

In the name of God



The Effects of the Ketogenic Diet on Gut Microbiota

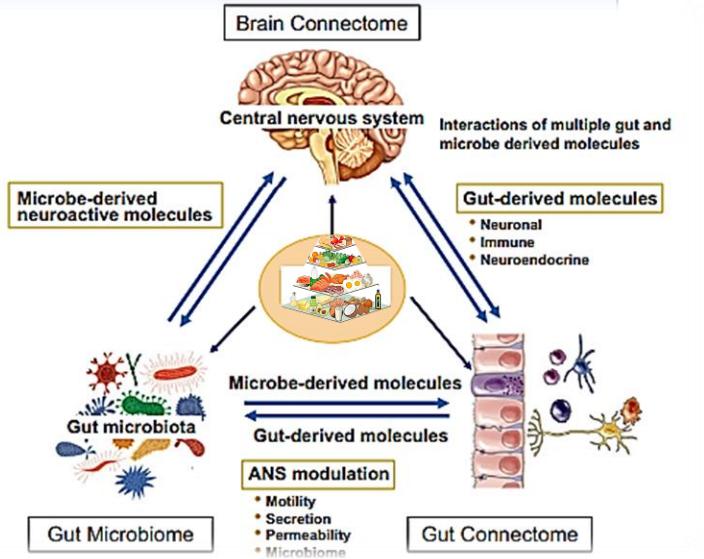
From Metabolic Reprogramming to Host–Microbe Signaling and the Gut–Brain Axis

Supervisor:

Dr. fazeli

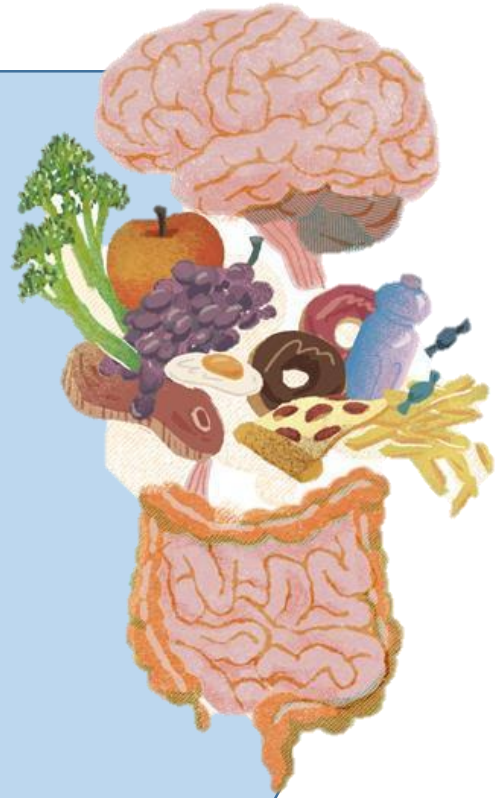
Presenter:

Saeede sadat Hosseini



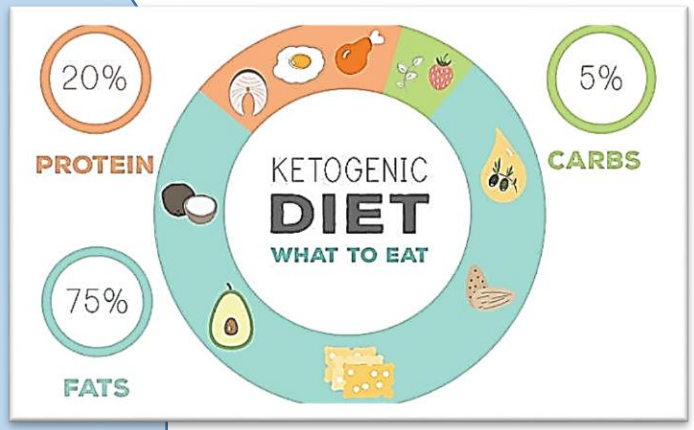
Outline:

- Ketogenic diet and host metabolism
- Microbial ecology and metabolic activity
- Immune regulation and intestinal barrier
- Gut–brain communication
- Translational evidence and limitations



What is the Ketogenic Diet (KD)?

A high-fat, very-low-carbohydrate, moderate-protein dietary pattern



Types of Ketogenic Diet:

Diet	Main characteristic
Classic KD	High fat; typically 4:1 or 3:1 fat:(protein + carbohydrate) by weight
MCT Diet	Uses medium-chain triglycerides to facilitate ketone production
Modified Atkins Diet	Low carbohydrate, higher protein, less restrictive
LGIT	Low-glycemic carbohydrates rather than strict macronutrient ratios
VLCKD	Very-low-calorie ketogenic approach, mainly used in metabolic/obesity settings
Mediterranean KD	Ketogenic framework combined with Mediterranean food patterns

Core metabolic shift:

Glucose dependence ↓ → Fatty-acid oxidation ↑ → Ketogenesis ↑

Abbreviation:

- **KD:** Ketogenic Diet
- **MCT:** Medium-Chain Triglycerides
- **LGIT:** Low-Glycemic Index Treatment ·
- **VLCKD:** Very-Low-Calorie Ketogenic Diet

From Carbohydrate Restriction to Hepatic Ketogenesis

Reduced carbohydrate availability

↓

Decreased insulin-to-glucagon ratio

↓

Increased adipose lipolysis

↓

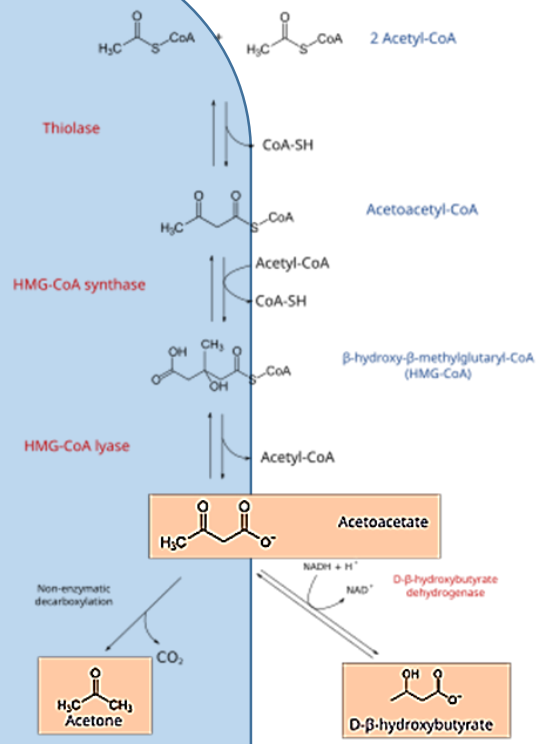
Hepatic fatty acid β-oxidation

↓

Acetyl-CoA → Ketone bodies (BHB, AcAc, Acetone)

↓

BHB crosses BBB via MCT1 → neuronal ketolysis → ATP

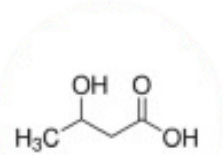


Abbreviation:

- **BHB:** β-Hydroxybutyrate
- **AcAc:** Acetoacetate
- **MCT1:** Monocarboxylate Transporter 1

BHB as Master Signaling Molecule:

1. **HDAC inhibition → histone hyperacetylation → gene expression changes**
2. **Histone lysine β-hydroxybutyrylation (Kbhb) → novel epigenetic mark**
3. **NLRP3 inflammasome inhibition → ↓ IL-1β, ↓ IL-18**
4. **GPR109A activation → ALDH1A → Retinoic Acid → Treg + IL-10**
5. **Nrf2 activation → ↑ SOD, ↑ Catalase, ↑ HO-1 → ↓ oxidative stress**

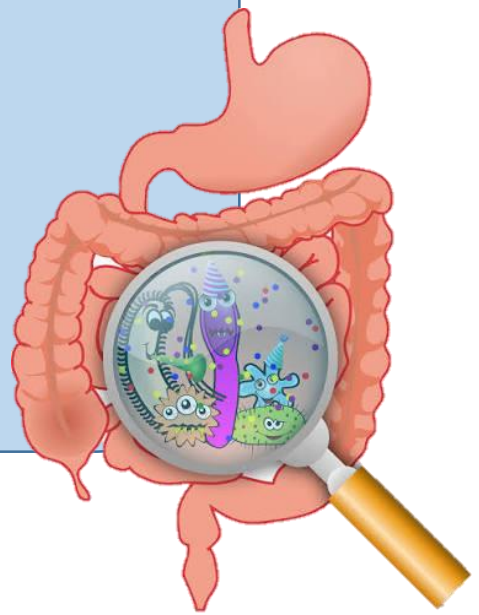


Abbreviation:

- **HDAC:** Histone Deacetylase
- **Kbhb:** Histone Lysine β-Hydroxybutyrylation
- **NLRP3:** NLR Family Pyrin Domain Containing 3
- **GPR109A:** G-Protein Coupled Receptor 109A
- **ALDH1A:** Aldehyde Dehydrogenase 1 Family Member A
- **Nrf2:** Nuclear Factor Erythroid 2-Related Factor 2
- **HO-1:** Heme Oxygenase-1

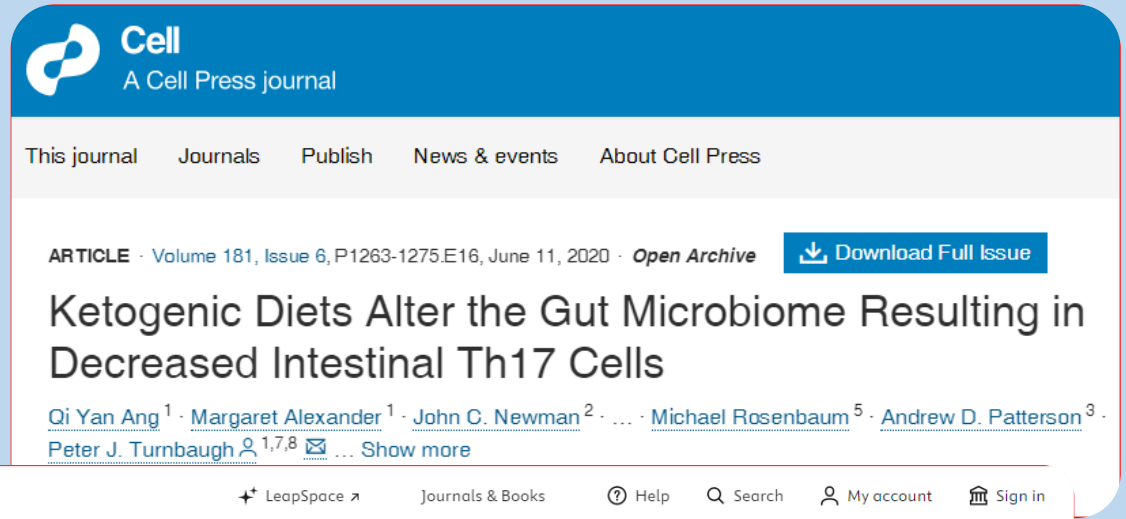
Diet as an Ecological Pressure on the Gut Microbiota

- **Substrate availability:** fiber, fat, protein
- **Bile acid secretion and composition**
- **Intestinal transit and luminal pH**
- **Host physiology and microbial interactions**
- **Cross-feeding networks shape microbial communities**



BHB: Selective Antimicrobial Effect

- **Directly inhibits *Bifidobacterium* growth (in vitro & in vivo)**
  - **Mechanism:** disruption of membrane potential and intracellular pH
  - **Selective:** not all bacteria equally affected
- **BHB secreted into intestinal lumen from bloodstream**
- ***Bifidobacterium*: potent inducer of Th17**
- **Reduction is not universally beneficial**





Akkermansia and *Parabacteroides*: Potential Functional Players

➢ ***Akkermansia muciniphila*:**

· **Mucin-associated bacterium**

· **Degrades mucin → short-chain fatty acids**

· **Strengthens barrier integrity**

· **Increases with KD in some studies**

➢ ***Parabacteroides spp.:***

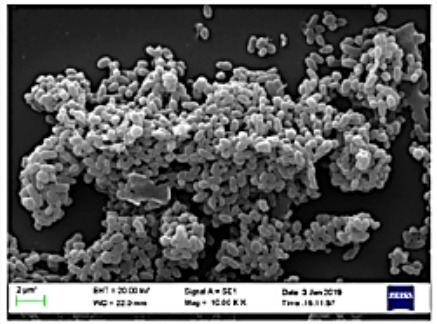
· **Metabolically versatile anaerobes**

· **Produce succinate, acetate**

· **Context-dependent effects on immunity**

· **Increase with KD in some studies**

Akkermansia muciniphila



Scanning electron micrograph of *Akkermansia muciniphila*[1]

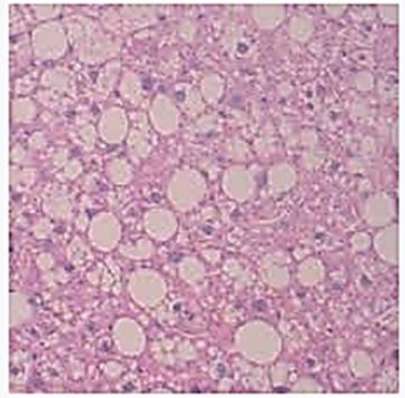
Scientific classification

Domain:	Bacteria
Kingdom:	Pseudomonadati
Phylum:	Verrucomicrobiota
Class:	Verrucomicrobiia
Order:	Verrucomicrobiales
Family:	Akkermansiaceae
Genus:	*Akkermansia*
Species:	***A. muciniphila***

Binomial name

Akkermansia muciniphila
Derrien et al. 2004

Parabacteroides



Parabacteroides distasonis, a species of *Parabacteroides* within the human gut microbiome

Scientific classification

Domain:	Bacteria
Kingdom:	Pseudomonadati
Phylum:	Bacteroidota
Class:	Bacteroidia
Order:	Bacteroidales
Family:	Tannerellaceae
Genus:	***Parabacteroides*** Sakamoto and Benno 2006[1]

Akkermansia and *Parabacteroides*

➢ *Akkermansia muciniphila:*

· Outer membrane protein Amuc_1100 → TLR2 → barrier integrity

· ↑ MUC2, ↑ tight junctions

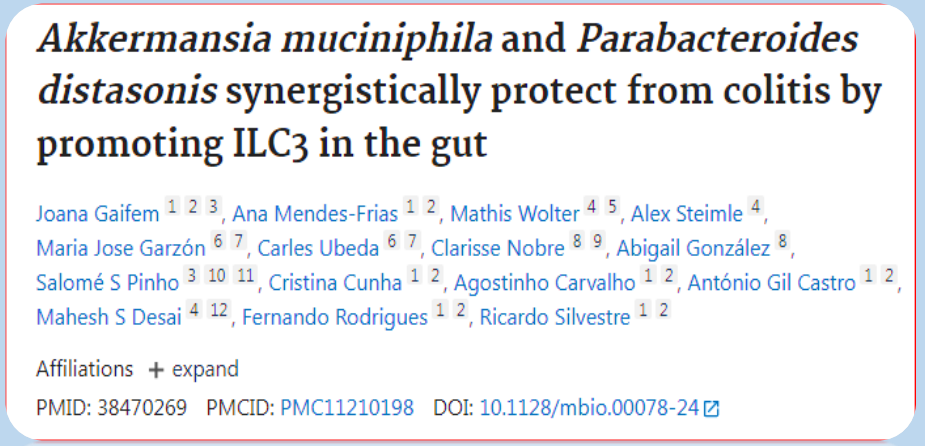
· ↑ Treg, ↓ inflammation

➢ *Parabacteroides distasonis:*

· Succinate → propionate → GPR41

· ↑ ILC3 → IL-22 → barrier

· Synergy with *Akkermansia*



***Akkermansia muciniphila* and *Parabacteroides distasonis* synergistically protect from colitis by promoting ILC3 in the gut**

Joana Gaifem [1 2 3], Ana Mendes-Frias [1 2], Mathis Wolter [4 5], Alex Steimle [4], Maria Jose Garzón [6 7], Carles Ubeda [6 7], Clarisse Nobre [8 9], Abigail González [8], Salomé S Pinho [3 10 11], Cristina Cunha [1 2], Agostinho Carvalho [1 2], António Gil Castro [1 2], Mahesh S Desai [4 12], Fernando Rodrigues [1 2], Ricardo Silvestre [1 2]

Affiliations + expand

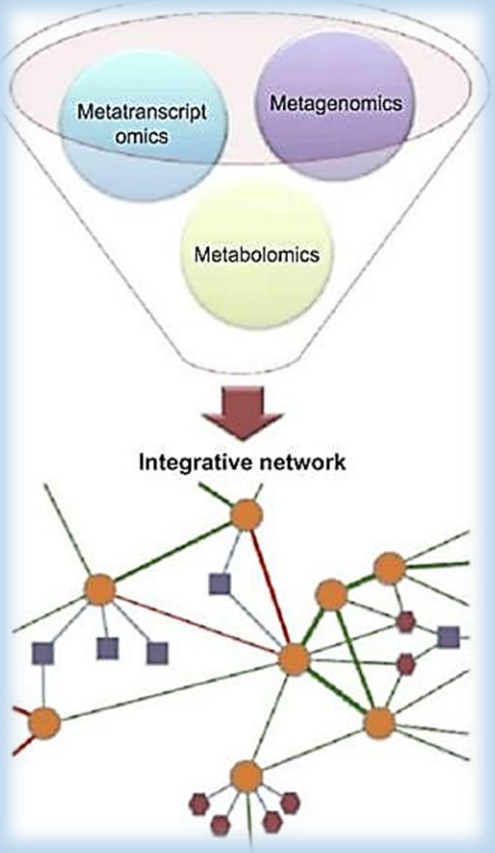
PMID: 38470269 PMCID: PMC11210198 DOI: 10.1128/mbio.00078-24

Abbreviation:

- **Amuc_1100:** Outer Membrane Protein of *Akkermansia muciniphila*
- **TLR2:** Toll-Like Receptor 2
- **Treg:** Regulatory T cells
- **GPR41:** G-Protein Coupled Receptor 41
- **ILC3:** Group 3 Innate Lymphoid Cells

Taxonomy Is Not Function

- **Relative abundance ≠ absolute abundance**
- **Microbial genes ≠ gene expression**
- **Metabolite production depends on substrates**
- **Cross-feeding shapes microbial networks**
- **Integrative multi-omics improves interpretation**



Short-Chain Fatty Acids (SCFAs): Microbial Metabolites with Host Effects

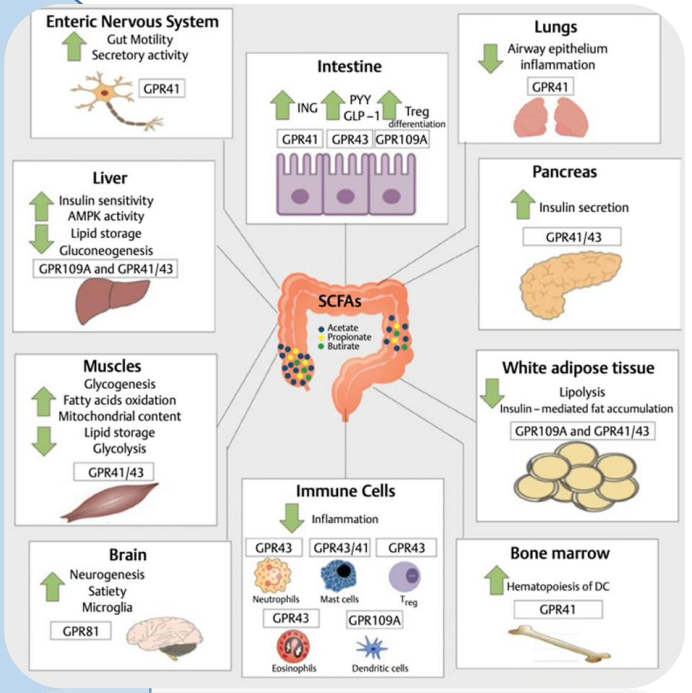
· Acetate (C2) → GPR43 → lipogenesis

· Propionate (C3) → GPR41 → gluconeogenesis, satiety

· Butyrate (C4) → GPR109A, HDAC inhibition → Treg, barrier

❑ **Produced through microbial fermentation of fiber**

❑ **KD → variable SCFA responses**



Abbreviation:

- **SCFA:** Short-Chain Fatty Acids
- **GPR43:** G-Protein Coupled Receptor 43
- **GPR41:** G-Protein Coupled Receptor 41
- **GPR109A:** G-Protein Coupled Receptor 109A

Bile Acids: A Link Between Dietary Fat and Microbial Metabolism

- Dietary fat stimulates bile secretion
- Microbial BSH deconjugates bile acids
- 7α-dehydroxylation → secondary bile acids (DCA, LCA)
- FXR / TGR5 signaling → metabolic + immune effects

KD → Bile Acid Remodeling → Host Signaling

High dietary fat
↓
Altered bile-acid secretion and composition
↓
Microbial BSH activity
↓
Modification of bile-acid pool
↓
FXR / TGR5 signaling
↓
Metabolic + immune effects

Abbreviation:

- **BSH:** Bile Salt Hydrolase
- **DCA:** Deoxycholic Acid
- **LCA:** Lithocholic Acid
- **FXR:** Farnesoid X Receptor
- **TGR5:** Takeda G-Protein-Coupled Receptor 5

Bile Acid Remodeling: Molecular Details

· BSH (Bile Salt Hydrolase):

· *Bacteroides*, *Clostridium*, *Lactobacillus*

· Deconjugation → free bile acids

· 7α-dehydroxylase:

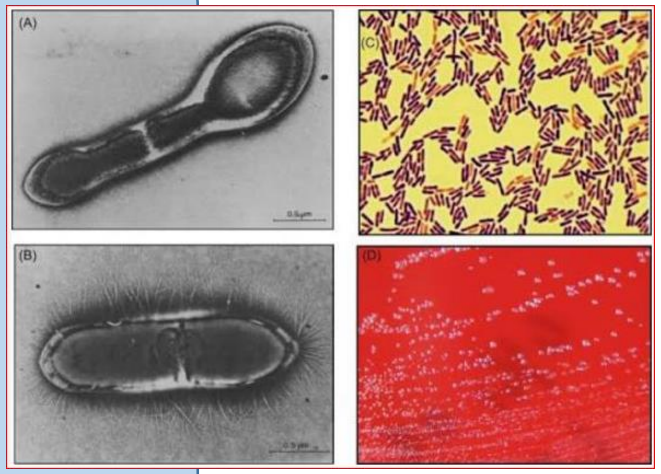
· *Clostridium scindens*

· DCA, LCA production

· FXR/TGR5 signaling:

· FXR: ↓ bile acid synthesis, ↓ lipogenesis

· TGR5: ↑ GLP-1, ↑ thermogenesis



Clostridium scindens

Scientific classification

Domain:	Bacteria
Kingdom:	Bacillati
Phylum:	Bacillota
Class:	Clostridia
Order:	Eubacteriales
Family:	Clostridiaceae
Genus:	*Clostridium*
Species:	***C. scindens***

Binomial name

Clostridium scindens
(Bokkenheuser et al. 1984)

Synonyms

Eubacterium sp. VPI12708

Abbreviation:

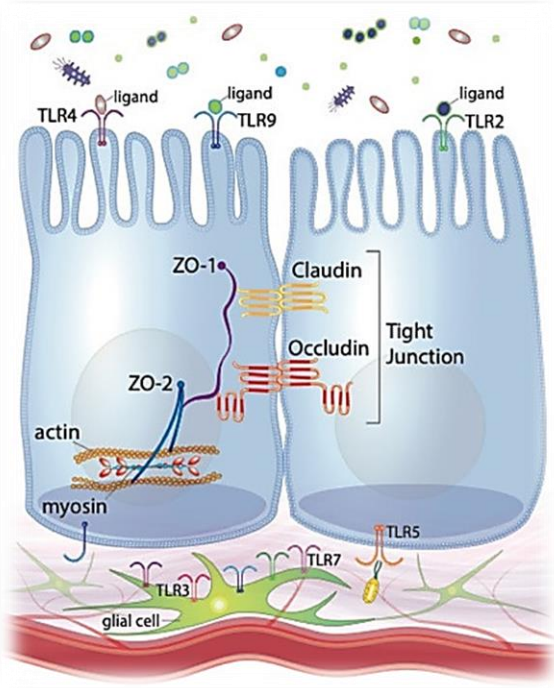
- **GLP-1:** Glucagon-Like Peptide-1

The Intestinal Barrier: A Multilayered Interface

- **Mucus layer:** MUC2, IgA, antimicrobial peptides
- **Epithelial cells:** enterocytes, goblet, Paneth, M cells
- **Tight junctions:** ZO-1, Occludin, Claudins
- **Immune surveillance:** DCs, macrophages, ILCs

➢ **KD effects:**

- BHB and butyrate enhance barrier integrity
- ↑ MUC2, ↑ RegIIIγ, ↑ tight junction proteins
- ↓ LPS translocation

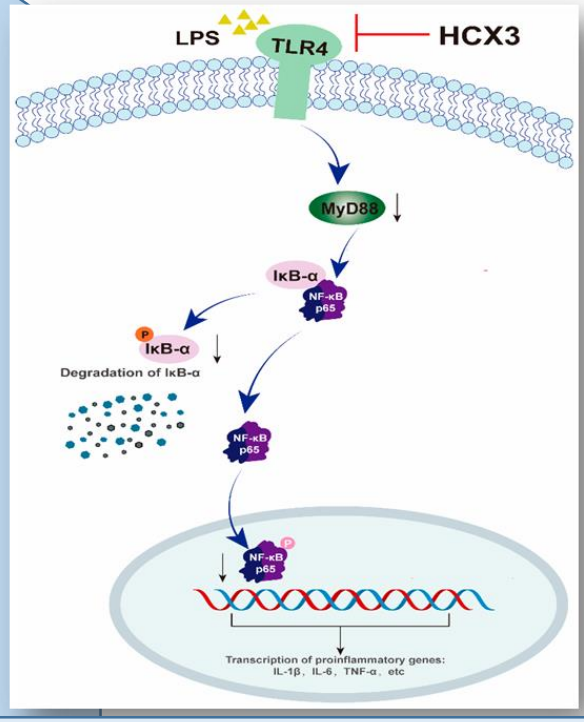


Abbreviation:

- **ZO-1:** Zonula Occludens-1
- **DC:** Dendritic Cells
- **ILC:** Innate Lymphoid Cells
- **RegIIIγ:** Regenerating Islet-Derived 3 gamma

Microbial Products and Innate Immune Signaling:

- LPS (lipopolysaccharide) from Gram-negative bacteria
- LBP-CD14-TLR4/MD-2 recognition
- MyD88 → NF-κB ; TRIF → IRF3
- Pro-inflammatory cytokines: TNF-α, IL-1β, IL-6
- Context-dependent inflammatory outcomes

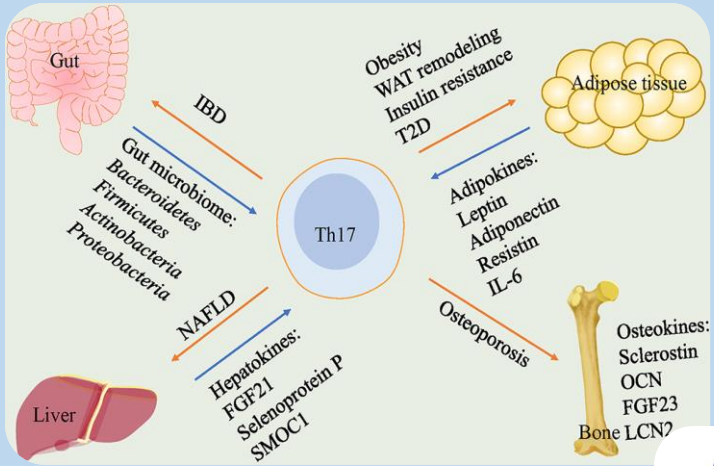


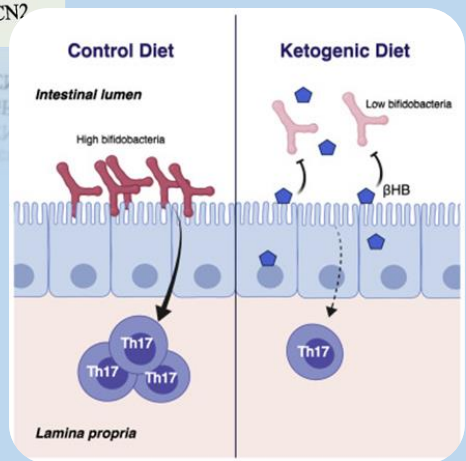
Abbreviation:

- **LBP:** LPS-Binding Protein
- **MD-2:** Myeloid Differentiation Factor 2
- **MyD88:** Myeloid Differentiation Primary Response 88
- **NF-κB:** Nuclear Factor kappa B
- **TRIF:** TIR-Domain-Containing Adapter-Inducing Interferon-β
- **IRF3:** Interferon Regulatory Factor 3

Th17 Cells at the Host–Microbe Interface

- Adaptive CD4+ T-cell subset, RORγt-associated
- IL-17A and IL-17F production
- Protective roles in mucosal defense
- Pathogenic potential in chronic inflammation





KD effect:

- Ketogenic feeding changes microbial composition
- BHB inhibits selected *bifidobacteria*
- Reduced intestinal Th17 cells in experimental models
- Human causality remains incompletely established

Abbreviation:

- **RORγt:** Retinoic Acid Receptor-Related Orphan Receptor Gamma t

ILC3: Innate Lymphoid Cells at the Mucosal Interface

· RORγt+ innate lymphoid cells

· Rapid responses to IL-23 and IL-1β

· IL-22 and context-dependent IL-17A production

· Barrier protection and inflammatory potential

KD in DSS colitis:

KD → Microbiota remodeling → ↓ Colonic ILC3 → ↓ IL-17A/IL-18/IL-22 → Improved experimental colitis



Abbreviation:

- **DSS:** Dextran Sulfate Sodium

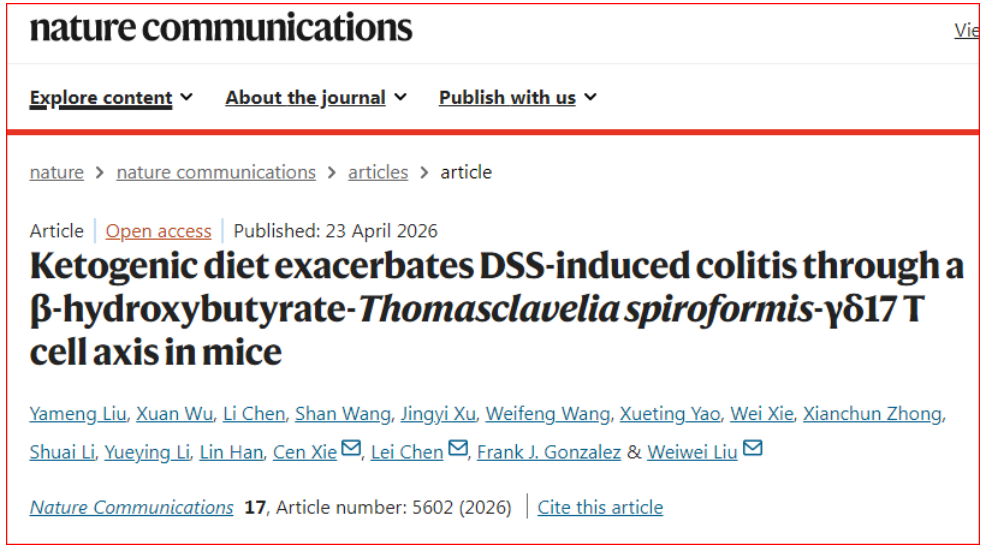
Immune Modulation Is Context-Dependent

- IL-17A can support antimicrobial defense
- IL-22 can promote epithelial protection
- Excessive signaling may drive pathology
- Reduced signaling may impair host defense
- Disease model and tissue context matter



A Context-Dependent Pro-Inflammatory Pathway in a Mouse Model

- DSS-induced colitis model
- Luminal β-hydroxybutyrate
- Expansion of *Thomasclavelia spiroformis*
- γδ17 T-cell activation and IL-17A
- Findings should not be generalized to all patients



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Ketogenic diet exacerbates DSS-induced colitis through a β-hydroxybutyrate-*Thomasclavelia spiroformis*-γδ17 T cell axis in mice

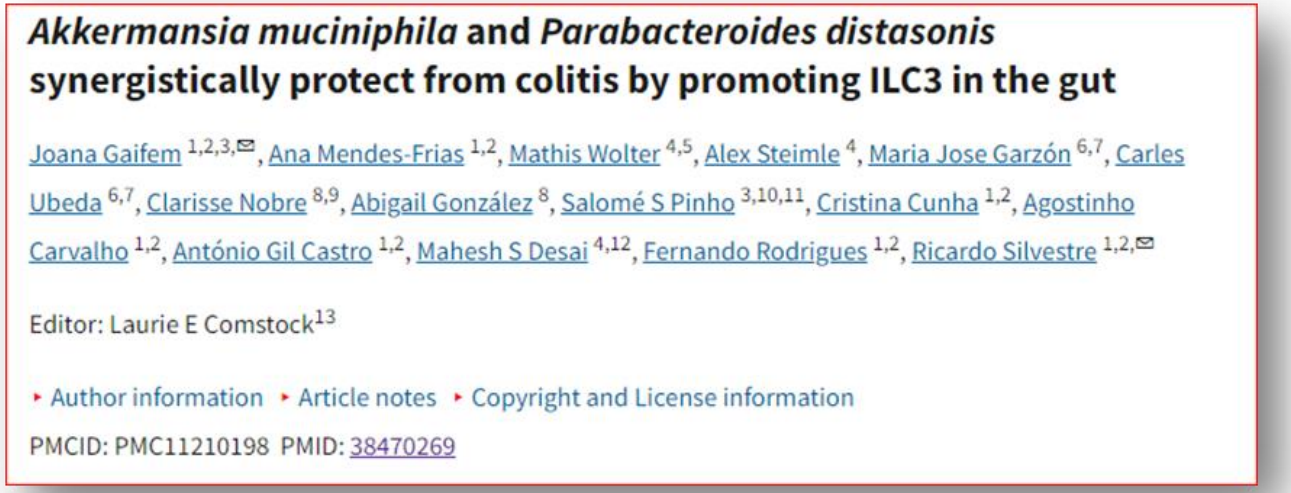
Yameng Liu, Xuan Wu, Li Chen, Shan Wang, Jingyi Xu, Weifeng Wang, Xueting Yao, Wei Xie, Xianchun Zhong, Shuai Li, Yueying Li, Lin Han, Cen Xie, Lei Chen, Frank J. Gonzalez & Weiwei Liu

Nature Communications **17**, Article number: 5602 (2026) | Cite this article

A Complementary Immune Mechanism

Mouse DSS-colitis model:

KD
→Microbiota remodeling
↓ →Colonic ILC3
↓ →IL-17A / IL-18 / IL-22-associated responses
→Improved experimental colitis



***Akkermansia muciniphila* and *Parabacteroides distasonis* synergistically protect from colitis by promoting ILC3 in the gut**

Joana Gaifem [1,2,3], Ana Mendes-Frias [1,2], Mathis Wolter [4,5], Alex Steimle [4], Maria Jose Garzón [6,7], Carles Ubeda [6,7], Clarisse Nobre [8,9], Abigail González [8], Salomé S Pinho [3,10,11], Cristina Cunha [1,2], Agostinho Carvalho [1,2], António Gil Castro [1,2], Mahesh S Desai [4,12], Fernando Rodrigues [1,2], Ricardo Silvestre [1,2]

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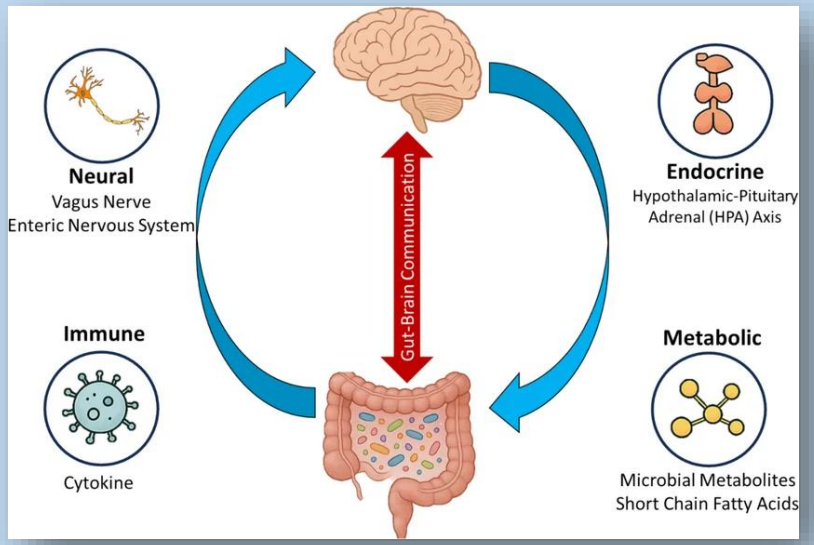
Microbial Function Depends on Context

- **Species and strain differences**
- **Host immune status**
- **Intestinal environment (pH, oxygen, substrates)**
- **Disease-specific microbial interactions**
- **Functional evidence is stronger than abundance alone**



The Microbiota–Gut–Brain Axis

- **Neural communication:** Vagus nerve, ENS
- **Endocrine signaling:** HPA axis, GLP-1, CCK
- **Immune mediators:** Cytokines
- **Microbial metabolites:** SCFAs, tryptophan, bile acids
- **Bidirectional host-microbe-brain interactions**



Abbreviation:

- **ENS:** Enteric Nervous System
- **HPA:** Hypothalamic-Pituitary-Adrenal Axis
- **GLP-1:** Glucagon-Like Peptide-1
- **CCK:** Cholecystokinin

Tryptophan Metabolism:

- **Serotonin pathway:** Tryptophan → 5-HTP → Serotonin (mood, sleep)
- **Kynurenine pathway:** Tryptophan → Kynurenine → Kynurenic acid (neuroprotective) or Quinolinic acid (neurotoxic)
- **Microbial indole pathway:** Tryptophan → Indoles → AhR ligands (barrier, immunity)

Microbiota influences substrate availability and metabolite production.

Abbreviation:

- **5-HTP: 5**-Hydroxytryptophan
- **AhR:** Aryl Hydrocarbon Receptor
- **IDO**: Indoleamine 2,3-Dioxygenase
- **TDO:** Tryptophan 2,3-Dioxygenase

GABA/Glutamate Balance:

- **Glutamate:** major excitatory neurotransmitter
- **GABA:** major inhibitory neurotransmitter

KD → ↑ hippocampal GABA:Glutamate ratio

Mechanisms:

- **Ketone metabolism → ↑ GABA synthesis**
- **Mitochondrial function → ↑ energy for neurotransmission**
- **Microbiota-dependent amino acid pathways**
- **Ion channel modulation**

Gut Microbiota Mediates Anti-Seizure Effects in Mouse Models

KD → Gut Microbiota → Seizure Resistance

Mouse models:

KD

↓

↑*Akkermansia* + *Parabacteroides*

↓

Altered amino-acid metabolism

↓

Altered systemic and hippocampal metabolites

↓

↑Hippocampal GABA : Glutamate ratio

↓

Reduced seizure susceptibility



Key findings:

· **Germ-free models:** no anti-seizure effect without microbiota

· **FMT from KD mice to germ-free mice:** transfers protection

· **Antibiotic depletion:** abolishes anti-seizure effect

· Microbiota is ONE contributor, not the only mechanism

Abbreviation:

- **FMT:** Fecal Microbiota Transplantation

Clinical Outcomes of KD:

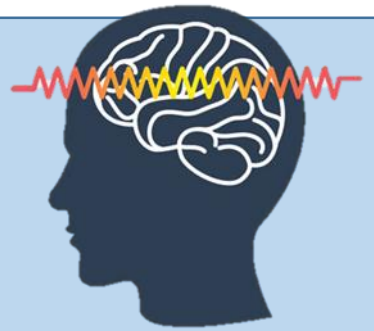
➢ **Drug-Resistant Epilepsy (DRE):**

· ~50% reduction in seizure frequency in ~50% of patients

· 10-15% become seizure-free

· Microbiota-dependent anti-seizure effects in mice

· Clinical response varies



➢ **Alzheimer's Disease (AD) and MCI:**

· Improved memory, ADAS-Cog, executive function

· MCTs show potential cognitive benefits

· Evidence remains limited

· Medical supervision is essential

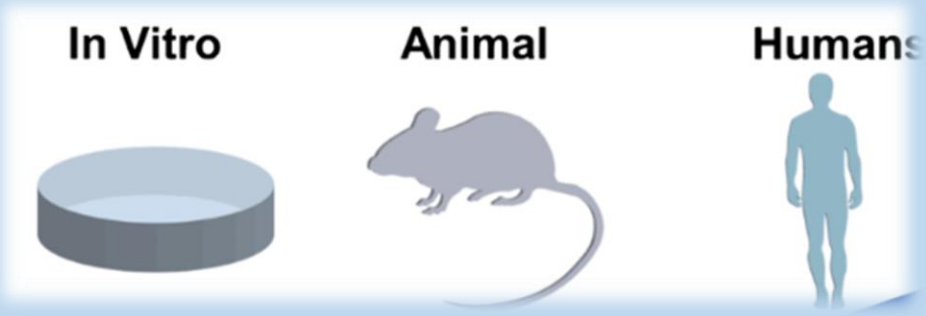


Abbreviation:

- **MCI:** Mild Cognitive Impairment
- **ADAS-Cog:** Alzheimer's Disease Assessment Scale-Cognitive Subscale
- **MCT:** Medium-Chain Triglycerides

Translating Preclinical Findings to Humans

- Mouse models enable causal experiments (Germ-free, FMT, antibiotics)
- Human microbiomes are more heterogeneous
- Diet adherence varies
- Clinical outcomes require direct measurement
- Mechanistic plausibility is not clinical proof



Human Randomized Trial: Microbiome and Metabolic Responses

- **Ketogenic diet altered gut microbial beta diversity**
- **Dietary carbohydrate restriction ≠ KD**
- **Metabolic outcomes also changed**
- **Atherogenic lipoprotein profile increased over 4 weeks**
- **Microbiome change ≠ universal benefit**

ARTICLE · Volume 5, Issue 8, 101667, August 20, 2024 · *Open Access* Download Full Issue

Ketogenic diet but not free-sugar restriction alters glucose tolerance, lipid metabolism, peripheral tissue phenotype, and gut microbiome: RCT

Aaron Hengist [1,9,10] · Russell G. Davies [1,9] · Jean-Philippe Walhin [1] · … · Françoise Koumanov [1] · Dylan Thompson [1] · Javier T. Gonzalez [1,10,11,12] … Show more

Affiliations & Notes · Article Info

Potential Limitations and Trade-Offs

- **Reduced fermentable fiber in some diet patterns**
- **Changes in microbial metabolite production**
- **Individual variation in lipid response**
- **Long-term effects remain incompletely characterized**
- **Diet quality matters as much as macronutrient ratio**
- **"Keto flu" (headache, fatigue, nausea)**
- **Micronutrient deficiencies (Ca, Vit D, Mg)**
- **Risk of kidney stones in children**



Personalized Nutrition: The Future

- **Responders vs. non-responders to KD**
- **Predictive biomarkers:** baseline microbiome, lipid profile, BHB levels, genetics
- **Future: diet design based on individual microbiome**
- **Multi-omics integration:** metagenomics + metabolomics + proteomics
- **Fiber as a key modulator of KD effects**



Conclusions

- KD affects more than energy metabolism
- Changes ecological and metabolic environment of gut microbiota
- Microbial metabolites, host ketone signaling, intestinal immunity, and gut-brain axis interact
- Outcomes depend on dietary composition, host physiology, and disease context
- Microbiota is one contributor, not the only mechanism
- KD is not universally beneficial or universally harmful

The end...

References

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Thank You



