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NHGRI Short Course in Genomics

Exploring the Microbiome and Its Connection to Metabolic Syndrome

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The Forefront of Genomics®

Forward

"We can compare the gut of a person with inflammatory bowel disease to a dying coral reef or a fallow field: a battered ecosystem where the balance of organisms has gone awry."
*(***Ed Yong,** *I Contain Multitudes: The Microbes Within Us and a Grander View of Life)*

This quote from Ed Yong illustrates how the study of the human microbiome is comparable to the way in which ecologists study complex communities. While people are probably most familiar with the human microbiome, every ecological niche on Earth has its own collection of distinctive microorganisms. This includes coral reefs and barnyard soils, as well as hostile environments like hot springs or acidic outflows from mining operations. These microbial communities are critical to important planet-wide processes like carbon sequestration, nitrogen fixation and the breakdown of toxic chemicals. These wildly differing environments and functions reflect another important feature of the microbiome: diversity. Despite a bias for focusing on the bacterial component of the microbiome, microbial communities are complex and draw organisms from across the tree of life, including fungi, viruses, protists and metazoans.

Bacteria are often the focus of microbiome studies because microbiologists have developed robust tools for growing and identifying bacteria. Part of this stems from our frequently adversarial relationship with bacteria. Pathogens like *Yersinia pestis*, the causative agent of the Black Plague, have fundamentally shaped human history. The careers of famous microbiologists like Louis Pasteur (1822-1895), Robert Koch (1843-1910) and Alexander Fleming (1881-1955) were built on understanding and eradicating bacterial infections. While modern life wouldn't be possible without medical advances to treat bacterial infections, it's important to understand that bacteria far more often play a beneficial role in the world. Unlike pathogenic bacteria, which usually act alone, beneficial bacteria often function as a community made up of tens or hundreds of different microbes. Consortia of bacteria (and also fungi) are indispensable for making bread, cheese, yogurt, kimchi and many other foods. The microbiome is important to human health and the development of a strong immune system. Microbial communities are critical for nitrogen fixation and the health of our crops and livestock.

This collection of lesson plans is designed to introduce students to the microbiome through discussions of current science and hands-on experiments.

- **A Glimpse into the Microbiome provides an overview of the microbiome** starting with the ecological paradigms that defined early microbiome science and finishing with the impact of the microbiome on human health.

- **Exploring the Microbiome and Its Connection to Metabolic Syndrome** offers a detailed look at the current science linking the microbiome to a constellation of health problems called metabolic syndrome. Studies connecting obesity, diabetes and hypertension to the microbiome are some of the most frequently cited examples of microbiome-mediated health conditions.

- **You Are What You Eat — Exploring the Microbiome Through Inquiry-Based Labs** teaches students important concepts like the scientific method, sterile technique and reproducibility.

- **Microbiome Virtual Lab Exploration!** gives student the opportunity to analyze real microbiome data using web-based analysis tools.

Taken together, these lesson plans can be adapted to a variety of settings, student populations and educational goals. We hope students will be inspired to learn more about the hidden communities of microbes that shape human health and the environment.

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Exploring the Microbiome and Its Connection to Metabolic Syndrome

How to use this resource

This resource is meant to provide a glimpse into how resident microbioata can impact our overall health. It is intended for advanced high school students and college students. Students should be introduced briefly to some of the general concepts of these journals to make them more accessible. These topics include: microbes, genetics, proteomics and immunity.

Timeframe

Time needed for "Introduction: What is metabolic syndrome?"
Estimated "time per article - 60 minutes

1. Brief lecture and article introduction (5-10 minutes)
2. Read each article and answer provided questions (20-30 minutes)
   a. Consider doing this in breakout groups or as a class if this is during class time.
   b. Assign the article as homework.
3. Article discussion (15 minutes)
   a. If as a class, discuss the articles in small pieces and help answer questions to clarify topics.
4. Lecture recap and closing comments (5 minutes)

Introduction: What is metabolic syndrome? - 15 minutes

American Heart Association: https://www.heart.org/en/health-topics/metabolic-syndrome

American Heart Association information flyer: https://www.heart.org/-/media/files/health-topics/answers-by-heart/what-is-metabolic-syndrome.pdf?la=en

Questions

1. What is metabolic syndrome?
2. What health risks are associated with metabolic syndrome?
3. What are the diagnostic criteria for metabolic syndrome?
4. What treatment options are available?
5. How can you reduce your risk of metabolic syndrome?

Article 1: Gut microbiota, low-grade inflammation, and metabolic syndrome

Chassaing, B. Gewirtz, A.T. (2014) "Gut microbiota, low-grade inflammation, and metabolic syndrome." *Toxicol Pathol*., pp. 42(1):49-53. doi:10.1177/0192623313508481.

Weblink: https://journals.sagepub.com/doi/pdf/10.1177/0192623313508481

Overview: This article discusses alterations in gut microbiota and their contribution to inflammation. The investigators hypothesize that this chronic low-grade inflammation may promote metabolic syndrome.

Questions

1. What is inflammation?
2. How does obesity contribute to systemic inflammation?
3. How diverse is the gut microbiome?
4. What is the function of pathogen recognition receptors (PRRs)?
5. What does flagellin do?
6. What is colitis?
7. What is the purpose of TLR5? What is observed in mice when a mutation is introduced in the gene encoding TLR5?
8. What does T5KO mean? What is the relationship between TK50 mice and obesity?
9. What qualities of metabolic syndrome could be observed in T5KO mice?
10. How was the metabolic syndrome phenotype eliminated in these mice? How did food restriction affect the mice?
11. How do chronically high levels of cytokines influence insulin and leptin?
12. What is low-grade inflammation and how did it impact the mice? How is this related to colitis or metabolic syndrome?
13. What is the current thinking on gut microbiota differences between residents of developed and developing countries?

Article 2: Human gut microbes associated with obesity

Ley, R.E., Turnbaugh, P.J., Klein., S, Gordon, J.I. (2006) “Microbial ecology: human gut microbes associated with obesity.” *Nature*. 444(7122) pp. 1022-1023. doi:10.1038/4441022a.

Weblink: https://www.ncbi.nlm.nih.gov/pubmed/17183309

Alternative weblink via University of Maryland – Centers for Bioinformatics and Computational Biology:
http://www.cbcb.umd.edu/confcour/CMSC828G-materials/Ley-etal-2006-Nature.pdf

Overview: This article discusses the relationship of two groups of intestinal bacteria: Bacteriodetes and Firmicutes. Their relationship and abundance on the human gut may offer insight into the impact of microbes on obesity.

Questions

1. What happens to germ free mice if they receive a gut microbe transplant from normal mice?
2. What happens to Bacteroidetes and Firmicutes levels with obesity?
3. What is the significance of using the 16s ribosome to study microbe diversity in the stool of individuals in this study?
4. What happens to levels of Bacteroidetes and Firmicutes with weight loss?
5. According to this study, did the type of diet or weight loss have the greatest impact on microbiota change?
6. What happens to the gut microbiota composition of a recipient if the donor is of a different species?

Article 3: Alterations of the gut microbiome in hypertension

Yan, Q., Gu, Y., Li X., et al. (2017) "Alterations of the Gut Microbiome in Hypertension." *Front Cell Infect Microbiol*. 2017;7, pp. 381. doi:10.3389/fcimb.2017.00381.

Weblink: https://www.ncbi.nlm.nih.gov/pubmed/28884091

Overview: Investigators compared fecal samples of patients with primary hypertension against comparable healthy control groups. They observed that there are significant differences between the gut microbial diversity in individuals with hypertension.

Questions

1. What metabolic impact does gut microbiota have on cardiovascular health?
2. What is hypertension?
3. What were the criteria of the patients and controls in this study?
4. Was there a difference in the diversity of gut microbes for hypertensive and control patients? How is this significant?
5. What is TMAO and how does it influence atherosclerosis?
6. What health problems are associated with Klebsiella species? How did levels vary in hypertensive and control subjects?
7. How did levels of Streptococcus vary in hypertensive and control subjects?
8. What microbes were observed to be found in higher concentrations in both hypertensive and type 2 diabetics?
9. Can pharmaceutical drugs have an impact on your gut microbiome?

Article 4: Intestinal immunomodulatory Cells (T Lymphocytes): A bridge between gut microbiota and diabetes

Li Q., Gao, Z., Wang, H., et al. (2018) "Intestinal Immunomodulatory Cells (T Lymphocytes): a bridge between gut microbiota and diabetes. mediators inflamm. 9830939. doi:10.1155/2018/9830939.

Weblink: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5866888/

Overview: This article discusses the impact of the immune system on gut microbiota and the contribution of this relationship on diabetes mellitus.

Questions:

1. What are some diseases currently studied that are thought to be impacted by the gut microbiome?
2. What is the current theory on the connection between diabetes and the gut microbiome? What do Li et al. believe the potential link is between these two?
3. What is an intestinal immunomodulatory cell? How do gut microbiota influence these?
4. How many species of bacteria live in the human intestinal tract? What taxa make up the majority of the intestinal microflora?
5. What is diabetes mellitus? What type of diabetes is investigated in this article?
6. What is the significance of the nonobese diabetic (NOD) mice experiment cited in this article? Why was the environment significant?
7. Which taxa ratios were found to be disrupted in diabetic patients?
8. How is diversity modified in the gut microbiome in Type 1 diabetes? Was there an impact on pathogenic bacteria?
9. What are some functions of Th1 and Th2 cells? How do IL-12, IFN- γ and IL-4 impact these cells?
10. What effects do gut microbiome metabolites have on Th1 and Th2 cells?
11. What are Treg cells? What did Tang et al. discover about Lactobacillus murinus?
12. What type of molecule is butyrate? What is its relationship to Niacr1 and Gpr109A?
13. What did Sokolova et al. observe in serum levels of type 2 diabetes mellitus patients compared to a healthy control group?
14. Why is it important to study IL-4 in insulin resistance?
15. How is IL-10 secreted and why is it significant for insulin activity?
16. How are Treg cells and Th17 associated with Type 1 diabetes mellitus?
17. What is the relationship between IICs and T lymphocytes? Do you think this is the only link to diabetes mellitus?

Standards (based on NGSS)

- HS-LS2-2 Ecosystems: Interactions, Energy, and Dynamics
  Use mathematical representations to support and revise explanations based on evidence about factors affecting biodiversity and populations in ecosystems of different scales.provide specific functions within multicellular organisms.
- HS-LS2-6 Ecosystems: Interactions, Energy, and Dynamics
  Evaluate the claims, evidence, and reasoning that the complex interactions in ecosystems maintain relatively consistent numbers and types of organisms in stable conditions, but changing conditions may result in a new ecosystem.

Further Reading

Hypertension: Salt: the microbiome, immune function and hypertension
https://www.nature.com/articles/nrneph.2017.166

Gut microbiome in obesity, metabolic syndrome, and diabetes
https://pubmed.ncbi.nlm.nih.gov/30338410/

Microbial ecology: human gut microbes associated with obesity
https://www.ncbi.nlm.nih.gov/pubmed/17183309

Gut microbiota as a potential target of metabolic syndrome: the role of probiotics and prebiotics
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5655955/

Linking gut microbiota, metabolic syndrome and economic status based on a population-level analysis
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6154942/

Gut microbiome and metabolic syndrome
https://www.sciencedirect.com/science/article/abs/pii/S1871402115300679

Gut microbiota, low-grade inflammation, and metabolic syndrome
https://journals.sagepub.com/doi/pdf/10.1177/0192623313508481

The gut microbiota and metabolic disease: current understanding and future perspectives
https://onlinelibrary.wiley.com/doi/pdf/10.1111/joim.12508

Metabolic endotoxemia initiates obesity and insulin resistance
https://diabetes.diabetesjournals.org/content/56/7/1761

Alterations of the gut microbiome in hypertension
https://www.ncbi.nlm.nih.gov/pubmed/28884091

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