



# PURINES (A/G) AND PYRIMIDINES (C/T) SENSORS AND EXTRACELLULAR MESSENGERS FOR LIFE.

JUDY A. MIKOVITS, PhD

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“VACCINATION IS NOT IMMUNIZATION, IT’S EXTERMINATION/STERILIZATION”

# Hematopoietic Stem Cell : the Orchestrator of the Development of Humans

## TGF $\beta$ : The Conductor of the 1 Billion Blood Cells Produced Each Day

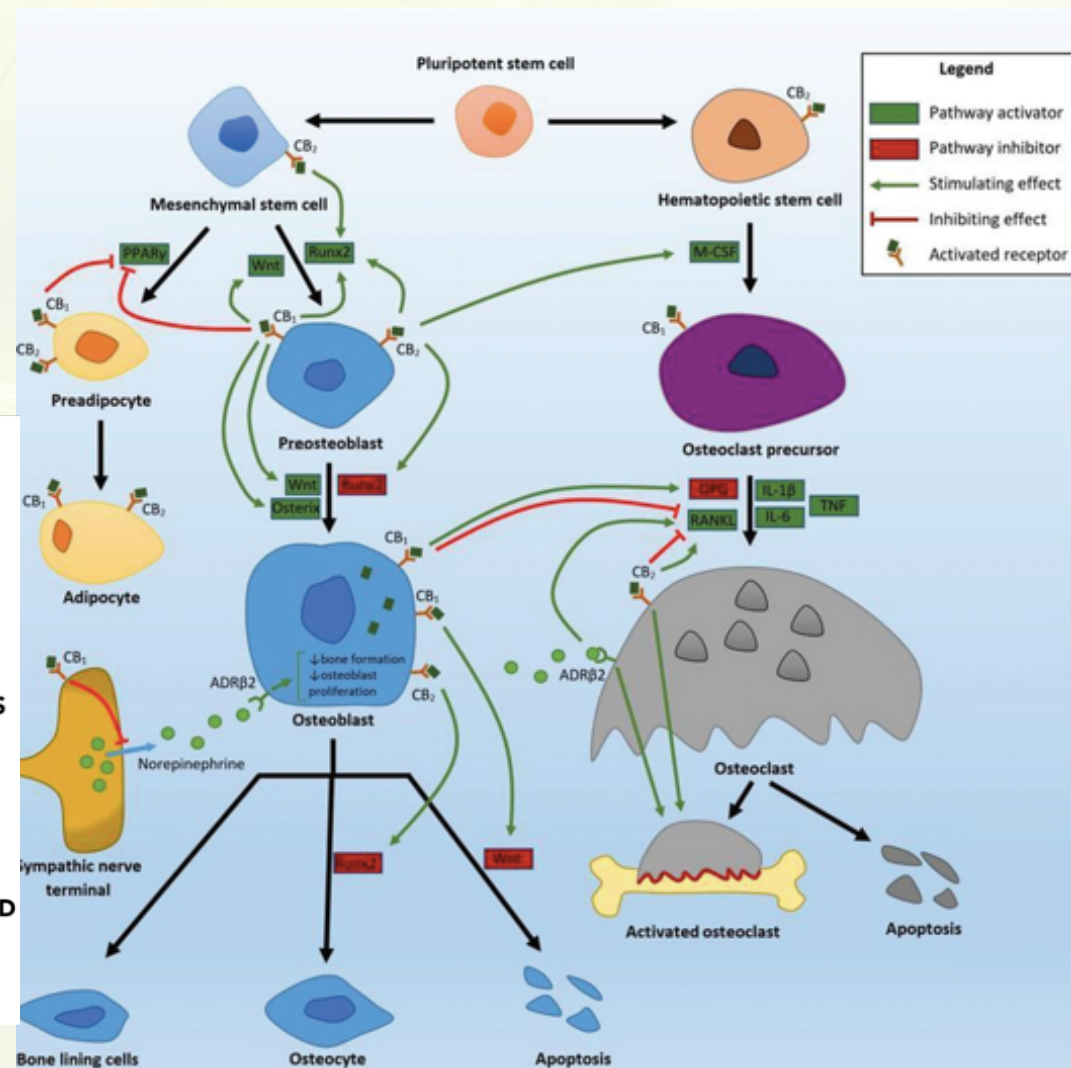
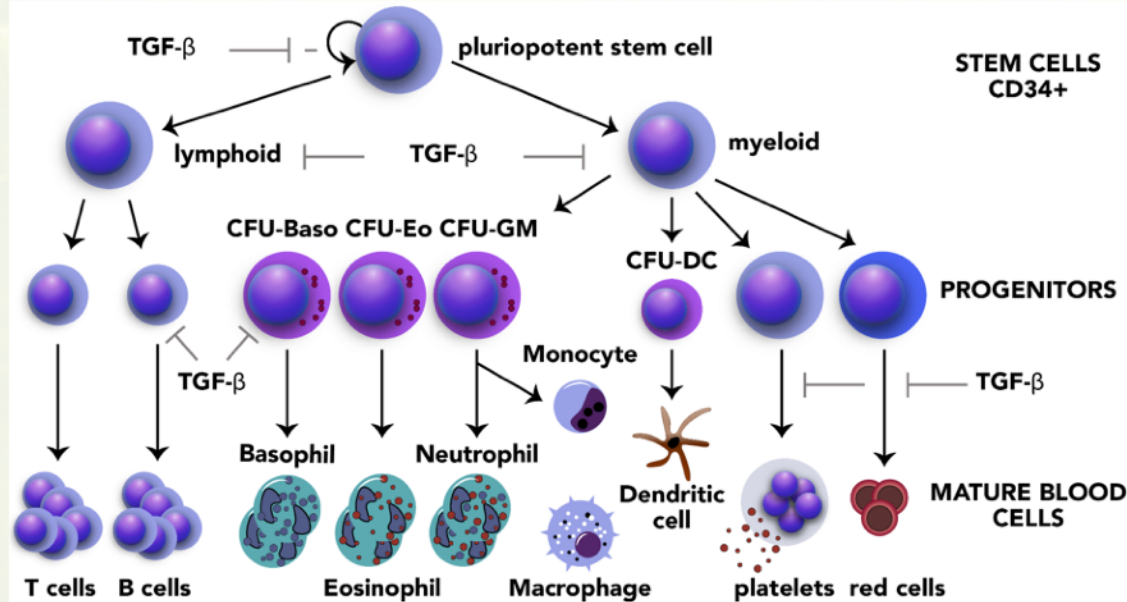
Trends in Neurosciences

### Review

## Ion Channel Functions in Early Brain Development

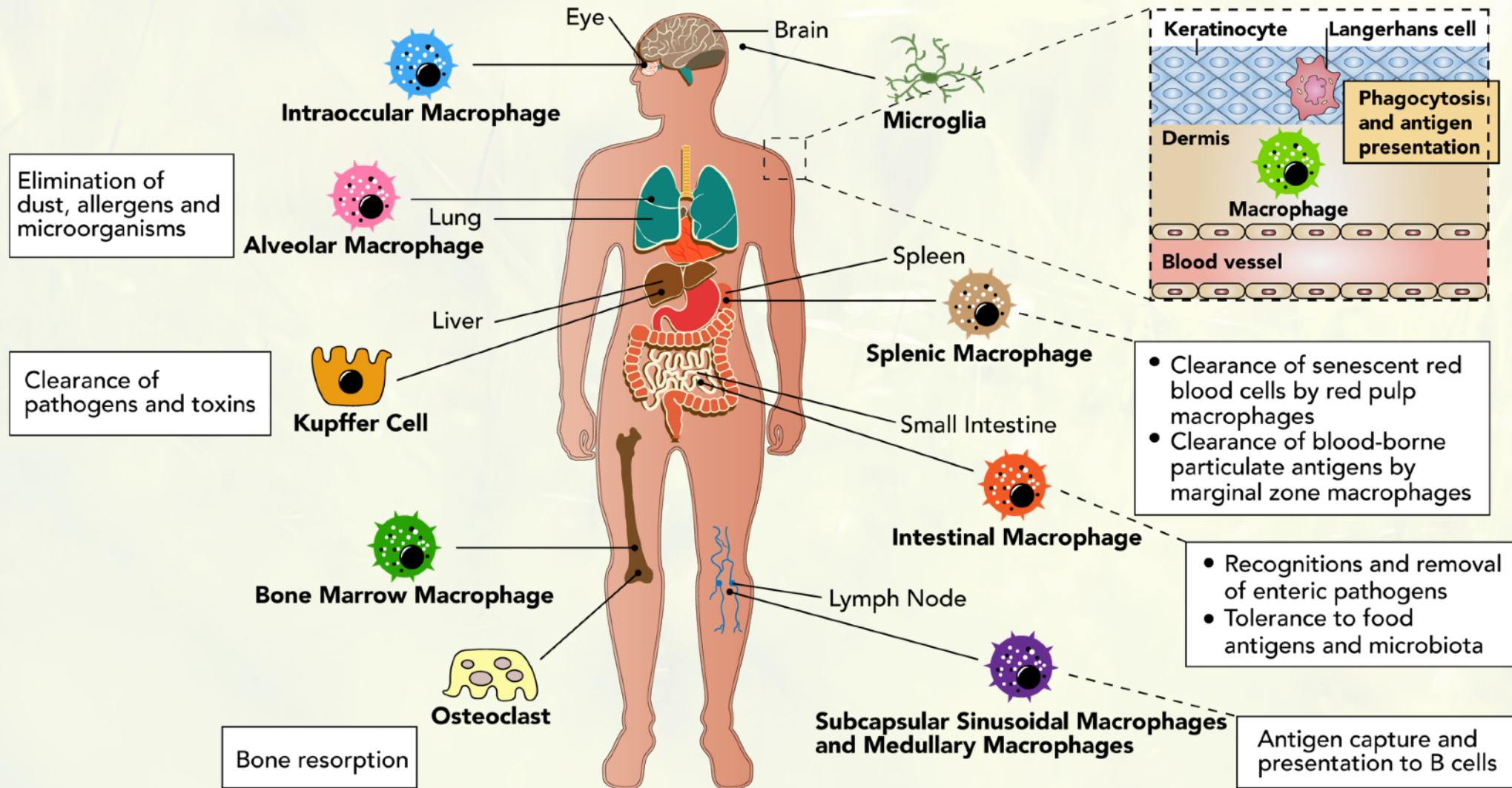
Richard S. Smith<sup>1,\*</sup> and Christopher A. Walsh<sup>1,\*</sup>

### TGF Beta: a Master Regulator of the Hematopoietic Stem Cell

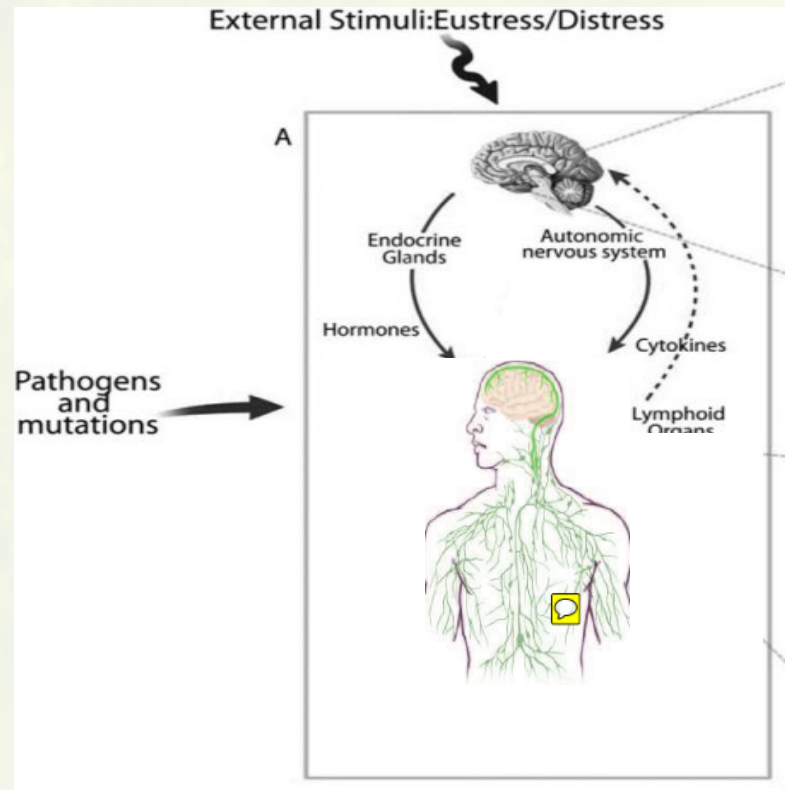




# Tissue macrophage stem cells: key homeostatic communication between purine/pyrimidine sensors and signaling via ECS



# The brain and immune system are inextricably linked from conception



**Stimuli**  
Loss of cell: cell communication,  
matrix breakdown, infections,  
vascular damage.



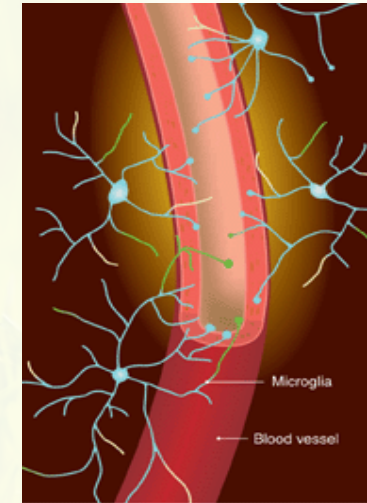
**Homeostasis**  
Phagocytosis of  
debris, neurotrophis

others

**Damage**  
Neurotoxins, phagocytosis of  
normal neurons, apoptosis



**Parkinson's  
Disease  
ALS, Alzheimers  
ME/CFS, Cancer**

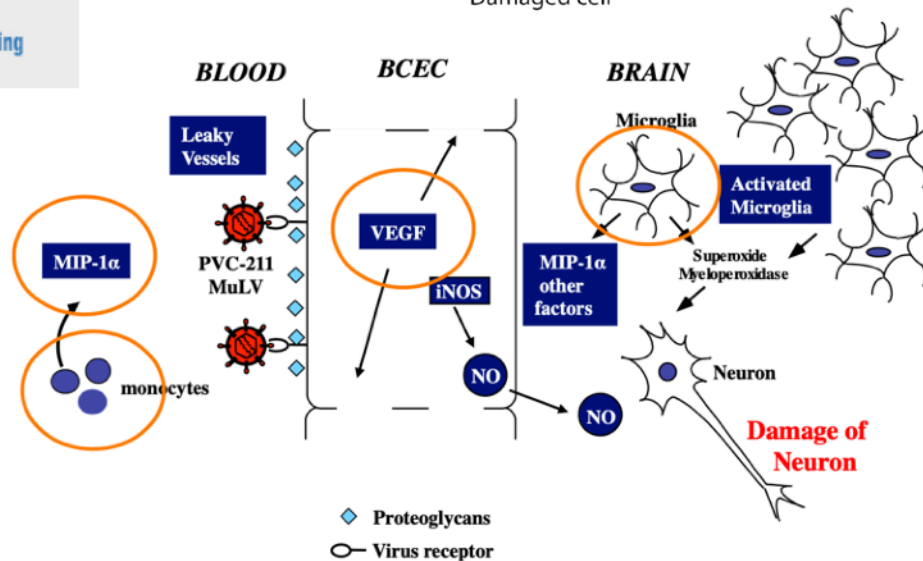
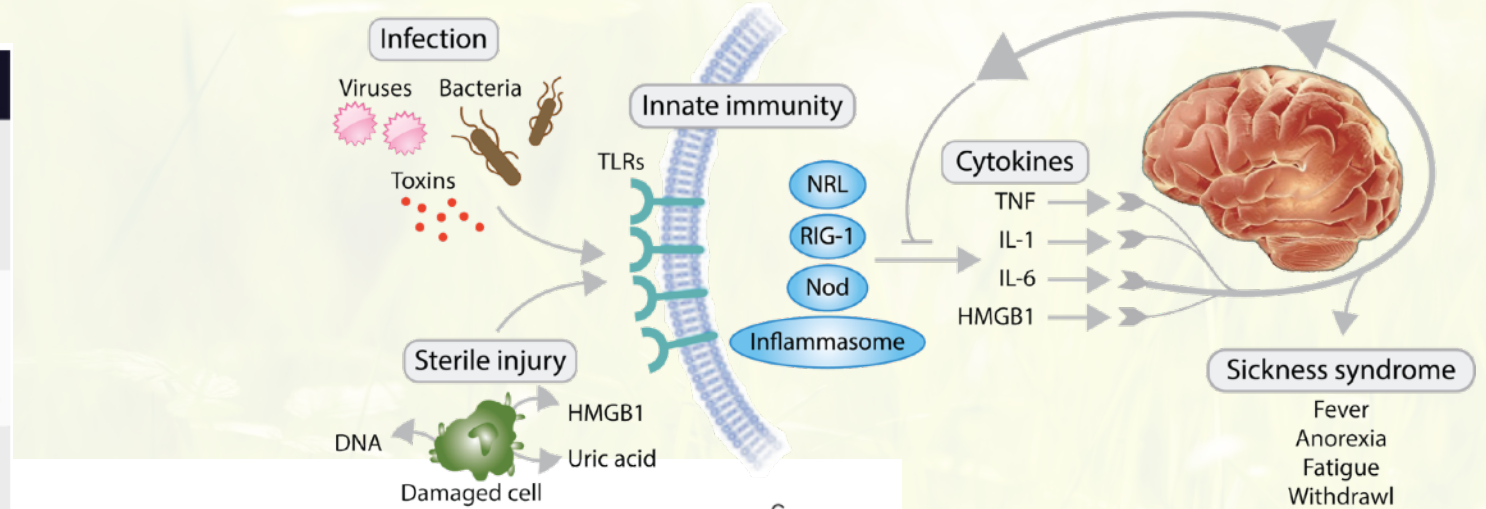
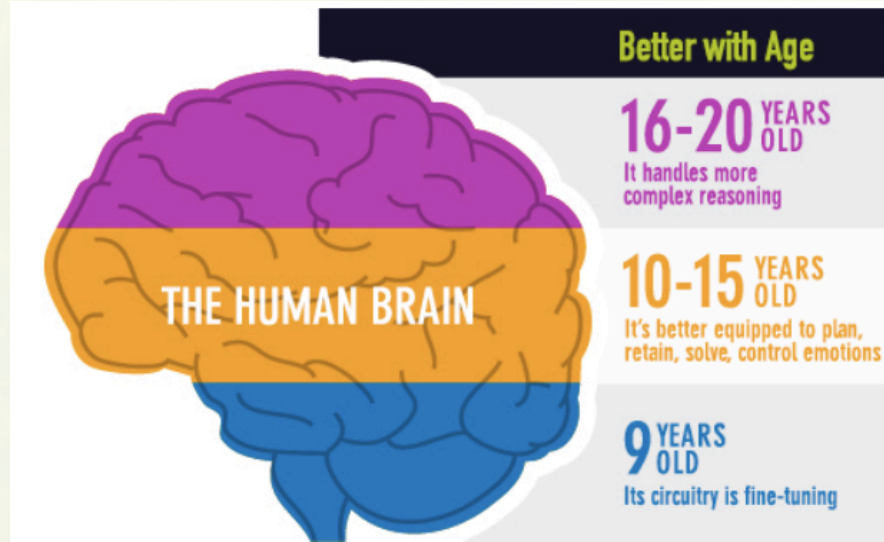


Fetler, L and S Amigorena,  
Science 2005, 309:392

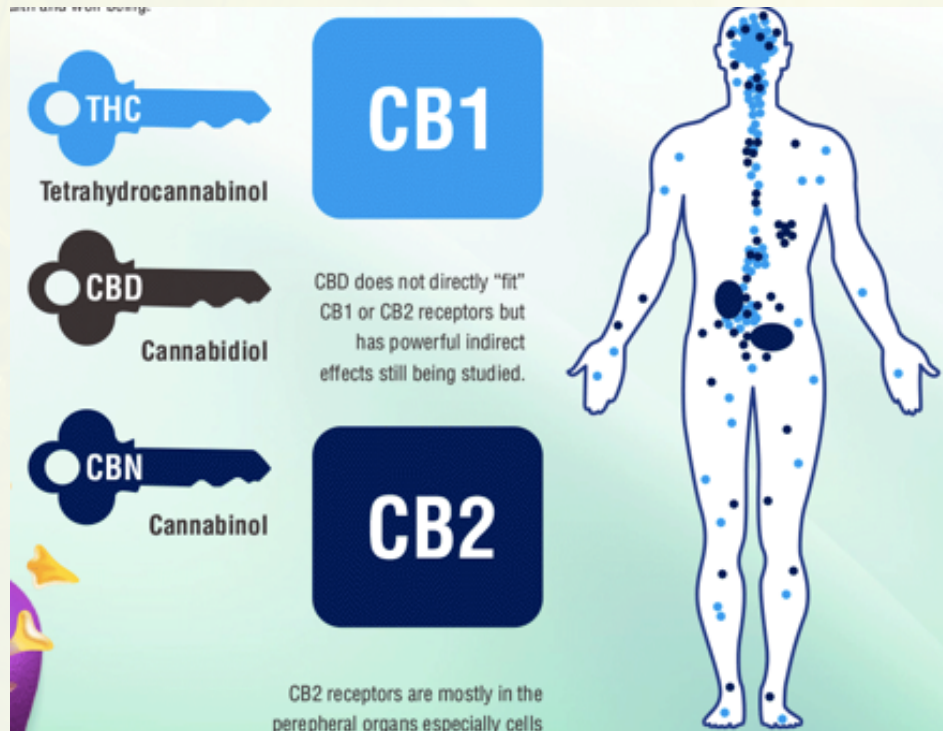




# Better With Age: the Immune System Is Not Static, It Changes/Refines With Age

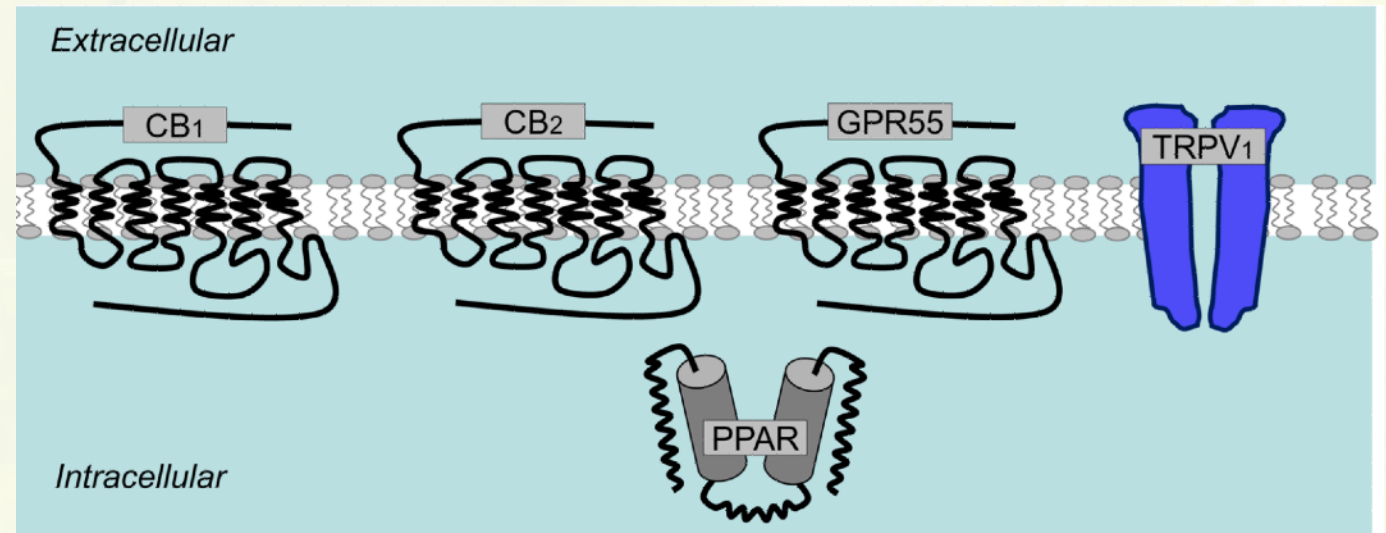


# ECS... A SIGNALING SYSTEM THAT HELPS TO MODULATE ALL OTHER PHYSIOLOGICAL, BEHAVIORAL, AND ENERGETIC PROCESSES IN THE BODY.



Anxiety  
Depression  
Sleep Disorders

Pain  
Itch  
Wound healing



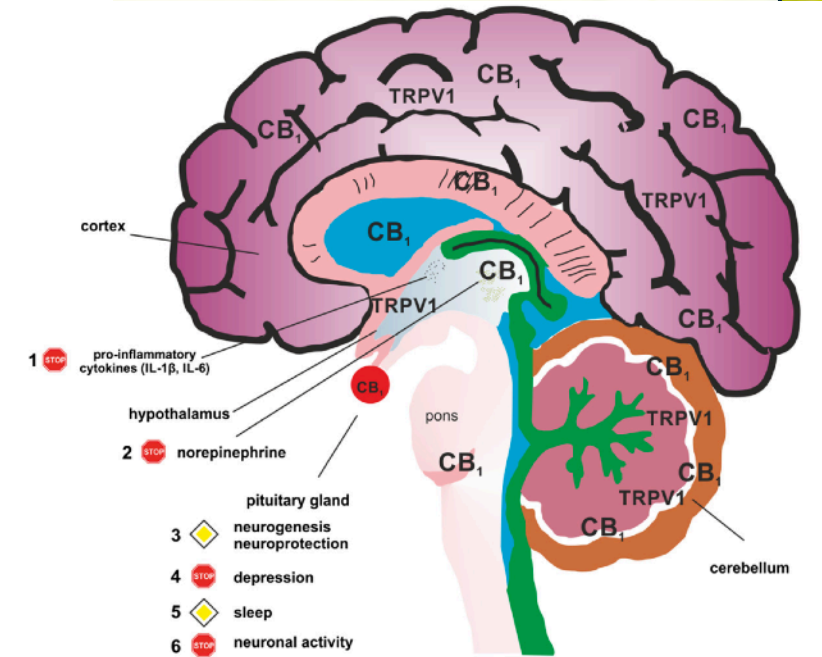
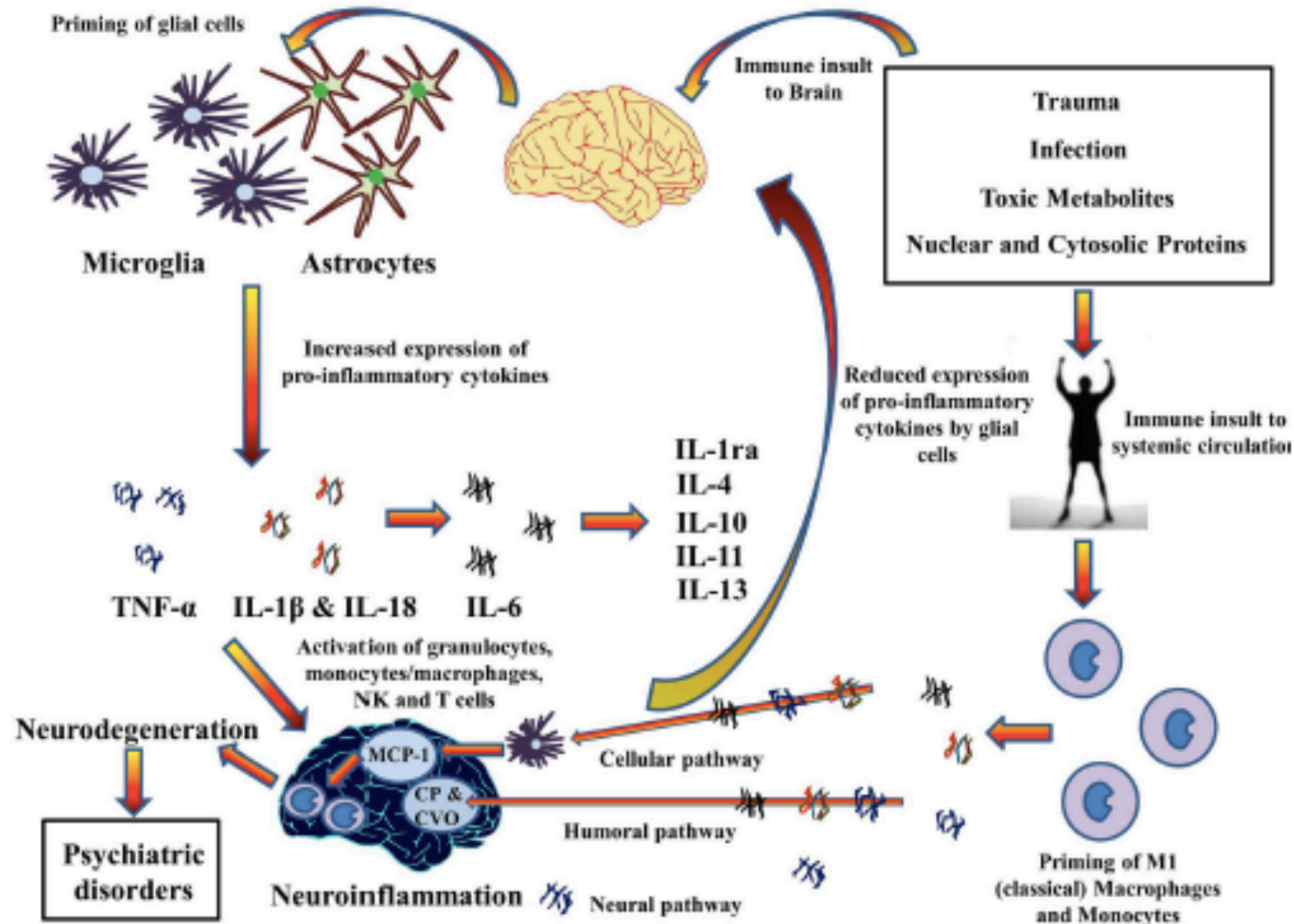
- *neuroprotection & plasticity*
- *immunity & inflammation*
- *apoptosis & carcinogenesis*
- *pain and emotional memory*
- *Supports detoxification:*
  - *repairs Fibrosis*
  - *fatty Liver disease*





# Synergies of purinergic and endocannabinoid system limit neuroinflammation

## Trauma response

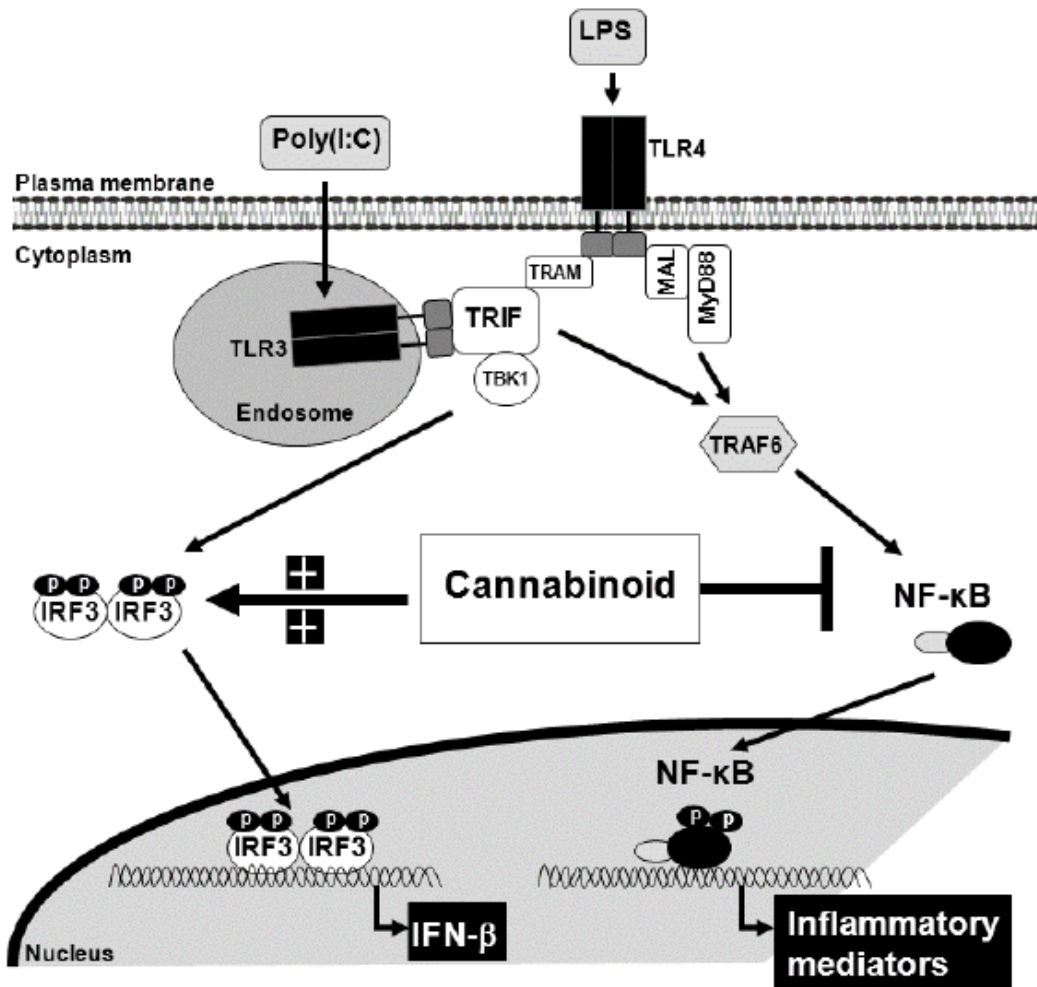


**Review Article**  
Published: 07 October 2014  
Doi: 10.3389/fnins.2014.00315



# All Cannabinoids Are Terpenes Healthy Lipid/Fat

## THE DIMMER SWITCH ON THE FLAME



CANNABIS is NOT a DRUG!  
IT'S Food!! Nourish CELLS

ALL Plants (HEMP & CANNABIS)  
Removed from US 1938!

**Drug  
Metabolism  
Reviews**

<http://informahealthcare.com/dmr>  
ISSN: 0360-2532 (print), 1097-9883 (electronic)

Drug Metab Rev, 2014; 46(1): 86-95  
© 2014 Informa Healthcare USA, Inc. DOI: 10.3109/03602532.2013.849268

**informa**  
healthcare

REVIEW ARTICLE

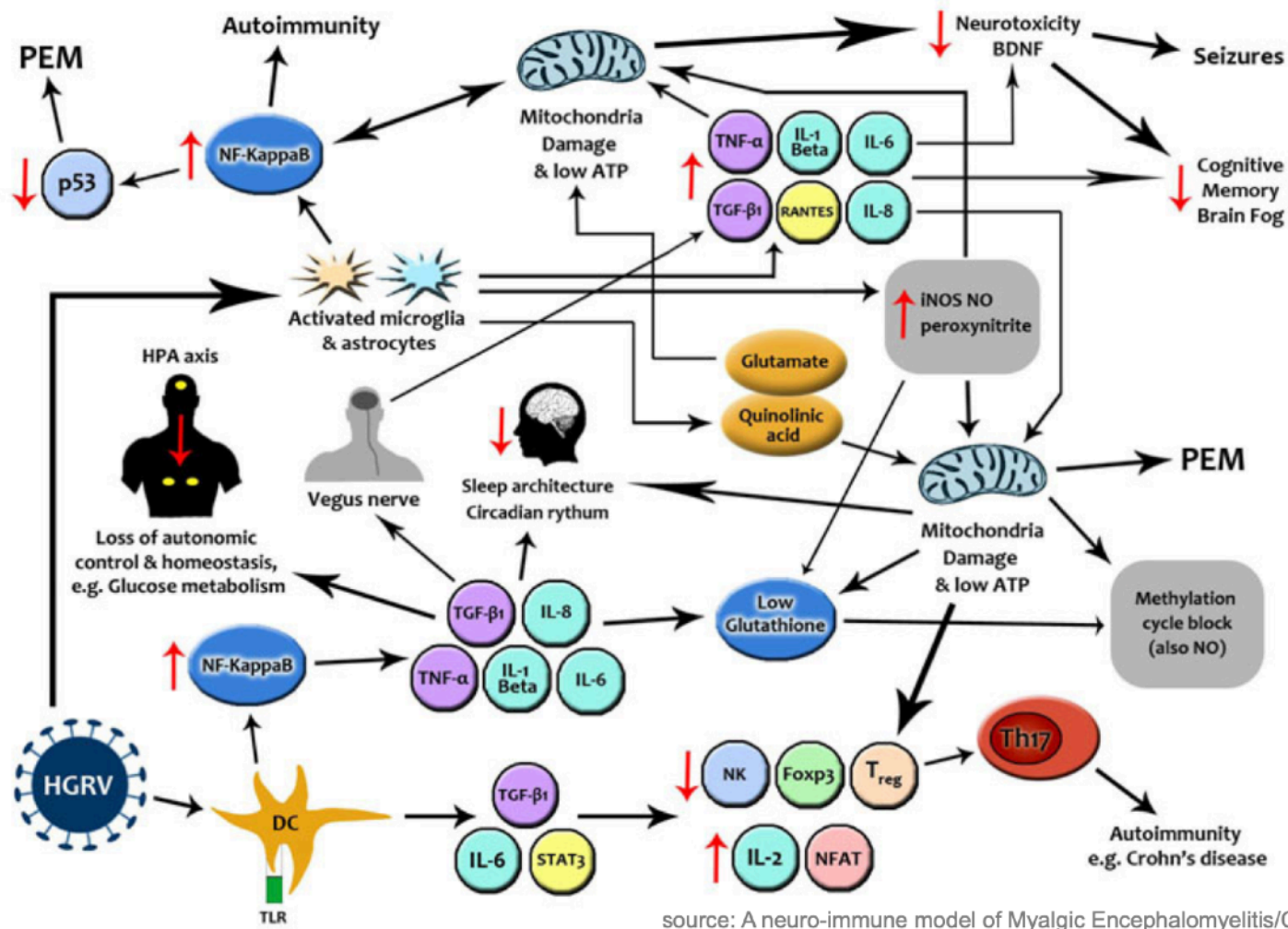
Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review

**GOD GIVEN LIPID/FAT  
SIGNALING SYSTEM  
in EVERY Cell MEMBRANE**



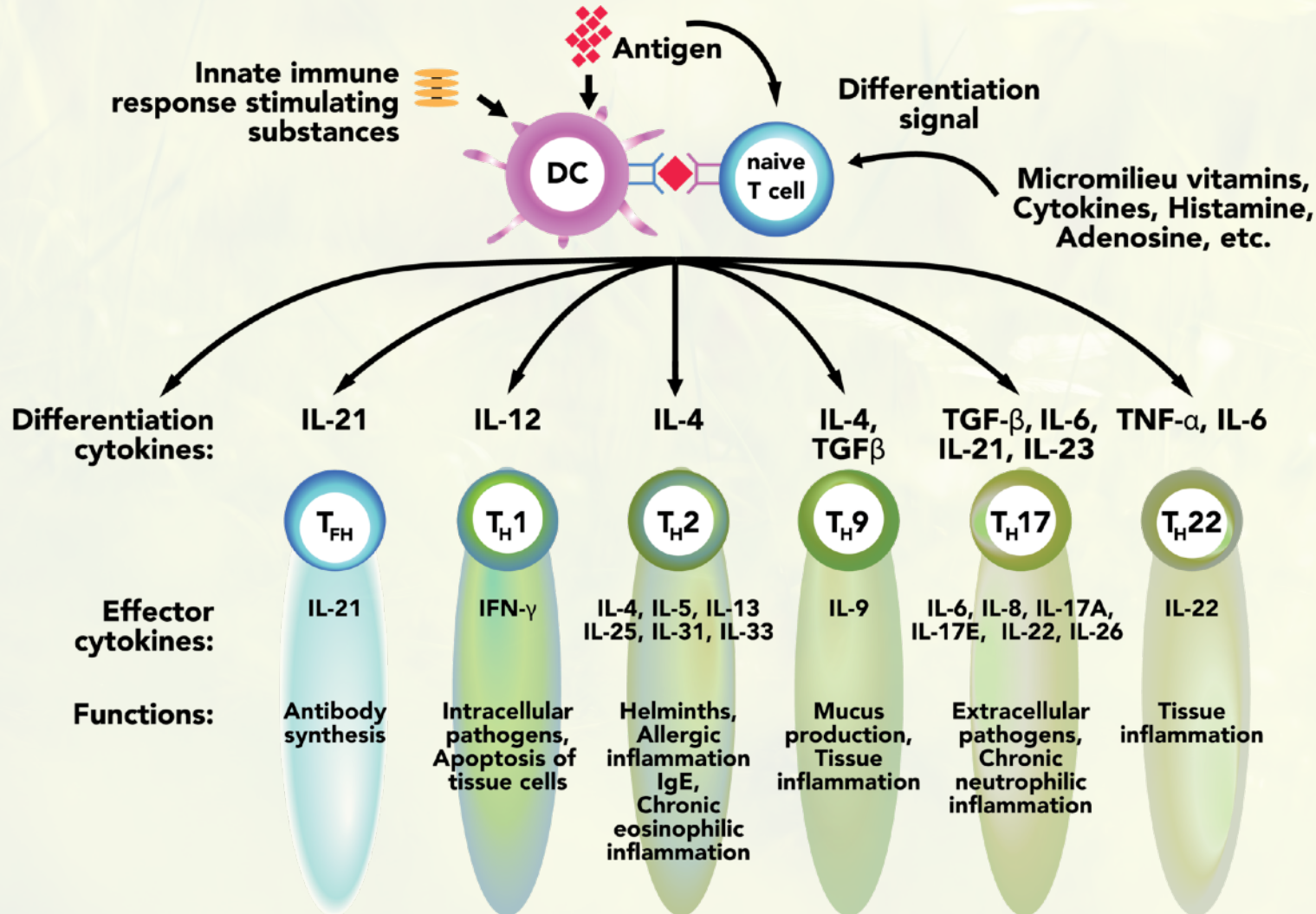


# Summary



source: A neuro-immune model of Myalgic Encephalomyelitis/Chronic fatigue syndrome; Morris & Maes; Metab Brain Dis. 2012 Jun 21

# Plasmacytoid (pDC) key for healthy antibody and Helper TCell responses



**Every  
Inoculation  
Bypasses  
The Innate  
Immune  
System**





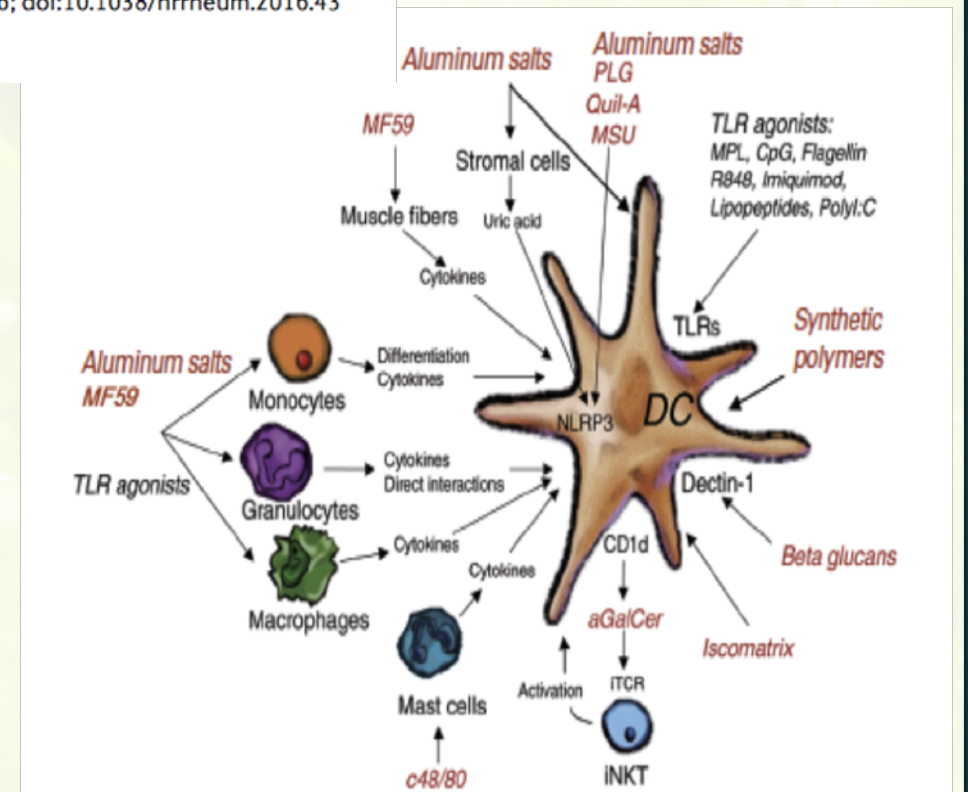
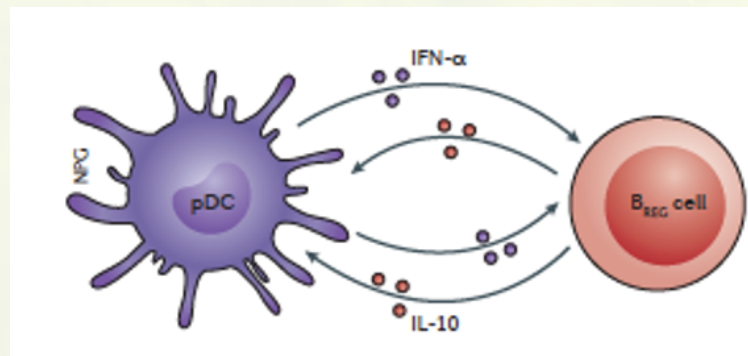
# LUPUS IS AN AUTO-INFLAMMATORY DISEASE ... ANTIBODIES CAUSING THE IMMUNE SYSTEM TO ATTACK THE SKIN, JOINTS, BLOOD AND KIDNEYS.

## Symptoms include:

- Skin rashes/ Inflammation
- Arthritis/ Joint Pain
- Extreme Fatigue
- Anemia/ Blood Disorders
- Kidney Damage
- Immune Disorder
- Antinuclear Antibodies
- CVID: Antibody Deficiency

Nature Reviews Rheumatology | Published online 24 Mar 2016; doi:10.1038/nrrheum.2016.43

## SYSTEMIC LUPUS ERYTHEMATOSUS Compromised pDC-B<sub>REG</sub> cell crosstalk



**Unintended** Consequences of Inappropriate Innate Immune Activation?



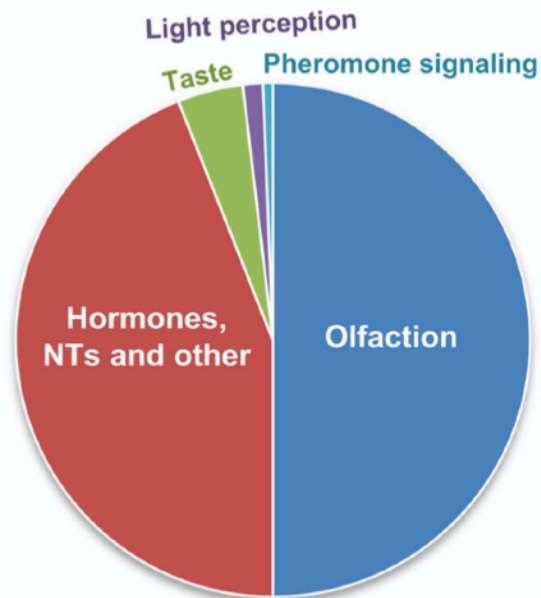
# LOSS OF SENSES (TASTE/SMELL) FROM POISON/VIRUS DYSREGULATION OF HOMEOSTASIS OF PURINERGIC (GPER) AND ENDOCANABINOID SIGNALING (ECS)



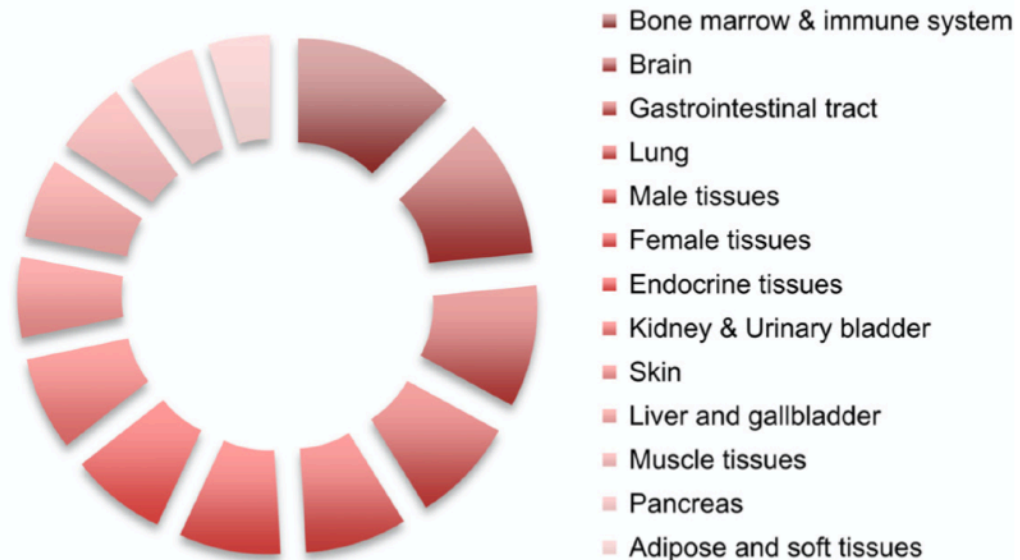
## $G_{i/o}$ -Protein Coupled Receptors in the Aging Brain

Patrícia G. de Oliveira<sup>1\*</sup>, Marta L. S. Ramos<sup>1\*</sup>, António J. Amaro<sup>2</sup>, Roberto A. Dias<sup>1,2</sup> and Sandra I. Vieira<sup>1,2\*</sup>

A GPCRs main functions



B Tissue distribution of  $G_{i/o}$ -coupled GPCRs





# Trans Receptor Potential (TRP) Cation signaling across membrane

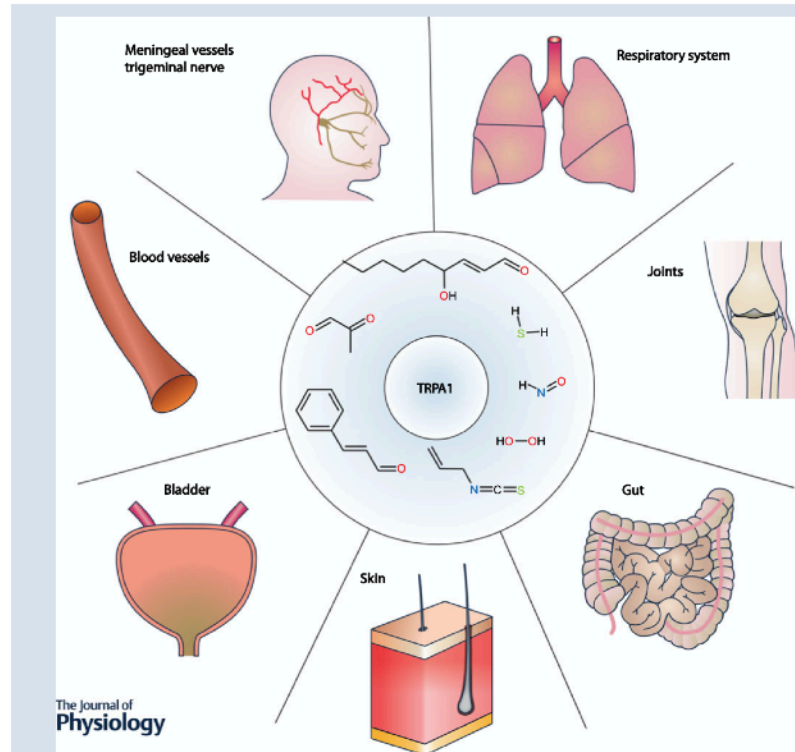
*J Physiol* 594.15 (2016) pp 4151–4169

SYMPOSIUM REVIEW

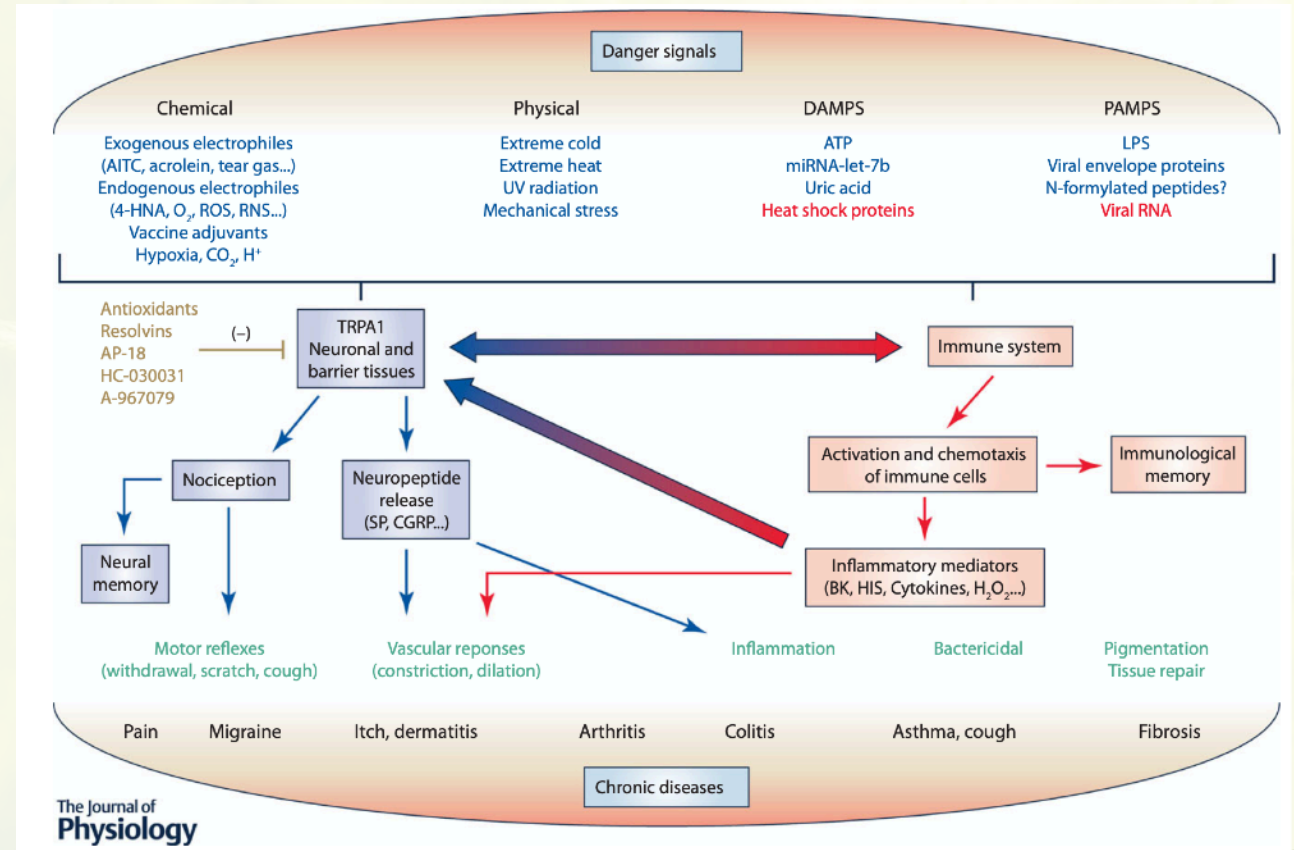
## TRPA1 channels: molecular sentinels of cellular stress and tissue damage

Félix Viana

*Instituto de Neurociencias de Alicante, Universidad Miguel Hernández-CSIC, Alicante, Spain*



The Journal of  
Physiology



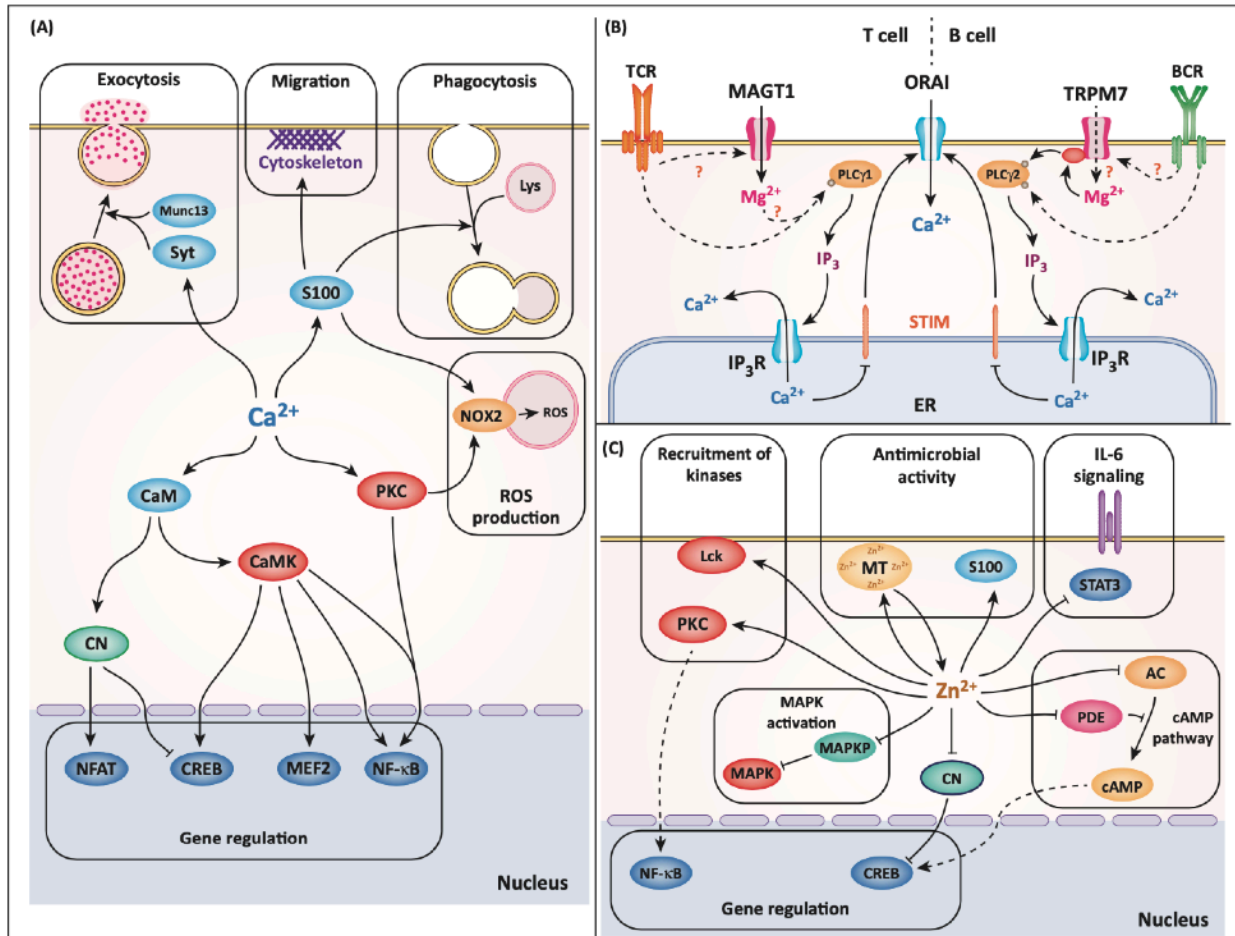
The Journal of  
Physiology



# Dysregulation of Cation Signaling Causes Acquire Immune Deficiency Dysfunction (AIDS)

## Review

Trends in Immunology July 2014, Vol. 35, No. 7



TRENDS in Immunology

## Review

CellPress

## Divalent cation signaling in immune cells

NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health.

Emir TLR, editor. Neurobiology of TRP Channels. 2nd edition. Boca Raton (FL): CRC Press/Taylor & Francis; 2017. doi: 10.4324/9781315152837-9

### Chapter 9 TRP Channels in the Heart

Marc Freichel, Michael Berlin, Alexander Schürger, Ilka Mathar, Lucas Bacmeister, Rebekka Medert, Wiebke Frede, André Marx, Sebastian Segin, and Juan E. Camacho Londoño.

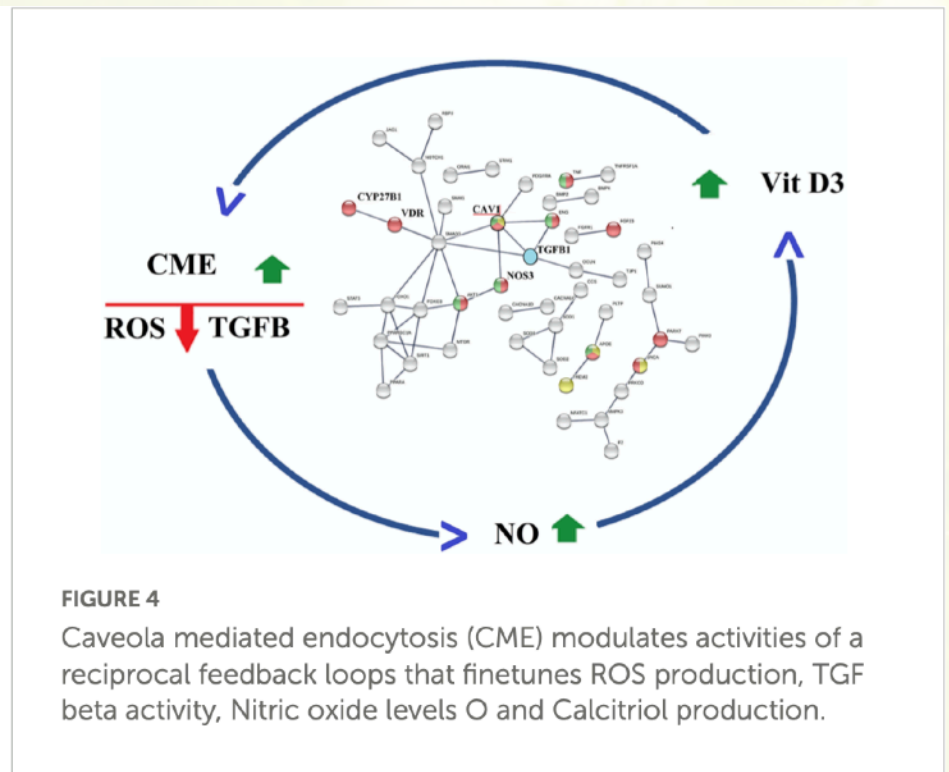
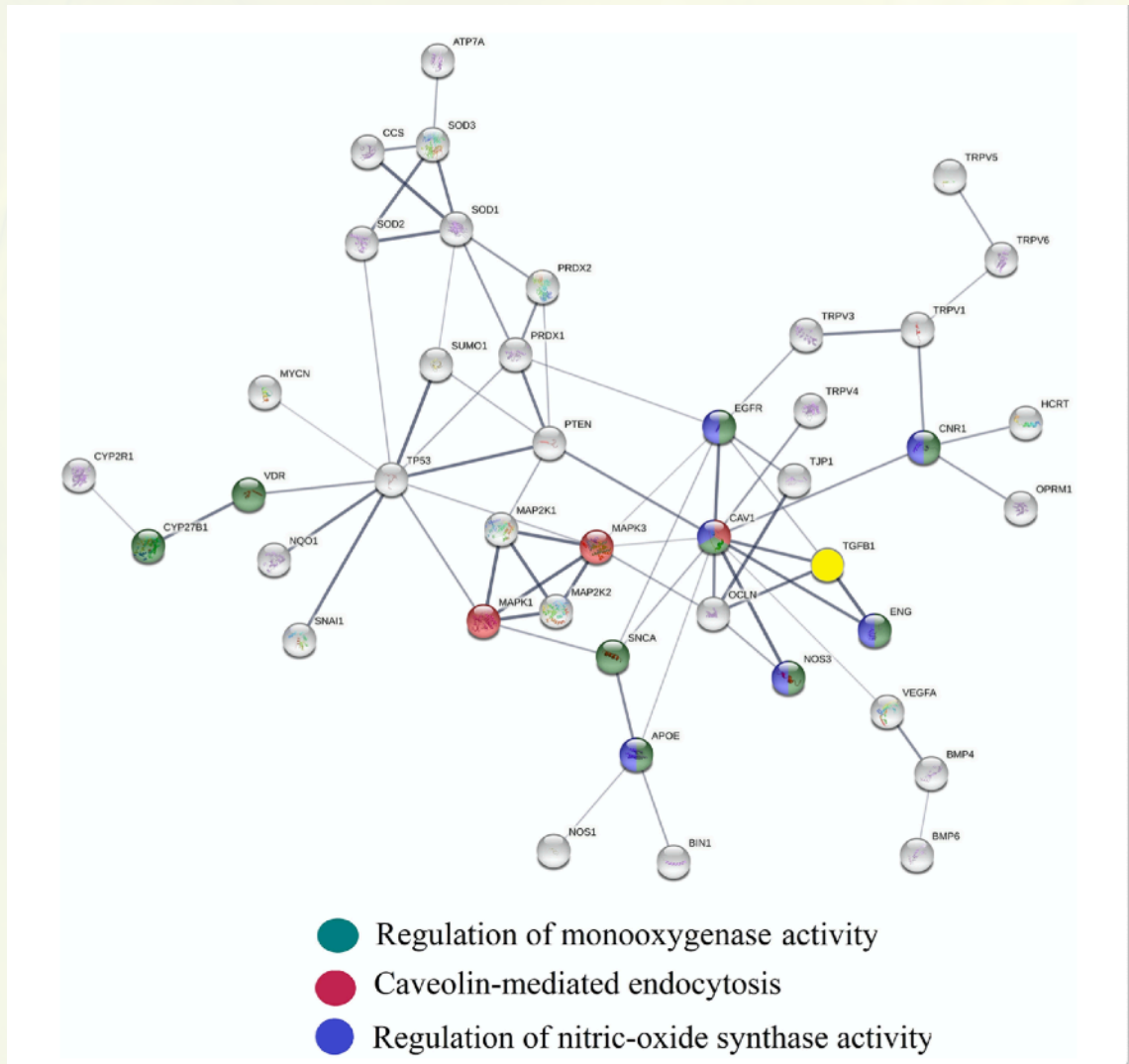
#### 9.1. Introduction

Calcium is an important second messenger in cardiac function. It is not only critical for the excitation-contraction coupling and relaxation of the heart (Bers, 2002), but it is also important for the activation of signal transduction pathways responsible for hypertrophic cardiac remodeling and heart failure, for example, by controlling gene transcription via  $\text{Ca}^{2+}$ -dependent signaling as well as for cardiac development, cardiac energy homeostasis, and eventually for death (Frey et al., 2000; Frey et al., 2004; Roderick et al., 2007). In beating cardiomyocytes, cycling changes in cytosolic  $\text{Ca}^{2+}$  concentration are the results of a timely coordinated interplay of voltage-gated  $\text{Ca}^{2+}$  channels, sodium-calcium-exchangers, ryanodine receptors, and the SERCA-ATPase (Bers, 2008). However, the channels and pumps mediating the fast  $\text{Ca}^{2+}$  cycle during beat-to-beat cardiac action are not only relevant for physiological cardiac functions but also for pathological processes such as development of pathological cardiac remodeling and development of heart failure. These pathological processes are essentially triggered by neuroendocrine stimuli such as noradrenaline, adrenaline, and angiotensin II, which subsequently lead to activation of G protein-dependent signaling pathways in cardiomyocytes that evoke  $\text{Ca}^{2+}$  entry and  $\text{Ca}^{2+}$ -dependent processes (e.g., activation of calcineurin/nuclear factor of activated T cells [NFAT], CaM-kinase, and protein kinase C inducing the development of myocyte growth and cardiac hypertrophy) (Heineke and Molkentin, 2006). Although the action of these sympathetic neurohormones represents an adaptive response that initially preserves cardiac function, the processes triggered by persistent activation during long-term cardiac stress lead to cardiac failure in many cardiovascular disease entities, including arterial hypertension and ischemic or valvular heart diseases. The sources of the  $\text{Ca}^{2+}$  elevation and the mechanisms whereby  $\text{Ca}^{2+}$  leads to calcineurin activation under repetitive  $\text{Ca}^{2+}$  concentration changes during the contraction cycle are still not entirely understood. Sustained elevation of diastolic  $\text{Ca}^{2+}$  has been identified as a mechanism (Dolmetsch et al., 1997) and can be achieved in

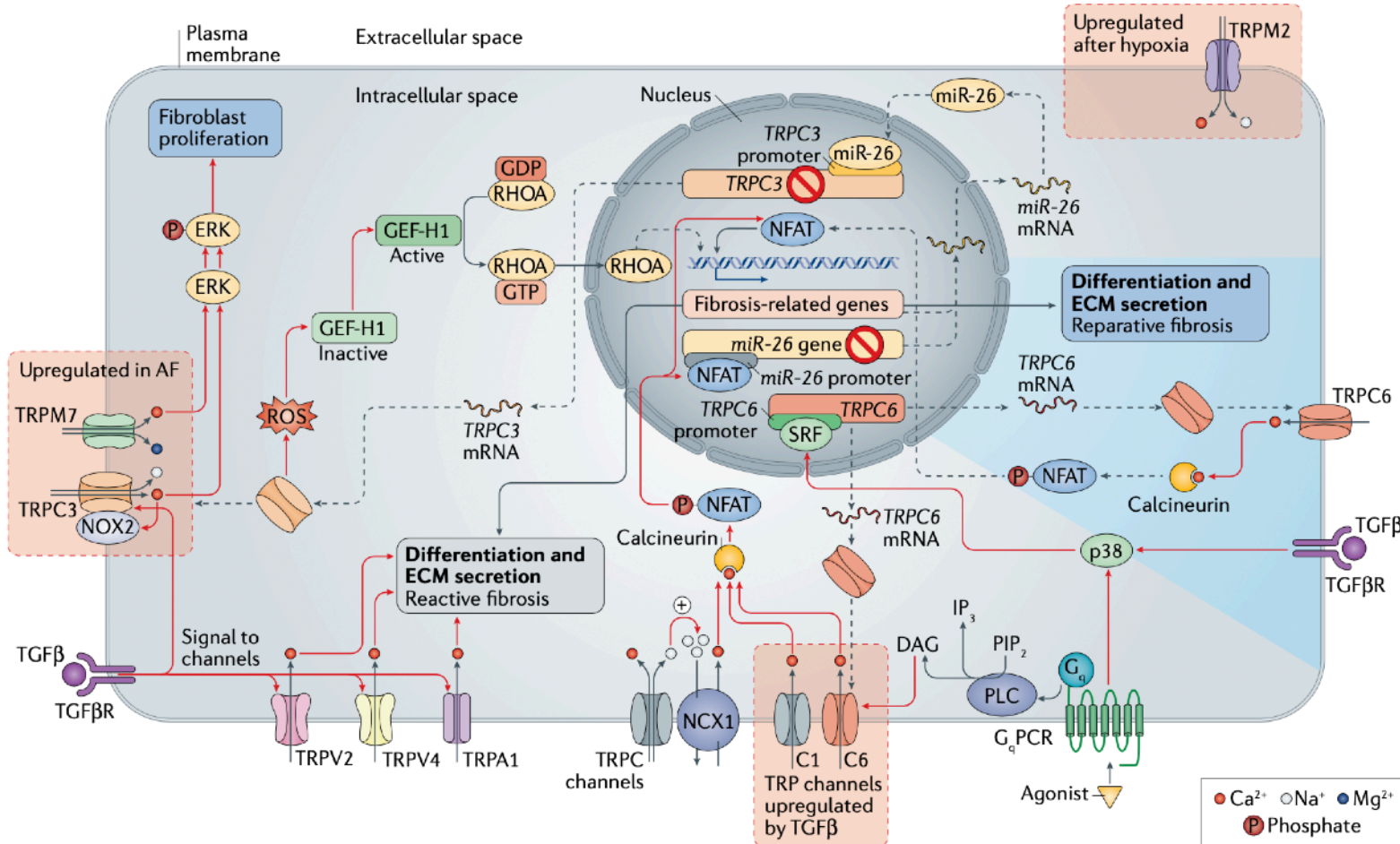




# CardioMiracle: living mineral water Foundation healing AIDS



# Fig. 3 | Roles of TRPC channels in ventricular cardiomyocytes.



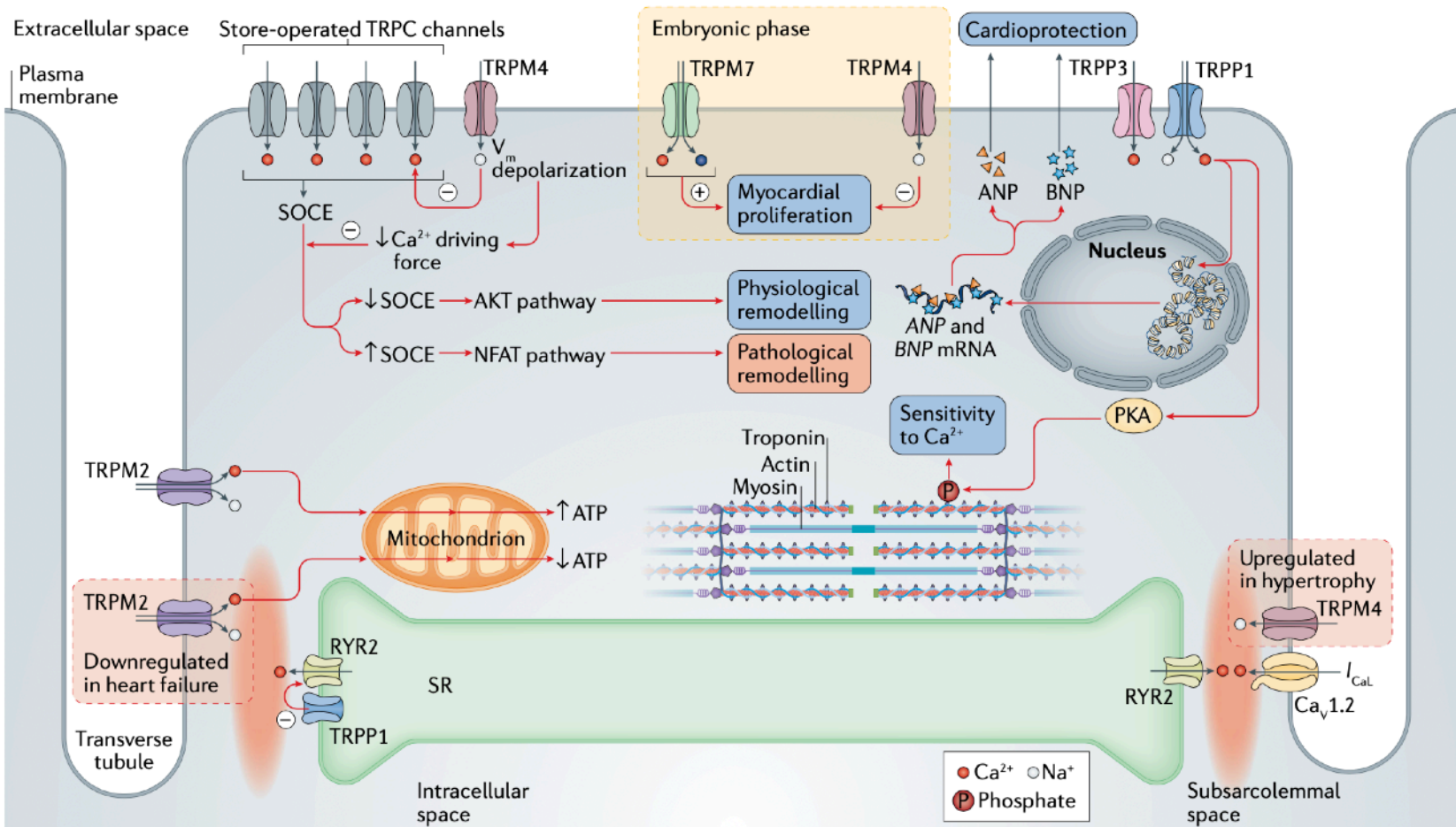
NATURE REVIEWS | **CARDIOLOGY**

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**Fig. 4 | Roles of TRPM and TRPP channels in ventricular cardiomyocytes.** TRPM2 channels participate in the maintenance of mitochondrial function. TRPM4 channels attenuate store-operated  $\text{Ca}^{2+}$  entry (SOCE) by depolarizing the membrane



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# THANK YOU FOR YOUR ATTENTION

