6th ANNUAL Functional Pharmacy Symposium

FUNCTIONAL MEDICINE Continuing Education

Fortifying the Immune System

The gut-immune interface

Lara Zakaria PharmD MS CNs CDN IFMCP

Disclosures

- Nothing to disclose

Objectives

- Review the power of the gut-immune interface
- Discuss best practices for fortifying/supporting the immune system by strengthening the gut-immune interface

What exactly is a healthy immune system

- Innate and adaptive
- Patterns of hypofunction
- Patterns of hyperreactivity
- Secretory IgA and barrier function

How strong is your defensive line?

Defense & Offense

Defense

- Physical barriers
- Chemical barriers
- Enzymatic barriers
- VALT/GALT/MALT/BALT/NALT

A “leaky barrier” is a significant gap in the defensive line

Offense

- Innate
- Adaptive

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Innate & Adaptive Immunity

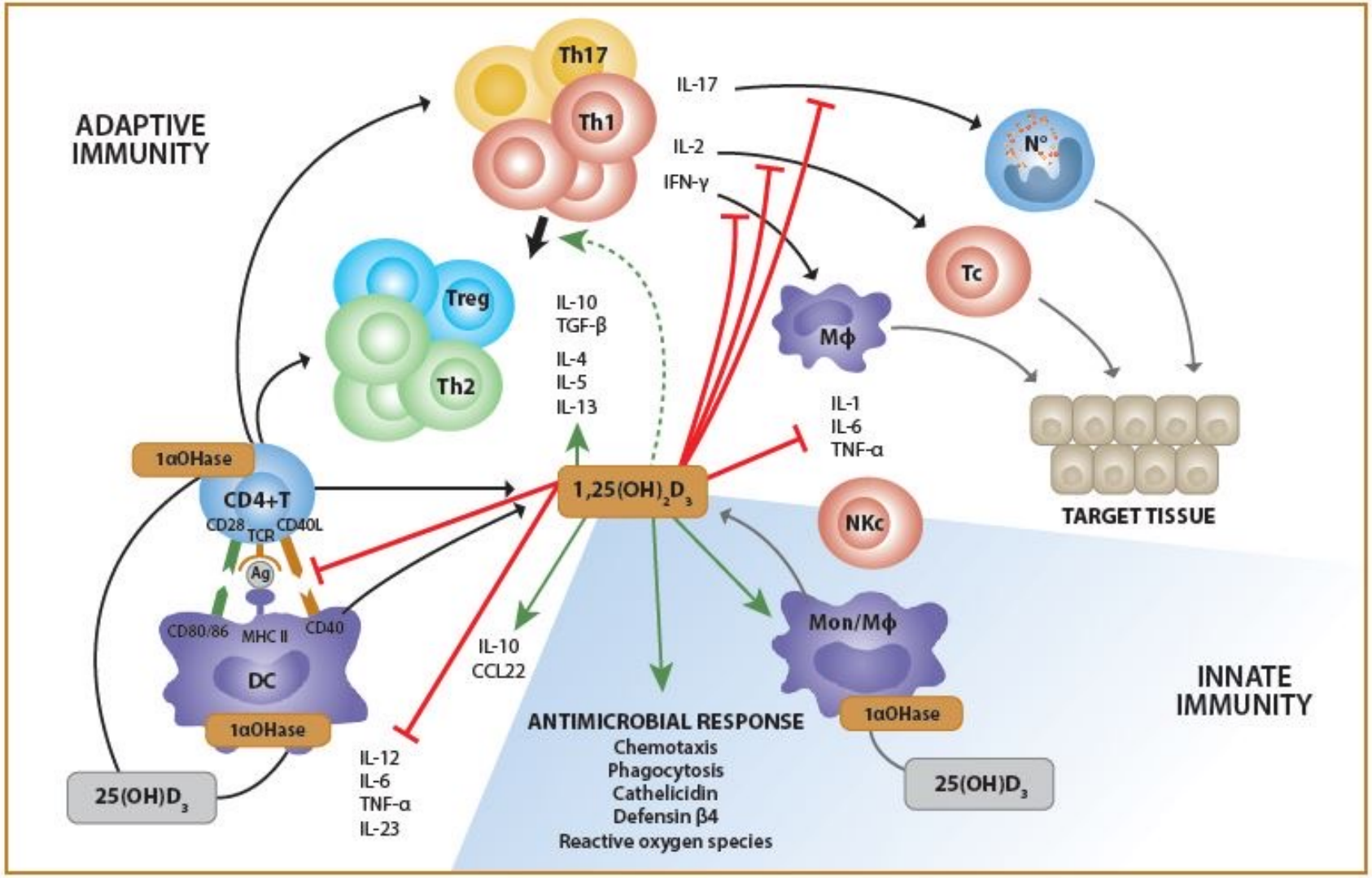


Figure 17: The Immunomodulatory Effects of Vitamin D3. 1,25(OH)2D3 targets different components of the innate and adaptive immune system. 1,25(OH)2D3 stimulates innate immune responses by enhancing the chemotactic and phagocytotic responses of macrophages as well as the production of antimicrobial proteins such as cathelicidin. On the other hand, 1,25(OH)2D3 also modulates adaptive immunity. At the level of the APC (like the DC), 1,25(OH)2D3 inhibits the surface expression of MHC-II-complexed antigen and of co-stimulatory molecules, in addition to production of the cytokines IL-12 and IL-23, shifting T cells from a Th1 and Th17 phenotype towards a Th2 phenotype. In addition, 1,25(OH)2D3 directly affects T cell responses, by inhibiting the production of Th1 cytokines (IL-2 and IFN-γ) and Th17 cytokines (IL-17 and IL-21), and by stimulating Th2 cytokine production (IL-4). 1,25(OH)2D3 favors Treg cell development via modulation of DCs and by directly targeting T cells. Finally, 1,25(OH)2D3 blocks plasma cell differentiation, IgG and IgM production and B cell proliferation. Adapted from *IBMS BoneKEy* (2011) 8, 178–186.

Supporting Immune Function: A Lifestyle and Nutrient Approach. Thomas G. Guilliams, Point Institute.

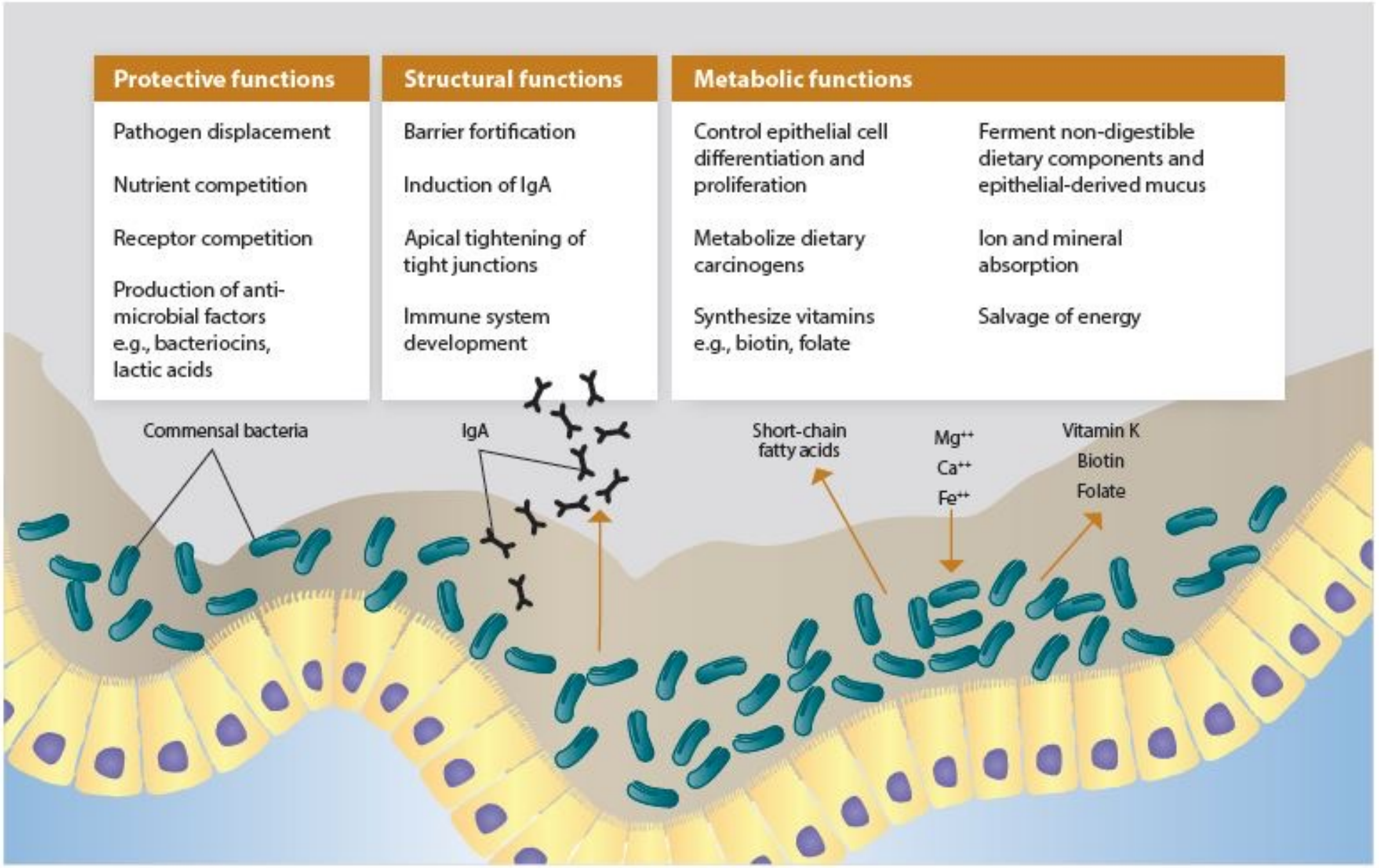
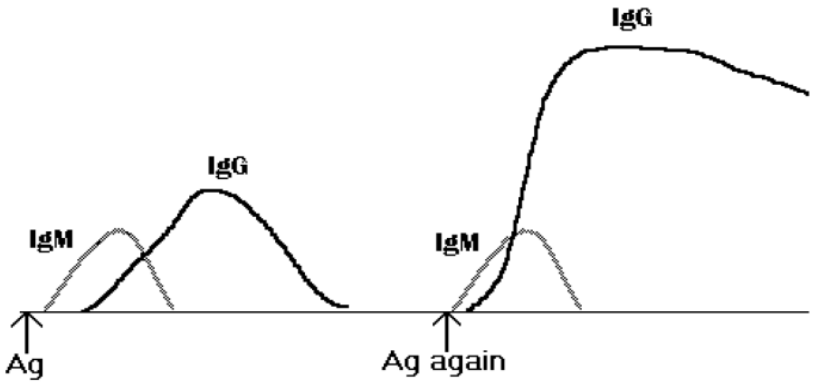


Figure 12: Multiple Benefits from Healthy Commensal Organisms.

Supporting Immune Function: A Lifestyle and Nutrient Approach. Thomas G. Guilliams, Point Institute.

Immunoglobulins



IgM	• Oldest antibody phylogenetically; 500 times more efficient than IgG at activating complement • First Ig to be produced in response to immune stimulation
IgA	• Made by plasma cells in lymphoid tissues near **mucous membrane** • **Secretory Component -** protective against invaders in the gut (first line of immunological defense)
IgG	• Most abundant in circulation • Plasma half-life of IgG is about **3 weeks** • **Opsonizing -** vital for clearance of most extracellular bacteria
IgE	• Promotes histamine-containing mast cells and basophils activation producing **Type I Immunopathology** • Protective for parasites

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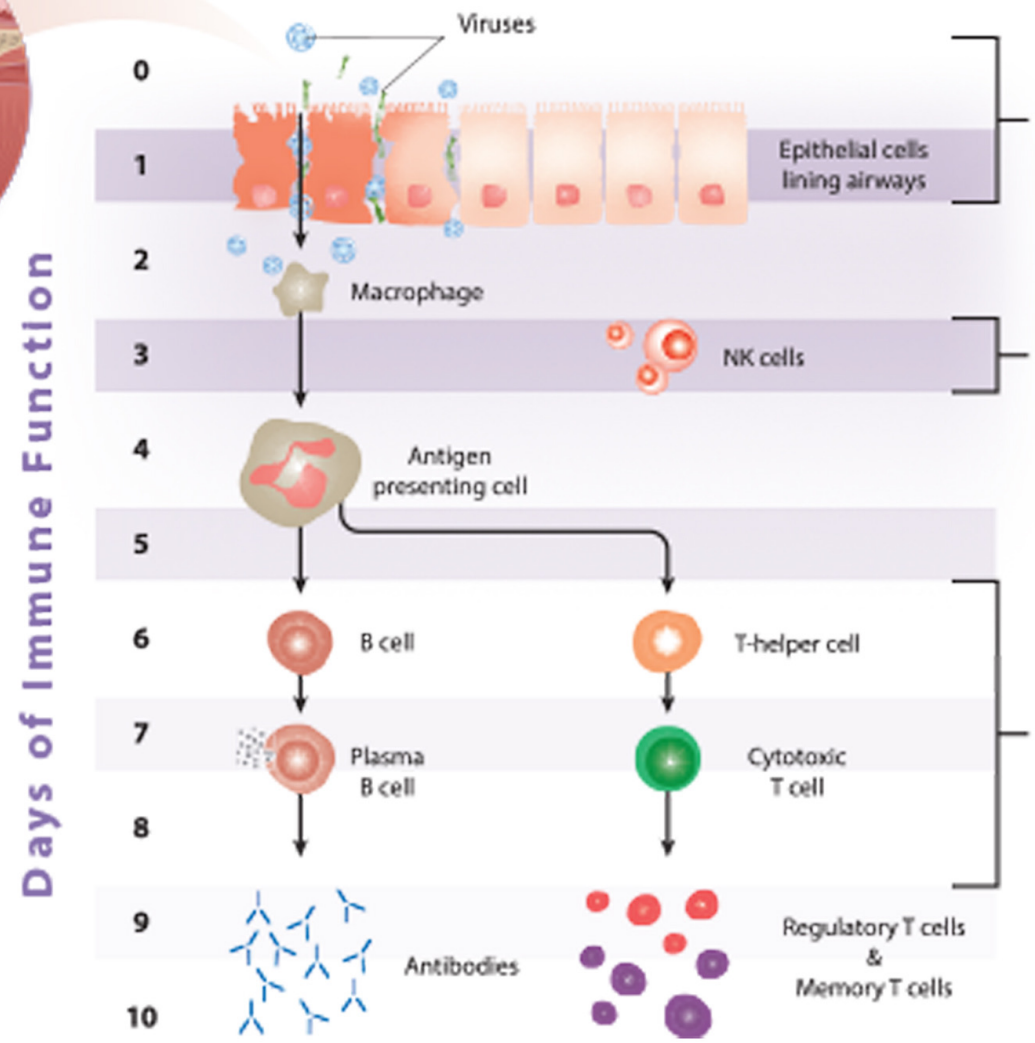
Immune Cascade



Epithelial Barrier Function

- NAC
- Quercetin
- Vitamin C
- Vitamin D
- Zinc

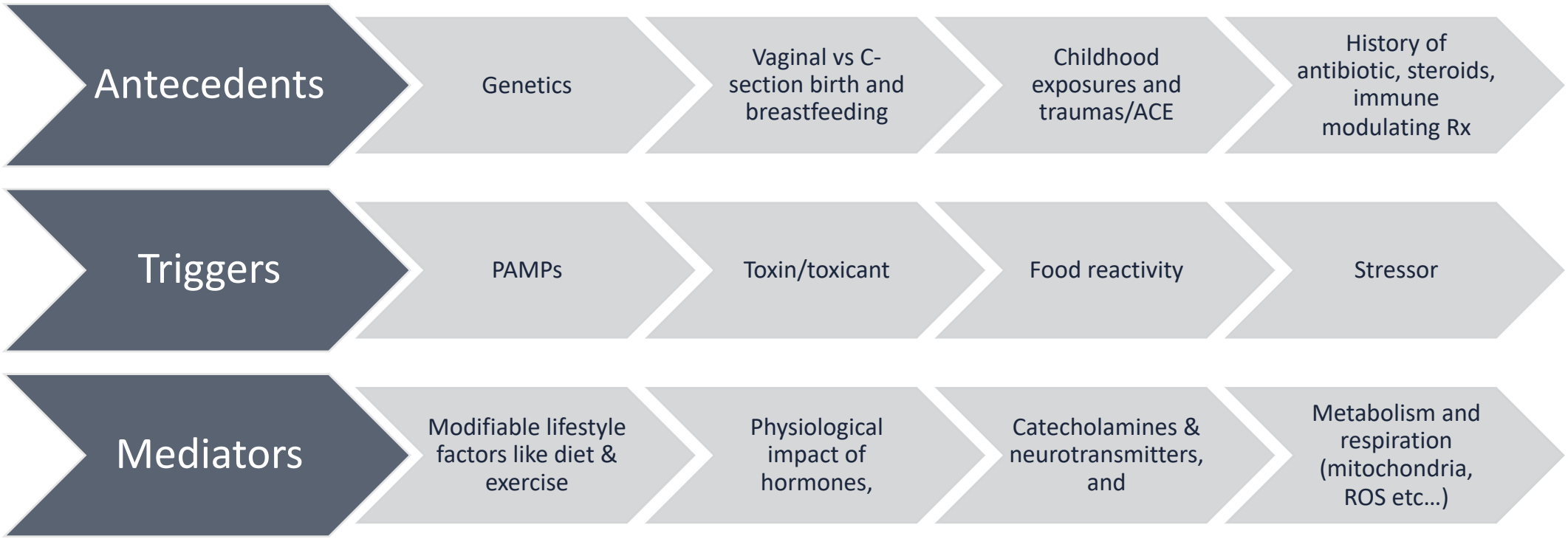
NK Cell Activity

- Quercetin
- Vitamin C
- Zinc

B-Cell and T-Cell Differentiation and Memory

- Quercetin
- Vitamin C
- Zinc

Functional Medicine: ATMs



PAMPs = pathogen associated molecular patterns

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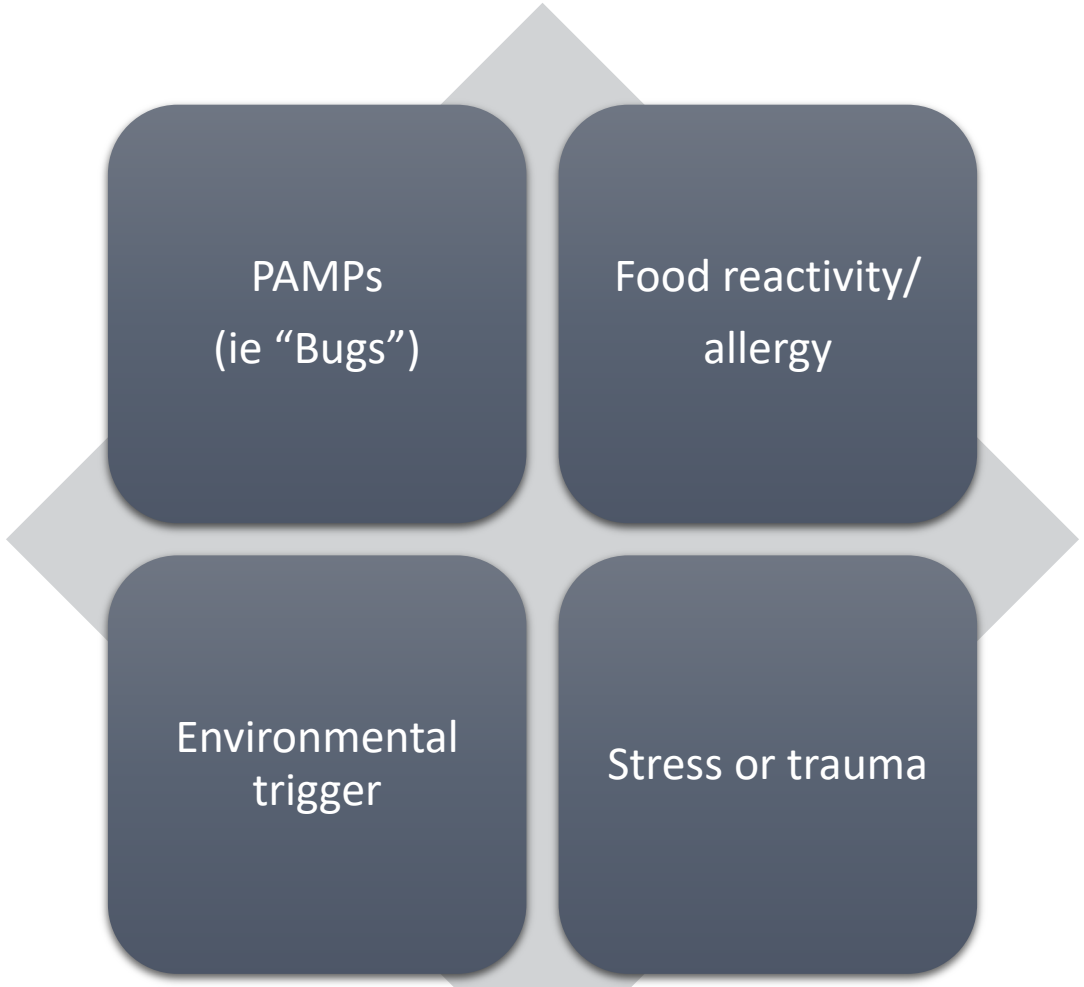
What's the tipping point?



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Immune Disease Drivers (ATMs)

- **GI Function**
  - Leaky gut
  - Dysbiosis
  - Malabsorption
  - Inflammation/food sensitivities
- **Diet**
  - Macronutrient imbalance
  - Micronutrient deficiencies
  - Phytonutrients deficiencies
- **Inflammation**
  - Insulin resistance/MetS
  - Hormonal dysregulation (estrogen dominance)
  - Injury/trauma
- **Stress**
  - Exercise
  - Stress management
  - Adrenal fatigue
- **Chronic toxin or allergen exposure**
  - Acute occupational
  - Chronic exposures (As, Hg, Pb, pesticides, air pollutants, etc)
  - Smoking, drug, and/or alcohol use
  - Food allergen
- **Chronic infection**
  - Viruses (EBV, CMV, etc…)
  - Tick-borne illness (Lyme, Babesia, Borellia etc..)
  - Fungal and mold

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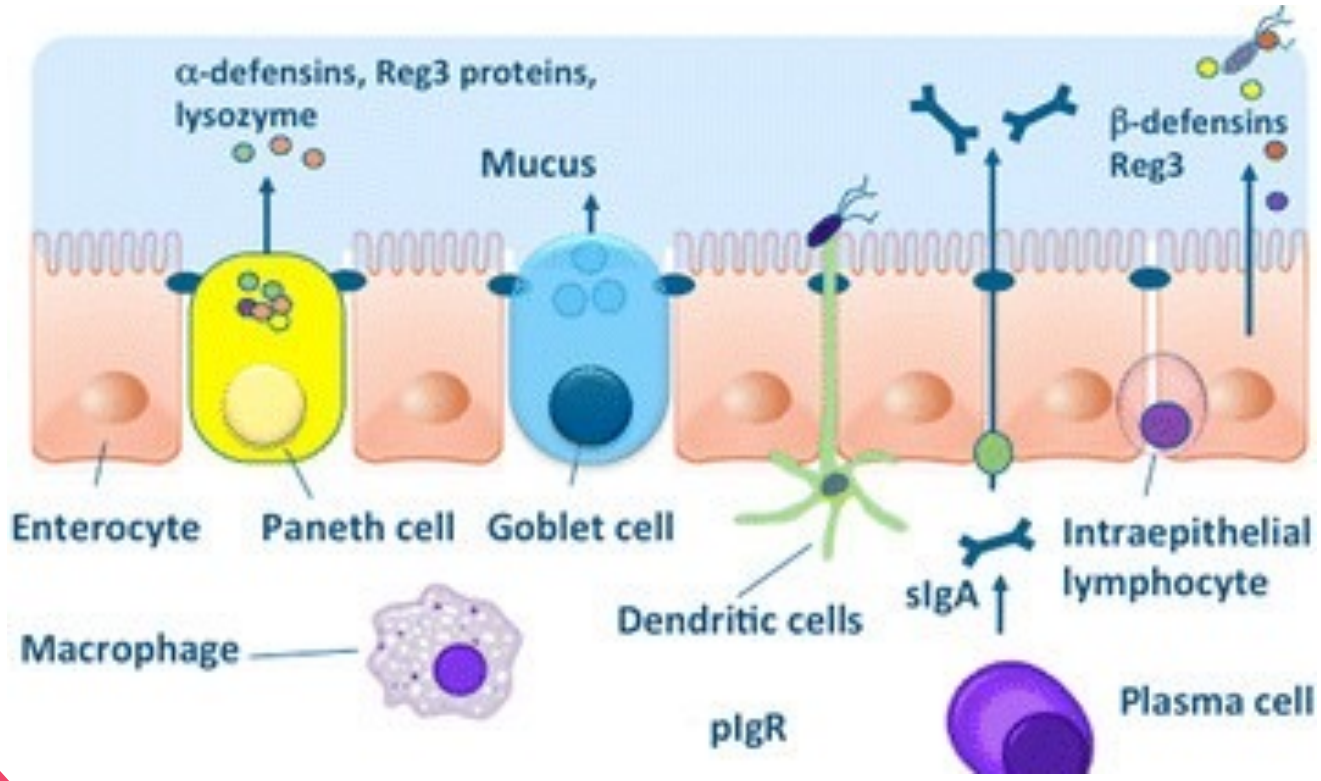
The gut-immune interface



- Significance of the connection between GI and immune
- Major site of host defense (mechanical, chemical, immunological)
- Comprises 7-80% of host immune cells reside in the GI

BMC Gastroenterol 2014

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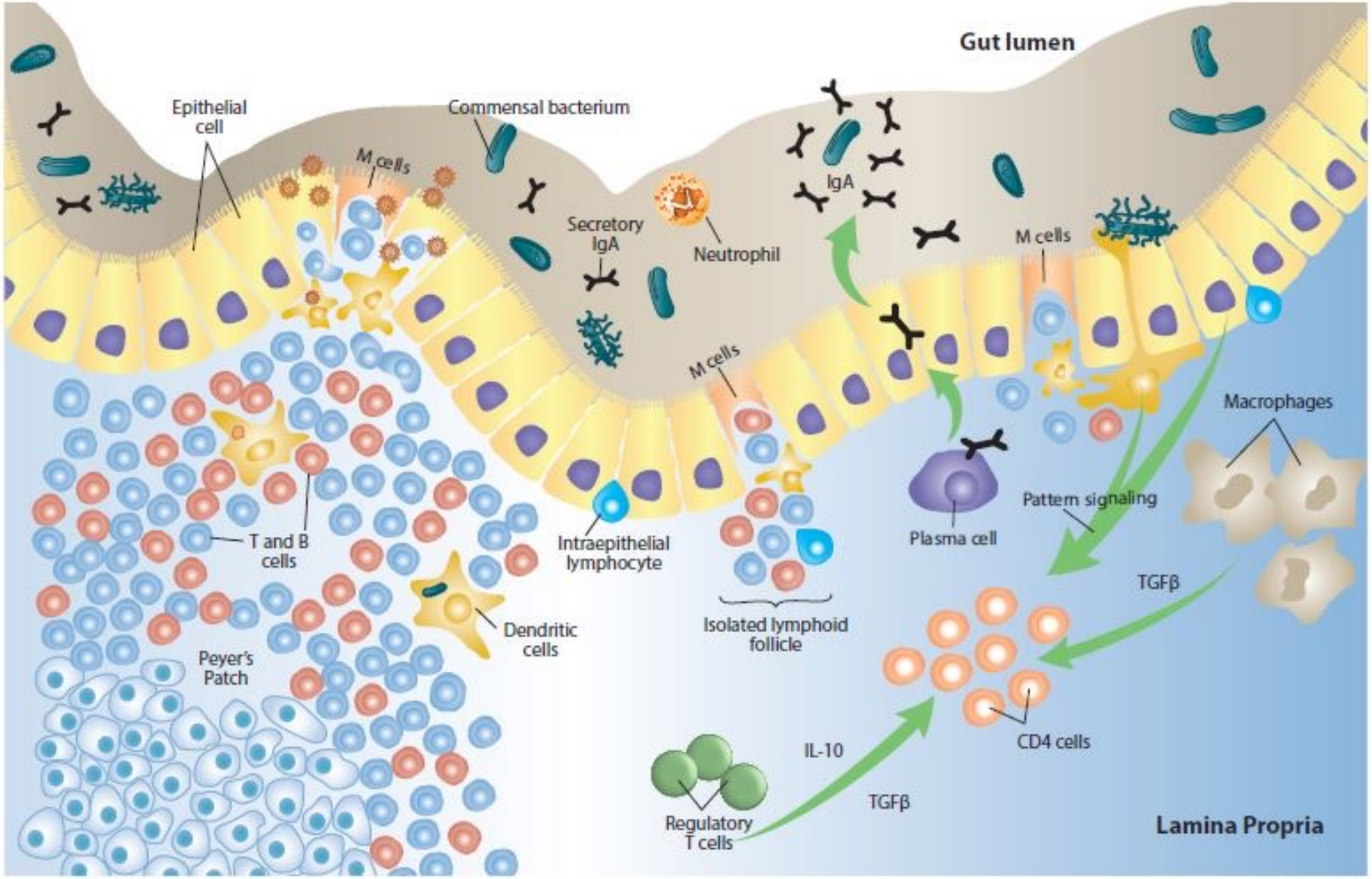

Figure 11: Basic Structures of the Gastrointestinal-Associated Lymphoid Tissue (GALT). See the text for detailed explanation.

Supporting Immune Function: A Lifestyle and Nutrient Approach. Thomas G. Guilliams, Point Institute.

A breach in the defensive line

- “Leaky gut” allows unprocessed antigens and organisms to pass between the epithelium
- Associated with autoimmune disease
- Permeability has been associated with endotoxemia and passage of pathogens into circulation

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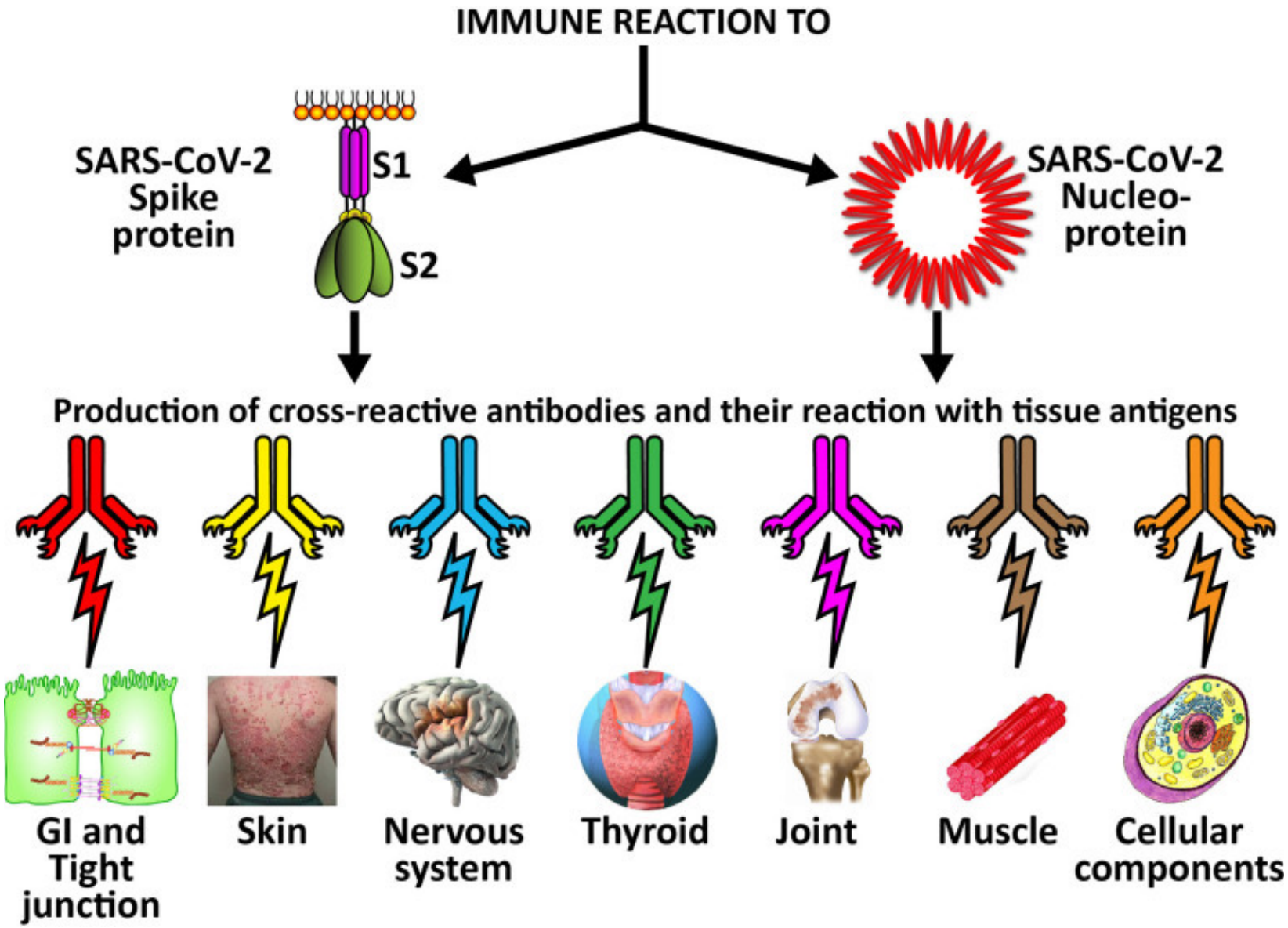

Front Immunol. 2021

frontiers in Immunology

ORIGINAL RESEARCH
published: 19 January 2021
doi: 10.3389/fimmu.2020.617089

Reaction of Human Monoclonal Antibodies to SARS-CoV-2 Proteins With Tissue Antigens: Implications for Autoimmune Diseases

Aristo Vojdani[1,2*], *Elroy Vojdani*[3] and *Datis Kharrazian*[2,4,5]

These cross-reactive interactions may lead to permeability of the lung barrier, gut-barrier, and the blood-brain barrier in susceptible individuals.

[…] Every single one of these identified risk factors [age, smoking, diabetes, cardiovascular, and respiratory diseases] is also associated with permeability of the immune barrier systems. **Permeability of the immune barriers may be the essential centerpiece risk factor that is associated with COVID-19 severity** […]

Permeability of these barriers may increase the spread of the virus throughout the body and potentially promote a systemic cytokine storm. Additionally, permeability of the immune barriers is also an independent mechanism that may promote immune dysregulation.

Front Immunol. 2021

Review

Potential beneficial role of probiotics on the outcome of COVID-19 patients: An evolving perspective

Luigi Santacroce [a, b, 1], Francesco Inchingolo [c, 1], Skender Topi [b], Raffaele Del Prete [a], Michele Di Cosola [d], Ioannis Alexandros Charitos [e, *], Monica Montagnani [f]

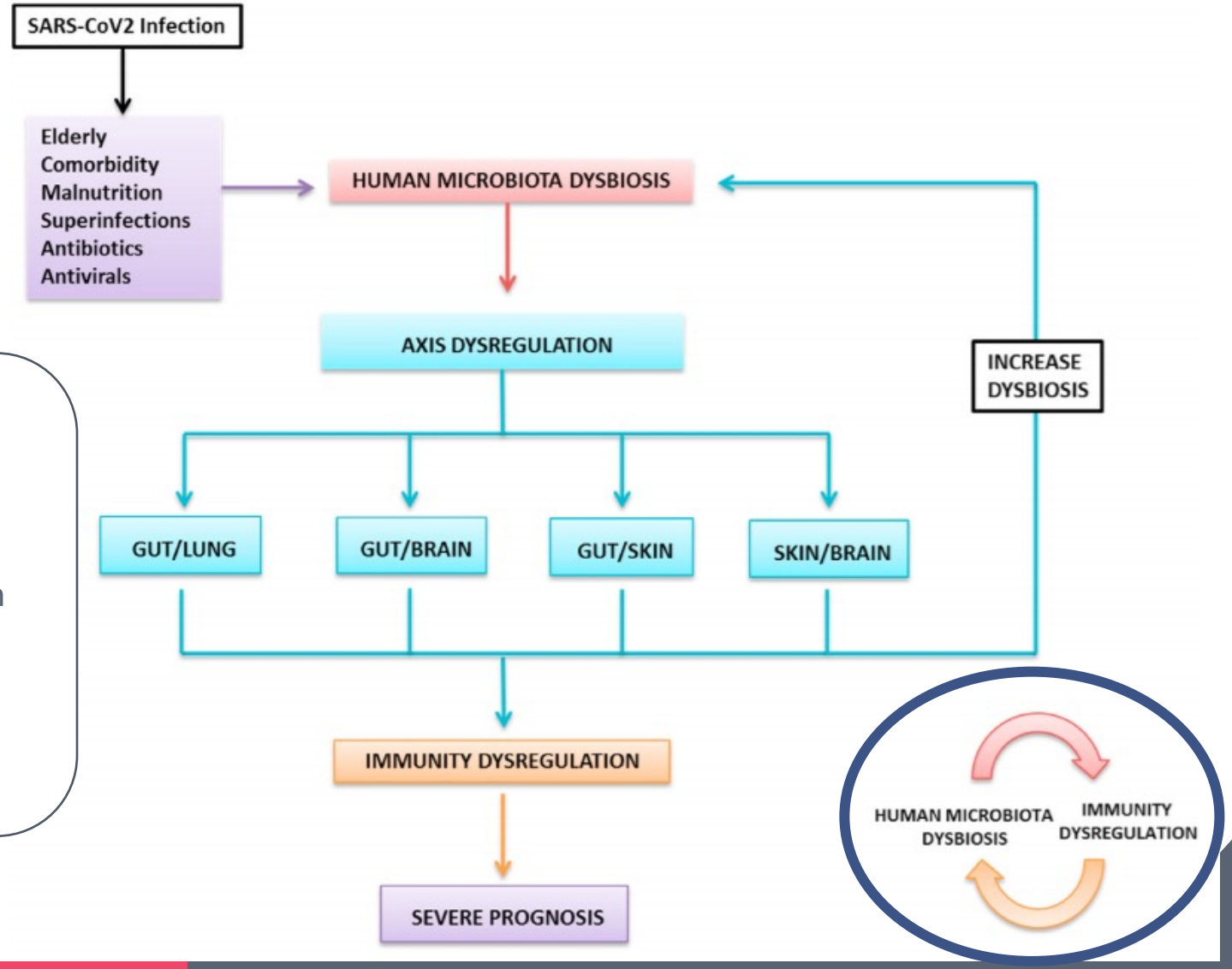

Fig 2 […] it is important to consider the patient's age, comorbidities, malnutrition, superinfections, antibiotics and antivirals which could result in further microbiota dysbiosis. This will lead to direct dysregulation of the human microbiota and of the intestinal, pulmonary, brain and skin axes. **Consequently, immune dysregulation will increase leading to continuous increased microbiota dysbiosis and immune dysregulation**. All this can contribute to a severe prognosis for the patients.

Diabetes Metab Syndr. 2021

The GI is a major site of immunity

- Gastric pH and digestive enzymes
- Barrier integrity (“the fence”)
- Microbiome
- Metabolome
- Glycome
- “Building the immune system” 70-80%
- sIgA regulation of the mucosal barrier and antigen response

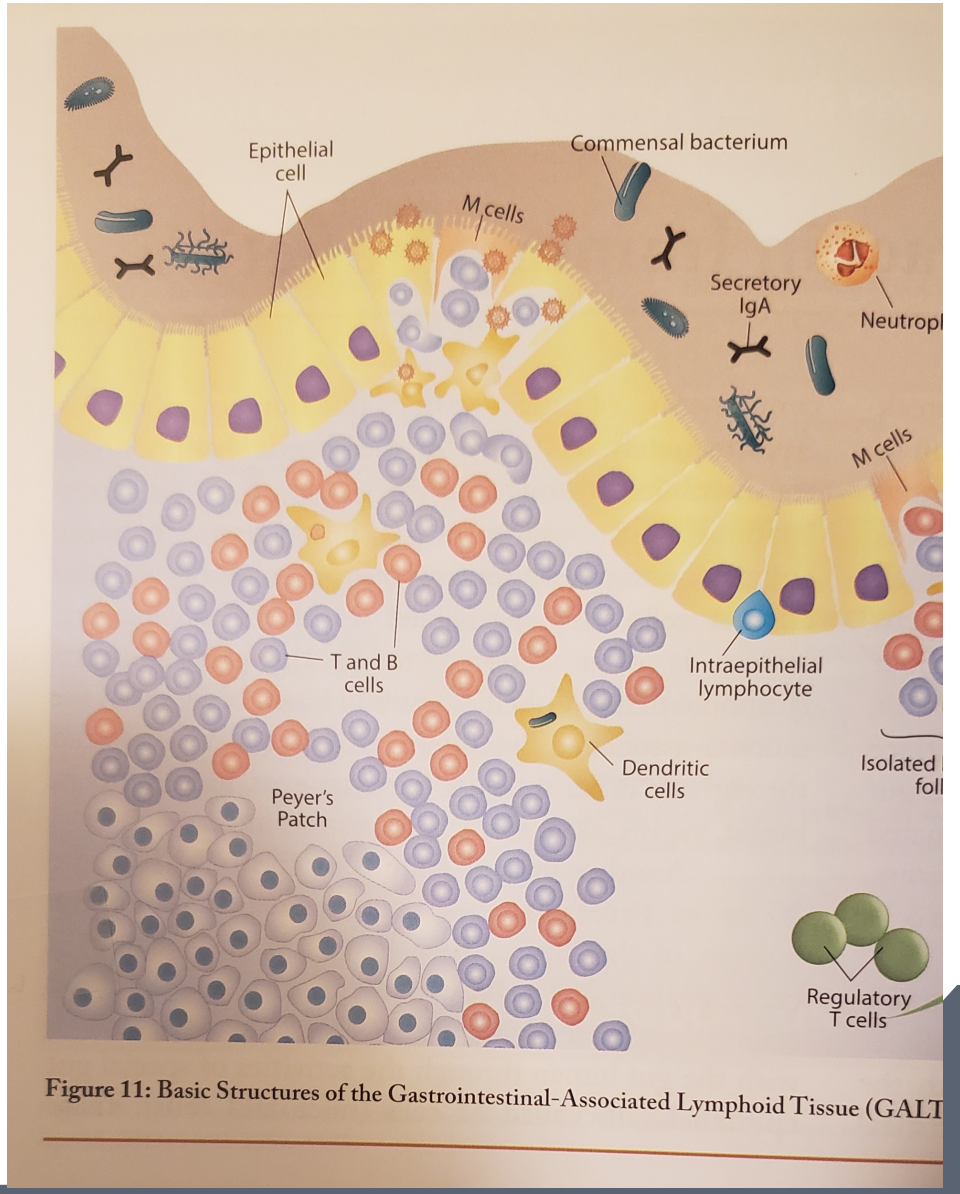

Figure 11: Basic Structures of the Gastrointestinal-Associated Lymphoid Tissue (GALT

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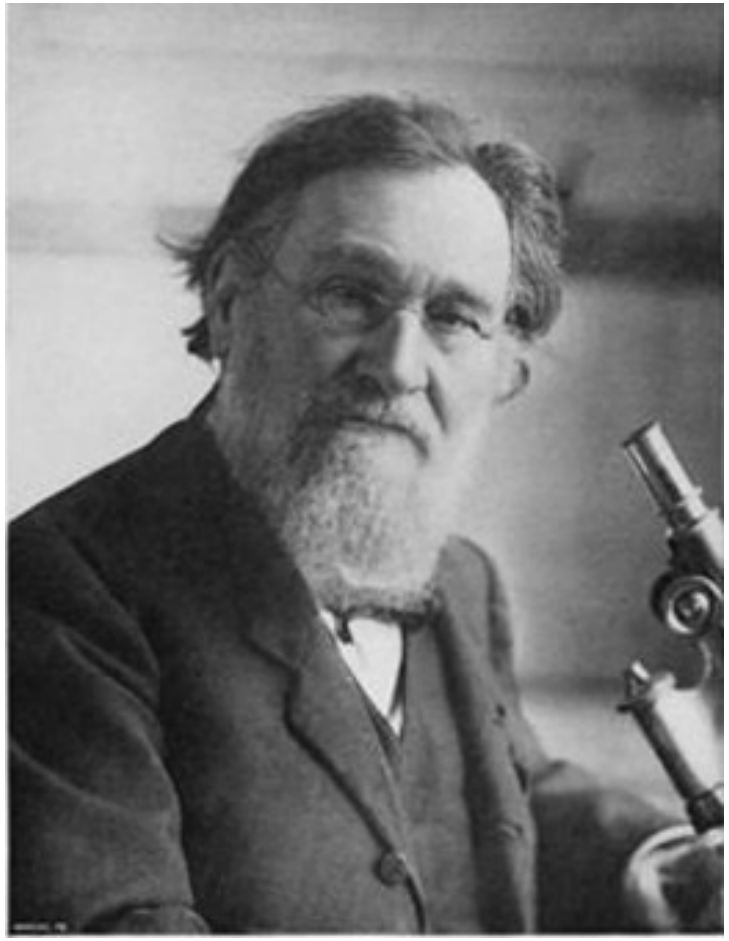
“Death Begins in The Colon”

Ellie Metchnikoff, Russian biologist

The rationale for the use of live microbes in the prevention and treatment of infections in 1907.

He hypothesized that replacing or diminishing the number of bacteria in the gut, you could normalize bowel health and prolong life.



Treatment Considerations: 4 vs 5R

Remove	• Food sensitivities, alcohol, aspirin, NSAIDS,PPIs • Antimicrobials for dysbiosis, infection, and/or parasites.
Replace	• Digestive support • May include digestive enzymes, or agents that promote improved motility and regular bowel movements.
Reinoculate	• Provide an environment where good bacteria can crowd out “bad guys” • Pre- and probiotics foods and supplements
Repair	• Support barrier repair through nutritional support • Anti-inflammatory, “seal and heal” nutrients and botanicals
Rebalance	• Lifestyle factors that influence bacterial balance, mucosal integrity, and immune response such as stress, sleep, exercise and relationships and assure ongoing gut health.

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Remove

1

Remove dietary triggers

- Food sensitivities and allergens, inflammatory foods, or triggers of dysbiosis
- Gluten, dairy, eggs, soy, corn, grains, shellfish, cross reactive foods, processed foods etc…

2

Decrease/eliminate Toxic exposure

- Water filtration, cookware, plastics, pesticides, heavy metals

3

Eliminate pathogens

- Antimicrobials (initiate medications or herbals)
- Probiotics/prebiotics *(?)*

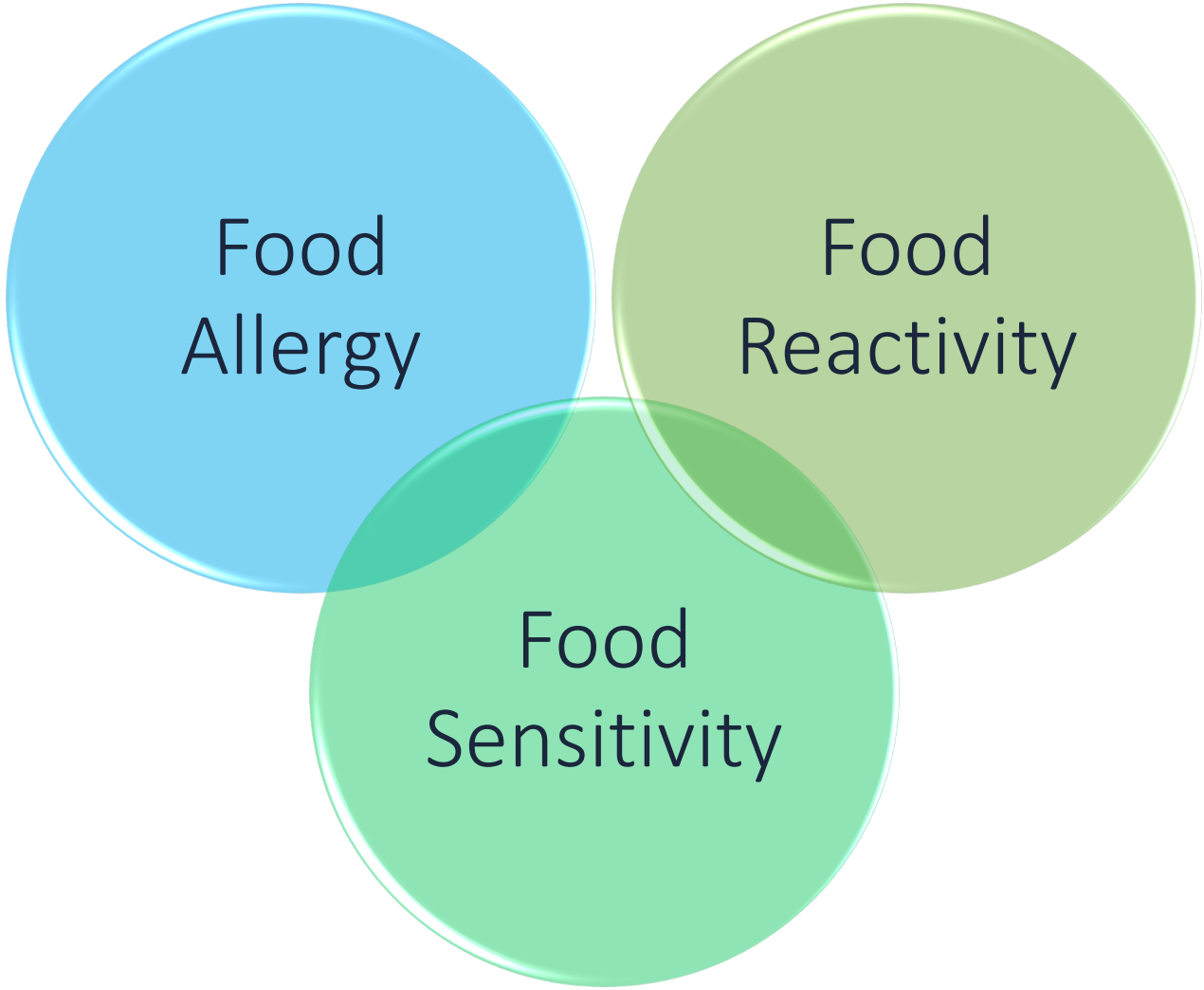
4

Remove stress

- Stress negative impact on digestion and absorption
- Address poor eating habits

Guilliams, TG. *Functional Strategies for the Management of Gastrointestinal Disorders*. 2016. The Roadmap Series. Point Institute.

Getting our terms clear



Remove: Antimicrobial Herbs

Berberine	• Evidence against all microbes
Wormwood & Black walnut	• Anti-parasitic
Grapefruit & Bearberry	• Anti-bacterial, anti-fungal
Caprylic acid	• Easily penetrates fatty cell membranes altering pathogen membrane fluidity
Oil of Oregano	• Anti-fungal
Allicin	• Anti-fungal
Olive Leaf Extract	• Antimicrobial, antiviral
Colloidal Silver	• Antimicrobial, antiviral

Guilliams, TG. *Functional Strategies for the Management of Gastrointestinal Disorders*. 2016. The Roadmap Series. Point Institute.

Replace

1

Assess Nutrient Status

- Maldigestion and Malabsorption

2

Replace digestive enzymes and HCL if necessary

- Treat underlying issue
- Support digestion
- Betaine HCL, pepsin, digestive enzymes, bitters, bile salts

3

Address Motility

- Constipation, diarrhea
- Bulk laxatives, stool softeners, motility agents (5-HTP, B6, Ginger), and stimulants

Guilliams, TG. *Functional Strategies for the Management of Gastrointestinal Disorders*. 2016. The Roadmap Series. Point Institute.

Digestion

Additional Tests			
	Result		Range
Secretory IgA	453	Low	510 - 2010 ug/g
Anti-gliadin IgA	209	High	0 - 100 U/L
Elastase-1	139	Low	>200 ug/g
Calprotectin	5		<50 ug/g
b-Glucuronidase	1892	High	<1123 U/mL
Steatocrit	33	Very High	<15 %
Fecal Occult Blood	Negative		Negative

“Reinoculate”

1

Prebiotics

- Mastic gum
- Guar Gum
- Rice Bran
- Arabinogalactan
- Pectin

2

Probiotics

- Target therapy/single organism
- Broad spectrum
- Spore-based
- *Saccharomyces boulaurdii*

3

Fiber-dense foods (30-45g +/day)

- Soluble
- Insoluble
- Resistant starch
- Short Chain Fatty Acids (SCFA)

4

Fermented foods

- Kefir, sauerkraut, kimchi, miso, and pickled vegetables

5

Other factors impacting the microbiome

- Exercise, stress

Guilliams, TG. *Functional Strategies for the Management of Gastrointestinal Disorders*. 2016. The Roadmap Series. Point Institute.

npj | Science of Food

www.nature.com/npjscifood

PERSPECTIVE OPEN

Check for updates

The potential application of probiotics and prebiotics for the prevention and treatment of COVID-19

Amin N. Olaimat[1]✉, Iman Aolymat[2], Murad Al-Holy[1], Mutamed Ayyash[3]✉, Mahmoud Abu Ghoush[1], Anas A. Al-Nabulsi[4], Tareq Osaili[4,5], Vasso Apostolopoulos[6], Shao-Quan Liu[7] and Nagendra P. Shah[8]

[…] probiotics L. gasseri, L. delbrueckii ssp. bulgaricus, B. bifidum, L. acidophilus strains induce IFN-alpha production by monocytes.

NK cells are important in the early immune response against viral infections, in particular through clearance of virus-infected cells. Lactobacillus probiotic strains are able to stimulate DCs to secrete IL-12, which in turn activates NK cells to secrete IFN-gamma, an essential cytokine for lung bacterial (S. aureus) and viral elimination.

Probiotics such as L. casei can also interact with Toll-like receptors (TLR) on the epithelial cells, thereby, enhancing the production of cytokines that play a major role in improving the epithelial cells productivity and preventing their apoptosis which enhances their survival and proliferation during restoration. Understanding the immune cell activation, cytokine profiles and immune modulation is crucial providing a clear path for managing viral infections.

Diabetes & Metabolic Syndrome: Clinical Research & Reviews 15 (2021) 295–301

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

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They [probiotics] seem effective in lowering inflammatory status, moreover in patients with chronic comorbidities such as cancer and diabetes, improving clinical outcomes.

[…] intestinal metabolites, mainly produced by bacterial fermentation of dietary fiber, such as short-chain fatty acids (SCFAs), significantly influence local gut immunity but also distant organs. SCFAs derived from gut are able to suppress lung inflammation.

Dendritic cells (DCs) […] stimulate T-cells [in the GALT and MALT] produce regulatory cytokines. […] T-cells move from the gut to the respiratory system, providing protection and stimulating an anti-inflammatory response […] shown to reduce ventilator-associated enteritis and pneumonia.

Diabetes Metab Syndr. 2021

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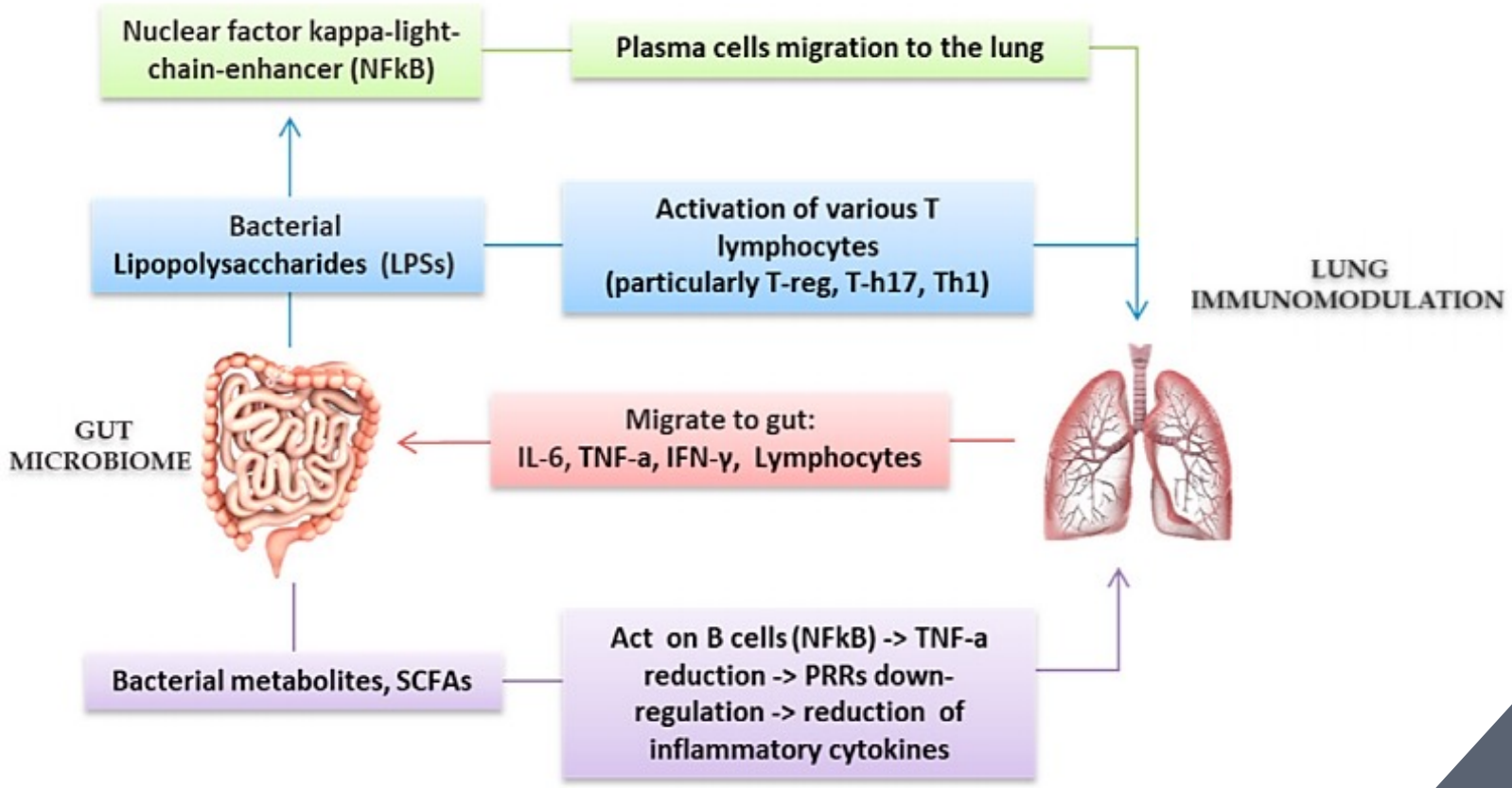

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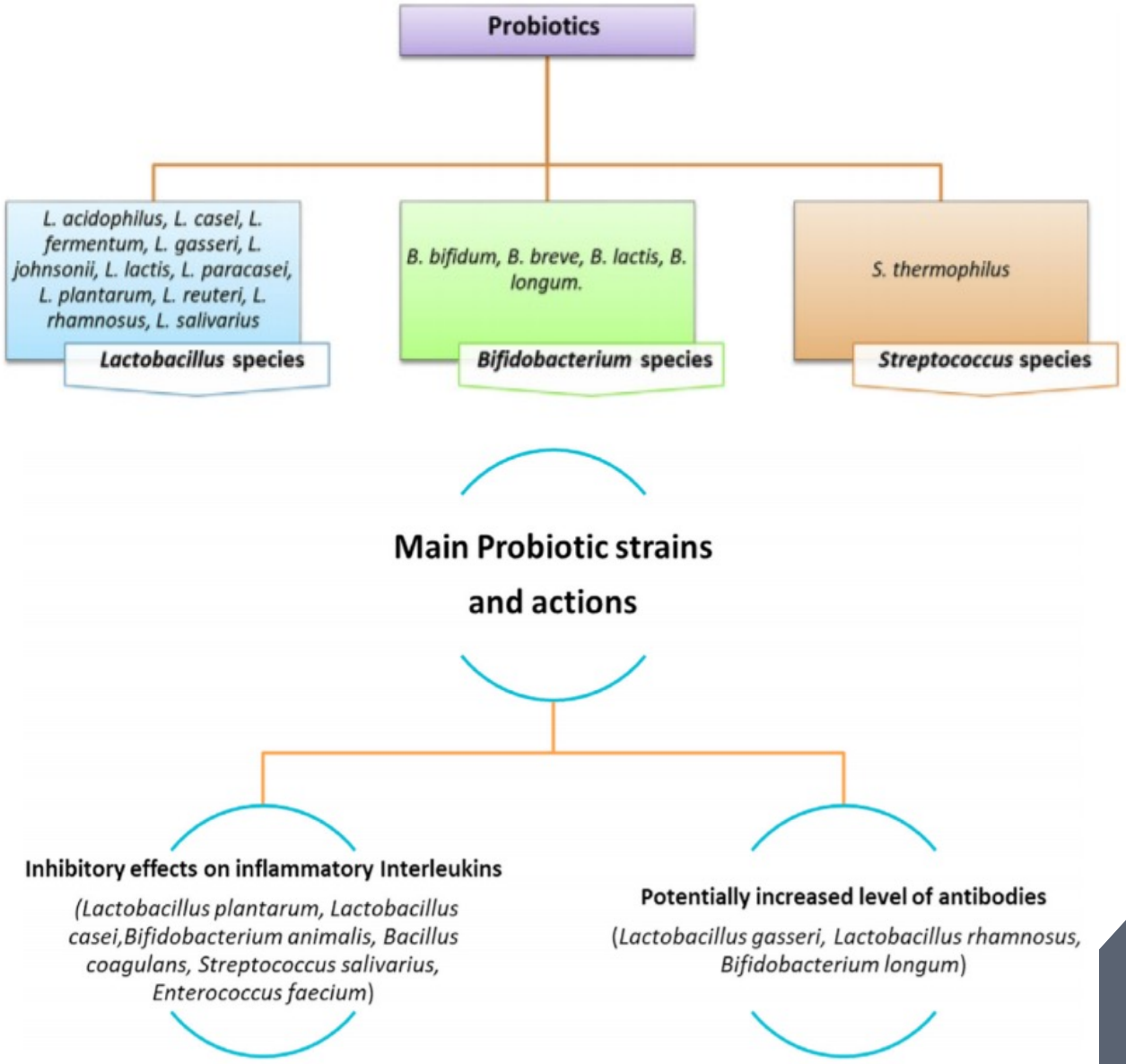
Compete with pathogens

Modulate epigenetic expression to enhance tight junction formation

Produce SCFA, organic acids, bacteriocins (against pathogens)

Modulate the immune system: Antiinflammatory effect via interleukins and promote production of antibodies



Diabetes Metab Syndr. 2021

Saccharomyces boulardii

A nonpathogenic, probiotic yeast.

Protects the intestinal epithelial cells and supports intestinal barrier function

Supports sIgA production

Directly inhibits colonization of harmful bacteria

Protects gastrointestinal tract during antibiotic therapy

Restores normal intestinal function in children and adults with diarrhea

Prevents traveler's diarrhea

Evidence against *C. difficile*

Evidence for use in Inflammatory Bowel Disease

Repair

Immune modulating

1

Zinc

- Protective of the mucosa and anti-ulcerative
- Useful for protecting against anti-inflammatory medications (NSAIDs) often associated with intestinal mucosal damage

2

Vitamin A

- Essential for maintaining the health of epithelial cells throughout the body
- Additional benefit of immune balance benefit

3

L-Glutamine

- Supports tissue repair and maintaining proper intestinal permeability
- Shown to have specific GI mucosal protective action
- Precursor for glutathione synthesis → Antioxidant support

Guilliams, TG. *Functional Strategies for the Management of Gastrointestinal Disorders*. 2016. The Roadmap Series. Point Institute.
Dig Dis Sci **57,** 1000–1012 (2012)
Life Sci. 2006;79(24):2245-2250

Repair *(Other agents worth considering)*

Mucin

- A glycoprotein, used to coat the intestinal lining and to neutralize intestinal antigens and sIgA

N-Acetyl Glucosamine- *GI tissue support*

- Promotes the production of health supportive structures for the cells of the intestinal lining
- Supports increased production of glycosaminoglycans (GAGs) for proper mucosal health and reduced intestinal permeability.

GI soothing

- DGL, Slippery Elm, Marshmallow, Chamomile, Okra, and Cat's Claw
- Provides comprehensive enhancement of intestinal function by coating and soothing the intestinal lining

Reduction of inflammation

- Omega-3 fatty acids
- Polyphenols like curcumin, boswellia, ginger, quercetin, rutin, rosemary, resveratrol, EGCG
- Can reduce the chronic inflammation of the intestinal lining

Guilliams, TG. *Functional Strategies for the Management of Gastrointestinal Disorders*. 2016. The Roadmap Series. Point Institute.

N-acetylcysteine NAC

NAC promotes glutathione production, has been demonstrated to be protective

NAC's antioxidant, anti-inflammatory, and immune-modulating activity along with safety status makes it a valuable tool in treatment and prevention of SARS-Cov-2. NAC enhances immunity, suppress viral replication, and reduces inflammation/cytokine storm

Acts as a natural mucolytic agent, mechanism is to decrease the viscoelastic properties of mucus by reducing disulfide bonds. As a result, reducing viscosity.

600-900 mg/BID

Ther Clin Risk Manag. 2020
Respir Res 2012

Vitamin D & COVID outcomes

2021 meta-analysis of 8209 patients reported 1.5 RR (positive COVID 19 test) when serum 25(OH)D levels <30 ng/ml

Six potential mechanisms:

- Antiviral mechanism
- Reduces proinflammatory cytokines
- Increases ACE2 concentrations and reduces ARDS mortality
- Reduces risk of endothelial dysfunction
- Reduces MMP-9 concentrations
- Reduces risk of bradykinin storm

Metabolism. 2021
Nutrients. 2020

International Journal of
Molecular Sciences

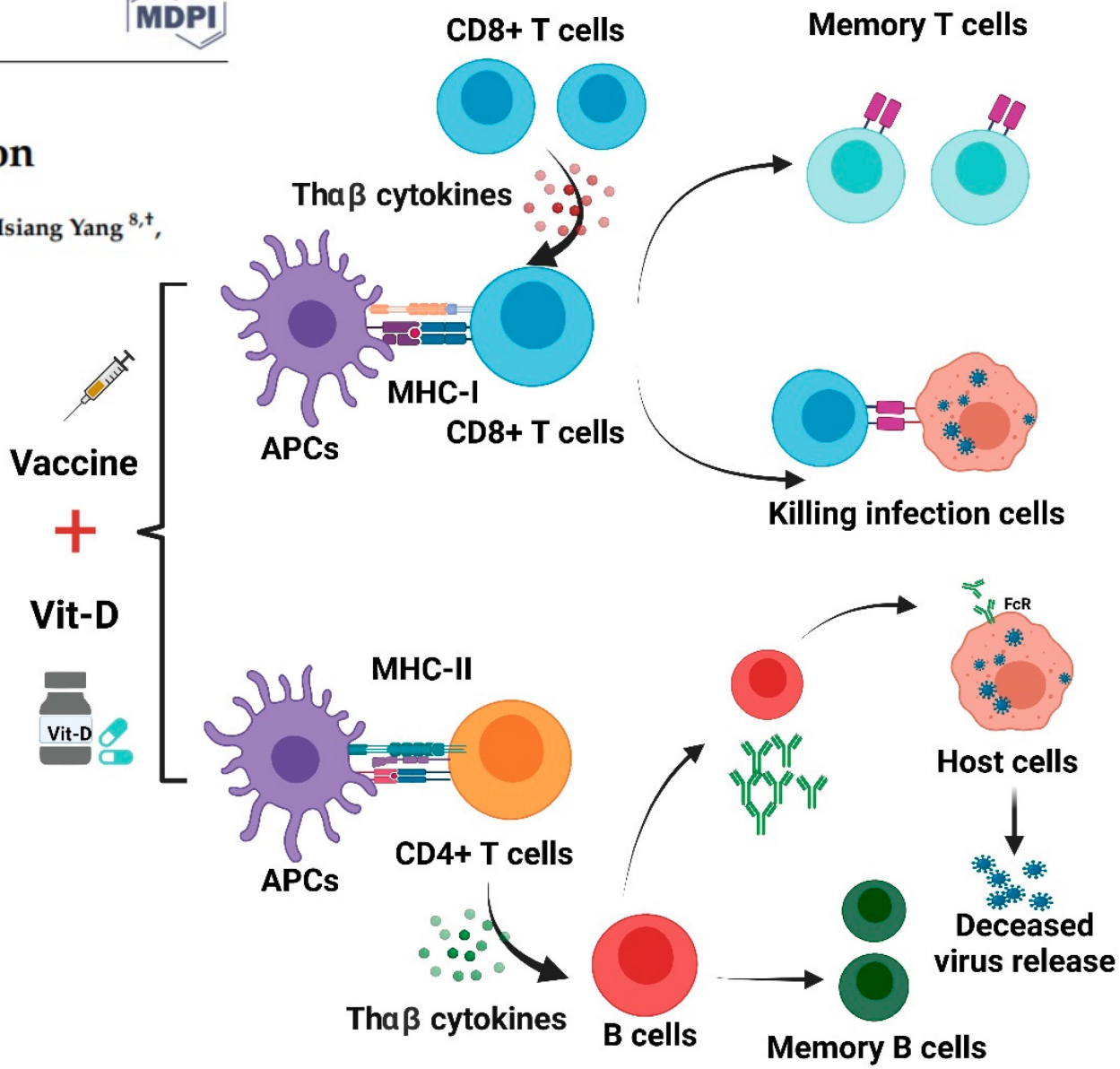
MDPI

Review

Putative Role of Vitamin D for COVID-19 Vaccination

Sheng-Kang Chiu [1,2,3,†], Kuo-Wang Tsai [4], Chia-Chao Wu [5,6], Cai-Mei Zheng [7], Chung-Hsiang Yang [8,†], Wan-Chung Hu [4,*], Yi-Chou Hou [9], Kuo-Cheng Lu [10] and You-Chen Chao [11]

Better vitamin D status was shown to improve seroconversion in response to influenza vaccinations



Pandemic Pre-Vaccination Protocol

Interventions that may improve the immune response to vaccination

If vacc
- Avoid acute st
- Obtain adequ
- Avoid anti-infla
- If active infecti

For all others, consid

Public Health Measures:
- Masks
- Distancing
- Hand washing

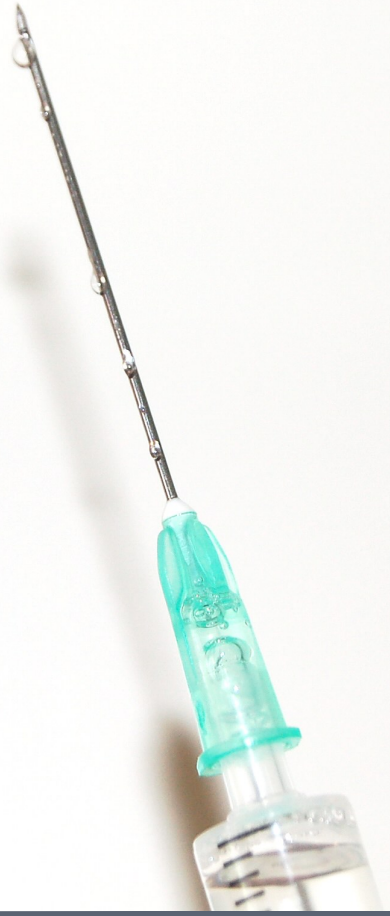
Address Lifestyle Factors:
- Sleep
- Exercise
- Nutrition
- Stress
- Relationships
- Gut health (IFM's "DIGIN" and "5R")

Additional Considerations:
- **Address Comorbidities (CDC List)**
- Enhance immune function
- Address inflammation
- Smoking cessation
- Weight loss
- Mind/body therapies
- Dietary fiber
- Optimize microbiota
- Address autoimmunity
- Address hormonal balance

Options to Improve Physiological Function:
- Curcumin
- Resveratrol
- Quercetin
- Melatonin
- *Green tea extract
- *Glutathione or *N-acetylcysteine
- *Andrographis
- *Berberine

***For conditions below, consider agents above:**
- Hypertension
- Diabetes
- CVD
- Hypertriglyceridemia
- Hyperinsulinemia
- Autoimmunity
- Obesity

Options to Support Immune Function:
- Vitamins A, C, D, E, B6, B12, Folate, Fe, Zn, Cu, Se
- Mushrooms
- Beta glucans
- Echinacea
- Quercetin
- Reservatrol



Printed with permission of the Institute for Functional Medicine
https://functionalmedicine.widen.net/s/jsx6jjtfvm/pandemic-pre-vaccination-protocol

Botanical Modulation of Arachidonic Acid Cascade

Cyclooxygenase (COX)	Lipooxygenase (LOX)	Phospholipase	Modulates cortisol → Phospholipase
• *Zingiber officinale* • *Curcuma longa* • *Ananas comosus* • *Salix nigra / alba* • *Gaultheria procumbens* • Quercetin (some weak activity)	• Quercetin • *Allium cepa /Allium sativum* • *Curcuma longa* • *Boswellia serrata* (specific for 5-LOX)	• *Glycyrrhiza glabra* • Quercetin	• *Glycyrrhiza glabra* • *Curcuma longa*

Guilliams, TG. *Functional Strategies for the Management of Gastrointestinal Disorders*. 2016. The Roadmap Series. Point Institute.

Useful Botanicals and Nutraceuticals

Bromelain & Digestive enzymes
Quercetin
Deglycyrrhizinated licorice/DGL (*Glycyrrhiza glabra*)
Slippery elm (*Ulmus fulva*)
Marshmallow (*Althaea officinalis*)
Ginger (*Zingiber officinale*) standardized to gingerols
Colostrum immunoglobulins
Serum Bovine-derived immunoglobulins
Glutamine
Vitamin A
Zinc
Vitamin C
NAC
Vitamin D

Rebalance

1

Anti-inflammatory diet

- Expand diet (safely)
- High fiber
- Anti-inflammatory fats
- Low antigen

2

Stress

- HPA axis support
- MMC and motility

3

Exercise

- Impact on IP
- Microbiome balance

4

Sleep

- Multiple mechanisms impact on GI health
- NT production (circadian rhythm impact on GI, melatonin, serotonin)

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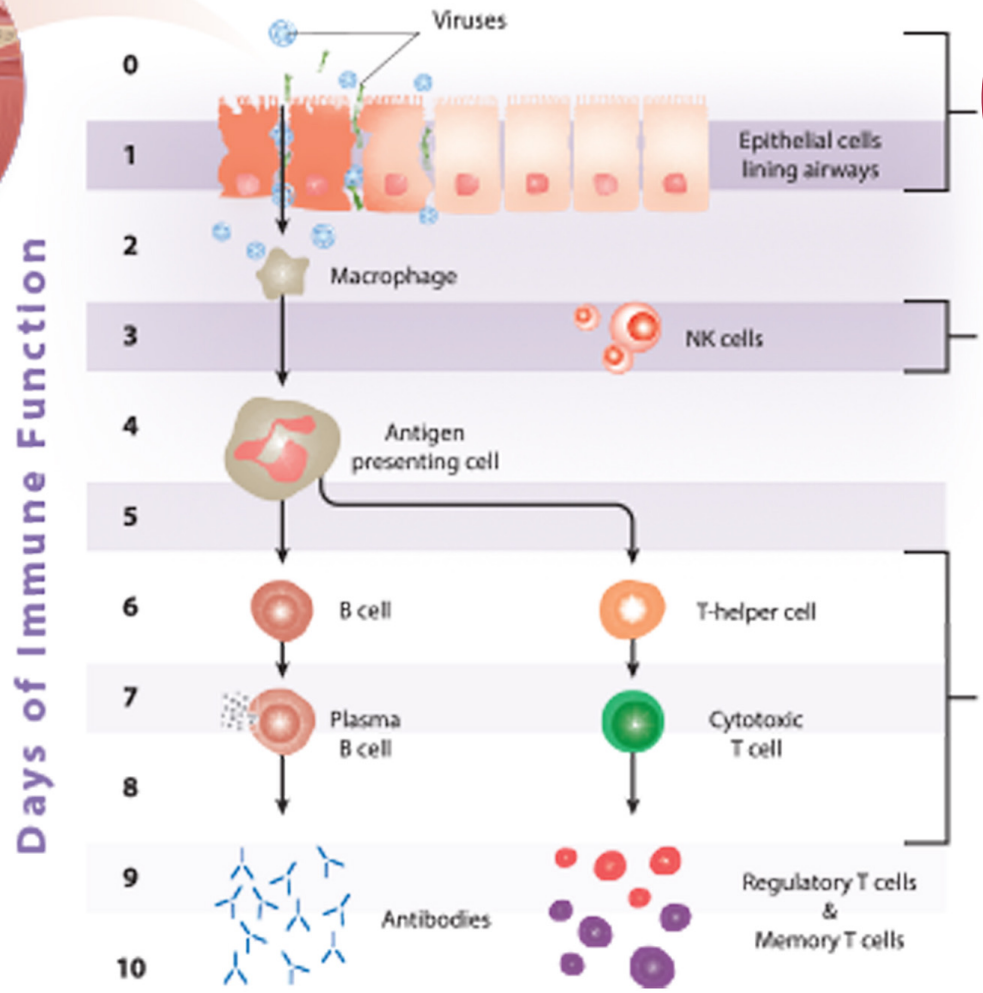
Immune Cascade



Epithelial Barrier Function

- NAC
- Quercetin
- Vitamin C
- Vitamin D
- Zinc

NK Cell Activity

- Quercetin
- Vitamin C
- Zinc

B-Cell and T-Cell Differentiation and Memory

- Quercetin
- Vitamin C
- Zinc

FUNCTIONAL MEDICINE
Continuing Education

Thank You!

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