

Brains on fire: the low down on neuroinflammation

MINDD MAPS forum

17th May 2015 Sydney

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The world today

- The era of information technology
- The era of scientific research
- The measures of financial wealth and success
- The 'contraction' of time
- The levels of stimulation and reward
- The decline of the natural world of forests, plants, wild life, the microbiome
- The challenge of balancing all of the above...

Overview: Governing system of the human mega-system- The Nervous System

➤ **Integrated neuronal functioning** needs:

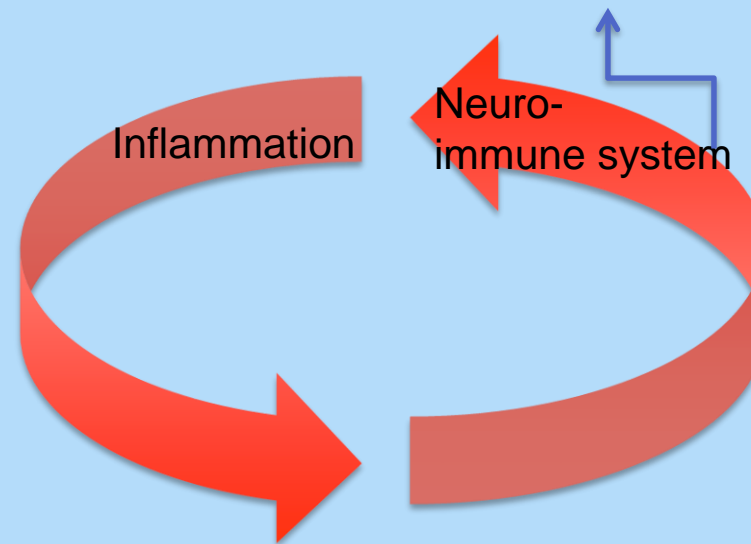
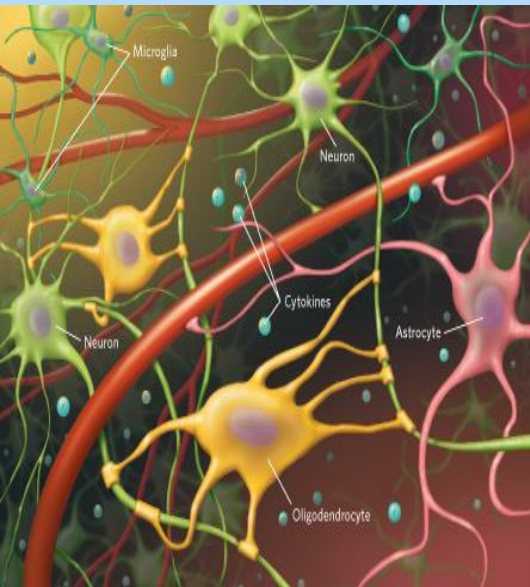
- i. Sleep
- ii. Detoxification of brain, CSF, lymph
- iii. Metabolic energy from mitochondrial transformation of food and air
- iv. Neurotransmitters function from nutrients and carbon dioxide
- v. Cell membrane function dictating nerve action potentials (as well as all cell signaling, cell membrane barriers i.e. brain & gut) and insulation from electromagnetism, receiving frequencies as information
- vi. Balanced neuro inflammation from central and peripheral tissue input, the neuro immune system and gut as the second brain
- vii. Integrated neural circuits: dysfunctional or under developed patterns
- viii. Emotional mental resilience

Overview: Governing system of the human mega-system- The Nervous System

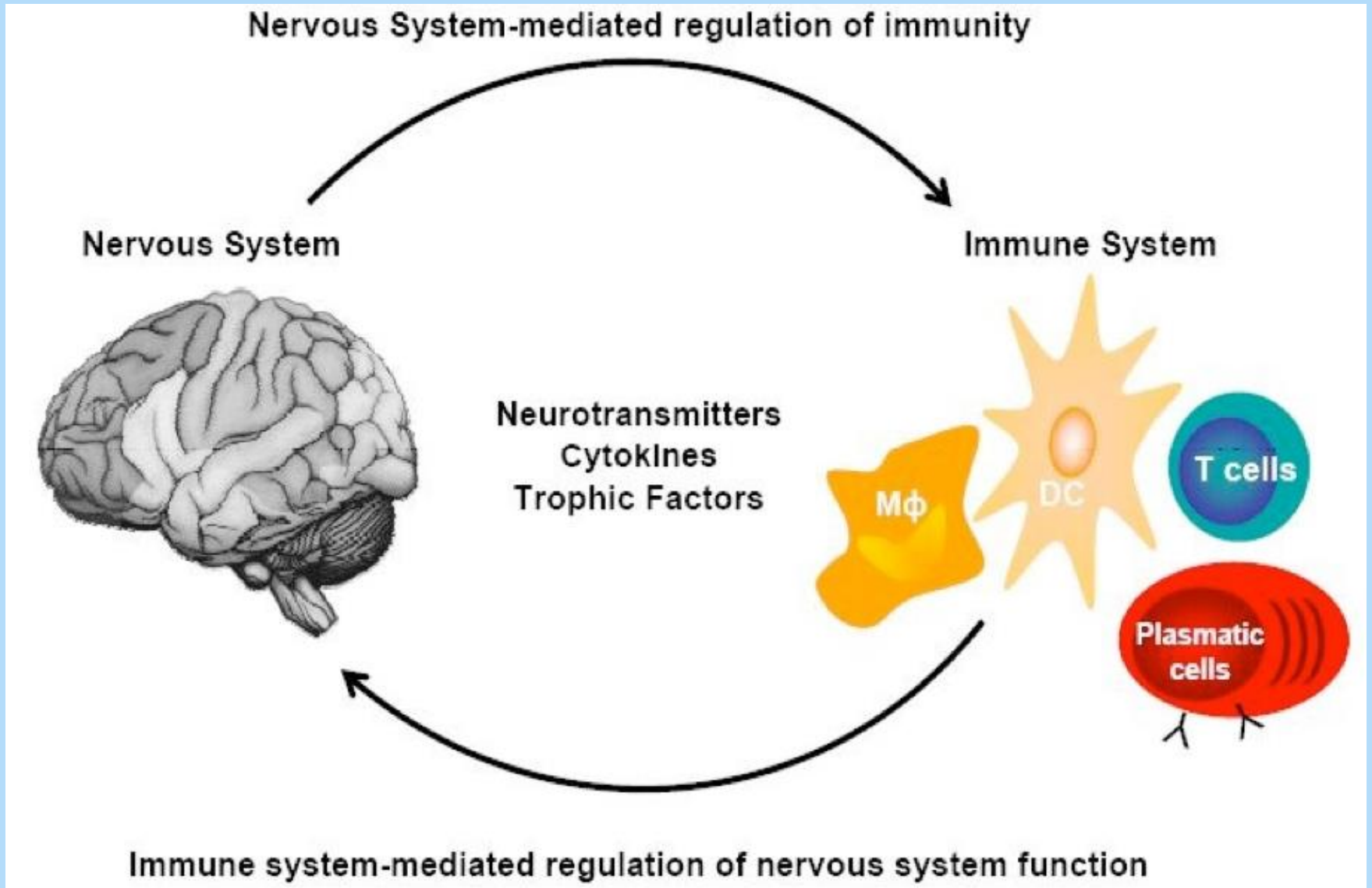
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Neuro- Inflammation

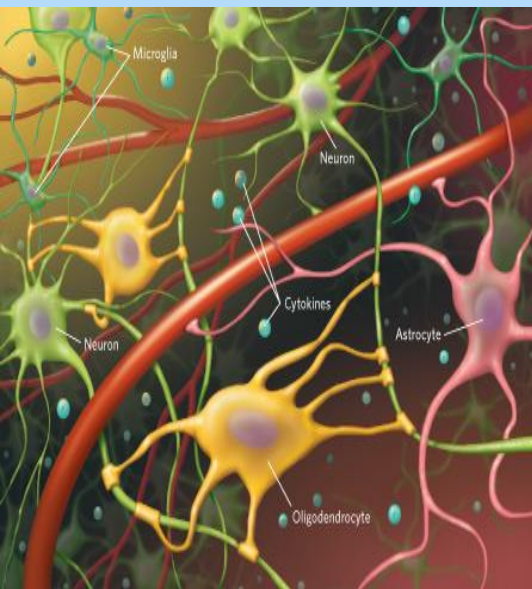
- Intricate communication between nervous and immune system
- Shared cellular messengers and receptors
- Immune feed back to nerves AND 'top down' neural control of immune cells



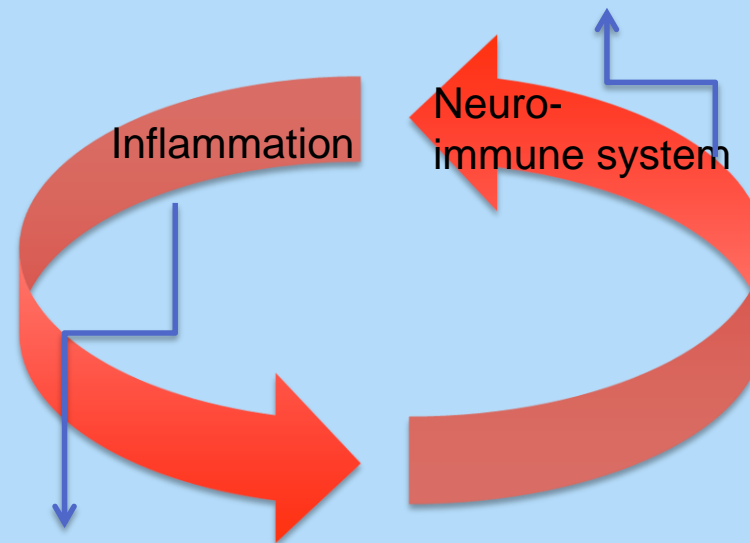
The neuro-immune system: a single entity



Components of a chronic infection state: the total sum of inflammation

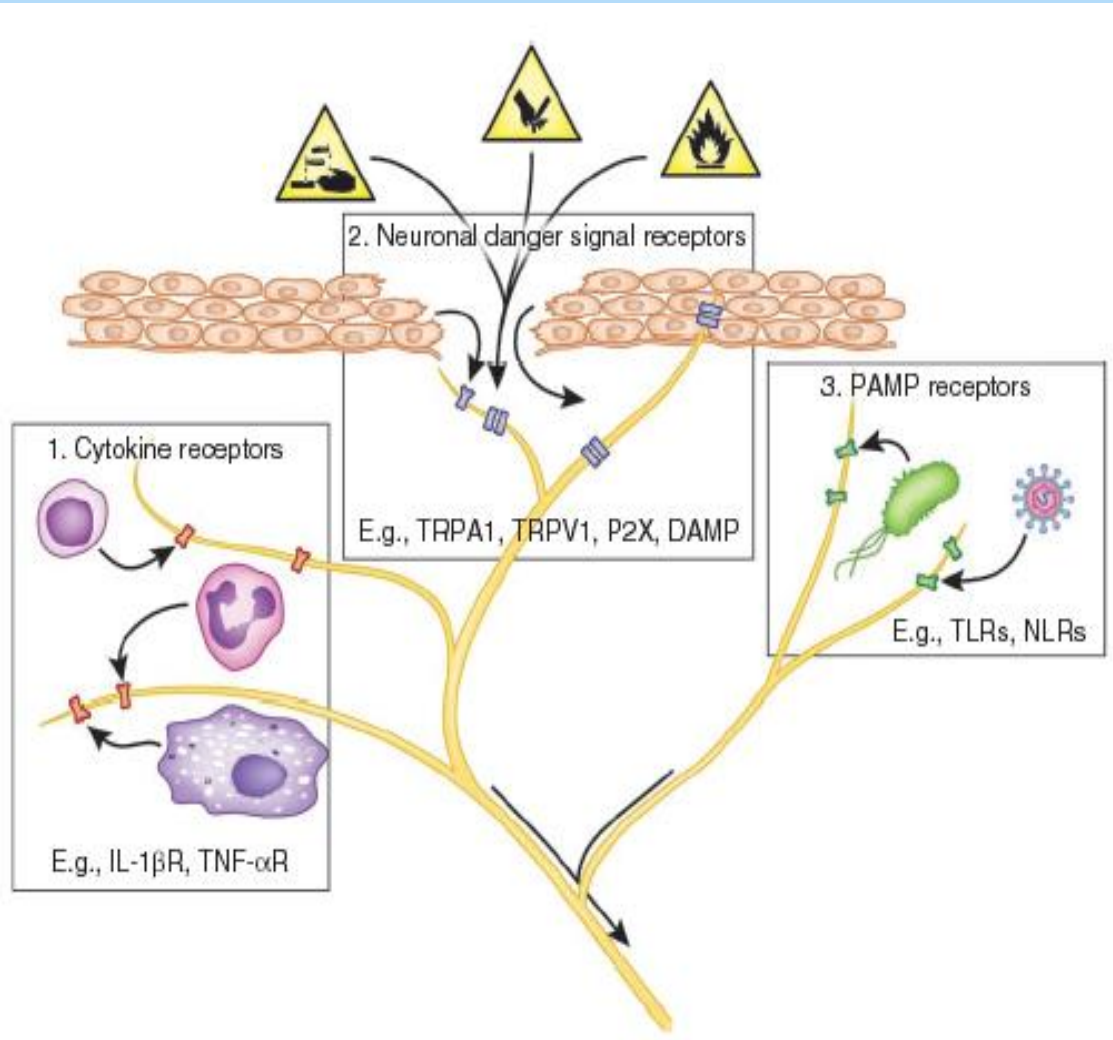


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- Peripheral tissues- may produce localised inflammation
- Central tissues- may produce systemic inflammation
- All adds to total load of inflammation and neuro-inflammation. From tissue microbial loads & all endogenous toxins to external environmental loads & sensory inputs
- Upregulated vicious cycles of numerous cytokines

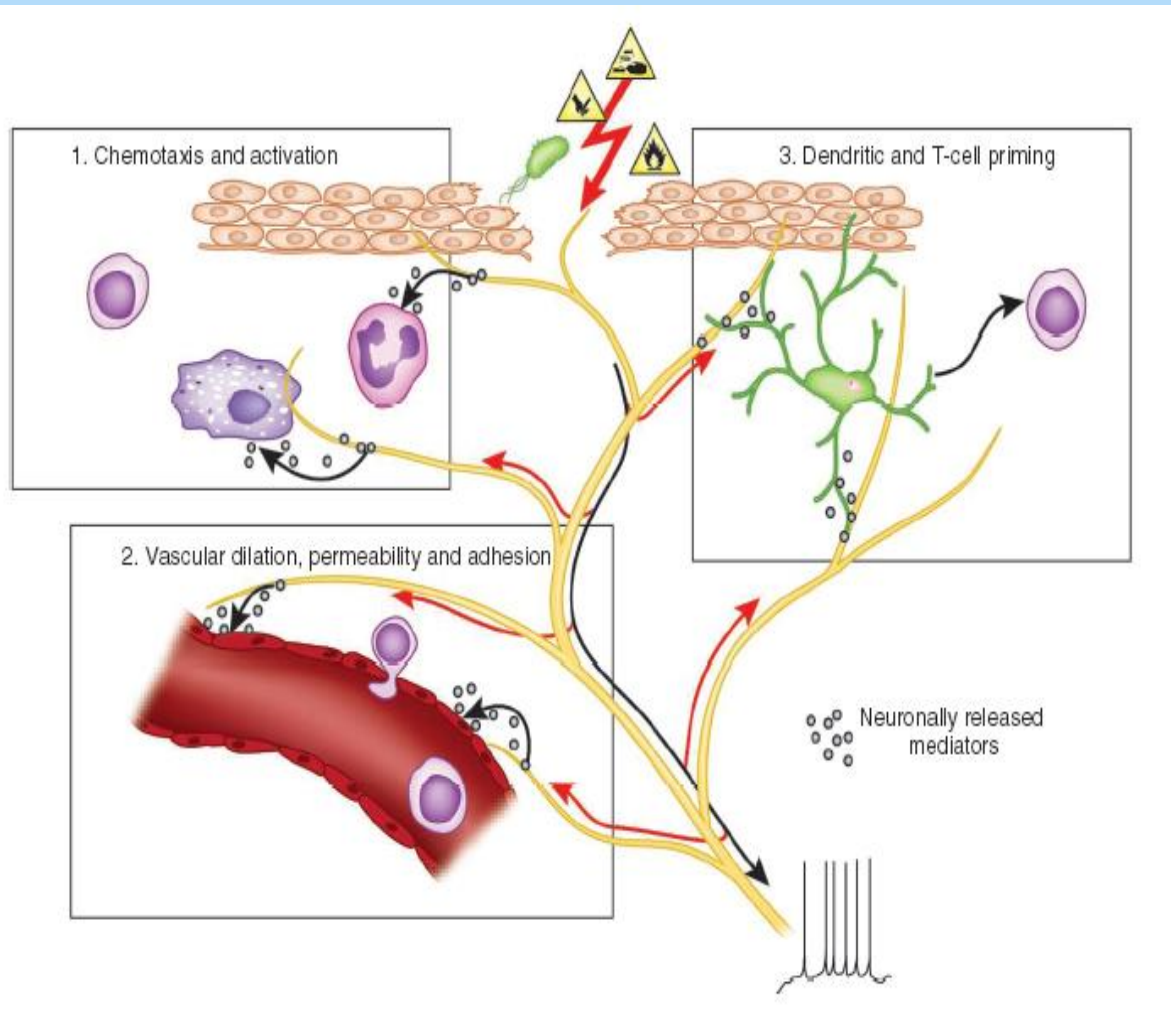
Total inputs to inflammation occurs through the nervous system



The signals

- inflammatory cytokines
- environmental noxious stimuli
- pathogens

Total inputs to inflammation occurs through the nervous system



The responses

- chemotaxis activation
- vascular leakage, endo-thelial dysfunction
- dendritic cell priming driving Th2 or Th17 subtypes

The total load of sensory inputs into the nervous system drive neural responses

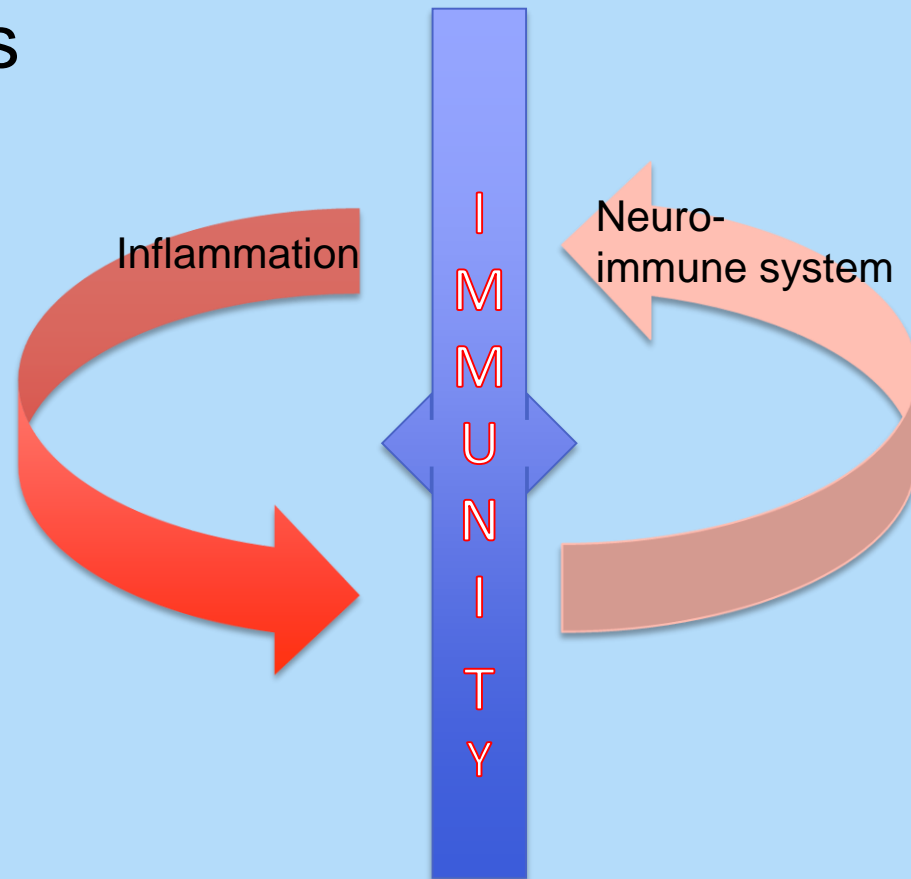
- All neurological inputs through the senses- taste, touch, smell, sound, vision
- Additional senses of the environment through the brainstem- emotions, barometric pressure, electrical frequencies
- All inputs through the gut/ enteric nervous system- food antigens, allergens, pathogens, toxins
- All inputs through the skin and other membrane systems

The outputs of the neural responses translates to:

- Stress/ danger response including emotions
- Pain and other neurological symptoms
- Acute immune response
- Chronic and altered immune responses
 - Chronic inflammation
 - Allergy
 - Autoimmunity
 - Leaky cell membranes and poor barrier functions

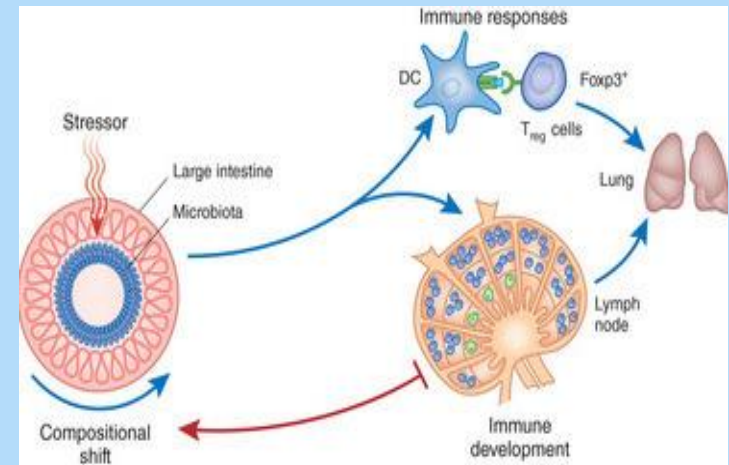
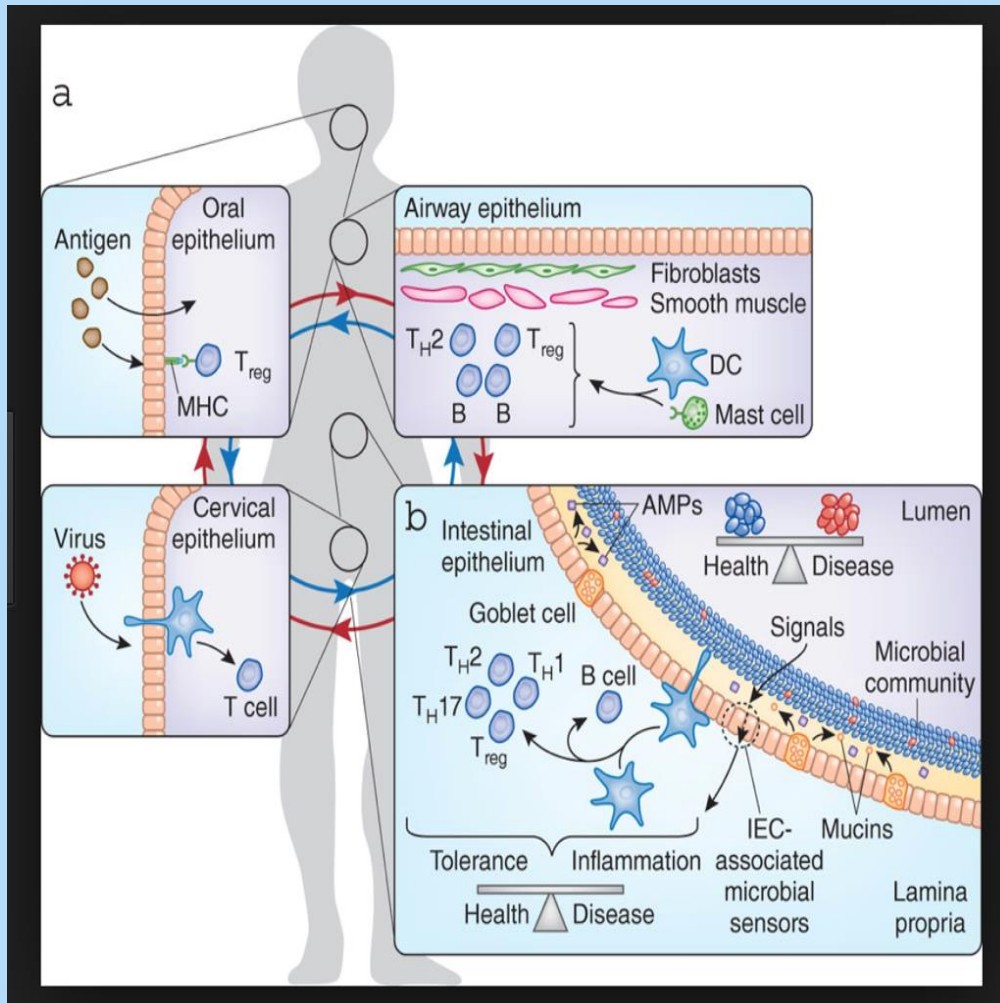
The interphase between infection, inflammation and our nervous system:

Mucosal immunity in the skin, gut, blood brain barrier, mucus membranes



The future of mucosal immunology: studying an integrated system- wide organ. Gill N et al. Nature Immunology 2010; 11: 558- 560

Mucosal immunity: housing platform for the neuro-immune system



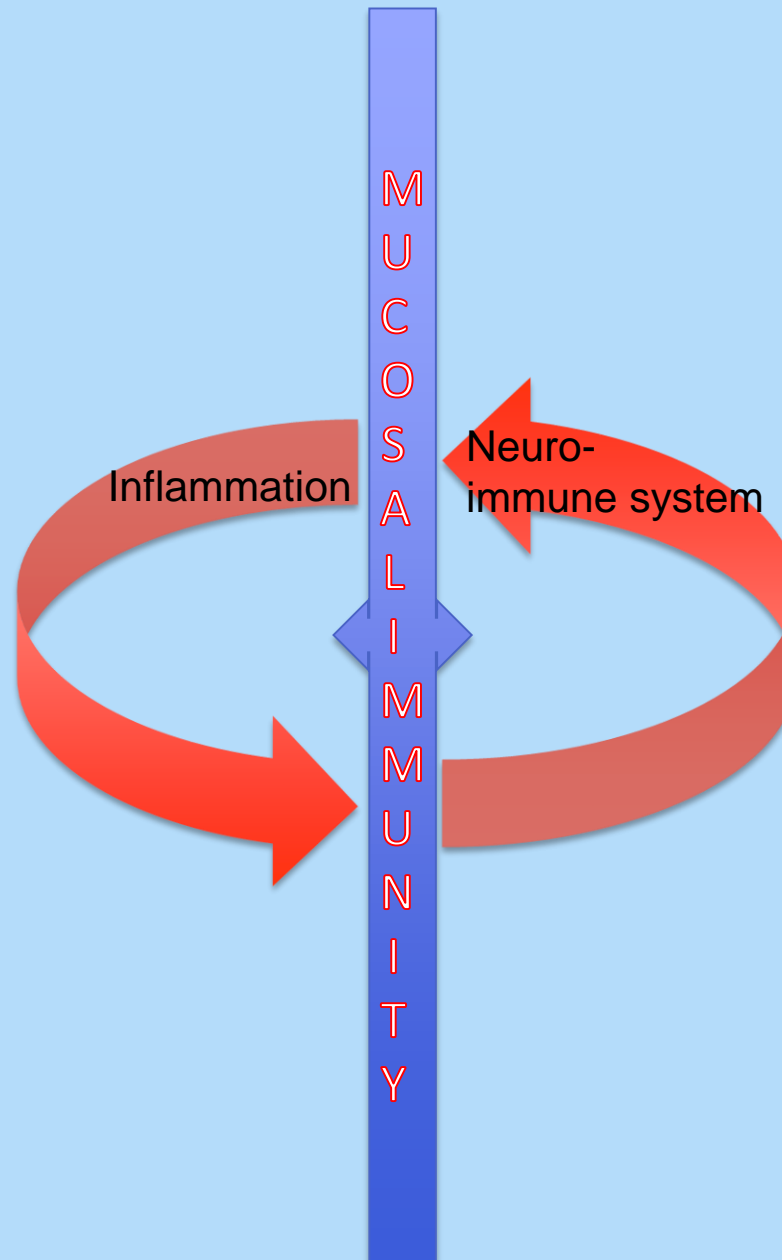
The future of mucosal immunology: studying an integrated system-wide organ. Gill N et al. Nature Immunology 2010; 11: 558- 560

Mucosal dendritic cells shape mucosal immunity. Sun Young C et al. Exp & Molecular Medicine 2014; 46: e84

How pathology
arises in a chronic
infection state:

Dependent on
mucosal immunity

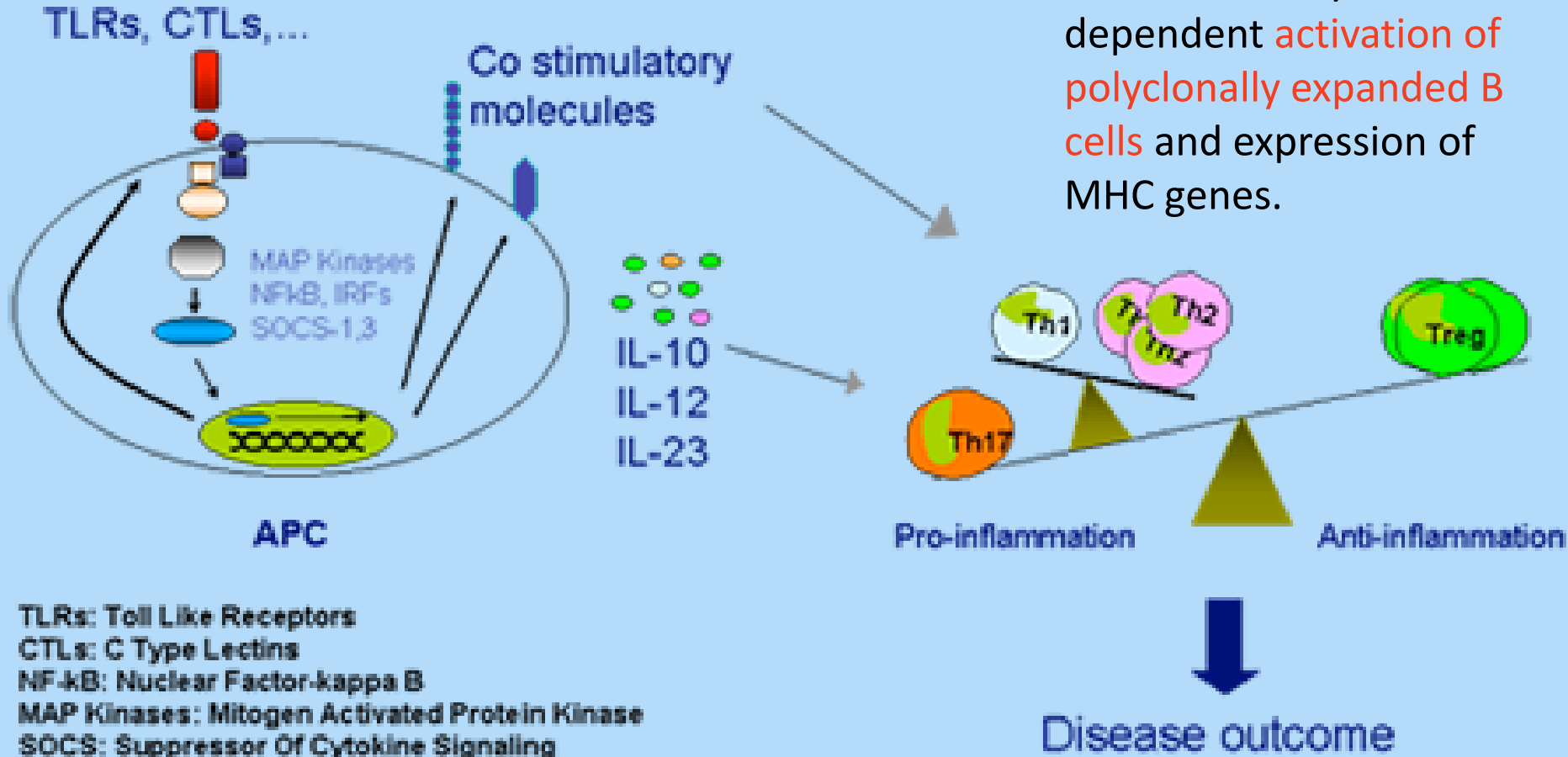
"If I could live my life
over again, I would
devote it to proving
that germs seek their
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tissue." Rudolph
Virchow (1821-1902)



What did Virchow mean by diseased tissue? 'The Terrain'

- There is so much evidence of worsening **microbiomes**- constipation, GI disorders, antibiotic resistance, bacterial and fungal dysbiosis, mental health issues
- There is so much evidence of worsening **immune dysfunction**- allergy, autoimmunity and chronic infections
- There is so much evidence of **mitochondrial** and energy dysfunction- chronic fatigue, psychiatric disease, neurological diseases and degeneration, cognitive dysfunction
- What does it actually mean to be 'toxic'?

The terrain of immune dysfunction



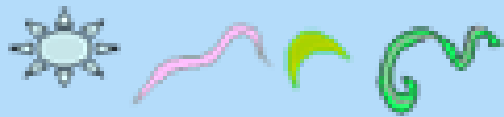
Chronicity of an infection is influenced by TLR dependent **activation of polyclonally expanded B cells** and expression of MHC genes.

TLRs: Toll Like Receptors
 CTLs: C Type Lectins
 NF- κ B: Nuclear Factor-kappa B
 MAP Kinases: Mitogen Activated Protein Kinase
 SOCS: Suppressor Of Cytokine Signaling
 APC: Antigen Presenting cell

Newell et al . TLR mediated B cell activation results in ectopic CLIP expression that promotes B cell dependent inflammation. J Leukocyte Biology 2010

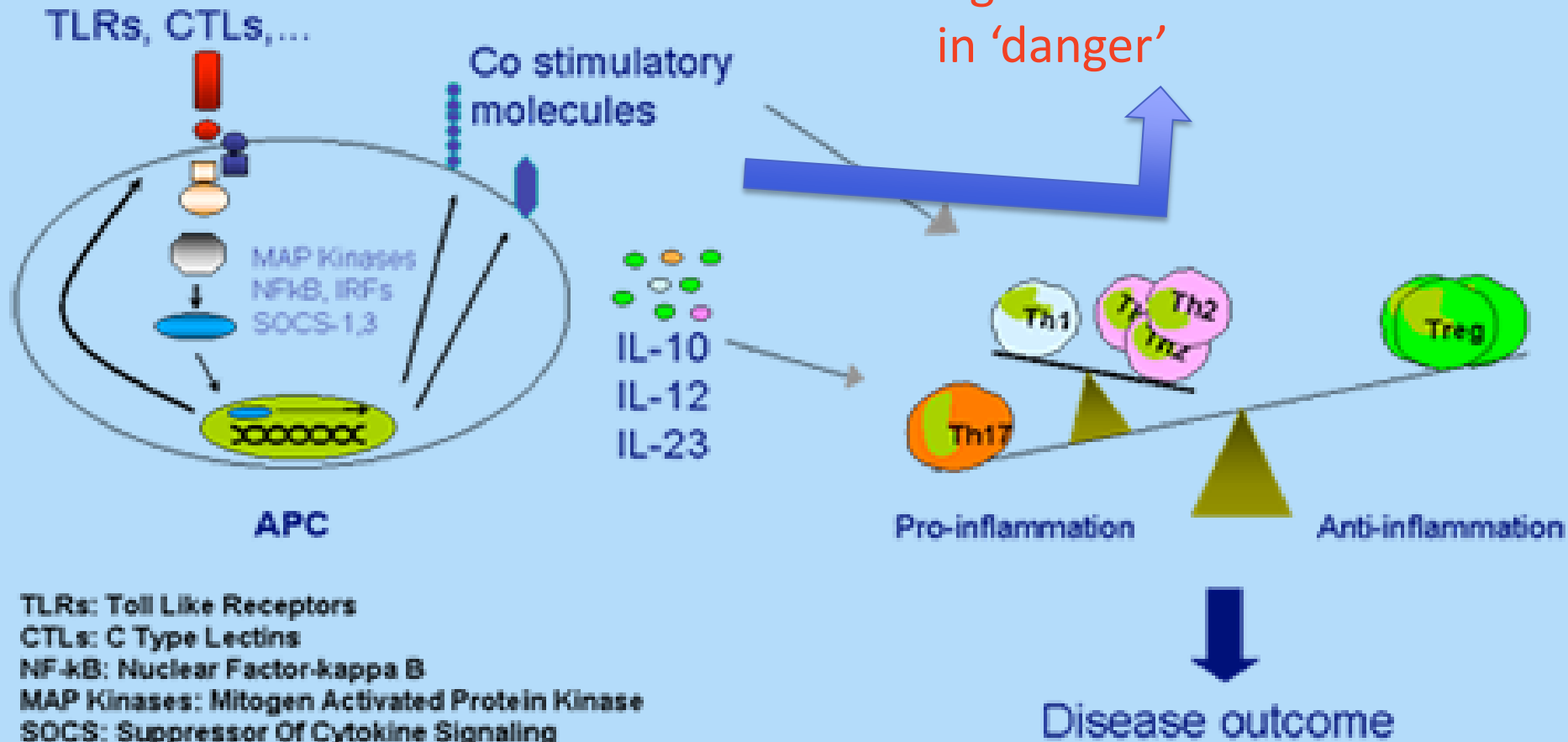
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This is the loss of immune tolerance



.....concomittant infections

‘Co stim’ molecules= danger signals i.e. any molecular signal that tells the cell it is in ‘danger’

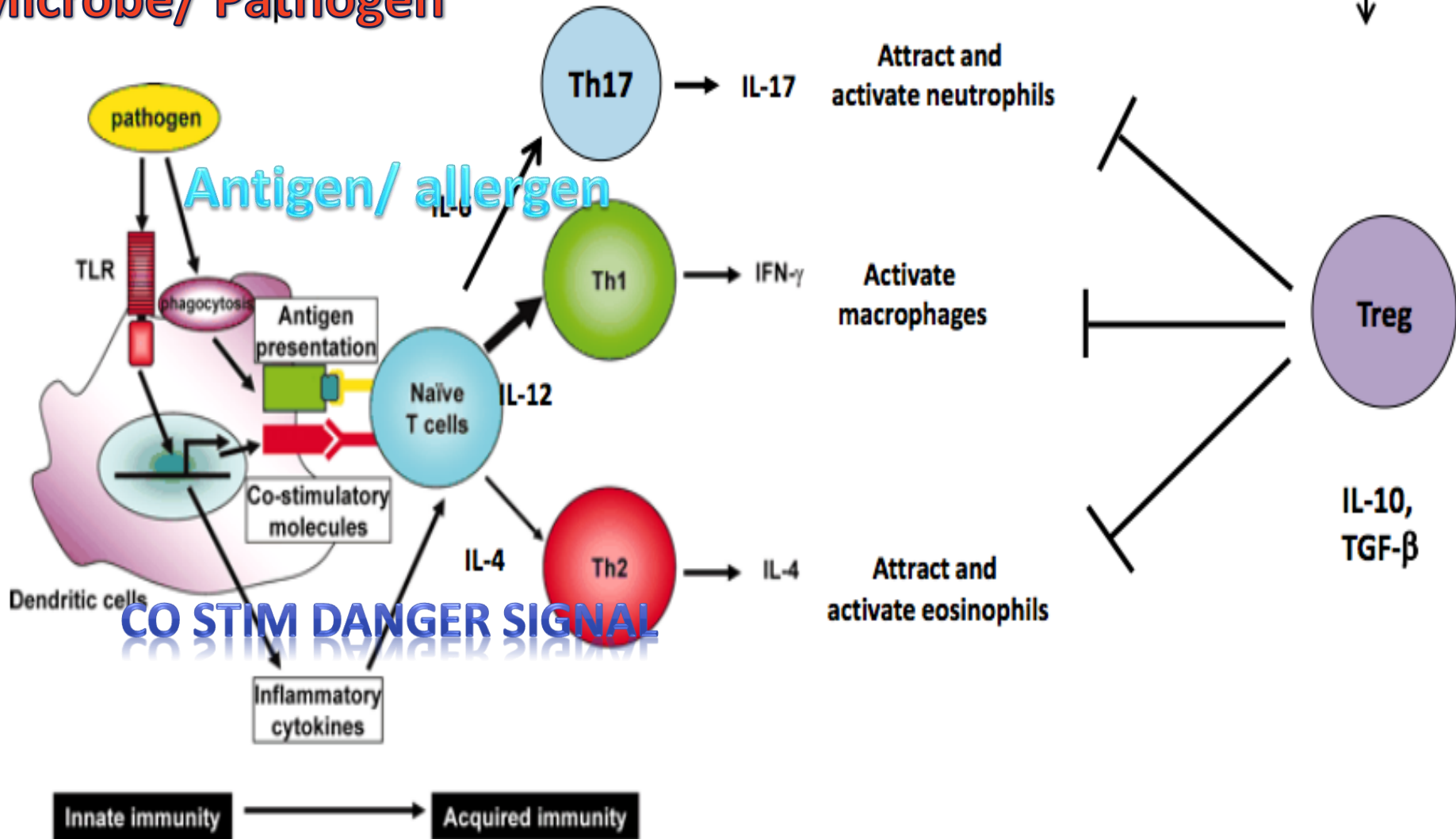


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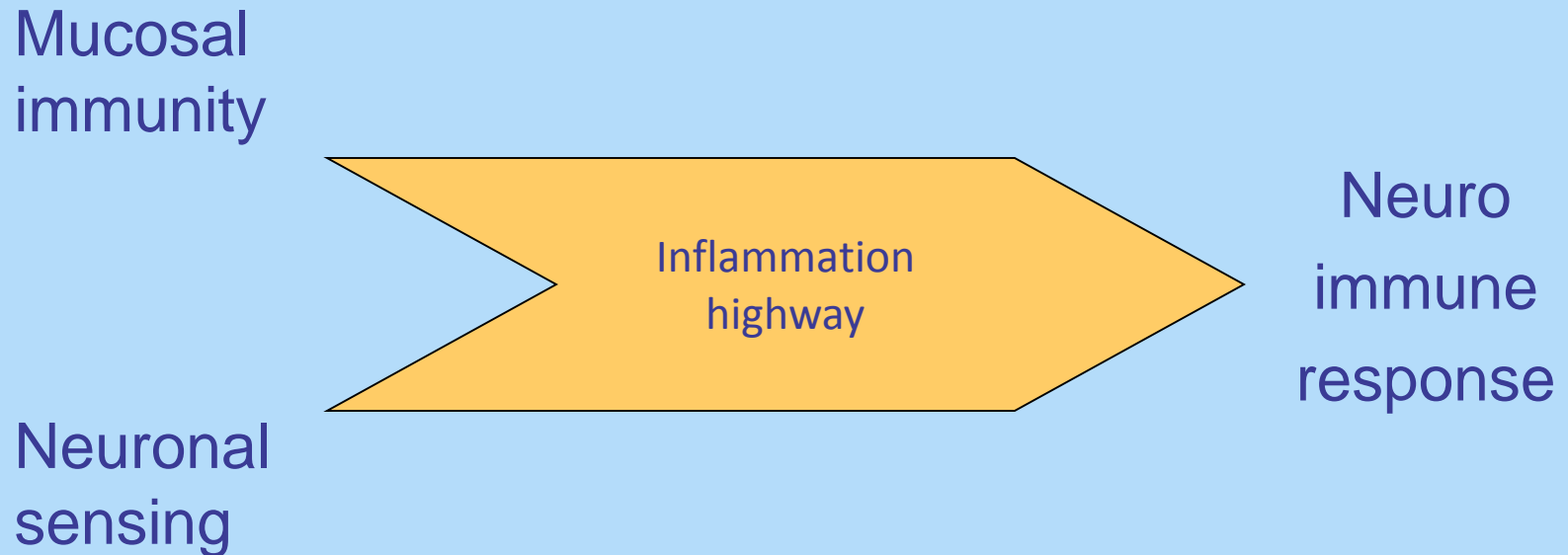
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Microbe/ Pathogen



Modified from Takeda & Akira,

Danger signals lead to loss of immune tolerance



Matzinger P. The Danger Model: A renewed sense of self. Science 2002; 296: 301-305

Matzinger lecture on Death, damage and immunity:

http://www.youtube.com/watch?v=1eSiAUHDhyA&feature=youtube_gdata_player

Danger Signals

- Danger signals are environmental toxins are 'co-stim' factors as described by Immunologist Matzinger

Damage to cells → danger signals → interference of cell membranes, disturbance of mitochondria, activation of microglia

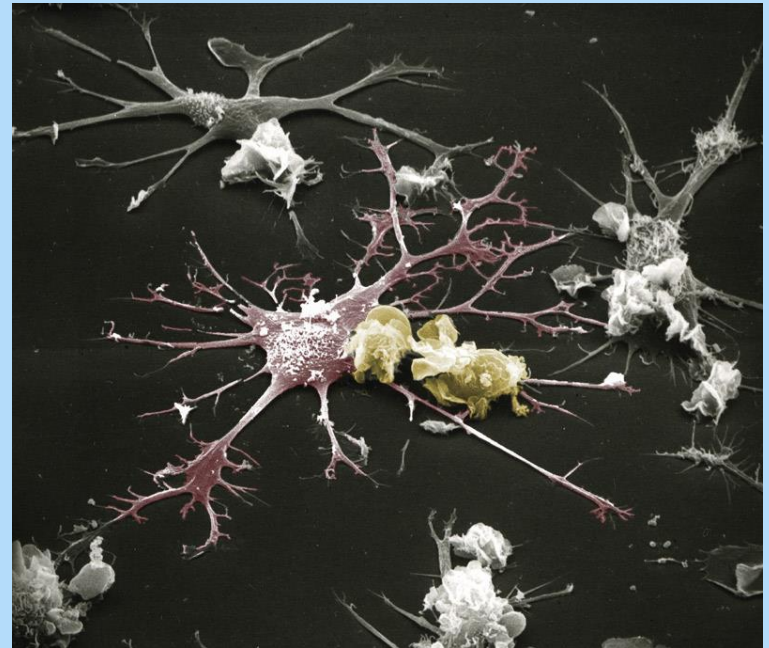
Activation of microglia → activation of immune responses eventually → loss of self tolerance

Matzinger P. Friendly and dangerous signals: is the tissue in control? Nat. Immunol. 2007; 8: 11–13

Matzinger P. The Danger Model: A renewed sense of self. Science 2002; 296: 301-305.

Mucosal Immunity

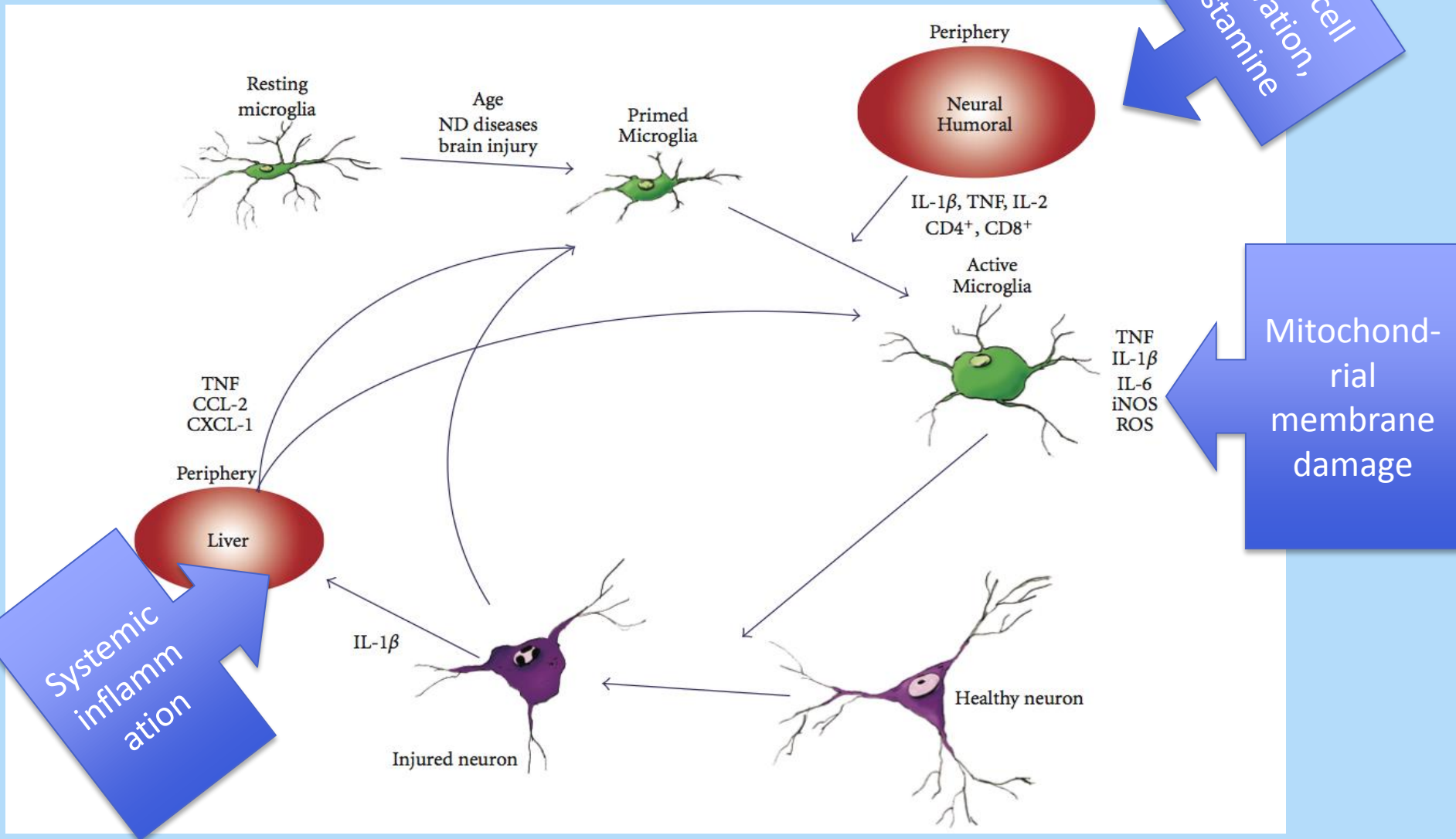
- Dendritic cells: activated by danger signals from injured cells such as those exposed to pathogens, toxins, mechanical damage
- Exist not only in lymphoid tissue but all over the body's mucosal membranes and skin (Langerhans)
- Mucosal DCs can also process circulating antigens



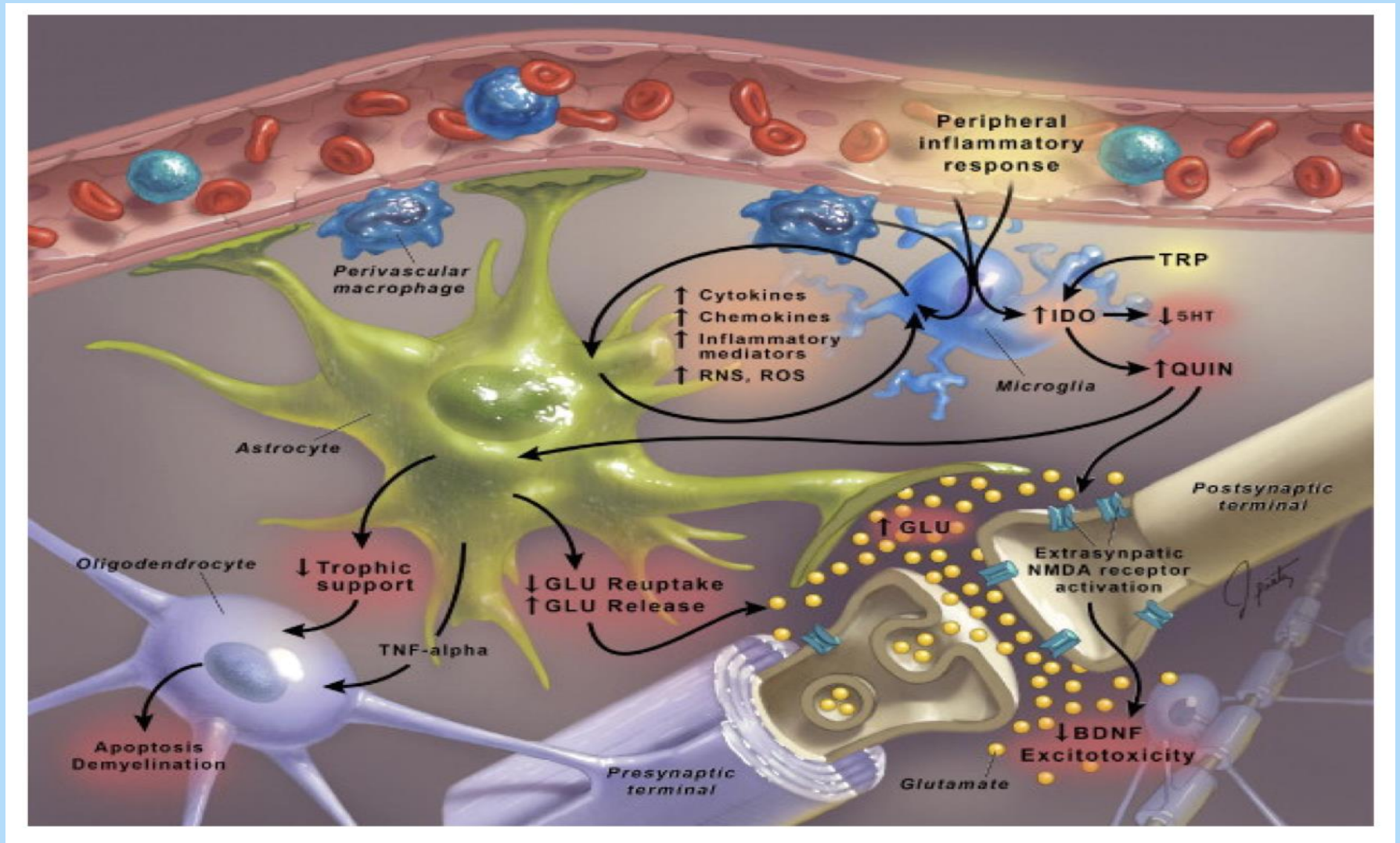
Microglia- the dendritic cells of the nervous system

- Microglia are the main innate immune cell in the nervous system
- Microglia can be activated (primed) but do not exert a pro inflammatory cascade.
- Only when there is central or peripheral inflammation does the primed microglial come into an active state which triggers stronger inflammation. E.g. Acute liver phase response- elevation of CRP, ESR, ferritin- are examples pro inflammation stimuli which can trigger secretion of pro inflammatory cytokines in a primed brain.
- This leads to blood brain barrier disruption, which further allows the extravasation/ flow of pro inflammatory cytokines and immune cells which further activate microglia.
- All this leads to increasing neuro dysfunction- degeneration in adults and poor development in children.
- Factors which activate microglia are the same as those that activates allergy responses and mitochondrial responses

The terrain of microglial cells



The terrain of microglial cells



Inflammation and its discontents. Miller AH . Biological Psychiatry 2009; 65: 732- 741

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Our environment sensing organs talk to the nerves

Gut

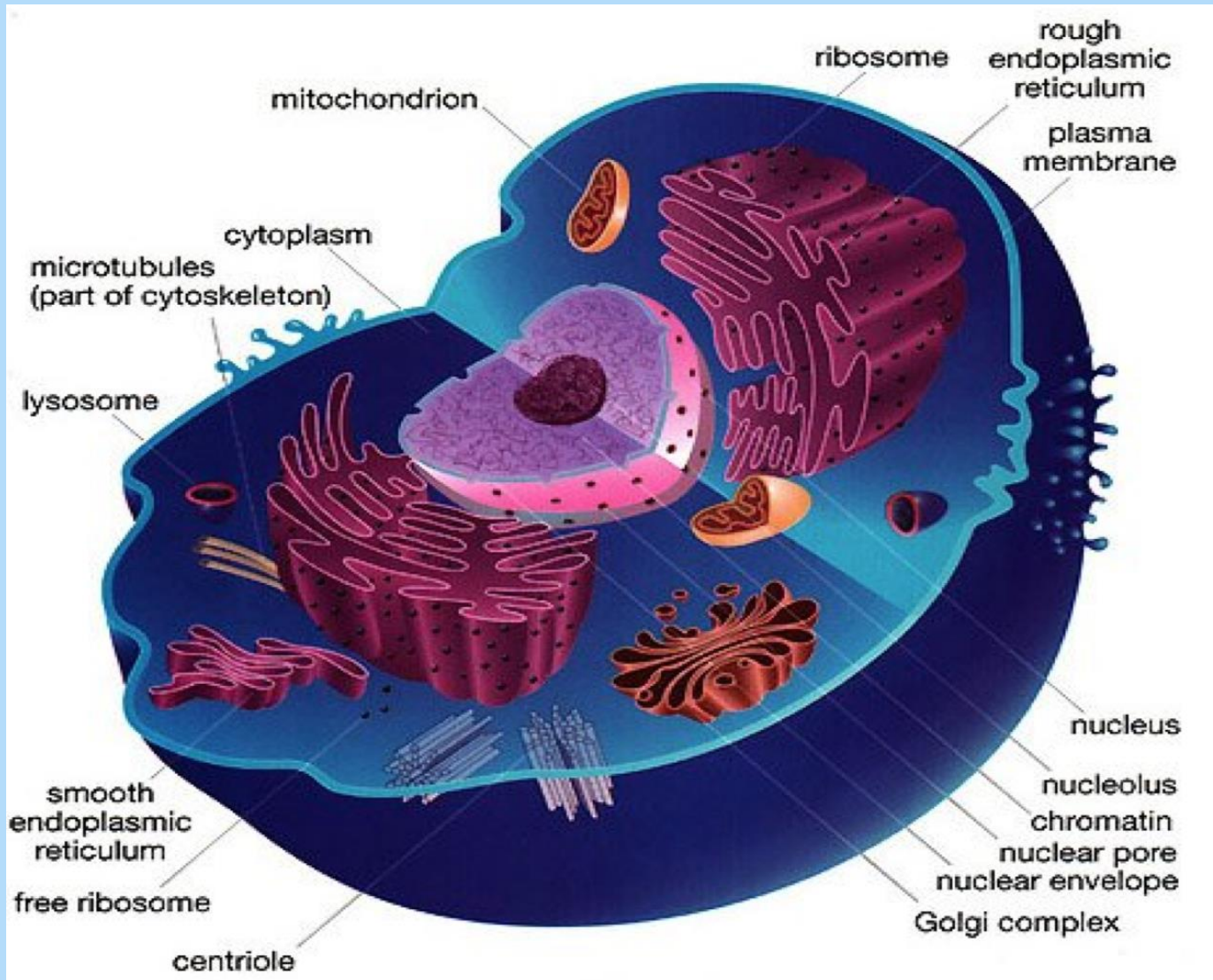
Lungs

Skin

Mucus membranous areas e.g. GU tract

There is constant cross talk between neurally mediated events and immune mediated events: the autonomic nervous system and the immune system function as a unit. The ANS is the most vulnerable and earliest part of the nervous system that is laid down in utero.

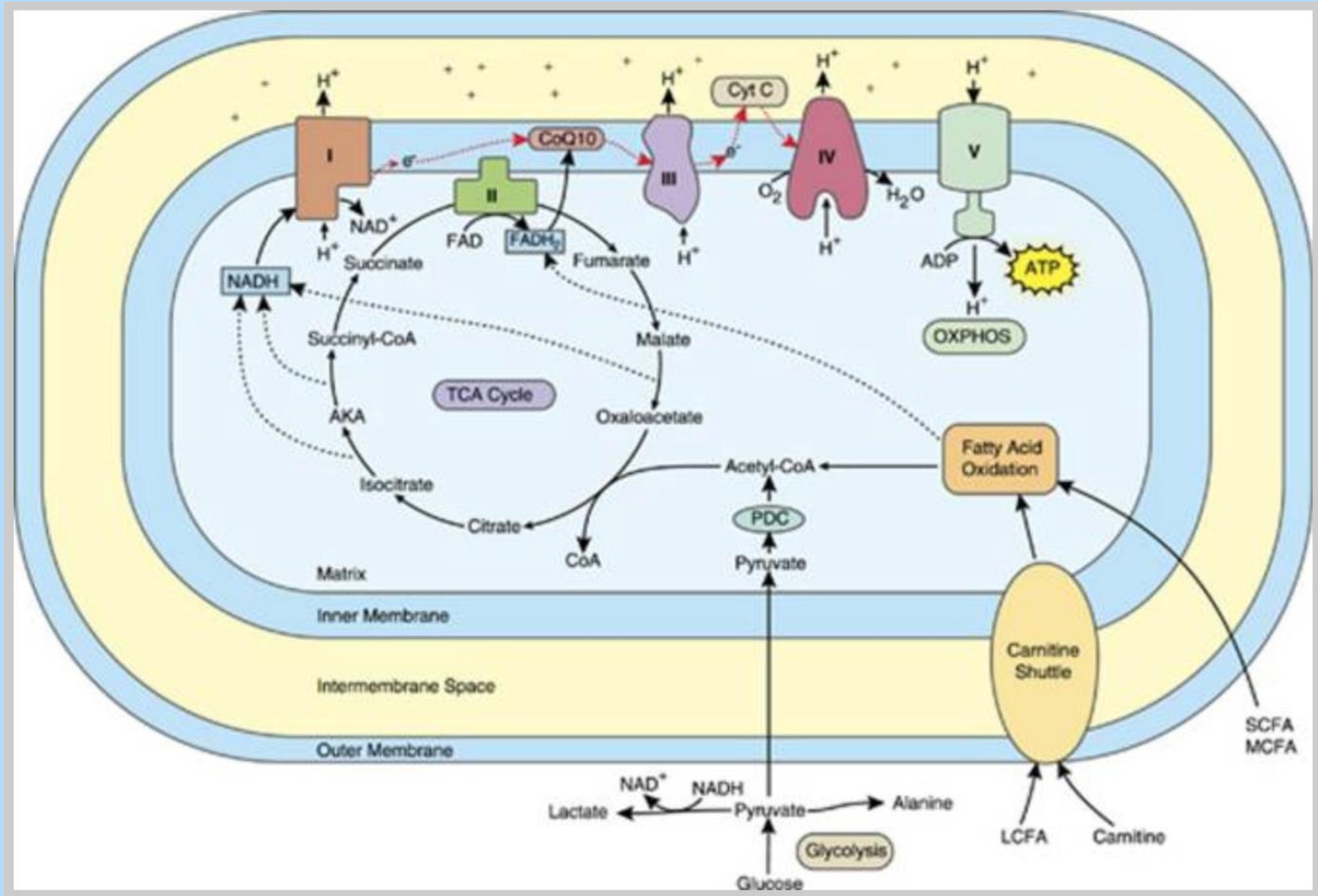
The terrain of mitochondria



Mitochondria

- Mitochondria are the powerhouse of the cell
- Produce ATP which is the currency for energy in a cell and thus the whole body – 100 trillion cells
- Each cell has a varied number of mitochondria depending how much energy that cell needs according to its function (e.g thousands)
- They have their own DNA and genome, inheritance is both maternal and paternal
- But mitochondria don't just make energy, they broadcast metabolism to the rest of the cell – akin to signals from an air traffic control tower

Life on the mitochondrial membranes



Mitochondrial dysfunction in autism spectrum disorders. A systematic review and meta analysis. Rossignol DA et al. Mol Psychiatry 2012; 17 (3):290- 314

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The 'cell danger response' of mitochondria

- A metabolic response that protects the cells and host from harm- evolutionary conservation
- Triggered by encounters with chemicals, physical and biological threats which **exceed the cellular capacity for homeostasis**
- This mismatch leads to alterations in cellular electron flow, oxygen consumption, redox potential, membrane fluidity, carbon and sulfur resource allocation, protein folding, vitamin availability, metal homeostasis, pterin and polyamine metabolism

Metabolic features of the cell danger response. Naviaux RK. Mitochondrion 2014; 16: 7-17

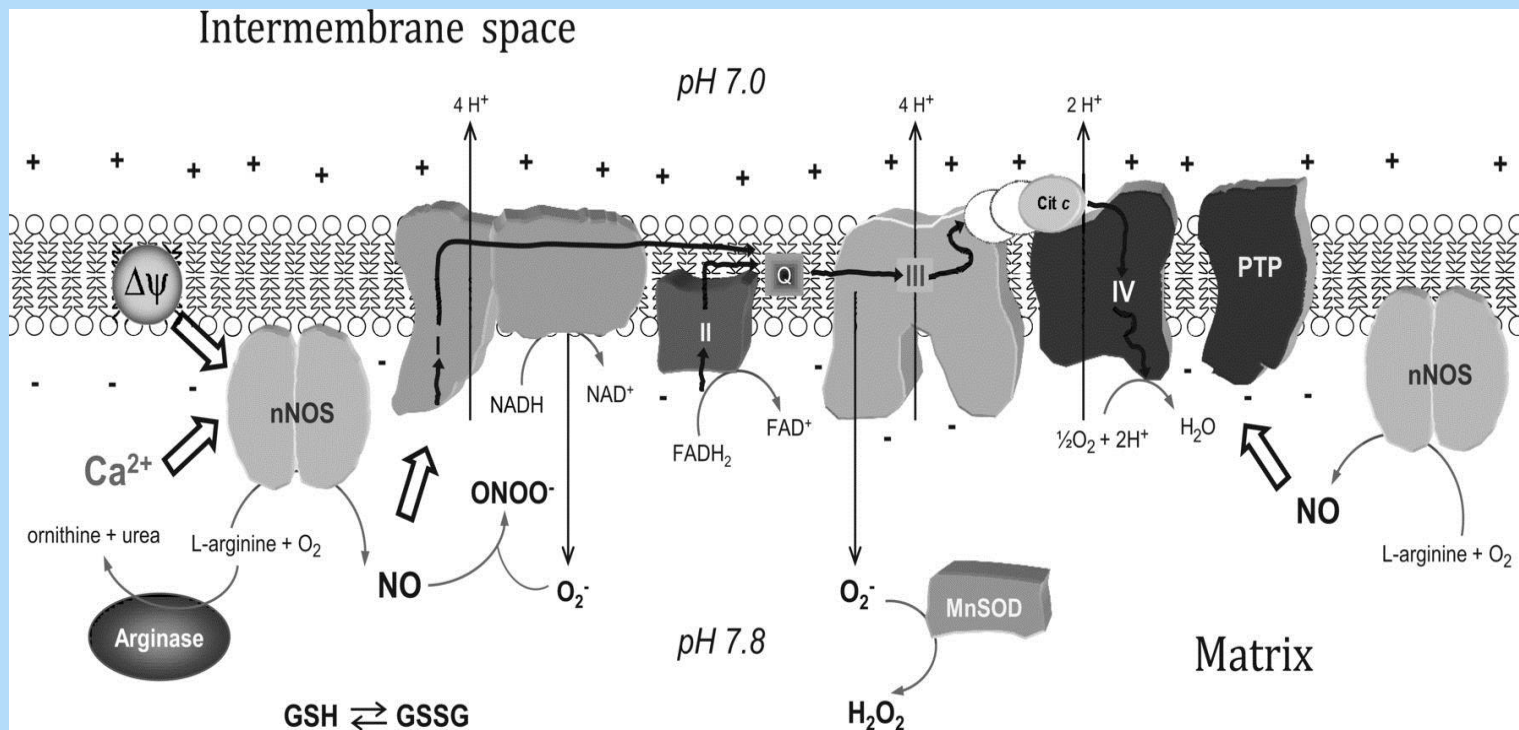
Understanding the cell danger response

- ATP has two different functions: inside versus outside the cell
- Inside the cell- an energy carrier molecule
- Outside the cell- a signaling molecule 'a mitokine'
- Mitochondria have two completely different functions:
 - Cellular defense and communication
 - Guardian of the membrane gradients which powers metabolism and bioenergetic flow of Life
- The cell danger response is maintained by extracellular nucleotides- purinergic signals (ATP, ADP, AMP, Adenosine) and mitokines

Metabolic features of the cell danger response. Naviaux RK. Mitochondrion 2014; 16: 7-17

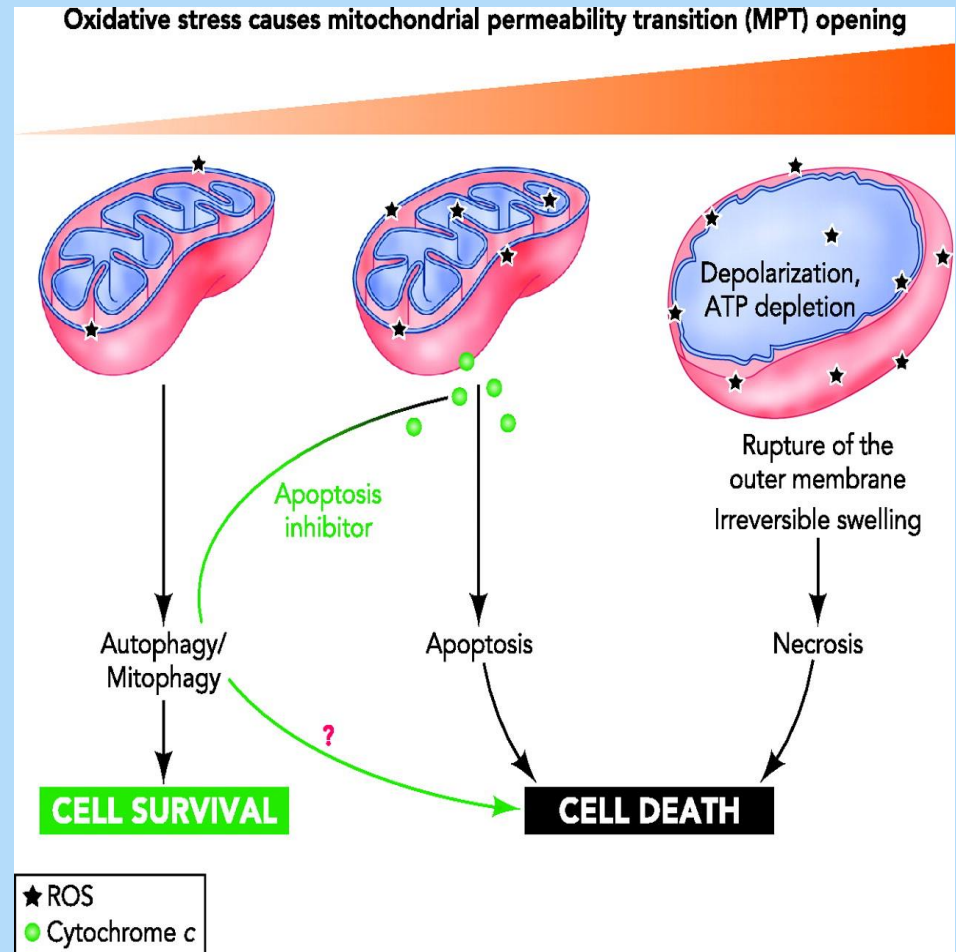
Mitochondria as the **biggest source of ROS** and triggers of the inflammasome

- Leaked ATP
- ATP metabolites
- Excess ROS
- Mitochondrial membrane damage



Reducing mitochondrial damage and immune activation

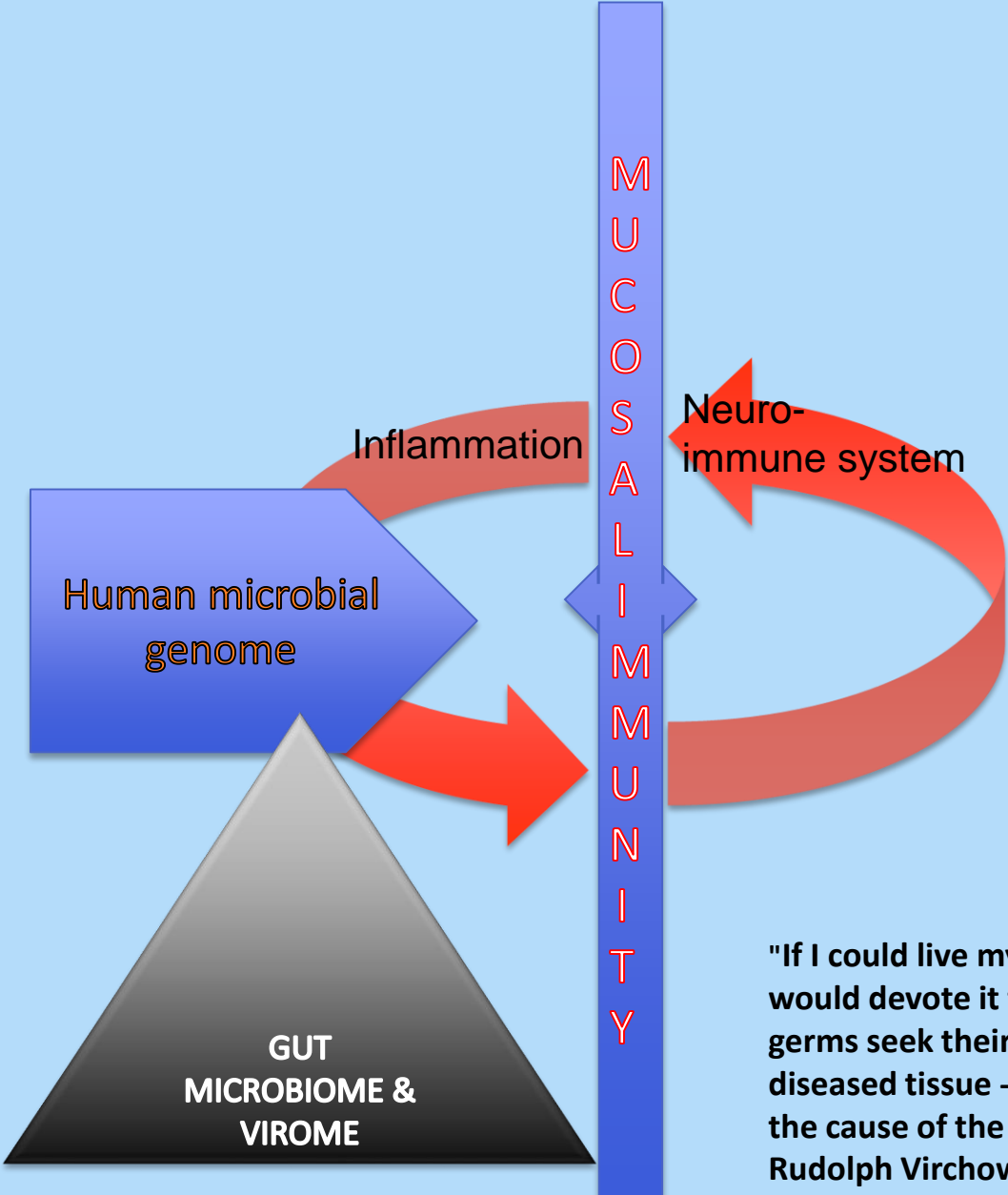
- Inflammasome triggers can be reduced by mitophagy
- Reduce oxidative damage to mt DNA
- Reduce electron leakage in endoplasmic reticulum
- Caloric restriction



What influences the constant conversation between everyday triggers of inflammation and the neuro immune system?

The combination of our genome and total microbial presence inside the body.

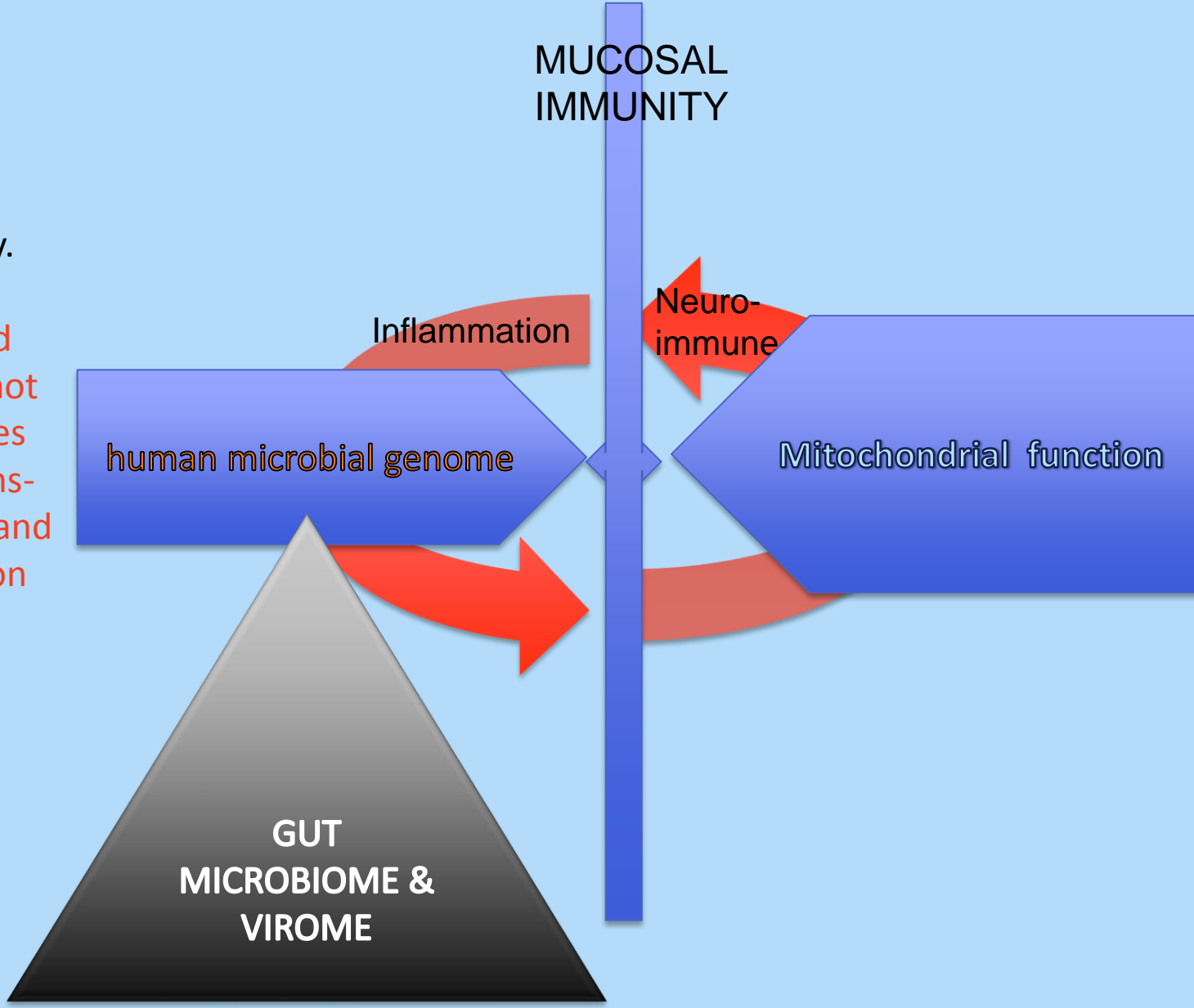
This symbiotic balance rests hugely on the terrain of the gut microbiome



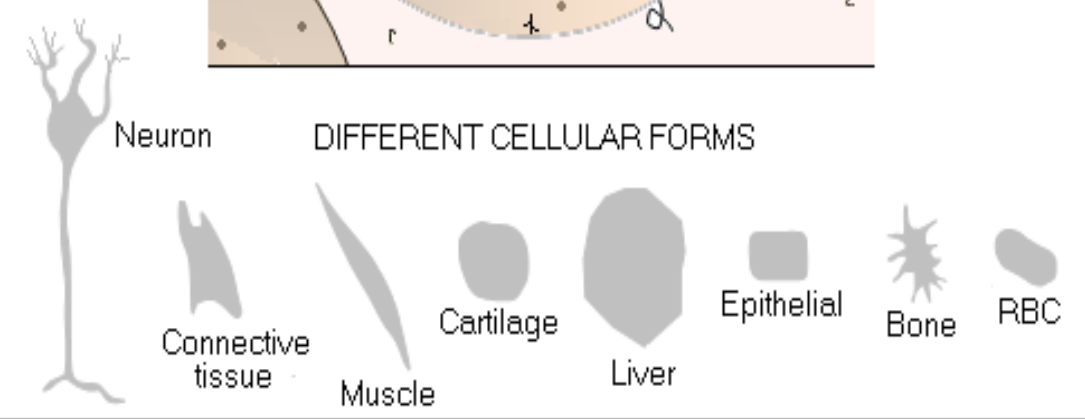
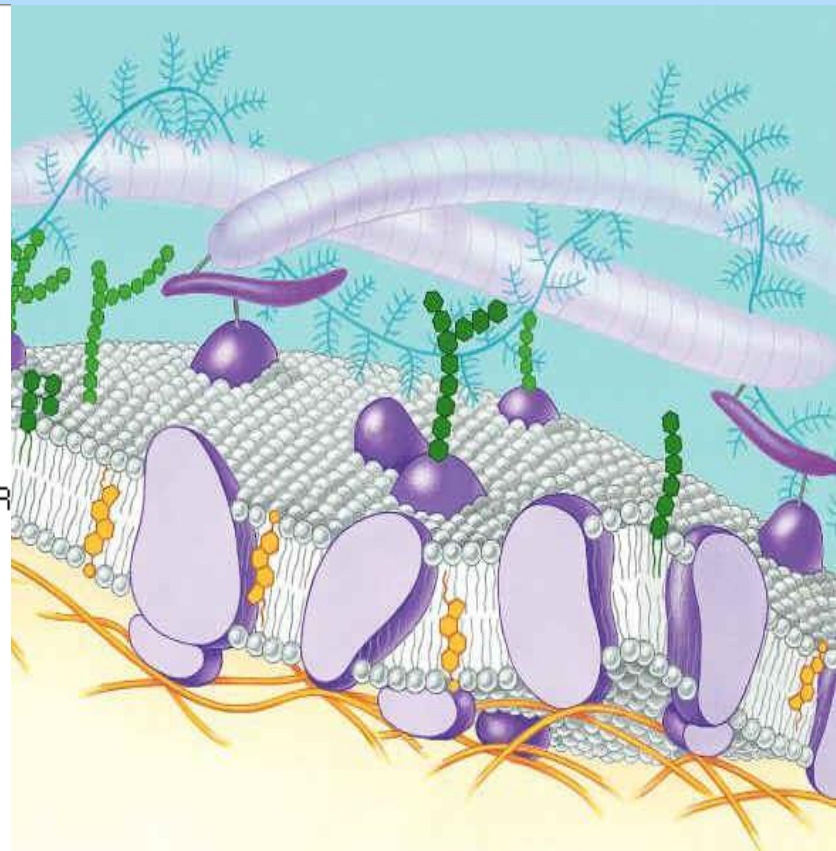
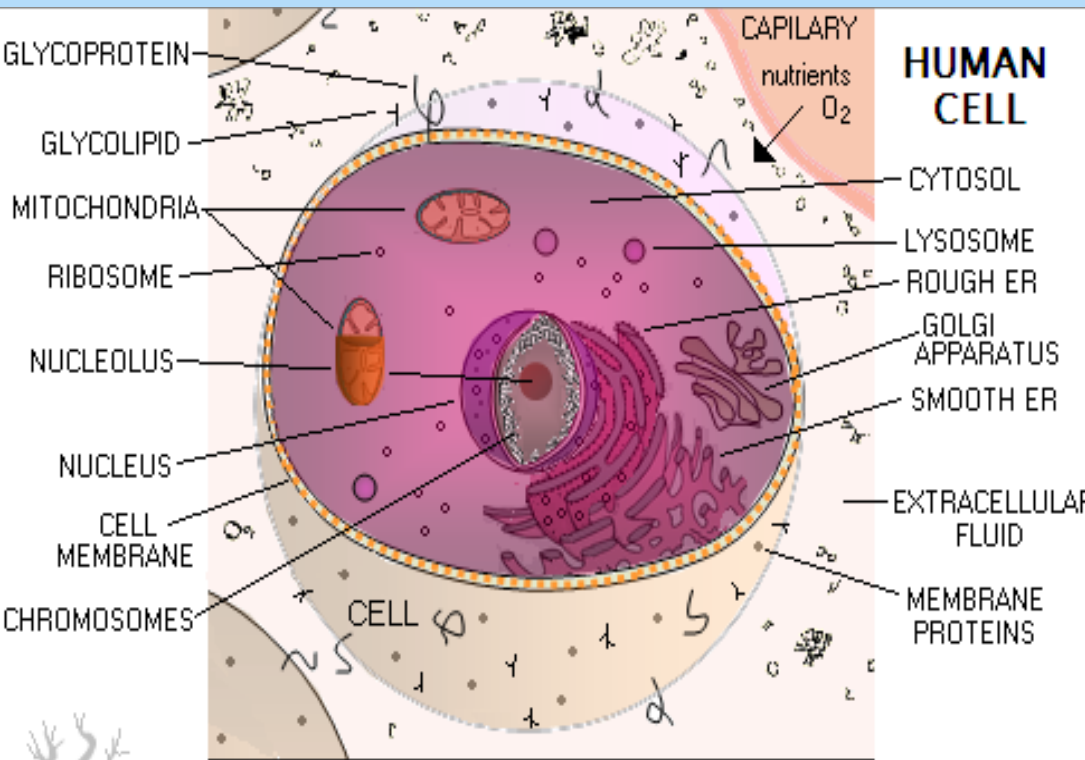
"If I could live my life over again, I would devote it to proving that germs seek their natural habitat, diseased tissue - rather than being the cause of the diseased tissue." -- Rudolph Virchow (1821-1902)

Mitochondrial and membrane function conducts this interplay.

Mucosal immunity and membrane integrity: not only immune responses but all barrier functions-sensing and signaling and cell membrane function



Beyond biochemistry: inner LIFE on our membranes



More than just mucosal immunity: membrane medicine

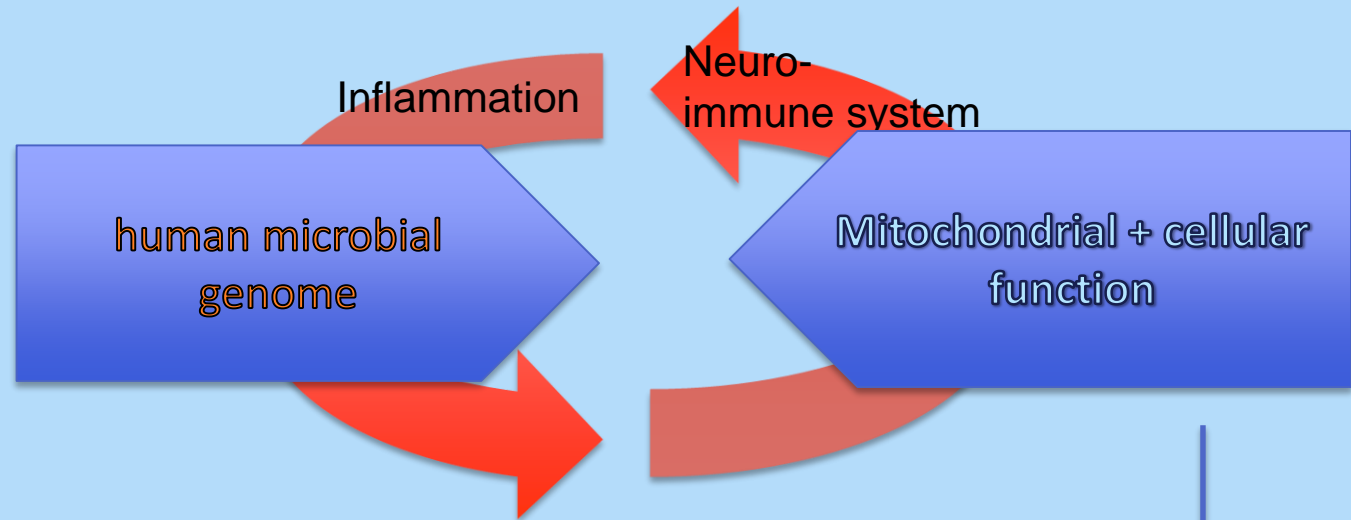
Endothelial membranes: the largest organ in the body governing coagulation, platelet function, immune function, control of blood volume and electrolyte content in intravascular and extravascular spaces

Mitochondrial membranes: mitokine signalling, bioenergetic function of all organs. Organs with the most mitochondria are the brain and muscles

Cell membranes in general, with a focus on neuronal membranes: with signaling as a key function, how do nerves and brains work without impeccable communication?

The pillars of functional medicine + nutrition

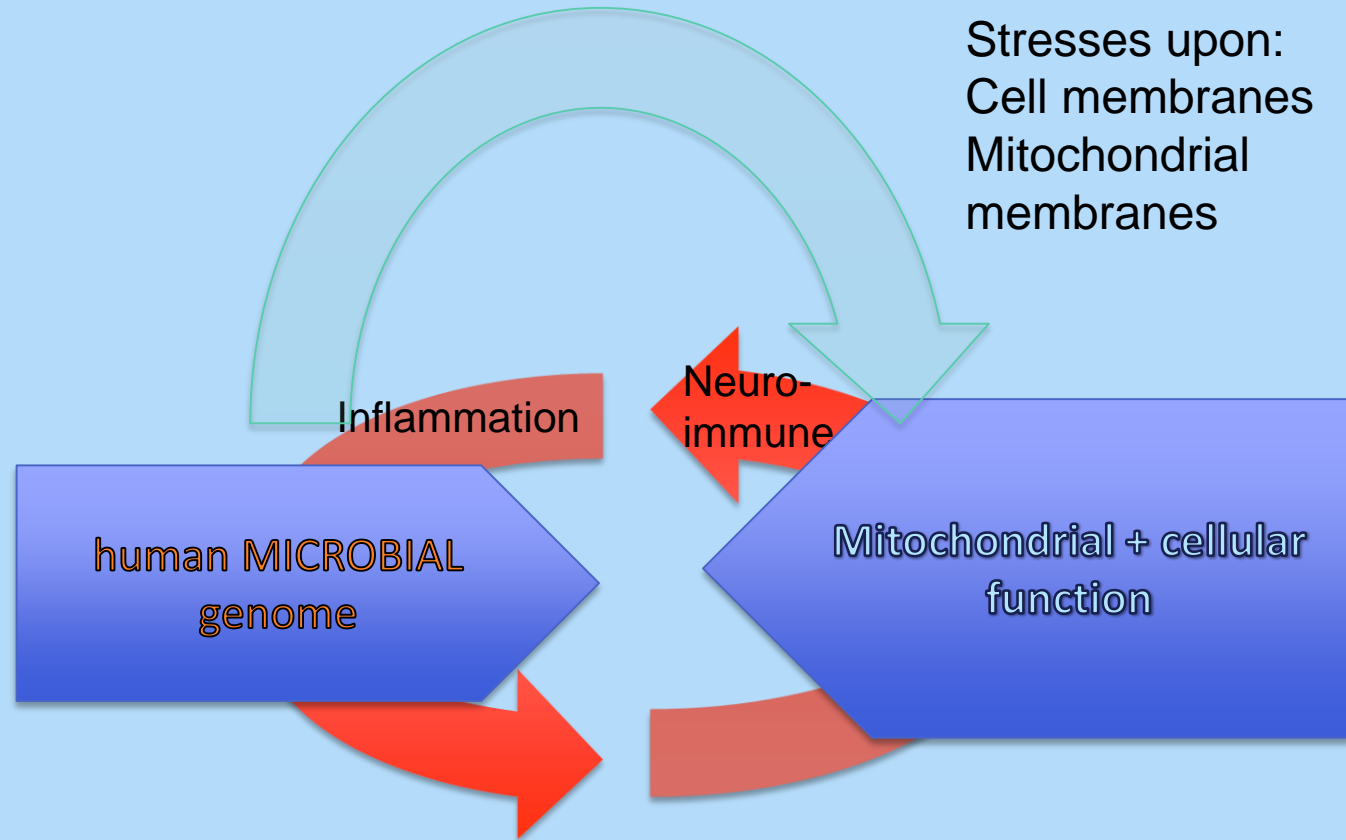
Cell membrane support
=
Mitochondrial support
=
Brain and nerve support
=
Peripheral and whole body organs support



- Essential fat nutrition: the problem with low fat diets and vegetable oils
- Mitochondrial nutrition
- Using fats as energy supply: the problem with carbohydrates and insulin
- Methylation

Cleaning up the terrains

Acquired
mitochondrial
dysfunction:
- Dietary
- Oxidative
- Microbial
- Xenobiotic



Mitochondrial medicine arrives to prime time in clinical care. Nutritional biochemistry and mitochondrial hyperpermeability meets disease pathogenesis and clinical intervention. Vasquez A. Alt Ther Health Med 2014; 20 (s1): 26-30

The total terrains of dysfunction

- Immune dysfunction and loss of immune tolerance due to bombardment of dendritic immune cells with toxins and pathogens, alongside exposure to antigens and allergens.
- Mitochondrial dysfunction and increasing cell danger responses from environmental toxins alongside loss of cell membrane nutrition and function.
- The body's microbiome and loss of ecosystem thus imbalance of viruses, bacteria, fungi, parasites.

the interactome

This entire 'interactome' leads to overall neural dysfunction

The terrain of neural dysfunction

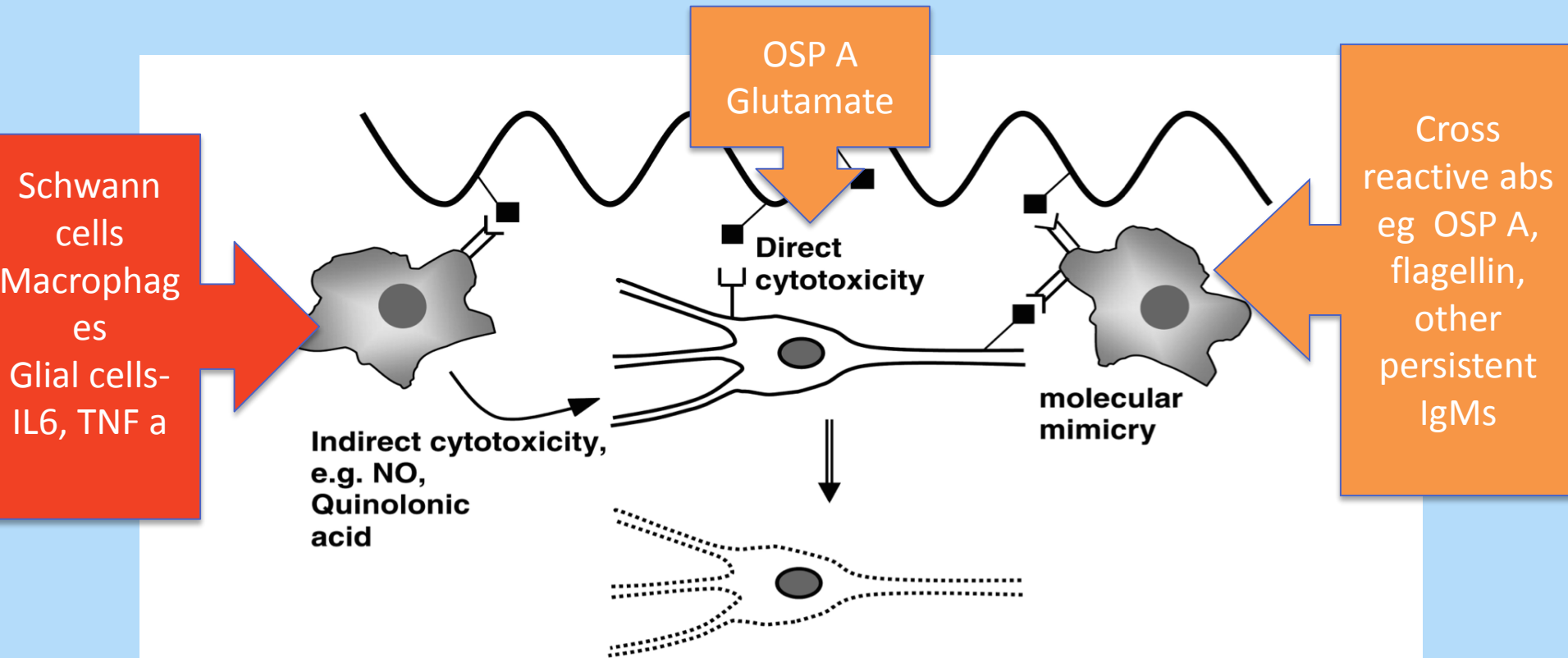


Figure 3. The neural dysfunction in neuroborreliosis. Three principal mechanisms that lead to the injury of neuronal cells: (1) the secretion of cytotoxic substances by leucocytes and glial cells, (2) direct cytotoxicity, and (3) autoimmune-triggered processes through molecular mimicry.

'The terrain' and neuro inflammation

- How does being chronically toxic (oxidative responses) disrupt neurological function and brain development?
- Inflammation
- Excito- toxicity
- Reduced mitochondrial respiratory chain function
- Membrane lipid abnormalities & poor signaling
- Cell danger responses

- 'Many roads can lead to Rome'
- **The total load really counts**

Guidelines – key mitochondrial supports

- ✧ Co enzyme Q 10 10mg/kg/d
- ✧ L- Carnitine 50mg/kg/d
- ✧ Nicotinamide 7.5mg/kg/d
- ✧ Vitamin C 30mg/kg/d
- ✧ Vitamin E 25IU/ kg/d
- ✧ Alpha lipioic acid 10mg/kg/d
- ✧ Pantothenic acid 10mg/kg/d
- ✧ Thiamine 15mg/kg/d
- ✧ Other mitochondrial support: moderate exercise, increased hydration, limited fasting

Taken from Kennedy Krieger Institute. R Kelly, Division of Metabolism, Dept of Pediatrics, Johns Hopkins Medical Institutions

Guidelines - Cell membrane nutrition

- ✧ **NO trans fats or hydrogenated vegetable oils**
- ✧ High fat: saturated, monounsaturated and polyunsaturated fats), moderate protein nutrient dense diet (fat sol vits A,D,E,K)
- ✧ Phosphatidylcholine 3-4 g per day
- ✧ Phosphatidylserine 300mg per day
- ✧ Butyric acid 3-6 g per day
- ✧ Omega 6 FA: Omega 3 FA 4:1 ratio
- ✧ Methylation support
- ✧ Sulfation support
- ✧ Minerals, antioxidants- carotenoids and flavonoids

Guidelines - Mucosal immunity nutrition

- ✧ Butyric acid- ghee, dietary fibre, nutritional supplements up to 4/d
- ✧ Retninoic acid/ vitamin A- fish, butter, full cream grass fed organic diary, supplements 2-25,000 IU per day
- ✧ Vitamin D- sunshine, supplements several 1000 iu per day : more contentious re vitamin D receptor dysfunction and immune dysregulation
- ✧ Zinc- larger doses that the recommended daily intake
- ✧ Gelatin, amino acids, short chain fatty acids, glycosaminoglycans- a global approach with food like meat stock, bone broth and high quality protein sources
- ✧ Lactofermented food

Guidelines - Supporting immune tolerance

- ✧ Reduce environmental 'co- stim' factors on the dendritic cells
- ✧ Food allergies and sensitivities trigger dendritic cells
- ✧ Other food proteins can trigger intestinal cell damage eg. Lectins, gluten
- ✧ Clear out potential triggers from medications, household personal and ingested chemicals, alcohol, water
- ✧ Reducing the total toxic load which leads to interference in cell and mitochondrial membranes which activate immune responses to cause loss of self tolerance

membranes: life in balance

