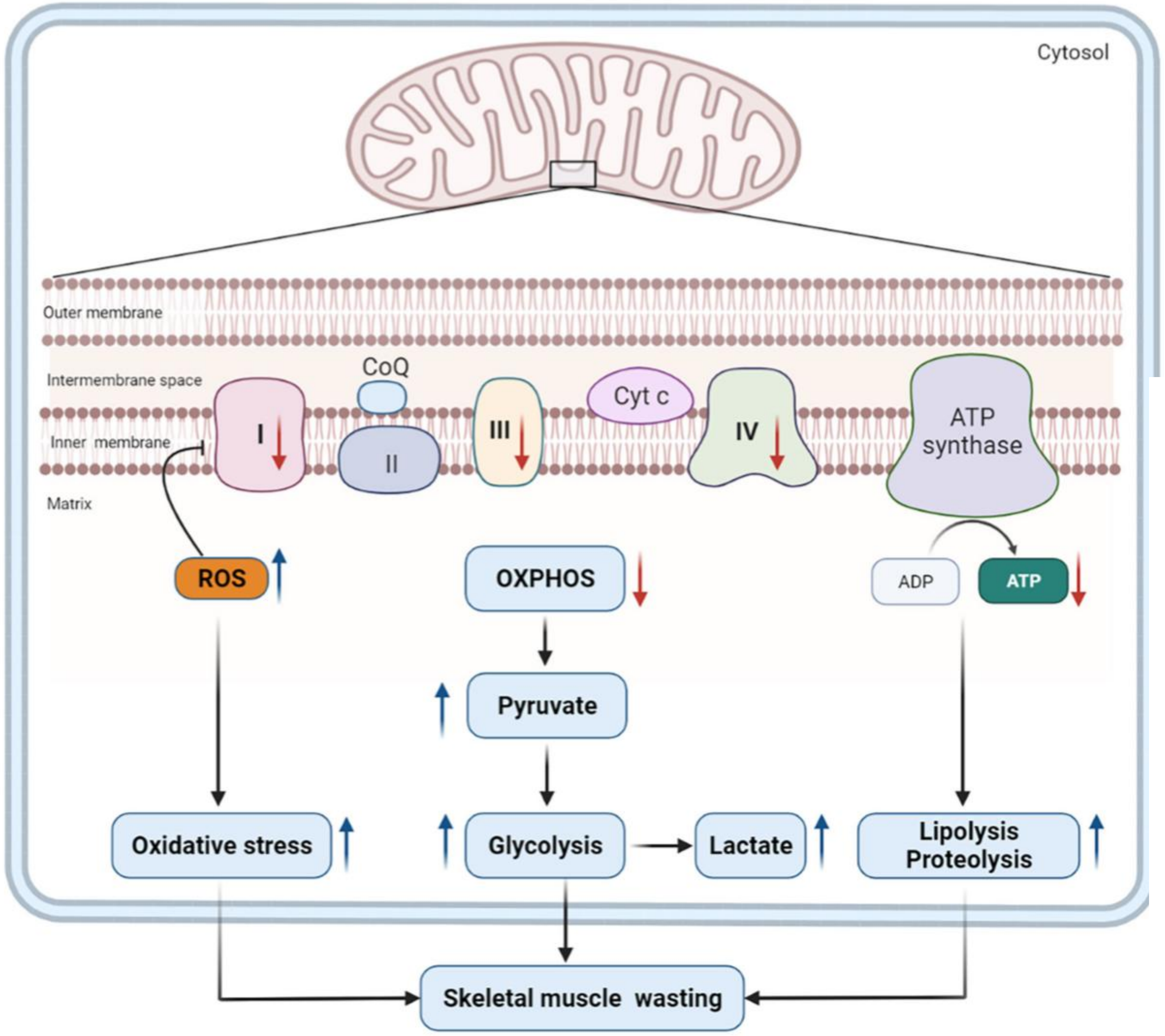


Figure 3

Grade 3 (severe sarcopenia) rectus femoris. (A) MSUS short axis view, (B) anatomical image, (C, D) histology. MSUS, musculoskeletal ultrasound.



Frontiers in Nutrition

REVIEW
published: 13 July 2022
doi: 10.3389/fnut.2022.941097

Hypercatabolism and Anti-catabolic Therapies in the Persistent Inflammation, Immunosuppression, and Catabolism Syndrome

Jinlin Zhang[1†], Wenchen Luo[1†], Changhong Miao[1] and Jing Zhong[1,2,3,4*]

[1] Department of Anesthesiology, Zhongshan Hospital Fudan University, Shanghai, China, [2] Fudan Zhangjiang Institute, Shanghai, China, [3] Department of Anesthesiology, Zhongshan Wusong Hospital, Fudan University, Shanghai, China, [4] Shanghai Key Laboratory of Perioperative Stress and Protection, Shanghai, China

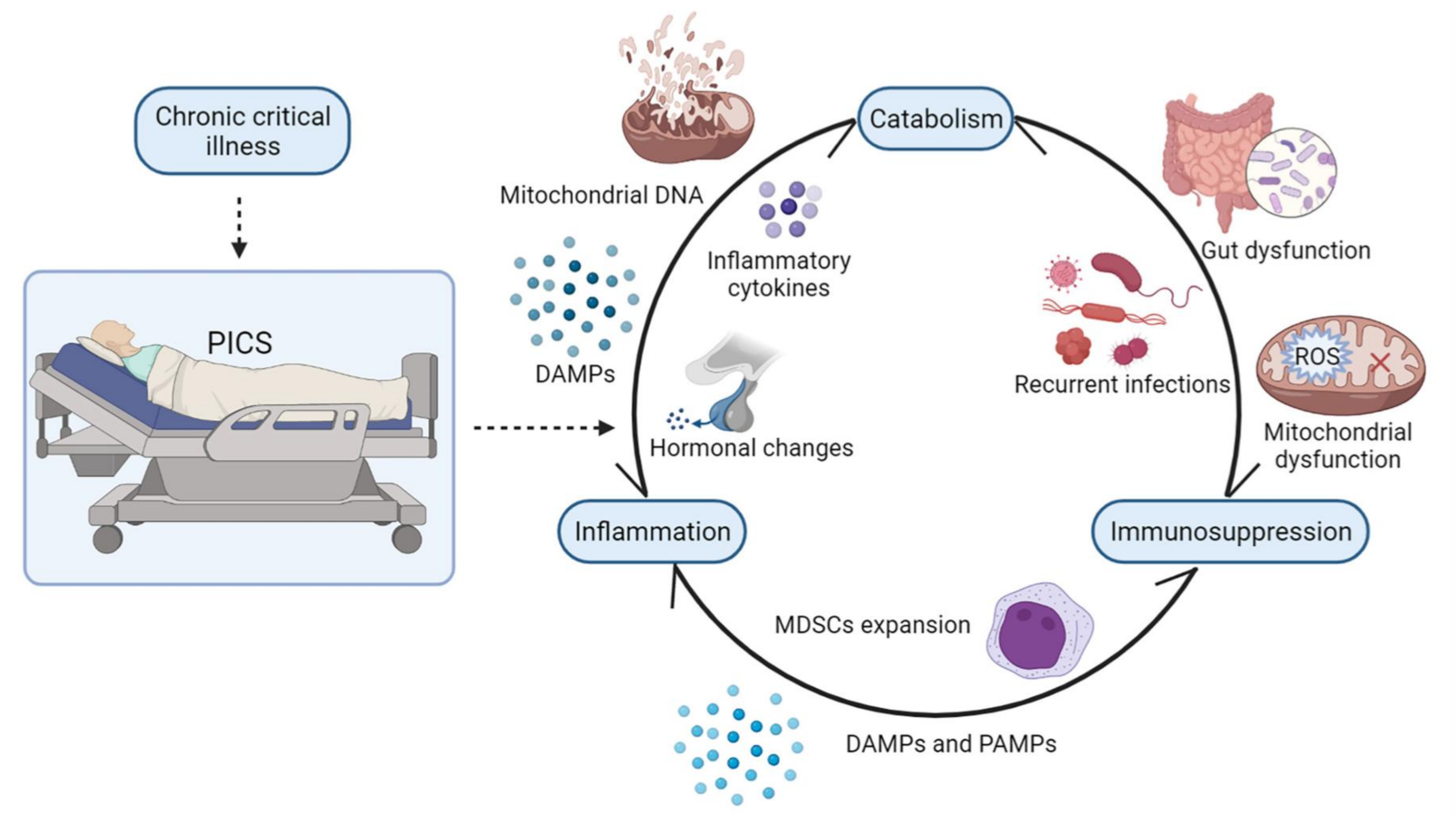
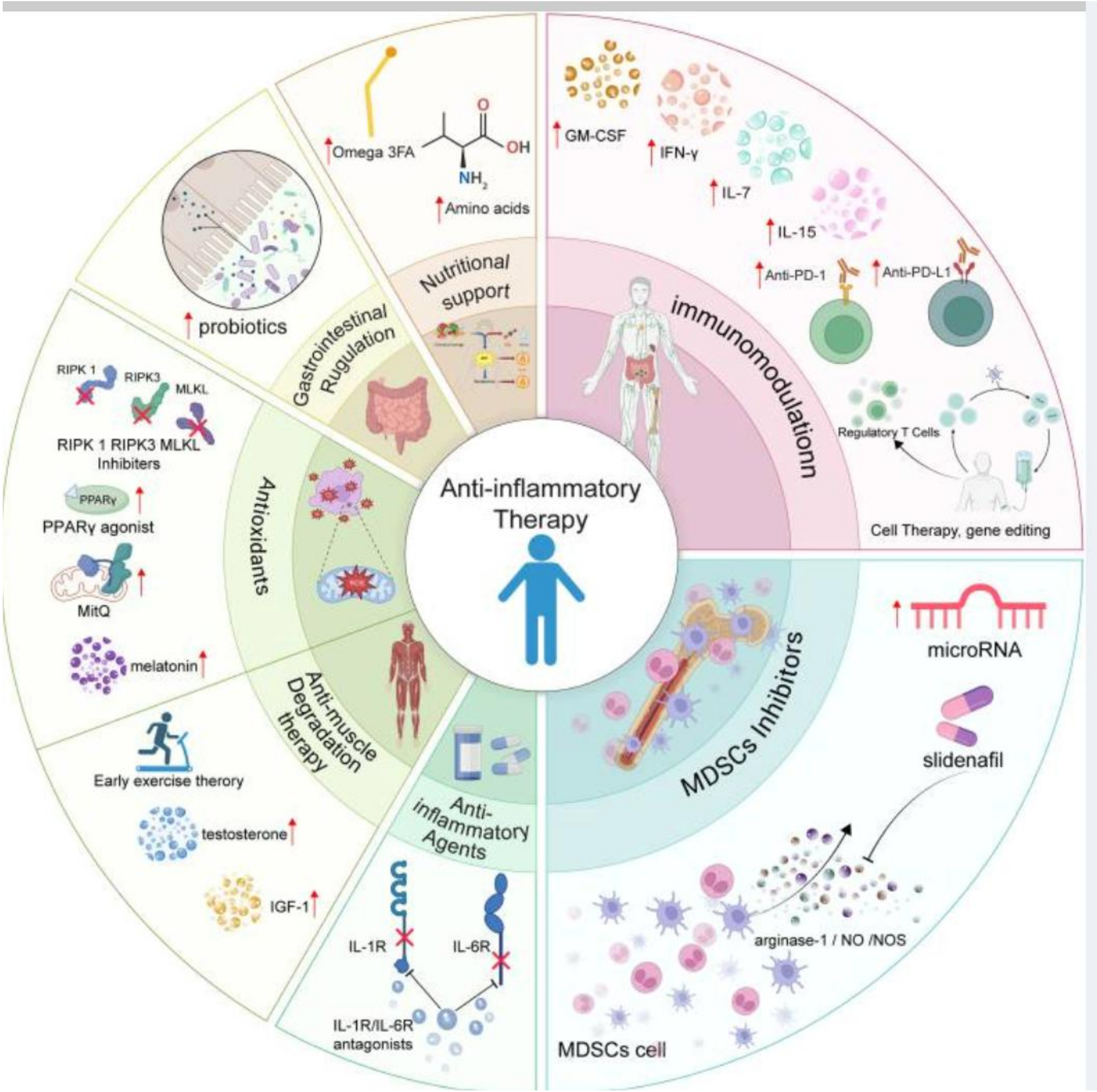


FIGURE 3 | The vicious cycle of PICS. There is a strong interaction between persistent inflammation, immunosuppression, and catabolism. In PICS, ongoing catabolism results in malnutrition and muscle wasting, and its decomposition products such as mitochondrial DNA and other DAMPs may drive persistent low-grade



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▸ J Inflamm Res. 2025 Feb 14;18:2267–2281. doi: 10.2147/JIR.S504694

Inflammatory Response and Anti-Inflammatory Treatment in Persistent Inflammation-Immunosuppression-Catabolism Syndrome (PICS)

Dacheng Xiong [1,2], Huixian Geng [1,2], Xuechun Lv [1,2], Shuqi Wang [1,2], Lijing Jia [1,2,✉]

Summary diagram of potential anti-inflammatory treatments for Persistent Inflammation, Immunosuppression, and Catabolism Syndrome (PICS). This diagram illustrates a multifaceted approach to anti-inflammatory therapy for PICS, incorporating immunomodulation, nutritional support (amino acids, Omega-3), gastrointestinal regulation

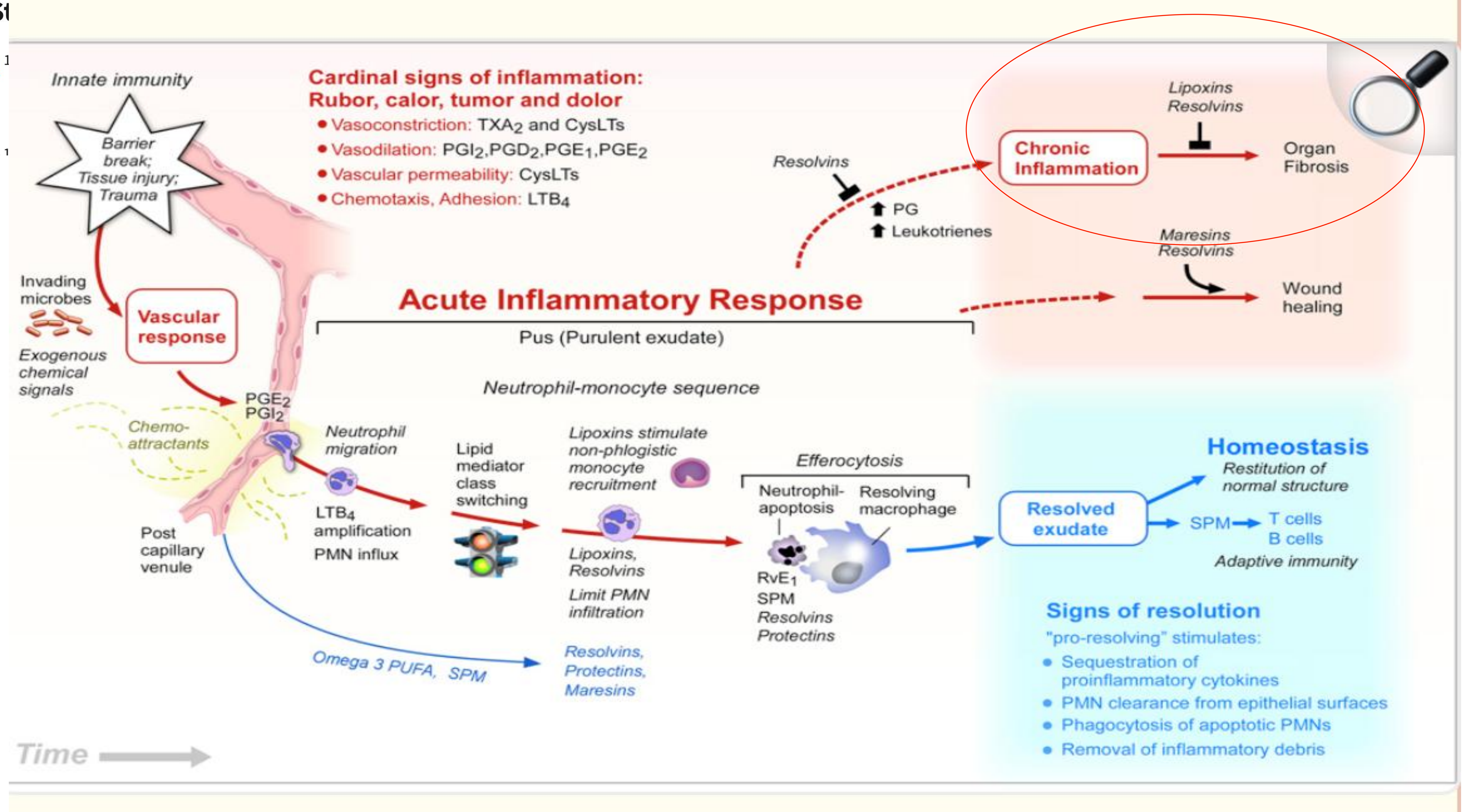
Journal of Clinical Medicine MDPI

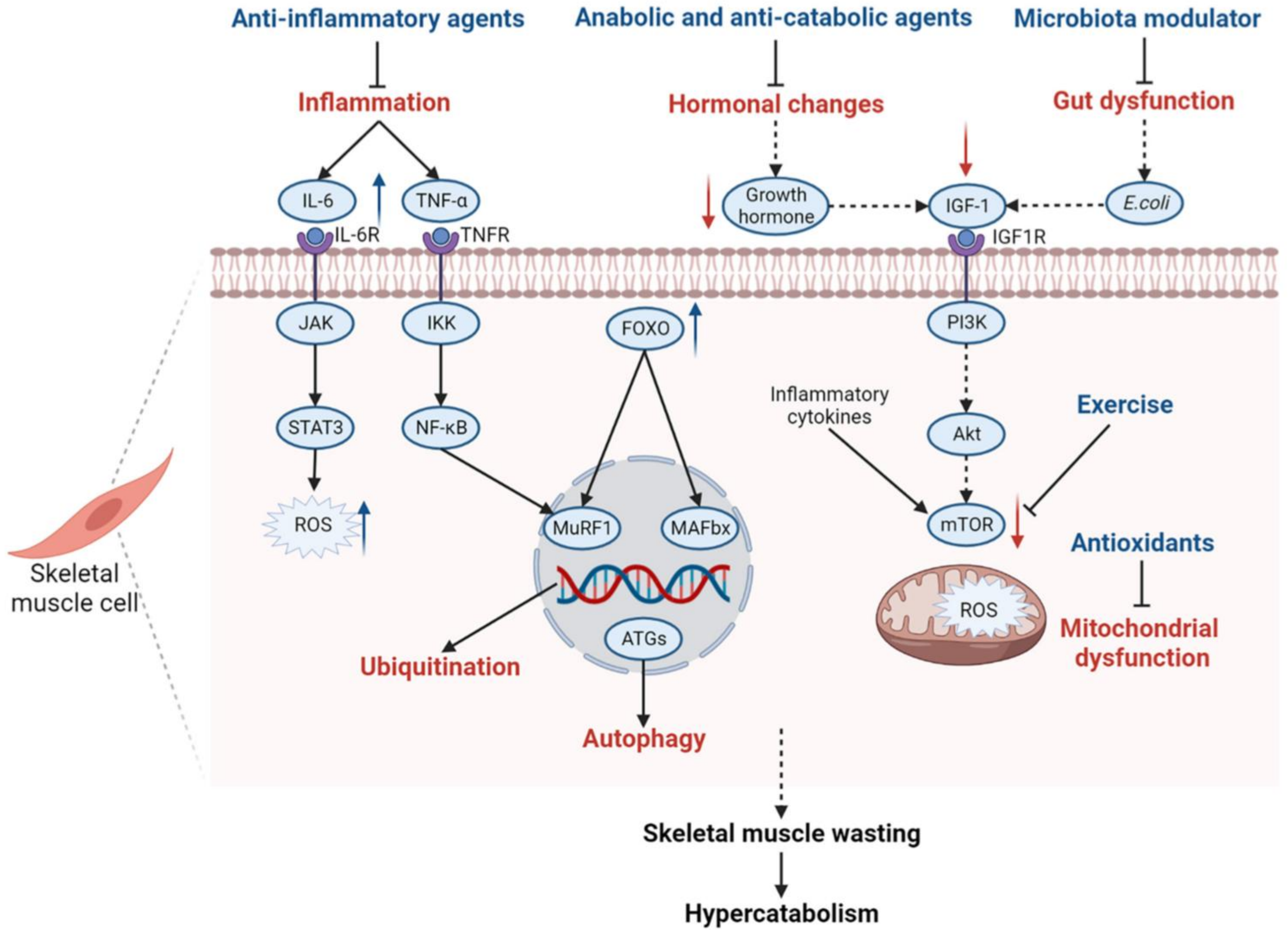
▸ J Clin Med. 2021 May 25;10(11):2294. doi: 10.3390/jcm10112294

Chronic Critical Illness and PICS Nutritional St

Martin D Rosenthal [1]

Moore [1]



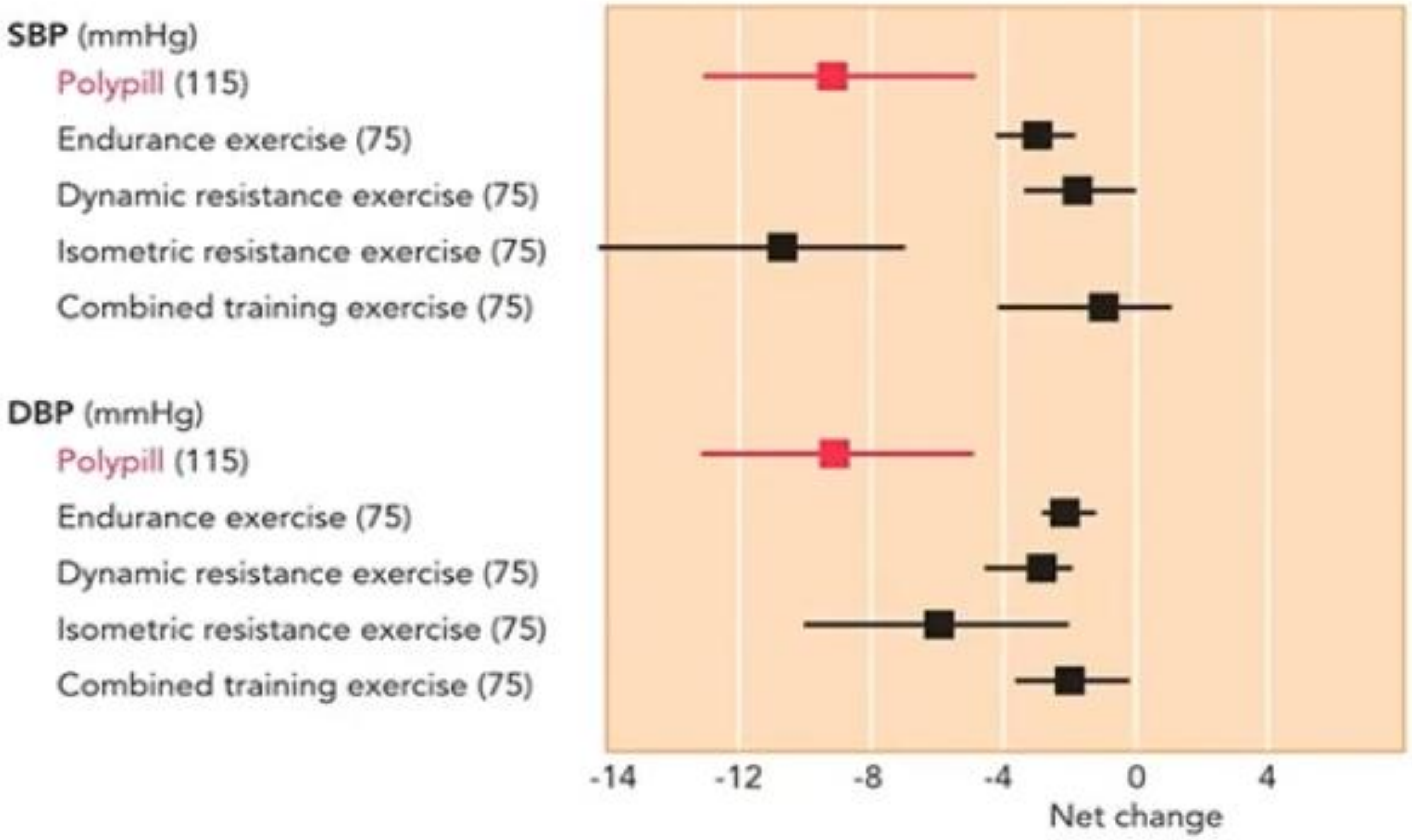


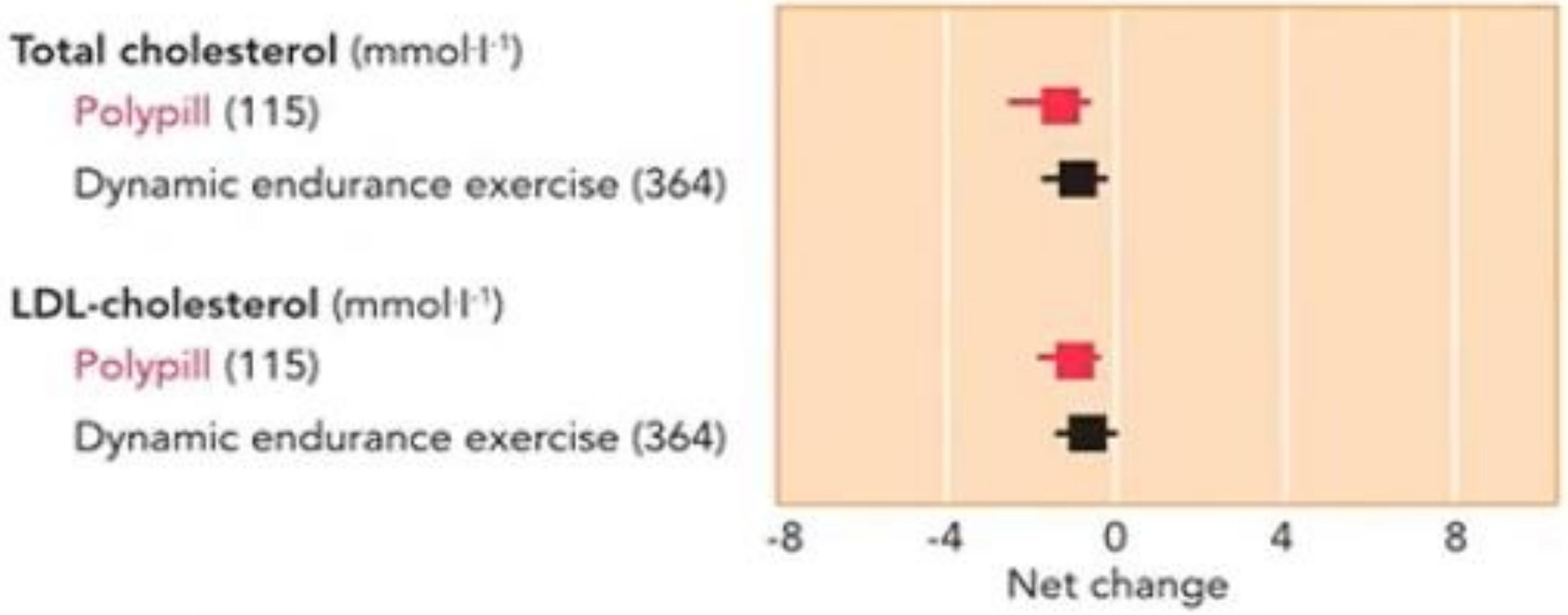
Anti-inflammatory agents
Anabolic and anti-catabolic agents
Microbiota modulator
Inflammation
Hormonal changes
Gut dysfunction
IL-6
TNF-α
Growth hormone
IGF-1
E.coli
IL-6R
TNFR
IGF1R
JAK
IKK
FOXO
PI3K
STAT3
NF-κB
Inflammatory cytokines
Exercise
Akt
ROS
MuRF1
MAFbx
mTOR
Antioxidants
Skeletal muscle cell
ROS
Mitochondrial dysfunction
ATGs
Ubiquitination
Autophagy
Skeletal muscle wasting
Hypercatabolism

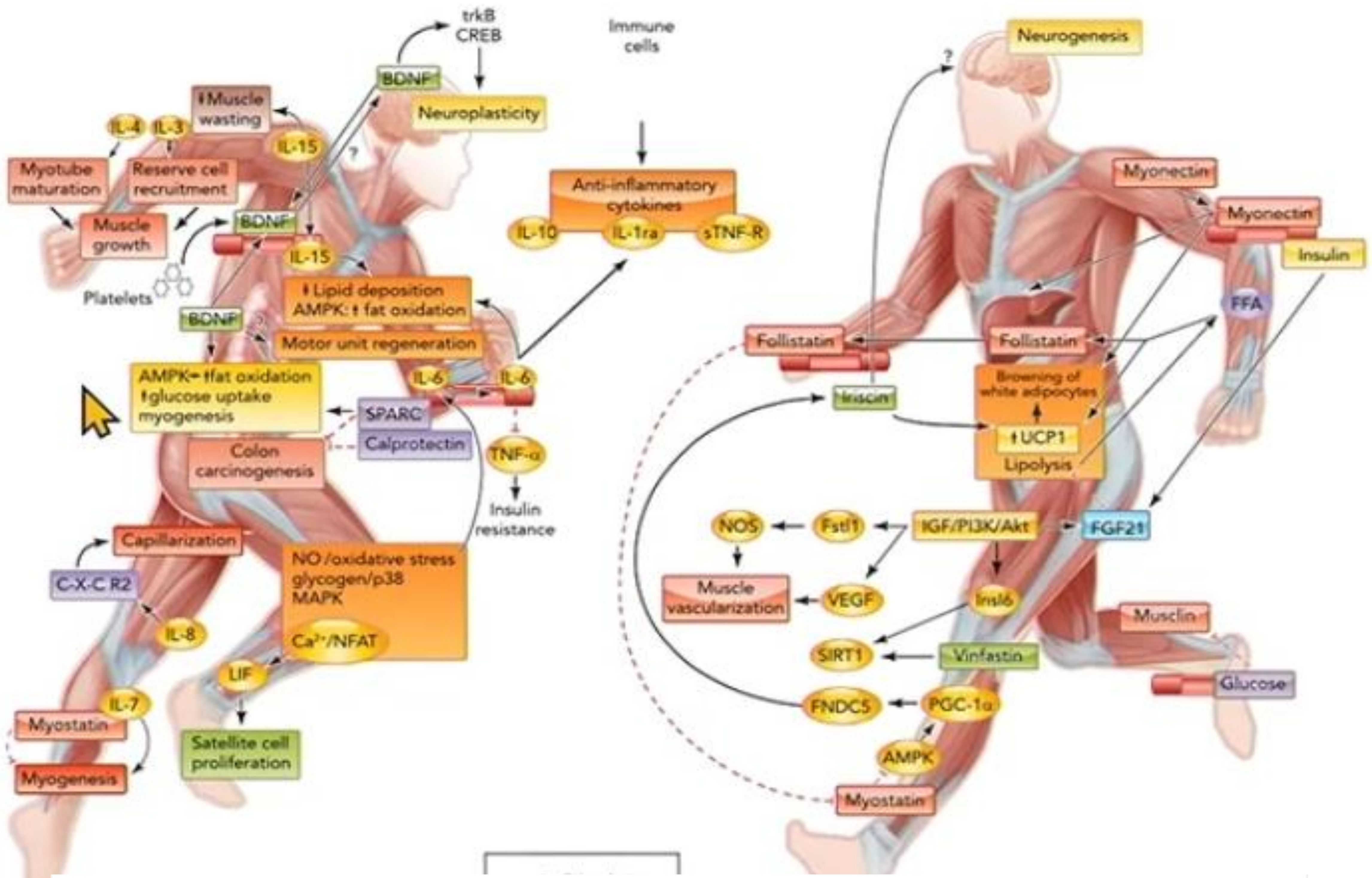
REVIEWS
PHYSIOLOGY 28: 330–358, 2013; doi:10.1152/physiol.00019.2013

Exercise is the Real Polypill

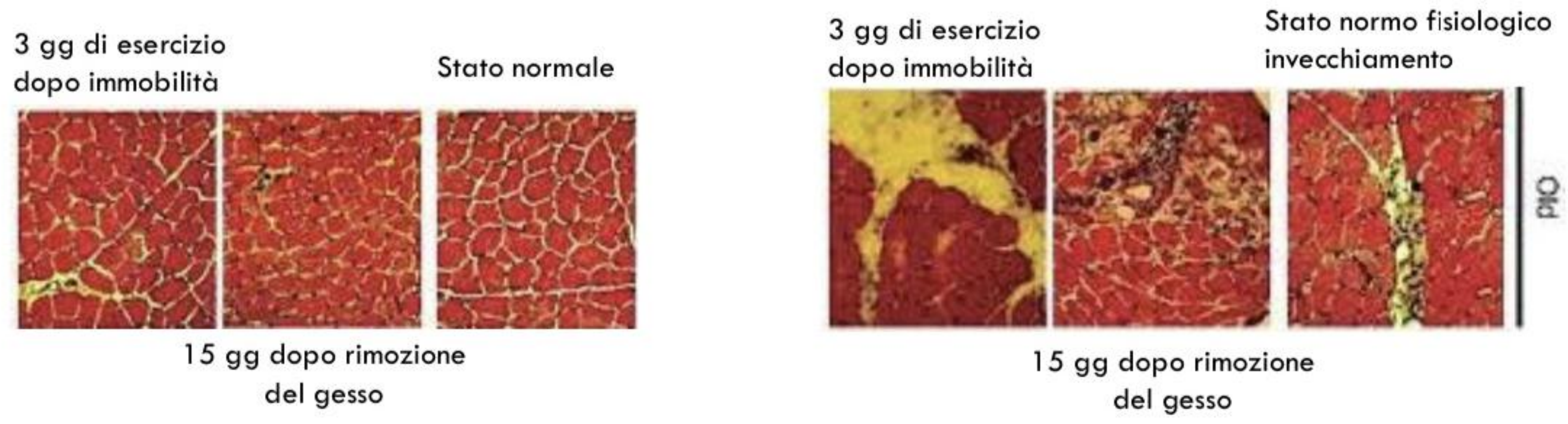
Carmen Fiuza-Luces,[1,2]
Nuria Garatachea,[3]
Nathan A. Berger,[4] and
Alejandro Lucia[1,2]







Polypill: FDC of statin, 3 blo … spirin



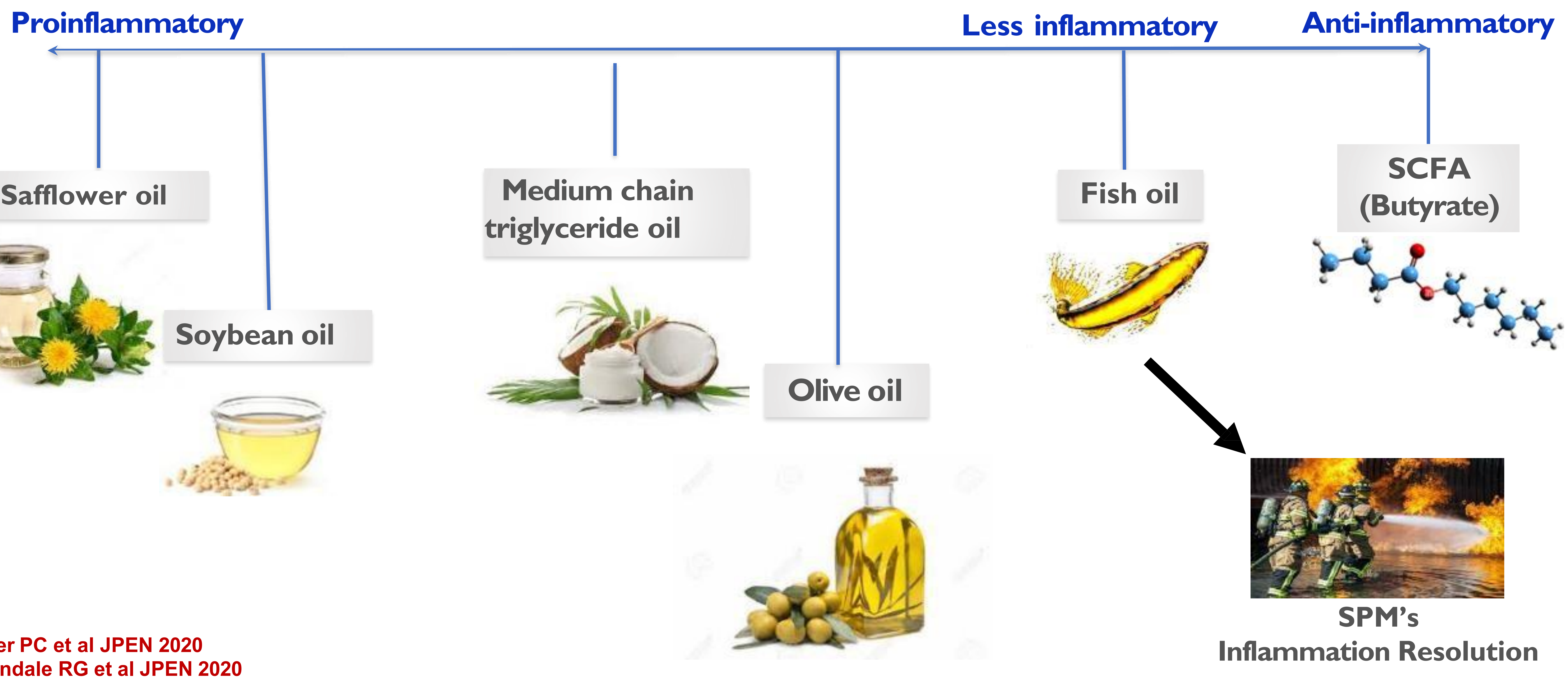
Carlson, Morgan E., et al. "Molecular aging and rejuvenation of human muscle stem cells." *EMBO molecular medicine* 1.8-9 (2009): 381-391.

		Day 1〜2 Early Acute	Day 3〜7 Late Acute	Day 7〜 Subacute
Acute Phase Treatment & Interventions		Emergency Operation Fluid resuscitation Vasopressors Mechanical Support	Definitive treatment Continuation of Acute interventions	Transition to long-term interventions/treatment
Physiotherapy			Early mobilization	Rehabilitation
Nutrition Therapy	**Rationale**	Maintenance of gut microbiota and mucosal barrier functions	Prevent muscle loss	Recovery of physical and cognitive/mental functions
	Route	Early enteral nutrition	Enteral nutrition and/or Parenteral Nutrition	Enteral nutrition and/or Parenteral Nutrition
	Provision targets	Energy: ≦ 70% of REE	Energy: 80-100% of mREE* Protein: 1.0-1.2 g/kgBW/day	Energy: ≧ 100% of mREE* Protein: ≧ 1.0-1.2 g/kgBW/day

Feeding strategy

Oshima and Hatakeyama *Journal of Intensive Care* (2024) 12:29

Relative Inflammation Scale



Calder PC et al JPEN 2020
Martindale RG et al JPEN 2020
Vanek VW et al Nutr Clin Pract 2012

Should modulation of inflammation be a goal in ICU settings ?

Original Investigation | Nutrition, Obesity, and Exercise

Association of Baseline Inflammation With Effectiveness of Nutritional Support Among Patients With Disease-Related Malnutrition

A Secondary Analysis of a Randomized Clinical Trial

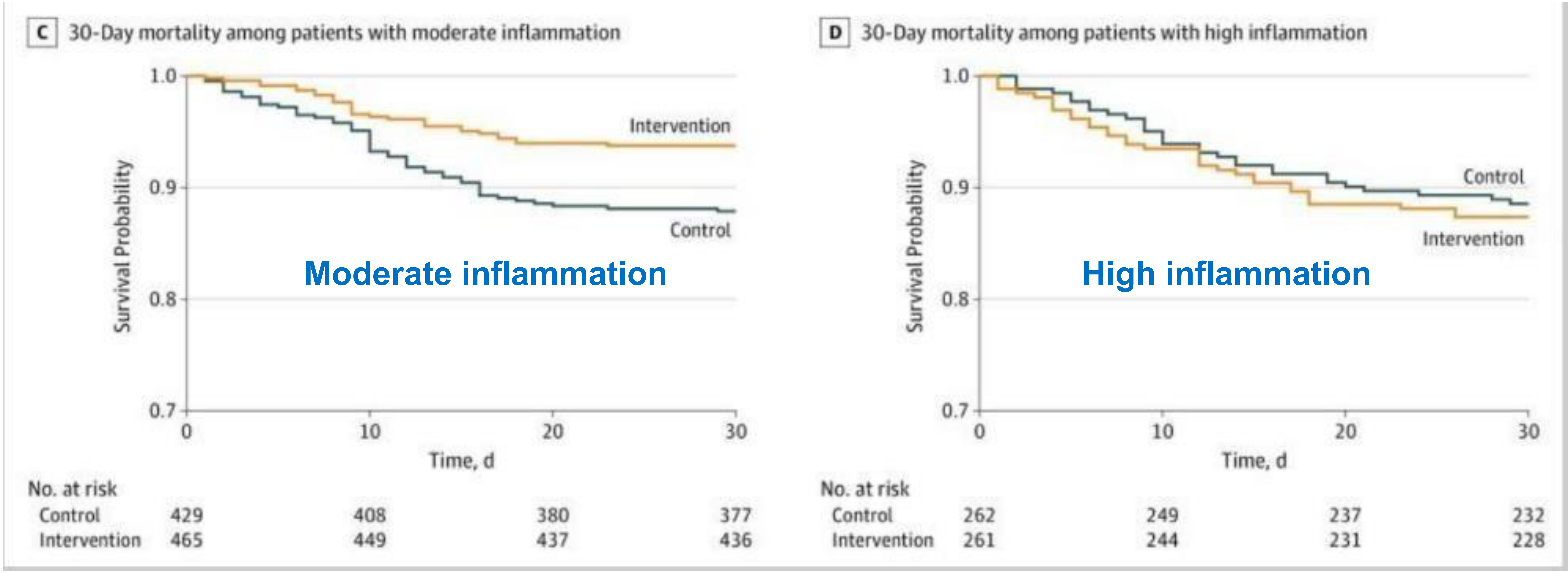
JAMA 2020

Meret Merker, MD; Martina Felder, BMSc; Louise Gueissaz, BMSc; Rebekka Bolliger, MD; Pascal Tribolet, MSc; Nina Kägi-Braun, MD; Filomena Gomes, PhD; Claus Hoess, MD; Vojtech Pavlicek, MD; Stefan Bilz, MD; Sarah Sigrist, MD; Michael Brändle, MD; Christoph Henzen, MD; Robert Thomann, MD; Jonas Rutishauser, MD; Drahomir Aujesky, MD; Nicolas Rodondi, MD, MAS; Jaques Donzé, MSc; Zeno Stanga, MD; Beat Mueller, MD; Philipp Schuetz, MD, MPH

- **RCT 8 Swiss Hospitals N=1950**
- **Personalized nutrition vs SOC hospital food**
  - protocol-guided individualized nutritional support to reach protein and energy goals (intervention group) or standard hospital food (control group).
- **End points**
  - **30 day mortality (primary)**
  - **Level of inflammation based on CRP (3 levels, low-moderate-high)**
- **Results**
  - **Personalized nutrition decreases mortality across entire study groups**
  - **Highest level of inflammation reported no benefit or effect of nutritional support**

What happened here?

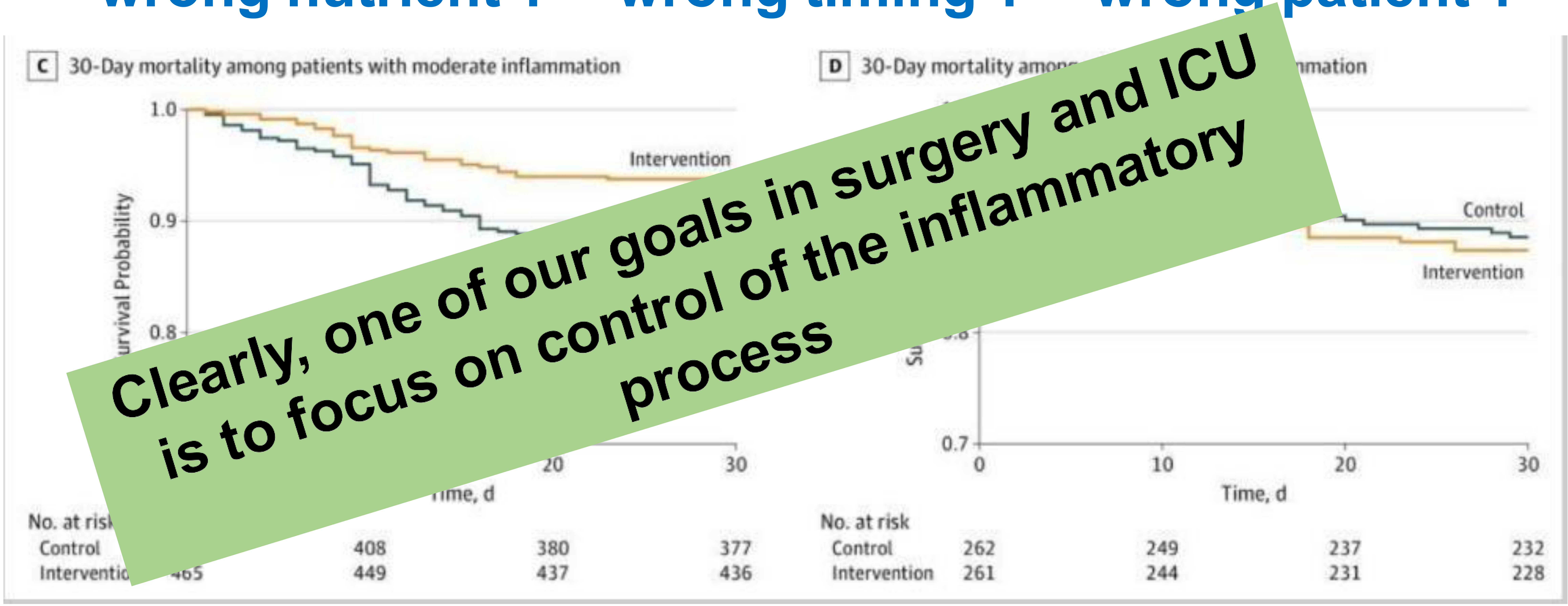
wrong nutrient ? wrong timing ? wrong patient ?



Merker M, et al. "Association of Baseline Inflammation with effectiveness of Nutritional Support…" JAMA Network Open. 2020; 3(3):e200663.

What happened here?

wrong nutrient ? wrong timing ? wrong patient ?



Merker M, et al. "Association of Baseline Inflammation with effectiveness of Nutritional Support…" JAMA Network Open. 2020; 3(3):e200663.

Specialized Proresolving Mediators (SPMs) in Patient Care 2024

Where to begin?

General Surgery

Cancer

Intensive Care

CV Disease

Trauma

Burns

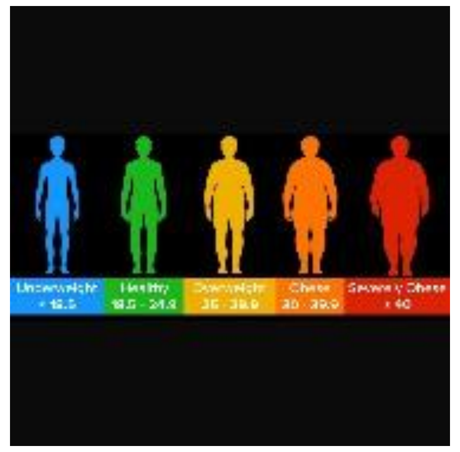
Traumatic Brain Injury, neurosurgery, neurodegenerative diseases

Pain

Bacterial and viral Infections

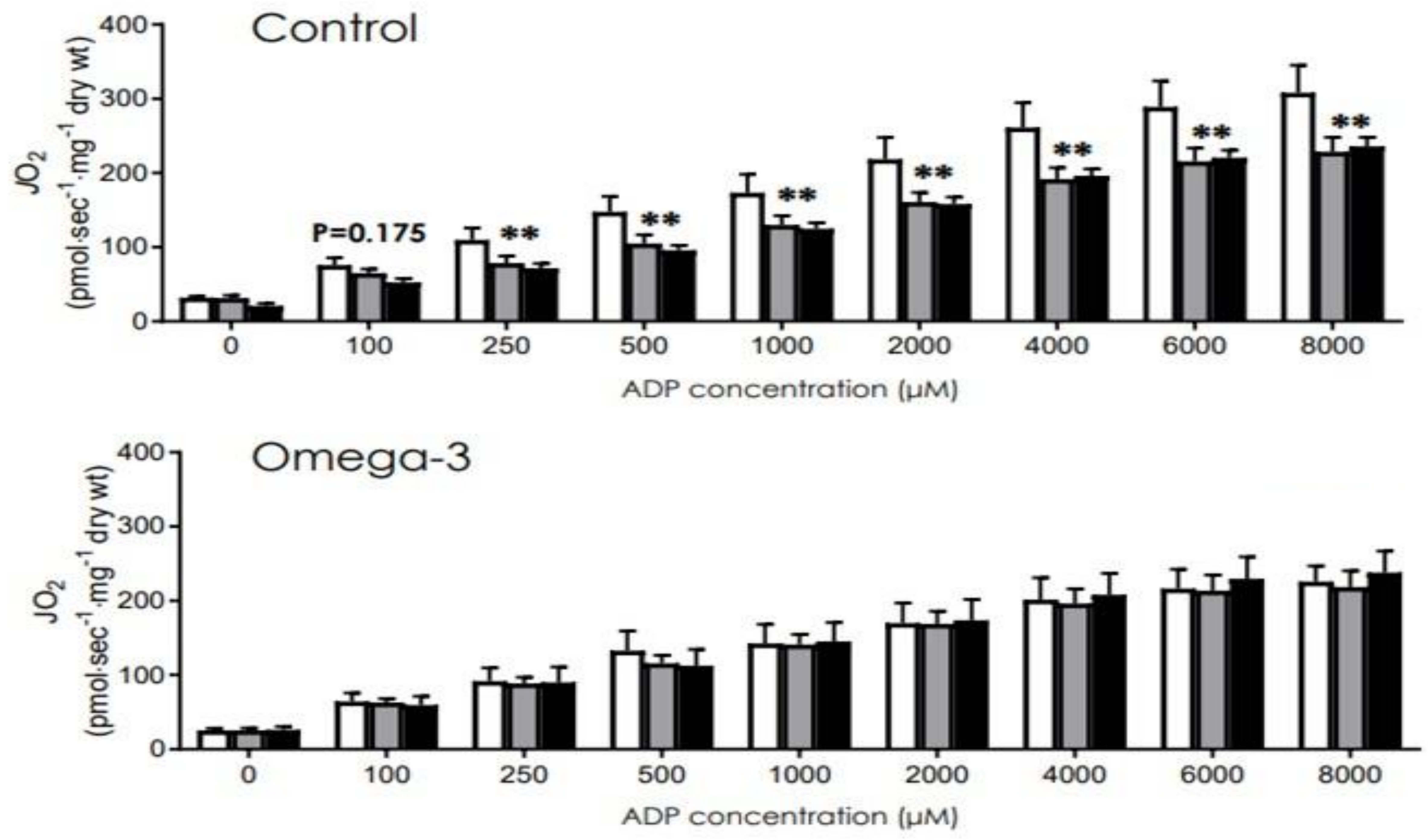
Orthopedic Surgery

Tissue regeneration



Chronic inflammatory Diseases

Omega-3 fatty acids protect against declines in mitochondrial respiration



Miotto PM et al FASEB J 2019

Note: no decrease in mitochondrial respiration in Omega 3 FA group

★ **4 wk 5 gm FO supplement pre immobilization and 2 weeks during immobilization**

SPMs and Muscle Regeneration

Muscle injury models of traumatic or surgical loss of skeletal muscle leads to chronic inflammation and fibrosis

- Macrophage and neutrophil infiltration
  - Macrophages are critical regulators of tissue repair – lack of polarization to M2
- Lack of M1 transition to M2 leads to limited regeneration

RvD1

- Limited degree of inflammation
- Enhanced regeneration
- Enhanced PMN clearance
- Modulated stem cell response

Tx with Maresin 1

- Augments macrophage polarization (conversion from M1 to M2)
- Ameliorates fibrosis
- Improved myogenesis
- Enhanced recovery of muscle strength

Resolvin D1 supports skeletal myofiber regeneration via actions on myeloid and muscle stem cells

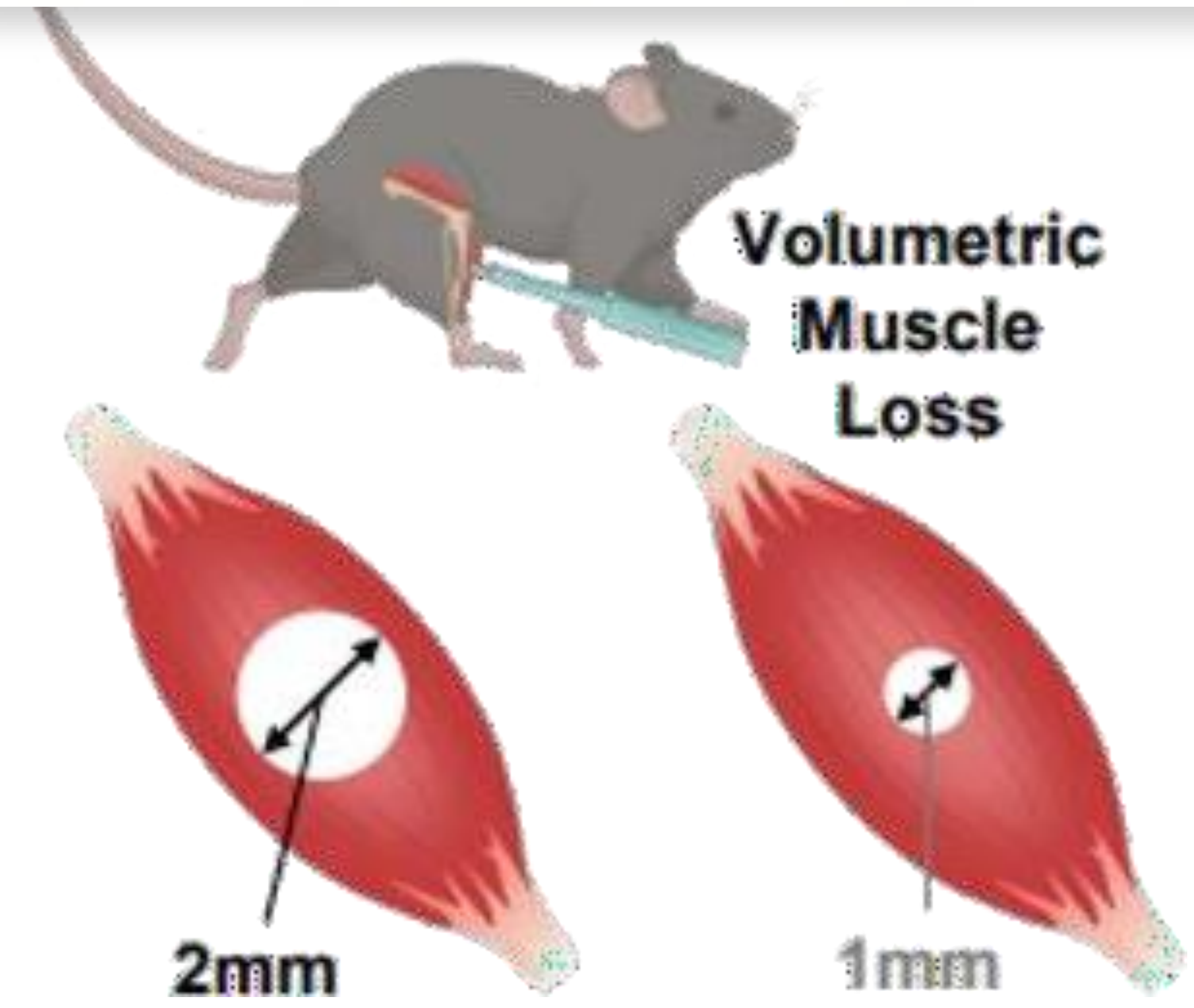
JCI Insight 2020

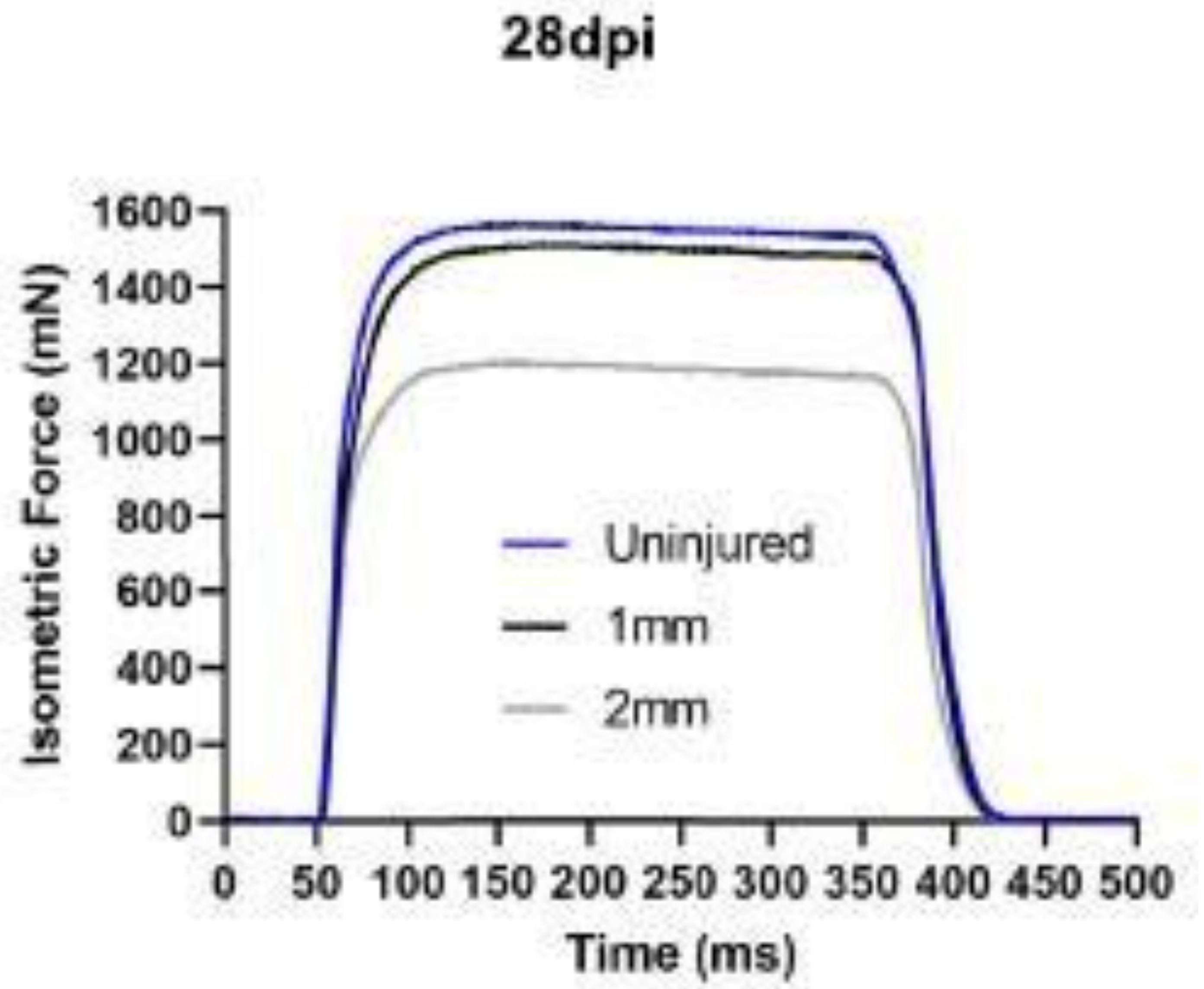
James F. Markworth,[1,2] Lemuel A. Brown,[1] Eunice Lim,[1] Carolyn Floyd,[1] Jacqueline Larouche,[3] Jesus A. Castor-Macias,[3] Kristoffer B. Sugg,[2,4] Dylan C. Sarver,[2,5] Peter C.D. Macpherson,[1] Carol Davis,[1] Carlos A. Aguilar,[3] Krishna Rao Maddipati,[6] and Susan V. Brooks[1,3]

Maresin 1 Repletion Improves Muscle Regeneration After Volumetric Muscle Loss

Jesus A. Castor-Macias[1,2,7], Jacqueline A. Larouche[1,2,7], Emily C. Wallace[1], Bonnie D. Spence[1], Alec Eames[1], Benjamin A. Yang[1,2], Carol Davis[3], Susan V. Brooks[1,3], Krishna Rao Maddipati[4], James F. Markworth[5], Carlos A. Aguilar[1,2,6,*]

eLife 2023





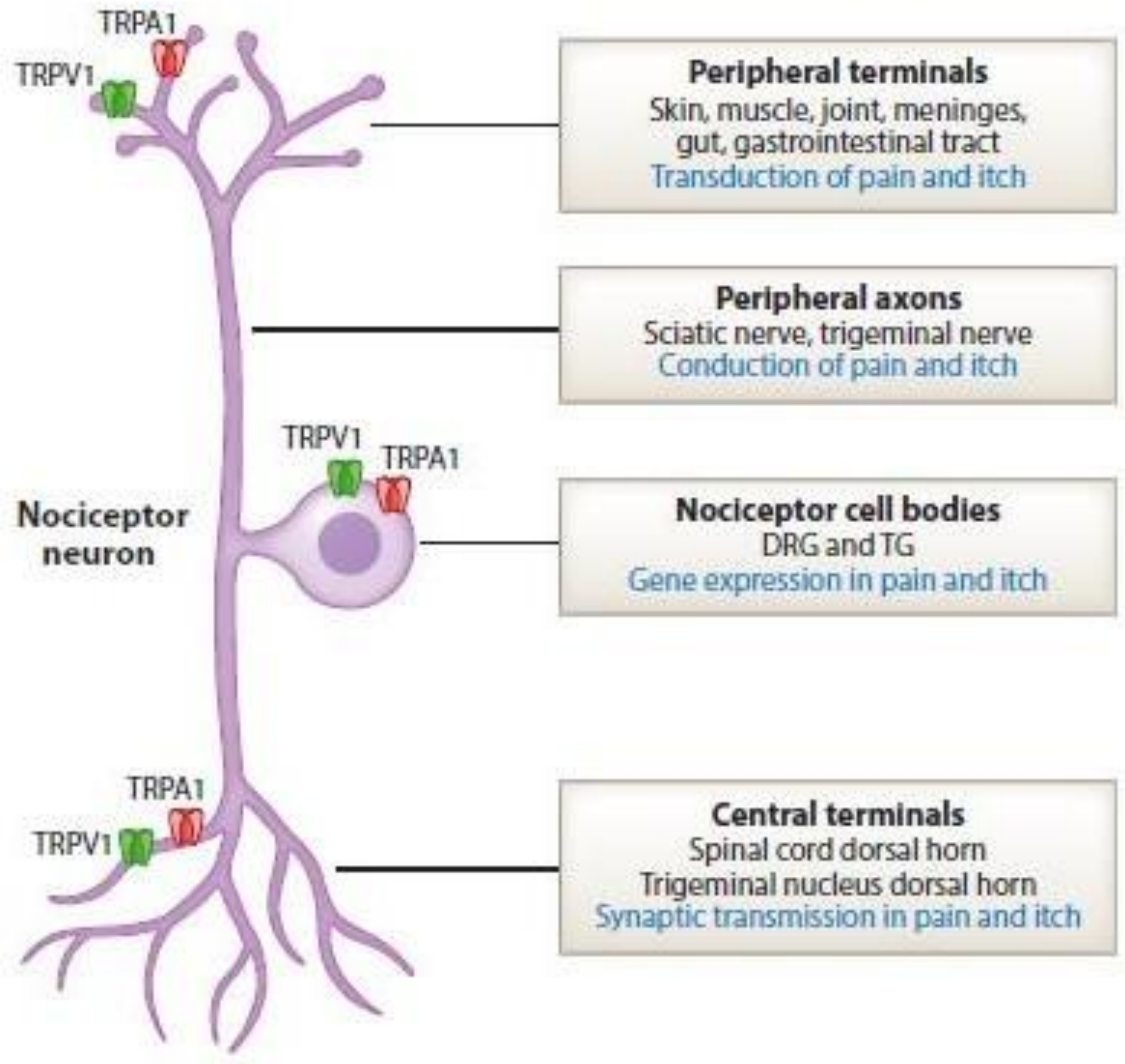
SPMs and multiple benefits in realm of pain control !

- Opioids and NSAIDS have potential detrimental side-effects post op
- Animal models:
  - Decrease pain in inflammatory models – incisional, bone fracture
  - Neuropathic pain – thoracotomy, amputation
  - Multiple models
    - RvD1 RvD2 decrease muscle incisional pain
    - RvD1 and RvD2 decrease post thoracotomy pain
    - RvD1, RvD2, and MaR1 tibial bone fracture model decrease pain
  - Systemic treatment with RvD1 prevented cognitive decline

1) SPMs do not interfere with normal pain perception
2) SPMs serve to restore homeostatic balance without suppressing physiologic pain

Ji RR Ann Rev Pharm Tox 2023

SPMs in Pain models



Ji RR. Ann Rev Pharm and Toxicology 2023

Table 1 Beneficial effects of synthetic SPMs in the control of pain, itch, and inflammatory diseases

Pain/itch model	SPM(s)	Species, route	Effect(s)	Reference(s)
Inflammatory pain				
Capsaicin (TRPV1)	RvE1, RvD2/D3, MaR1, NPD1	mice, IPL	Spontaneous pain ↓	55, 58, 59
Mustard oil (TPA1)	RvD1, RvD2	mice, IPL	Spontaneous pain ↓	57, 58
Formalin	RvE1, NPD1, RvD5	mice, IT	Spontaneous pain ↓	55, 59, 84
Carrageenan	RvD1, RvE1, LXA4, LXB4	mice/rats, IT/IV	Heat and mechanical pain ↓	55, 68
CFA	RvD1, RvD2, RvE1, NPD1	mice, IT	Heat hyperalgesia ↓	55, 58, 59
Visceral pain	RvD2	mice/rats, IP	Visceral pain ↓	60
Bladder pain	RvD2	rats, IT	Mechanical pain ↓	71
Low back pain	LXA4, MaR1	rats, IT	Mechanical pain ↓	72, 73
Vulvodynia	MaR1	mice, topical	Mechanical pain ↓	65
Osteoarthritis	17(*R*)-HDHA, AT-RvD1	rats, IP	Spontaneous and mechanical pain ↓	41, 61
Rheumatoid arthritis	MaR1, AT-RvD1	mice/rats, IP	Mechanical pain ↓	63, 64
Neuropathic pain				
Nerve injury (CCI)	RvE1, MaR1, NPD1	mice, IT	Mechanical and heat pain ↓	83, 87, 88
Spinal cord injury	LXA4	mice, IT	Mechanical allodynia ↓	86
Chemotherapy	RvD1, RvD2, MaR1	mice, IT	Mechanical allodynia ↓	84
Diabetic neuropathy	3-oxa-PD1$_{n-3}$ DPA	mice, IT	Mechanical allodynia ↓	85
Postoperative pain				
Muscle retraction	RvD1, RvE1	rats, IT	Mechanical allodynia ↓	78
Thoracotomy	RvD1, RvD2	rats, IT	Mechanical and nocifensive pain ↓	79
Tibial bone fracture	RvD1, RvD2, MaR1	mice, IV/IT	Mechanical pain ↓	46
Cancer pain				
Oral cancer pain	RvD2	mice, IP	Mechanical and spontaneous pain ↓	96
Bone cancer pain	RvD1, RvE1	mice, IT	Mechanical and thermal pain ↓	95
Dermatitis and itch				
Eczema	LXA4	human, topical	Infantile eczema severely ↓	128
Psoriasiform itch	RvD3	mice, topical	Scratching ↓	124
Cancer itch	3-oxa-PD1$_{n-3}$ DPA	mice, IT	Scratching ↓	85

Specialized pro-resolving mediators: biosynthesis and biological role in bacterial infections

Paul M. Jordan and Oliver Werz

Department of Pharmaceutical/Medicinal Chemistry, Institute of Pharmacy, Friedrich-Schiller-University Jena, Jena, Germany

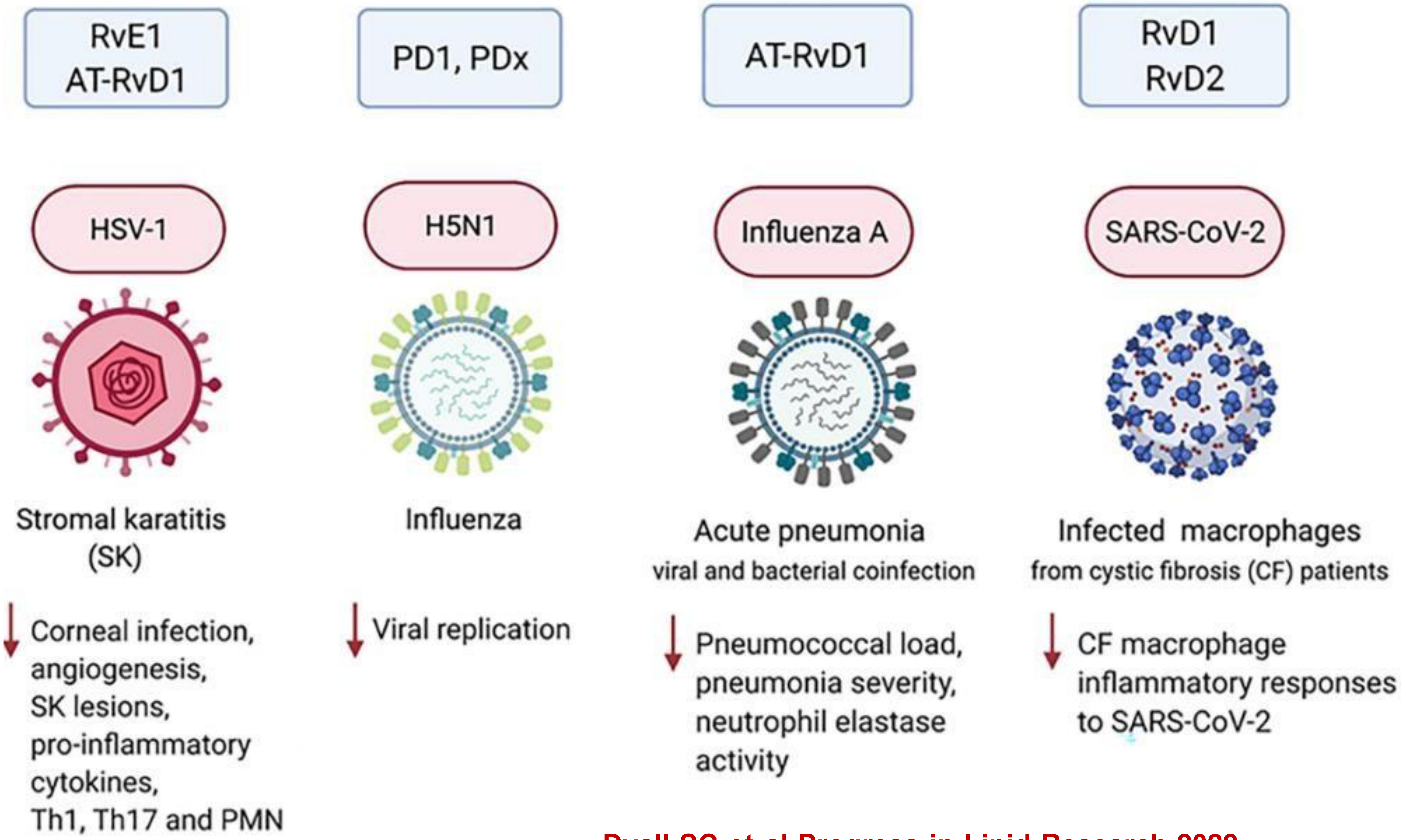
The FEBS Journal 2021

- **SPMs are physiologic immunoresolvents that actively resolve inflammation by:**
  - **Limiting neutrophil influx**
  - **Stimulating phagocytosis**
  - **Enhanced bacterial killing and clearance**
  - **Efferocytosis of apoptotic neutrophils and cellular debris by macrophages (M2)**

- **SPMs:**
  - **prevent collateral tissue damage**
  - **promote tissue repair and regeneration**
  - **lower antibiotic requirements *without* side effects**

The FEBS Journal 2021

Viral Infections: functions of SPMs



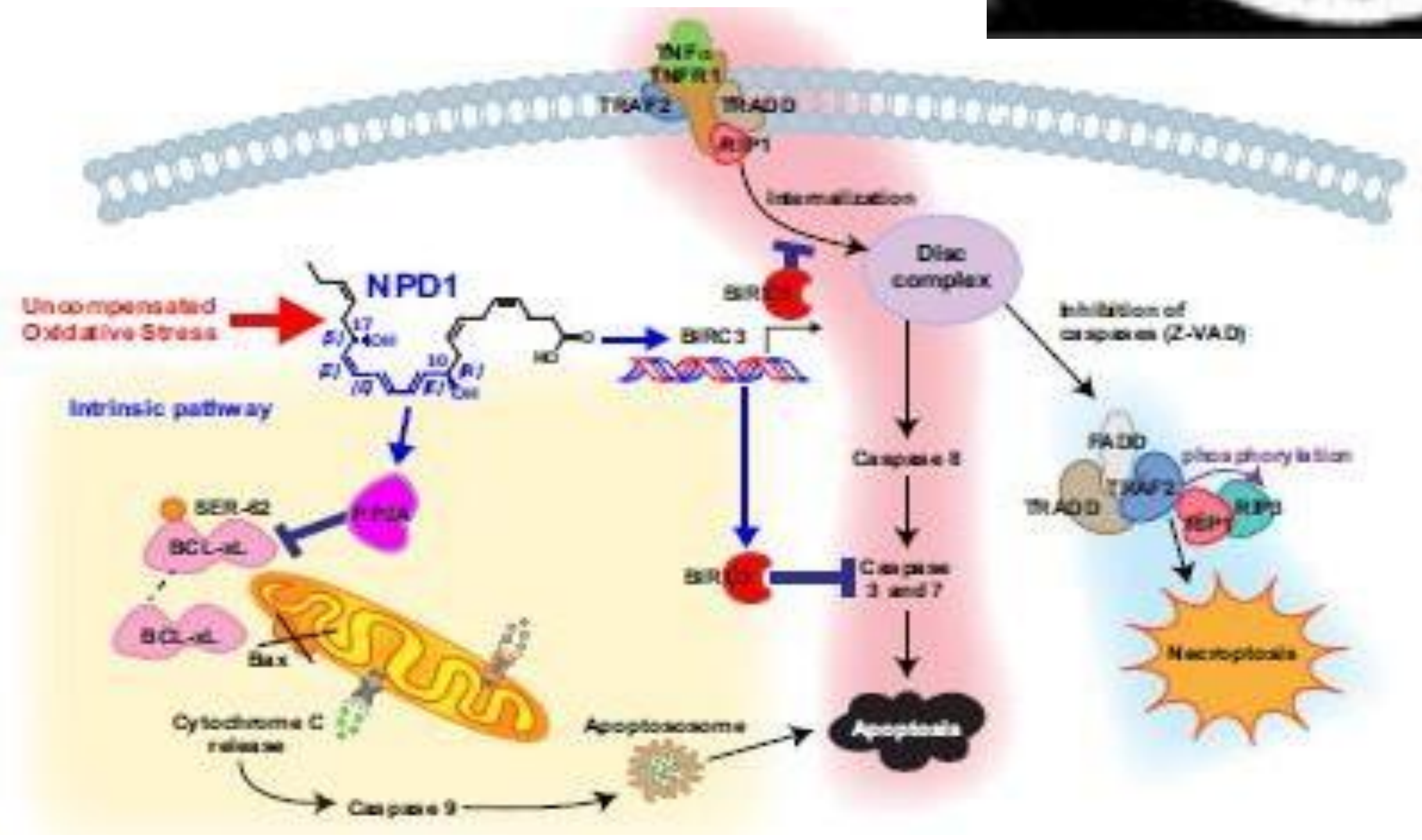
Dyall SC et al Progress in Lipid Research 2022

SPMs: Stroke, TBI, CNS Hemorrhage, Post-op Cognitive Decline

"Neuroinflammation"

- SPM (NPD1) counteracts pro-inflammatory microenvironment following brain injury "Neuroprotective"
- Elovanoids- new "pro-homeostatic" lipid class

- **SPM's Decrease:**
  - Stroke damage
  - PMN entering into injured brain
  - induction of COX-2 and NFkB
  - Injury (cell death) in the penumbra
  - Neuroinflammation
- **Increase CNS cell survival**
  - Activation of pro-apoptotic pathway
  - Induction of pro-survival proteins



Terrando N et al FASEB J 2013, Asatryan A, Bazan NG J Biol Chem 2017 Bazan NG et al NY Acad Science 2017, Jun B et al Sci Reports 2017 Bhattacharjee S et al Sci Adv 2017, Valente M et al Molecules 2022

SPM = specialized pro-resolving mediator; NPD1 = neuroprotectin D1; COX-2 = cyclooxygenase-2; PMN = polymorhonuclear; CNS = central nervous system

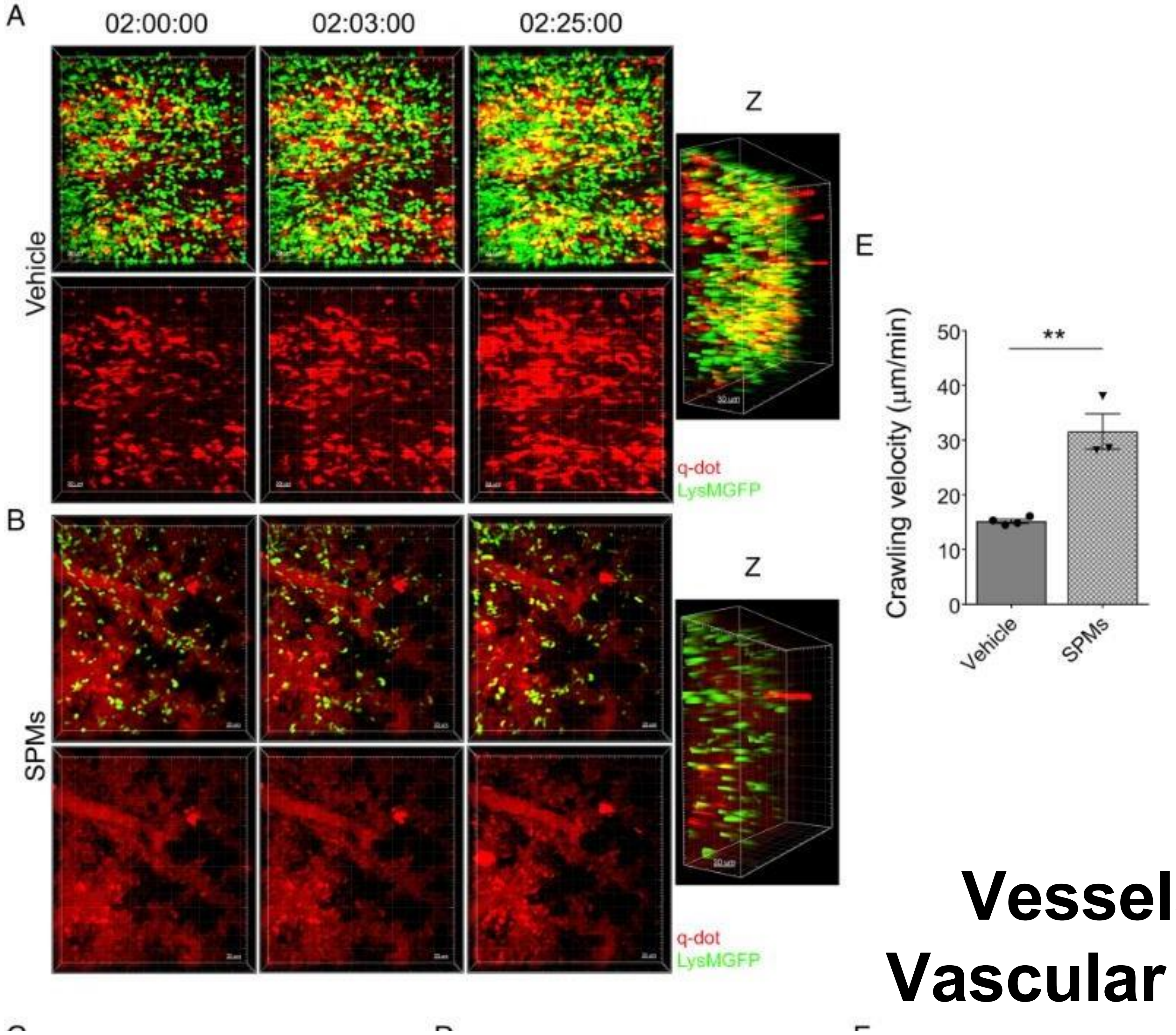
What about Transplant ?

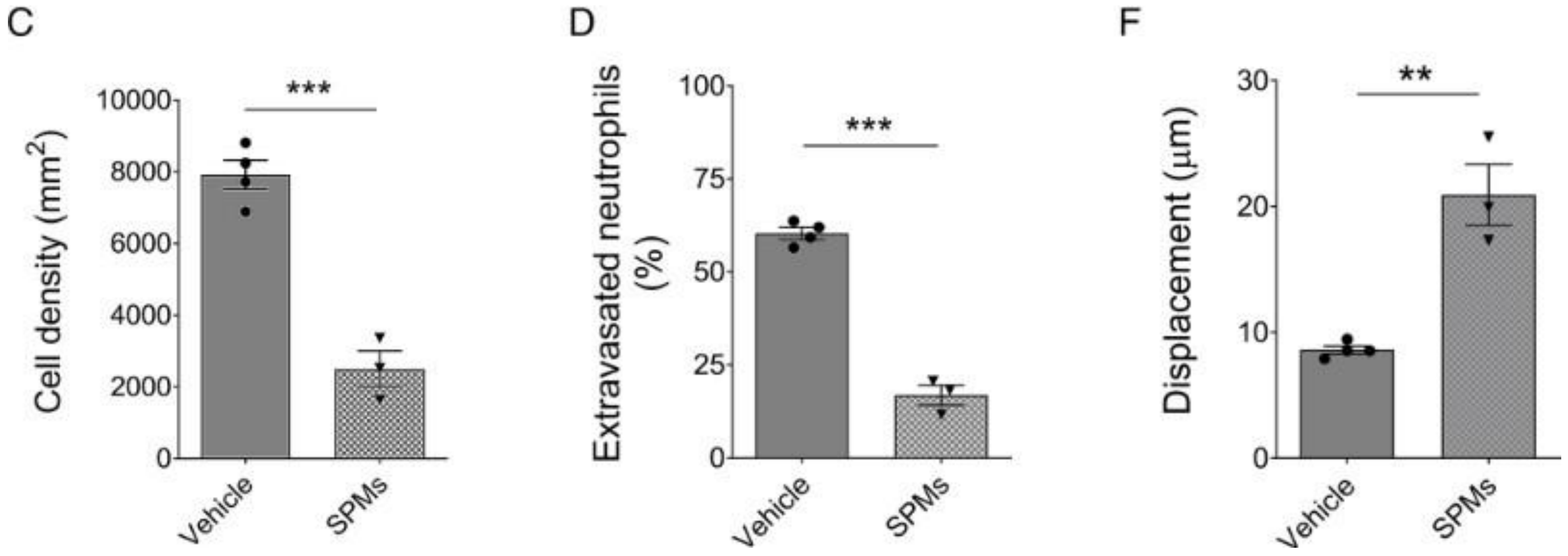
PNAS

RESEARCH ARTICLE | IMMUNOLOGY AND INFLAMMATION

Resolvin D1 prevents injurious neutrophil swarming in transplanted lungs

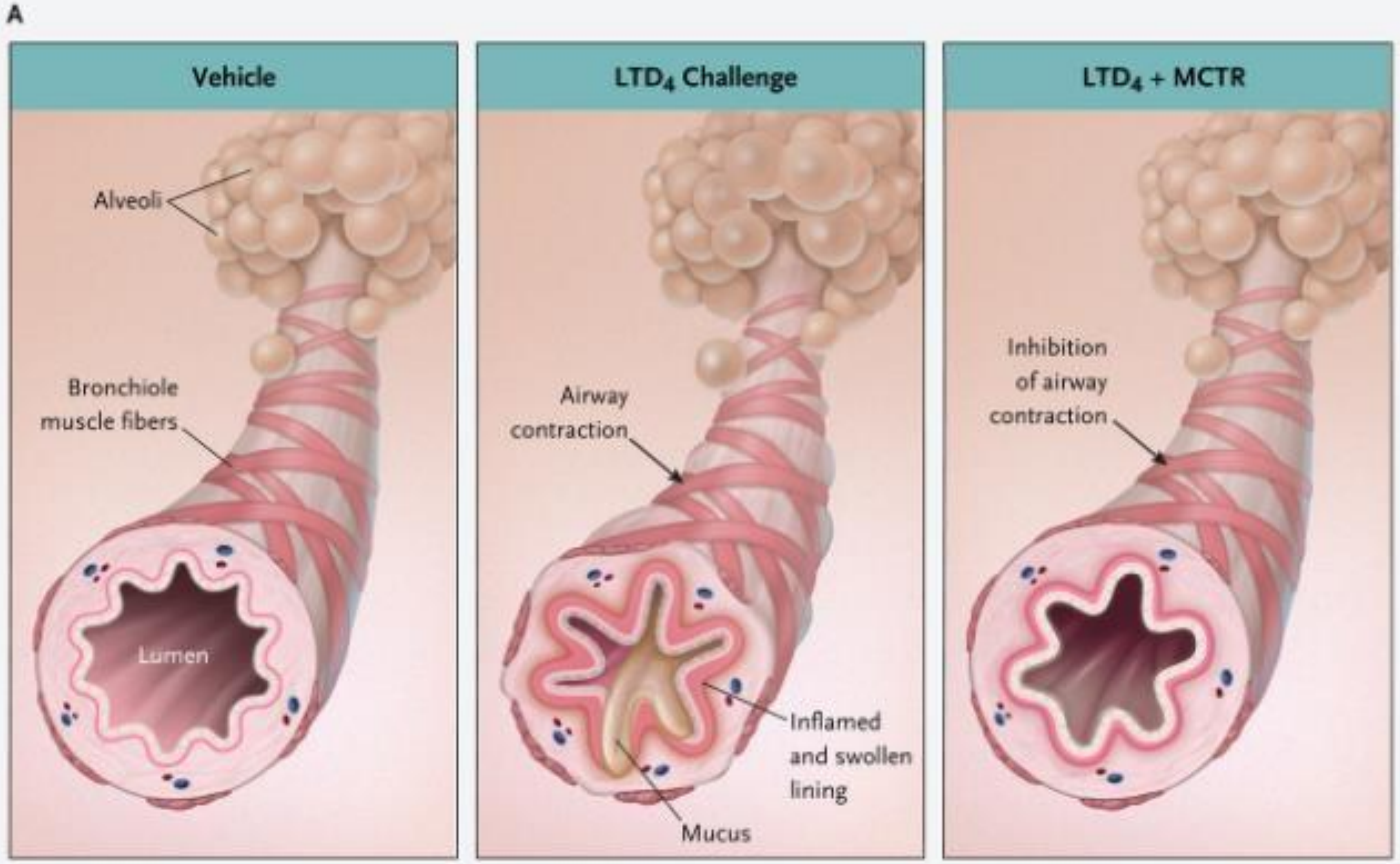
Wenjun Li[a,1], Hailey M. Shepherd[a,1], Yuriko Terada[a], Ashley E. Shay[b], Amit I. Bery[c], Andrew E. Gelman[a,d], Kory J. Lavine[c], Charles N. Serhan[b] and Daniel Kreisel[a,d,2]



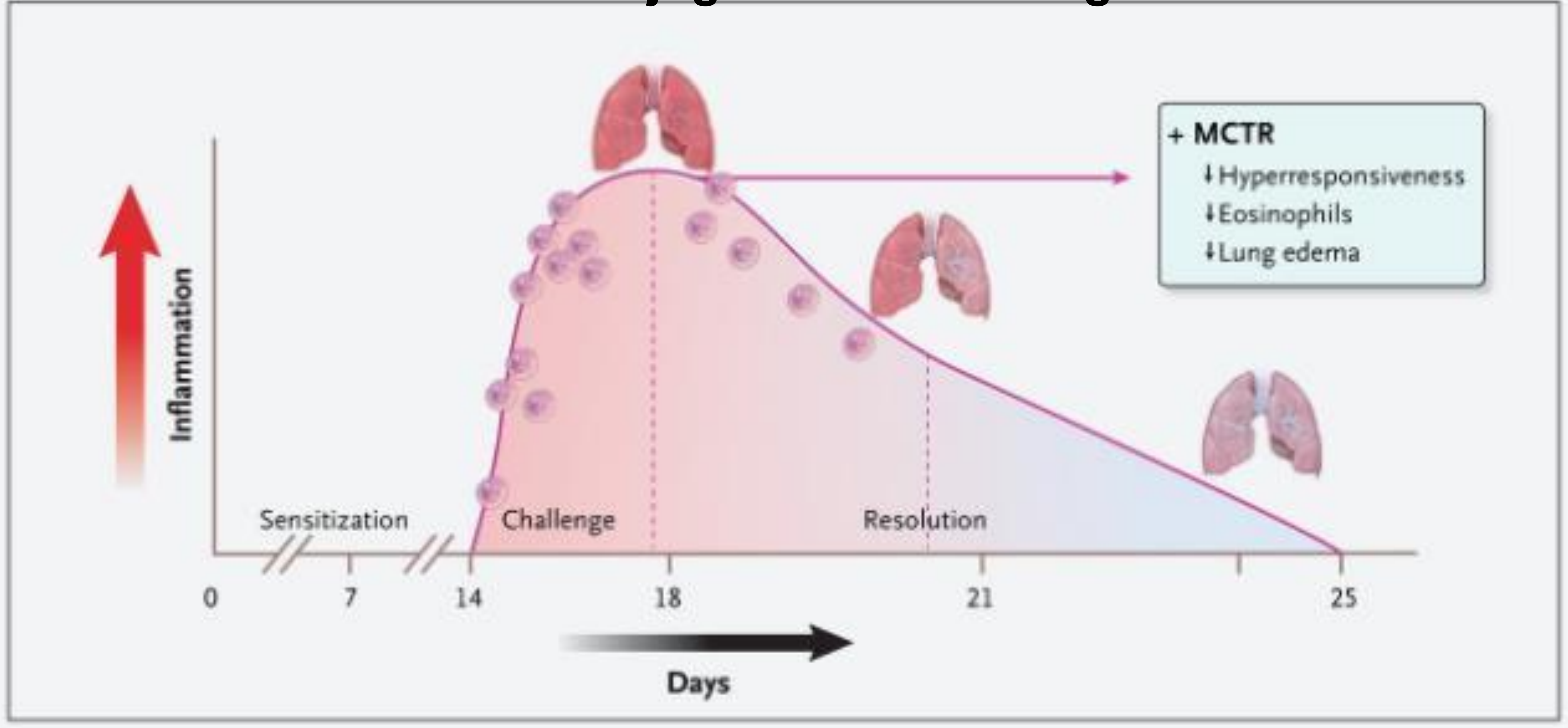


Vessels red : Neutrophils - Green
Vascular leakage diminished with RD1

Li W et al PNAS 2023



B **MCTR – Maresin conjugates in tissue regeneration**



What about reactive airway disease ?

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor*

Balancing the Effect of Leukotrienes in Asthma

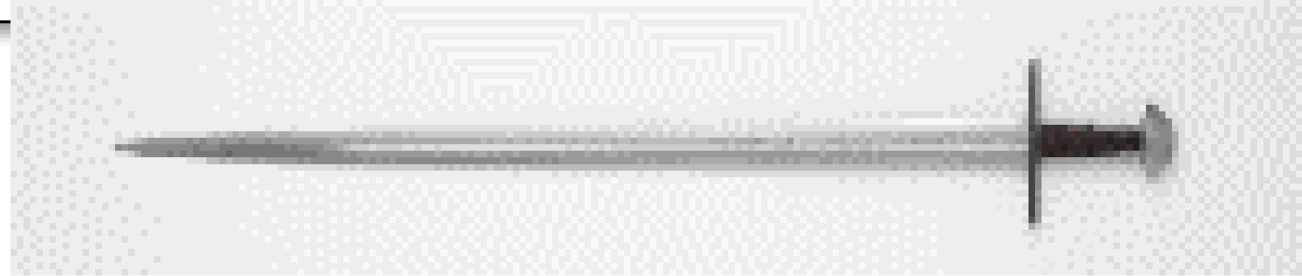
Catherine Godson, Ph.D.

Godson C NEJM 2020

Resolvins suppress tumor growth and enhance cancer therapy

Journal of Experimental Medicine 2018

Megan L. Sulciner,[1,2,3*] Charles N. Serhan,[4*] Molly M. Gilligan,[1,2,3*] Dayna K. Mudge,[1,2,3*] Jaimie Chang,[1,2,3] Allison Gartung,[1,2,3] Kristen A. Lehner,[1,2,3] Diane R. Bielenberg,[5] Birgitta Schmidt,[6] Jesmond Dalli,[4] Emily R. Greene,[1,2,3] Yael Gus-Brautbar,[1,2,3] Julia Piwowarski,[1,2,3] Tadanori Mammoto,[5] David Zurakowski,[7,8] Mauro Perretti,[12] Vikas P. Sukhatme,[3,9] Arja Kaipainen,[13] Mark W. Kieran,[10,11*] Sui Huang,[14*] and Dipak Panigrahy[1,2,3*]



- Cancer treatment is a double edge sword:
  - Cancer therapy reduces tumor burden by killing tumor cells
  - Treatment creates tumor cell debris that stimulates inflammation and tumor growth
    - Increase metastatic disease in animal models

- Debris-stimulated tumors were inhibited by anti-inflammatory and pro-resolving lipid mediators
  - Resolvin D1 (RvD1), RvD2, or RvE1

- Enhancing endogenous clearance of tumor cell debris is a new therapeutic target in cancer therapy

L’importanza degli omega 3

Metanalisi Pradelli et al 2020

Meta-analisi di confronto tra NP arricchita con acidi grassi omega-3 e NP senza omega-3 (standard) in pazienti adulti ospedalizzati

p<0,0000 1

Riduzione significativa del 40% del rischio di infezioni

(24 studi con 2.154 pazienti)

p<0,0000 1

Riduzione significativa della degenza in ospedale di 2,14 giorni

(26 studi con 2.182 pazienti)

P<0,01

Riduzione significativa della degenza in terapia intensiva di 1,95 giorni

(10 studi con 882 pazienti)

P=0,0000 4

Riduzione significativa del 56% del rischio sepsi

(9 studi con 1.141 pazienti)

Pradelli L, Mayer K, Klek S, et al. ω-3 Fatty-Acid Enriched Parenteral Nutrition in Hospitalized Patients: Systematic Review With Meta-Analysis and Trial Sequential Analysis. JPEN J Parenter Enteral Nutr. 2020;44(1):44-57

L’importanza degli omega 3

Costo-efficacia

L‘aumento dell‘efficacia clinica con la Nutrizione Parenterale con acidi grassi Omega-3 porta a una significativa riduzione del costo medio per paziente adulto in tutte le strutture ospedaliere europee e statunitensi indagate.

Pazienti ospedalizzati in Italia (Pradelli et al, JPEN 2020)

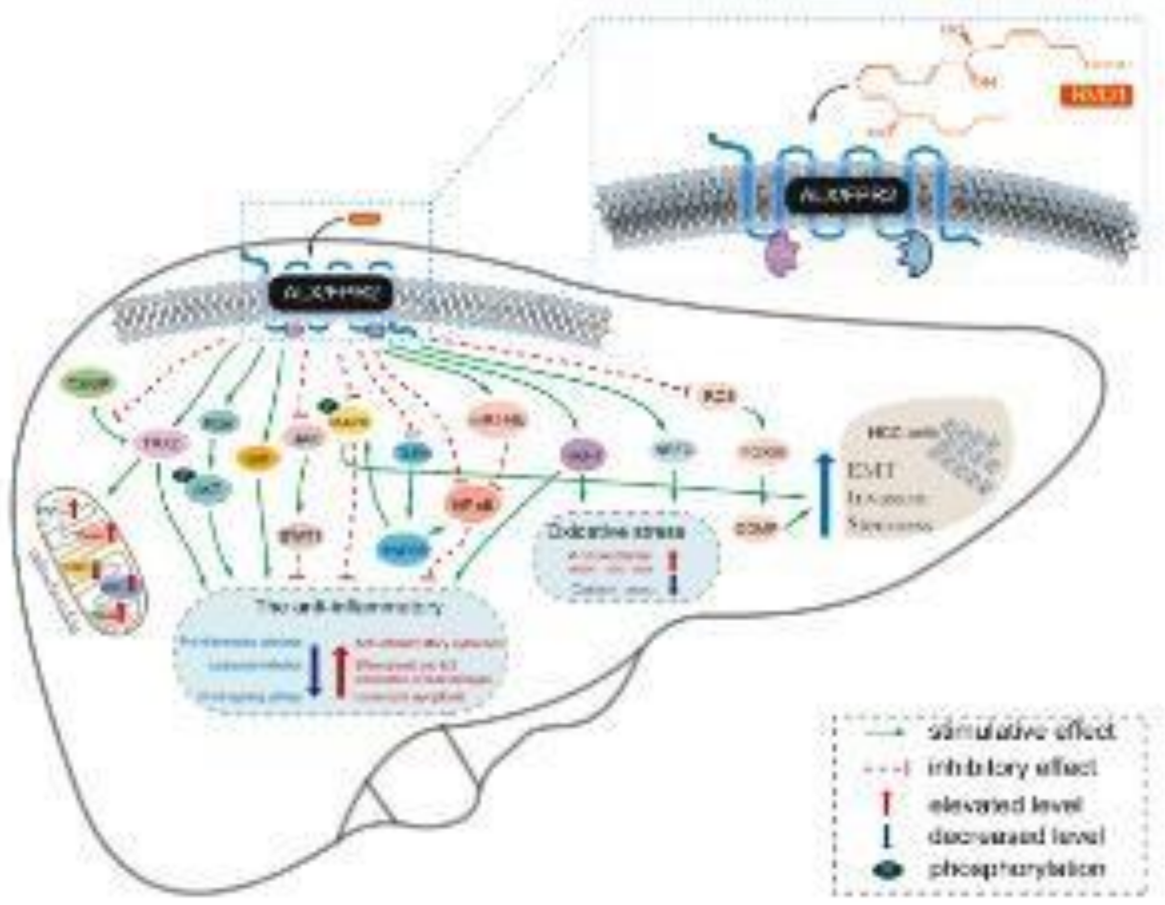
Costo medio ± SD (€)	PN	Infezione	Degenza	Totale
PN con ω-3	938 ± 523	396 ± 760	27,549 ± 25,442	28,883 ± 25,533
PN Standard (senza ω-3)	589 ± 338	657 ± 887	29,378 ± 25,647	30,624 ± 25,741
∆	349 ± 189	-261 ± 1,152	-1,829 ± 483	**-1,741 ± 1,284**

Pazienti in terapia intensiva in Italia (Pradelli et al, Critical Care 2020)

Costo medio ± SD (€)	PN	Infezione	Degenza	Totale
PN con ω-3	918 ± 557	531 ± 838	37,928 ± 31,886	39,377 ± 31,934
PN Standard (senza ω-3)	579 ± 362	833 ± 923	41,308 ± 31,886	42,719 ± 31,915
∆	339 ± 202	-302 ± 1,242	-3,380 ± 0	**-3,342 ± 1,254**

What is the evidence that animal models have shown to be potentially clinically relevant in intensive care patients ?

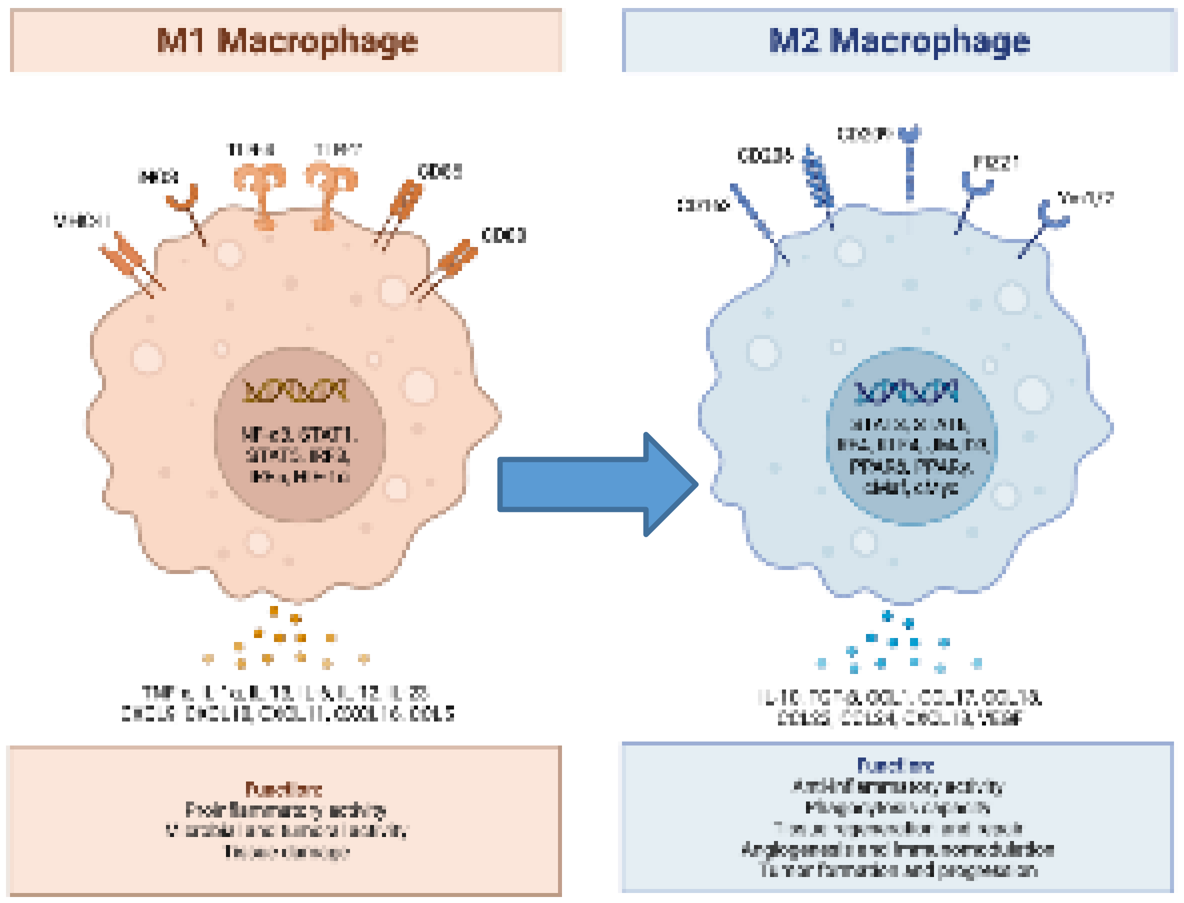
- **Improves muscle metabolism in several inflammatory diseases, injury, tissue loss [(1)], stimulates muscle regeneration in animal model**
- **RvD1 inhibits mitochondrial damage in cardiac ischemia [(3)]**
- **RvD1 therapeutic target for ARDS [(4)]**
- **RvE3 ameliorates diet and stress induced insulin resistance [(5)]**
- **RvD1 reported to decrease post-op cognitive decline [(6)]**
- **RvD1 improves acute hepatic injury, I/R, NAFLD, fibrosis, Ca[(2)]**



1. Engelen MPKJ et al Am J Clin Nutr 2022
2. Yang M et al Prostaglandins lipid mediators 2022
3. Zhang J et al 2022
4. Molaei E et al Euro J Pharm 2021
5. Shimizu T et al FASEB journal 2022
6. Terrando N et al FASEB J 2013

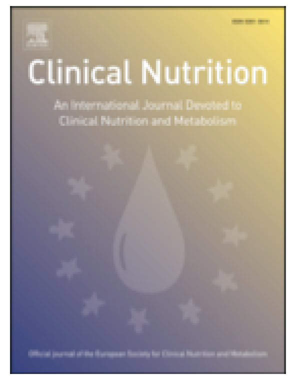
What is the evidence that SPM's have a potential to be clinically relevant in the ICU ?

- **Decreases postop edema pain, neuropathic pain, cancer pain etc (1)**
- **SPM serum profiles linearly correlated with outcomes in obesity, pregnancy and ICU(2)**
- **SPMs are key to appropriate host response both viral and bacterial infections (3, 4)**
  - **Enhance bacterial killing by macrophages and neutrophils**
  - **Increase antimicrobial peptides**
  - **Disrupts biofilm production**
  - **Potentiates action of antibiotics**
- **Accelerates removal of inflammatory and necrotic debris (5,6)**
  - **Seen in cancer therapy (radiation and chemo) trauma, and surgery**
- **Enhances conversion M1 to M2 macrophages (resolution macrophages) (7)**



1. Ji RR et al Ann Rev Pharm and Toxicololgy 2022
2. Dalli J Molecular Biol 2017, Dali J CCM 2017
3. Chiang N et al Essays in Biochem 2020
4. Thornton JM et al Molecules 2021
5. Baidoo JNE Int J Molecular Sci 2021
6. Sulcinar ML et al J Exp Med 2018
7. Shay AE et al PNAS 2021

OREGON HEALTH & SCIENCE UNIVERSITY
OHSU



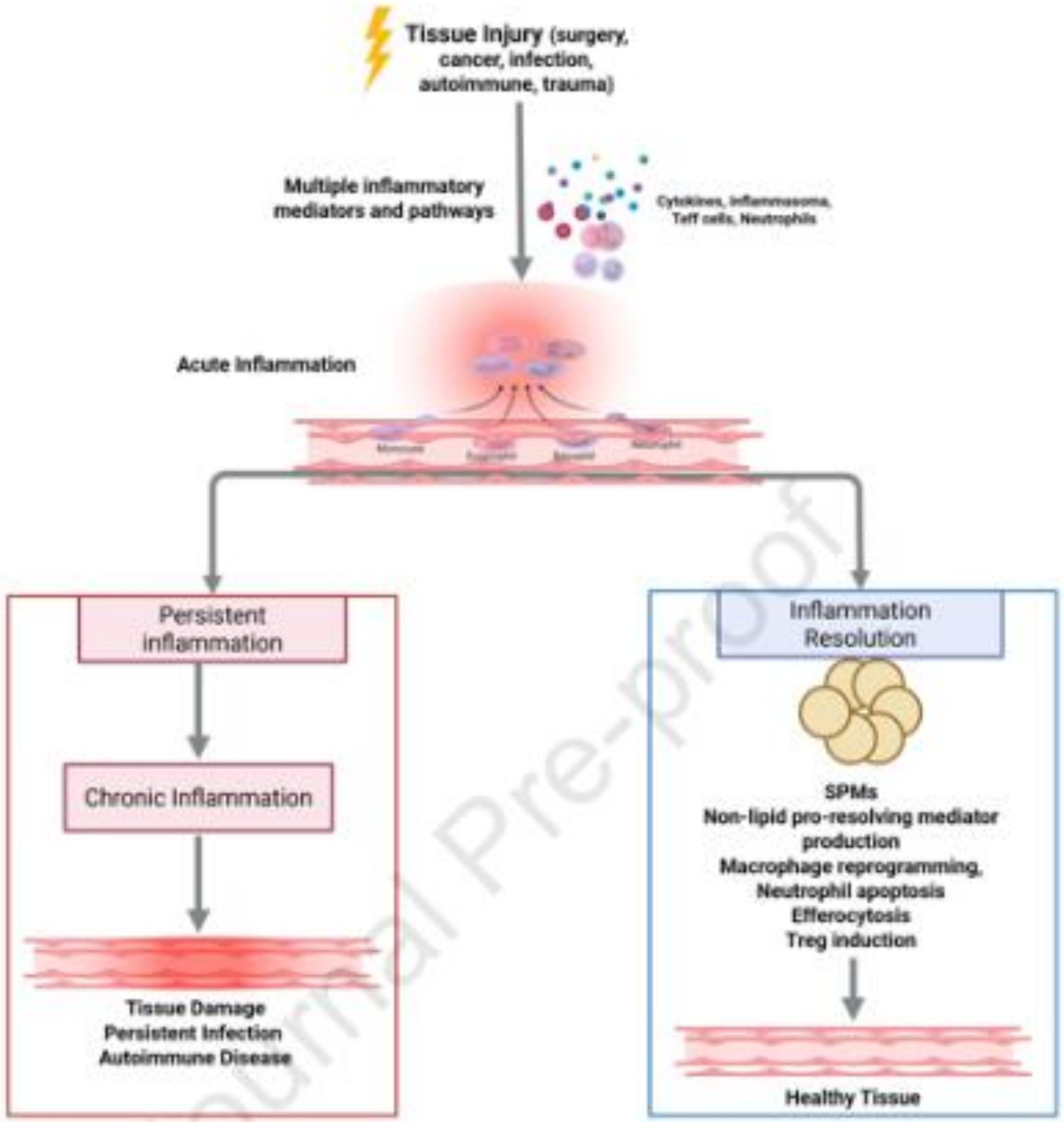
Integrating Downstream Mediators of Omega-3 Fatty Acids into Enteral Nutrition for Improved Patient Care: An Expert Panel Consensus

Robert Martindale, MD, PhD, Manpreet S. Mundi, MD, Dan Waitzberg, MD, PhD, Elisabeth De Waele, MD, PhD, Marialaura Scarcella, MD, Michele Umbrello, MD, Philip C. Calder, PhD, DPhil, Jesmond Dalli, PhD, Zudin Puthucheary, MD, PhD, Arthur R.H. van Zanten, MD, PhD

Table 3: Evidence of SPMs-mediated inflammation resolution in disease states.

Disease Area	SPMs Involved	Mechanisms/Benefits	Preclinical/Clinical Evidence	References
Hypertension	RvD1, RvD2, RvE1, MaR1	Lower blood pressure, improved vasomotor function, reduced cardiac hypertrophy, decreased cytokine expression, increased NO and prostacyclin.	Preclinical (murine models of Ang II-induced hypertension)	[50-53]
Atherosclerosis	RvD1	Restored RvD1/LTB4 ratio, reduced plaque necrosis, and improved fibrous cap integrity.	Animal models and human lesion studies	[26]
Aortic Valve Disease	RvE1	Reduced valve calcification and inflammation, reversed arterial remodeling, associated with FADS polymorphisms.	Tissue and genetic studies	[17,28,54]
Infectious Diseases	RvE1, PD1, PDX, AT-RvD1	Enhanced microbial clearance, reduced inflammation, inhibited viral replication, effective in bacterial-viral co-infections.	Murine models (HSV, influenza, pneumonia)	[55-57]
Neurodegenerative Diseases	LXA4, LXB4, RvD1, PD1, MaR1	Suppressed monocyte activation, reduced migration across BBB, restored lipid mediator balance, correlated with disease severity.	Human samples and experimental BBB models	[58,59,61-63]
Pain Modulation	RvD1, RvD2, MaR1	Reduced inflammatory and neuropathic pain, preserved normal nociception, and restored balance in pain pathways.	Animal models (incisional, fracture, thoracotomy pain)	[67]
Cancer	RvD1, RvD2, MaR1	Reduced pro-inflammatory signaling, modulated macrophage polarization (M2 to M1), decreased VEGF production, and limited angiogenesis.	Preclinical studies on tumor progression and TAMs	[69,70]
Obesity and Metabolic Syndrome	RvD1, RvD2	Improved insulin sensitivity, reduced inflammatory cytokines, improved autophagy, and ER stress response.	Preclinical and clinical studies in obese subjects and mice	[14,77]

Journal Pre-proof



The role of lipid emulsions containing omega-3 fatty acids for medical and surgical critical care patients

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Critical Care Medicine 2024

Shorter ICU stay

ICU length of stay significantly reduced by 1.95 days[27]

Shorter hospital stay

Hospital length of stay significantly reduced by 2.14 days[27]

Lower relative risk of infections

40% significant reduction in relative risk of infection rate in non-ICU and ICU patients[27]

Lower relative risk of sepsis

56% significant reduction in the risk of sepsis[27]

27. Pradelli L et al. JPEN J Parenter Enteral Nutr. 2020;44(1):44-57

ICU, intensive care unit; PN, parenteral nutrition

Key Take Home Messages

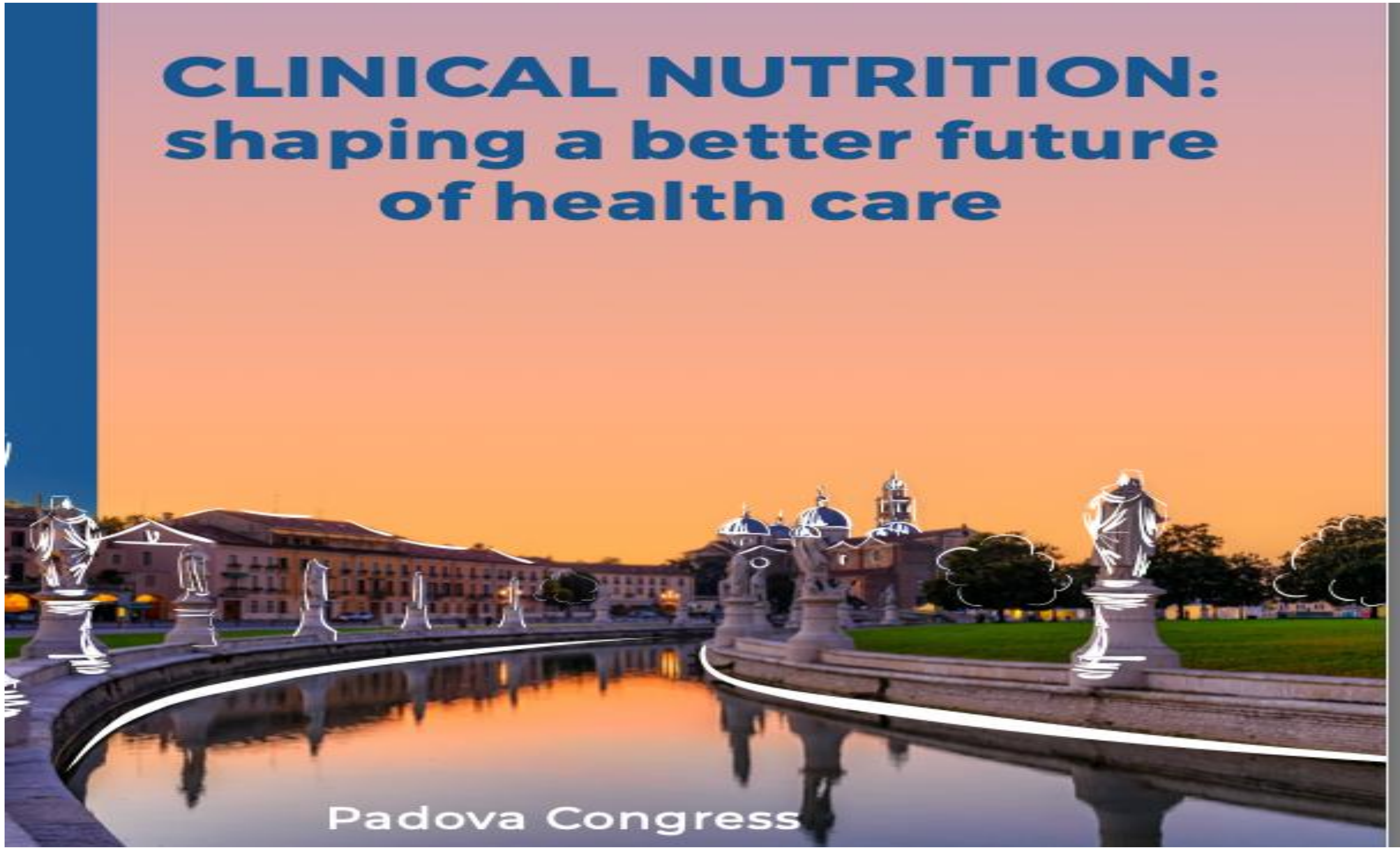
- Lo stato infiammatorio è un processo Biosintetico attivo

- *L'avvio ed il potenziamento della risoluzione dello stato infiammatorio è dovuta a molteplici e noti meccanismi di azione*

- Gli SPMs offrono una riposta plausibile a molte domande ancora aperte riguardo ai meccanismi a valle degli acidi grassi Omega tre (Immunonutrizione).

- Gli SPMs porteranno ad un nuovo insieme di Terapie nutrizionali mirate, basate sulla modulazione dell'immunità e sul metabolismo di precisione per i pazieti in ICU.

GRAZIE



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