Module 3:

Leaky Gut & Endotoxemia

Rebel health

Build Your Resilient Gut

MICROBIOME & BEYOND

with

Kiran Krishnan

Study session:

What *is* Leaky Gut?

Leaky gut, or **increased intestinal permeability**, occurs when the gut lining becomes damaged or weakened, allowing toxins, microbes, and undigested food particles to pass into the bloodstream, leading to inflammation, immune responses, and a host of systemic health problems.

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The Mighty Mucosa: First Line of Defense

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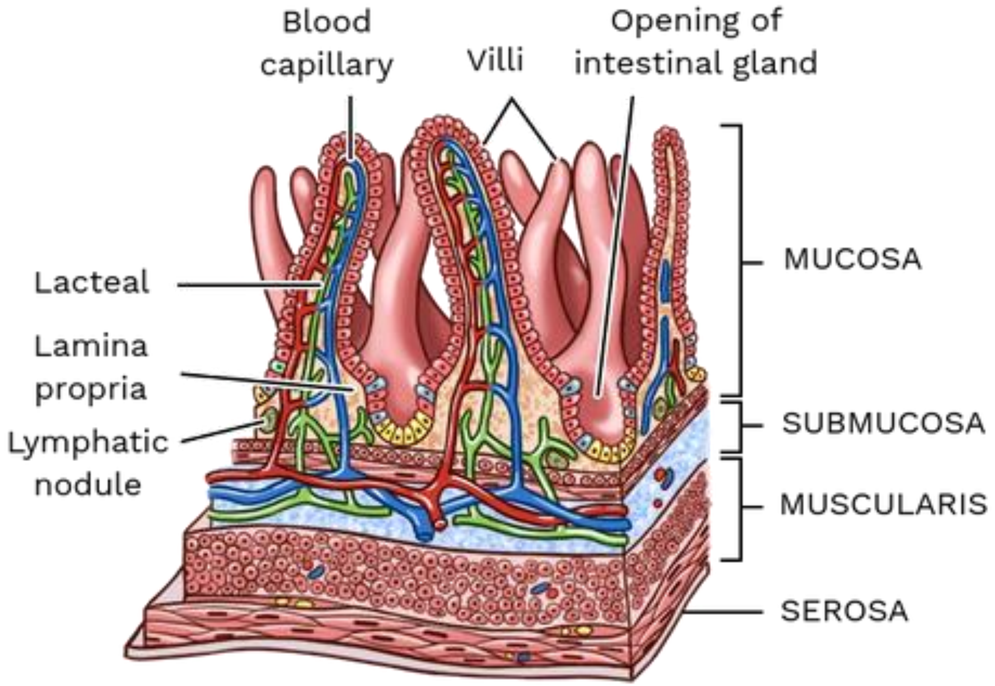
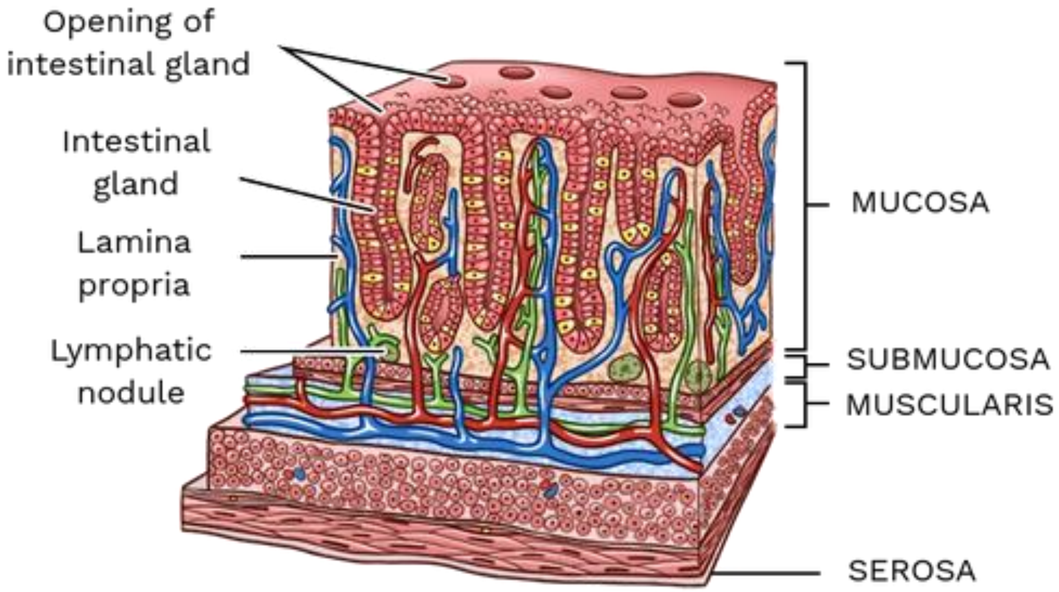
- The **gut mucosal barrier** is the first line of defense, covering roughly 400 square meters (basketball court!)
- It is composed of a complex layer of **mucin**, which protects the epithelial cells beneath it - preventing direct contact between gut microbes, food particles, and the gut lining
- There is a robust immune presence in the mucosa, including:

  - **SIgA** - Immunoglobulins secreted into the mucus, binds/neutralizes pathogens
  - **Defensins** - Antimicrobial peptides produced by epithelial cells, combat pathogens
  - **IAP (Intestinal Alkaline Phosphatase)** - Enzyme in the musical layer that detoxifies harmful substances like LPS, helps maintain a healthy microbiome, and supports tight junction integrity
  - **GALT (Gut-Associated Lymphoid Tissue)** - Part of mucosal immune system, contains 70% of the body's immune cells, constantly sampling the gut to maintain immune balance
  - **Mast Cells & Dendritic Cells** - Regulate immune responses and inflammation in the gut, determining which substances should trigger an immune reaction

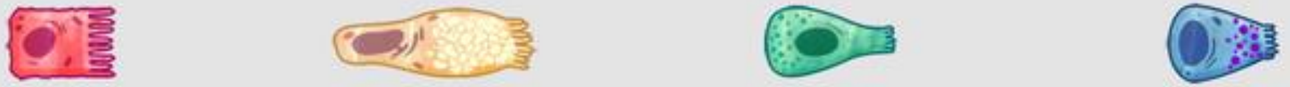


Small Intestine



Large Intestine

Cells of Intestines



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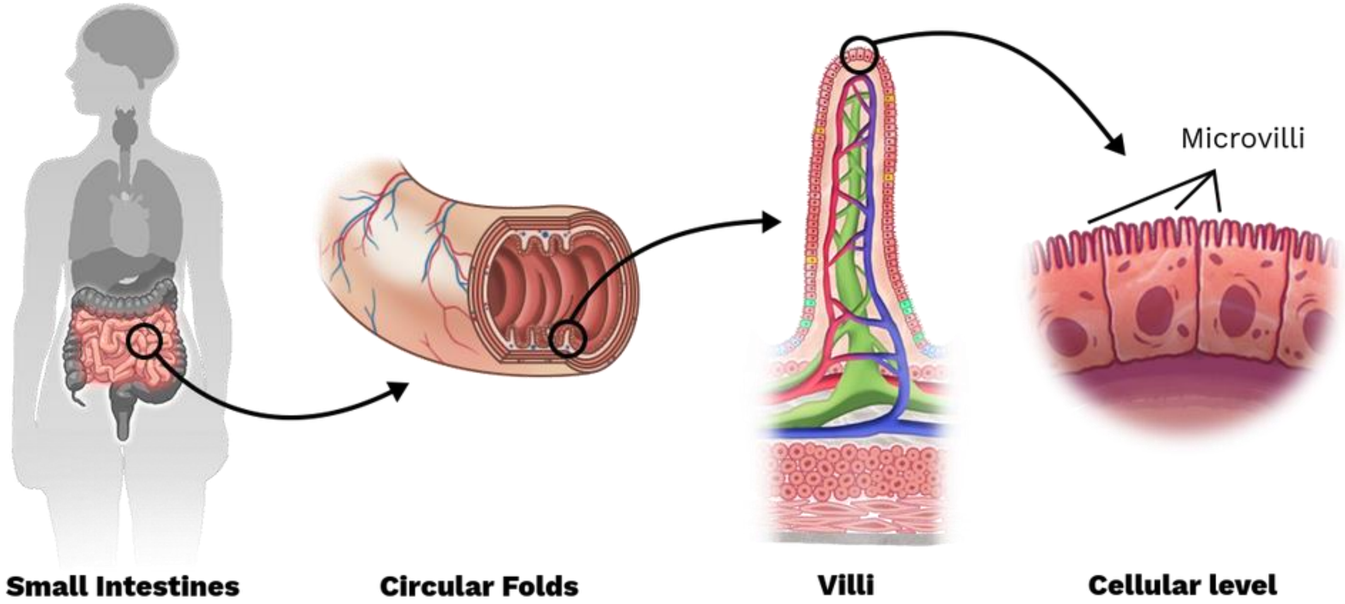

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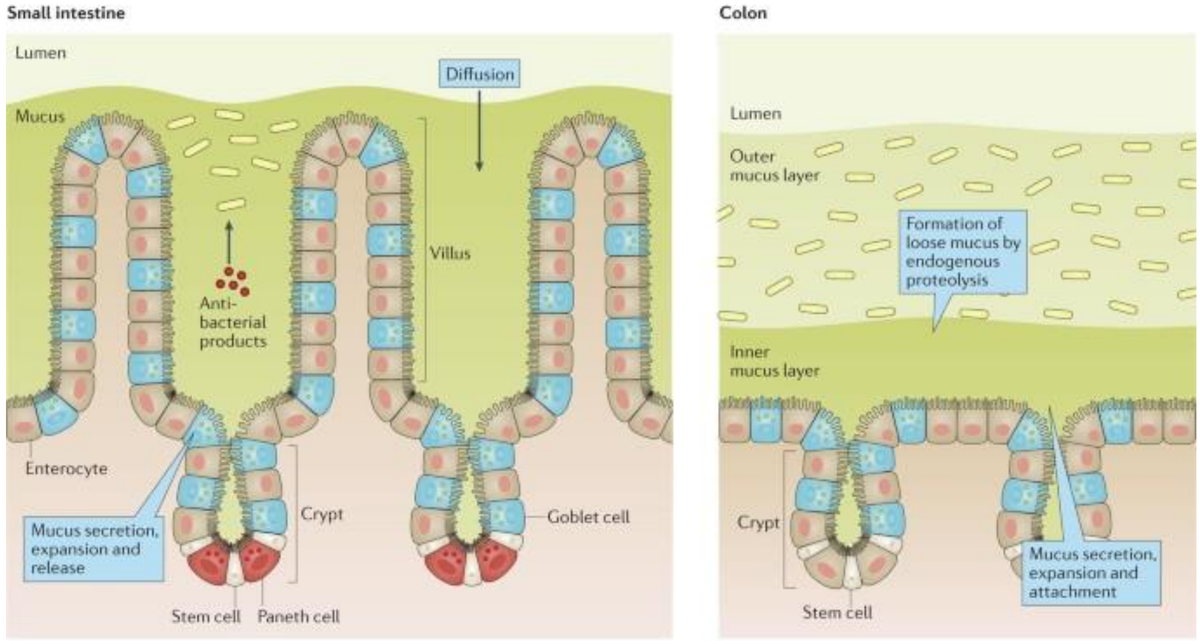

Johansson, M., Hansson, G. Immunological aspects of intestinal mucus and mucins. *Nat Rev Immunol* **16**, 639–649 (2016). https://doi.org/10.1038/nri.2016.88

The Epithelial Cells & Tight Junctions

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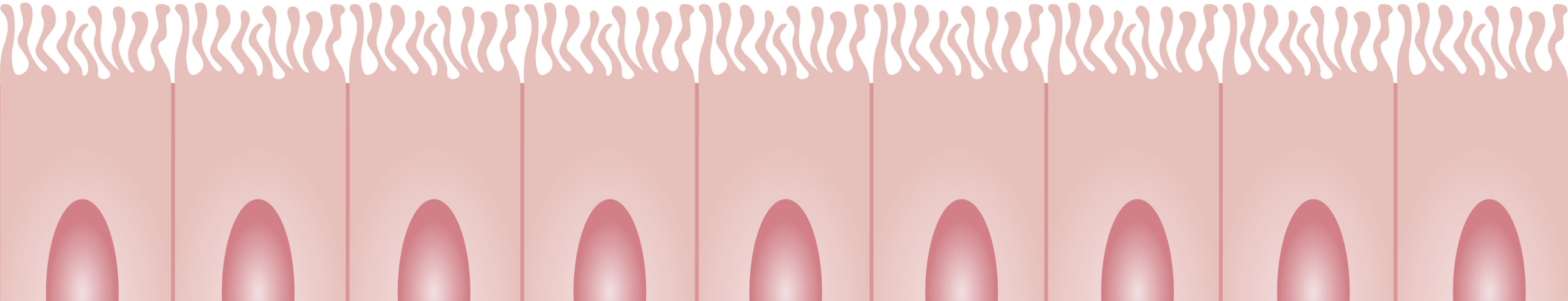
- The epithelial layer is the physical barrier between the gut (outside of our body) and our body (blood stream), which controls what enters circulation from the digestive tract and is responsible for most nutrient absorption
- **Tight junctions** act as gatekeepers, controlling what enters the bloodstream from the gut. When this barrier is compromised, it is possible for toxins, undigested food particles, and microbes to pass through
- The protein **zonulin** regulates the opening and closing of tight junctions. Elevated levels of zonulin have been linked to increased permeability in conditions like celiac disease
- When the mucosal barrier and tight junctions are compromised, it leads to immune chaos - creating inflammatory responses that have effects throughout the body



Study session:

Consequences of Leaky Gut

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It Starts in the Gut, But it Doesn't Stay There…

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- **Autoimmune Conditions:** Hashimoto's, Rheumatoid Arthritis, Lupus, MS, and *dozens* mor
- **Chronic Inflammatory Conditions:** IBS, IBD, Ulcerative Colitis, Crohn's,etc…
- **Sensitivities**: Includes MCAS, Histamine Intolerance, Chemical Sensitivity, Food Sensitivities, etc…
- **Skin Conditions**: Eczema, Psoriasis, Acne, Rosacea, etc…
- **Brain & Cognitive Dysfunction:** Brain Fog, Anxiety, Depression, Alzheimer's, Chronic Fatigue, etc…
- **Metabolic Disorders:** Obesity, Insulin Resistance, Metabolic Syndrome, T2 Diabetes
- **Chronic Pain:** Arthritis, Fibromyalgia, Muscle Pain, etc…
- **Hormonal Imbalance:** PCOS, Infertility, Low Libido, Low Energy, Adrenal Dysfunction, etc…
- **Nutrient Deficiencies**: Vitamins, Minerals, Proteins, Fatty Acids, etc…
- **Respiratory Issues:** Asthma, Allergies, etc…
- **Immune System Dysregulation:** Frequent Infections, Chronic Low-Grade Infections, Poor Illness Recovery, etc…
- **Cardiovascular Issues:** Hypertension, Atherosclerosis - both linked to systemic inflammation

And the BIG Consequence: Metabolic Endotoxemia

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Metabolic endotoxemia occurs when **endotoxins**, primarily **lipopolysaccharides (LPS)** from the outer membrane of **gram-negative bacteria**, leak into the bloodstream due to increased intestinal permeability - contributing to a *host* of chronic health conditions & symptoms including:

- Chronic low-grade inflammation
- Insulin resistance, elevated blood sugar, T2D
- Obesity, weight gain, increased visceral fat
- Cardiovascular disease
- Cognitive dysfunction/Brain disorders
- Liver disease (NAFLD, fibrosis, cirrhosis, etc…)
- Hormone imbalance (PCOS, etc…)
- Autoimmune disease

Metabolic endotoxemia is estimated to affect approximately 50% of the western population

What is an Endotoxin?
AKA - Lipopolysaccharide (LPS)

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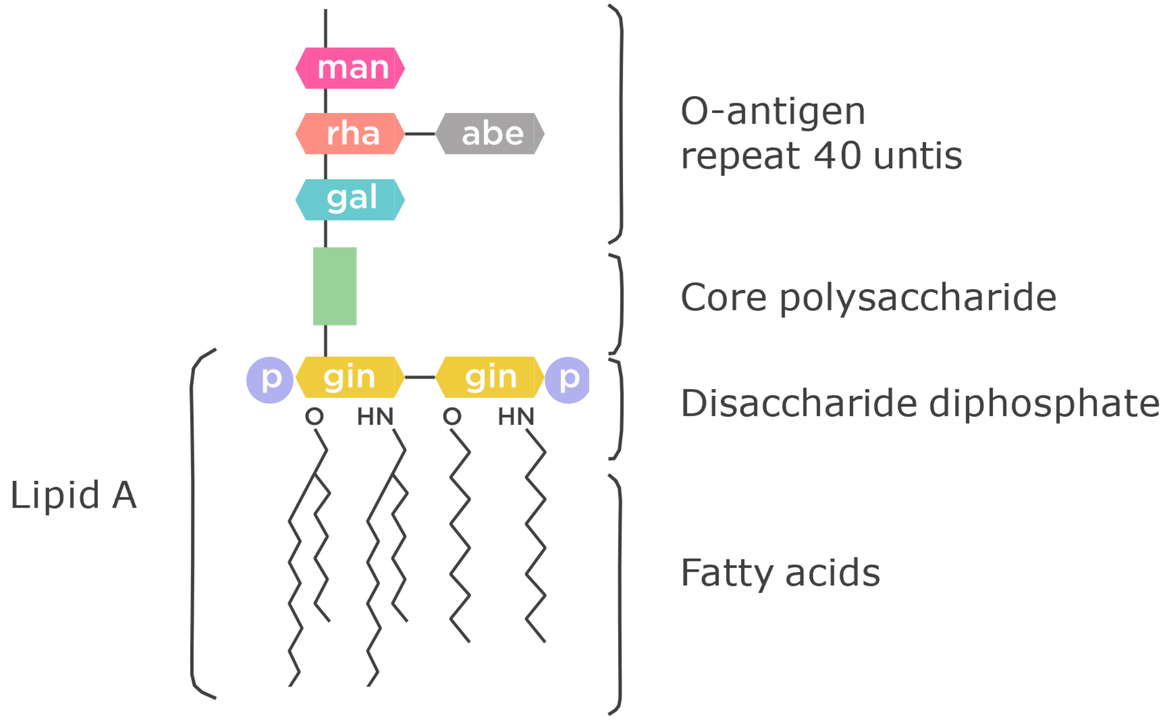
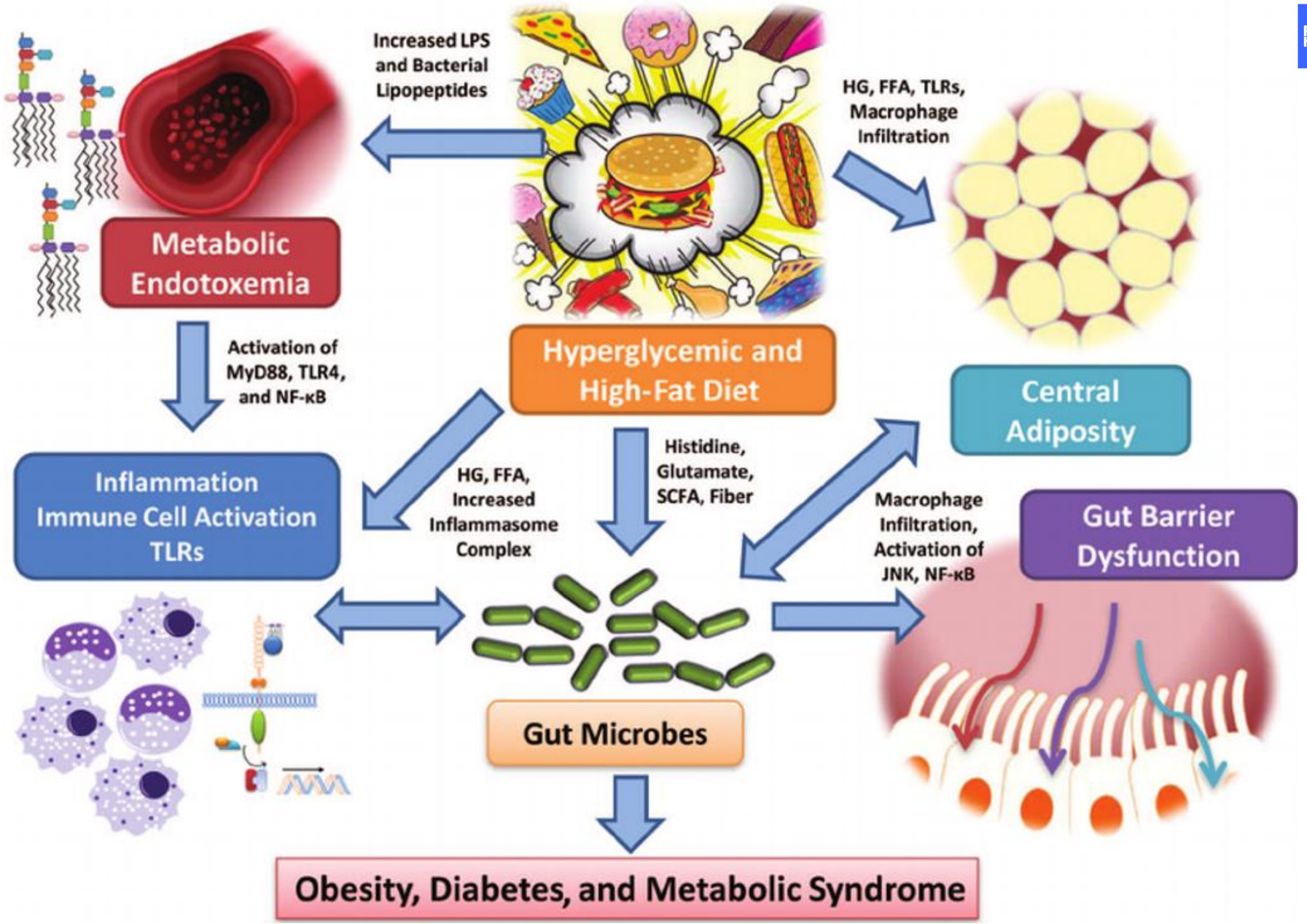
- Inflammatory immunogens
- Component of gram-negative bacterial outer cell wall
- Adhesin for colonization of host
- Diversity of antigenic strains
- Circulates at low-grade levels in healthy individuals
- Toxicity mainly mediated by the lipid-A component



Structure of Lipopolysachharide

http://caltagmedsystems.blogspot.com/2013/05/uscn-specialist-elisa-kit-manufacturer.html


Increased LPS and Bacterial Lipopeptides
HG, FFA, TLRs, Macrophage Infiltration
Metabolic Endotoxemia
Activation of MyD88, TLR4, and NF-κB
Hyperglycemic and High-Fat Diet
Central Adiposity
Inflammation Immune Cell Activation TLRs
HG, FFA, Increased Inflammasome Complex
Histidine, Glutamate, SCFA, Fiber
Macrophage Infiltration, Activation of JNK, NF-κB
Gut Barrier Dysfunction
Gut Microbes
Obesity, Diabetes, and Metabolic Syndrome

“Conclusion: Our results suggest that a high postprandial endotoxemia precedes the development of Type 2 diabetes mellitus. Our results also showed the potential use of LPS plasma levels as a biomarker predictor of T2DM development.”

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Randomized Control Trials

Postprandial endotoxemia may influence the development of type 2 diabetes mellitus: From the CORDIOPREV study

Antonio Camargo [a, b, 1], Rosa Jimenez-Lucena [a, b, 1], Juan F. Alcala-Diaz [a, b], Oriol A. Rangel-Zuñiga [a, b], Sonia Garcia-Carpintero [a, b], Javier Lopez-Moreno [a, b], Ruth Blanco-Rojo [a, b], Javier Delgado-Lista [a, b], Pablo Perez-Martinez [a, b], Ben van Ommen [c], Maria M. Malagon [b, d], Jose M. Ordovas [e, f, g], Francisco Perez-Jimenez [a, b], Jose Lopez-Miranda [a, b, *]

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SUMMARY

Background & aims: Insulin resistance (IR) and impaired beta-cell function are key determinants of type 2 diabetes mellitus (T2DM). Intestinal absorption of bacterial components activates the toll-like receptors inducing inflammation, and this in turn IR. We evaluated the role of endotoxemia in promoting inflammation-induced insulin resistance (IR) in the development of T2DM, and its usefulness as predictive biomarker.
Methods: We included in this study 462 patients from the CORDIOPREV study without T2DM at baseline. Of these, 107 patients developed T2DM according to the American Diabetes Association (ADA) diagnosis criteria after a median follow-up of 60 months (Incident-DIAB group), whereas 355 patients did not developed it during this period of time (Non-DIAB group).
Results: We observed a postprandial increase in lipopolysaccharides (LPS) levels in the Incident-DIAB at baseline ($P < 0.001$), whereas LPS levels were not modified in the Non-DIAB. Disease-free survival curves based on the LPS postprandial fold change improved T2DM Risk Assessment as compared with the previously described FINDRISC score (hazard ratio of 2.076, 95% CI 1.149–3.750 *vs.* 1.384, 95% CI 0.740–2.589). Moreover, disease-free survival curves combining the LPS postprandial fold change and FINDRISC score together showed a hazard ratio of 3.835 (95% CI 1.323–11.114), linked to high values of both parameters.
Conclusion: Our results suggest that a high postprandial endotoxemia precedes the development of T2DM. Our results also showed the potential use of LPS plasma levels as a biomarker predictor of T2DM development.
Clinical trials.gov.identifier: NCT00924937.

Endotoxemia, Obesity & Cardiovascular Risk

Review | A L NEVES and others | *Molecular link between obesity and CV risk* | 51:2 | R51–R64

Metabolic endotoxemia: a molecular link between obesity and cardiovascular risk

Ana Luísa Neves[1], João Coelho[1], Luciana Couto[2], Adelino Leite-Moreira[1] and Roberto Roncon-Albuquerque Jr[1]

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Abstract

Obesity is associated with significantly increased cardiovascular (CV) risk and mortality. Several molecular mechanisms underlying this association have been implied, among which the intestinal barrier has gained a growing interest. In experimental models of obesity, significant alterations in the intestinal barrier lead to increased intestinal permeability,

Key Words
- endotoxemia
- obesity
- cardiovascular diseases

Endotoxemia & Alzheimer's Connection

frontiers in Immunology

PERSPECTIVE
published: 04 September 2017
doi: 10.3389/fimmu.2017.01064

Microbiome-Derived Lipopolysaccharide Enriched in the Perinuclear Region of Alzheimer's Disease Brain

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***Correspondence:**
Walter J. Lukiw

Abundant clinical, epidemiological, imaging, genetic, molecular, and pathophysiological data together indicate that there occur an unusual inflammatory reaction and a disruption of the innate-immune signaling system in Alzheimer's disease (AD) brain. Despite many years of intense study, the origin and molecular mechanics of these AD-relevant pathogenic signals are still not well understood. Here, we provide evidence that an intensely pro-inflammatory bacterial lipopolysaccharide (LPS), part of a complex mixture of pro-inflammatory neurotoxins arising from abundant Gram-negative bacilli of the human gastrointestinal (GI) tract, are abundant in AD-affected brain neocortex and hippocampus. For the first time, we provide evidence that LPS immunohistochemical signals appear to aggregate in clumps in the parenchyma in control brains, and in AD, about 75% of anti-LPS signals were clustered around

Physiology

Role of gut barrier dysfunction and endotoxemia in development of colon cancer cachexia

Melissa J Puppa, James P White, Shuichi Sato, John W Baynes, and James A Carson

Published Online: 1 Apr 2010

Tools Share

Abstract

Cachexia, accounts for ~30% of all cancer-related deaths, and up to 50% of deaths in patients with gastrointestinal cancers. $Apc^{Min/+}$ mice have been used as a model of colorectal cancer that become cachetic at 4–5 months of age. Gut barrier dysfunction (GBD) is an increase in the permeability of intestinal epithelium which can allow bacteria to breach the gut barrier and induce an inflammatory response. The purpose of this study was to determine if GBD is associated with cachexia in the $Apc^{Min/+}$ mouse. Mice were administered FITC-dextran, FD4, (MW 4000 Da) by gavage and blood sampled 1h later via retraorbital stick. Plasma endotoxin was measured with the limulus assay at 12wk and 19wk of age. There was a 27% decrease in body weight of the $Apc^{Min/+}$ mice at 20 wks compared to the C57/BL6 wild type. Plasma FD4 was increased in the $Apc^{Min/+}$ mice at 20wk compared to 14wks (6.9±2.4 μg/ml, n=10 vs 0.5±.5μg/ml, n=7). Endotoxin was greater at 19wks than 12wk $Apc^{Min/+}$ mice (10.5±3EU/ml, n=9 vs 2.02±.8EU/ml, n=4). Mesentaric lymphs were taken at the 20wks were significantly larger in the $Apc^{Min/+}$ mice compared with wild type mice (38±2.4mg, n=6 vs 24.4±1.7mg, n=9). Tumor number between 12 and 20 weeks was not different but, 20wk $Apc^{Min/+}$ mice had an 8 fold greater number of large tumors. From these results, we hypothesize that GBD and resultant endotoxemia induce the pro-inflammatory state that leads to development of cachexia in ApcMin/+ mice.

“From these results, we hypothesize that gut barrier dysfunction and resultant endotoxemia induce the pro-inflammatory state that leads to the development of cachexia.”

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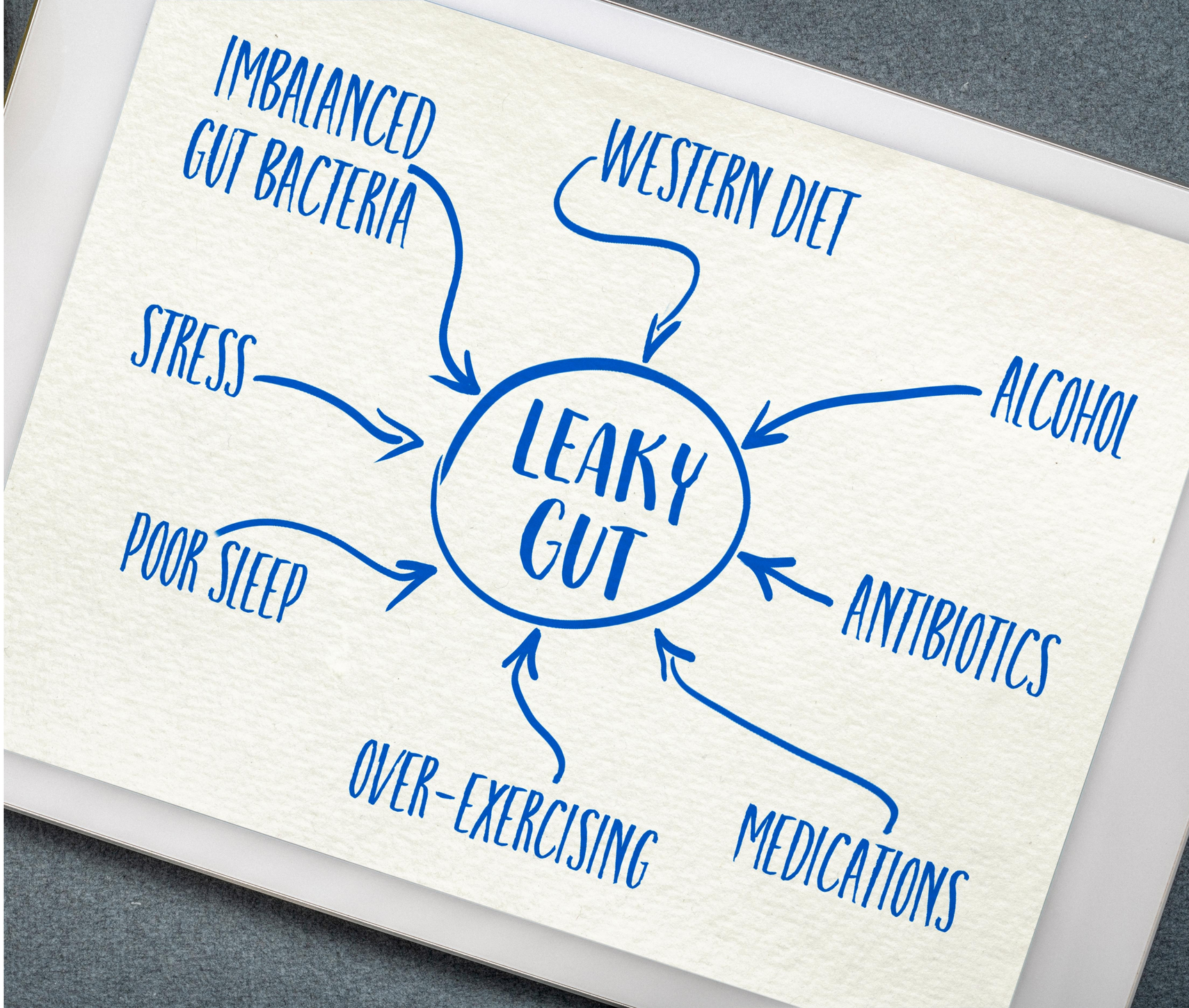
MICROBIOME & BEYOND

CONDITION	MECHANISM
Leptin Resistance	LPS enters and causes inflammation in the enteric nervous system leading to a disruption in the gut-brain axis of communication.
Chronic Constipation	LPS enters the enteric nervous system and causes disruption in signals for gastric emptying and bowel motility.
Mood and Appetite Disorders	LPS disrupts ghrelin function which has a direct impact on appetite and mood,
Depression	LPS can migrate to the blood-brain barrier and cause inflammation along with inhibition of dopamine receptors.
Cognitive Decline	Inflammation in the blood brain barrier leads to cognitive decline.
Loss of Memory and Recall	LPS can get into the amygdala and hippocampus which disrupts memory function.
Depression	LPS can increase the turnover of serotonin in the synapse and CNS reducing the concentration in those regions.
Anorexia Nervosa	The reduction of serotonin in the synapse and CNS is proposed as a possible mechanism for anorexia.
Anxiety	LPS disrupts key communication between the hypothalamic-adrenal-pituitary axis thereby increasing the expression of corticosteroid releasing hormone.
Chronic Pain	Elevated LPS in sensory neurons in the dorsal root stimulate nociceptors.
Parkinson's	Intra-cranially LPS causes microglial activation and neuronal loss.
Hypogonadism (low testosterone)	Increased circulating LPS and the subsequent chronic immune activation has feedback inhibition of testosterone production. GELDING theory.
Autoimmunity	Chronic activation of the innate immune system in various tissues leads to the by-stander effect where self-tissues inadvertently become targeted by the immune system.

Root Causes of Leaky Gut & Metabolic Endotoxemia



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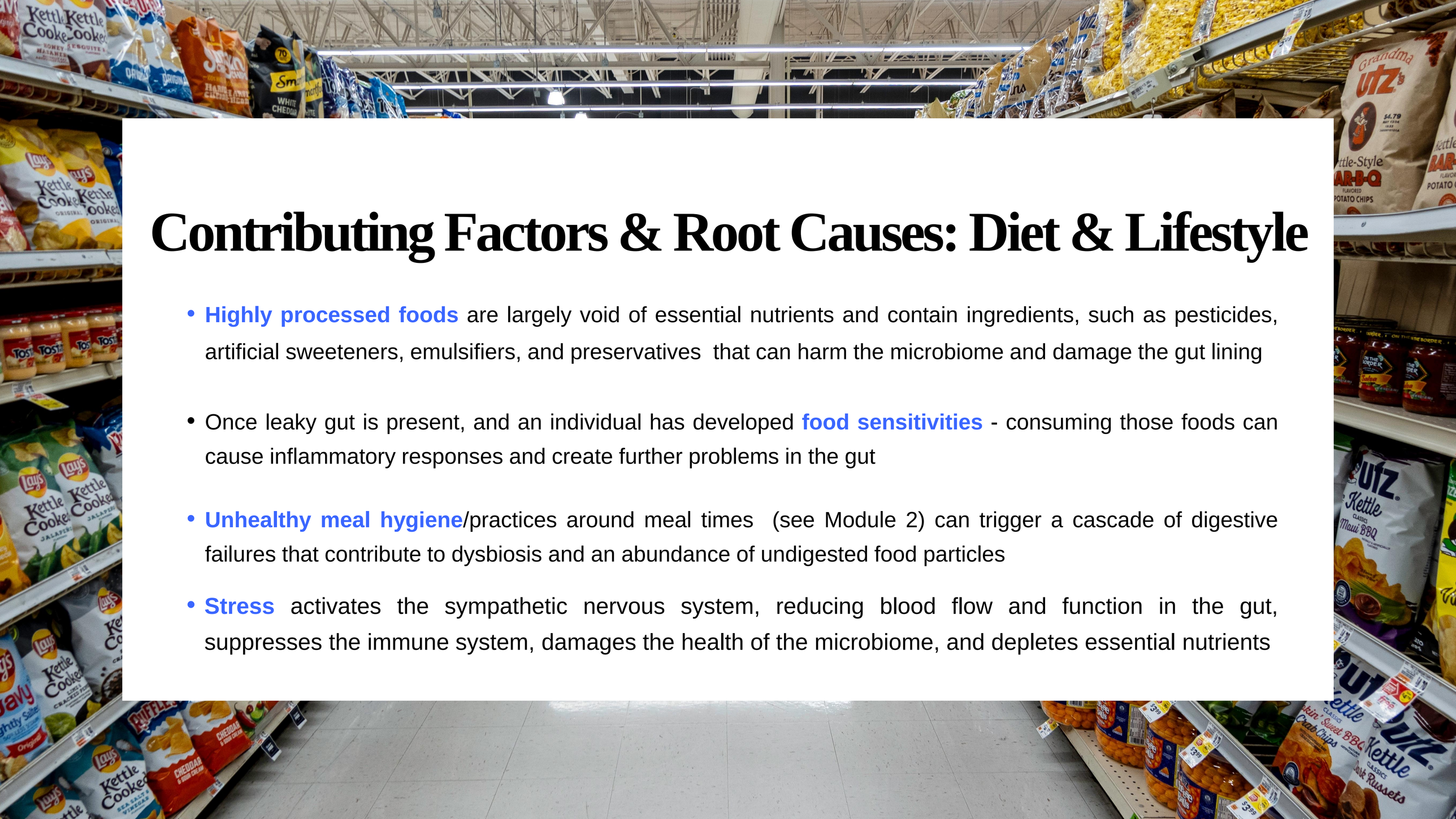


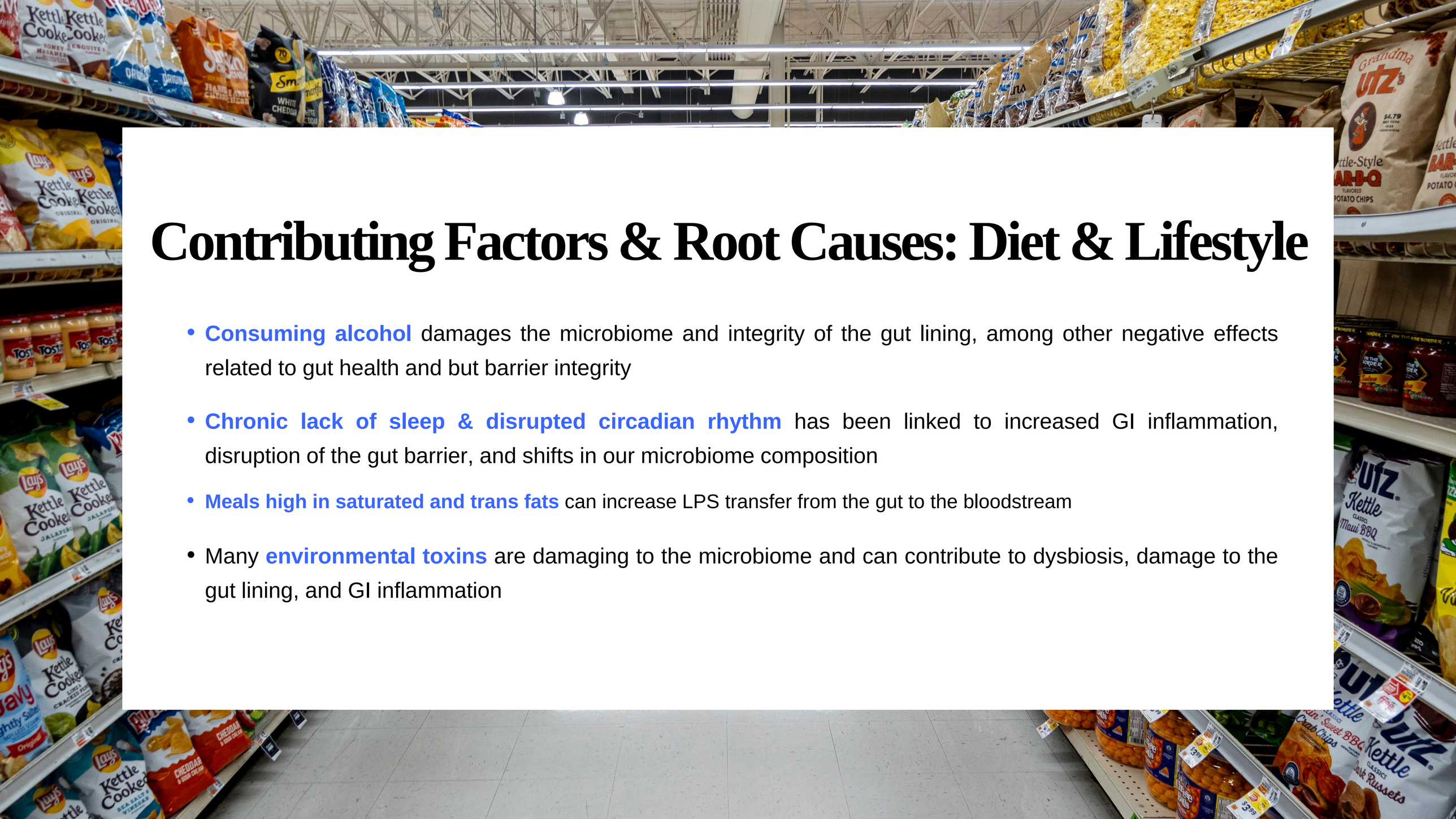
Contributing Factors & Root Causes: Diet & Lifestyle

- **Highly processed foods** are largely void of essential nutrients and contain ingredients, such as pesticides, artificial sweeteners, emulsifiers, and preservatives that can harm the microbiome and damage the gut lining

- Once leaky gut is present, and an individual has developed **food sensitivities** - consuming those foods can cause inflammatory responses and create further problems in the gut

- **Unhealthy meal hygiene**/practices around meal times (see Module 2) can trigger a cascade of digestive failures that contribute to dysbiosis and an abundance of undigested food particles

- **Stress** activates the sympathetic nervous system, reducing blood flow and function in the gut, suppresses the immune system, damages the health of the microbiome, and depletes essential nutrients



Contributing Factors & Root Causes: Diet & Lifestyle

- **Consuming alcohol** damages the microbiome and integrity of the gut lining, among other negative effects related to gut health and but barrier integrity
- **Chronic lack of sleep & disrupted circadian rhythm** has been linked to increased GI inflammation, disruption of the gut barrier, and shifts in our microbiome composition
- **Meals high in saturated and trans fats** can increase LPS transfer from the gut to the bloodstream
- Many **environmental toxins** are damaging to the microbiome and can contribute to dysbiosis, damage to the gut lining, and GI inflammation

Contributing Factors & Root Causes: Dysbiosis, GI Environment & Imbalances

- **Pathogenic organisms** release toxins (like LPS) that can damage and degrade the gut lining
- An absence of beneficial microbes leads to **deficiency in SCFAs**, particularly butyrate - which is essential for maintaining healthy cells in the gut lining
- **Infections/overgrowths** like **SIBO** (Small Intestinal Bacterial Overgrowth) and **candida** can produce toxins and cause inflammation that weaken the gut lining
- An absence of beneficial microbes reduces the thickness and integrity of the mucosal layer

Contributing Factors & Root Causes: Dysbiosis, GI Environment & Imbalances

- The microbiome is responsible for the **production, support, and regulation of essential compounds, molecules, and peptides**, such as mucin, defensins, SIgA, HIFs, dendritic cells, and *much* more - when this is inadequate due to dysbiosis, the integrity of the gut barrier is compromised and immune chaos ensues

- In the absence of adequate beneficial SCFA-producing microbes (and therefore a lack of butyrate), the gut environment will see an **increase in oxygen**. This is bad for beneficial organisms and more hospitable to pathogenic overgrowth - contributing to leaky gut

Contributing Factors & Root Causes: Medications, Toxins, Antibiotics, & Over-Sterilization

- Pesticides, heavy metals, and many other chemicals and pollutants can harm the microbiome and damage the gut lining
- Alcohol, NSAIDs (ibuprofen, etc…), and other medications are common triggers to increased intestinal permeability
- Antibiotics kill beneficial bacteria, which are essential for maintaining healthy gut barrier integrity - overuse allows harmful bacteria to flourish, contributing to leaky gut
- Lack of exposure to microbes from the environment (dirt, pets, nature, etc…) reduces microbial diversity, which weakens the gut barrier
- Excessive use of antibacterial products, mouthwash, and over-sterilization can harm the microbiome, contributing to dysbiosis and increased gut permeability

Study session:

So What Do We Do?

REDUCING METABOLIC ENDOTOXEMIA & REPAIRING LEAKY GUT

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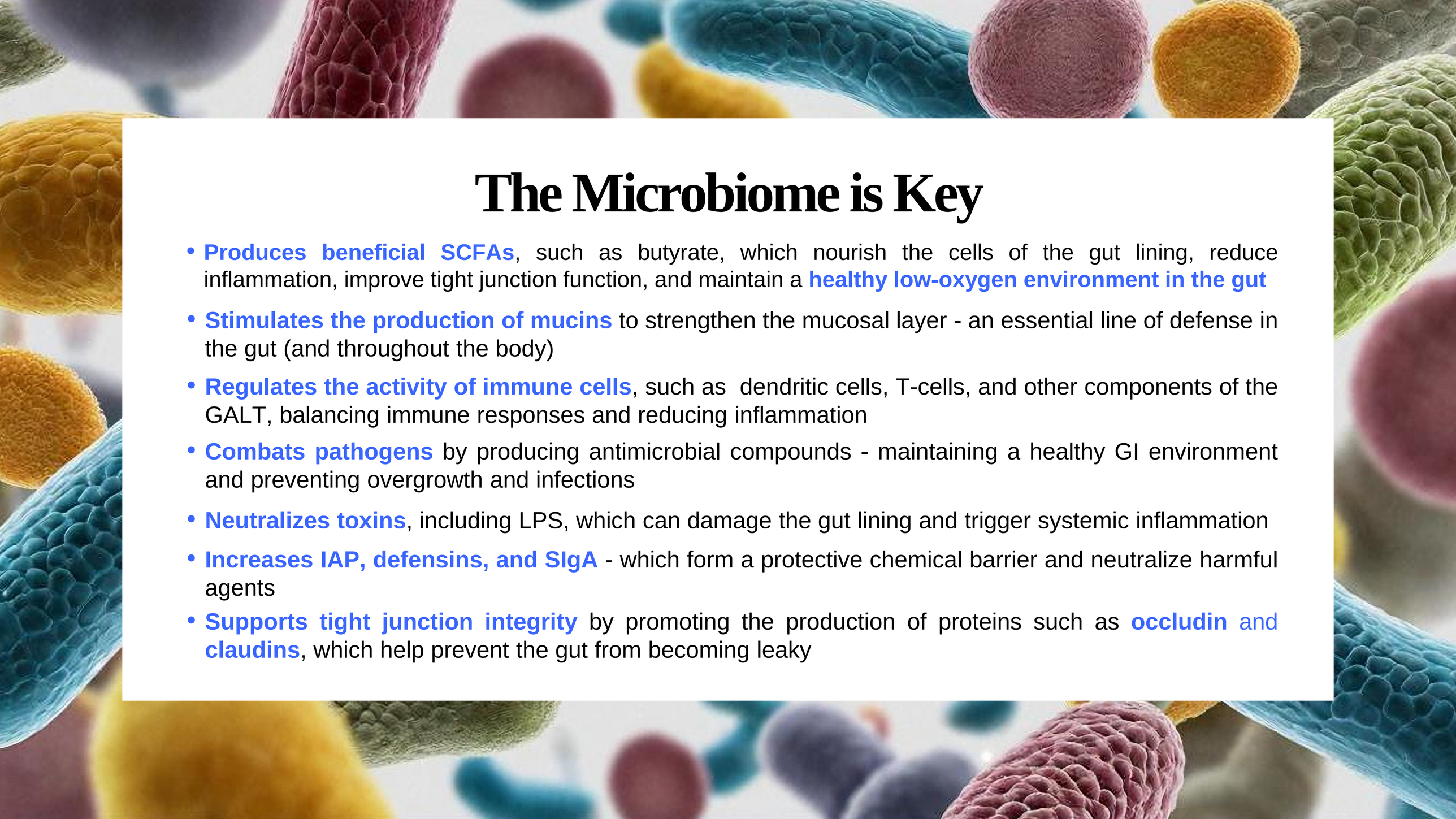
Build Your Resilient Gut

MICROBIOME & BEYOND



The Microbiome is Key

- **Produces beneficial SCFAs**, such as butyrate, which nourish the cells of the gut lining, reduce inflammation, improve tight junction function, and maintain a **healthy low-oxygen environment in the gut**
- **Stimulates the production of mucins** to strengthen the mucosal layer - an essential line of defense in the gut (and throughout the body)
- **Regulates the activity of immune cells**, such as dendritic cells, T-cells, and other components of the GALT, balancing immune responses and reducing inflammation
- **Combats pathogens** by producing antimicrobial compounds - maintaining a healthy GI environment and preventing overgrowth and infections
- **Neutralizes toxins**, including LPS, which can damage the gut lining and trigger systemic inflammation
- **Increases IAP, defensins, and SIgA** - which form a protective chemical barrier and neutralize harmful agents
- **Supports tight junction integrity** by promoting the production of proteins such as **occludin** and **claudins**, which help prevent the gut from becoming leaky

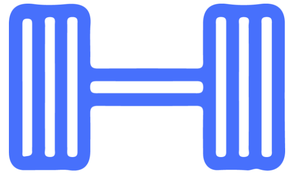
Remember the 5 Pillars to Cultivate a Healthy Microbiome

Pillar 1: FOOD

- Diverse - Colors - Polyphenols
- Fiber - All Types - 50g/day Goal
- Prebiotic Foods
- Low to Moderate Fat - Reduce Saturated/Trans
- Real Foods - Organic

Pillar 2: STRESS

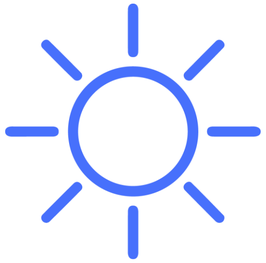
- Meditation/Mindfulness
- Breathing
- Nature
- Nervous System/Brain Retraining
- Yoga - Qigong - Tai Chi
- Trauma Therapy
- More JOY!



Pillar 3: LIFESTYLE

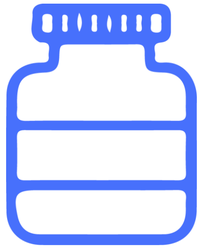
- Exercise - Strength!
- Sleep & Circadian Rhythm
- Meal Hygiene
- Connection/Community
- Intermittent Fasting (MMC!)

Remember the 5 Pillars to Cultivate a Healthy Microbiome



Pillar 4: EXPOSURE

- Pets - Dirt - Nature
- Minimal Antibiotics (Natural or Rx)
- Avoid Over-Sterilization
- Reduce Toxin Exposure



Pillar 5: SUPPLEMENTS

- Spore-based Probiotics (**MegaSporeBiotic**)
- Precision Prebiotics (**MegaPre**)
- Butyrate (**Tributyrin-X**)
- Targeted Digestive Support (as Needed)
- Microbiome Foundations Bundle!
- Microbiome Foundations Bundle!

Repairing Leaky Gut & Reducing Metabolic Endotoxemia

TARGETED SUPPLEMENTATION

MegaSporeBiotic™

- **Reduces leaky gut & endotoxemia (enhanced gut barrier function)**

- Increases microbial diversity and beneficial keystone strains
- **Boosts production of SCFAs** like butyrate and other beneficial metabolites
- Has significant hepatoprotective (liver) properties
- Reduces systemic inflammatory markers
- Produce antioxidants at the point of absorption/utilization in the gut

Repairing Leaky Gut & Reducing Metabolic Endotoxemia

TARGETED SUPPLEMENTATION

Tributyrin-X

- **Strengthens tight junctions/gut barrier function**
- Promotes microbiome diversity
- **Maintains a low-oxygen environment**, critical for the survival of beneficial microbes
- Reduces inflammation and oxidative stress in the gut - can stabilize mast cells & immune responses
- Preferred fuel source for the cells lining the colon (colonocytes)
- **Increases endogenous butyrate production**

Repairing Leaky Gut & Reducing Metabolic Endotoxemia

TARGETED SUPPLEMENTATION

MegaMucosa

- Contains immunoglobulins (IgG**)** to **neutralize toxins (including LPS)**
- Contains **polyphenols** for antioxidant and anti-inflammatory benefits
- Contains key amino acids (L-proline, L-serine, L-cysteine) that **support gut barrier repair and mucin production**

Repairing Leaky Gut & Reducing Metabolic Endotoxemia

TARGETED SUPPLEMENTATION

MegaIgG2000

- **Neutralizes, binds, and removes toxins, such as LPS (endotoxins)**
- **Supports gut barrier integrity** by protecting it from harmful pathogens and toxins
- Lowers gut inflammation by neutralizing inflammatory triggers
- Helps **seal the gut lining**, reducing intestinal permeability

Additional Supplements to Consider

- **Polyphenols** - Supports microbiome diversity, reduces inflammation, and can reduce LPS in the gut – Pomegranate Extract (**656mg of phenolic compounds per day**)
- **Zinc Carnosine** - Helps to repair the gut lining and reduce GI inflammation: **75mg 2 time per day**
- **L-Glutamine** - Fuels gut lining cells, promotes repair, and regenerates the intestinal barrier: **5g per day**
- **Quercetin** - Strengthens tight junctions, reduces gut inflammation, and stabilizes immune responses: **500mg – 1000mg daily**
- **N-Acetyl Glucosamine (NAG)** - Boosts mucin production to protect and repair the gut lining: **500mg – 1000mg**
- **Marshmallow Root** - Soothes and protects the gut lining, promoting healing and reducing irritation: **2-5ml per day of liquid extract**
- **DGL (Deglycyrrhizinated Licorice)** - Soothing for the gut lining, reduces inflammation, and protects the mucosal layer: **350mg taken before a meal, 3 times per day**

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Build Your Resilient Gut

MICROBIOME & BEYOND

THANK YOU