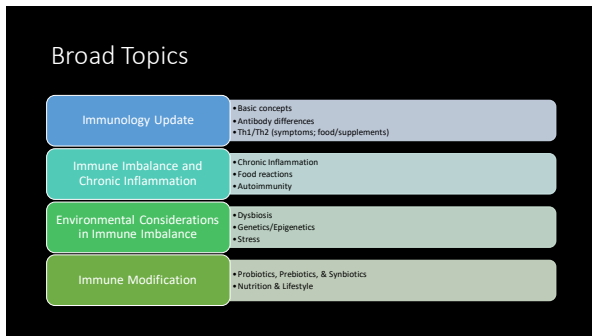
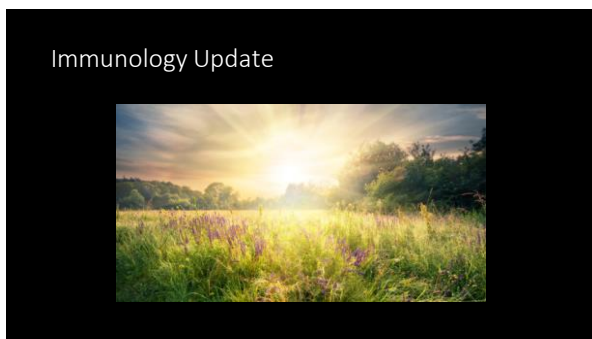




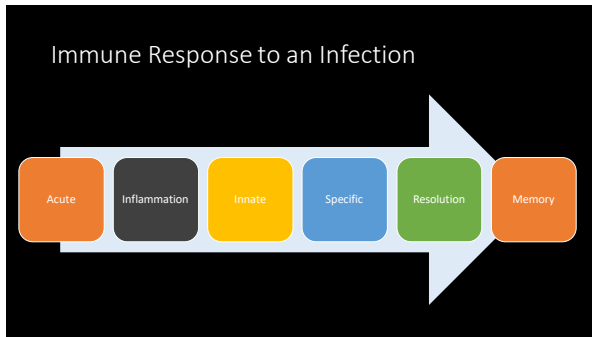
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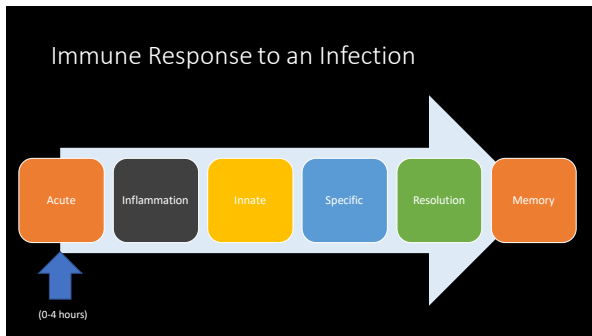
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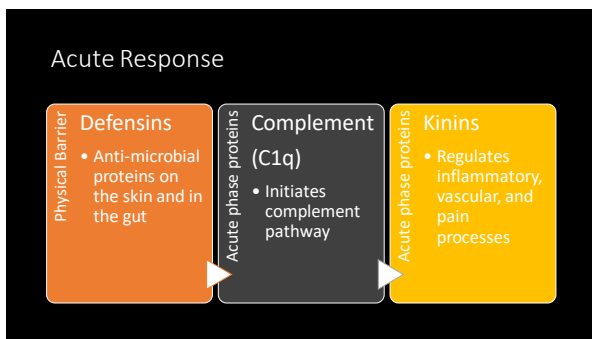
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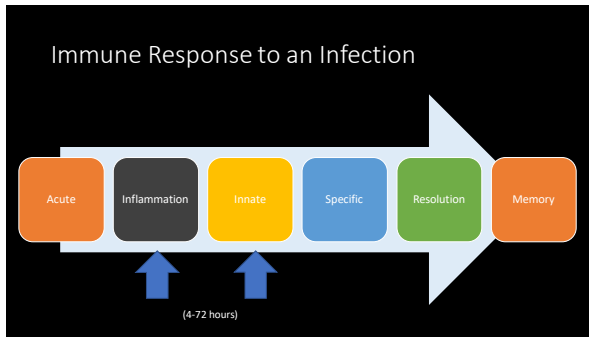
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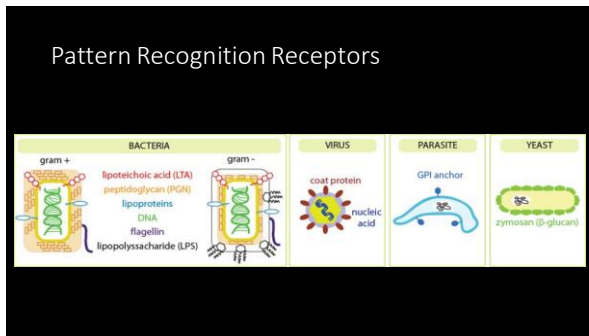
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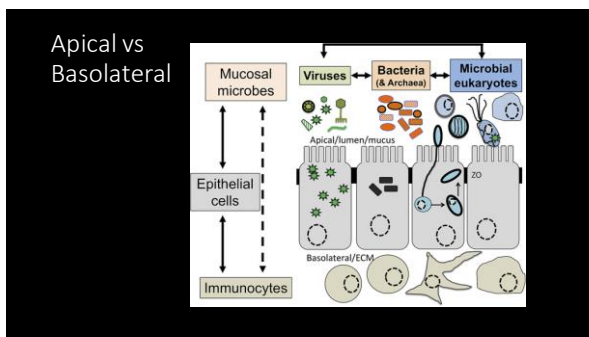
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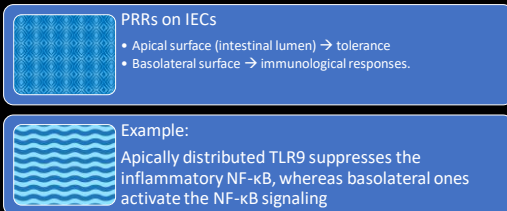


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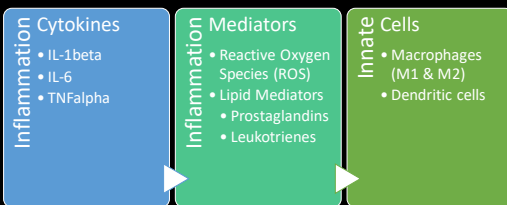
Pattern Recognition Receptors



Retinoic Acid, Leaky Gut, and Autoimmune Diseases. *Nutrients* **2018**, *10*, 1016; doi:10.3390/nu10081016

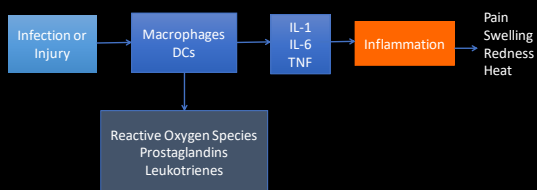
10

Inflammation and Innate Immune Response

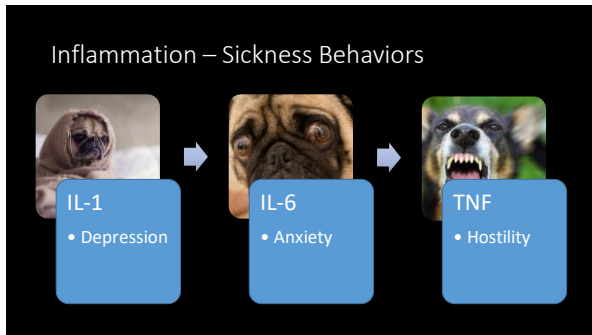


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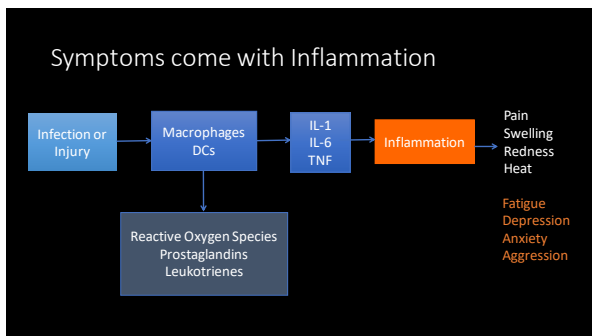
Inflammation and Innate Immunity



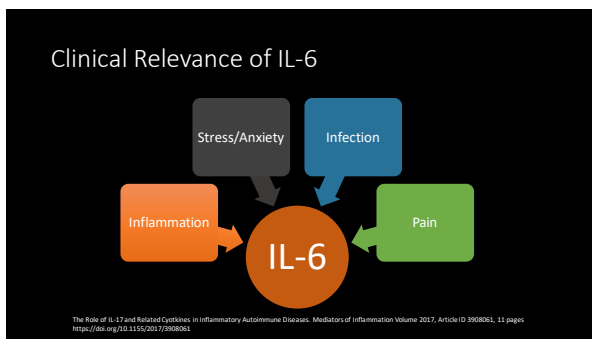
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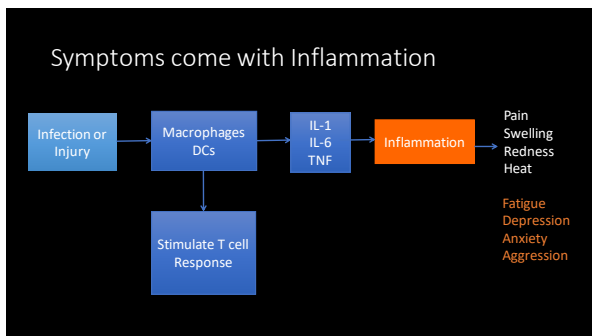
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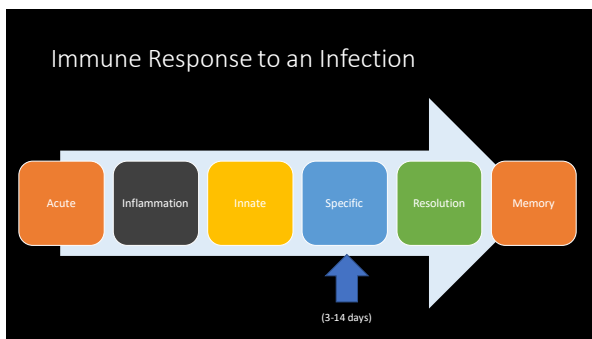
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16



17



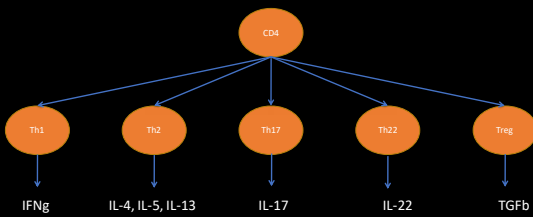
18

Types of Immune Responses (not comprehensive)

Reactions to:	T Cell Response
Bacteria and Virus	Th1
Worms (some parasites)	Th2
Fungi (some parasites and extracellular bacteria) *Autoimmunity*	Th17 Th22
Food	Treg/Th3

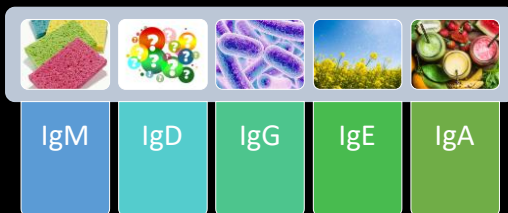
19

Specific Immunity - CD4 T cell Subtypes



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Antibodies



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Antibody Function



- Opsonization
 - Coat
- Neutralization
 - Block a function
- Fc Receptor mediated endocytosis
 - Increase uptake
- Antibody Dependent Cellular Cytotoxicity
 - Tag for destruction

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Antibodies – More complexity



IgM

IgD

IgG

• IgG1

• IgG2

• IgG3

• IgG4

IgE

IgA

• IgA1

• IgA2

• sIgA

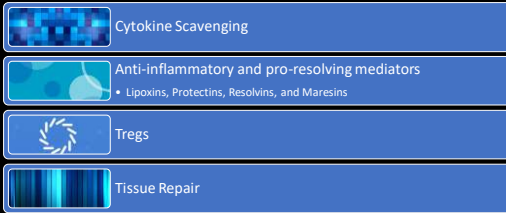
23

Antibodies

Reaction to:	T cell	Cytokine	Antibody
Bacteria and Virus	Th1	IFNgamma	IgG2, IgG3
Worms/Allergens	Th2	IL-4, IL-5, IL-13	IgE, IgG1, IgA2 (mucus)
Food	Th3/Treg	TGFbeta	IgA2, IgG4
Mold/ Autoimmunity	Th17	IL-17	IgG2, IgG3

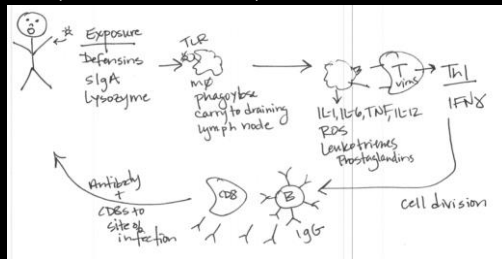
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Resolution



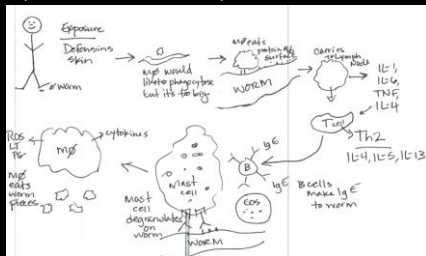
25

Complete Immune Response to Infection



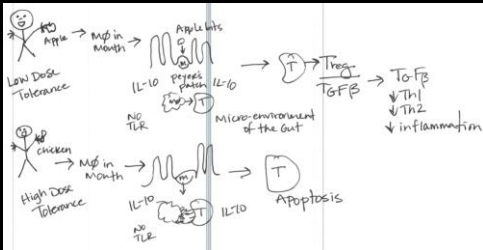
26

Complete Immune Response to Worms



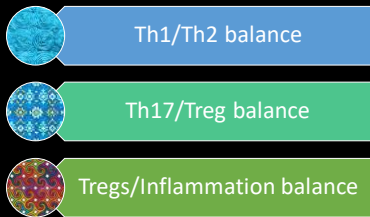
27

Complete Immune Response to Food



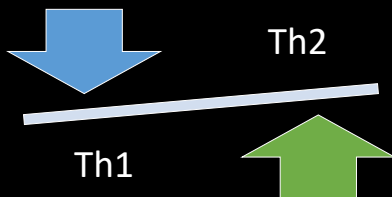
28

Balance



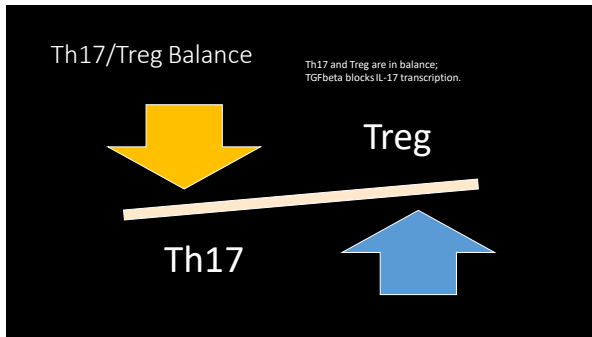
29

Th1/Th2 Balance

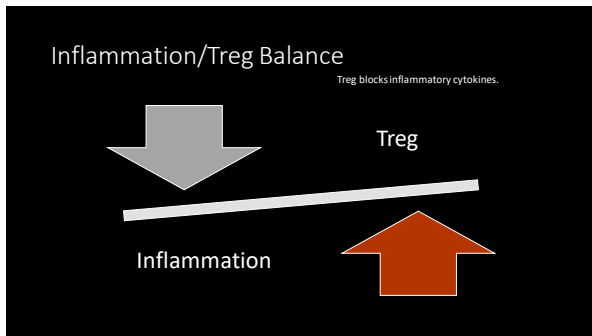


Th1 and Th2 are in balance;
IL-4 blocks IFNγ transcription and vice versa.

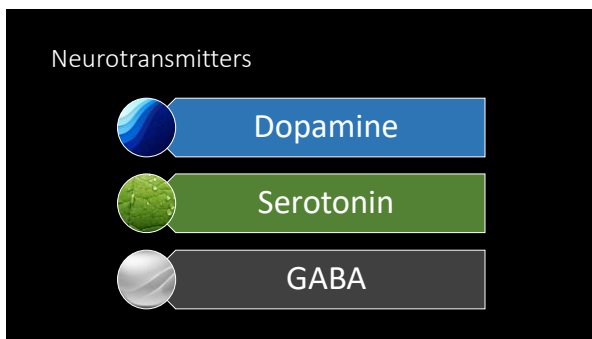
30



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32

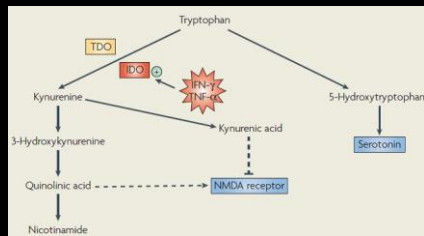


33

Cell	Express Receptors (not exhaustive)
CD4 T cell (Th1, Th2, Th17, Treg)	β adrenergic receptor Dopamine receptor Acetylcholine receptor 5HT receptor (serotonin) Opioid receptor
CD8 T cell (Kills infected cells)	Dopamine receptor 5HT receptor (serotonin)
B cell (Pathology and predictive)	Dopamine receptor
NK cell (Kills virally infected cells and cancer)	Dopamine receptor Opioid receptor
Macrophage IL-1, IL-6, and TNF	Dopamine receptor α and β adrenergic receptor
Dendritic cell IL-1, IL-6, and TNF	Dopamine receptor Opioid receptor

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IFN γ vs Serotonin (Kynurenine Pathway)

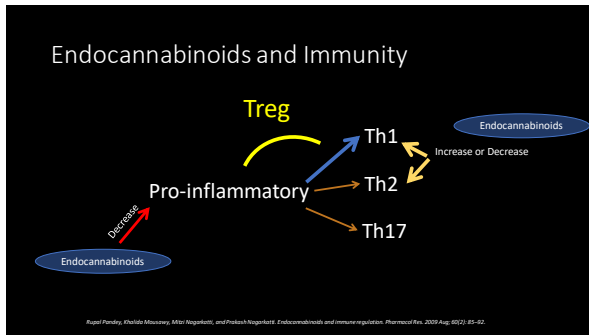


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Neurotransmitter Summary

Neuro-transmitter	Mood Effect	Gut Effect	Immuno Effect
Dopamine	Pleasure/Depression	Colon contraction	Can contribute to Th1, Th2, Th17 or Treg (misregulated in MS, Lupus, and IBD)
Serotonin	Happy/Anxiety	Bowel movements	Competes for Tryptophan with IFN γ - Th1
GABA	Relaxation/Depression/Mania	Intestinal motility; Pain reduction	Anti-inflammatory

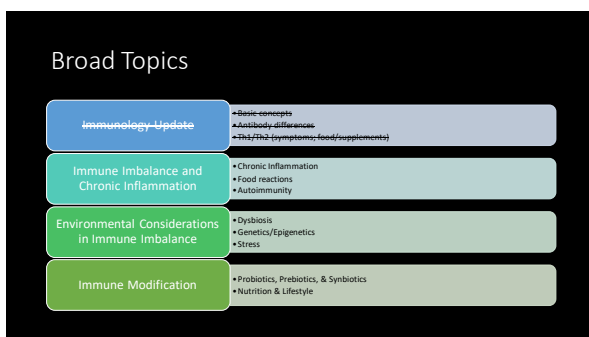
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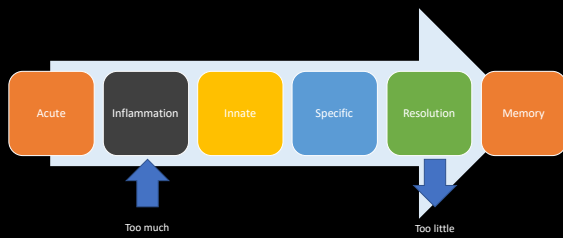
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Immune Imbalance and Chronic Inflammation



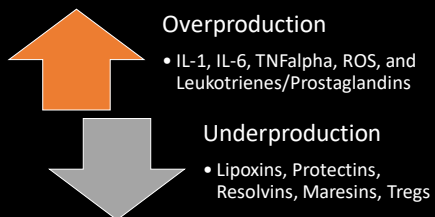
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Chronic Inflammation



41

Chronic Inflammation



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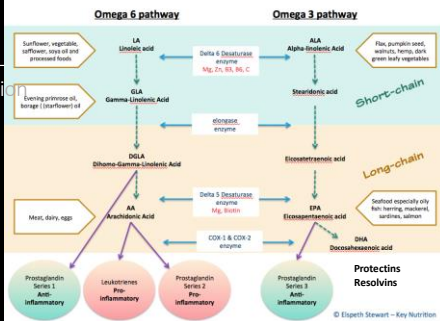
Chronic Inflammation - Overproduction



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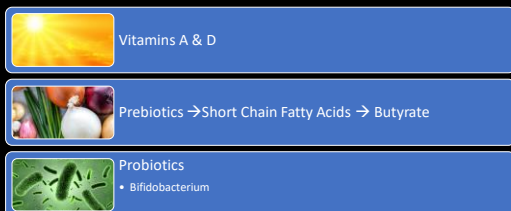
Chronic Inflammation - Underproduction

Standard American Diet



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Chronic Inflammation – Low Tregs



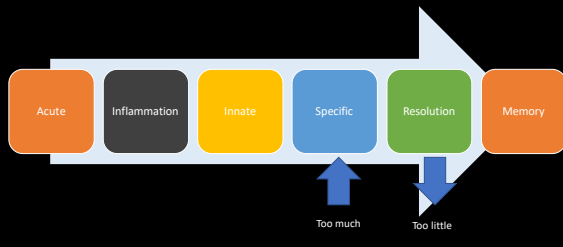
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Food Reactions



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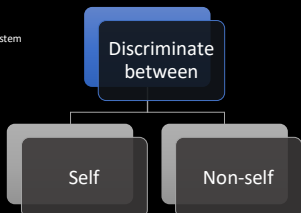
Autoimmunity



47

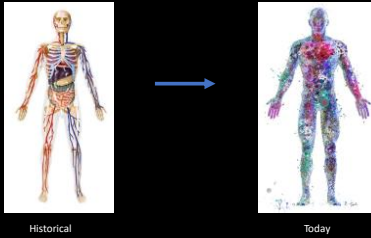
Autoimmunity

What the Immune System
is doing every day...



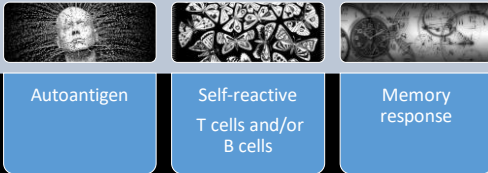
48

Immunological Self



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Autoimmunity



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Tolerance – T cell



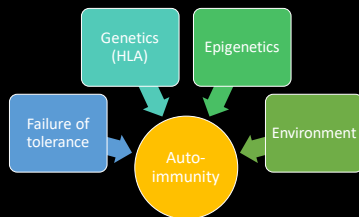
51

Tolerance



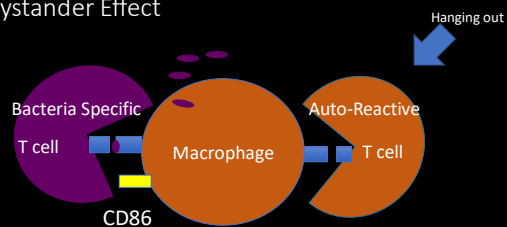
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Cause of Autoimmunity

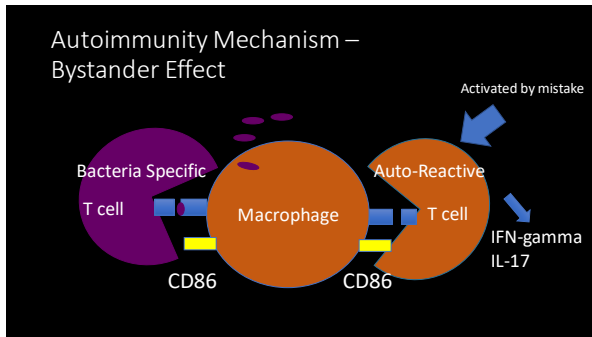


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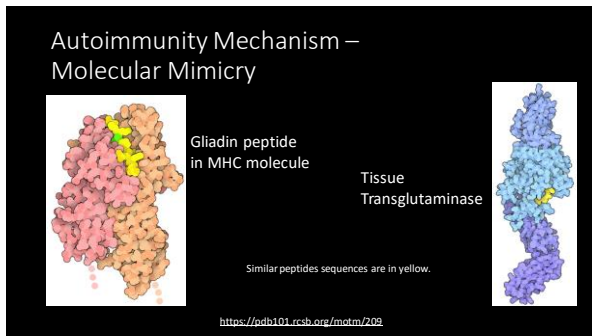
Autoimmunity Mechanism – Bystander Effect



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Autoimmunity – Autoantibodies

Preclinical

- Antibodies show up before disease starts

Clinical

- Antibodies part of pathology

Development of autoantibodies precedes clinical manifestations of autoimmune diseases. Journal of Autoimmunity 83 (2017) 95e112

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Autoimmunity - Autoantibodies

Disease	When Auto-Ab Appear Prior to Disease
Primary Biliary Cholangitis	0.9 – 19 years
Rheumatoid Arthritis	0.1 – 13.8 years
Systemic Lupus Erythmatosus	0.88 – 3. 68 years for ANA 1.1 – 8.1 years for Anti-dsDNA
Type 1 Diabetes	1.7 – 6 years

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Autoimmunity - Autoantibodies

Disease	When Auto-Ab Appear Prior to Disease
Autoimmune Thyroid Disease (Graves and Hashimoto's)	Up to 7 years
Multiple Sclerosis	1 – 3 years
Celiac	Not reported
IBD (Crohn's and UC)	About 4.5 years

Development of autoantibodies precedes clinical manifestations of autoimmune diseases. Journal of Autoimmunity 33 (2017) 95e112

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Example – Rheumatoid Arthritis



Rheumatoid Factor - RF

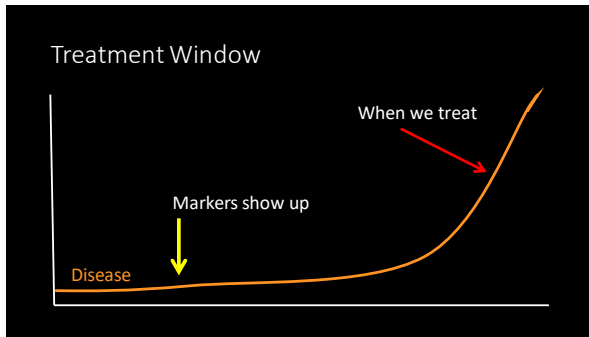
- People can have RA and not have RF
- Elderly people can have RF and not have RA



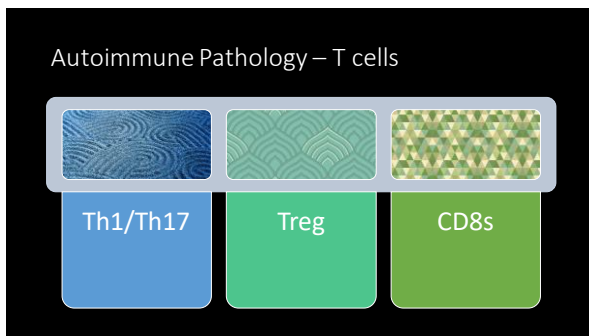
ACPA

- Specificity of 95% - if ACPA is present, RA is likely
- Found in 75% of people with RA
- Correlate with more aggressive disease

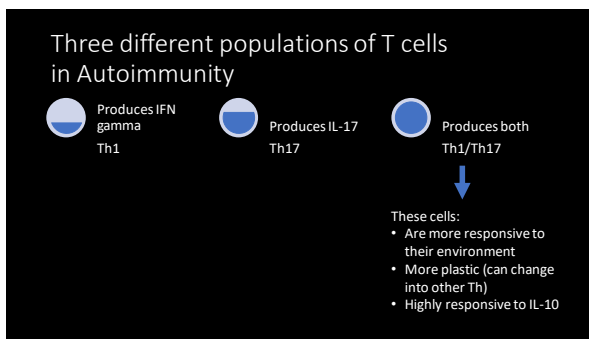
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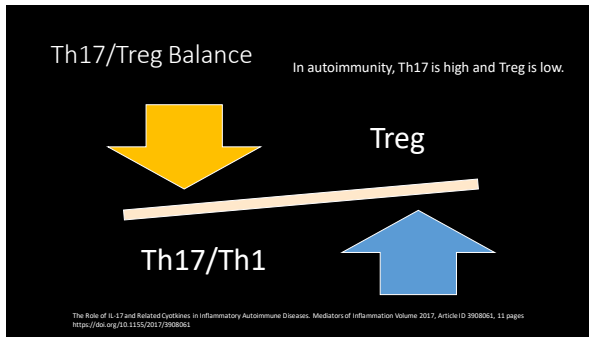
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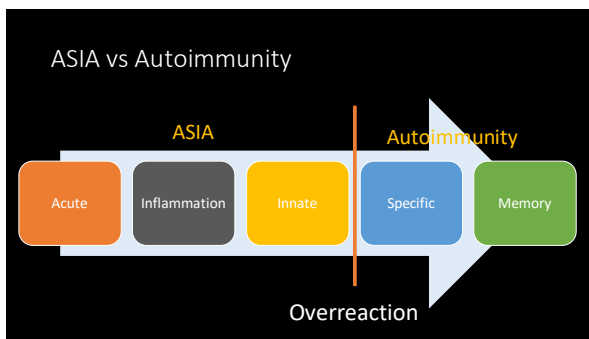
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Broad Topics

Immunology Update

- Basic concepts
- Antibody differences
- Th1/Th2 (symptoms, food/supplements)

Immune Imbalance and Chronic Inflammation

- Chronic inflammation
- Food reactions
- Autoimmunity

Environmental Considerations in Immune Imbalance

- Dysbiosis
- Genetics/Epigenetics
- Stress

Immune Modification

- Probiotics, Prebiotics, & Synbiotics
- Nutrition & Lifestyle

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Dysbiosis

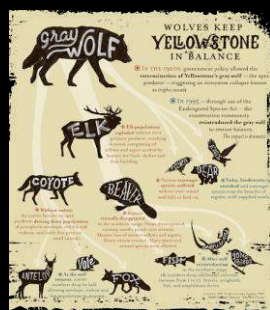


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Dysbiosis



Historically



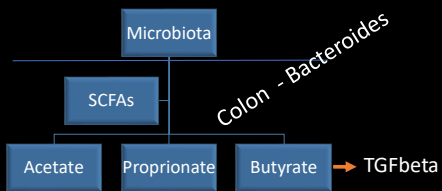
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Microbiome influencers

Vaginal or C-section	Breastfed	Type of Diet (meat or veg)	Pets (Type and number)	Siblings	City or rural
Culture	Geographical location	Genetic variability	Antibiotic use	Non-antibiotic pharmaceutical use	Exposure to chemicals
Hormones (time of month)	Health Status	Age	Preservatives in food	Stress level	Exercise

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Microbiome metabolites impact Tregs



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The health of the gut is essential!

Gut microbial metabolites can be proinflammatory or anti-inflammatory.

Cytokines in the gut circulate systemically.
• TGFbeta in the gut can have widespread effects.

Intestinal permeability can increase inflammation and decrease TGFbeta.

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Therapeutic Strategy



Decrease Th1



Decrease Th17



Decrease inflammation



Increase Treg!!!!

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Treating the Gut



Vitamin D



Vitamin A



Omega 3s (DHA)



Prebiotics/Probiotics

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Vitamin D



Vitamin D Receptors

- Macrophages, DCs, NKs, T cells, B cells



Immune cells express enzyme CYP27B1,

- Indispensable for the internal conversion of the circulating 25(OH)D



Functions

- Influences expression of cytokines and co-stim molecules

Immunomodulatory effect of vitamin D and its potential role in the prevention and treatment of thyroid autoimmunity: a narrative review. 04 October 2019. Journal of Endocrinological Investigation

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Vitamin D in Autoimmunity



In macrophages and DCs

- Down-regulates IL-12 which leads to Th1
- Down-regulates IL-23 which leads to Th17



Vitamin D promotes Treg response

Immunomodulatory effect of vitamin D and its potential role in the prevention and treatment of thyroid autoimmunity: a narrative review. 04 October 2019, Journal of Endocrinological Investigation

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Vitamin A



Vitamin A has 3 isomers

- 9 cis, 13 cis, all trans RA



Receptors

- RAR (Retinoic Acid Receptor)
- RXR (Retinoid X Receptor)



Receptors mix and match

- Dimerization
- Heterodimerization

Retinoic Acid, Leaky Gut, and Autoimmune Diseases. Nutrients 2018, 10, 1016; doi:10.3390/nu10081016

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Vitamin A Effects on B and T cells

B cells

CD19+CD24+CD38+

Breg

Production of IgA

T cells

CD4+CD25+ Tregs

Production of TGFbeta

Retinoic Acid, Leaky Gut, and Autoimmune Diseases. Nutrients 2018, 10, 1016; doi:10.3390/nu10081016

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Vitamin A, Intestinal Permeability, and Autoimmunity



Increases expression of TJ proteins



Retinoic acid –microbiome axis

- RA + Acetate from microbes → IgA secreting B cells

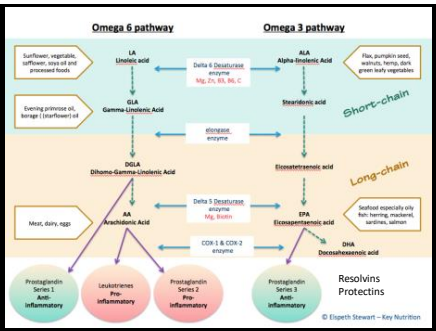


Can stimulate gut microbiome homeostasis
- Lactobacillus

Retinoic Acid, Leaky Gut, and Autoimmune Diseases. *Nutrients* 2018, 10, 1016; doi:10.3390/nu10081016

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Omega3s



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Genetics and Epigenetics

Genetics


- Differences in the DNA sequence that affect different proteins (SNPs – single nucleotide polymorphisms)

Epigenetics

- Differences in how the gene is expressed – when it is turned on, turned off, and how much protein is made

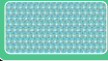
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Genetics and Immune Imbalance - Examples




Reactive Oxygen Species

- Genetic differences in the regulation of ROS – endogenous antioxidants and enzymes that make ROS
- Linked to CVD, blood pressure, Crohn's, infections, cancer



Vitamin D Receptor (VDR)

- VDR polymorphism determines how much vitamin d can be absorbed
- Linked to infections, cancers, arthritis, etc



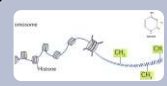
Human Leukocyte Antigen (HLA)

- Some HLAs bind to certain peptides better than others
- Linked to autoimmune disease


Canva, S., Villar, V.A.M. & Jose, P.A. Genetic polymorphisms associated with reactive oxygen species and blood pressure regulation. *Pharmacogenomics* 18, 115–134 (2018). <https://doi.org/10.1089/phgm.2017.0006>
 Costa-Rosa, C., Turbato, C., Coelho, B., et al. Association between Polymorphisms in Antioxidant Genes and Inflammatory Bowel Disease. *PLoS One*. 2017;12(11):e0169102. Published 2017 Jan 4. doi:10.1371/journal.pone.0169102

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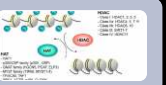
Epigenetics and Immune Imbalance



DNA methylation required for Treg maintenance



microRNA regulates mRNA in inflammatory disease



Histone deacetylases influence immune and inflammatory processes, mainly involving T cells

Mazzoni, R., Zwingel, C., Artico, M., et al. The emerging role of epigenetics in human autoimmune disorders. *Clin Epigenet* 11, 34 (2019). <https://doi.org/10.1186/s13148-019-0020-2>

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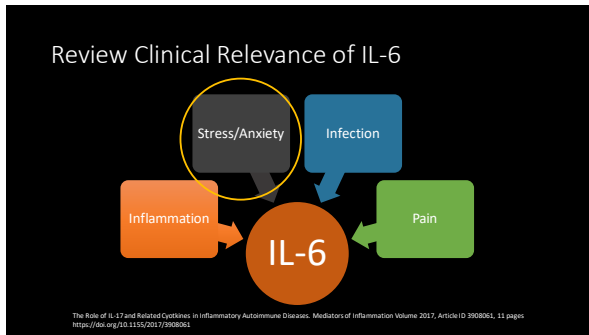
Stress and Chronic Inflammation



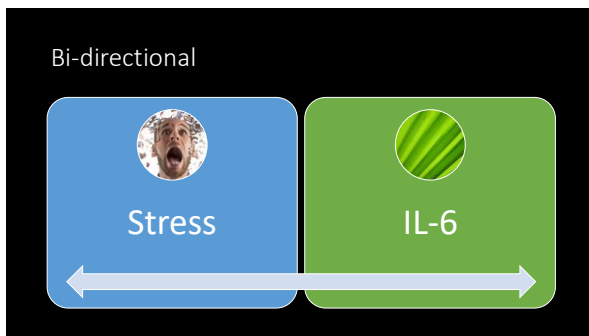
What is STRESS?

A particular relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her well-being... (Lazarus and Folkman)

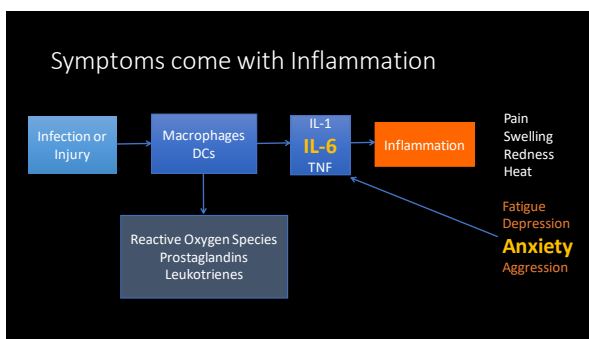
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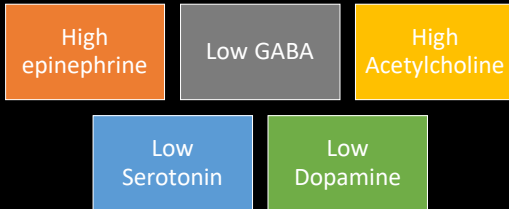


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Stress and Neurotransmitters

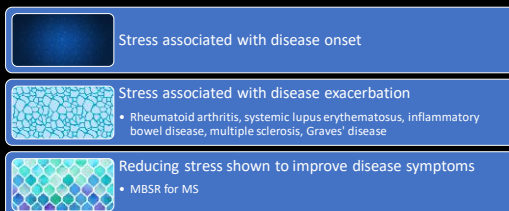


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Cell	Express Receptors (not exhaustive)
CD4 T cell (Th1, Th2, Th17, Treg)	β adrenergic receptor Dopamine receptor Acetylcholine receptor 5HT receptor (Serotonin)
CD8 T cell (Kills infected cells)	Dopamine receptor 5HT receptor (Serotonin)
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NK cell (Kills virally infected cells and cancer)	Dopamine receptor
Macrophage IL-1, IL-6, and TNF	Dopamine receptor α and β adrenergic receptor
Dendritic cell IL-1, IL-6, and TNF	Dopamine receptor

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Stress and Autoimmunity



The role of stress in the mosaic of autoimmunity: An overlooked association. [Autoreviews, 2018 Oct;17\(10\):967-983. doi: 10.1016/j.autrev.2018.04.005. Epub 2018 Aug 14.](https://doi.org/10.1016/j.autrev.2018.04.005)


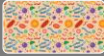

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Broad Topics

Immunology Update	<ul style="list-style-type: none"> Basic concepts Antibody differences Th1/Th2 (symptoms, food/supplements)
Immune Imbalance and Chronic Inflammation	<ul style="list-style-type: none"> Chronic inflammation Food reactions Autoimmunity
Environmental Considerations in Immune Imbalance	<ul style="list-style-type: none"> Dysbiosis Genetics/Epigenetics Stress
Immune Modification	<ul style="list-style-type: none"> Probiotics, Prebiotics, & Synbiotics Nutrition & Lifestyle

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Prebiotics / Probiotics / Synbiotics

	Prebiotics <ul style="list-style-type: none"> Types of dietary fiber that feed the friendly bacteria in your gut. This helps the gut bacteria produce nutrients
	Probiotics <ul style="list-style-type: none"> Live (?) microorganisms that are intended to have health benefits when consumed or applied to the body
	Synbiotics <ul style="list-style-type: none"> Synergistic combination of probiotics and prebiotics, which serve to improve the therapeutic benefits of probiotics by combining them with prebiotics to enhance their growth in the colon

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Prebiotic Foods



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Prebiotic Herbs



Curcumin

Ginger

Long Pepper

Black Pepper

Cinnamon

Oregano

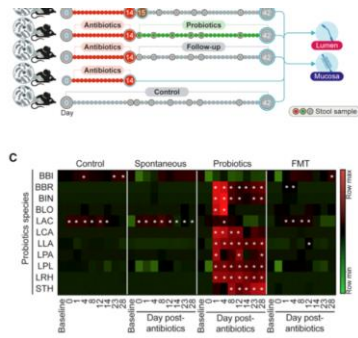
Rosemary

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Probiotics

- Historical
 - Probiotics thought to reconstitute the gut post antibiotics
- Today
 - Probiotics don't reconstitute and may actually delay reconstitution
 - May help symptoms

Cell 174, 1406–1423, September 6, 2018



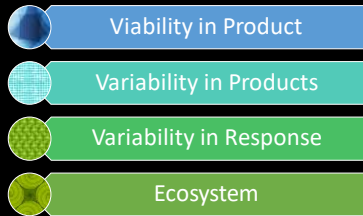
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Probiotics and Immune Function

						PMID
Lactobacillus plantarum DR7	Stressed adults	1x10 ¹⁰ cfu/day for 12 weeks	Placebo	Alleviated stress and anxiety	+ IFN-γ & TGF-α, IL-10	30822344
Lactobacillus plantarum IS-10506	Children w/ atopic dermatitis	10 ¹⁰ cfu/2x/day for 12 weeks	Placebo	Improved atopic dermatitis	+ IFN-γ, IL-4 & IL-17	29022387
Lactobacillus plantarum 299v	Men w/ stable coronary artery disease	20 billion CFU/day	None	Improved vascular endothelial function	+ IL-6 & IL-12	30355158
Bifidobacterium animalis	Healthy adults	Probiotic-containing yogurt (unknown dose) for 28 days + 5 non-brushing days	Placebo	Improved gingival health (after refraining from oral hygiene)	+ IL-1β	28753102
Bifidobacterium lactis HN019	Adults with metabolic syndrome	80 mL fermented milk with 2.72 x 10 ¹⁰ cfu/day for 45 days	Placebo	Improved lipid profile and reduced inflammation	+ TNF-α & IL-6	27126957

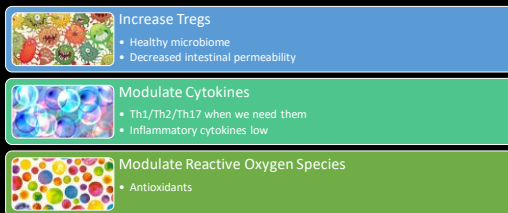
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Probiotics Issues



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Nutritional Strategy



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Nutrition



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Eat Antioxidants

What to Eat



What Antioxidants Do



Some antioxidants act as prebiotics.



Antioxidants quench oxidative stress.

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Eat Healthy Oils

What To Eat



What Healthy Oils Do



Medium Chain Triglyceride (MCT) oils act as antioxidants.






Oils quench oxidative stress and lower blood sugar which lowers inflammation.

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Don't eat pesticides.

What to Eat

-  Organic berries & vegetables you don't peel
-  Organic dairy
-  Organic Meats (fat)

Why to eat Organic






Pesticides kill healthy microbiota which control inflammation.



Pesticides are associated with neuroinflammation.

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Pesticides – Glyphosate


Round-up

Spraying


Well-water

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Pesticides - Glyphosate




Glyphosate show to be toxic to gut microbes in cattle, chickens, and marine turtles



Target enzyme for glyphosate is: 5-enolpyruvylshikimate 3-phosphate synthase

- Enzyme is active in plants, bacteria, and microbes, but not mammals
- Marketed as an herbicide



Lactobacillus and Bifidobacteria are killed by glyphosate.

- Glyphosate also causes Honey Bee dysbiosis
- Treat with Lactobacillus plantarum

Interaction of the herbicide glyphosate with its target enzyme 5-enolpyruvylshikimate 3-phosphate synthase in atomic detail. 1276-1380 • PNAS • February 13, 2003 • vol. 98 • no. 4
Glyphosate perturbs the gut microbiota of honey bees. PNAS | October 9, 2014 • vol. 111 | no. 41 | 10300-10310

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Don't eat (drink) BPAs

What to eat

- Fresh & frozen vegetables (no cans)
- Glass bottled sauces and beverages (no plastic)
- BPA-free labels




Why to avoid bpas

- BPAs linked to neurological disorders.
- BPAs kill healthy microbiota which decrease inflammation.



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Don't eat artificial sweeteners.

What to eat

-  Honey
-  Maple Syrup
-  Stevia

Why to avoid sweeteners

-  Spiking blood glucose increases inflammation.
-  Artificial sweeteners kill microbiota.



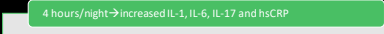

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Sleep



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Sleep

-  Sleep deprivation increases IL-6.
-  TNF can disrupt sleep, and disrupted sleep can increase TNF.
-  4 hours/night → increased IL-1, IL-6, IL-17 and hsCRP
-  Inflammatory disease increases cytokines because higher baseline

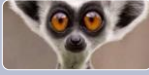
Mullington JM, Simpson NS, Meyer-Ewert HK, Haack M. Sleep loss and inflammation. *Best Pract Res Clin Endocrinol Metab.* 2010;24(5):779-794. doi:10.1016/j.beem.2010.08.014

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Sleep and the NLRP3 Inflammasome



Inflammasome is 'intracellular machine' that involves all IL-1 proteins



Sleep deprivation increases the NLRP3 inflammasome



Calm the inflammasome before people can sleep

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Summary



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Summary

Immunology Update	<ul style="list-style-type: none"> Basic concepts Antibody differences Th1/Th2 (symptoms; food/supplements)
Immune Imbalance and Chronic Inflammation	<ul style="list-style-type: none"> Chronic inflammation Food reactions Autoimmunity
Environmental Considerations in Immune Imbalance	<ul style="list-style-type: none"> Dysbiosis Genetics/Epigenetics Stress
Immune Modification	<ul style="list-style-type: none"> Probiotics, Prebiotics, & Synbiotics Nutrition & Lifestyle

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Summary



Nutrition can impact every aspect of the immune response.



The mind is as important as the body.
IL-6 effect.



Gut health (microbiota) is essential for immunity.

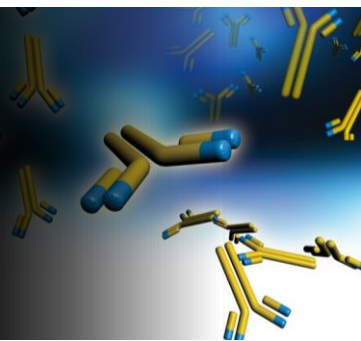
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Questions

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Immune Imbalances and Inflammation

Heather Zwickey, PhD



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