Immunology in Integrative Medicine

Function/Dysfunction
Lifestyle & Nutrients Solutions

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Partners

- *Financial support was provided for this course through an educational grant from KBMO Diagnostics and Your Financial Pharmacist.*

Disclosures

- Consultant: Ortho Molecular Products

- Speaker Fees for commercial entities in past 12 months
  - Genova Diagnostics
  - Labrix/Doctor's Data

  - There is No discussion of unapproved drugs.

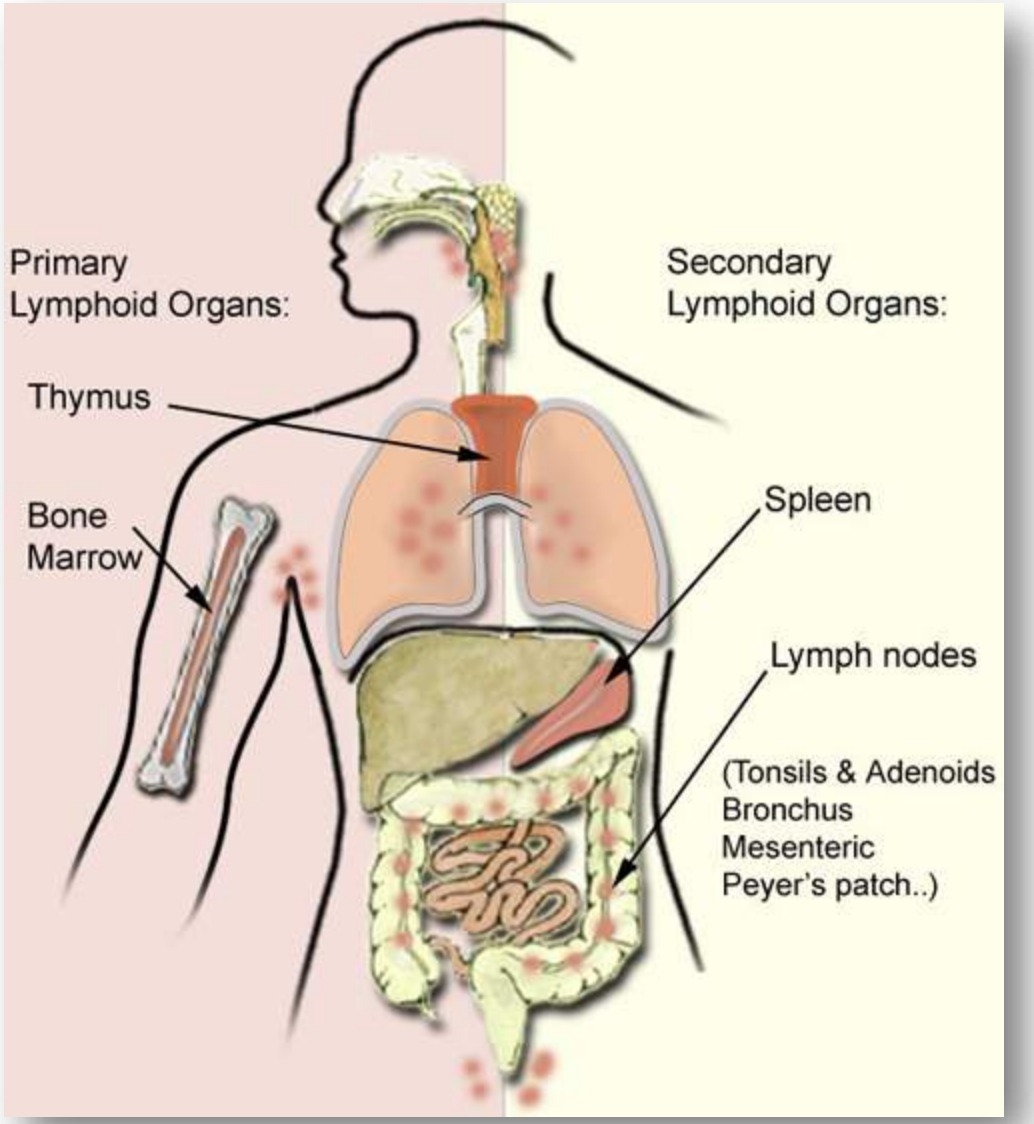
Overview & Objectives.

- Discuss some of the unique design challenges the immune system faces in mounting a strong defense against (potentially) harmful foreign substances- while attempting not to over-react on the one hand or cross-react with itself
- **Learning Objectives**
- Describe functions of the innate and adaptive immune system
- Discuss the role of mitochondrial function in relation to supporting the immune system
- Recognize the connection between the GI tract and immune function
- Define the differences between autoimmune and autoinflammatory conditions

Defining The Mechanism(s) of Intervention

- The immune system is involved in nearly every facet of human pathophysiology.
- Some therapies alter the course of the disease by modulation immune/autoimmune functions directly
- Some therapies modulate the mediators of the disease downstream of the trigger (i.e., inflammatory signals)
- Some therapies change epigenetic susceptibility to disease.
- Very often we don't have the ability to distinguish the difference- or the therapy modifies more than one of these categories.

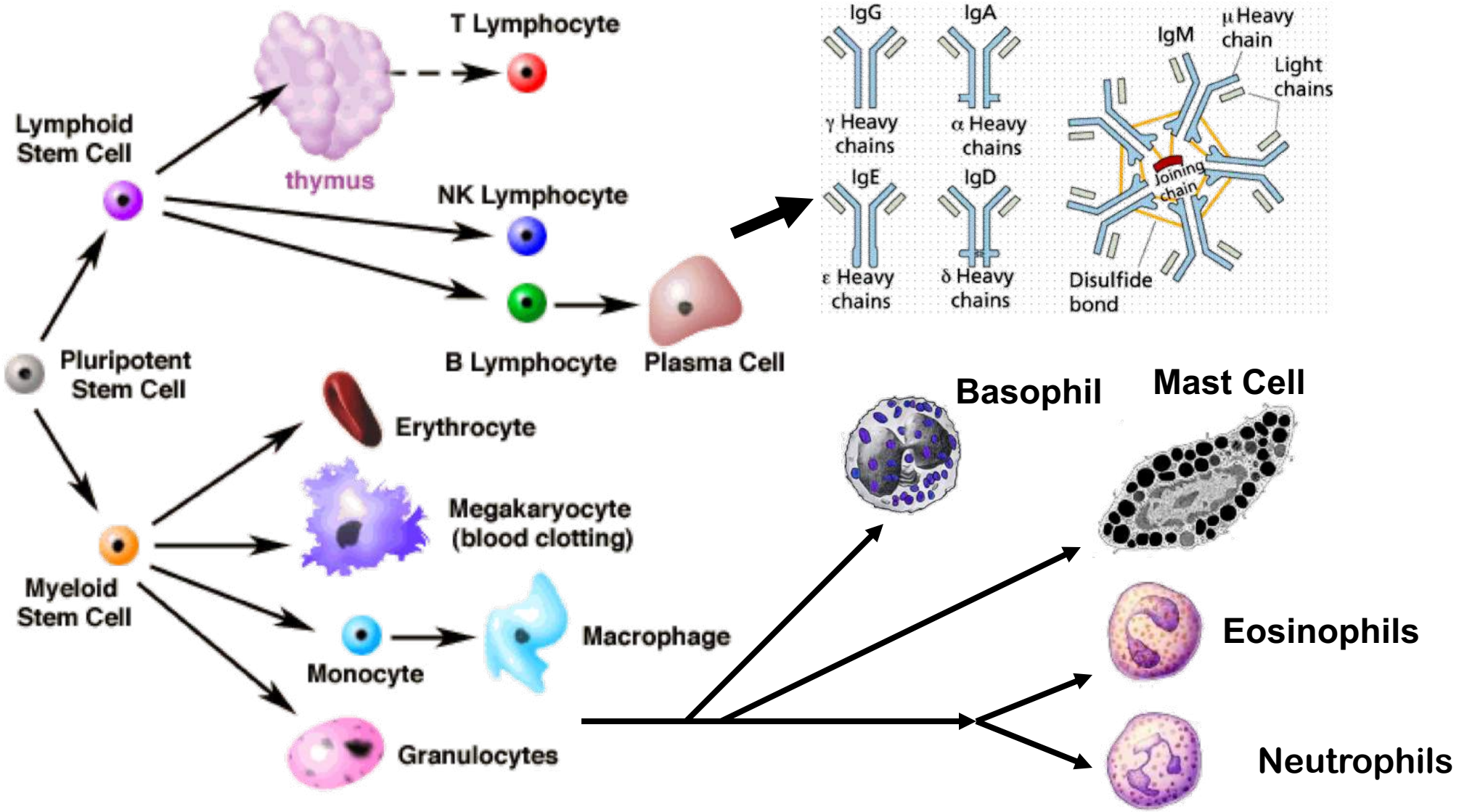
Functional immune-related tissues

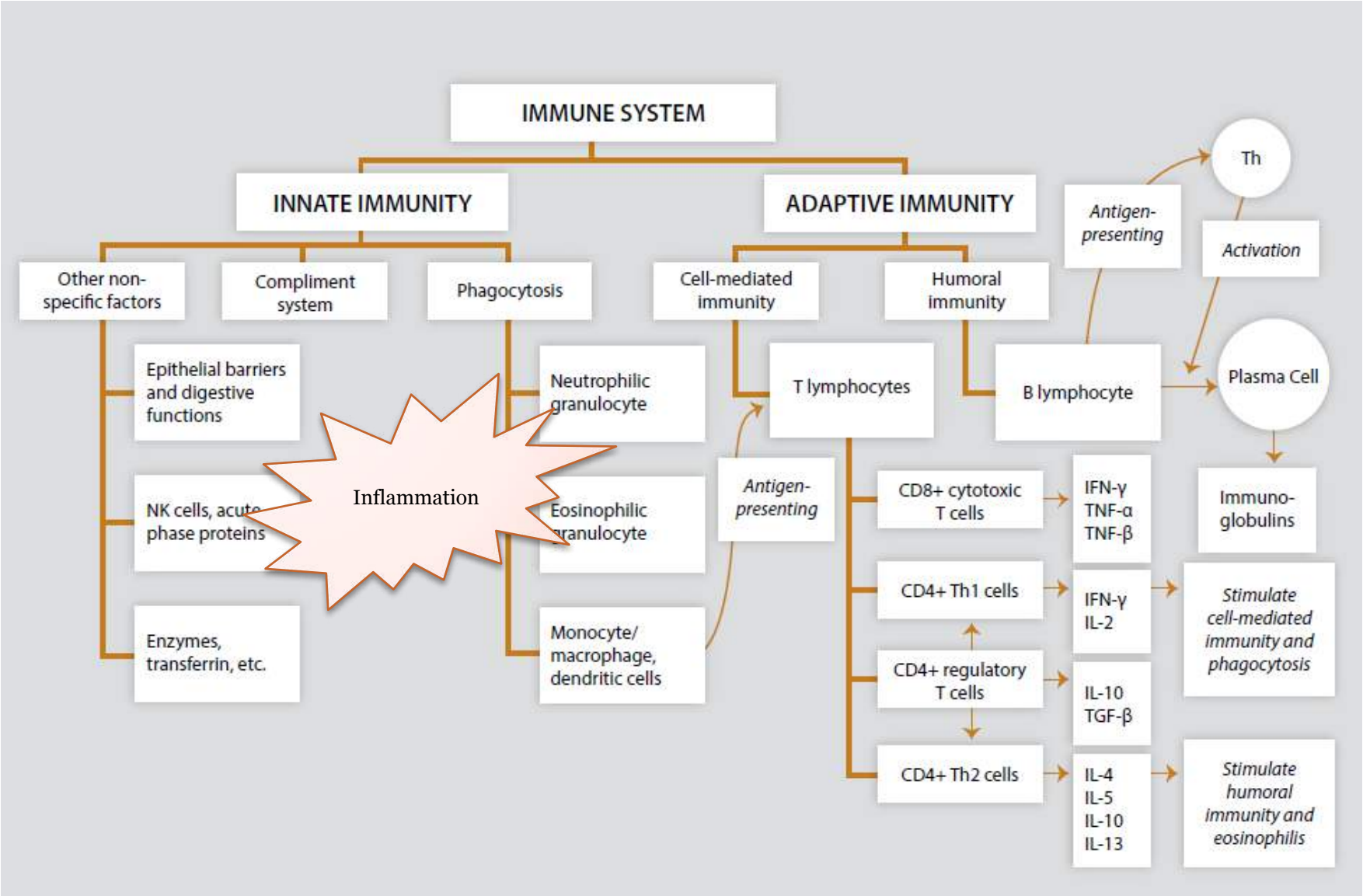


While the immune system cells (systemic or specialized) exist in nearly all tissues, there are certain Primary and Secondary Lymphoid organs/glands/tissues that are specifically designed to concentrate more global immune system functions (maturation, training, overwhelming pathogens).

- Examples of specialized cells include:
  - Kupffer Cells (liver)
  - Microglia (CNS)
  - Alveolar Macrophages (resp. tract)

Important Immune Cells



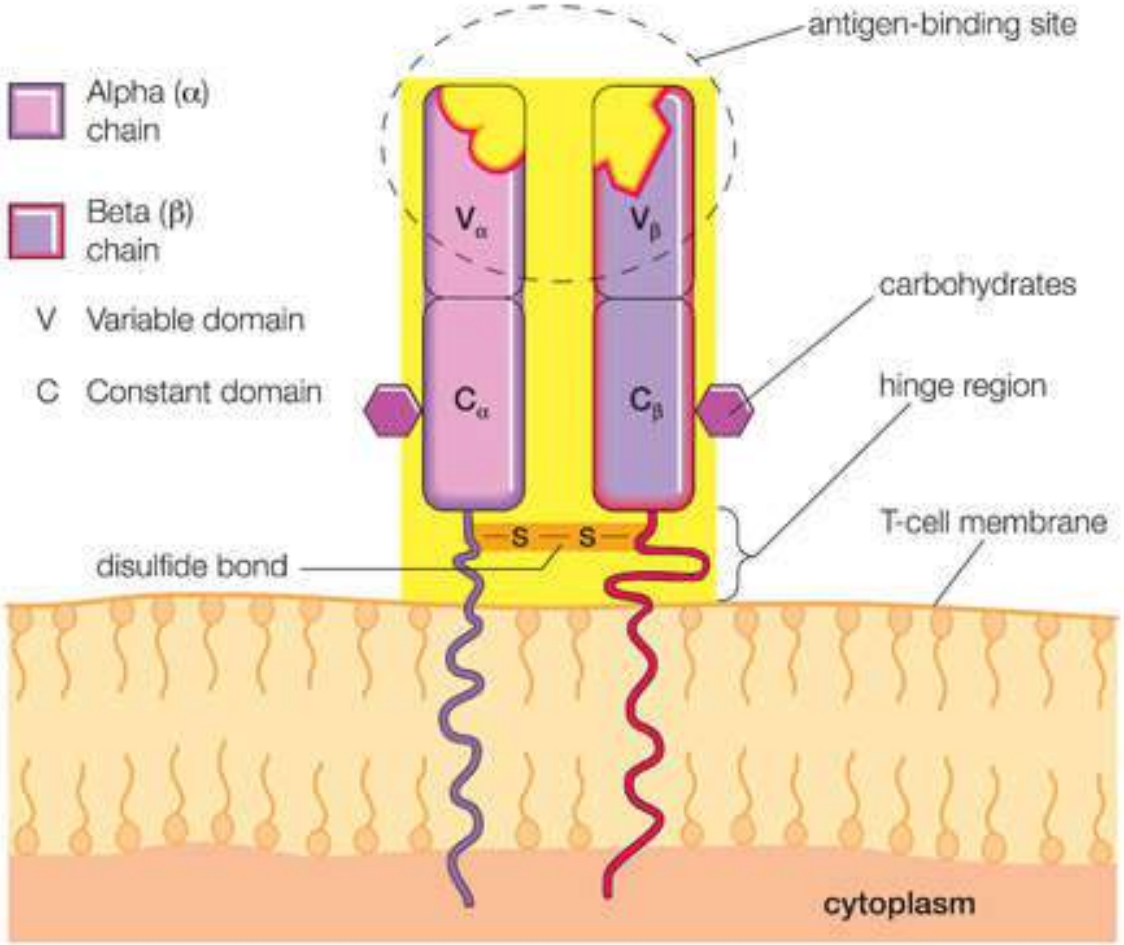

IMMUNE SYSTEM
INNATE IMMUNITY
ADAPTIVE IMMUNITY
Other non-specific factors
Compliment system
Phagocytosis
Cell-mediated immunity
Humoral immunity
Epithelial barriers and digestive functions
NK cells, acute phase proteins
Enzymes, transferrin, etc.
Neutrophilic granulocyte
Eosinophilic granulocyte
Monocyte/ macrophage, dendritic cells
Inflammation
T lymphocytes
B lymphocyte
Antigen-presenting
Antigen-presenting
Th
Activation
Plasma Cell
Immuno-globulins
CD8+ cytotoxic T cells
IFN-γ
TNF-α
TNF-β
CD4+ Th1 cells
IFN-γ
IL-2
Stimulate cell-mediated immunity and phagocytosis
CD4+ regulatory T cells
IL-10
TGF-β
CD4+ Th2 cells
IL-4
IL-5
IL-10
IL-13
Stimulate humoral immunity and eosinophilis

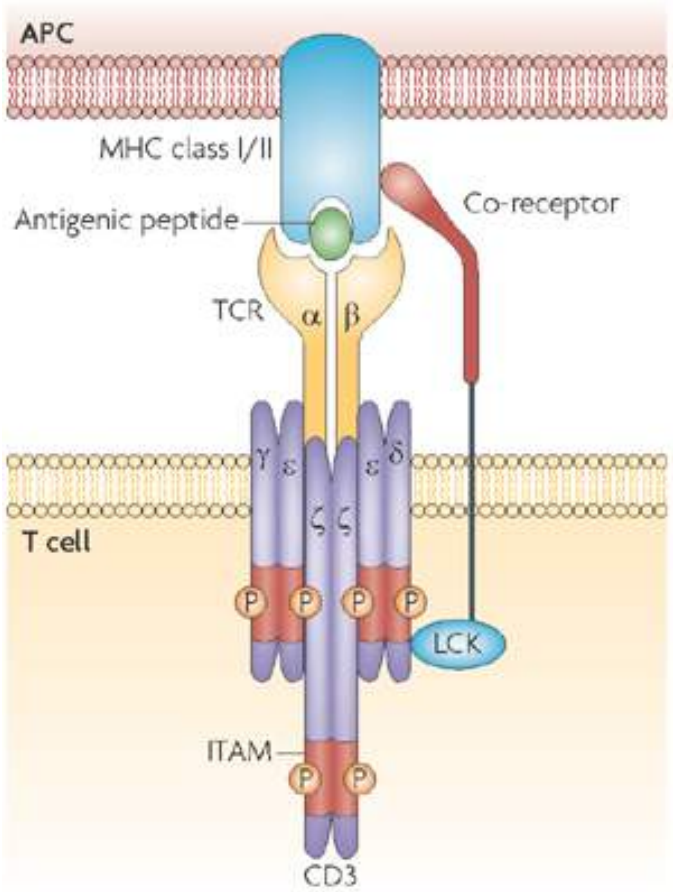
Simple Dichotomy? Time to Rethink!

TABLE 3-1 Innate and adaptive immunity

Attribute	Innate immunity	Adaptive immunity
Response time	Minutes/hours	Days
Specificity	Specific for molecules and molecular patterns associated with pathogens	Highly specific; discriminates even minor differences in molecular structure; details of microbial or nonmicrobial structure recognized with high specificity
Diversity	A limited number of germ line–encoded receptors	Highly diverse; a very large number of receptors arising from genetic recombination of receptor genes
Memory responses	None	Persistent memory, with faster response of greater magnitude on subsequent infection
Self/nonself discrimination	Perfect; no microbe-specific patterns in host	Very good; occasional failures of self/nonself discrimination result in autoimmune disease
Soluble components of blood or tissue fluids	Many antimicrobial peptides and proteins	Antibodies
Major cell types	Phagocytes (monocytes, macrophages, neutrophils), natural killer (NK) cells, dendritic cells	T cells, B cells, antigen-presenting cells

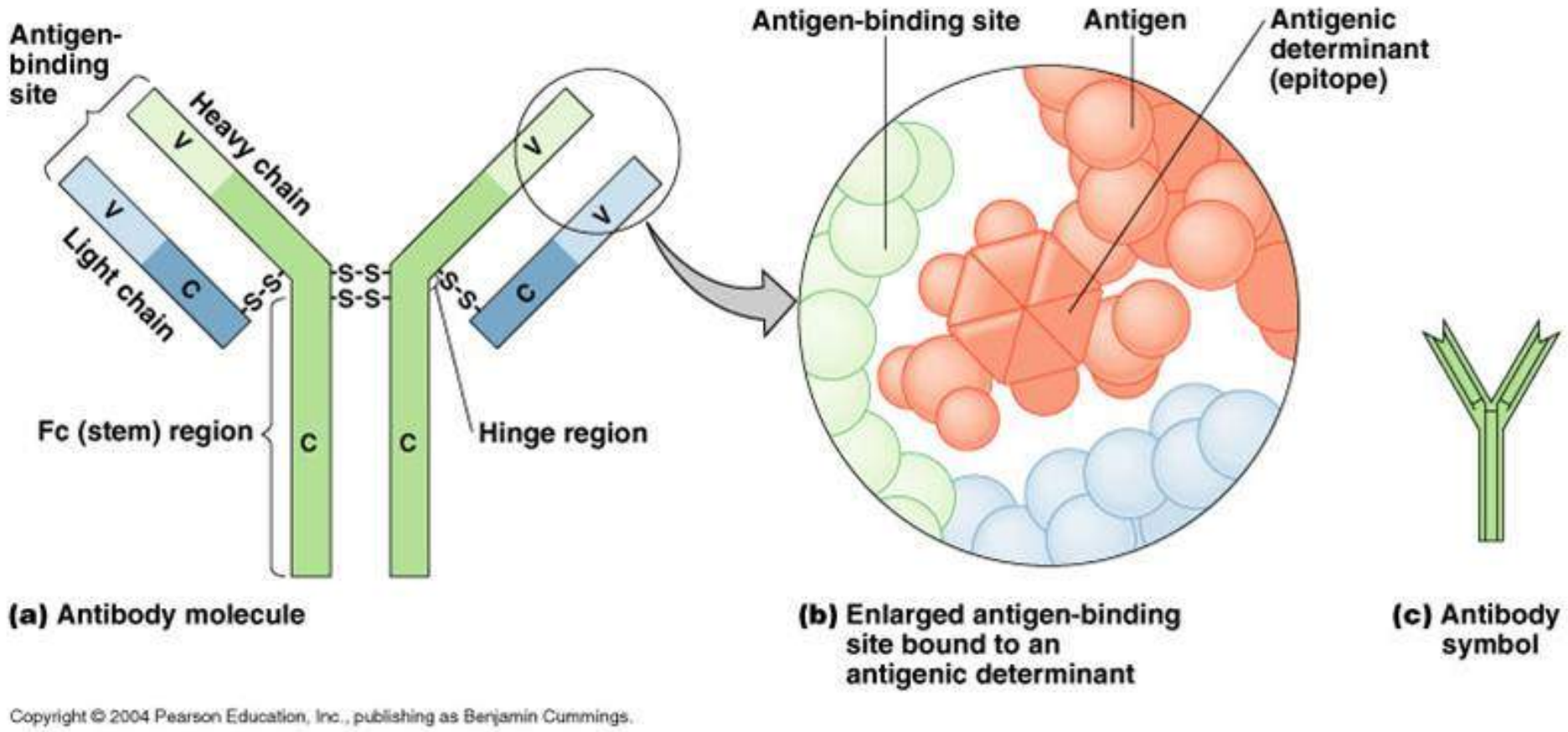
Basic Structure- T-cell Receptor



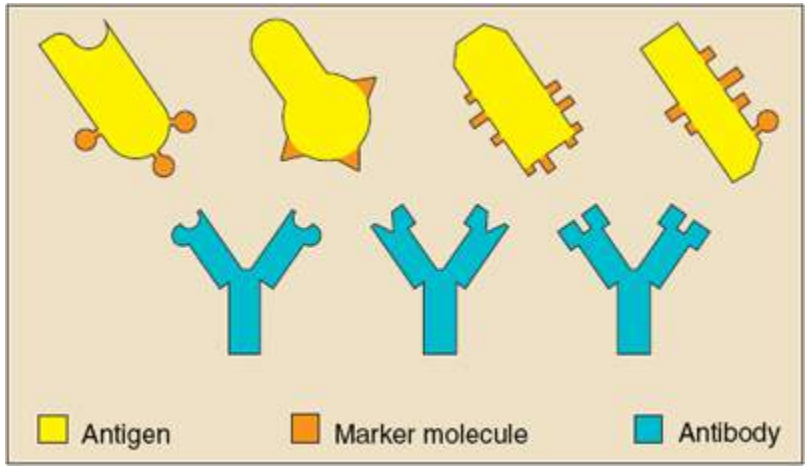


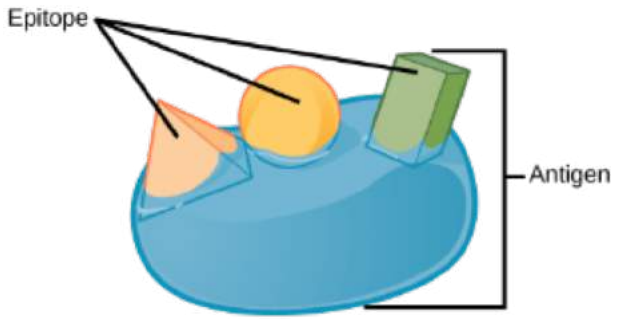
Nature Reviews | Immunology

Anatomy of an Antibody: Very Specific Recognition



The (adaptive) immune system conundrum

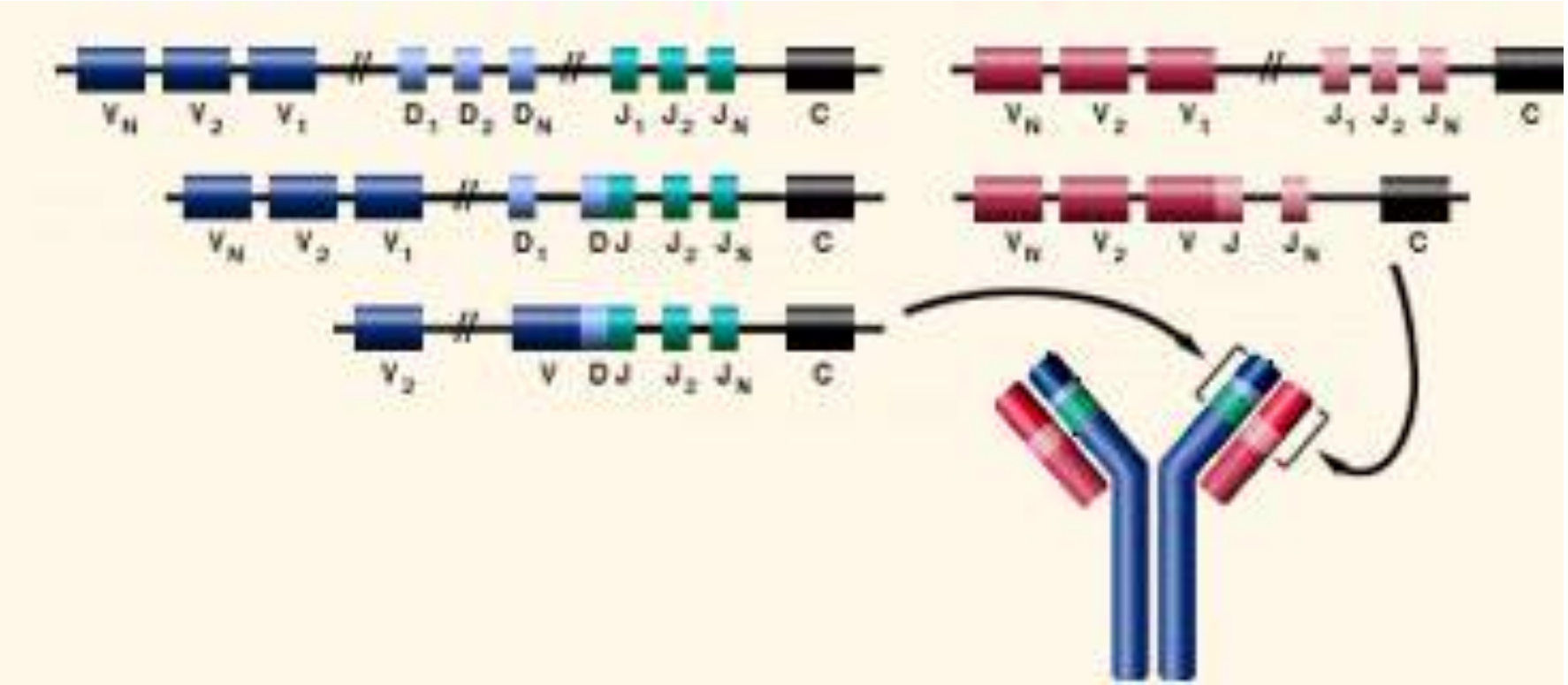




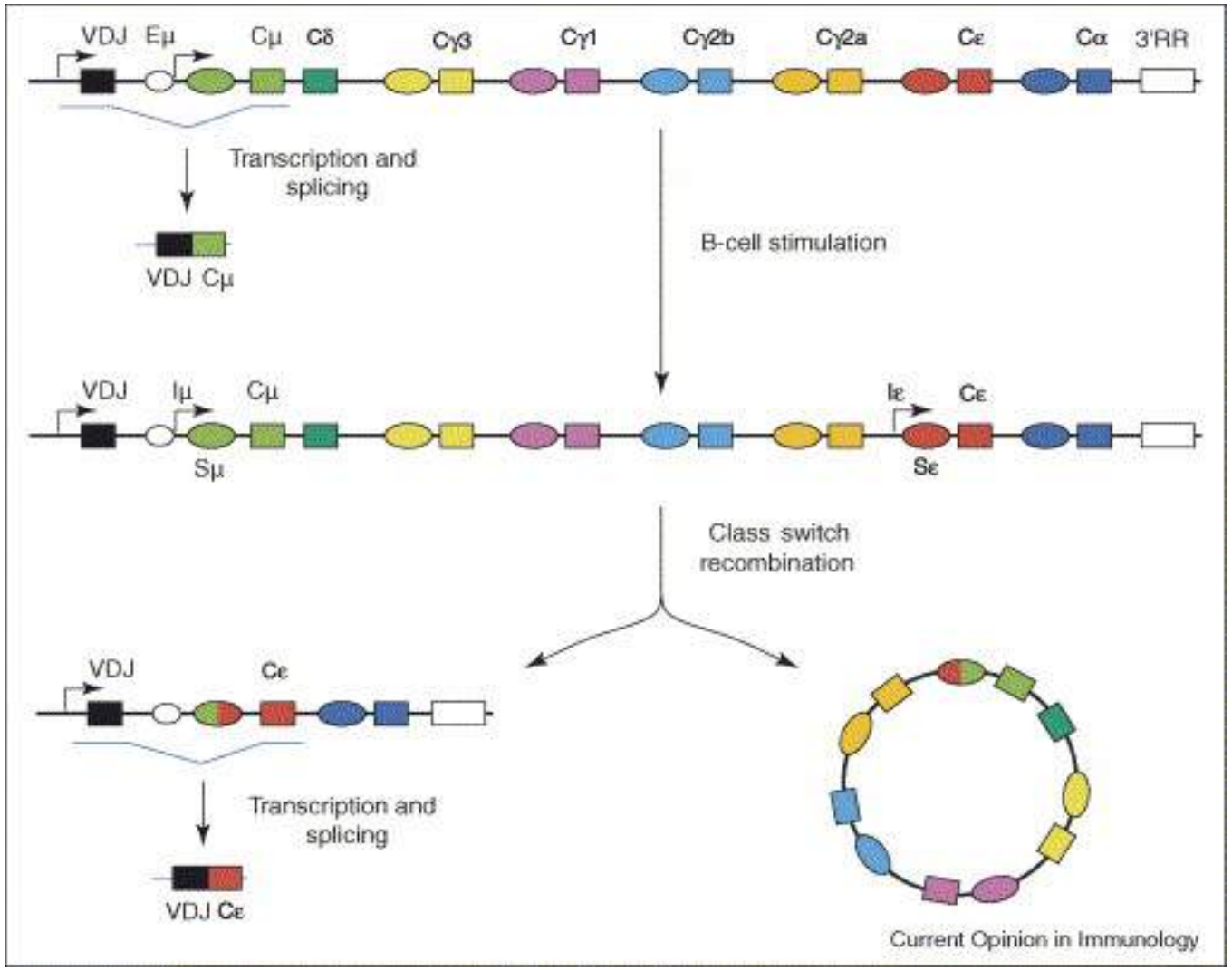
Each Antigen may contain multiple epitopes, Antibodies bind to epitopes, which are small portions of the antigen.

- A nearly infinite number of antigen epitopes exist.
- Ig and TCR are protein sequences made from a limited number of genes.
- How can an infinite number of antigen binding sites be formed with a finite number of genes
- How can this be accomplished in the absence of antigen?

Recombination:
The solution for limited genes

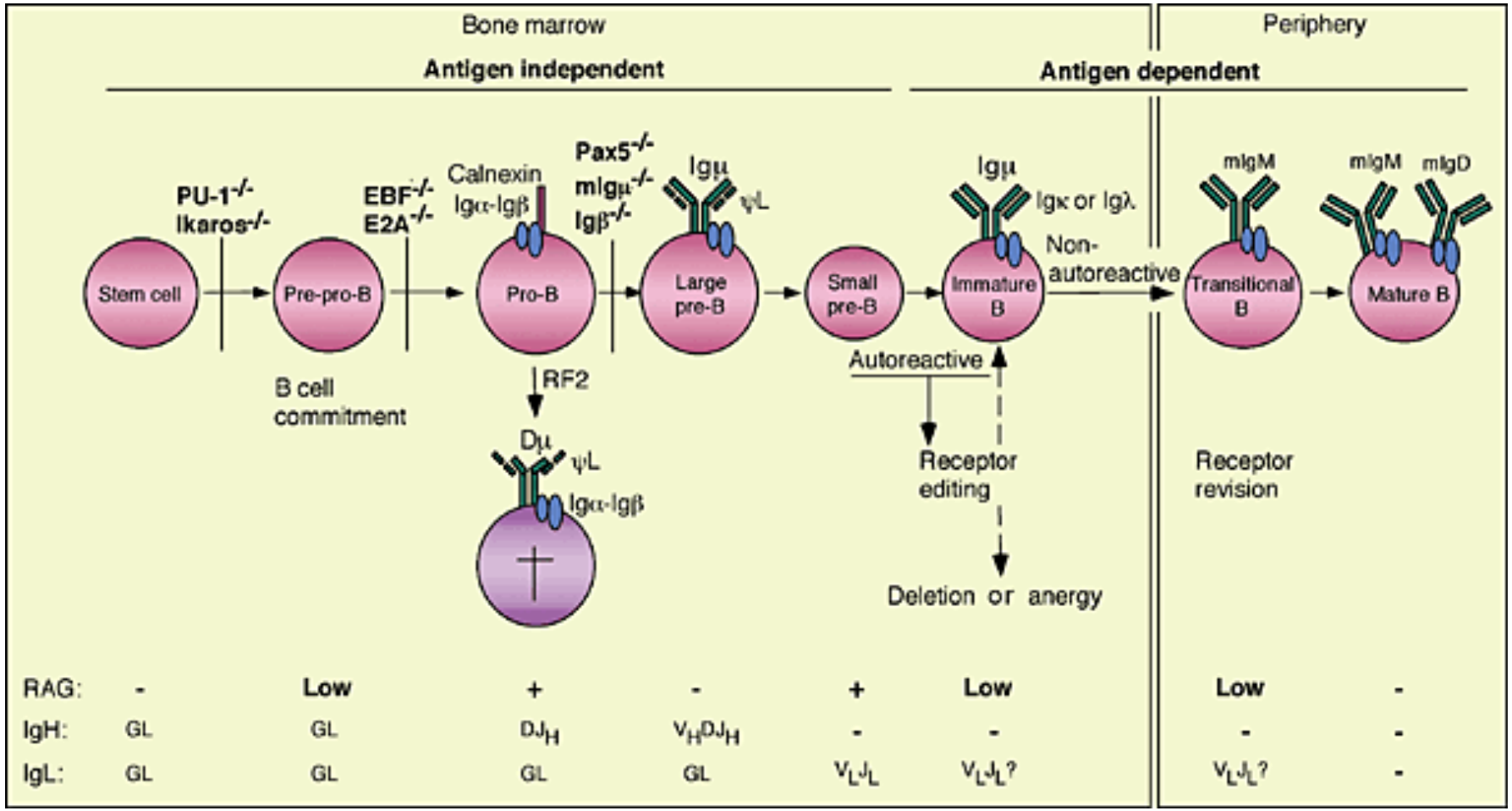


Class Switching: A second recombination



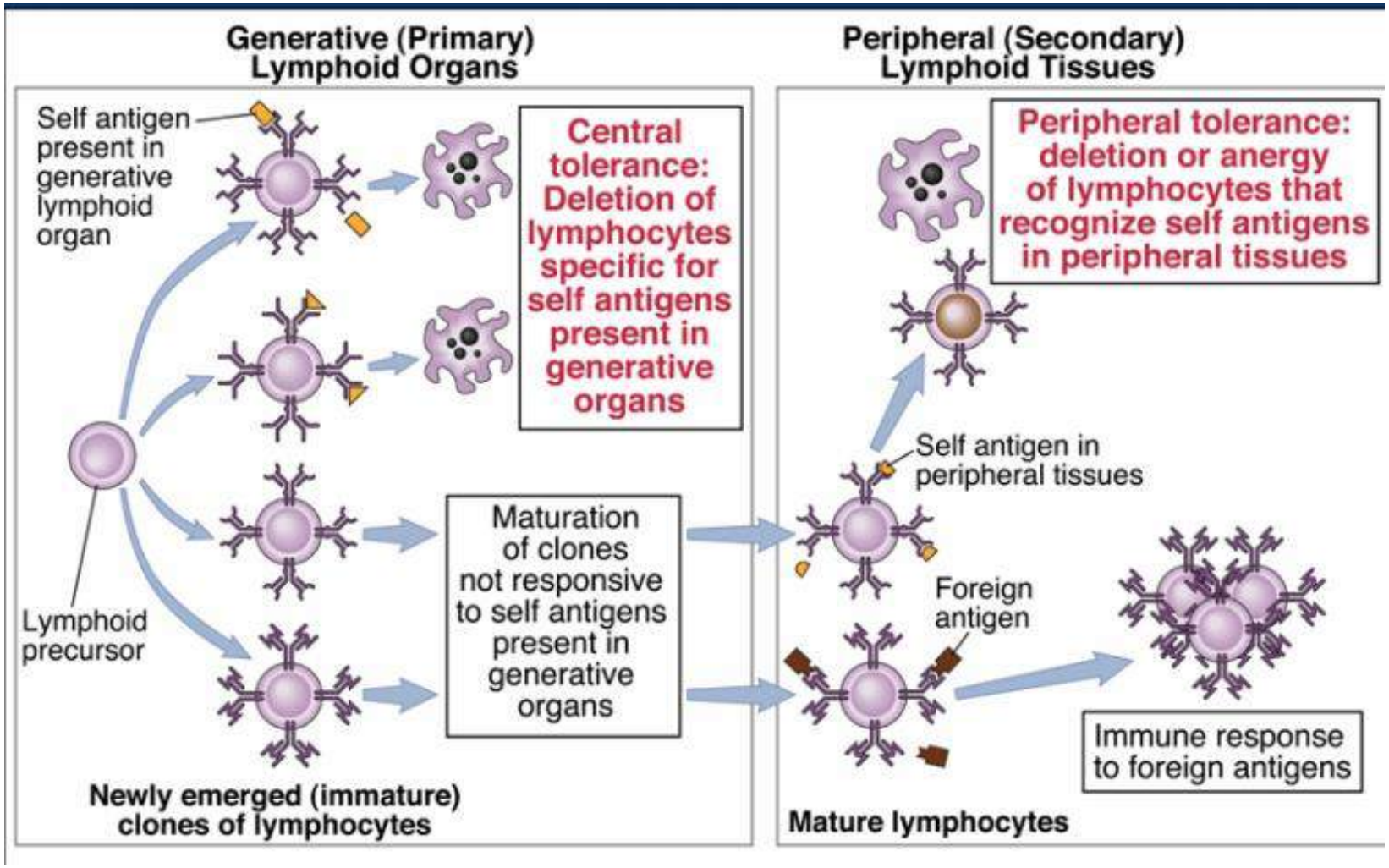
Current Opinion in Immunology
Volume 18, Issue 3, June 2006, Pages 249-254

Maturation and selection

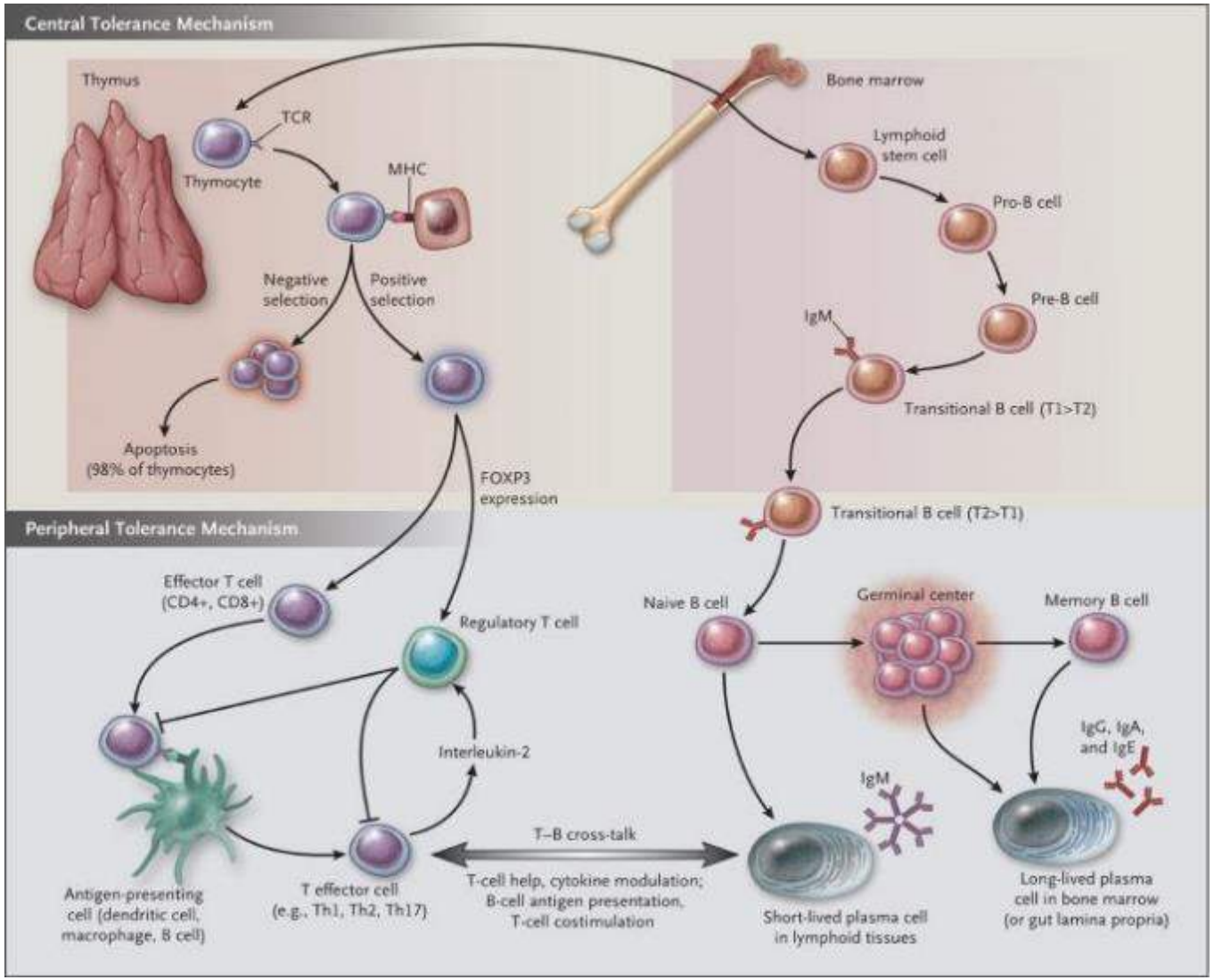


Nature Immunology **volume 1**, pages379–385(2000)

Self-tolerance is key!



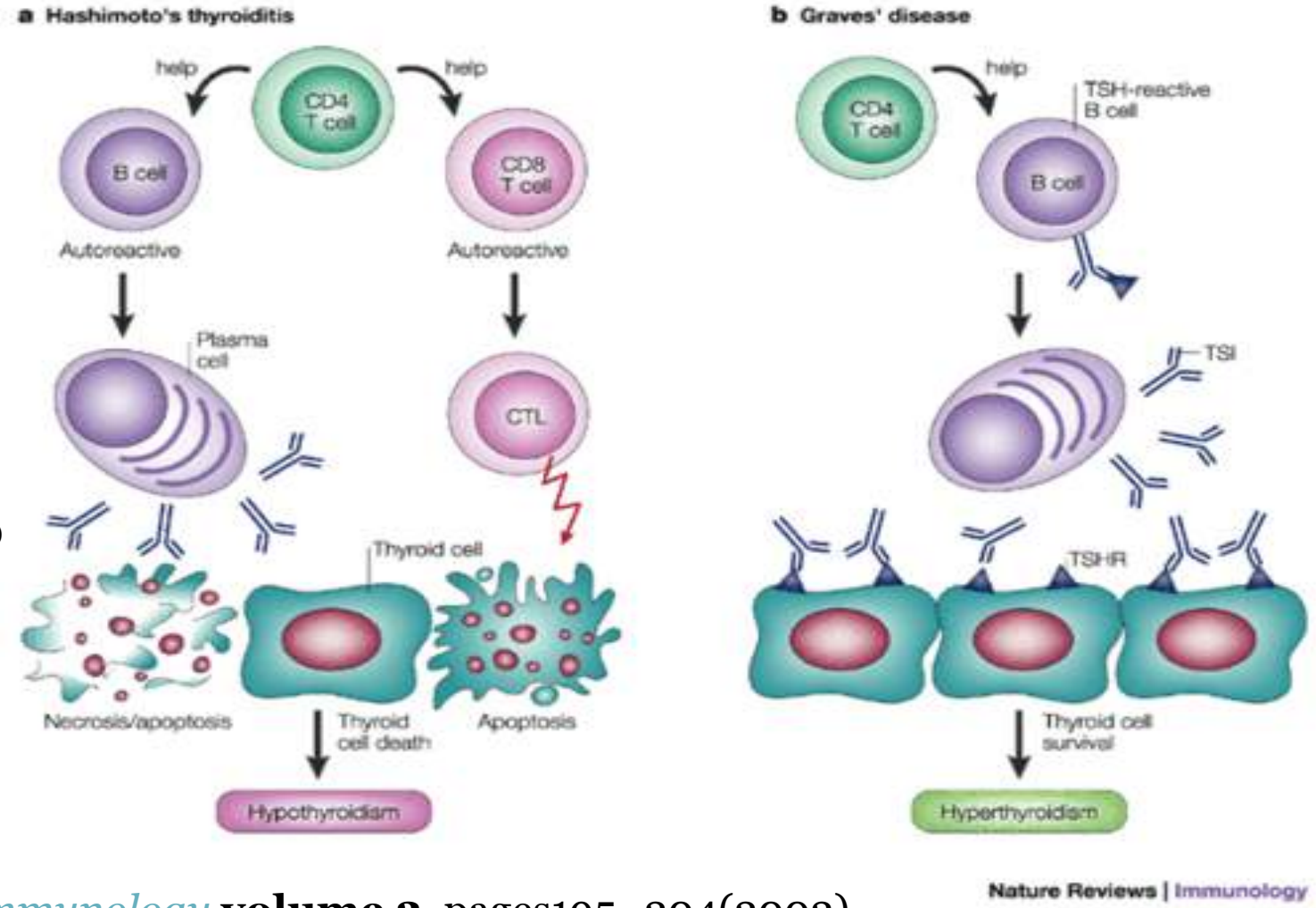
Central and Peripheral Tolerance Mechanisms in the Adaptive Immune System.



Cho JH, Gregersen PK. N Engl J Med 2011;365:1612-1623.

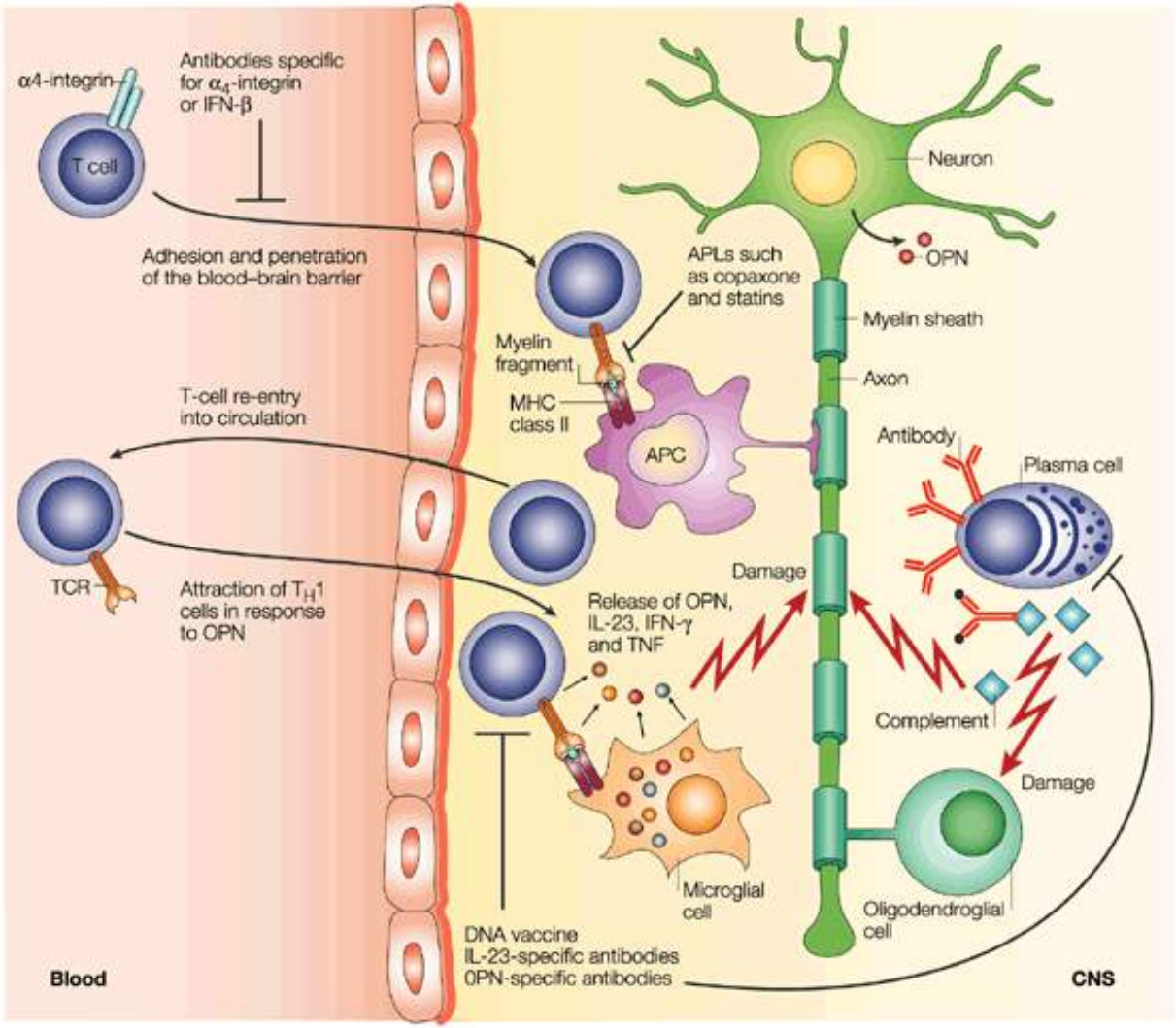
Thyroid autoantibodies

Anti-TPO



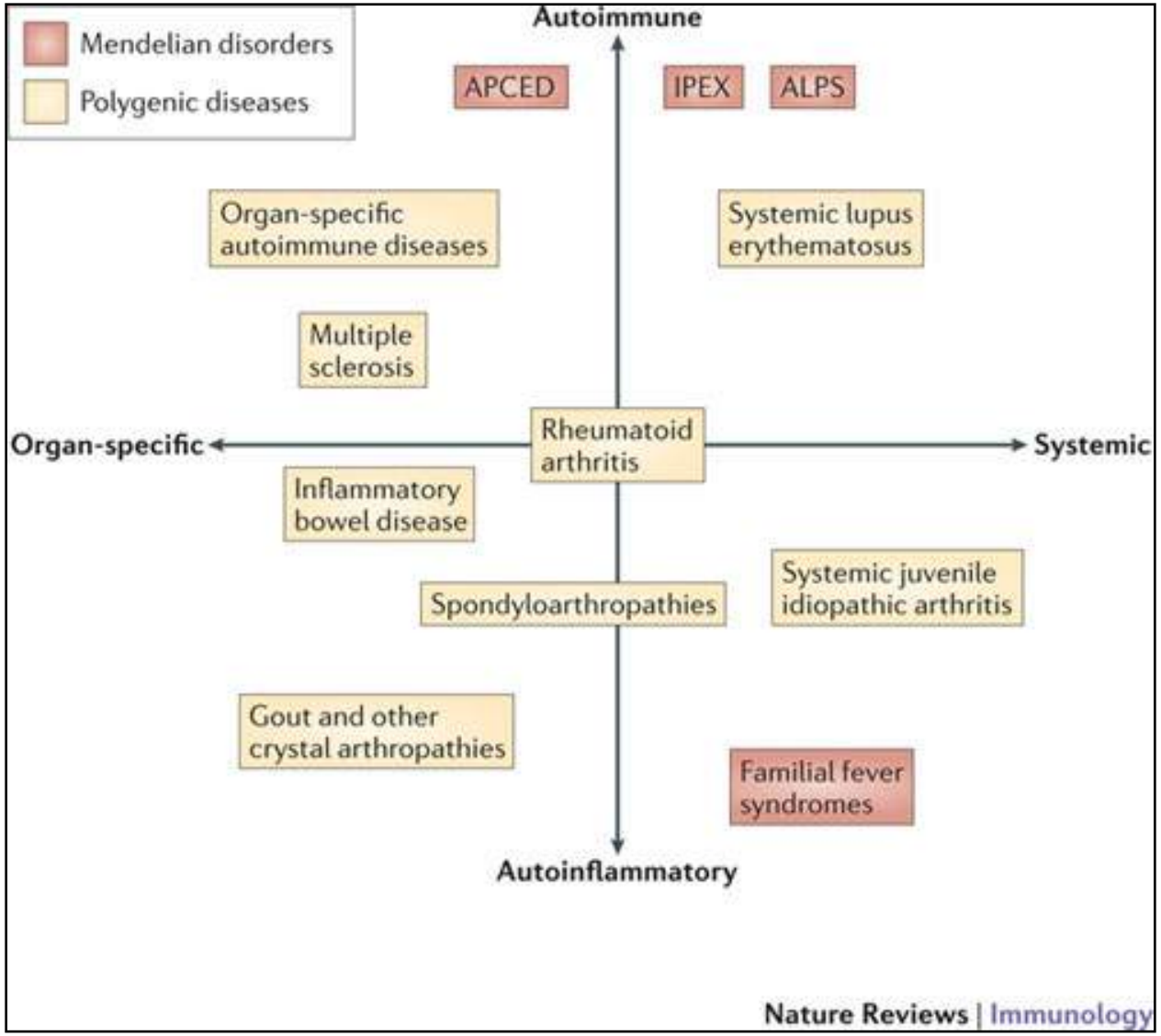
Nature Reviews Immunology **volume 2**, pages195–204(2002)

T-cells and Ig in MS

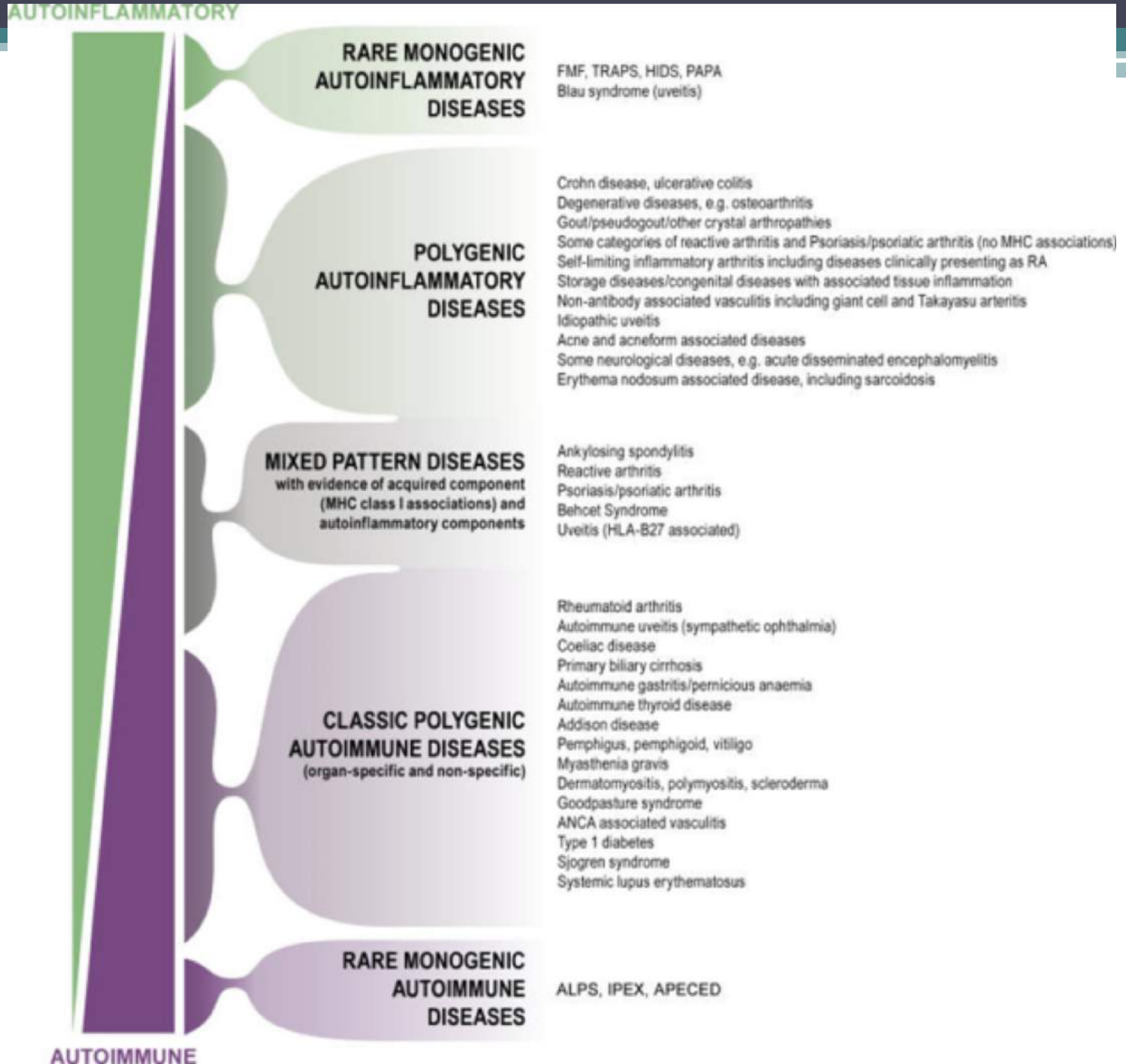


Nature Reviews Immunology **volume 3**, pages483–492(2003) Nature Reviews | Immunology

Autoimmunity vs. Autoinflammatory

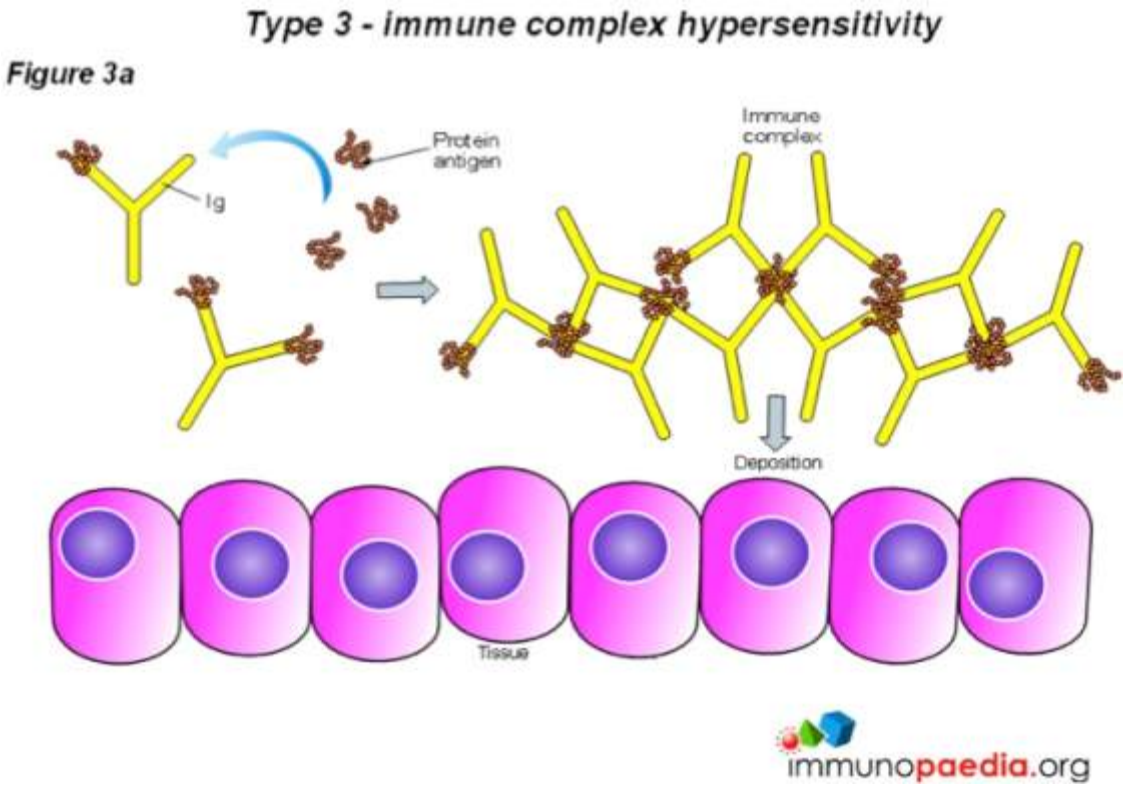


Nature Reviews Immunology
12, 570-580 (August 2012)



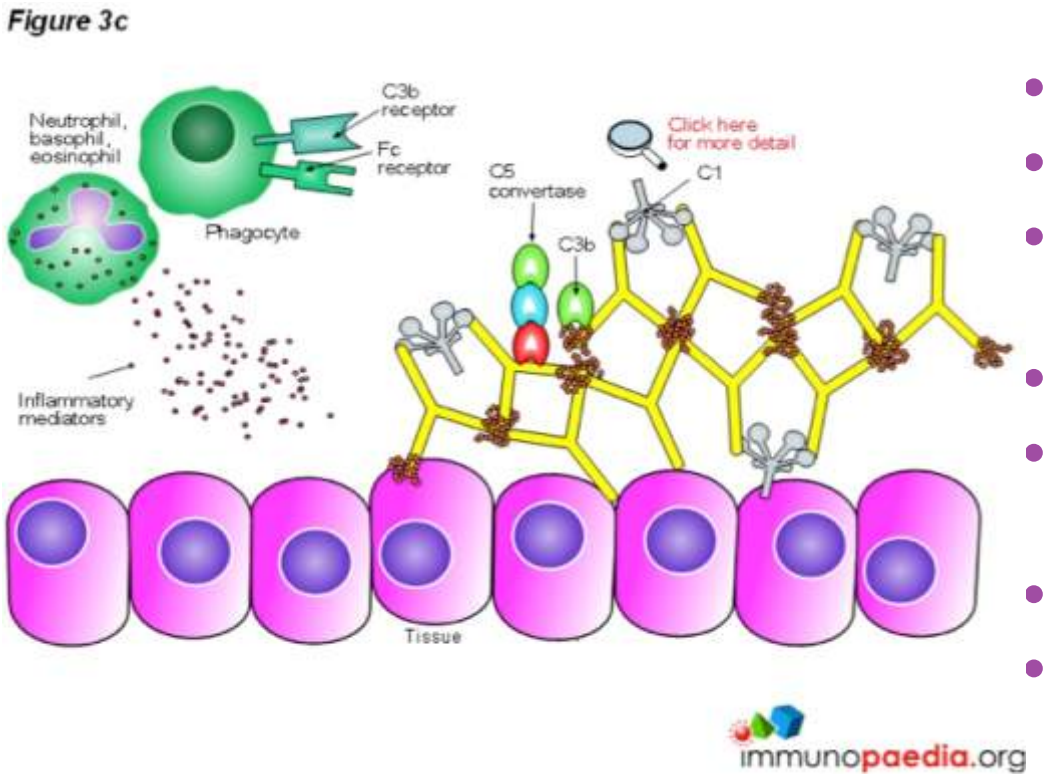
PLoS Med. 2006 August; 3(8): e297.

The “Immune-Complex”



- Insoluble immune complexes (aggregations of antigens and IgG and IgM antibodies) form in the blood and are deposited in various tissues (typically the skin, kidney and joints)

Immune complexes fix complement-drive inflammation



- Immune complex glomerulonephritis
- Rheumatoid arthritis
- Serum sickness
- Subacute bacterial endocarditis
- Symptoms of malaria
- Systemic lupus erythematosus
- Arthus reaction
- Farmer's Lung (Arthus-type reaction)

Education through sampling non-self
Friend or Foe?

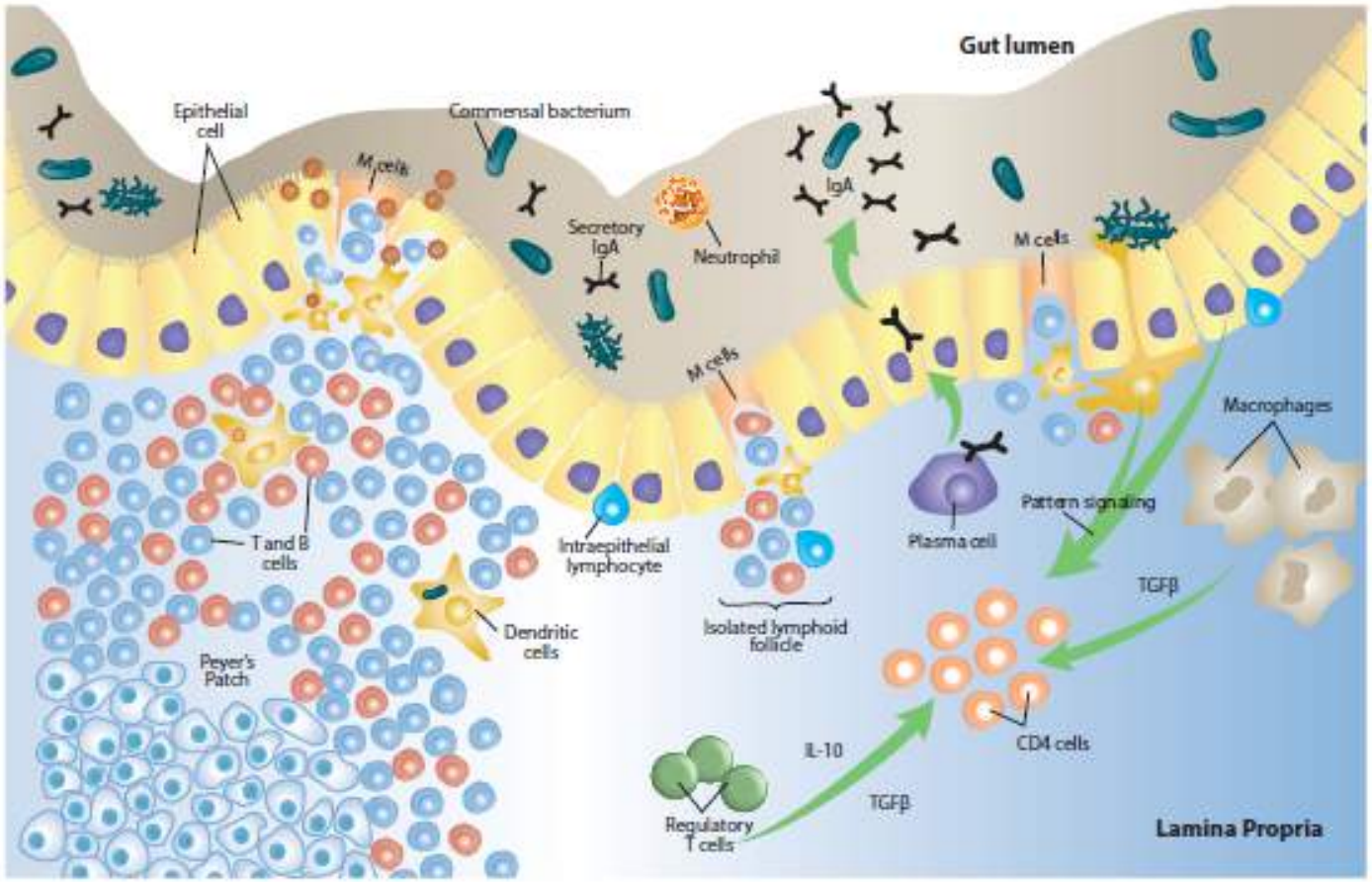
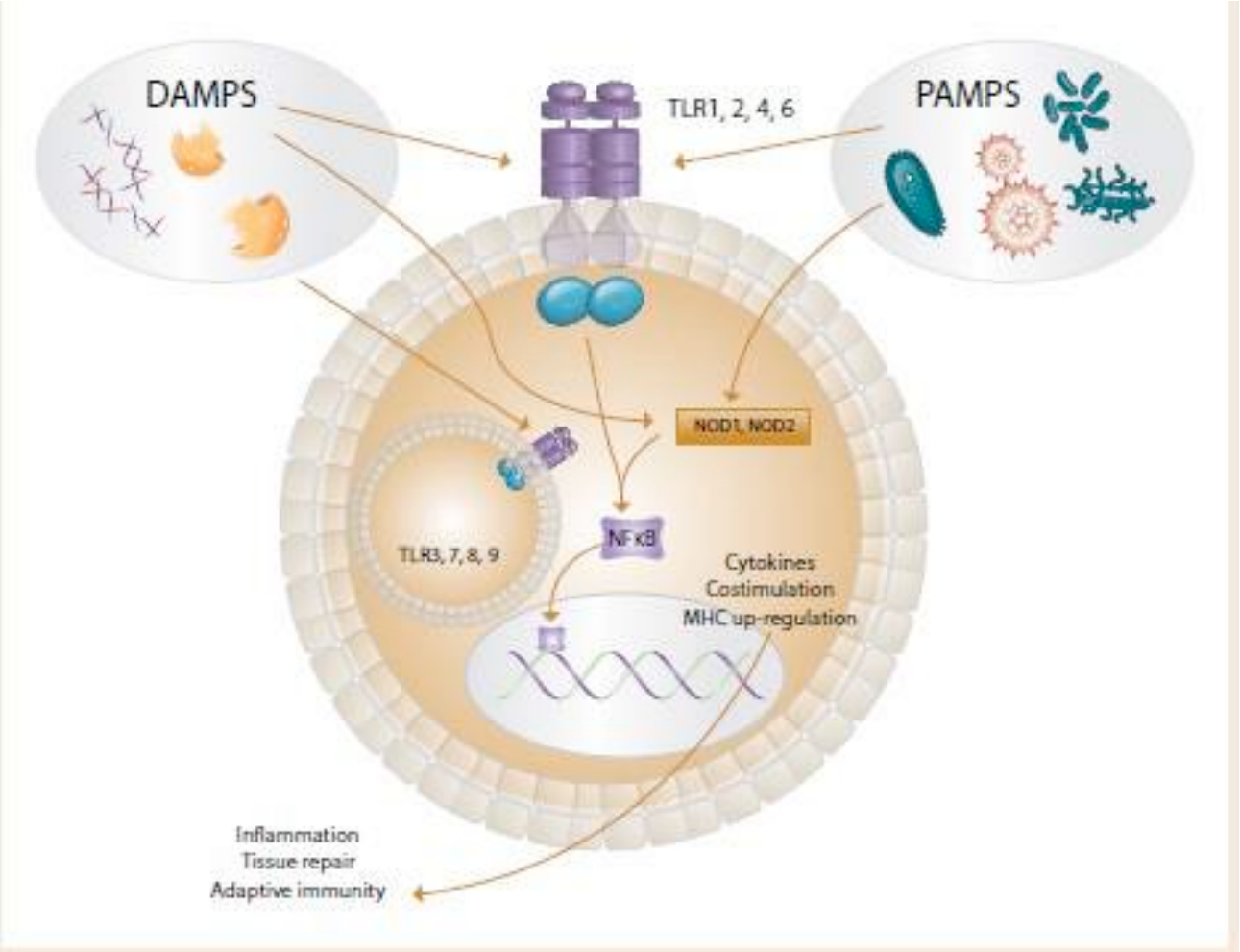


Figure 11: Basic Structures of the Gastrointestinal-Associated Lymphoid Tissue (GALT). See the text for detailed explanation.

Pattern Recognition Receptors



Guilliams: Supporting Immune Function: A Lifestyle and Nutrient Approach (2014)

Toll-like receptor family (TLRs)

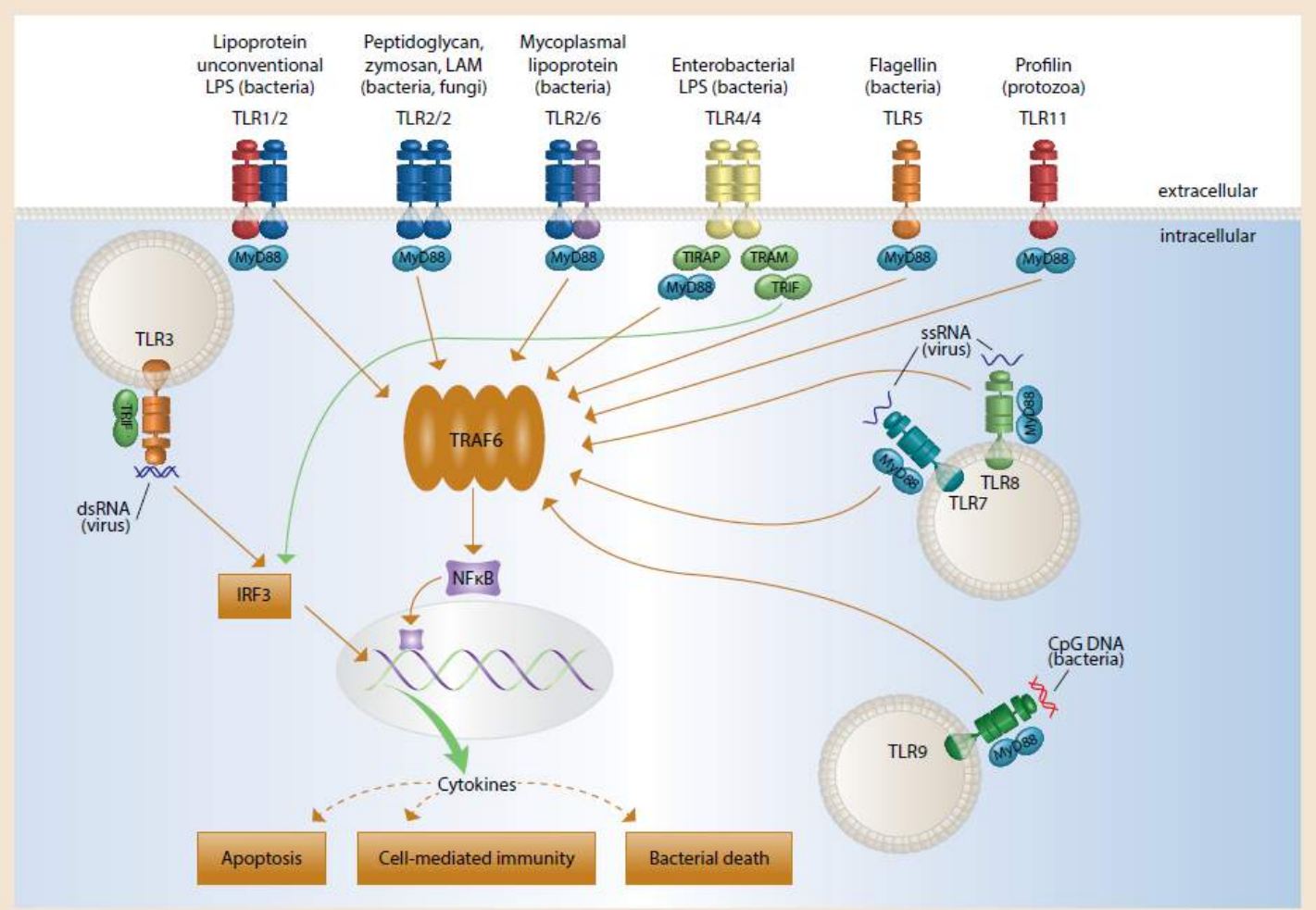
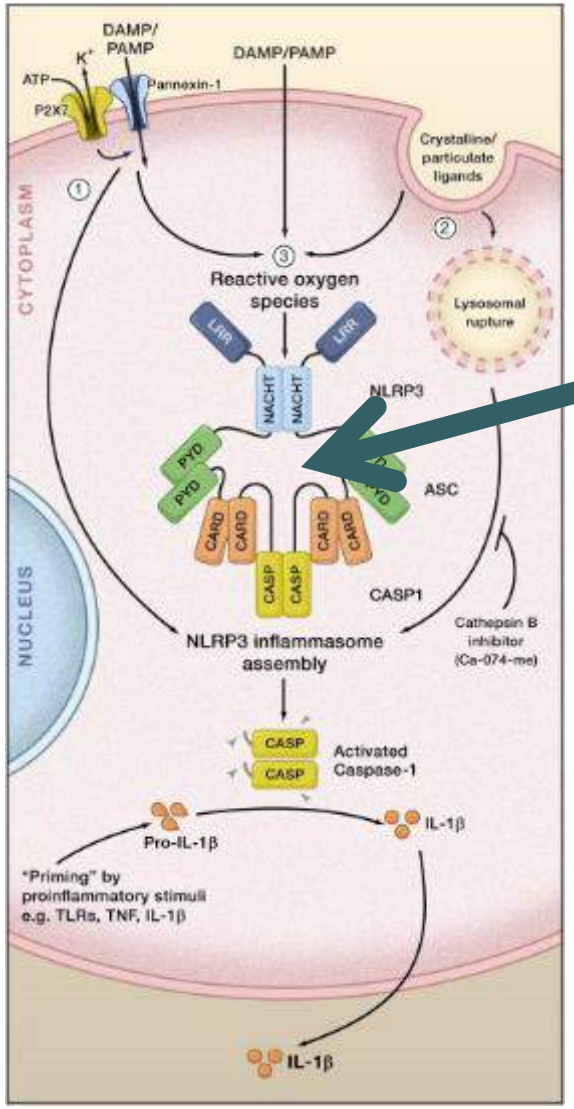
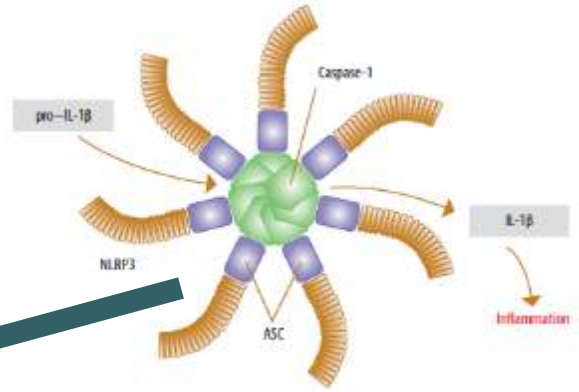


Figure: Toll-like receptor (TLR) signaling. This diagram shows the different types of TLRs, their locations and the patterns they recognize. See text for more details about the signaling pathways. Image adapted from Minireview: Toll-like Receptors (TLR)-www.abdserotec.com.

Inflammasome (NLRP3-type)

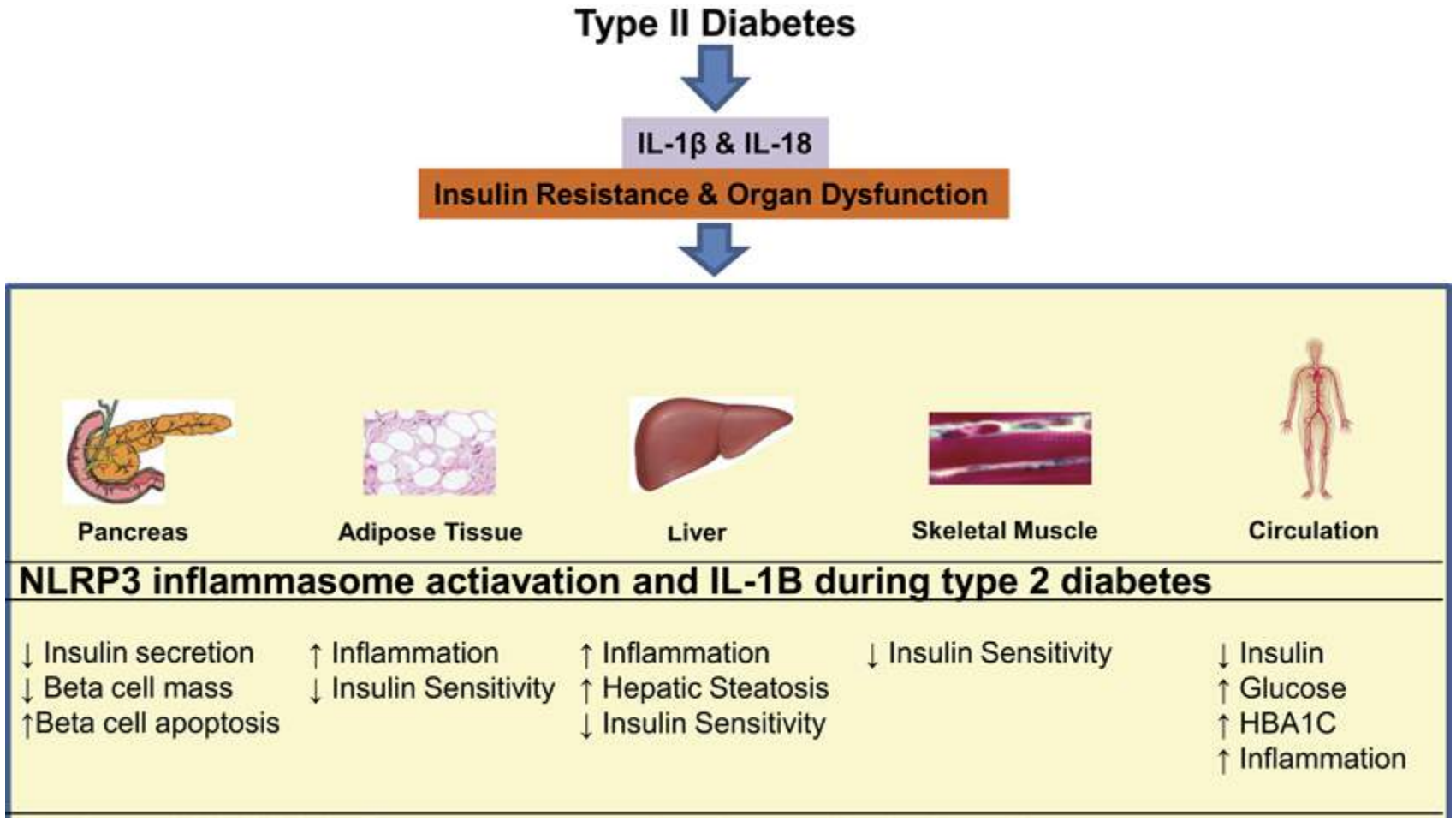




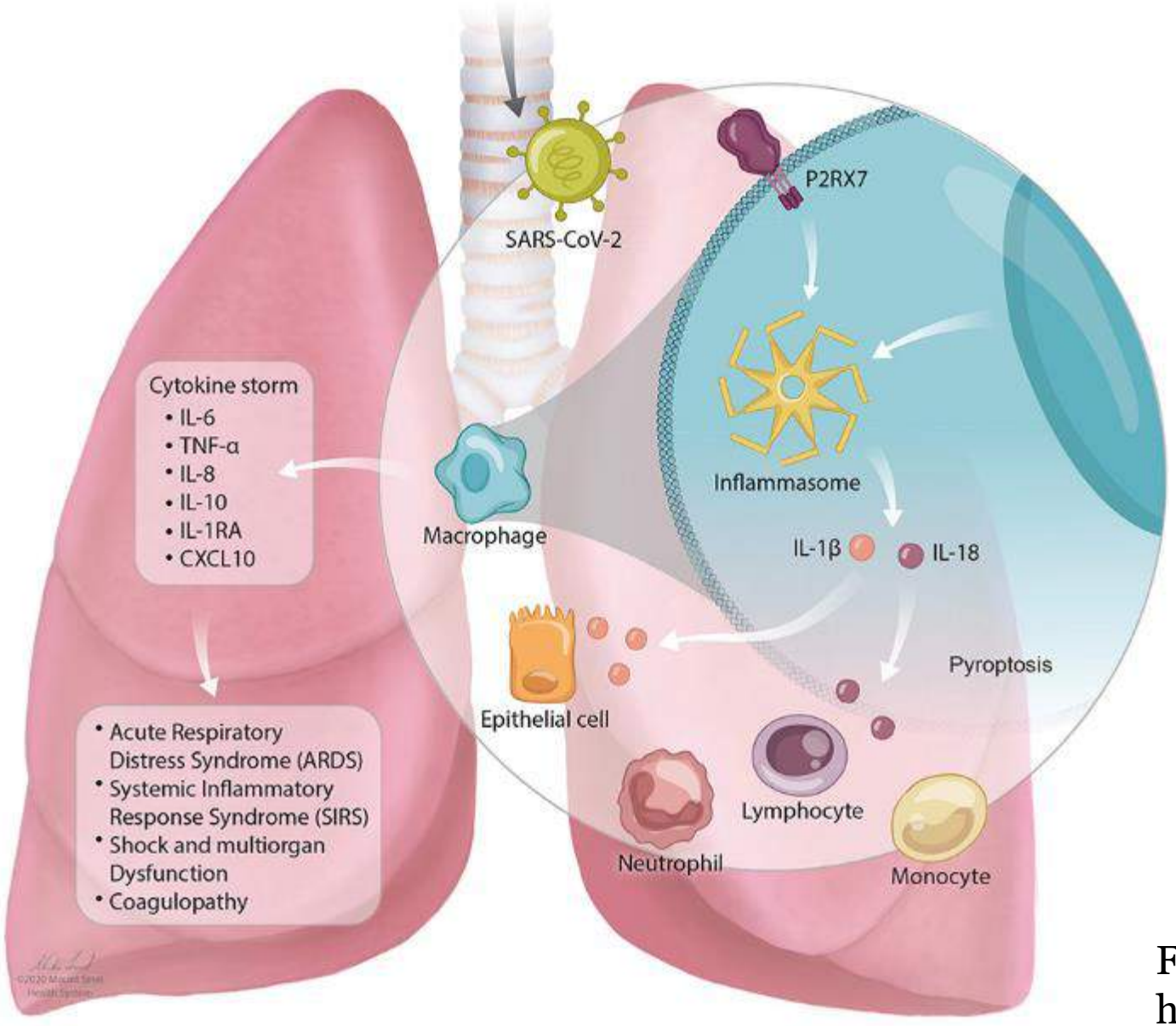
- Heptamer complex between caspase and NRLP3
- Caspase activates the release of IL-1b, furthering inflammatory cascade
- 3 potential triggers

Cell: Volume 140, Issue 6, 19 March 2010, Pages 821–832

Inflammasome and chronic disease



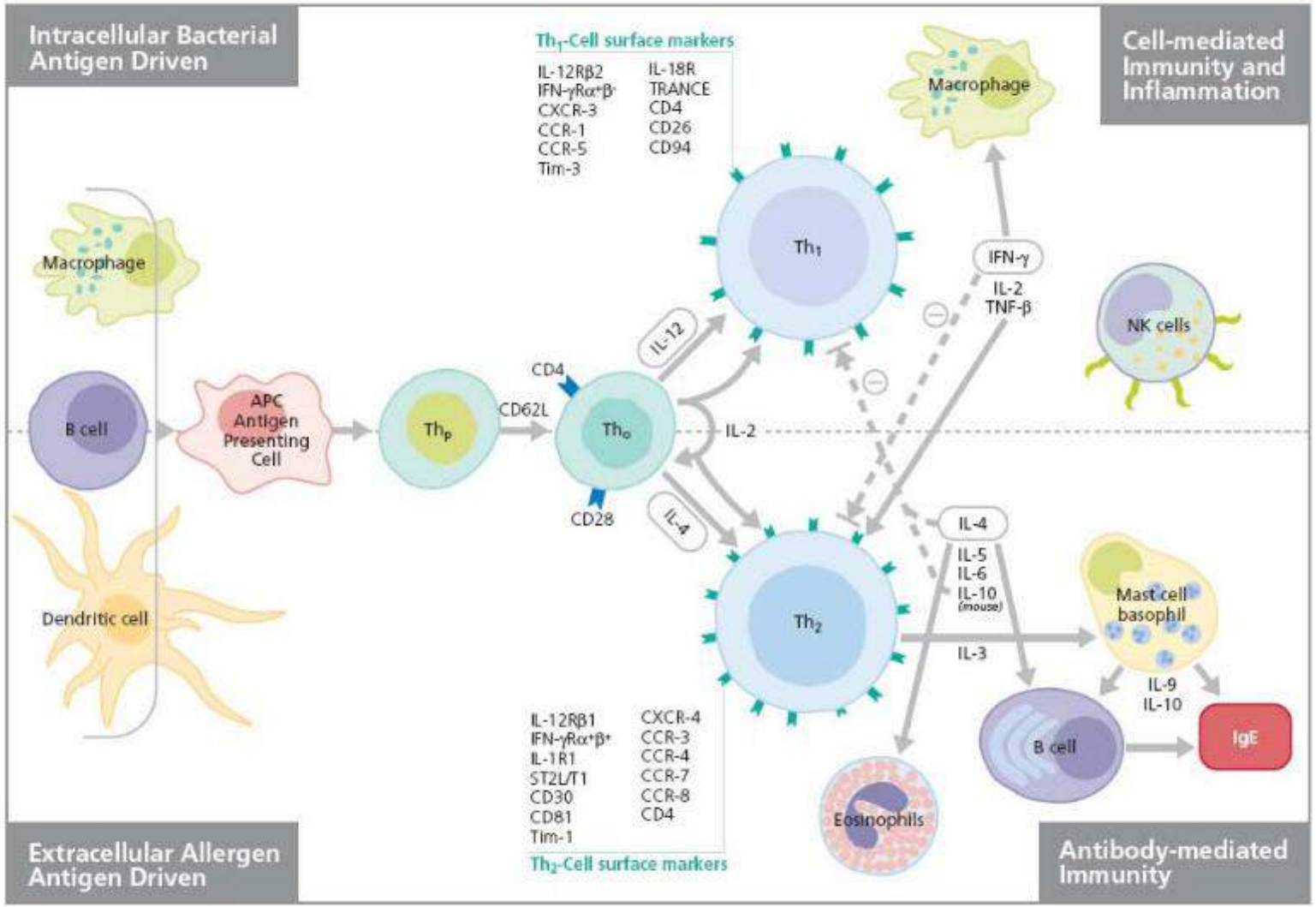
Front. Immunol., 08 March 2013



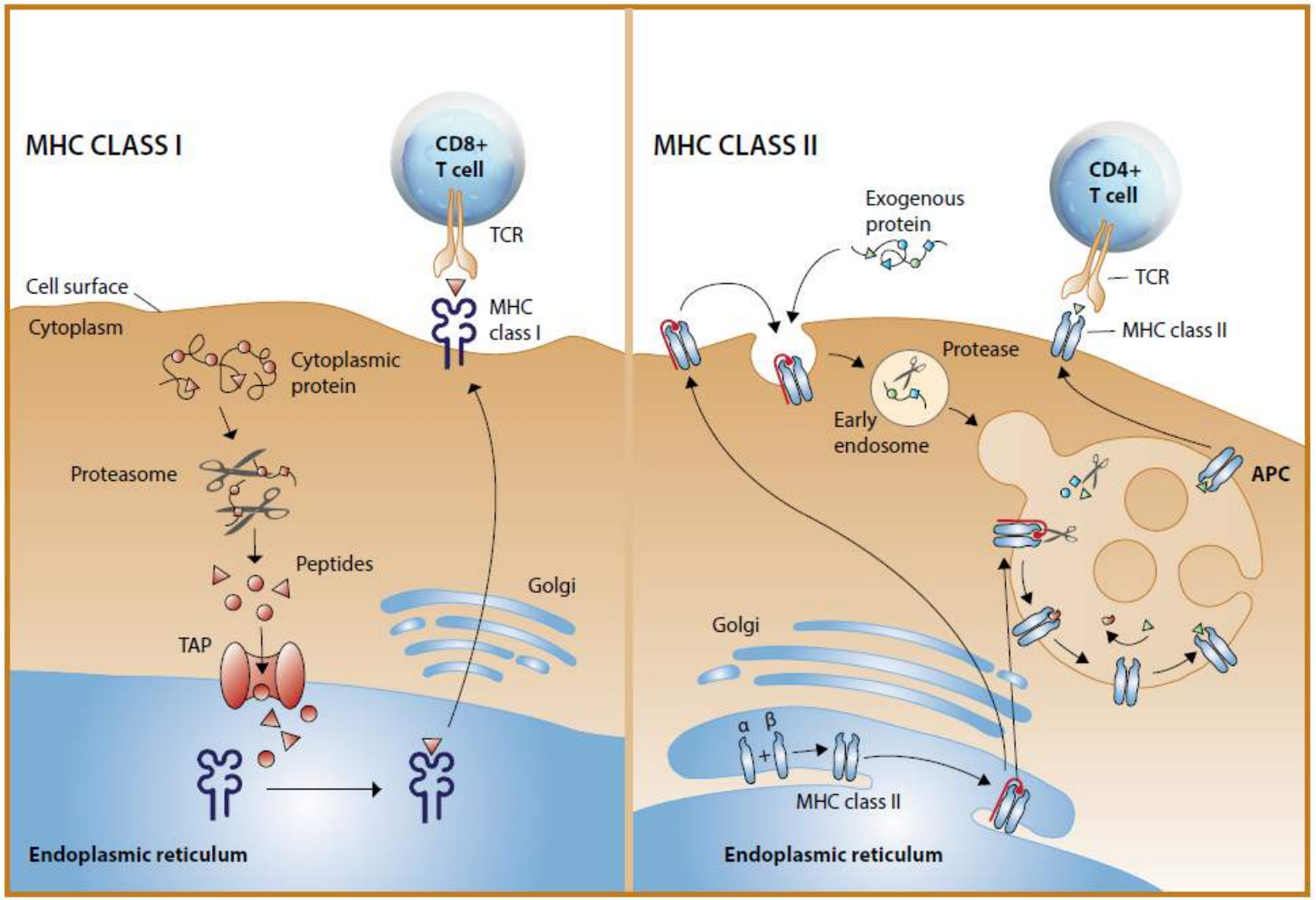
The NLRP3 inflammasome appears to mediate lung inflammation in SARS-CoV-2 infection.

Front. Immunol., 23 June 2020 | https://doi.org/10.3389/fimmu.2020.01518

Training the Adaptive Immune Cells

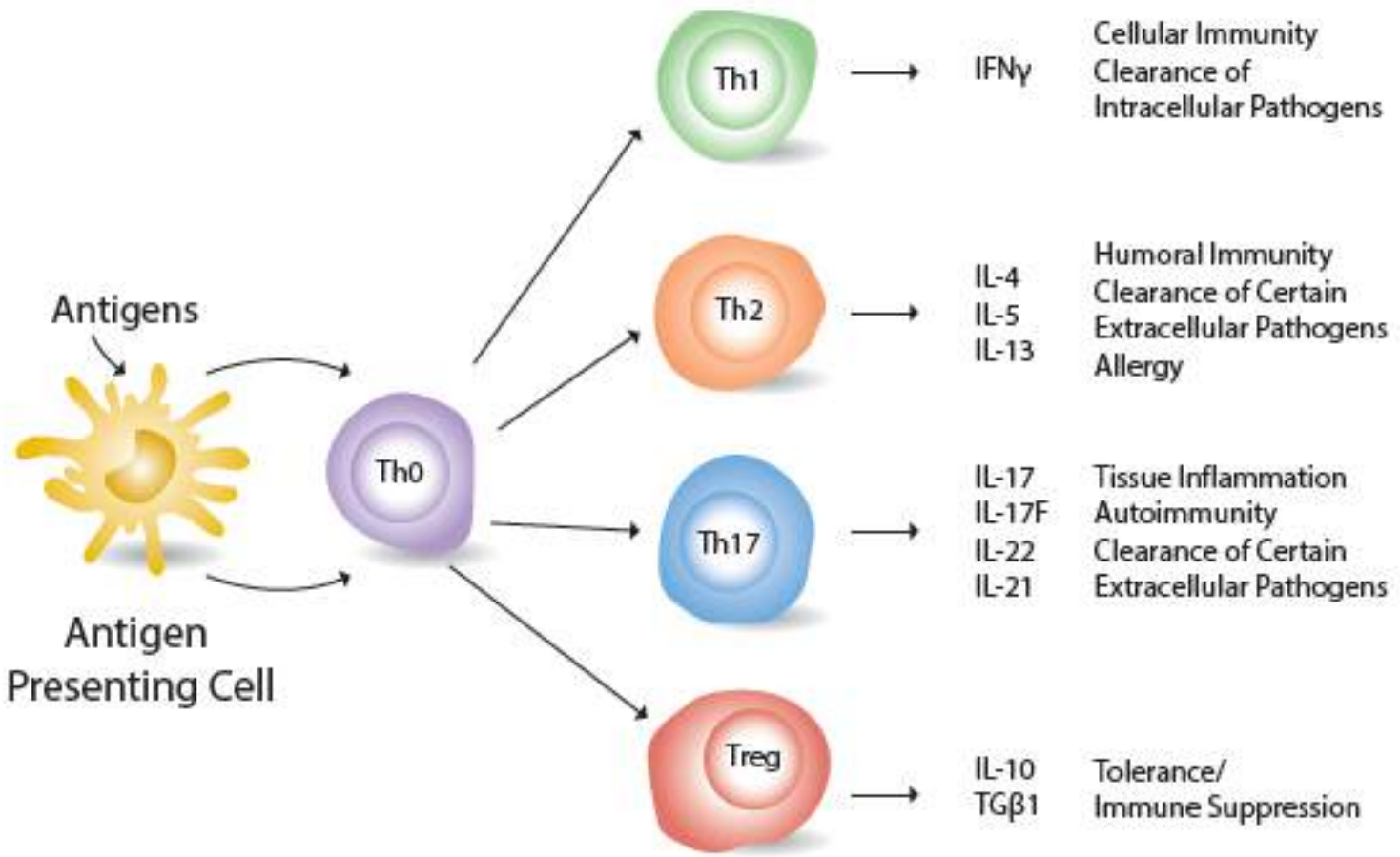


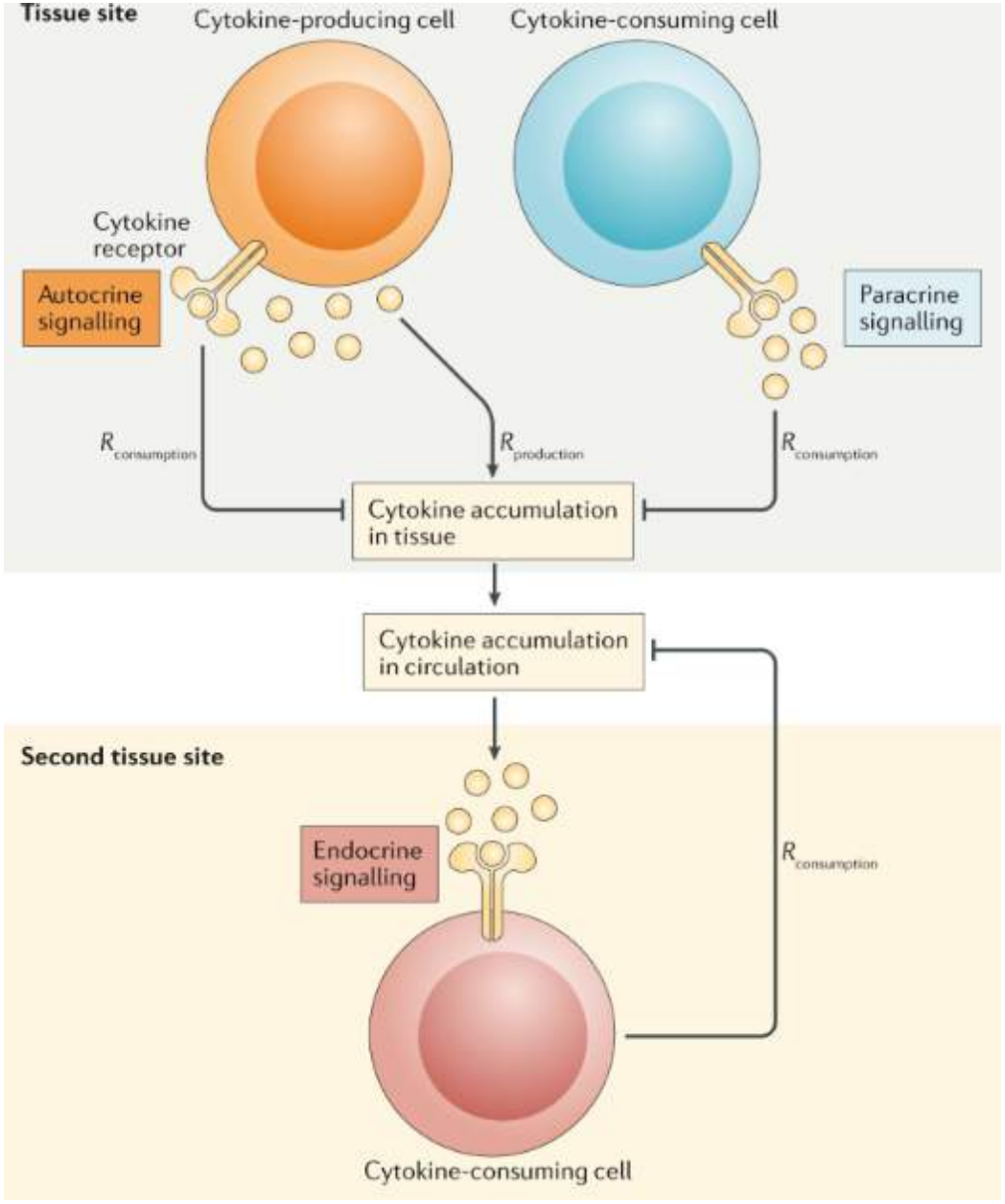
HLA: Major Histocompatibility Complexes



Guilliams: Supporting Immune Function: A Lifestyle and Nutrient Approach (2014)

But there is more….



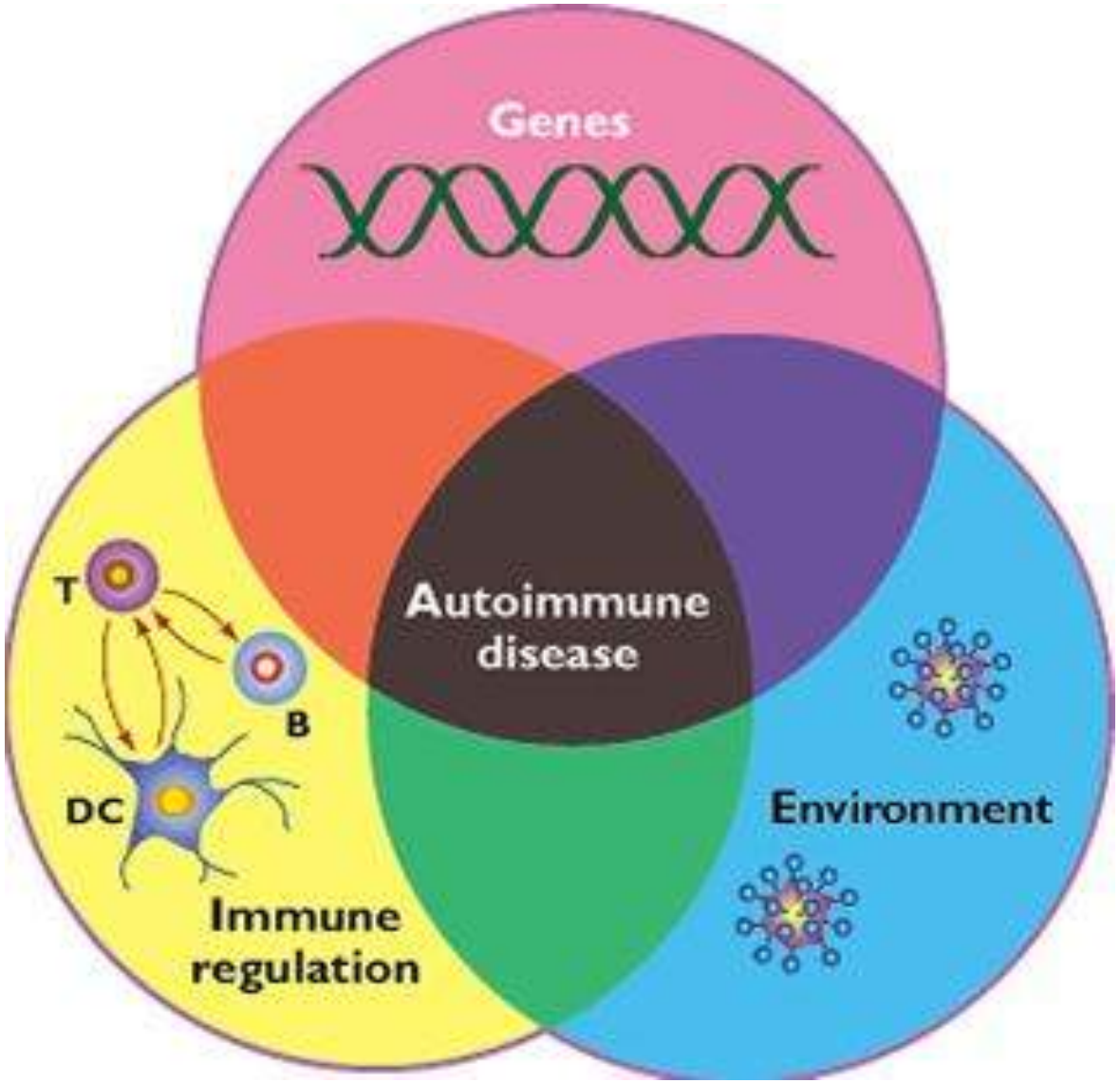


Cytokines are the messengers of the immune system

- Autocrine
- Paracrine
- Endocrine

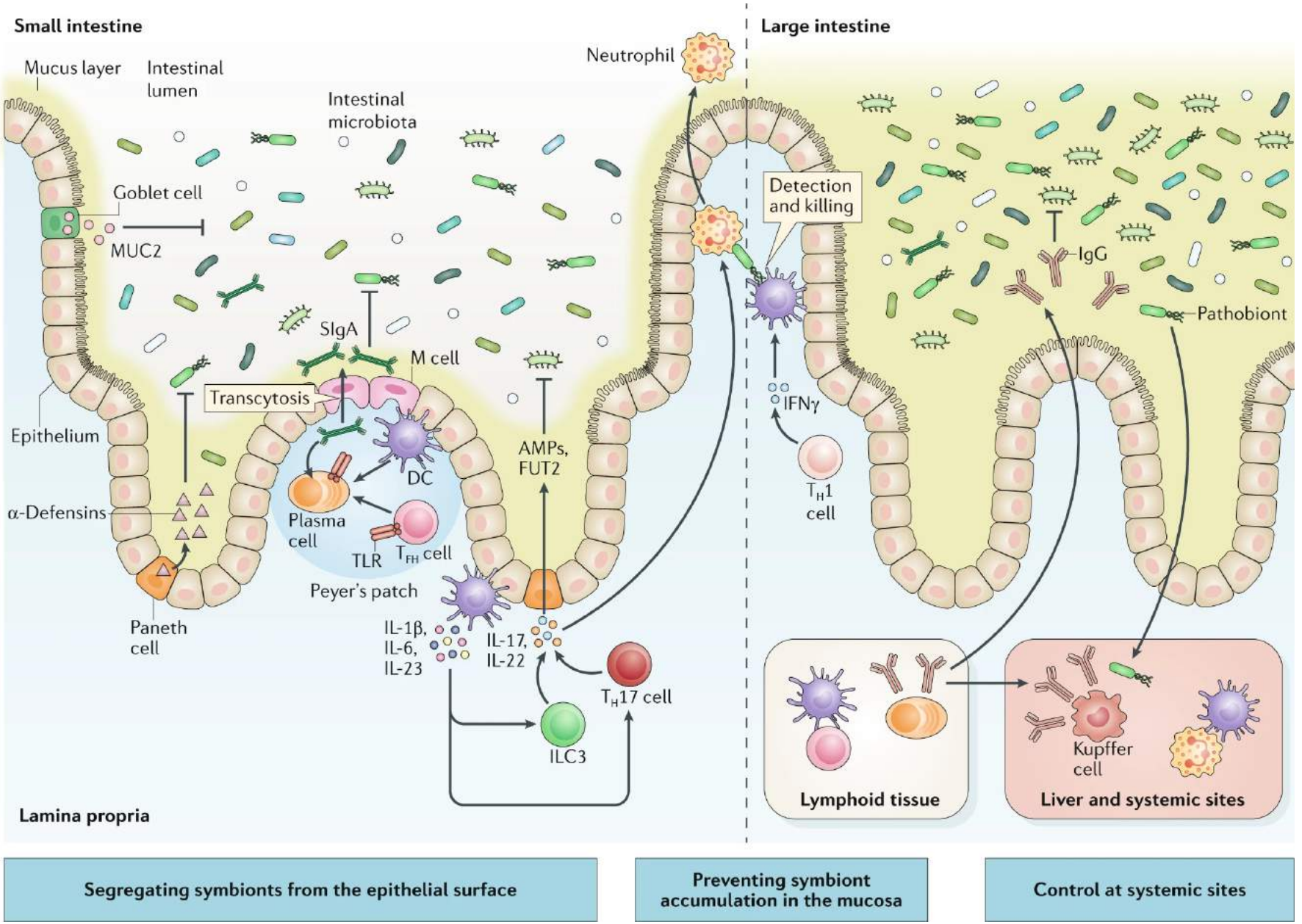
Nature Reviews Immunology **volume 19**, pages205–217(2019)

What can you control?

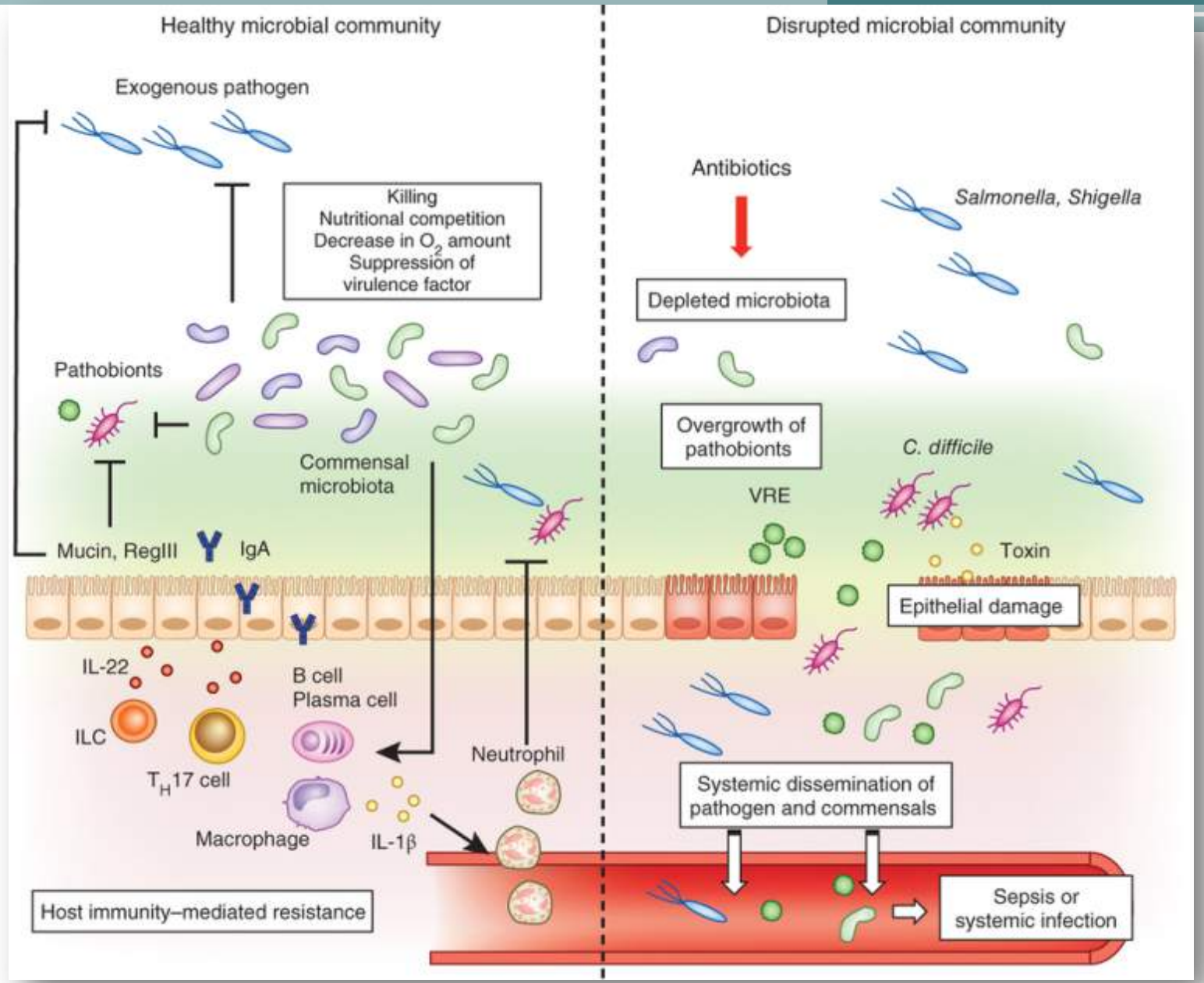


Keys to Supporting Immune Function

- Maintaining and protecting barrier functions
- Creating a commensal-friendly environment
- Maintaining appropriate hygiene practices
- Avoiding antigens and allergens in adulthood
- Building micronutrient and antioxidant reserve
- Maintaining and building cellular (mitochondrial) energy
- Maintaining adequate detoxification capacity
- Diminishing stress and cortisol-induced immune suppression
- Reducing chronic inflammatory triggers/mediators
- Using appropriate immune modulators to create balance and strengthen immune function



Nature Reviews Immunology
volume 20, pag es411–426(2020)



Nature Immunology 14, 685–690 (2013

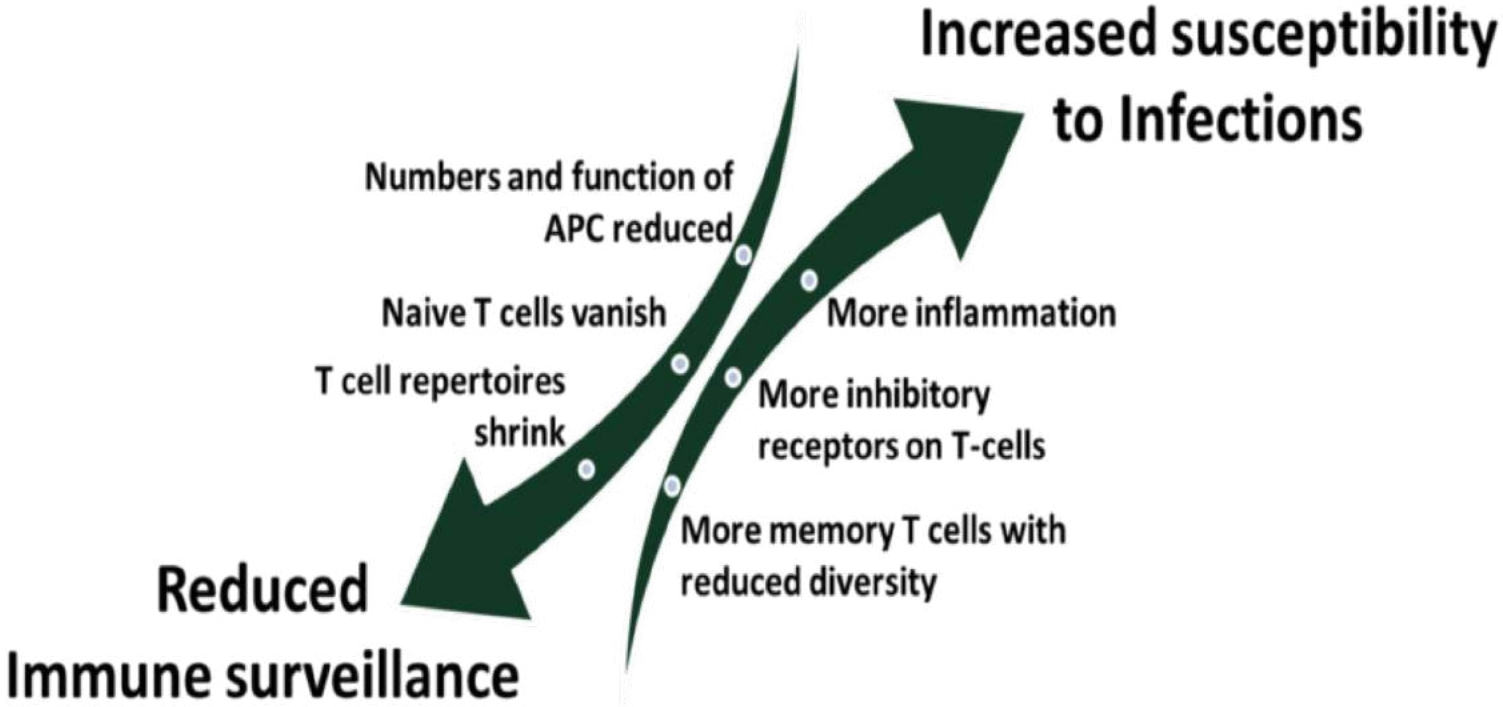
Immunosenescense

The loss of immune “reserve”

- Changes in immune function with age
- Influenced by years of immune training and stress
- Depletion of naïve cells in the Adaptive immune system
- NK-cells- more numerous but less active
- Decreased numbers of neutrophils/monocytes
- Changes in Gut microflora influence immune function
- “Inflammaging”- drive chronic diseases
- Increased frequency of auto-immune reactions
- Accumulations of HPA Axis Stress

Immuno-senescence

Altered Immune Function that are influenced by the “Aging Process”



Immunosenescence

- Reduced Ability to Mount an Immune Response (Depleted Immune Reserve)
  - Fewer numbers of most effector cells (neutrophils etc.)
  - Lower metabolic activity (killing capacity of most effector cells (NK cells)
- Reduced Surveillance Capacity and Discretion (Stranger vs Self)
  - Reduced Numbers of Naïve Lymphocytes to form a Adaptive Response to New Antigens
  - Poorer Control of Self-Tolerance System- Allowing more cross-reactivity, auto-immunity.

Immune System Changes with Time

- Influenced by years of immune training and stress
- Depletion of naïve cells in the Adaptive immune system
- NK-cells- more numerous but less active
- Decreased numbers of neutrophils/monocytes
- Changes in Gut microflora influence immune function
- “Inflammaging”- drive chronic diseases
- Increased frequency of auto-immune reactions
- Accumulations of HPA Axis Stress

ANTIOXIDANTS & REDOX SIGNALING
Volume 14, Number 8, 2011
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DOI: 10.1089/ars.2010.3228

COMPREHENSIVE INVITED REVIEW

Aging and Immune Function: Molecular Mechanisms to Interventions

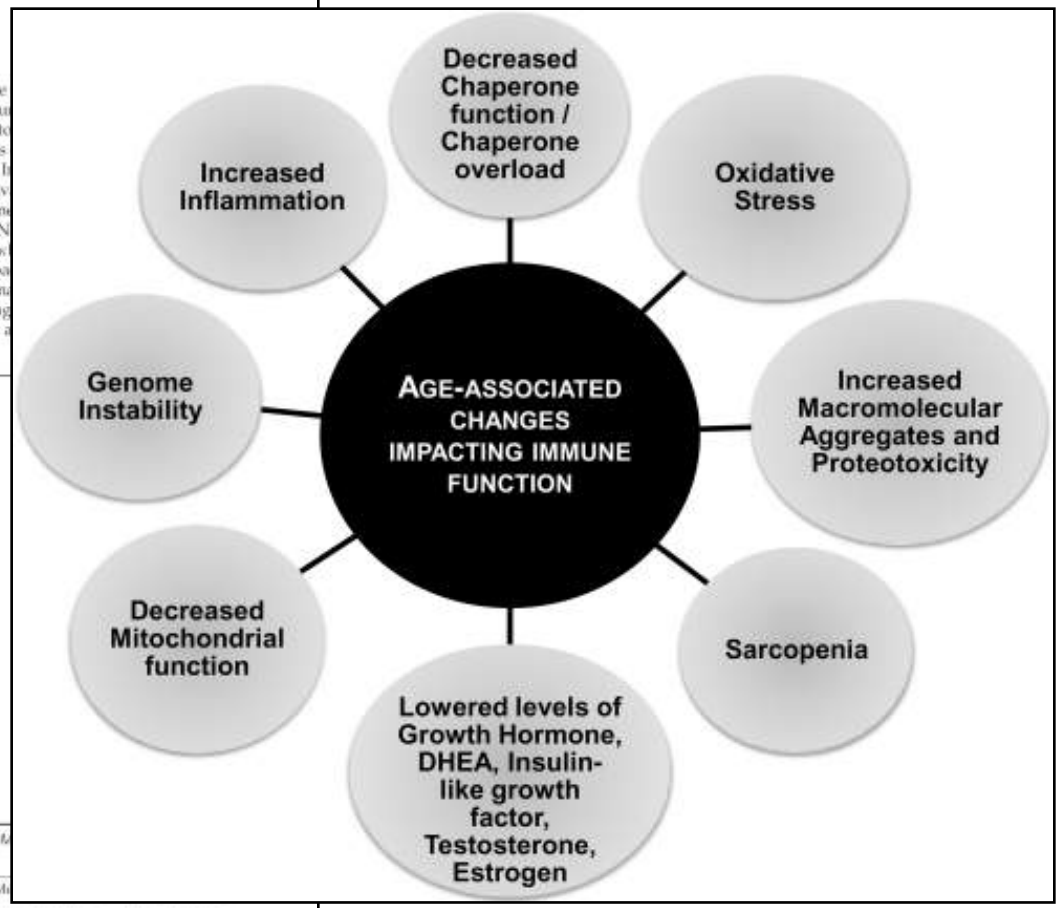
Subramaniam Ponnappan[1] and Usha Ponnappan[1,2]

Abstract

The immune system of an organism is an essential component of the defense
pathogenic stress. Age-associated immune dysfunction, also dubbed "immu
creased susceptibility to infections, increased onset and progression of auto
neoplasia. Over the years, extensive research has generated consensus in terms
defects within the immune system in various organisms, including humans. I
such as thymic involution, T cell repertoire skewing, decreased ability to activ
robust memory responses, have been shown to have a causative role in immun
the molecular mechanisms underlying the generation of proteotoxic stress, DN
of ubiquitin proteasome pathway, and regulation of transcription factor NFκ
have paved the way to delineating signaling pathways that cross-talk and impa
role of the immune system in combating infections, its effectiveness with age m
a predictor of longevity. It is therefore believed that a better understanding
immune senescence will lead to an effective interventional strategy aimed
individuals. *Antioxid. Redox Signal.* 14, 1551–1585.

Reviewing Editors: *Rommy von Bernhardi, Manuel Collado, Monica de la Fuente, M
Loebenstein, Anonymous, and Michael Toledano*

Departments of [1]Geriatrics and [2]Microbiology and Immunology, University of Arkansas for Ma



Antioxidants & Redox Signaling, 14(8):1151 (2011)

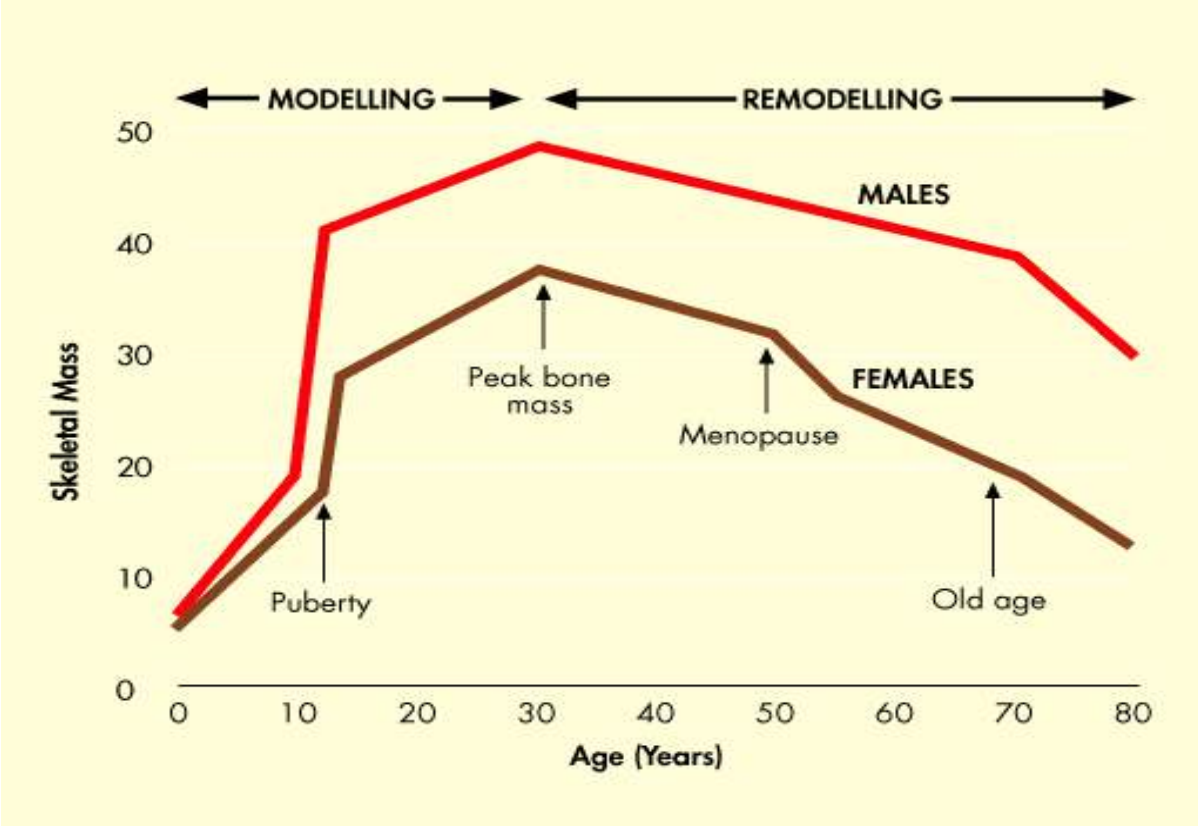
Immunosenescence

Depleted Immune Reserve Capacity

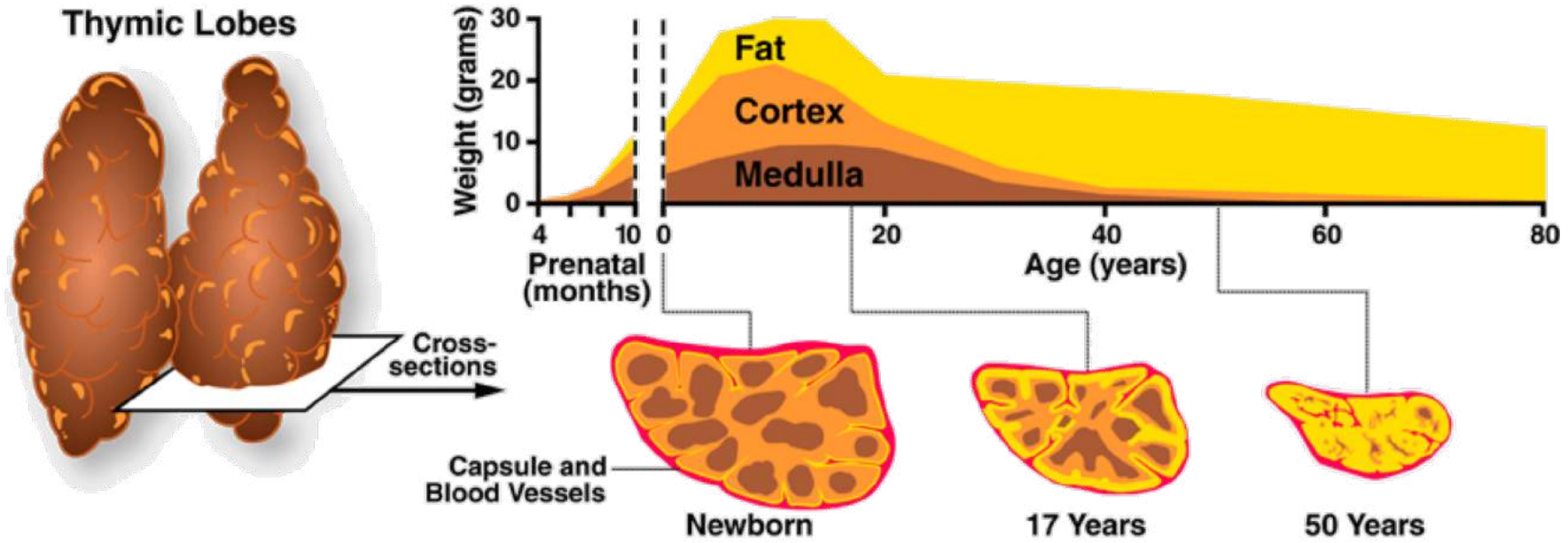
- A loss of immune system function that occurs coincident with the aging process; both advancing chronological time AND metabolic signals that can accelerate the aging process (ROS, stress, etc.)
- Diminishing Immune Metabolic Reserve at
  - The Effector Level (cells doing immediate work)
  - Cellular Reserve Level (bone marrow, thymus)
  - At the Organ Level (thymus, lymph nodes etc.)
  - At the Interface Level (GALT and related tissues)

Metabolic Reserve

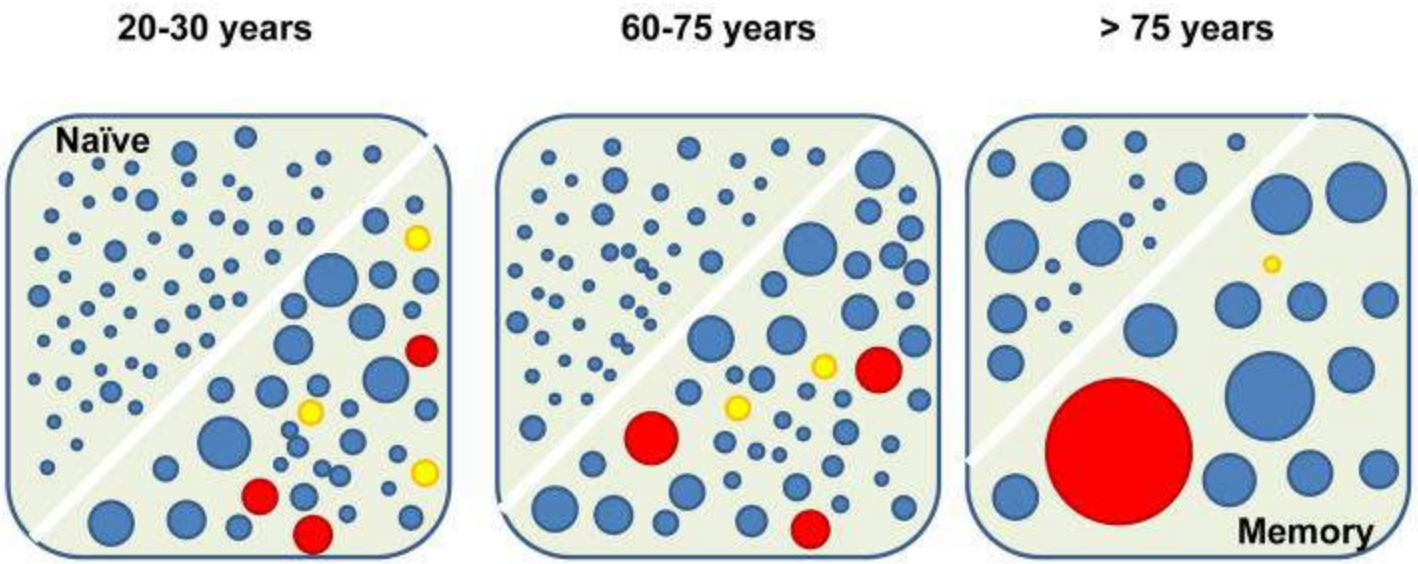
- The long-term (reserve) capacity to rebuild our resilience when it is challenged.



Depletion of Thymic reserve and Function over time



Larger numbers of fewer memory clones- fighting (some)old battles well.

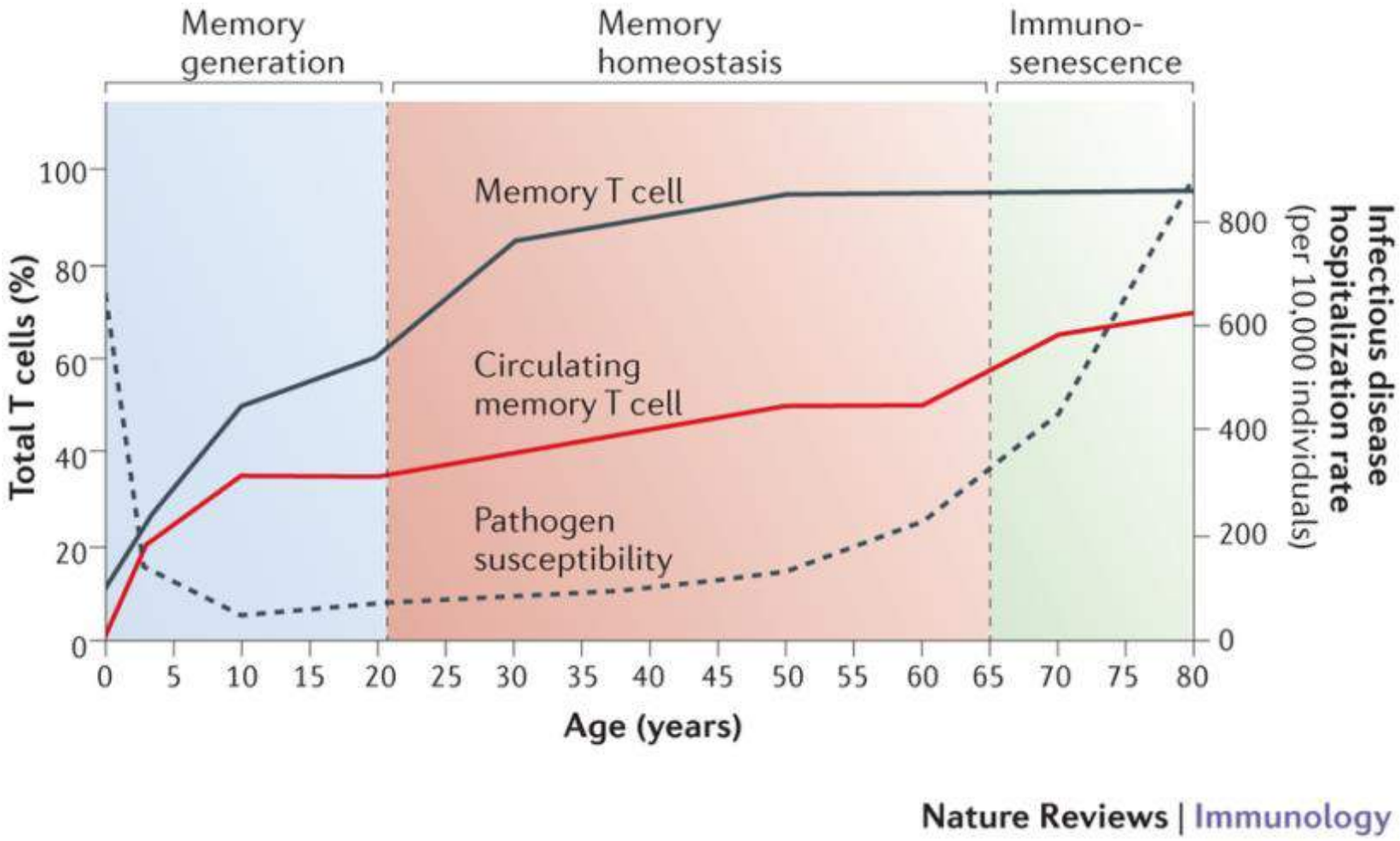


Age and the human CD4 T cell repertoire

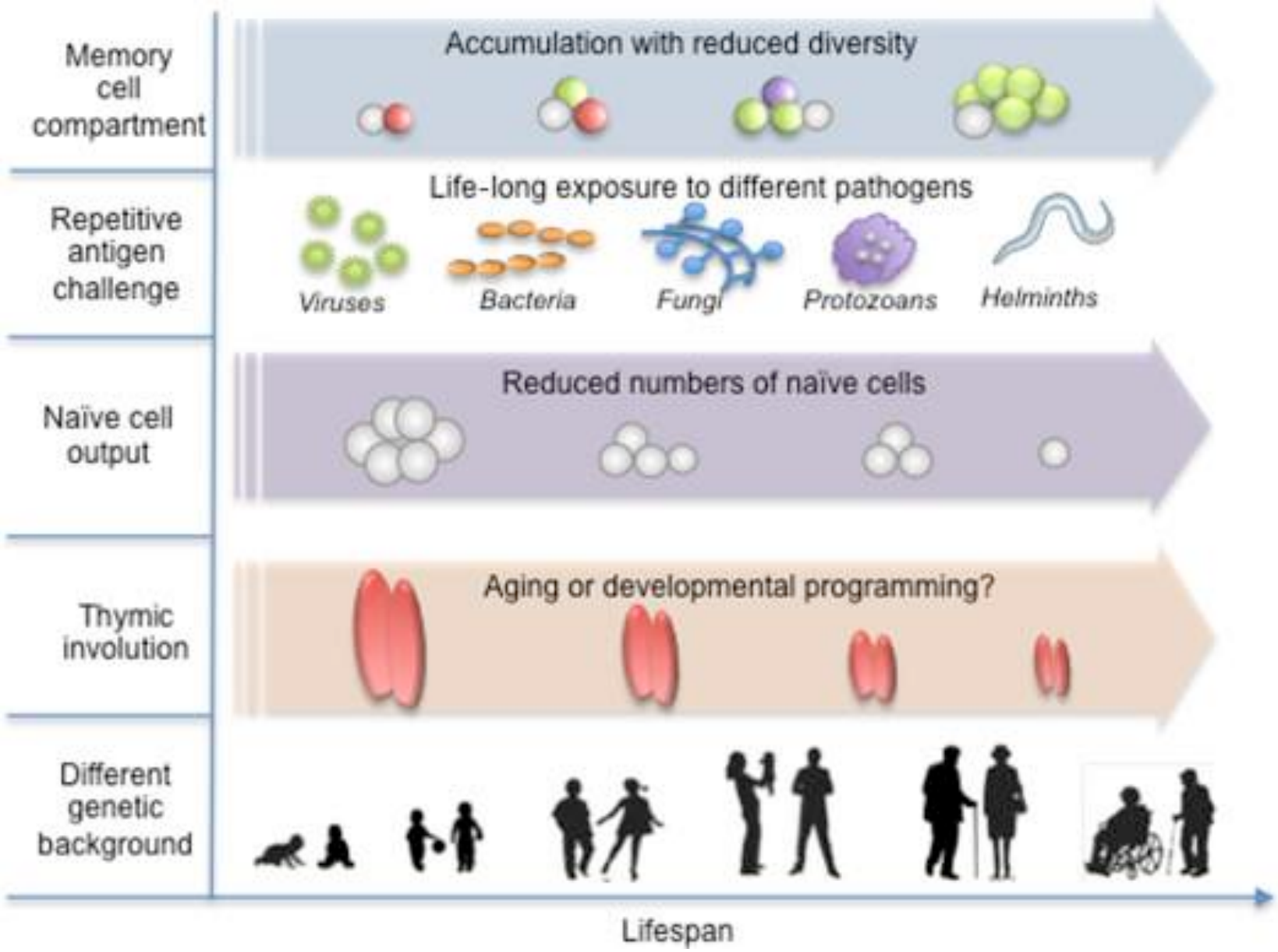
Circle size defines numbers of memory cells of same clone (against the same antigen). Yellow depicts anti-VZV clones, Red depicts anti-CMV clones; both due to long-term latent infections in the host. Aging does not decrease the number of memory cells, but decreases the number of different clonal groups of memory cells.

Nature Immunology 14, 428–436 (2013)

Losing

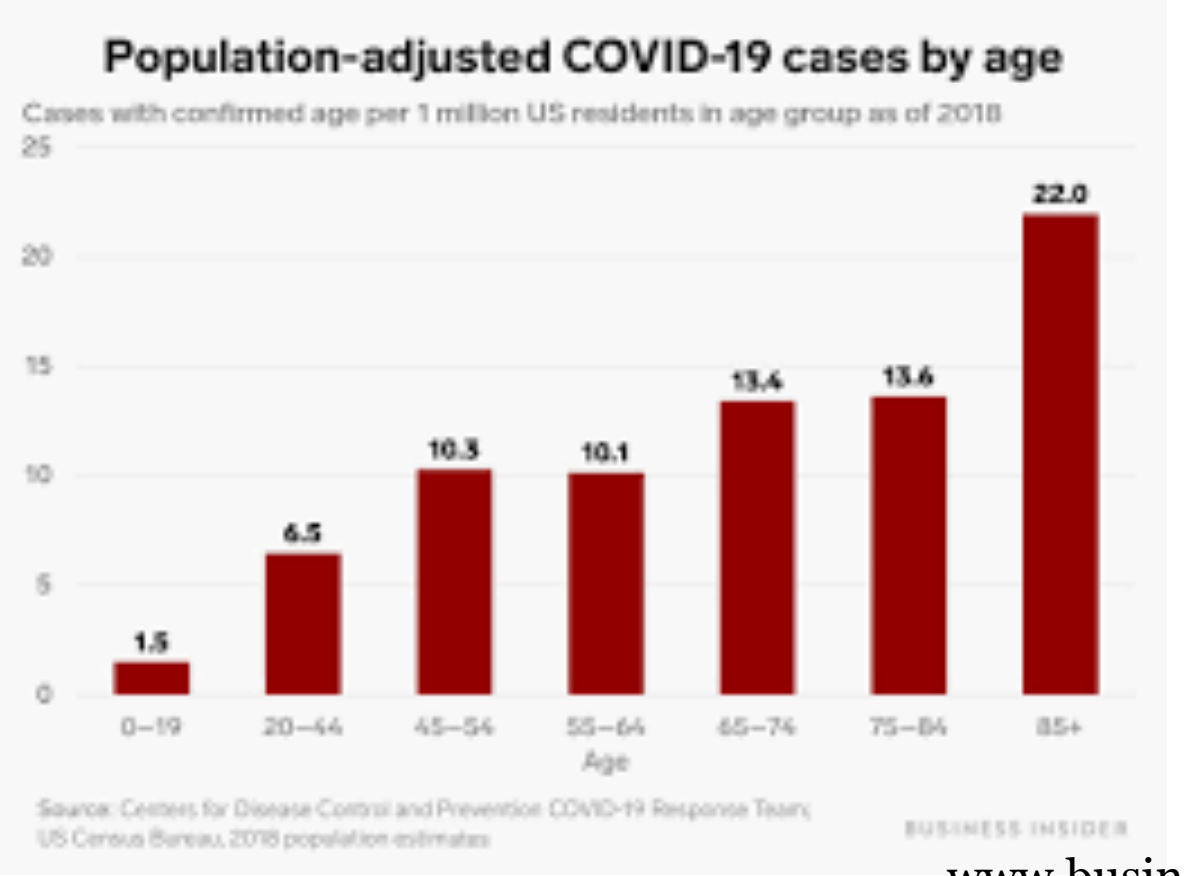


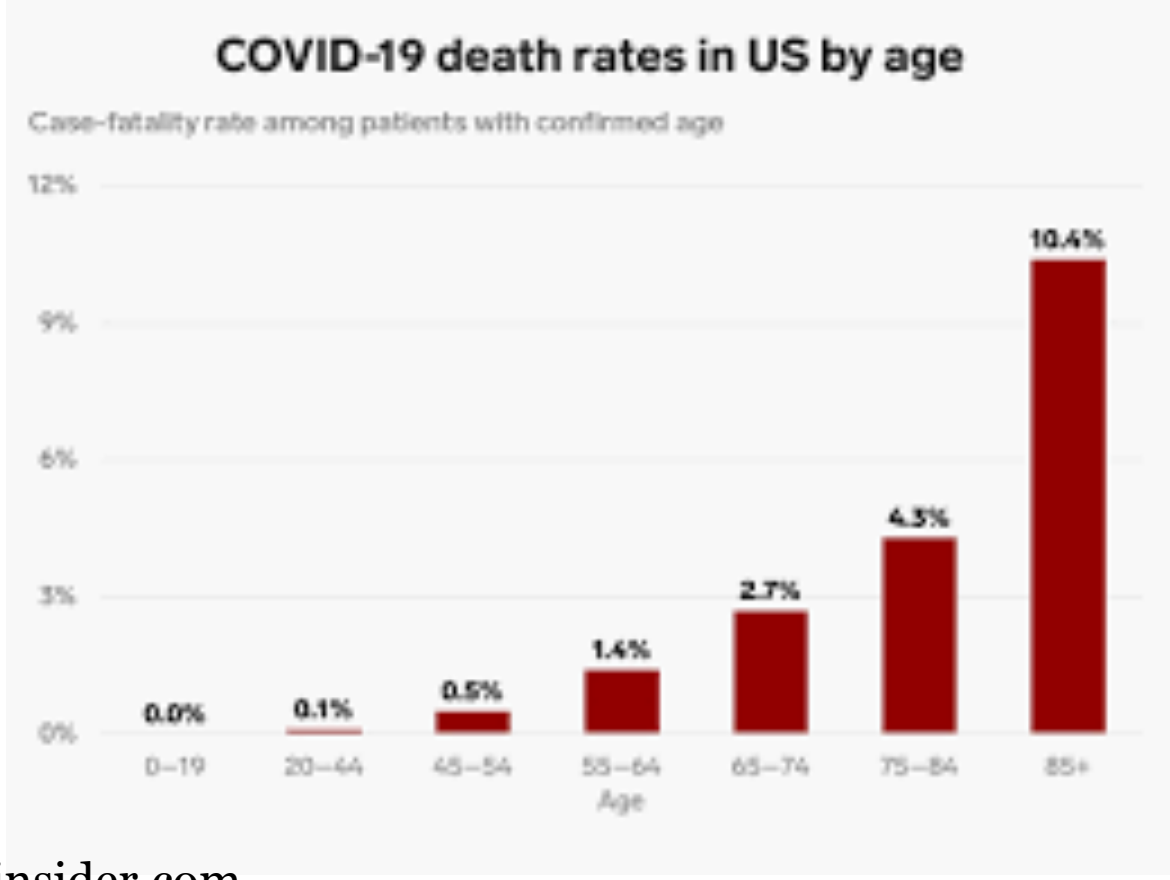
Nature Reviews Immunology 14, 24–35 (2014) doi:10.1038/nri3567



Handbook of the Biology of Aging (Eighth Edition) 2016, Pages 407-431

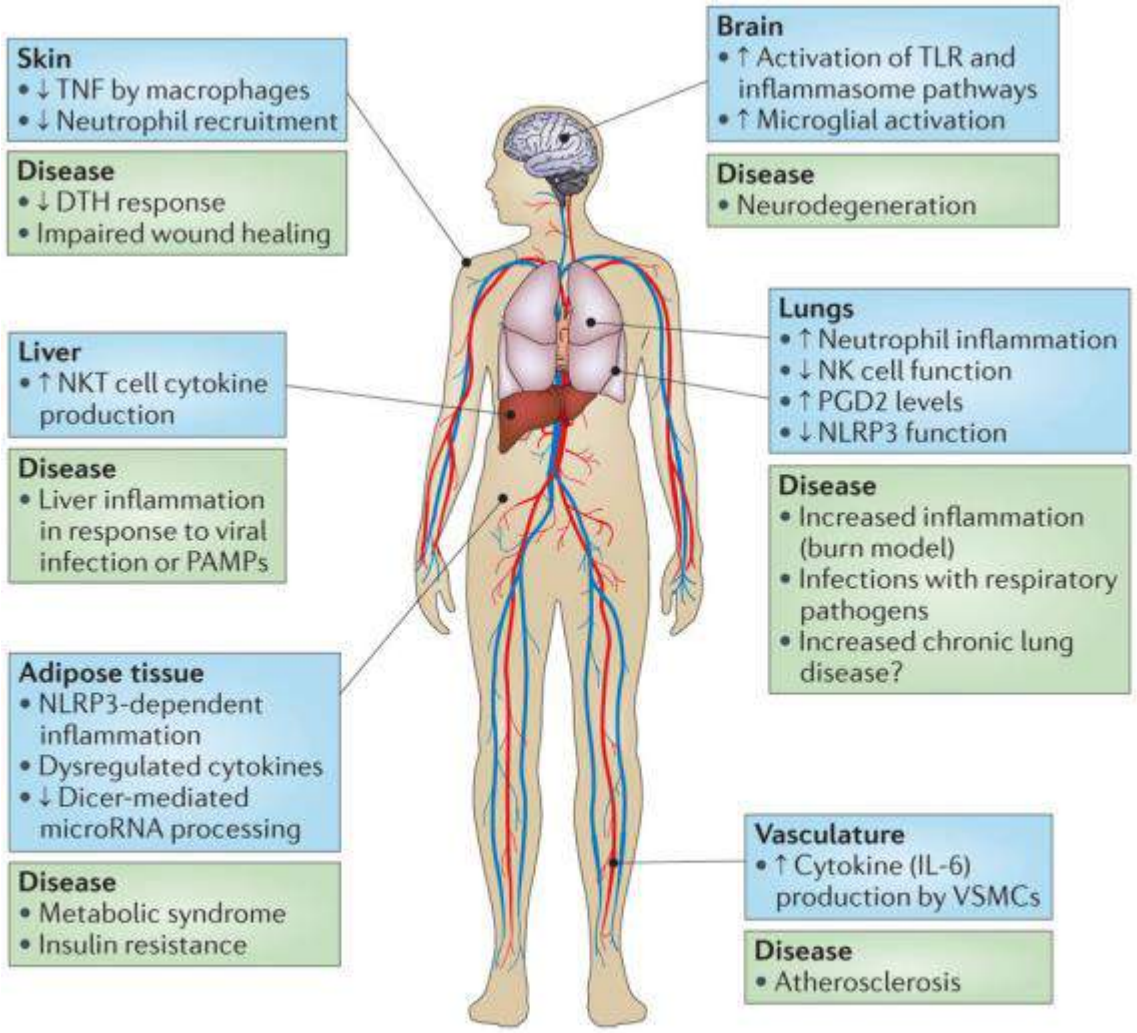
The Older are less capable of mounting response





www.businessinsider.com

The Aging Immune System and Chronic Disease

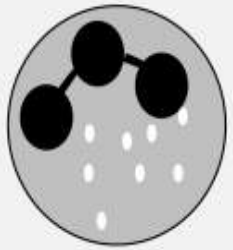


Nature Reviews Immunology 13, 875–887 (2013)
doi:10.1038/nri3547

Immunosenescence and cell function

INNATE IMMUNE RESPONSE : AGE-ASSOCIATED CHANGES NEUTROPHILS AND MACROPHAGES

NEUTROPHILS



DECREASED

- Chemotaxis
- Intra- & Extra-cellular killing
- FCR dependant killing
- Tumor cell toxicity
- Pathogen elimination
- ROS generation
- TLR 4 of mice (not humans)
- Phagocytosis (or no change)

MONOCYTES / MACROPHAGES

DECREASED

- Phagocytosis
- Surface expression of TLR1 and TLR4
- TLR induced up-regulation of CD80
- TLR 1 & 2 induced IL6 and TNFα production
- CD68^{+} Macrophages in bone marrow (percentage)
- Altered immuno-modulatory cytokines

INNATE IMMUNE RESPONSE : AGE-ASSOCIATED CHANGES NK CELLS AND DENDRITIC CELLS

NK CELLS

DECREASED

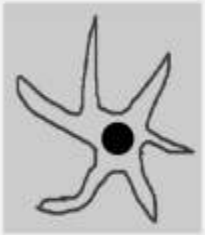
- CD69 expression
- IL 2 and IL12 mediated Chemokine production
- Calcium Mobilization
- Cytotoxicity
- IL2 dependant IFNγ production

INCREASED

- Numbers

No Change in antibody-dependant cytotoxicity

DENDRITIC CELLS

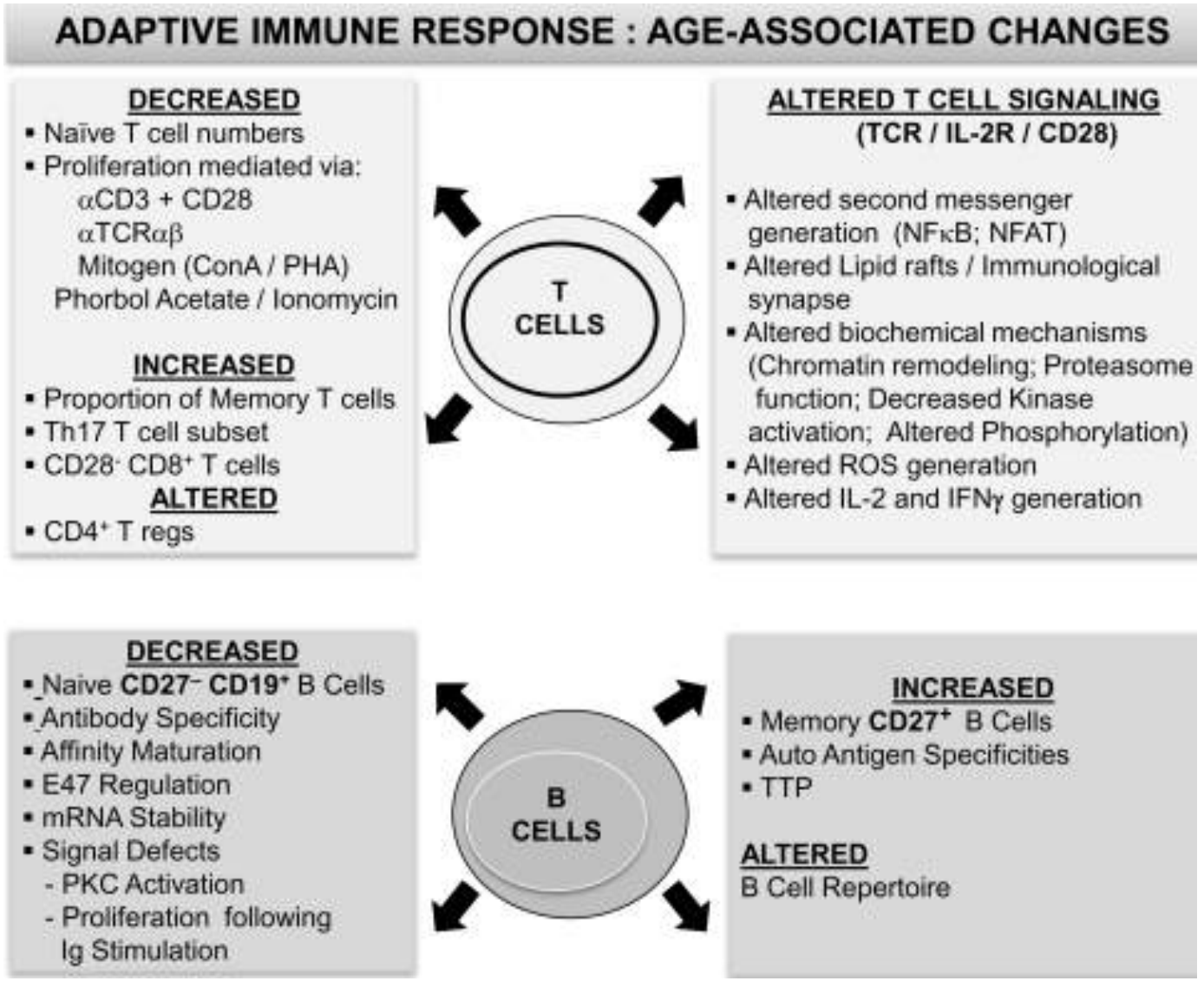


DECREASED

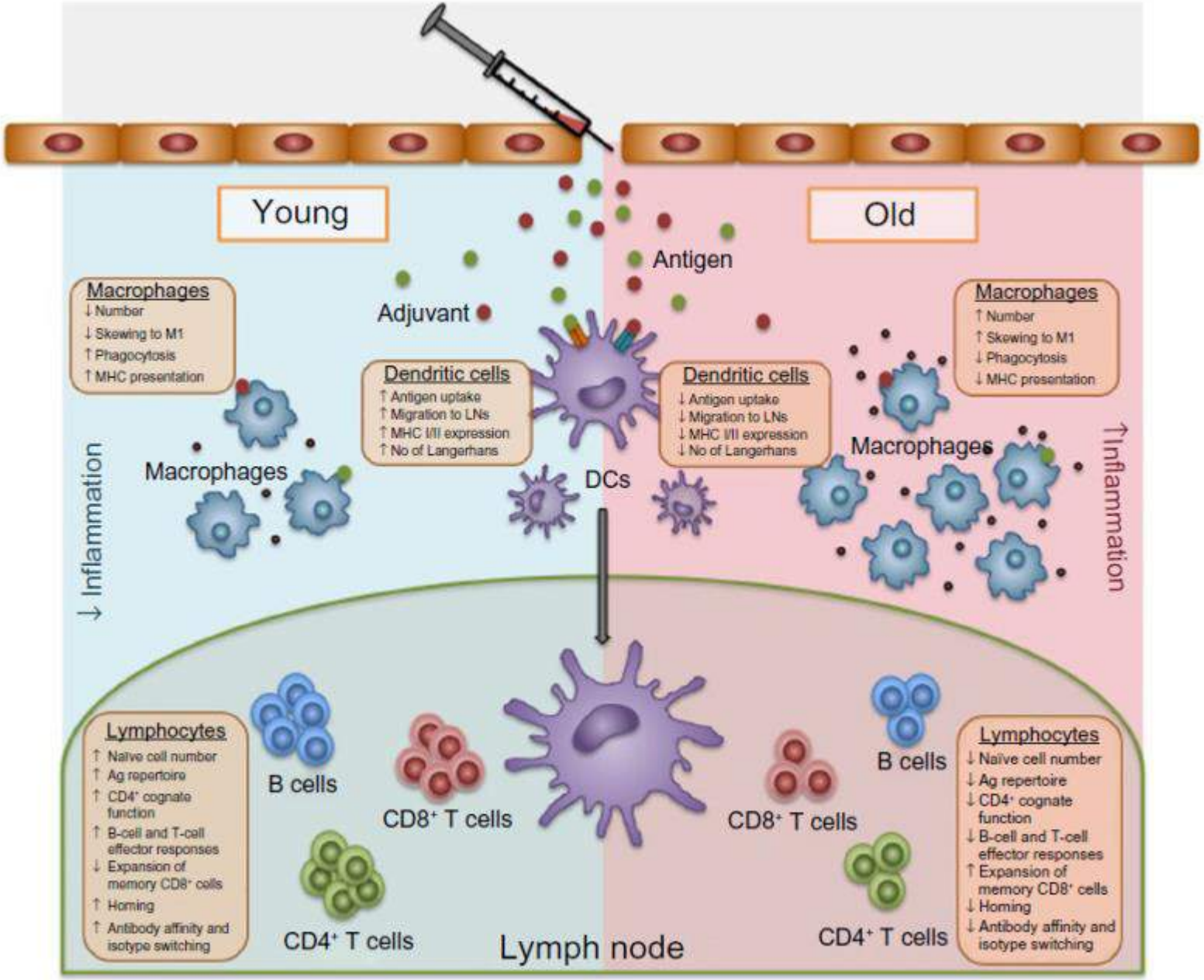
- Langerhans cell density in skin
- Processing capacity
- Micropinocytosis
- Phagocytosis,
- Migration
- TLR function
- LPS - induced IL12 production
- IFNα production

Antioxidants & Redox Signaling, 14(8):1151 (2011)

Immunosenescence and cell function

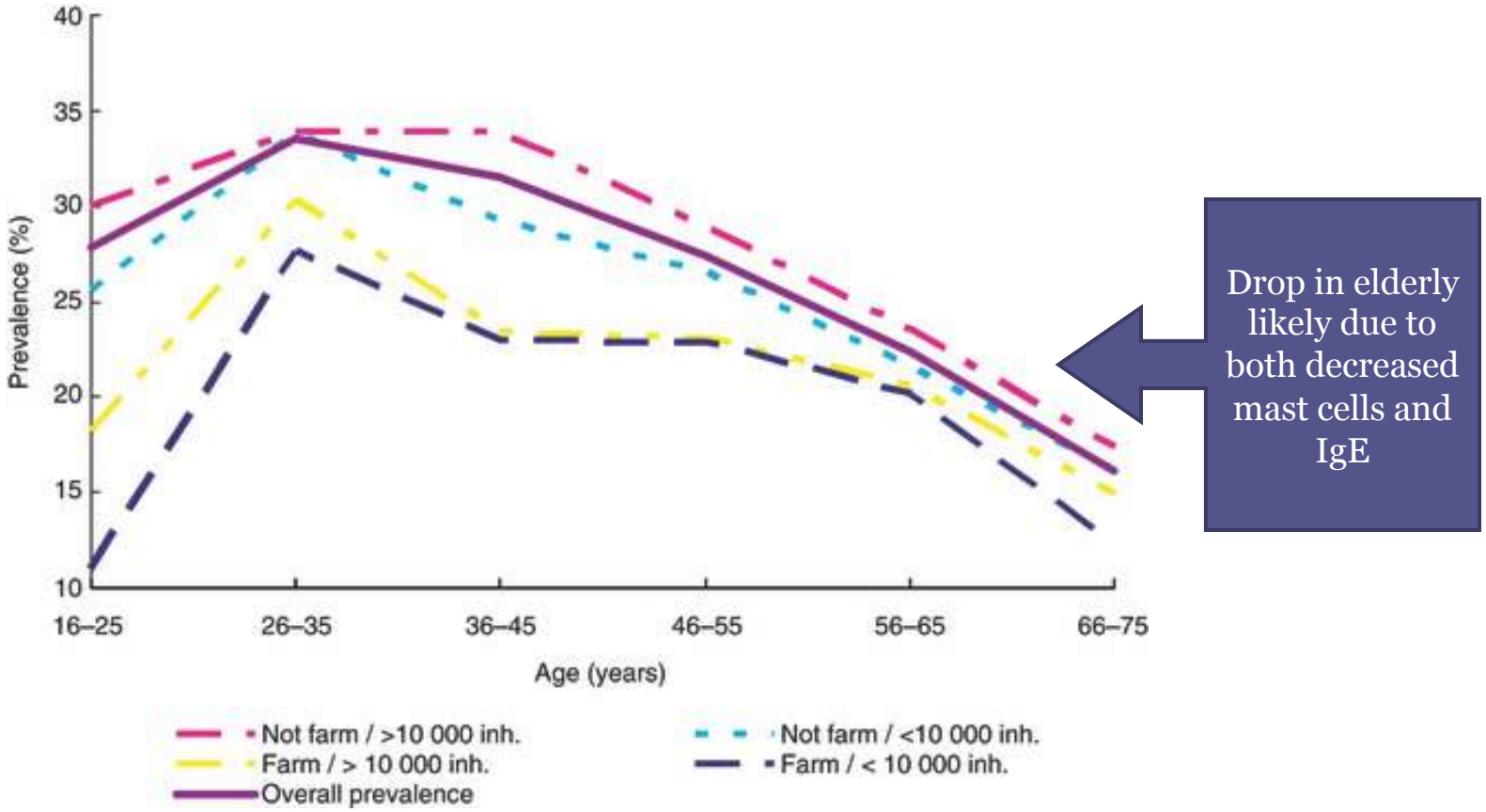


Antioxidants & Redox Signaling, 14(8):1151 (2011)



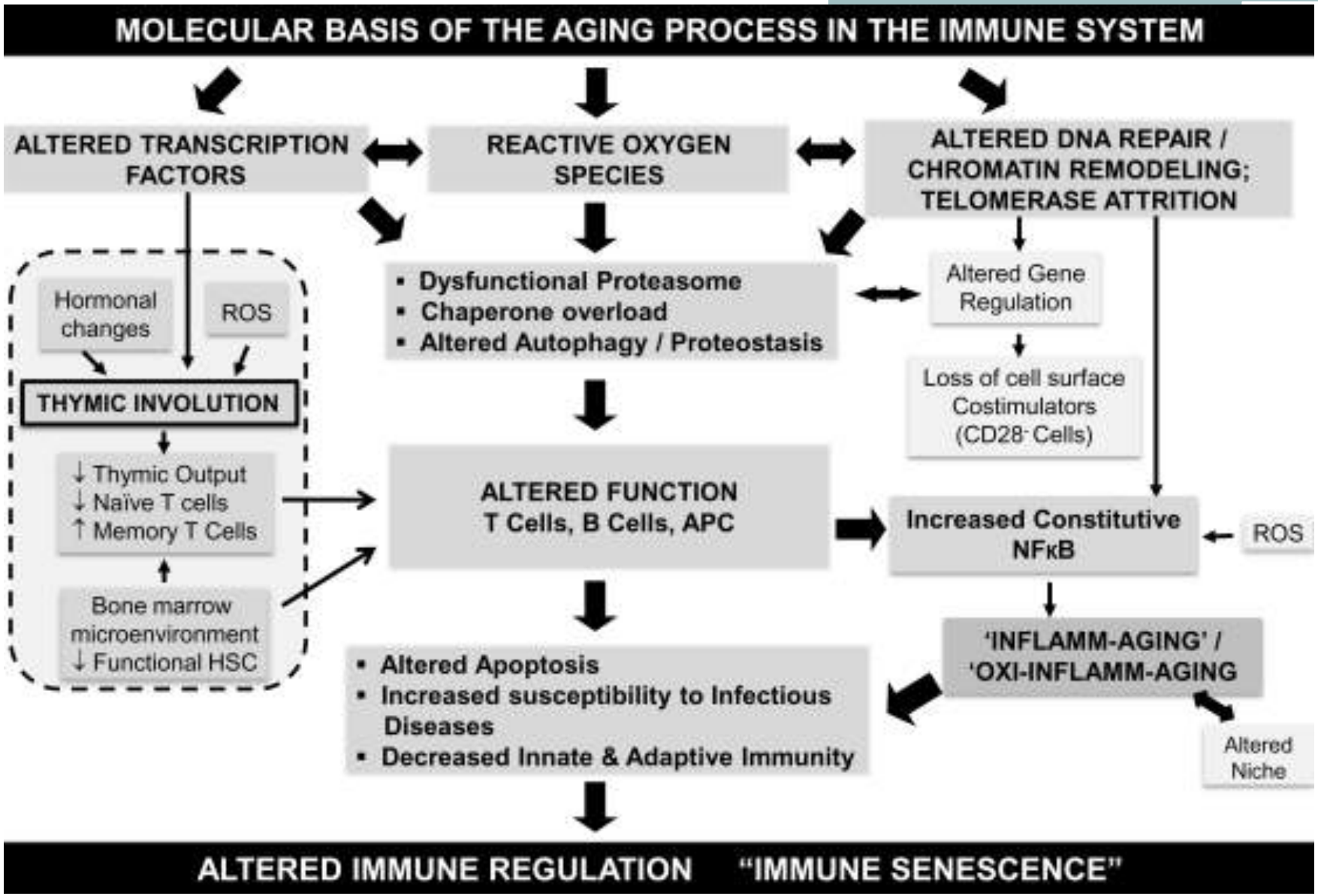
doi.org/10.2147/VDT.S63888

A silver-lining, perhaps



Drop in elderly likely due to both decreased mast cells and IgE

Prevalence of allergic rhinitis by age and childhood living on a farm and degree of urbanization. (>10 000 inh includes metropolitan Gothenburg.) *Allergy* 65(11):1397-403 · May 2010



Antioxidants & Redox Signaling, 14(8):1151 (2011)

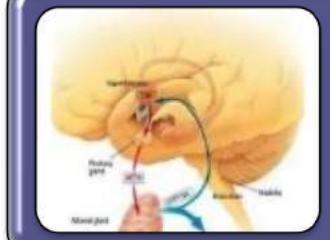
Slowing the Process and Consequences of Immunosenescence

- Rebuilding the Interfaces between self and stranger (Barriers: Gut, Lungs, Skin)
- Maintaining Metabolic Reserve- the earlier the better.
- Rebuilding Metabolic Reserve- Can it be done?
- Limit interaction with new antigenic load while immune system is weak
- Challenge the system with safe stimulators to increase immune resilience.

Everything happens at the interface!

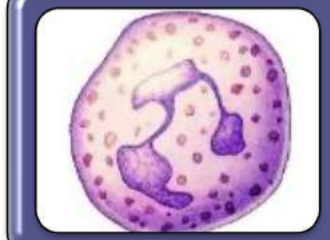
- Biological systems are designed to create discrete functional units
  - Tissues
  - Cells
  - Organelles
  - Genes
- All of which are equipped to modulate each other by signals at their interfaces
- Functional Interfaces require Intact Barriers

Coordinated Surveillance Systems: Protecting “Self” at the interfaces



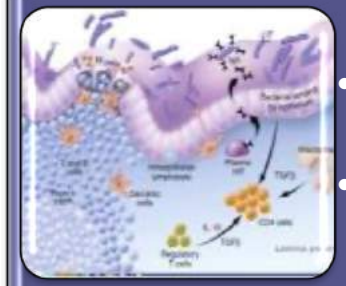
HPA Axis (Stress Response)

- Assessing threats from outside (interface with outside world)
- Compensating for internal imbalances



Immune System

- Surveillance of Self vs. Non-Self
- Highly coordinated by GC signals, highly concentrated in the Gut



Gastrointestinal Tract- GALT

- Maintaining Barrier Function (interface with outside world)
- Signal coordination to brain using direct and immune facilitated signals.

Breaches in the Barrier

- Immune System glands and cells are concentrated at interfaces between our body and the external environment
  - Skin
  - Respiratory Tract
  - Vagina
  - Mucosa-associated Lymphoid Tissue (MALT)
  - Gut-Associated Lymphoid Tissue (GALT)
  - ~75% of the immune system is in the gut!

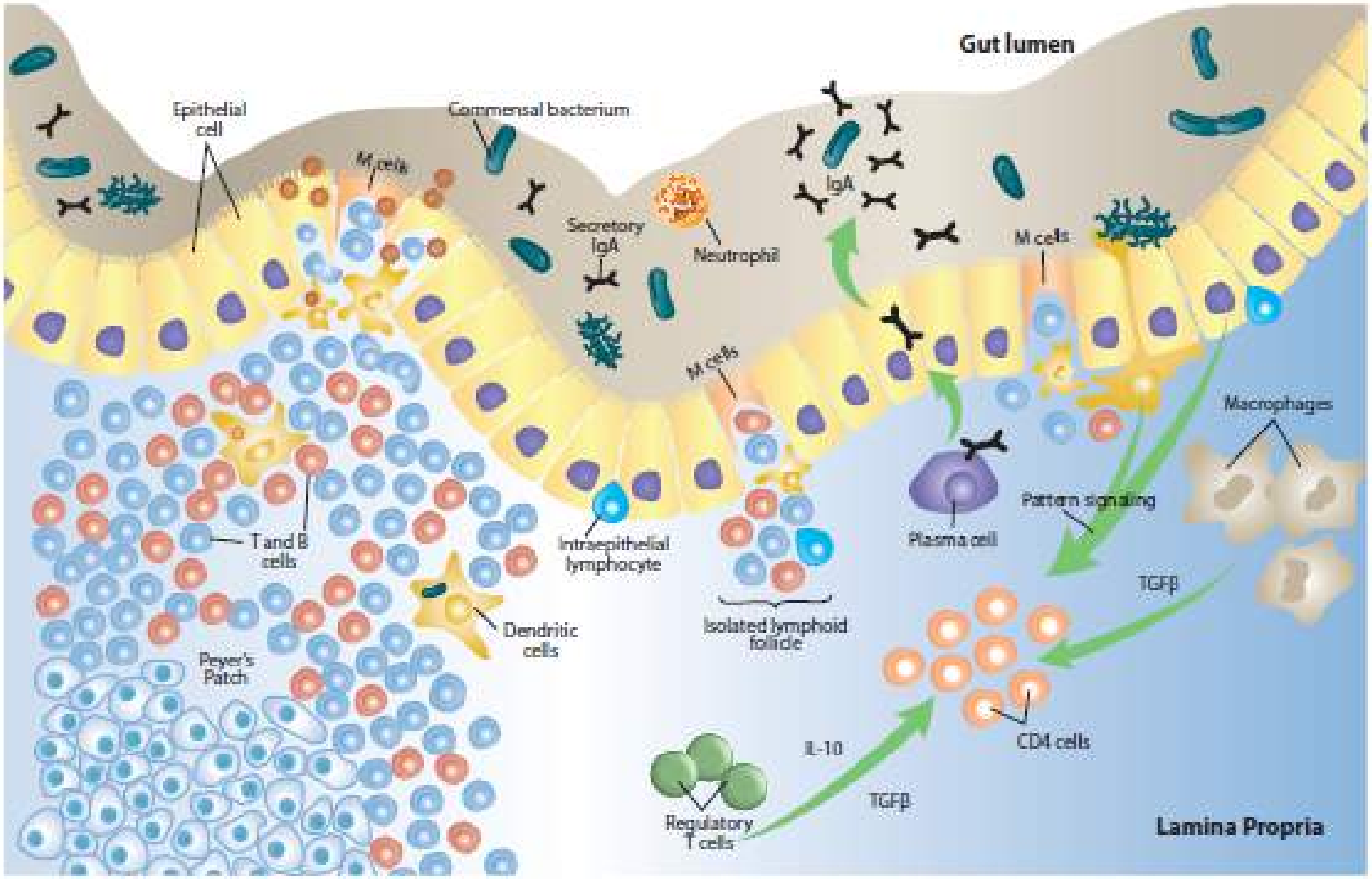


Figure 11: Basic Structures of the Gastrointestinal-Associated Lymphoid Tissue (GALT). See the text for detailed explanation.

GI Changes with Aging…..

- Decreased stomach acid and pancreatic enzymes: reduces macro and micronutrient absorption and increases potential for food or microbial antigenic burden
- Gut permeability: while healthy aging is not generally associated with changes in measures of gut permeability, increase inflammation and other diseases (IBD, T2D etc.) that increase permeability are more prevalent in the elderly
- Shift in the microbiota to a less diversity and more vulnerability

Building Metabolic Reserve

- Strong Immune Function and Regulation depends on:
  - Adequate Macronutrient Balance (More protein, The right fats and few simple sugars)
  - Adequate Micro-nutrient Reserve (cofactors for most enzymatic functions)
  - Strong Antioxidant Reserve (quenching ROS)
  - Mitochondrial Energy and Antioxidants

Simple Step: Are they consuming **and absorbing** enough nutrients?

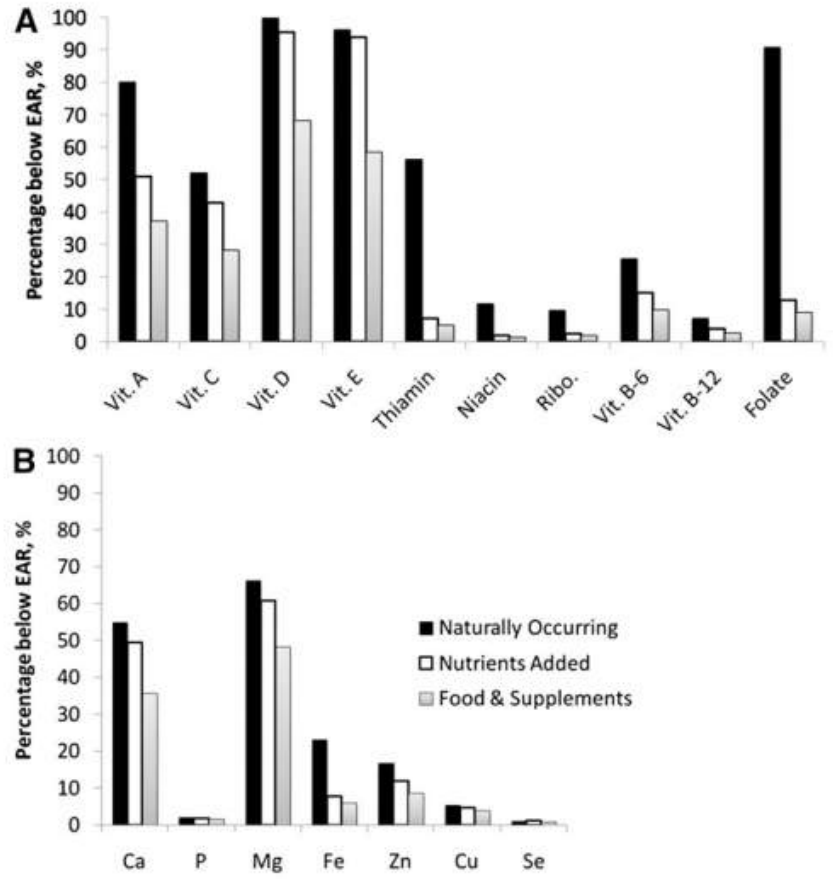
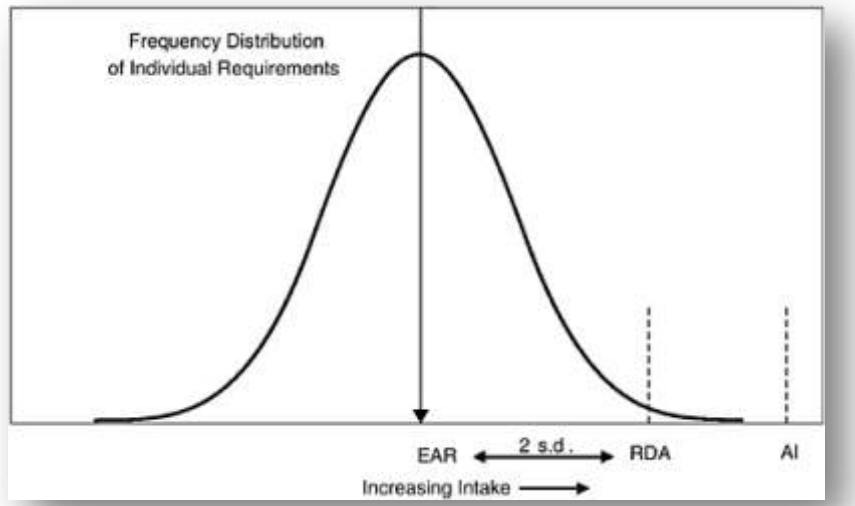


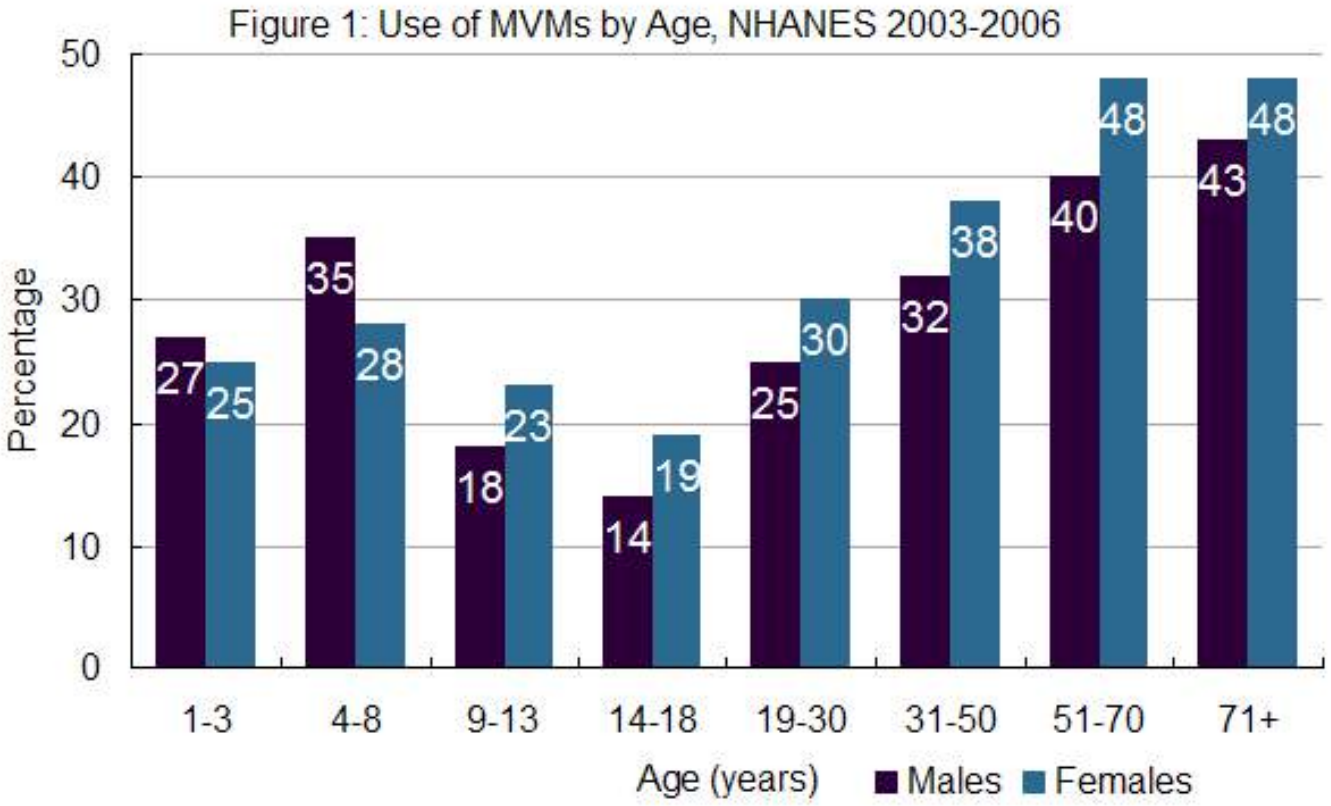
FIGURE 3 Percentage of the population with vitamin (*A*) and mineral (*B*) intakes below the below the EAR for individuals aged ≥19 y (data from NHANES 2003–2006; $n = 8860$). Usual intakes from foods (naturally occurring and that from naturally occurring plus added via enrichment and/or fortification) and dietary supplements were estimated by using the National Cancer Institute method with 2 d of reported intake. EAR, estimated average requirement.



The EAR (Estimated **<u>Average</u>** Requirement) is set by the IOM based on intake level expected to satisfy the needs of 50% of people.

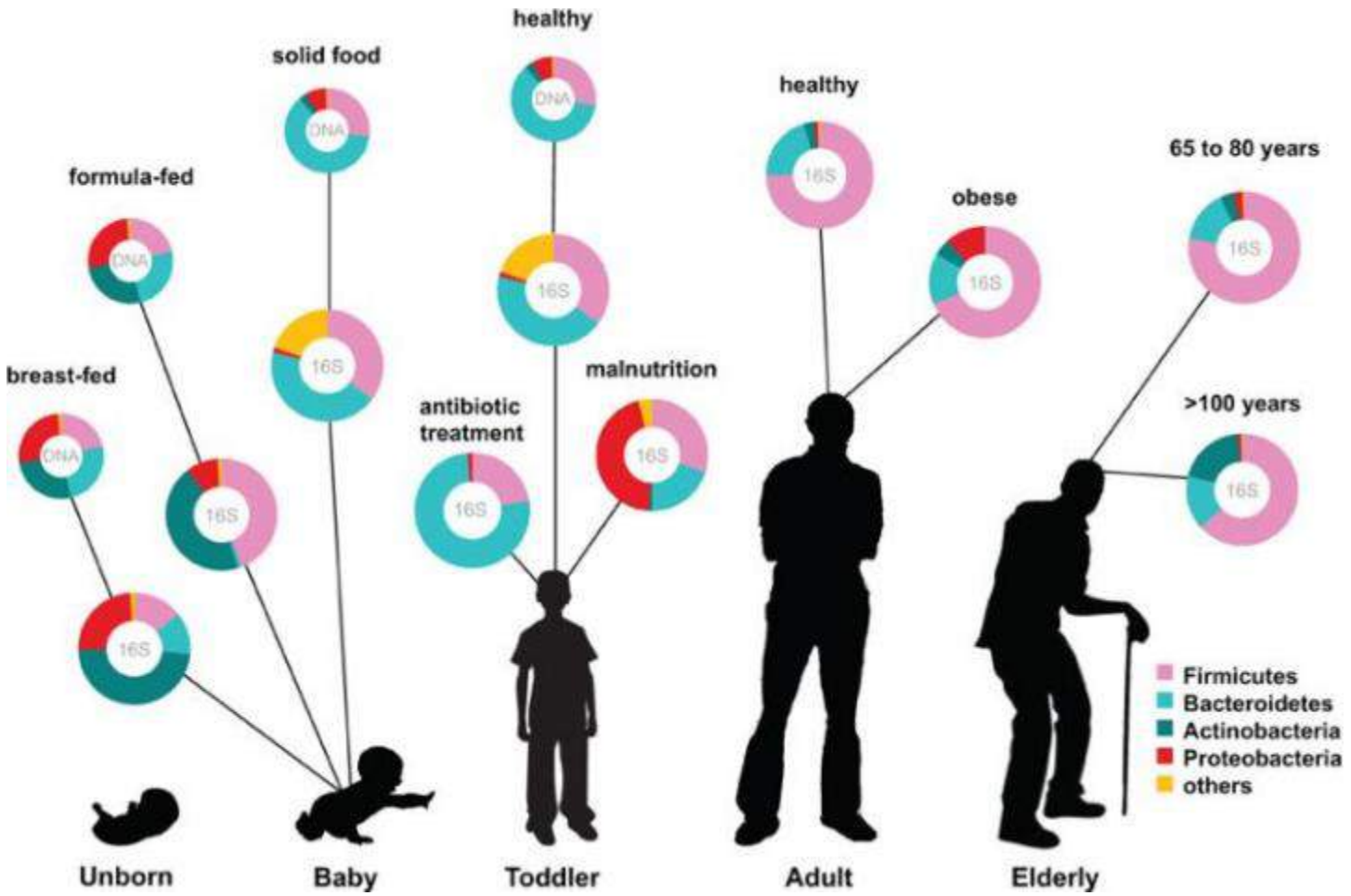
- RDA is set at 2 SD from the EAR, attempting to capture the needs for 98% of the population.
- AI are set by the IOM when research is limited on determining the EAR

Already taking supplements…



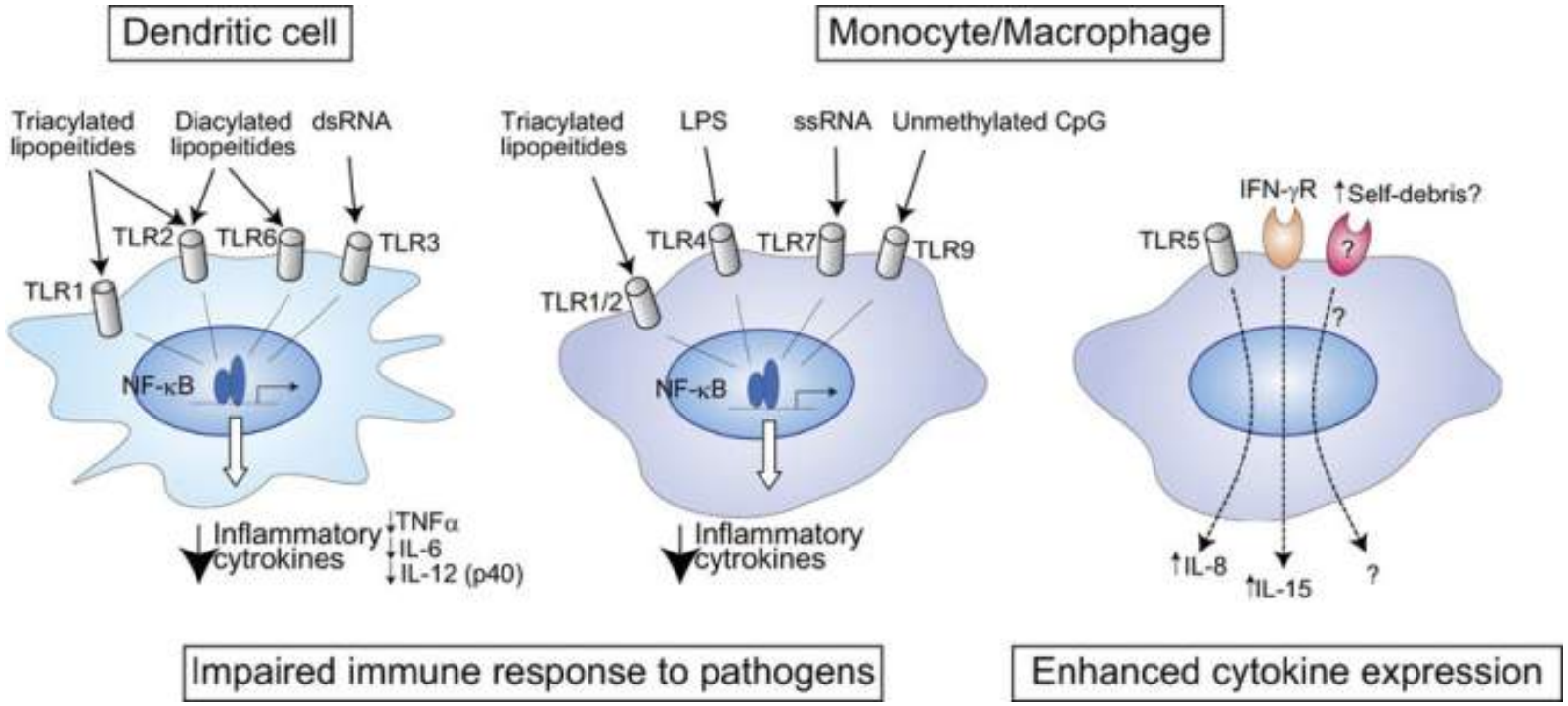
- Clinicians should be sure adequate quantities (and types) of B12, vitamin D3, A, calcium, magnesium
- Consider supplementation with protein powder to increase intake of protein

How does the microbiome change with age?

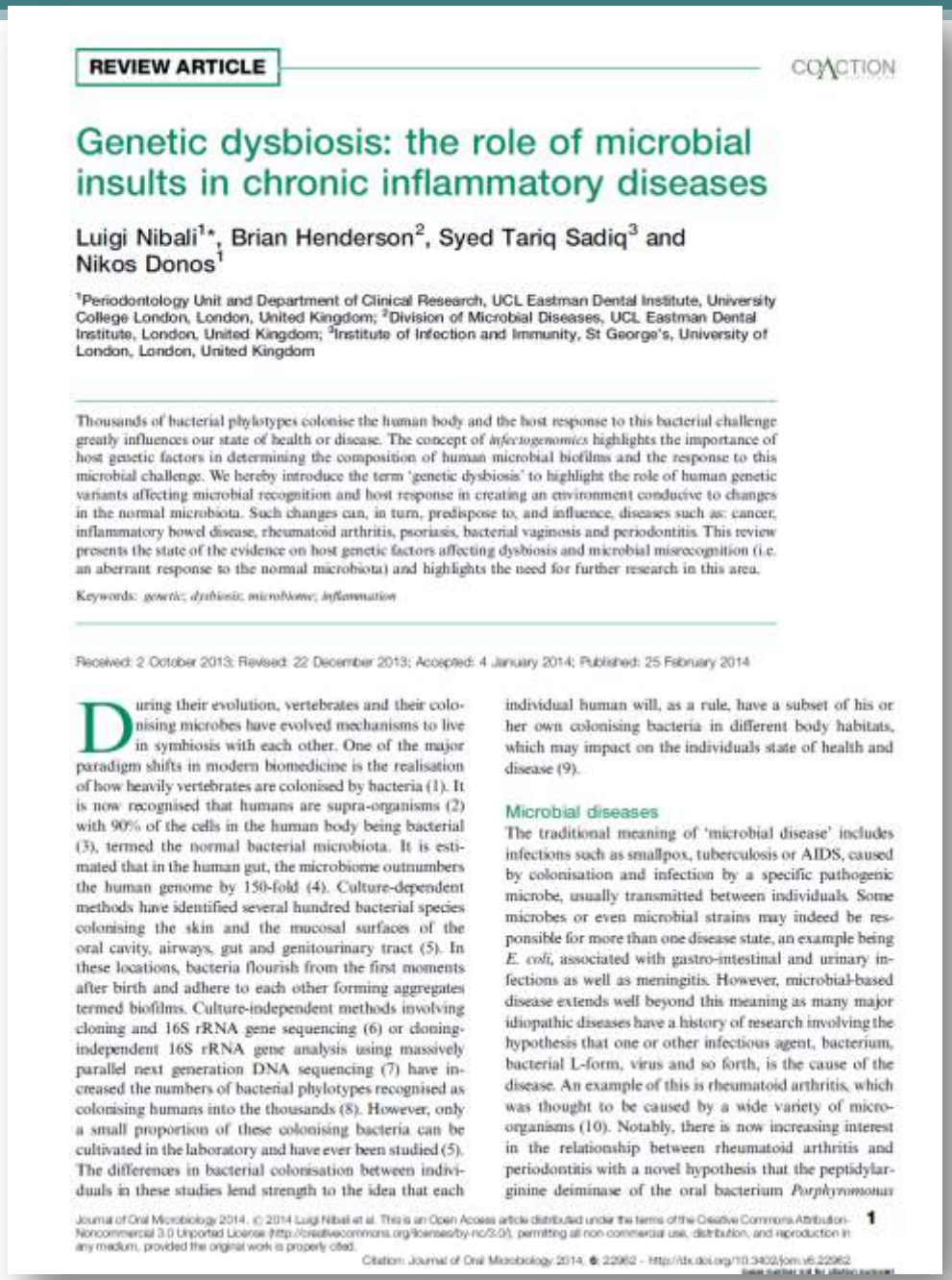


Front. Cell. Infect. Microbiol., 09 August 2012
http://dx.doi.org/10.3389/fcimb.2012.00104

Aberrant inflammatory response of a dendritic cell and macrophage with aging.



Aberrant inflammatory response of a dendritic cell and macrophage with aging. Toll-like receptors (TLRs) are a family of pattern-recognition receptors that have a key role in the innate immune system. TLRs are activated by specific ligands derived from pathogens and damaged cells, as shown. The expression and function of some TLRs are downregulated with aging, potentially impairing immune responses. **On the contrary, signaling mediated via TLR and IFNγ is activated, resulting in increased secretion of inflammatory cytokines.** IFN, interferon; LPS, lipopolysaccharide; dsRNA, double-stranded RNA; ssRNA, single-stranded RNA. doi:10.1038/npjamd.2016.18



REVIEW ARTICLE

COACTION

Genetic dysbiosis: the role of microbial insults in chronic inflammatory diseases

Luigi Nibali[1]*, Brian Henderson[2], Syed Tariq Sadiq[3] and Nikos Donos[1]

[1]Periodontology Unit and Department of Clinical Research, UCL Eastman Dental Institute, University College London, London, United Kingdom; [2]Division of Microbial Diseases, UCL Eastman Dental Institute, London, United Kingdom; [3]Institute of Infection and Immunity, St George's, University of London, London, United Kingdom

Thousands of bacterial phylotypes colonise the human body and the host response to this bacterial challenge greatly influences our state of health or disease. The concept of *infectogenomics* highlights the importance of host genetic factors in determining the composition of human microbial biofilms and the response to this microbial challenge. We hereby introduce the term 'genetic dysbiosis' to highlight the role of human genetic variants affecting microbial recognition and host response in creating an environment conducive to changes in the normal microbiota. Such changes can, in turn, predispose to, and influence, diseases such as: cancer, inflammatory bowel disease, rheumatoid arthritis, psoriasis, bacterial vaginosis and periodontitis. This review presents the state of the evidence on host genetic factors affecting dysbiosis and microbial misrecognition (i.e. an aberrant response to the normal microbiota) and highlights the need for further research in this area.

Keywords: *genetic; dysbiosis; microbiome; inflammation*

Received: 2 October 2013; Revised: 22 December 2013; Accepted: 4 January 2014; Published: 25 February 2014

During their evolution, vertebrates and their colonising microbes have evolved mechanisms to live in symbiosis with each other. One of the major paradigm shifts in modern biomedicine is the realisation of how heavily vertebrates are colonised by bacteria (1). It is now recognised that humans are supra-organisms (2) with 90% of the cells in the human body being bacterial (3), termed the normal bacterial microbiota. It is estimated that in the human gut, the microbiome outnumbers the human genome by 150-fold (4). Culture-dependent methods have identified several hundred bacterial species colonising the skin and the mucosal surfaces of the oral cavity, airways, gut and genitourinary tract (5). In these locations, bacteria flourish from the first moments after birth and adhere to each other forming aggregates termed biofilms. Culture-independent methods involving cloning and 16S rRNA gene sequencing (6) or cloning-independent 16S rRNA gene analysis using massively parallel next generation DNA sequencing (7) have increased the numbers of bacterial phylotypes recognised as colonising humans into the thousands (8). However, only a small proportion of these colonising bacteria can be cultivated in the laboratory and have ever been studied (5). The differences in bacterial colonisation between individuals in these studies lend strength to the idea that each individual human will, as a rule, have a subset of his or her own colonising bacteria in different body habitats, which may impact on the individuals state of health and disease (9).

Microbial diseases

The traditional meaning of 'microbial disease' includes infections such as smallpox, tuberculosis or AIDS, caused by colonisation and infection by a specific pathogenic microbe, usually transmitted between individuals. Some microbes or even microbial strains may indeed be responsible for more than one disease state, an example being *E. coli*, associated with gastro-intestinal and urinary infections as well as meningitis. However, microbial-based disease extends well beyond this meaning as many major idiopathic diseases have a history of research involving the hypothesis that one or other infectious agent, bacterium, bacterial L-form, virus and so forth, is the cause of the disease. An example of this is rheumatoid arthritis, which was thought to be caused by a wide variety of micro-organisms (10). Notably, there is now increasing interest in the relationship between rheumatoid arthritis and periodontitis with a novel hypothesis that the peptidylarginine deiminase of the oral bacterium *Porphyromonas*

Citation: Journal of Oral Microbiology 2014, 6: 22962 - http://dx.doi.org/10.3402/jom.v6.22962

We hereby introduce the term 'genetic dysbiosis' to highlight the role of human genetic variants affecting microbial recognition and host response in creating an environment conducive to changes in the normal microbiota. Such changes can, in turn, predispose to, and influence, diseases such as: cancer, inflammatory bowel disease, rheumatoid arthritis, psoriasis, bacterial vaginosis and periodontitis.

ANTIOXIDANTS & REDOX SIGNALING
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COMPREHENSIVE INVITED REVIEW

Aging and Immune Function: Molecular Mechanisms to Interventions

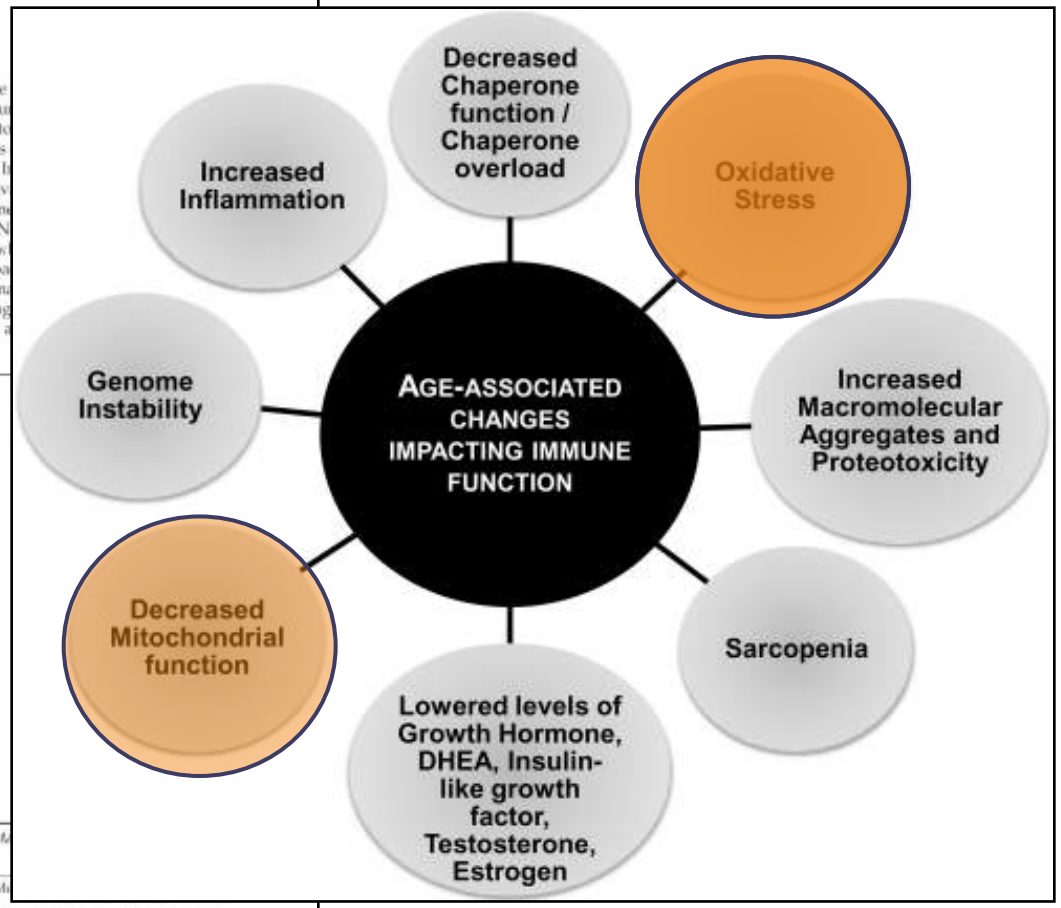
Subramaniam Ponnappan[1] and Usha Ponnappan[1,2]

Abstract

The immune system of an organism is an essential component of the defense
pathogenic stress. Age-associated immune dysfunction, also dubbed "immu
creased susceptibility to infections, increased onset and progression of auto
neoplasia. Over the years, extensive research has generated consensus in terms
defects within the immune system in various organisms, including humans. I
such as thymic involution, T cell repertoire skewing, decreased ability to activ
robust memory responses, have been shown to have a causative role in immun
the molecular mechanisms underlying the generation of proteotoxic stress, DN
of ubiquitin proteasome pathway, and regulation of transcription factor NFκ
have paved the way to delineating signaling pathways that cross-talk and impa
role of the immune system in combating infections, its effectiveness with age m
a predictor of longevity. It is therefore believed that a better understanding
immune senescence will lead to an effective interventional strategy aimed
individuals. *Antioxid. Redox Signal.* 14, 1551–1585.

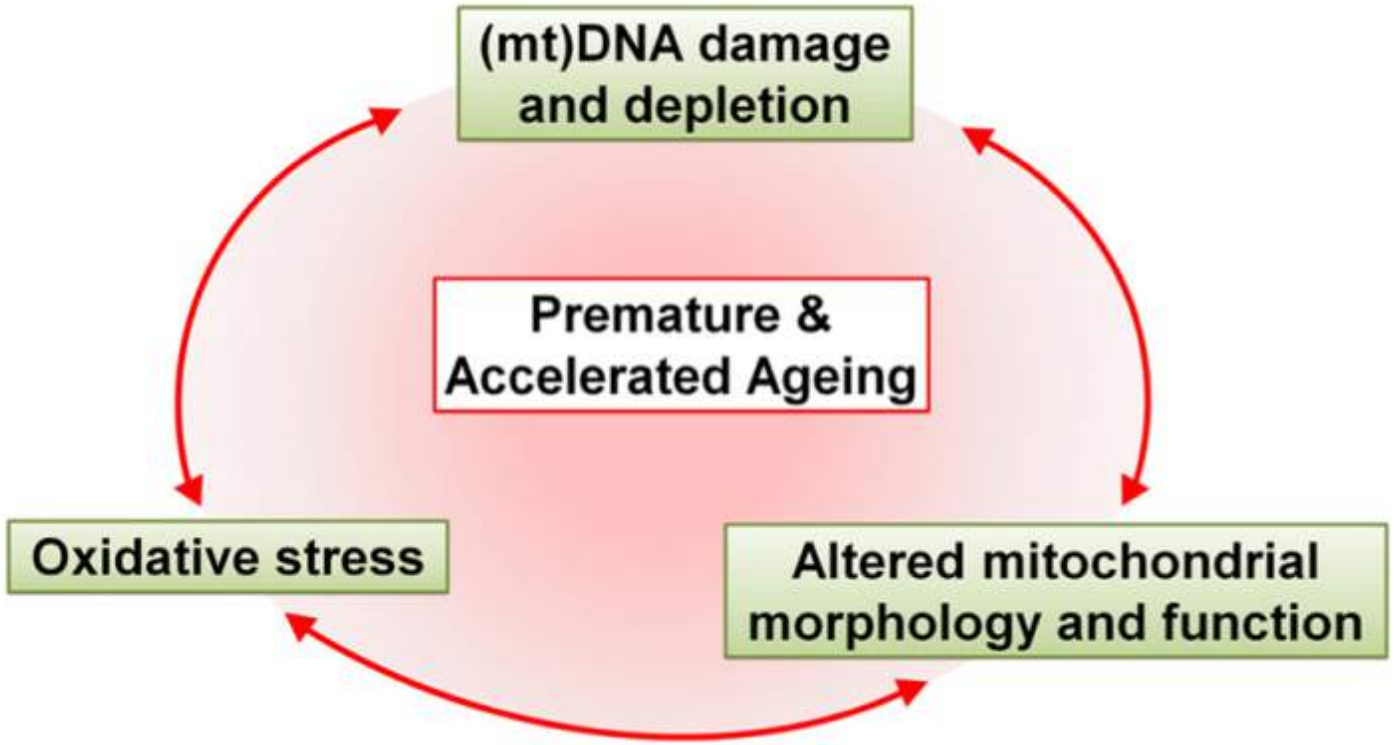
Reviewing Editors: *Rommy von Bernhardi, Manuel Collado, Monica de la Fuente, M
Loebenstein, Anonymous, and Michael Toledano*

Departments of [1]Geriatrics and [2]Microbiology and Immunology, University of Arkansas for Ma



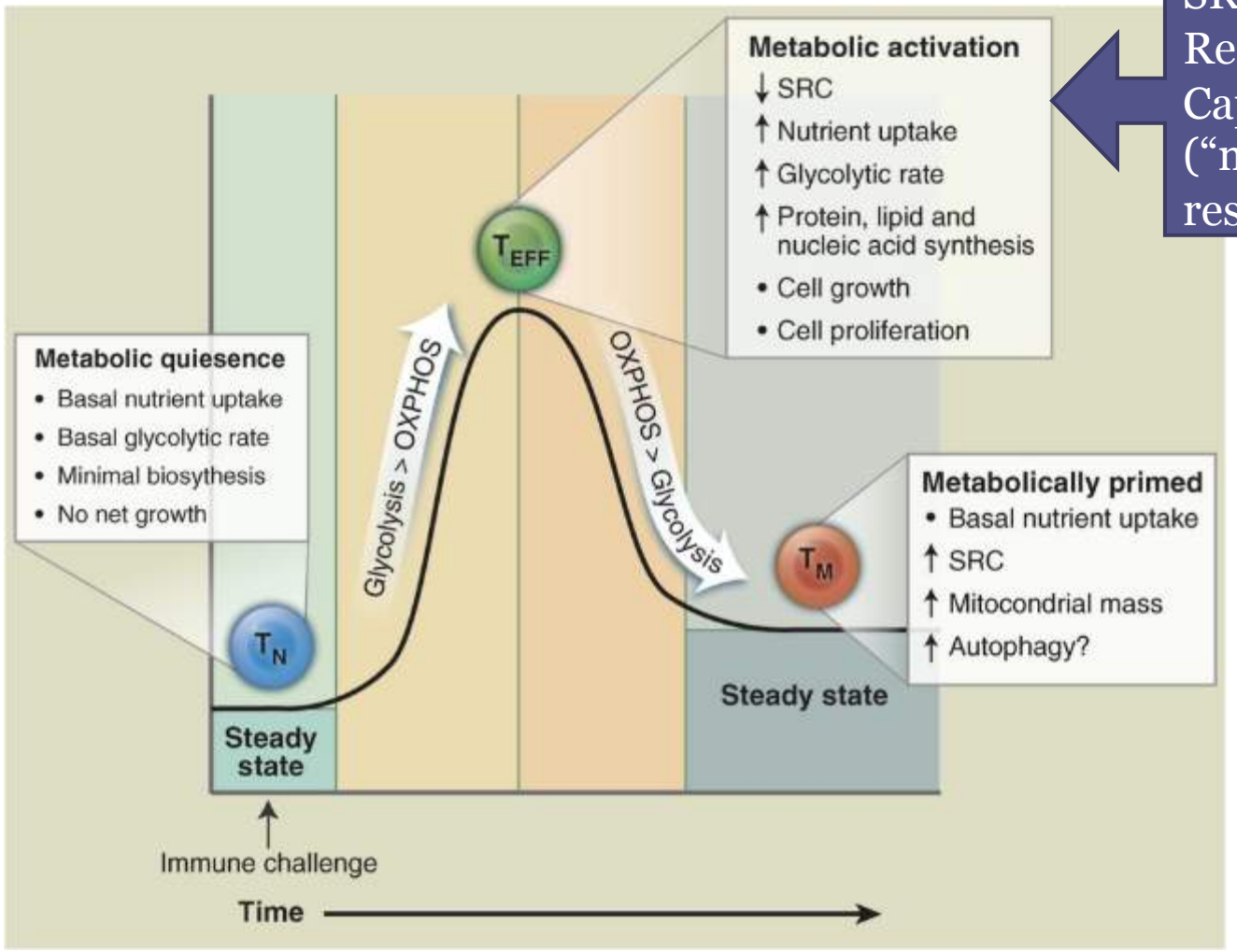
Antioxidants & Redox Signaling, 14(8):1151 (2011)

Mitochondria are key



Immune Cell Metabolic Activation

SRC= Spare Respiratory Capacity ("metabolic reserve")



Science 11 October 2013: Vol. 342 no. 6155

Mitochondria in innate immune responses

A. Phillip West, Gerald S. Shadel[§] and Sankar Ghosh[‖]*

Abstract | The innate immune system has a key role in the mammalian immune response. Recent research has demonstrated that mitochondria participate in a broad range of innate immune pathways, functioning as signalling platforms and contributing to effector responses. In addition to regulating antiviral signalling, mounting evidence suggests that mitochondria facilitate antibacterial immunity by generating reactive oxygen species and contribute to innate immune activation following cellular damage and stress. Therefore, in addition to their well-appreciated roles in cellular metabolism and programmed cell death, mitochondria appear to function as centrally positioned hubs in the innate immune system. Here, we review the emerging knowledge about the roles of mitochondria in innate immunity.

Programmed cell death
A common form of cell death that is also referred to as apoptosis. Many physiological and developmental stimuli cause apoptosis, and this mechanism is frequently used to delete unwanted, superfluous or potentially harmful cells, such as those undergoing transformation.

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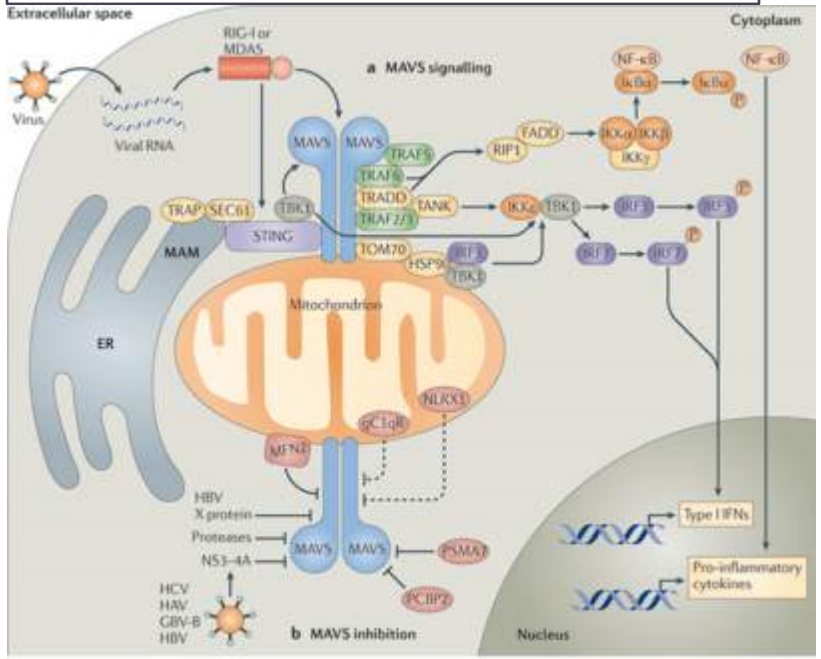
doi:10.1038/nri2975
Published online 20 May 2011

Following infection, microorganisms are initially sensed by pattern-recognition receptors (PRRs) of the innate immune system, which bind conserved molecular patterns that are shared by different classes of microorganisms. These pathogen-associated molecular patterns (PAMPs) include microbial structural components, nucleic acids and proteins. The list of PRRs known to sense PAMPs is extensive, and is comprised most notably of four families: Toll-like receptors (TLRs), nucleotide oligomerization domain (NOD)-like receptors (NLRs), C-type lectin receptors (CLRs) and retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs)[1–3] (BOX 1). PRR ligation triggers multiple signalling pathways that culminate in the activation of nuclear factor-κB (NF-κB), mitogen-activated protein kinases (MAPKs) and interferon regulatory factors (IRFs), which control the expression of pro-inflammatory cytokines and chemokines, type I interferons (IFNs) and co-stimulatory molecules[2,3,4]. The resulting pro-inflammatory state is necessary for the generation of a robust antimicrobial environment and for the proper activation of the adaptive immune response.

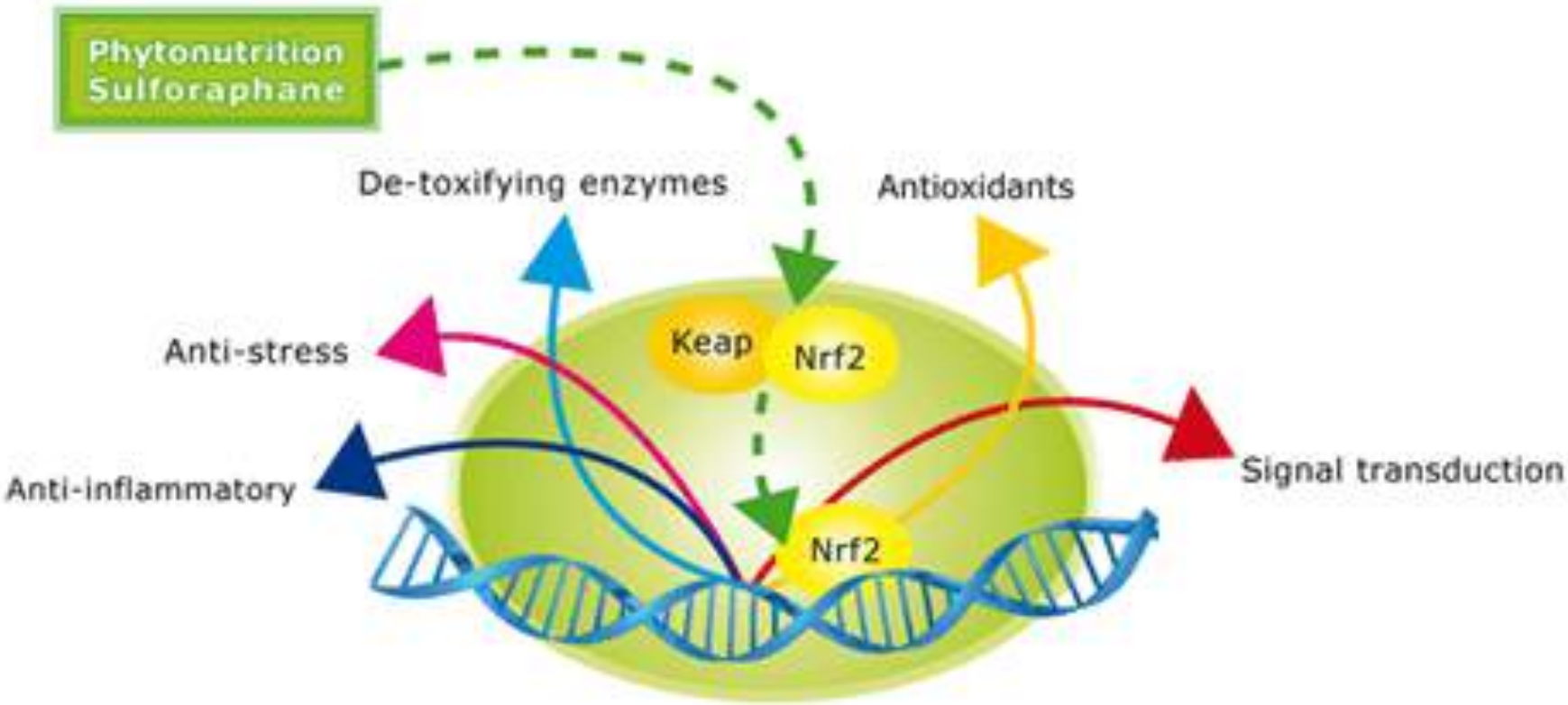
Mitochondria are dynamic double-membrane-bound organelles that are involved in a wide range of cellular processes, including ATP generation, programmed cell death and calcium homeostasis, as well as the biosynthesis of amino acids, lipids, nucleotides and haem. Although mitochondria possess their own genome (mitochondrial DNA (mtDNA)) that encodes 13 proteins of the oxidative phosphorylation machinery, 2 ribosomal RNAs and 22 transfer RNAs essential for translation in the mitochondria, most of the ~1,500 proteins comprising the mitochondrial proteome are nuclear encoded[5]. Many of these proteins function in oxidative phosphorylation or other metabolic pathways, but they also include those needed for replication and expression of mtDNA (that is, the mitochondrial transcription and translation machinery). Consequently, coordination between the mitochondrial and nuclear genomes is required for proper assembly and function of the mitochondrial network, and cellular signalling cascades mediate crosstalk between mitochondria and the nucleus[6]. The mitochondrial network forms a reticular branching structure that, through association with the cytoskeleton, is motile and undergoes regular fusion and division[7]. Mounting evidence suggests that mitochondrial dynamics regulate many aspects of mitochondrial biology and are influenced by a variety of metabolic and cellular signals[7].

Mitochondrial regulation of apoptotic signalling has been appreciated for some time; however, more recent evidence suggests that mitochondria also participate in various additional signalling pathways[7,8]. For example, research over the past several years has unveiled previously unappreciated roles for mitochondria in the innate immune response, and it is becoming increasingly apparent that mitochondria participate in RLR signalling, antibacterial immunity and sterile inflammation. Although mitochondrial control of apoptosis during infection is an important aspect of the mammalian innate immune response, this topic has been reviewed thoroughly by others[8,10] and therefore is not discussed further in this article. Instead, we review and discuss the involvement of mitochondria in innate immune signalling pathways and the mechanisms by which these organelles facilitate effector responses of the innate immune system.

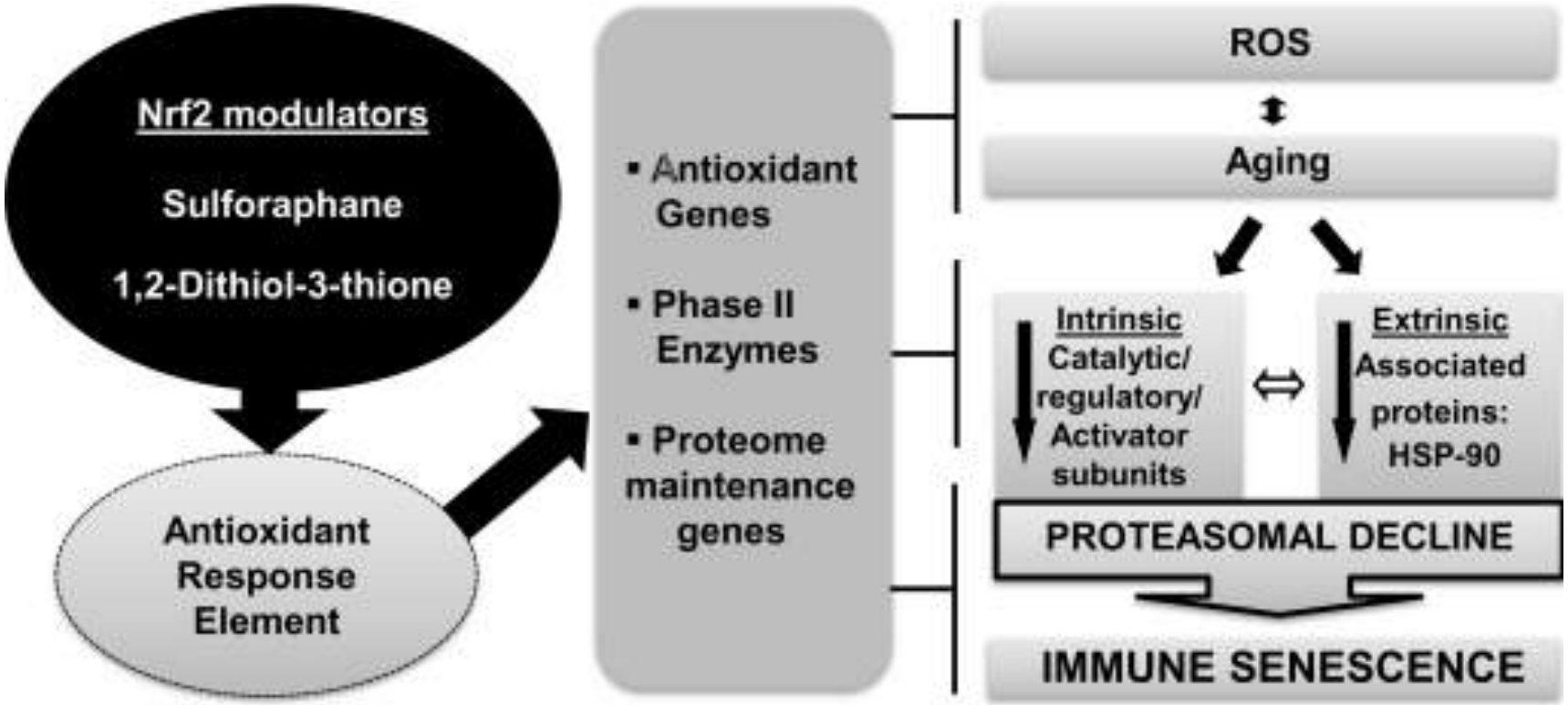
- In addition to regulating antiviral signalling, mounting evidence suggests that mitochondria facilitate antibacterial immunity by generating reactive oxygen species and contribute to innate immune activation following cellular damage and stress. Therefore, in addition to their well-appreciated roles in cellular metabolism and programmed cell death, mitochondria appear to function as centrally positioned hubs in the innate immune system.



Pleomorphic effects of NRF2

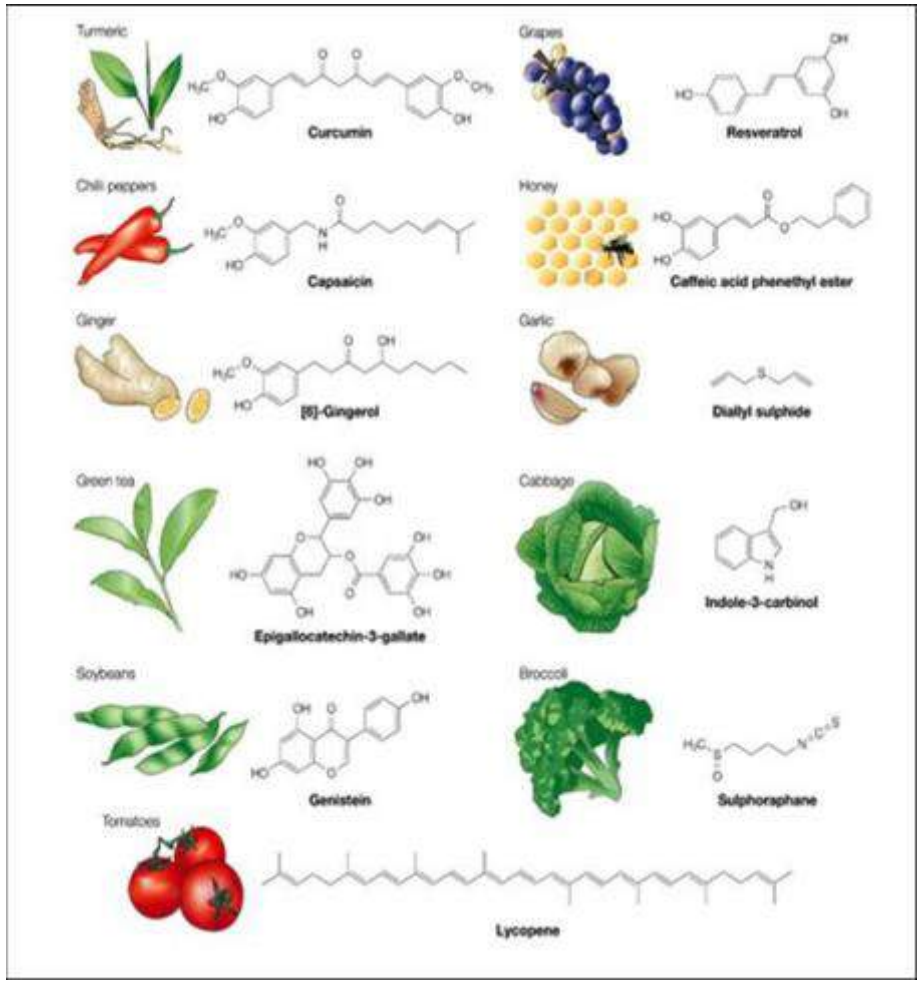


Nrf2 modulators and their mode of action in overriding immune dysfunction during aging.



Antioxid Redox Signal. 2011 April 15; 14(8): 1551–1585.

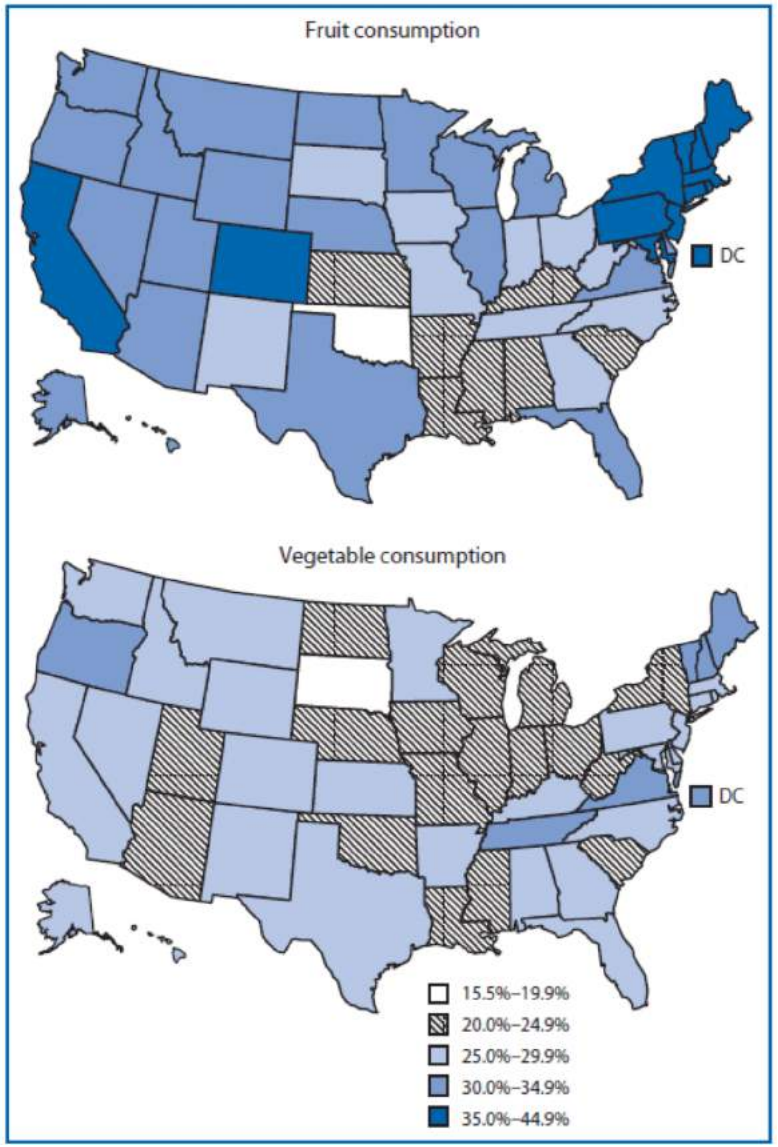
Powerful genomic signals*



Most common Nrf-2 modulators

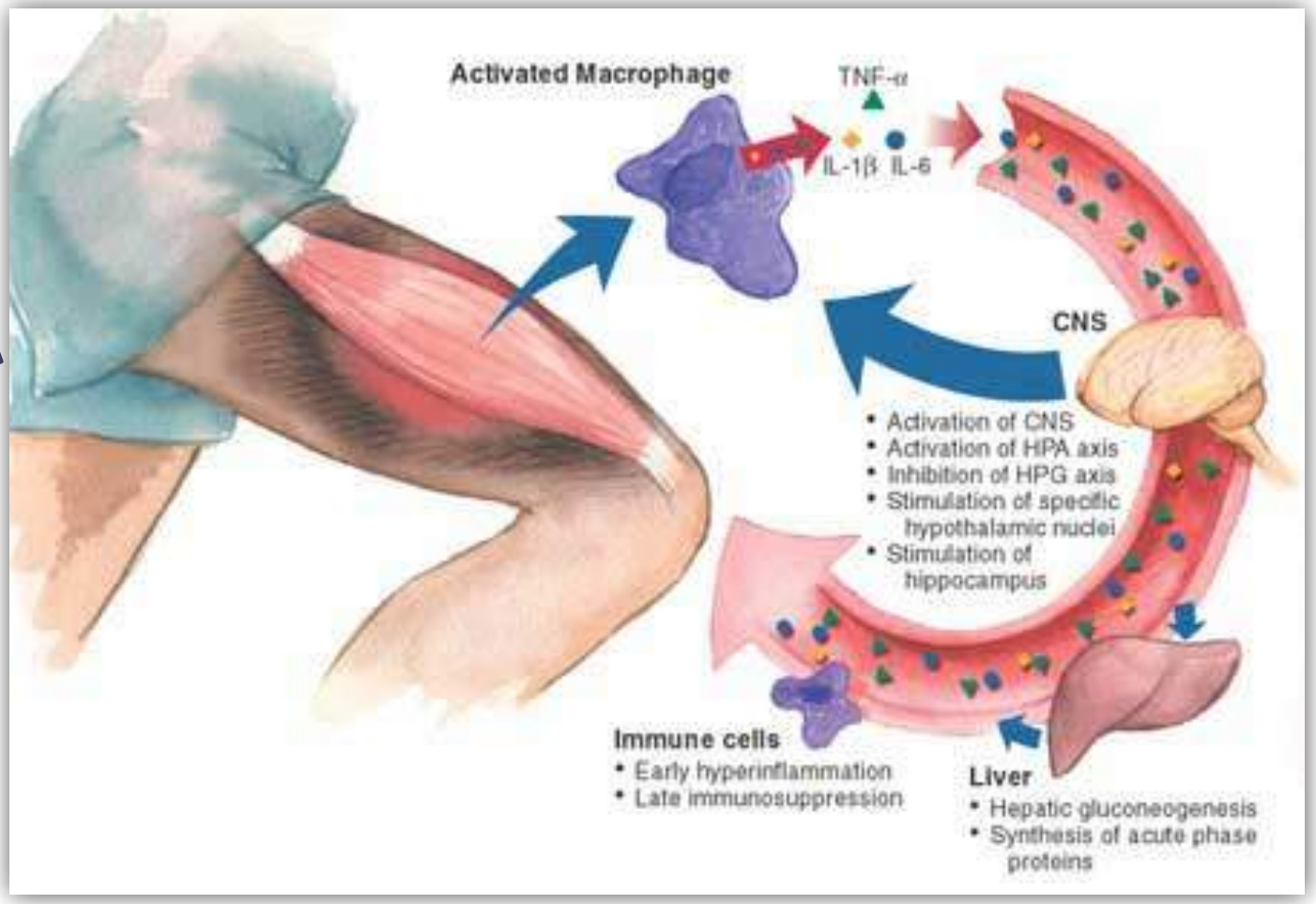
* Disclaimer: Must actually be eaten

We are simply not eating F&Vs



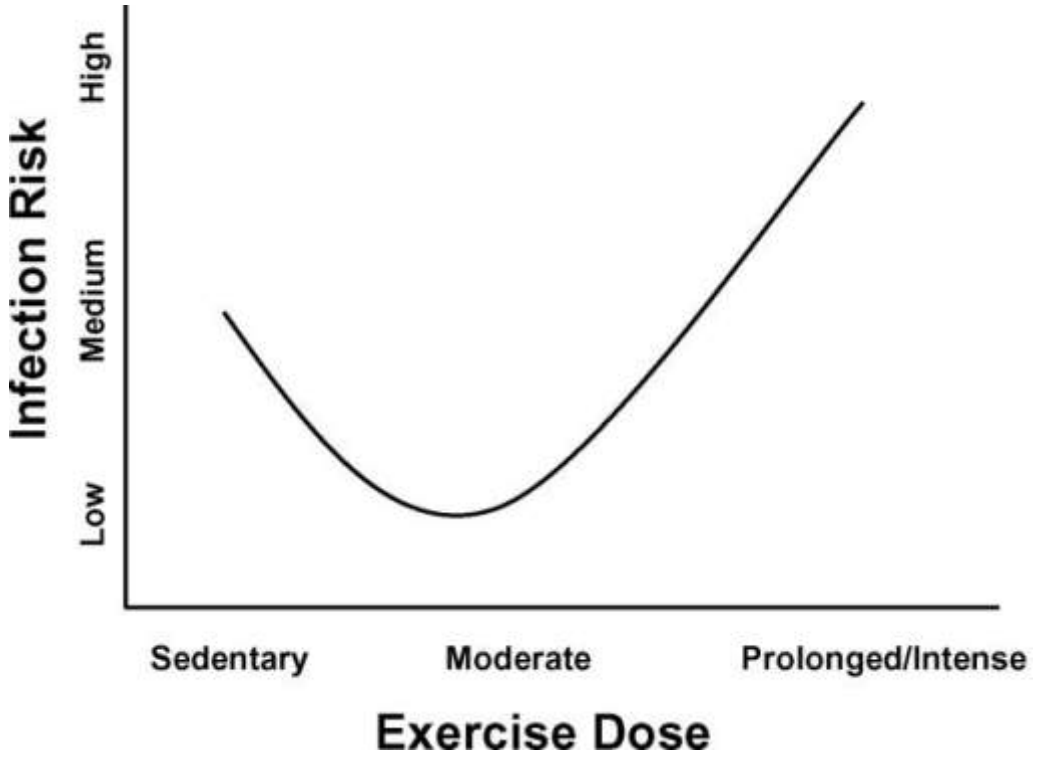
- CDC data showing the percent of adults (>18 yo) consuming either 2 or more fruit servings, or 3 or more vegetable serving per day.
- Low signal to calorie ratio- poor genomic signaling to protect against chronic disease

PA and Immune Function



Physical Activity/Exercise

- A typical J-shape (U-shape?) curve is often used to describe the exercise-immune system relationship.



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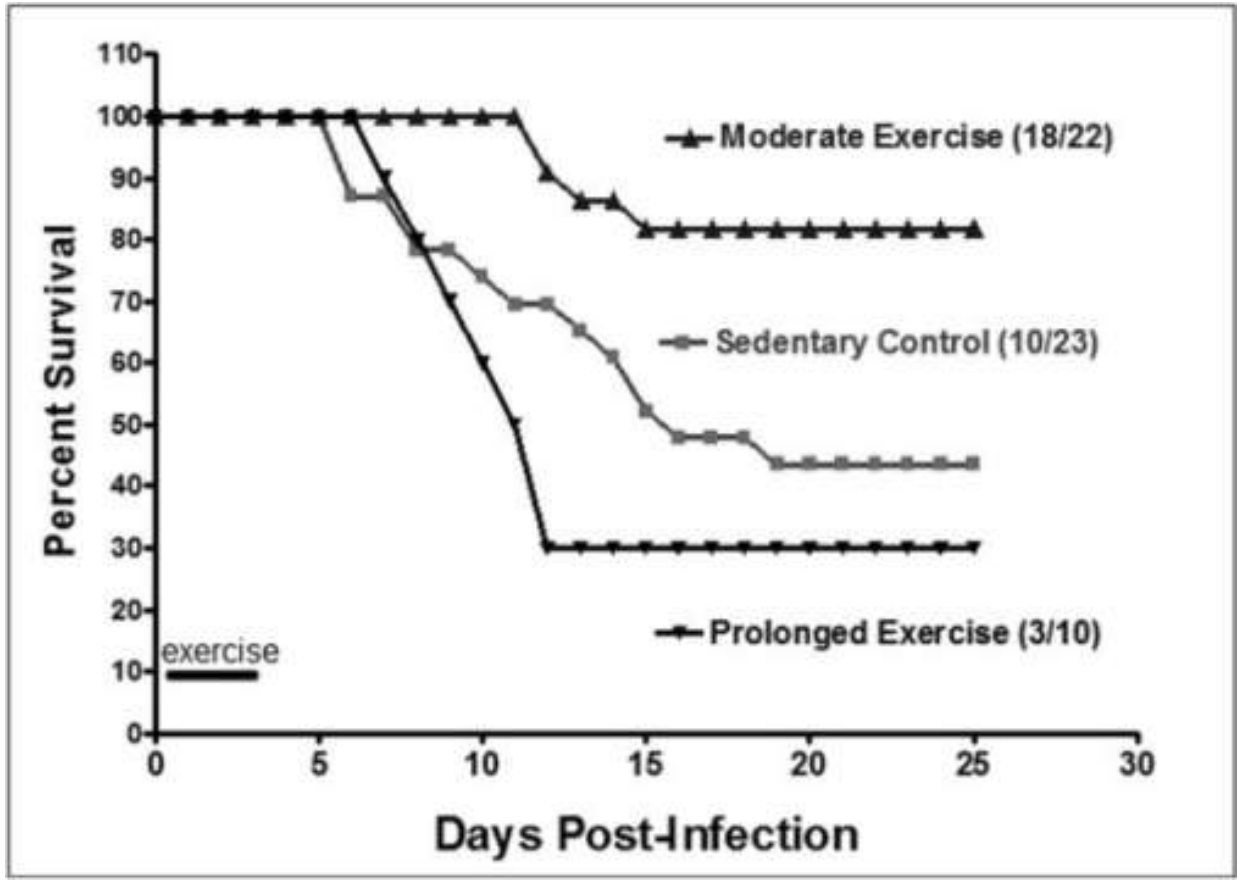
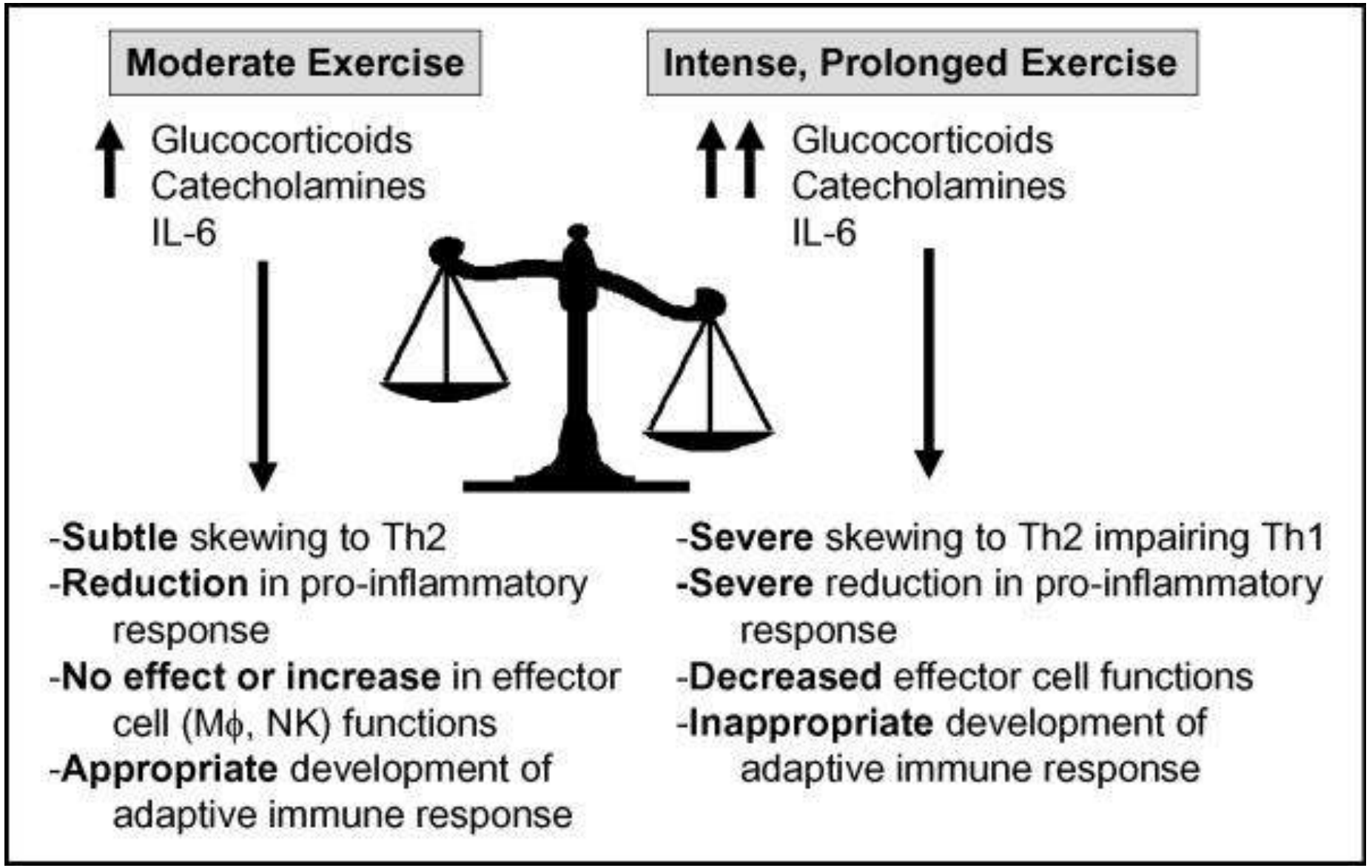
Intensity matters!



- Influence of exercise on mortality due to influenza (H1N1 Puerto Rico A/8/34) in male 20–24 wk old Balb/c mice. Mean survival was 14 ± 1, 17 ± 2, and 16 ± 3 days for control, moderate and prolonged exercise, respectively. There was a statistically significant difference between control and moderate exercise (log rank = 7.3; p = 0.007), but not between control and prolonged exercise (log rank = 1.1; p = 0.29). (Reprinted from Lowder T, Padgett DA, Woods JA. Moderate exercise protects mice from death due to influenza virus. *Brain Behav Immun*. 2005;19(5):377–80.



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Review

Exercise as a therapeutic tool to counteract inflammation and clinical symptoms in autoimmune rheumatic diseases

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ABSTRACT

Chronic inflammation is a common feature shared by several autoimmune rheumatic d
matoid arthritis, systemic lupus erythematosus, idiopathic inflammatory myopathies, a
ankylosing spondylitis. Therefore, blocking or reducing inflammation is one of the majo
in these diseases. In this context, exercise training has emerged as a potential ther
teracting systemic inflammation, thereby leading to better clinical outcomes. The aim
i) to provide a summary of the clinical effects of exercise training in selected autoim
eases; and ii) to discuss the potential anti-inflammatory role of exercise training in au
diseases, stressing the gaps in literature and the clinical and scientific perspectives in t

Contents

1. Introduction

Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), idiopathic inflammatory myopathies (IIM), systemic sclerosis (SSc), and ankylosing spondylitis (AS) are autoimmune rheumatic diseases that share common clinical features, including periodic pain, chronic fatigue, depression, reduced physical fitness, and, as a consequence, hypoactivity and poor health-related quality of li
ly, the main clinical signs and symptoms of these
strongly related to a sustained inflammatory cond

Glucocorticoids and immunosuppressive dru
stone of the treatment for autoimmune rheum
these medications may not be fully effective in h
gression of disabilities [4]. Moreover, the long-
drugs has been associated with several deleterio
bone and muscle mass wasting and cardiovascula

In this context, exercise training has as a n
strategy aimed at improving a variety of clinical sy
with autoimmune rheumatic diseases [1–5,12–14
line with a growing body of literature revealing th

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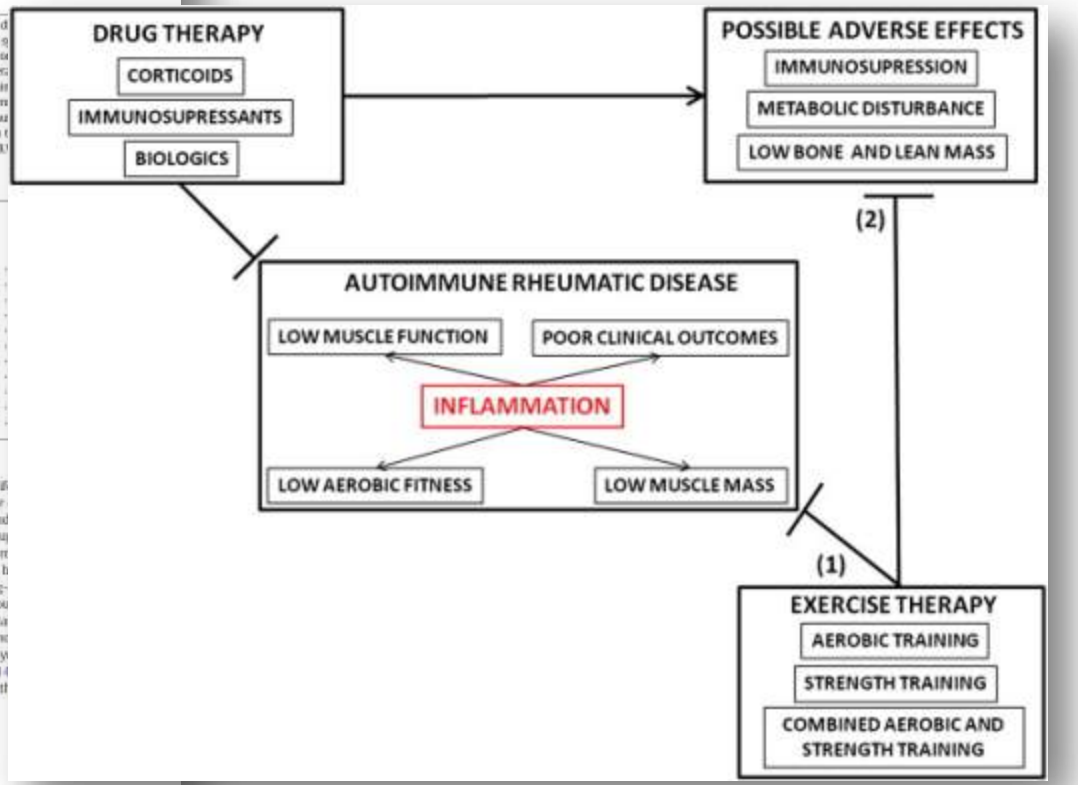
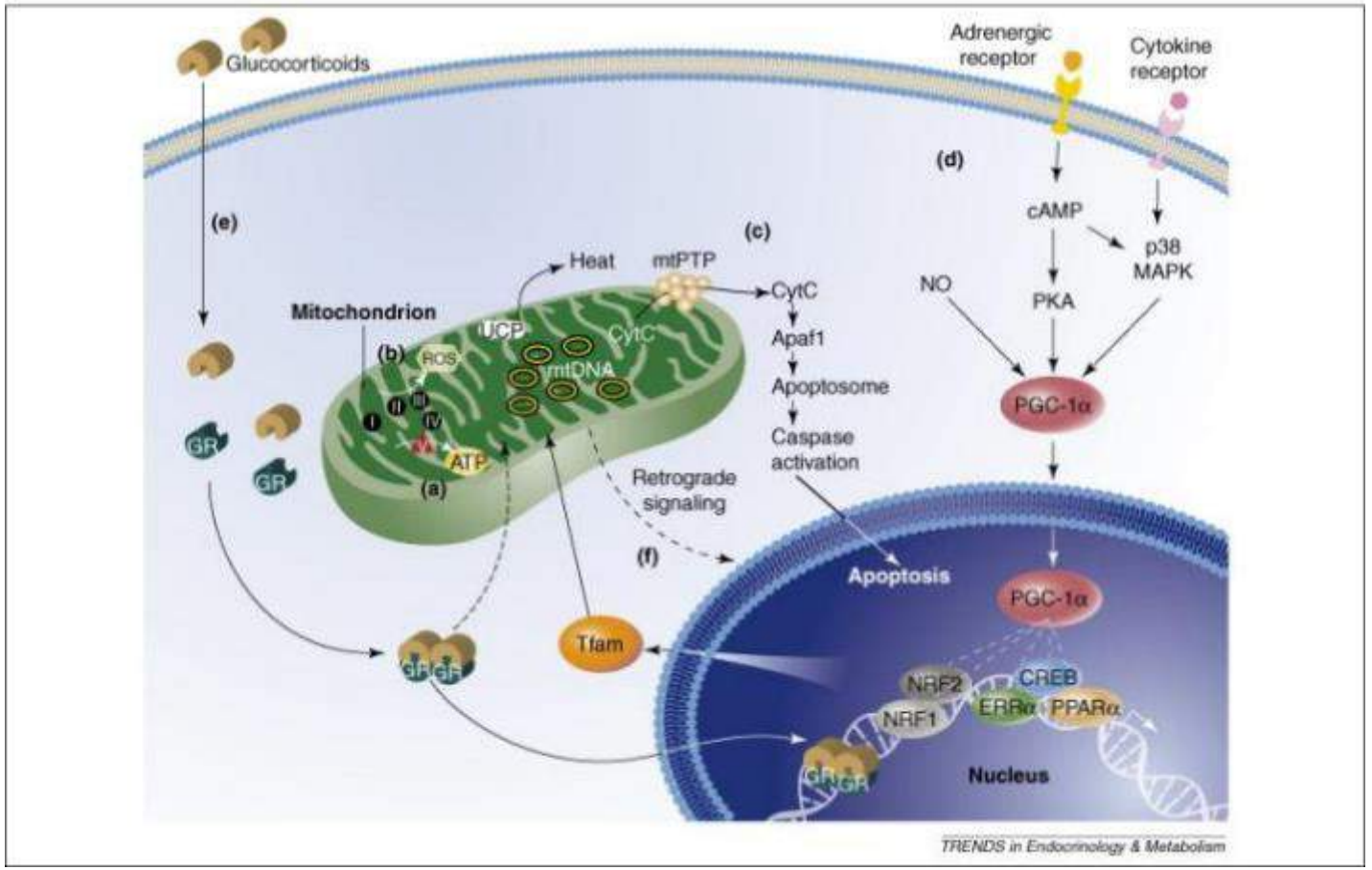
doi:10.1016/j.autrev.2012.06.007

- Excellent review of the limited data with proposed mechanism for how moderate exercise limits inflammatory process.

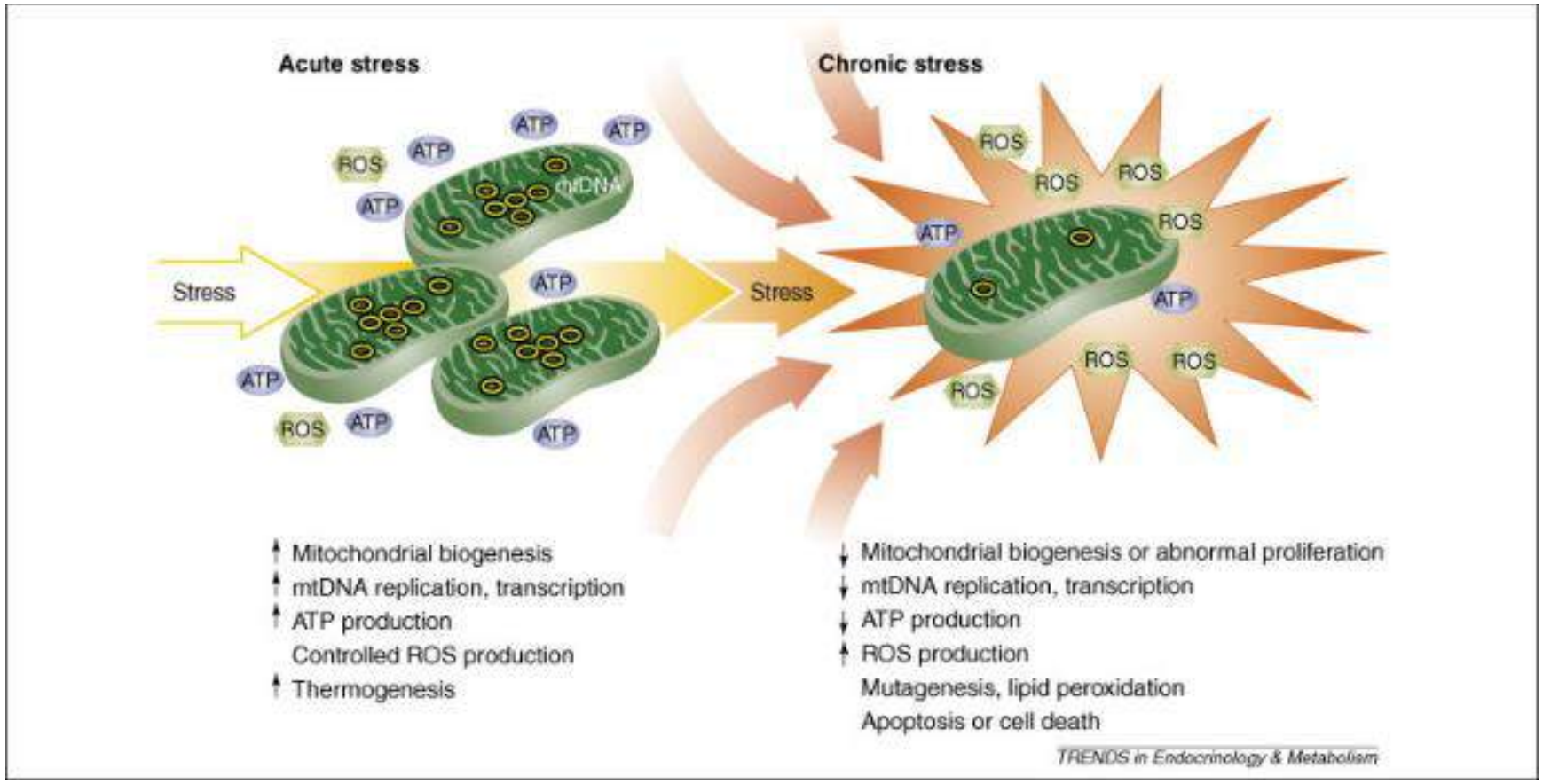


Stress and the Mitochondria



Trends in Endocrinology & Metabolism
Volume 18, Issue 5, July 2007, Pages 190-198

Biphasic response to Stress



Trends in Endocrinology & Metabolism Volume 18, Issue 5, July 2007, Pages 190-198

Building Immune Strength

- Maintaining and Protecting Barrier Function
- Creating a Commensal-friendly environment
- Avoiding antigens and allergens in adulthood
- Building Metabolic Reserve
  - Antioxidant Reserve
  - Micronutrient Reserve
  - Mitochondrial Energy
  - Detoxification Capacity
  - HPA axis resilience
- Reducing Chronic Inflammatory Triggers/Mediators
- Use of Appropriate Immuno-modulators to create balance and immune system strength

Keys to Supporting Immune Function

- Maintaining and protecting barrier functions
- Creating a commensal-friendly environment
- Maintaining appropriate hygiene practices
- Avoiding antigens and allergens in adulthood
- Building micronutrient and antioxidant reserve
- Maintaining and building cellular (mitochondrial) energy
- Maintaining adequate detoxification capacity
- Diminishing stress and cortisol-induced immune suppression
- Reducing chronic inflammatory triggers/mediators
- Using appropriate immune modulators to create balance and strengthen immune function

Thank You

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- Thomas Guilliams Ph.D.
- www.pointinstitute.org