

Transforming Diabetes Care

**Gut Bacteria and Diabetes:
What We Know and What We Don't**

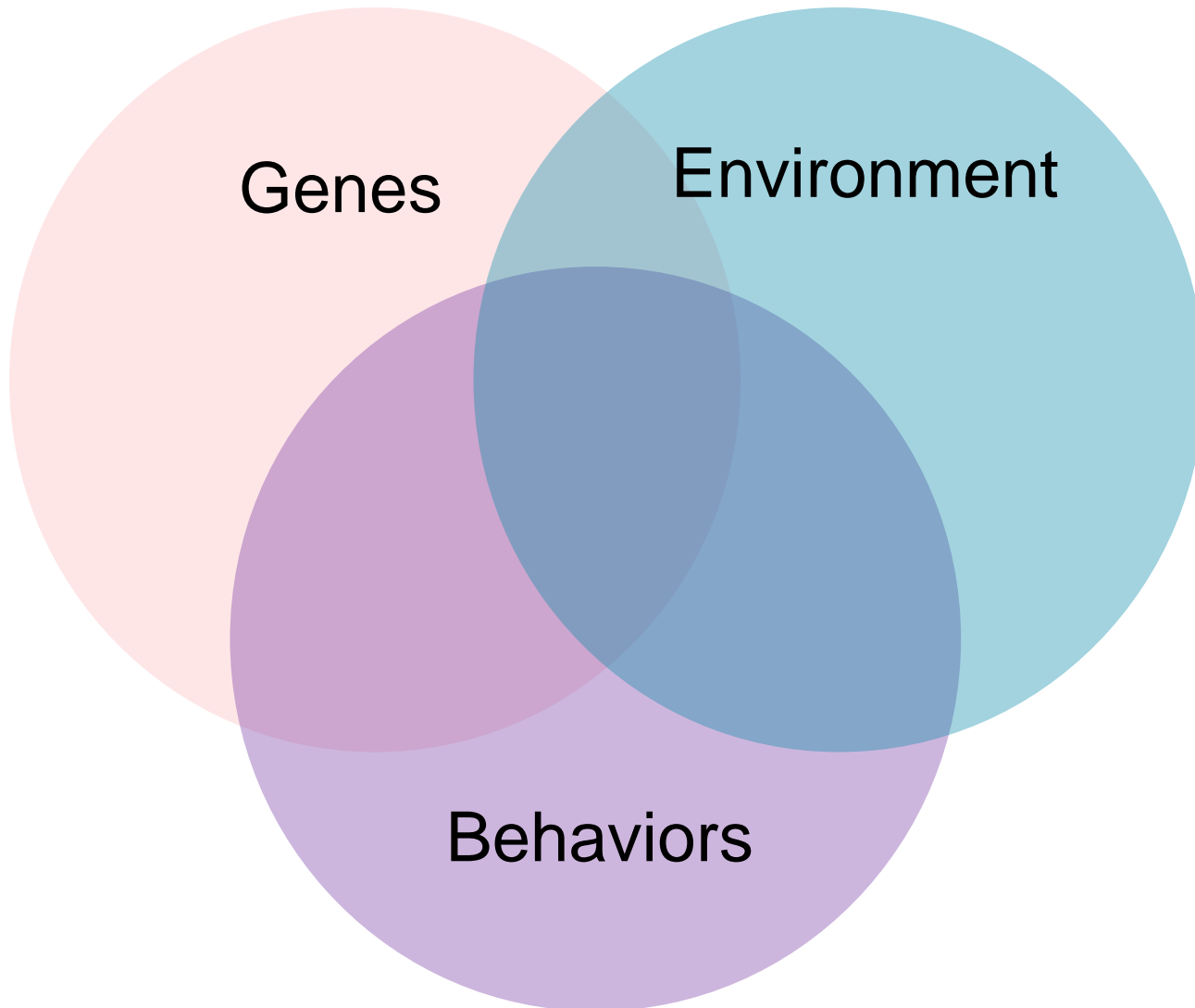
Kim Kelly, PharmD, BCPS, FCCP

Kelly Diabetes Associates, LLC

Cupertino, CA



Development of diabetes in humans





The interrelationship between organisms in the gut and the factors associated with diabetes is incredibly complex

What we're going to talk about

- The gut microbiome
- The role of the gut in immunity
- The role of the gut microbiome in type 1 diabetes
- The role of the gut microbiome in obesity and type 2 diabetes
- Can we affect diabetes development or progression through the microbiome?



Man as a magnificent structure...^{1,2}



The average human is a composite of species ... a 'super organism' which has:

- about 37.2 trillion human cells
- approximately 20,000 active genes
- ... but that's not all

1) <http://www.smithsonianmag.com/smart-news/there-are-372-trillion-cells-in-your-body-4941473/>

2) https://www.sciencedaily.com/terms/human_genome.htm

We function as scaffolding for numerous other organisms in a symbiotic relationship¹⁻³

- The cells in every person are outnumbered by bacterial cells in the gut alone by 100 to 1
- The genes in every person are outnumbered by bacterial genes by 1000 to 1
- The variety of organisms in man is more diverse than in any other naturally occurring colonization
- The bacteria in the gut collectively weigh almost 6 pounds
- The bacteria in the gut alone have a myriad of positive, neutral, and in some cases negative effects and are collectively referred to as the gut microbiome



1) Shreiner AB, et al. *Curr Opin Gastroenterol.* 2015; 31: 69–75

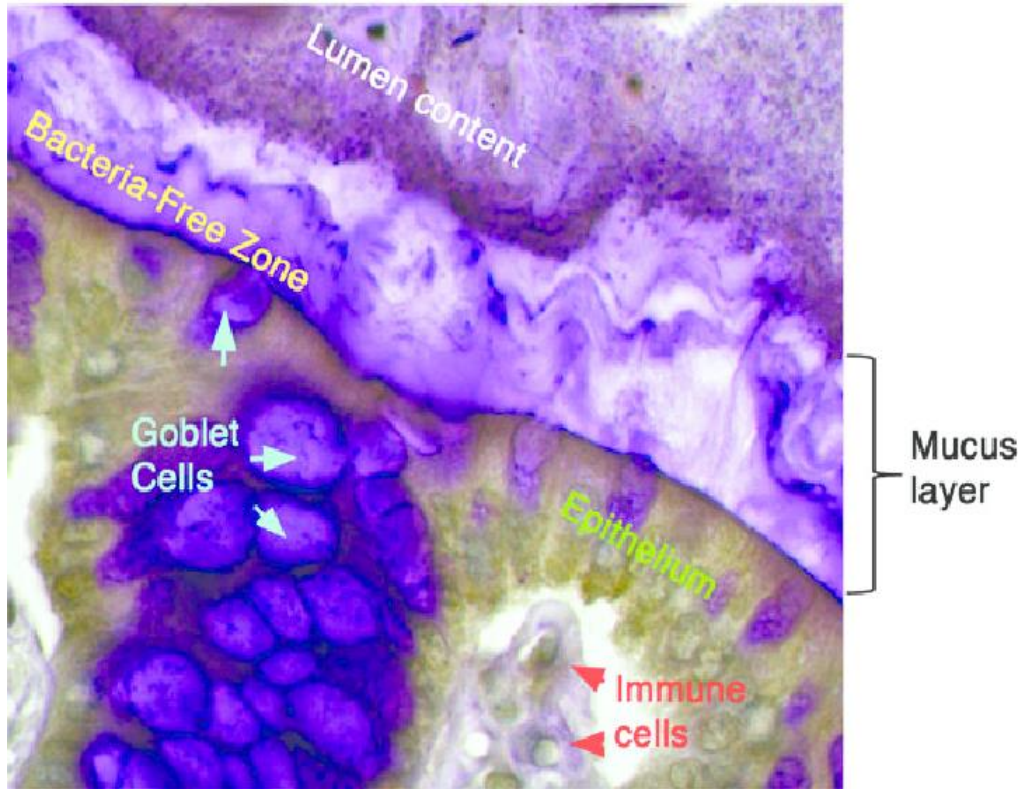
2) https://depts.washington.edu/ceeh/downloads/FF_Microbiome.pdf

3) <https://www.nih.gov/news-events/news-releases/nih-human-microbiome-project-defines-normal-bacterial-makeup-body>

So here's some things
we know about the
bacteria in YOU



Looking at the gut in cross section...



- Cells in the intestine are exposed to bacteria and food breakdown products all the time.
- In addition, the gut is a major place where non-self antigens are recognized by interaction with the immune system which is integrated with the intestinal cells

https://www.researchgate.net/figure/237097190_fig1_Fig-1-The-intestinal-mucus-layer-and-host-microbiota-interactions-Periodic-acid-Schiff

Polling Question

Which of the following affects the composition of the gut microbiome?

- a) The country you live in
- b) Cesarean section delivery
- c) Breastfeeding
- d) A & C
- e) All the above

“Tell me what you eat
and I will tell you what
you are”

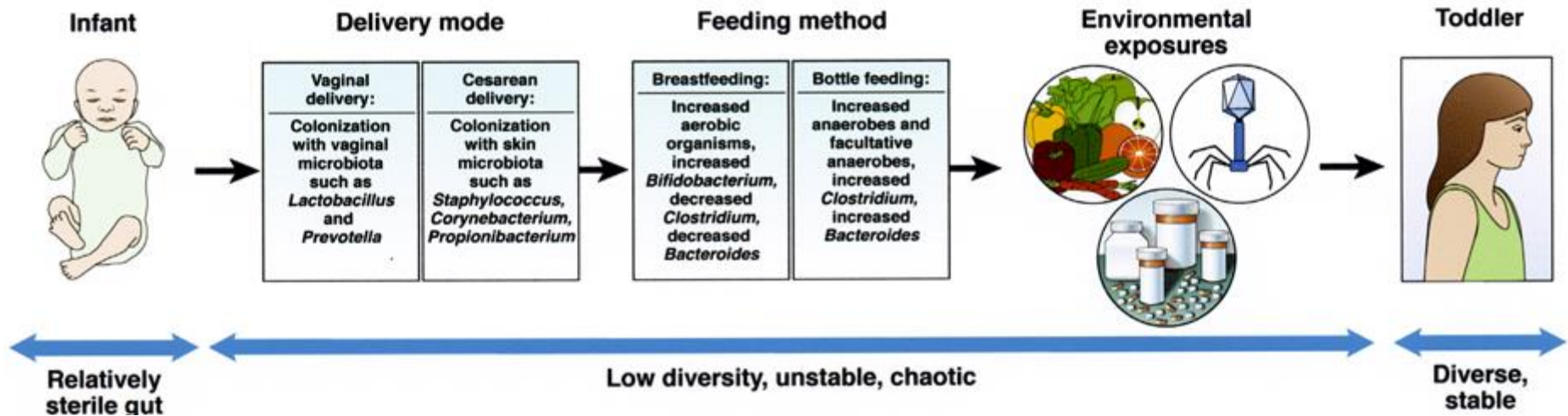


Jean Anthelme Brillat-Savarin

1755-1826

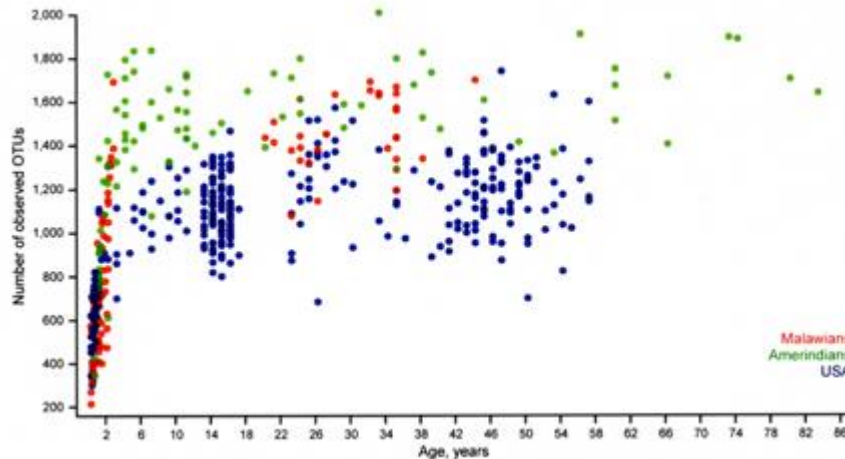
Brillat-Savarin is often considered as the father of low-carbohydrate diets. He considered sugar and white flour to be the cause of obesity and he suggested instead protein-rich ingredients

Many things affect the type of bacteria in the gut at any time



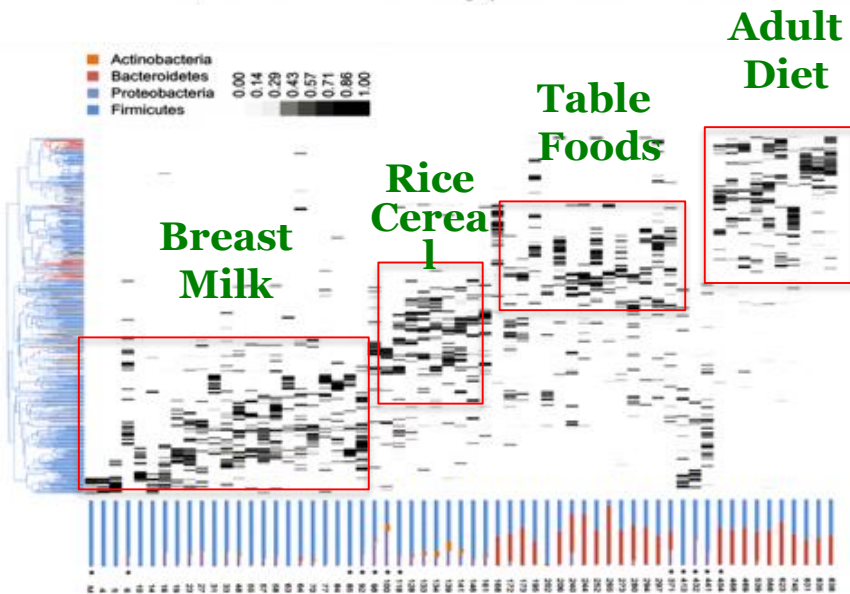
Albenberg LG and Wu GD, *Gasroenterology* 2014;146:1564

Shifts in gut bacteria:



with age and country

Yatsunenکو T., et al.
Nature 2012;486:222



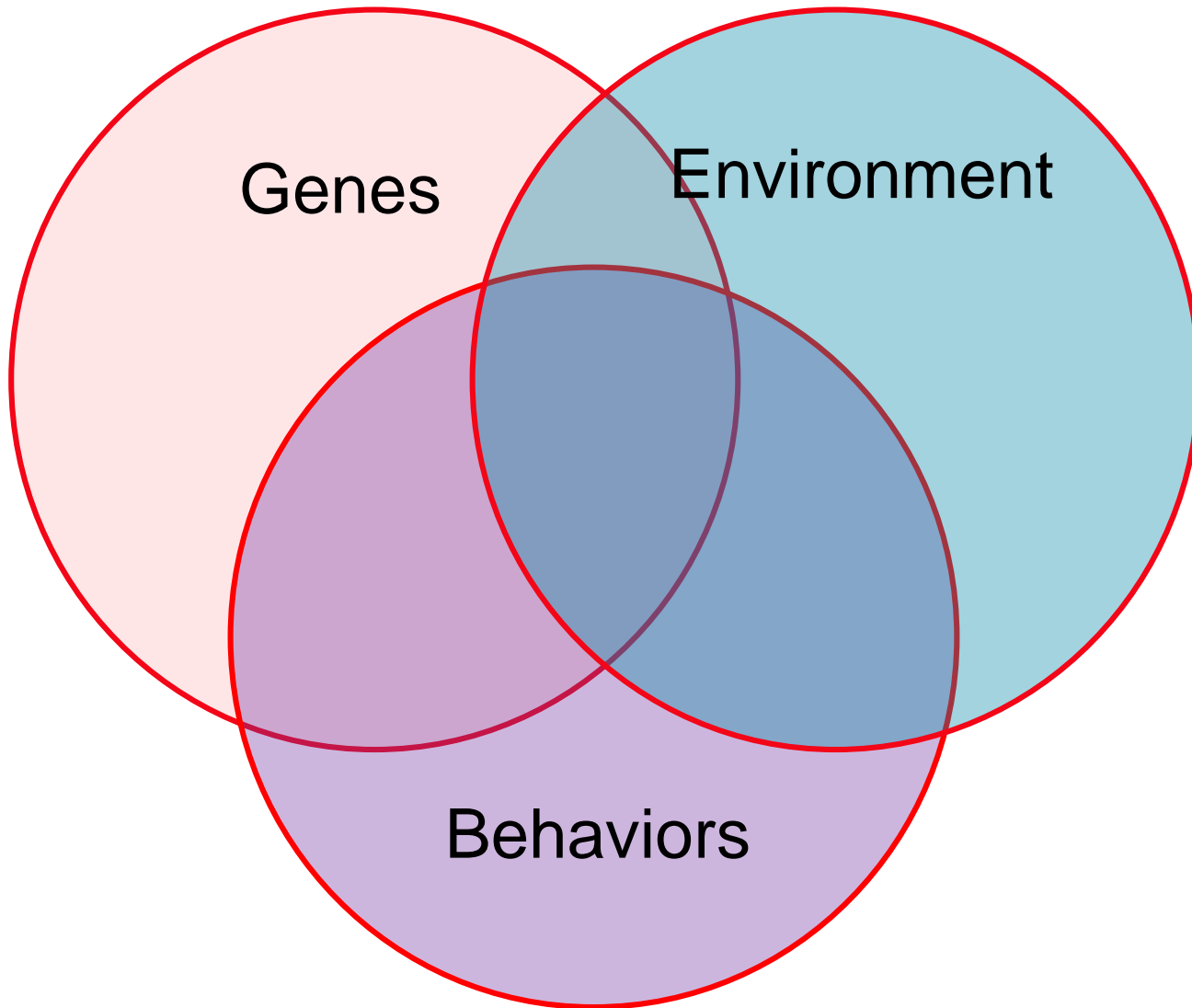
with different exposures

Koenig JE, et al.
Proc. Natl. Acad. Sci.
2011;108:4578



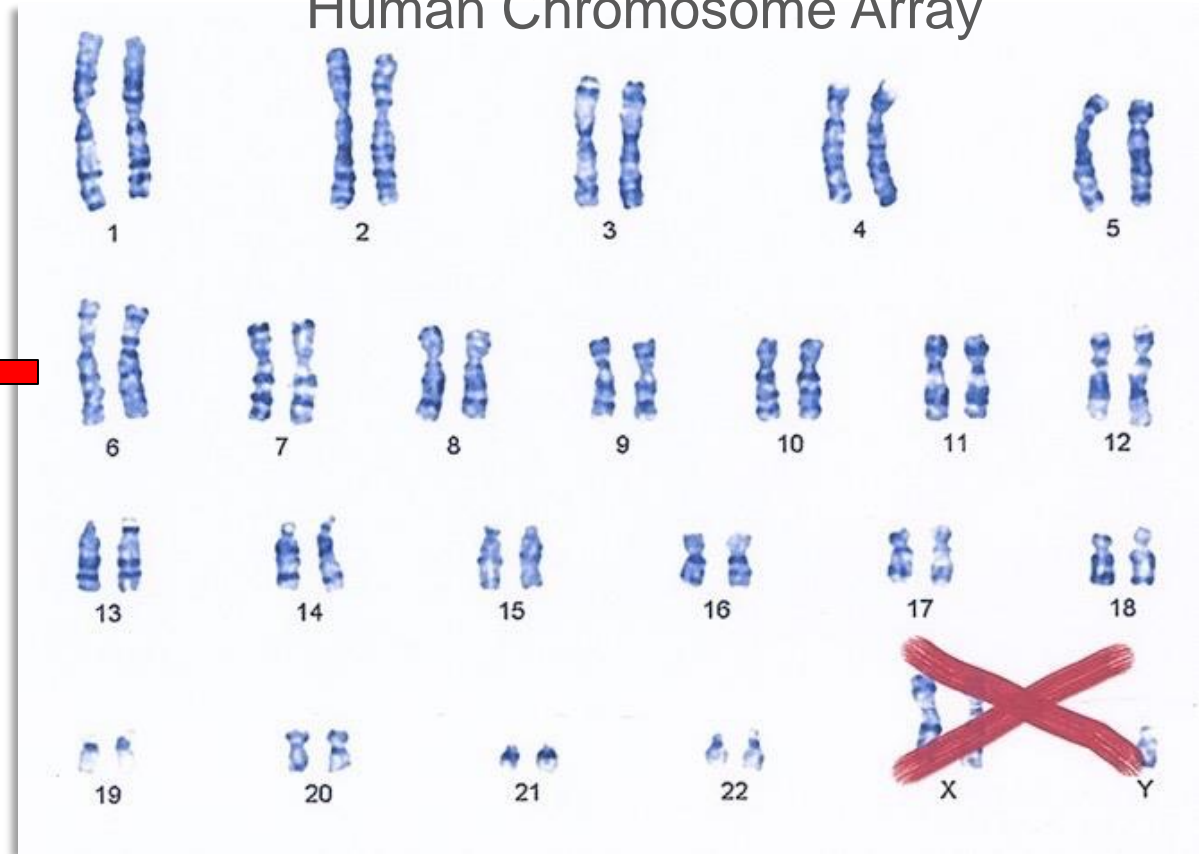
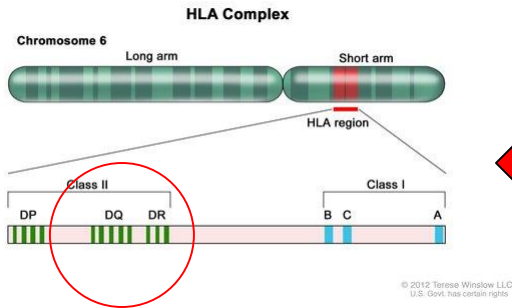
OK, I got the bacteria part, but how is that related to type 1 diabetes?

Development of diabetes in humans



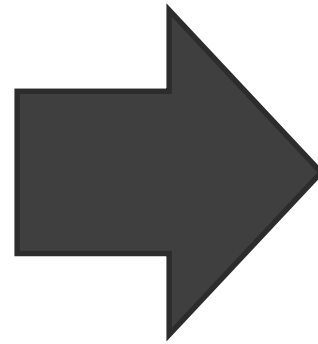
Genes play an important role

Human Chromosome Array



<https://ghr.nlm.nih.gov/art/large/hla.jpeg>

The negative view of bacteria has led to changes in our cleanliness behaviors



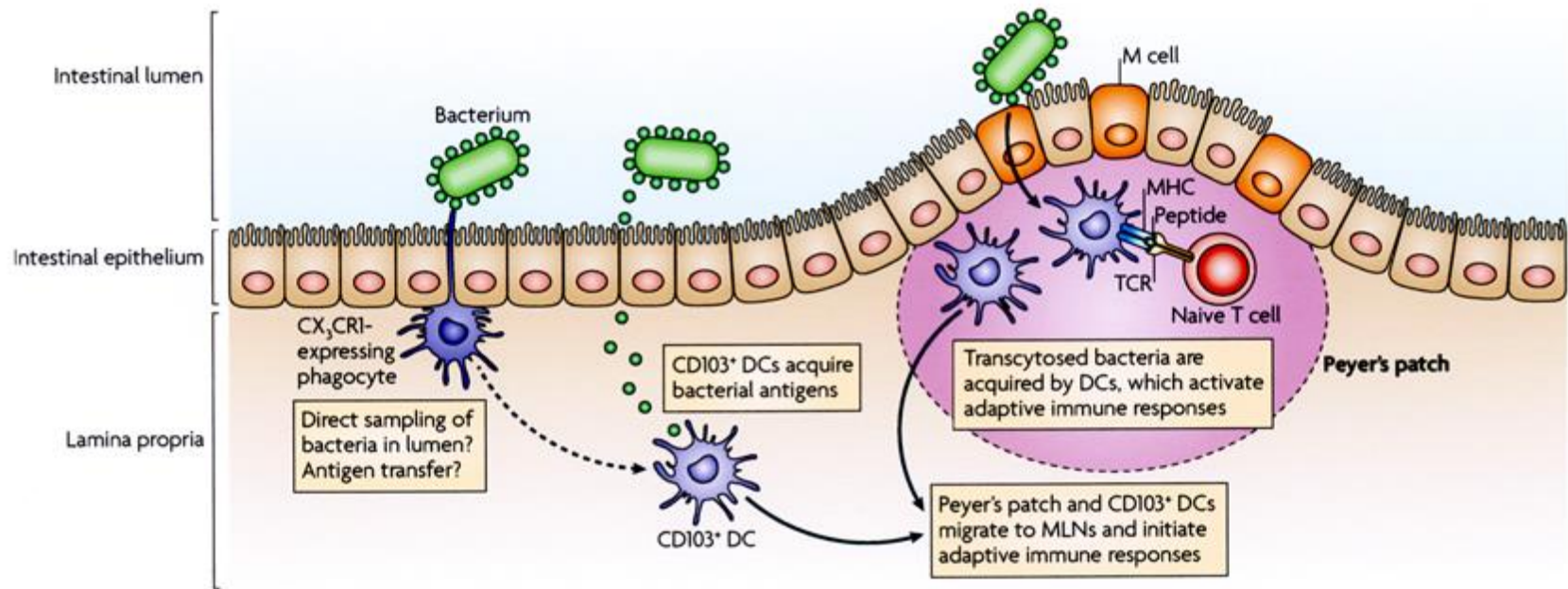
The Hygiene Hypothesis

- The **Hygiene Hypothesis** suggests that a lack of early childhood exposure to infectious agents, symbiotic microorganisms (such as gut flora, etc), viruses and parasites increases susceptibility to allergic and immune diseases by suppressing the natural development of the immune system. In particular, the lack of exposure is thought to lead to defects in the establishment of immune tolerance.



Okada H, et al. The 'hygiene hypothesis' for autoimmune and allergic diseases: an update, Clin. Exp. Immunol. 2010;160:1-9.

Immune system processes antigens



- Processing antigens that pass through the gut is pivotal to **immune tolerance**, **immune recognition**, and in some cases a **profound immune response** to those antigens

Cerf-Bensussan N, and Gaboriau-Routhiau V. Nature Reviews-Immunology 2010;10:735

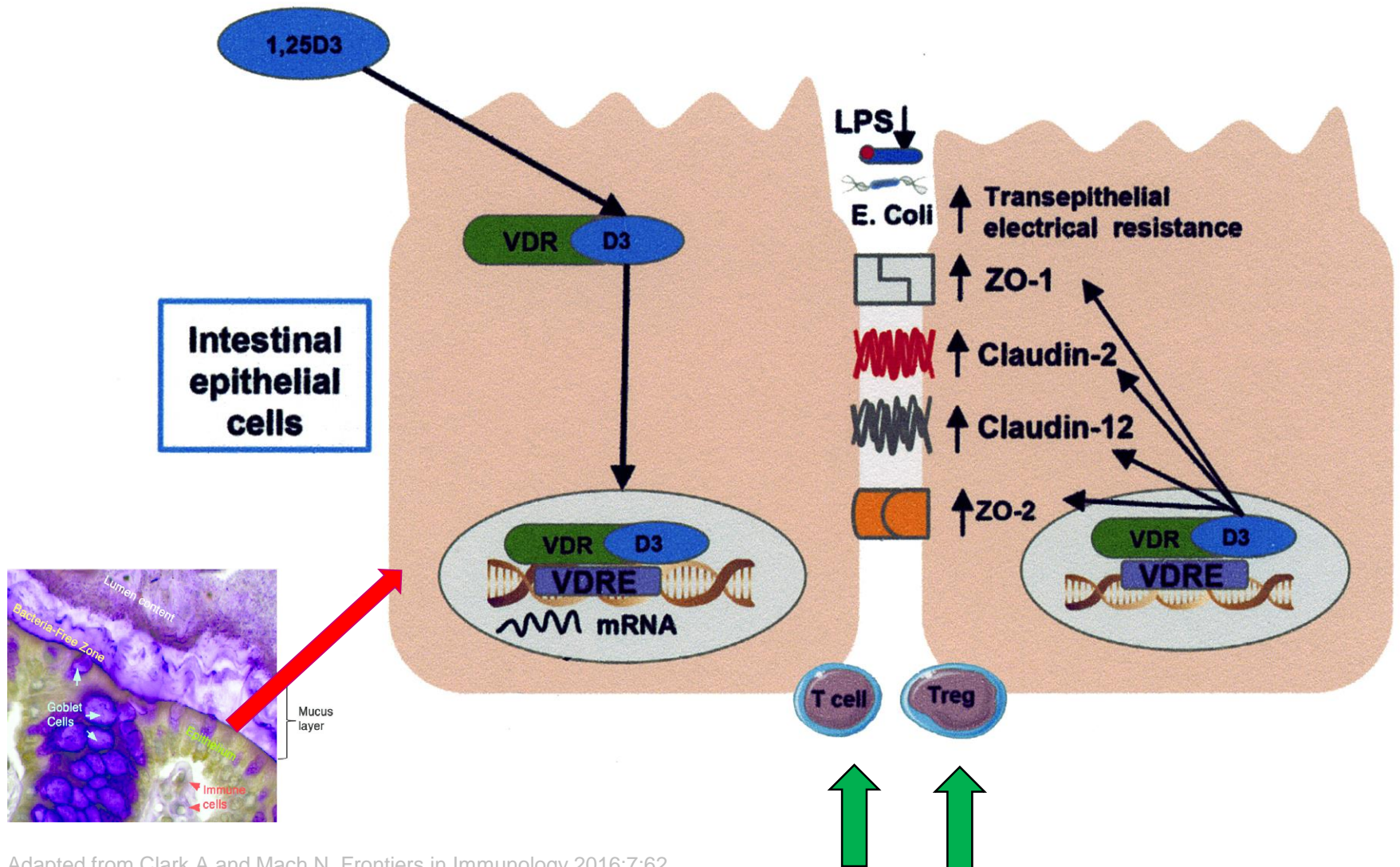
Immune system processes

Cross section of a mouse intestine stained to show epithelial cells (in red) and immune cells (in blue and green) and their proximity at every level.



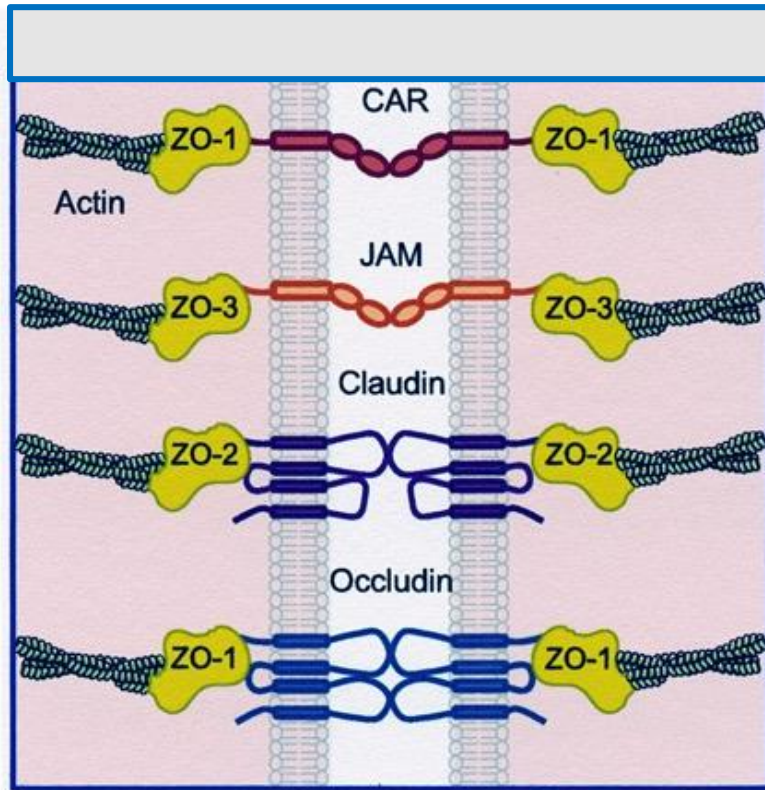
Fasano A., et al. American Journal of Pathology 2014;173:1243

Vitamin D plays a key role...

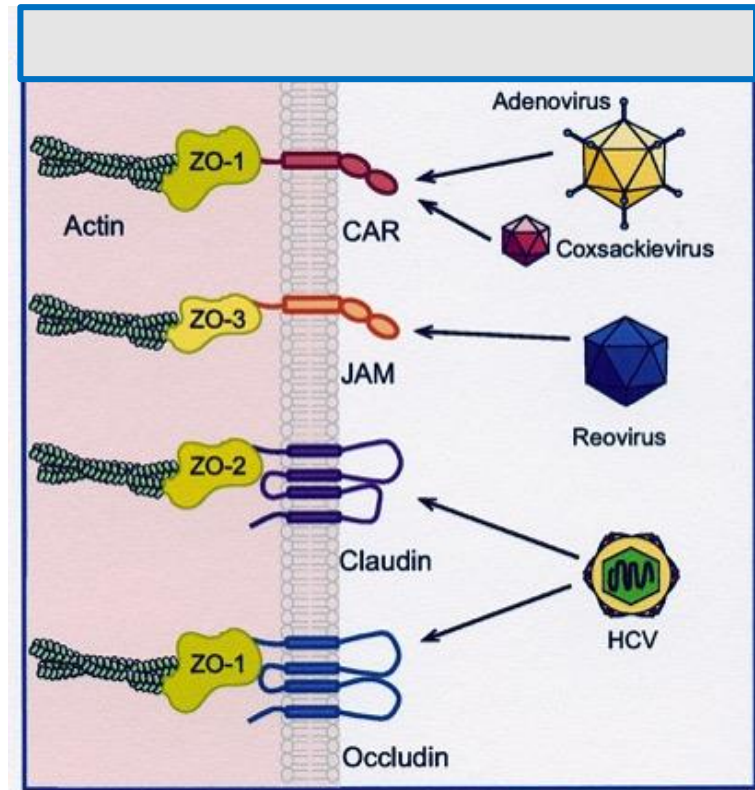


Adapted from Clark A and Mach N. Frontiers in Immunology 2016;7:62

Tight Junctions: vital to cells as structural support and to restrict passage of various compounds



Tight junctions between cell have several components



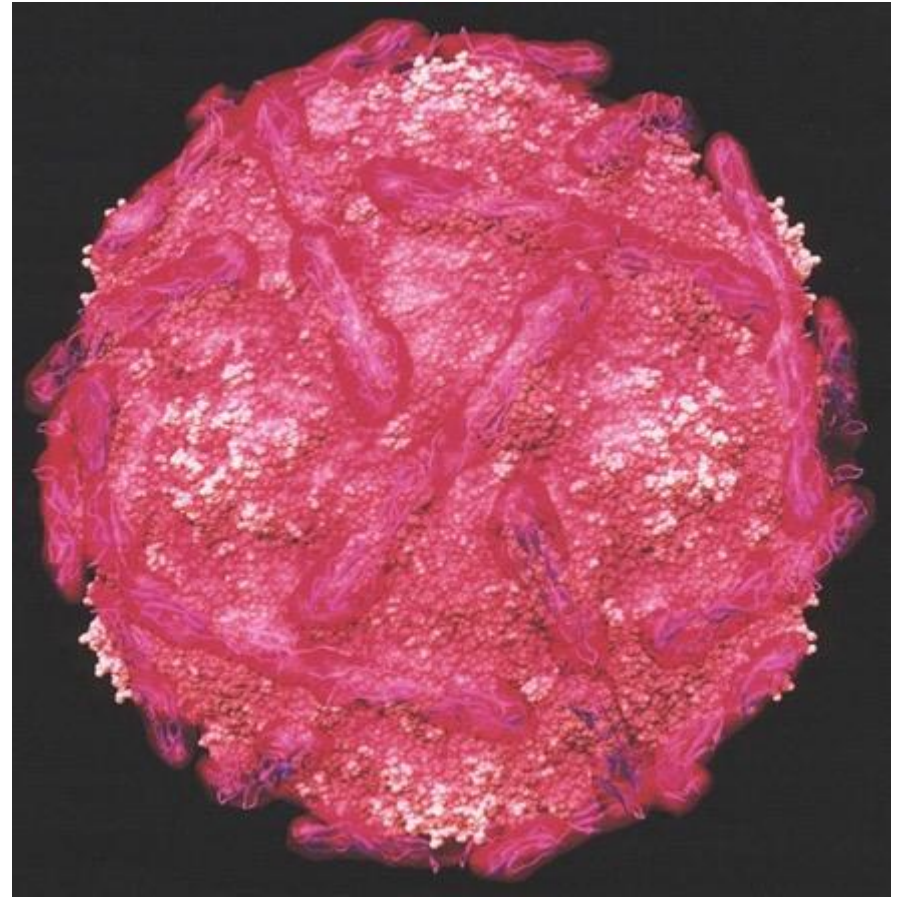
Some of the components are targets for viruses

Mateo M, et al. Journal of Cell Science (2015) 128, 431–439

Susceptibility to type 1 diabetes is both genetic and associated with a viral infection

One proposal for the auto-immune reaction is the establishment of a persistent enteroviral infection of beta cells that may represent an initiating event leading to changes such as chemokine secretion that facilitate the infiltration of immune cells

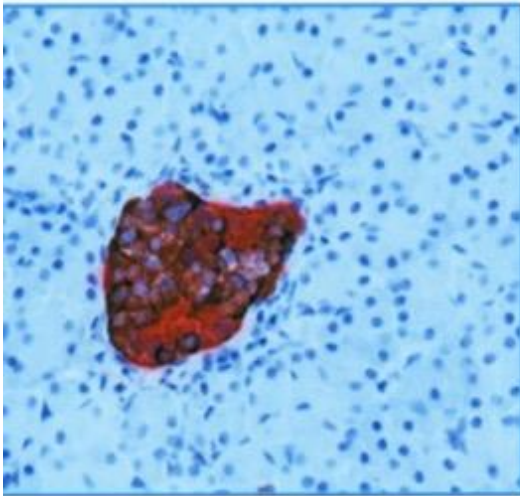
Willcox A, et al. Diabetologia 2011;54:2417-2420



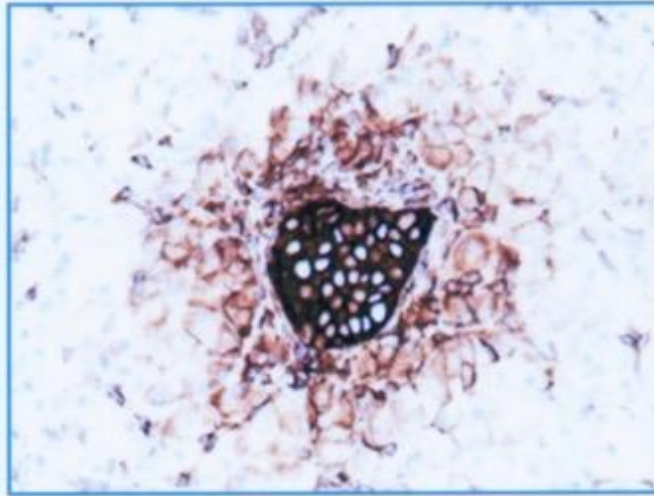
Artists conception of Enterovirus
(cover art from Diabetologia)

Enterovirus protein (VP1) in pancreatic islet cells

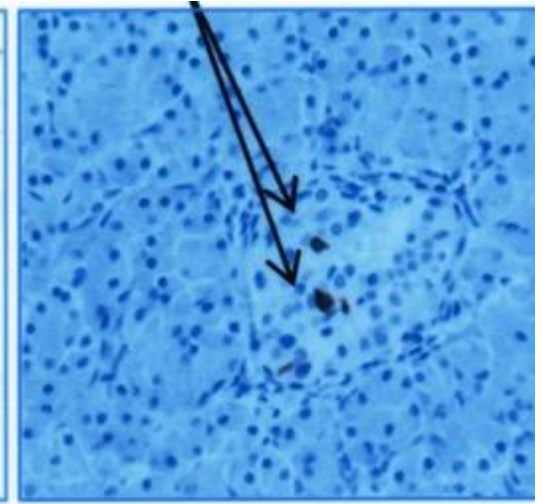
A



B



C VP1-positive cells



Pancreas islets from a person with type 1 diabetes. [A] stained for Insulin (brown) and glucagon (red), [B] Class 1 HLA molecules and Enteroviral protein. [C] cells positive for enteroviral protein (VP1) marked by arrows.

Krogvold L, et al Diabetes 2015;64:1682–1687

Polling Question

What are leverage points to enhance the role of the microbiome thus affecting the development of type 1 diabetes

- a) Sterilizing the gut with antibiotics
- b) Giving microorganisms orally
- c) Giving Vitamin D
- d) B & C
- e) All the above

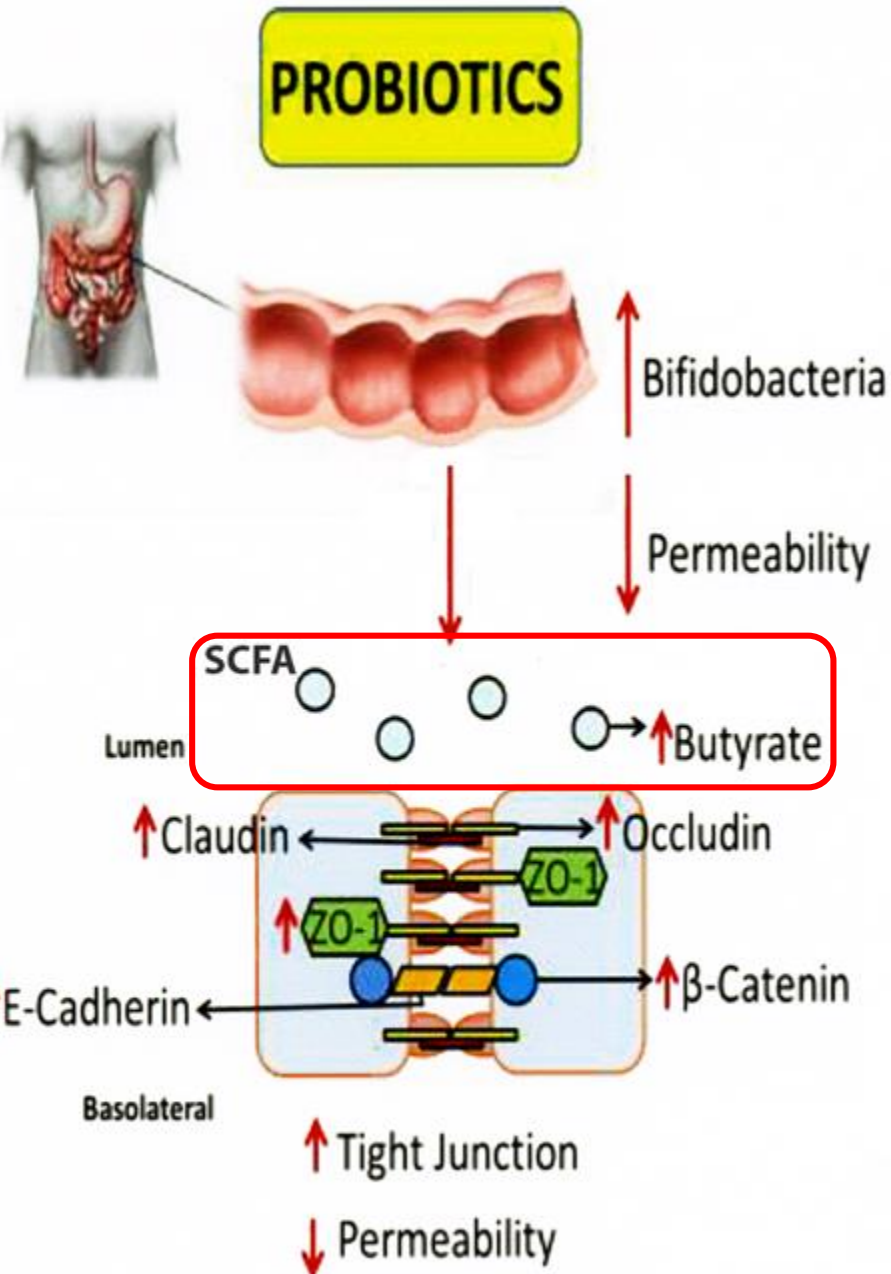
Some additional terms

- Probiotic- A supplement made up of one or more organisms (bacteria currently...) meant to purposefully seed these bacteria in the gut
- Prebiotic – food for your gut bacteria, not just food you eat, but often added ‘soluble fiber’ such as oligosaccharides





Is there anything we
can do to the
microbiome to affect
type 1 diabetes?

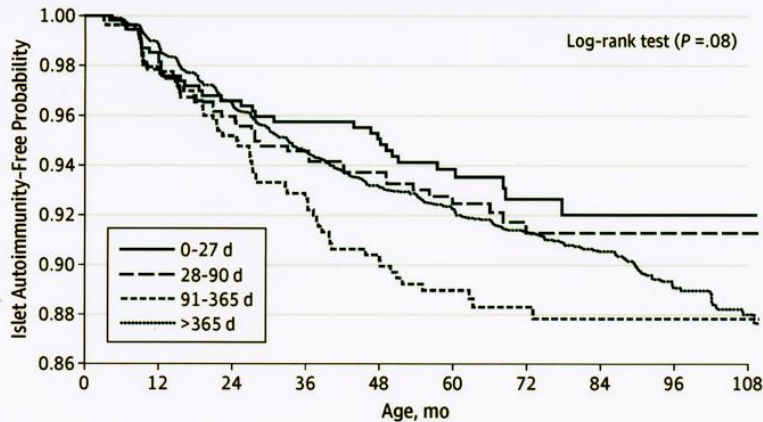


‘Probiotics’: feeding (and changing) your inner ‘biome ...

- Probiotics contain cultures of so-called ‘good’ bacteria.
- Probiotics can be capsules, powders, gels and liquids [e.g. acidophilus milk]
- With over 10,000 different organisms in the gut, some are beneficial (symbionts), some may cause disease (pathobionts) and some we just plain don’t know that much about...which ones are the right ones?

Probiotics can effect the development of type 1 diabetes: the TEDDY Study

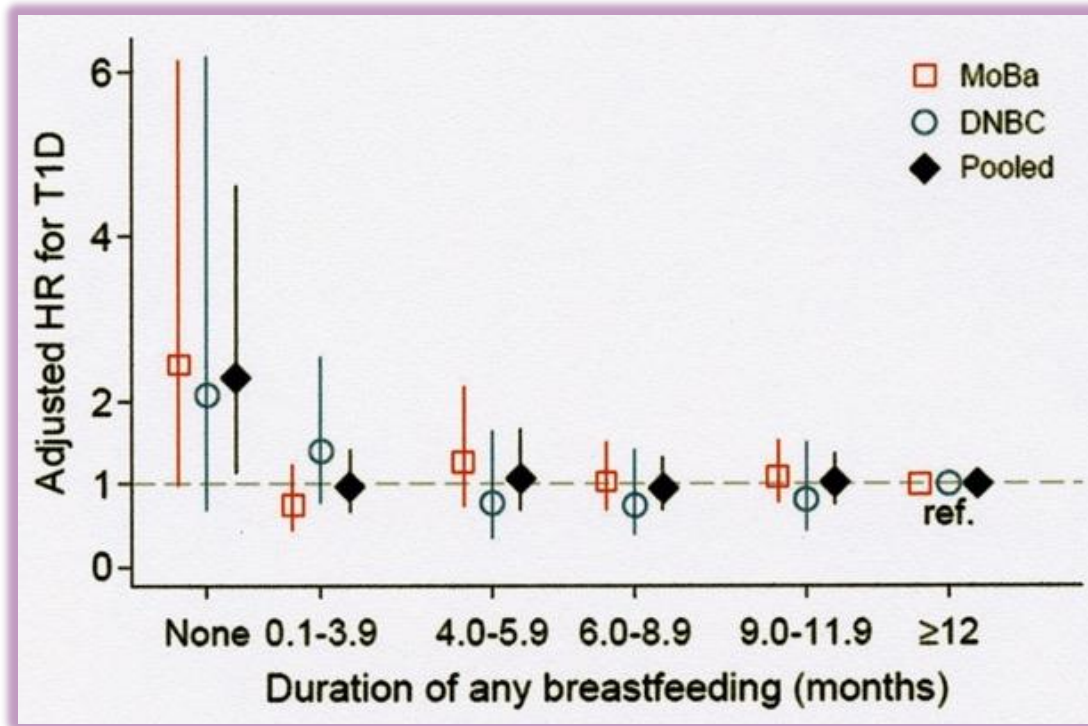
Figure. Islet Autoimmunity Risk by First Probiotic Exposure Age of the Child



No. at risk	0	12	24	36	48	60	72	84	96	108
0-27 d	540	521	478	438	412	306	184	104	48	5
28-90 d	556	537	493	455	414	318	203	111	56	5
91-365 d	538	519	466	420	389	303	202	132	72	24
>365 d	5839	5660	4972	4504	4145	3426	2521	1665	965	341

- Ongoing prospective cohort study started 2004; population was 7473 infants at high genetic risk for type 1 diabetes
- Details of infant feeding, probiotic supplementation and infant formula use monitored from birth

Breastfeeding associated with lower chance of developing type 1 diabetes



- Two cohorts from databases in Denmark and Norway
- From over 155,000 mother and child pairs, the lack of breastfeeding was associated with a 229% increase in the likelihood of developing type 1 diabetes.

What we're going to talk about

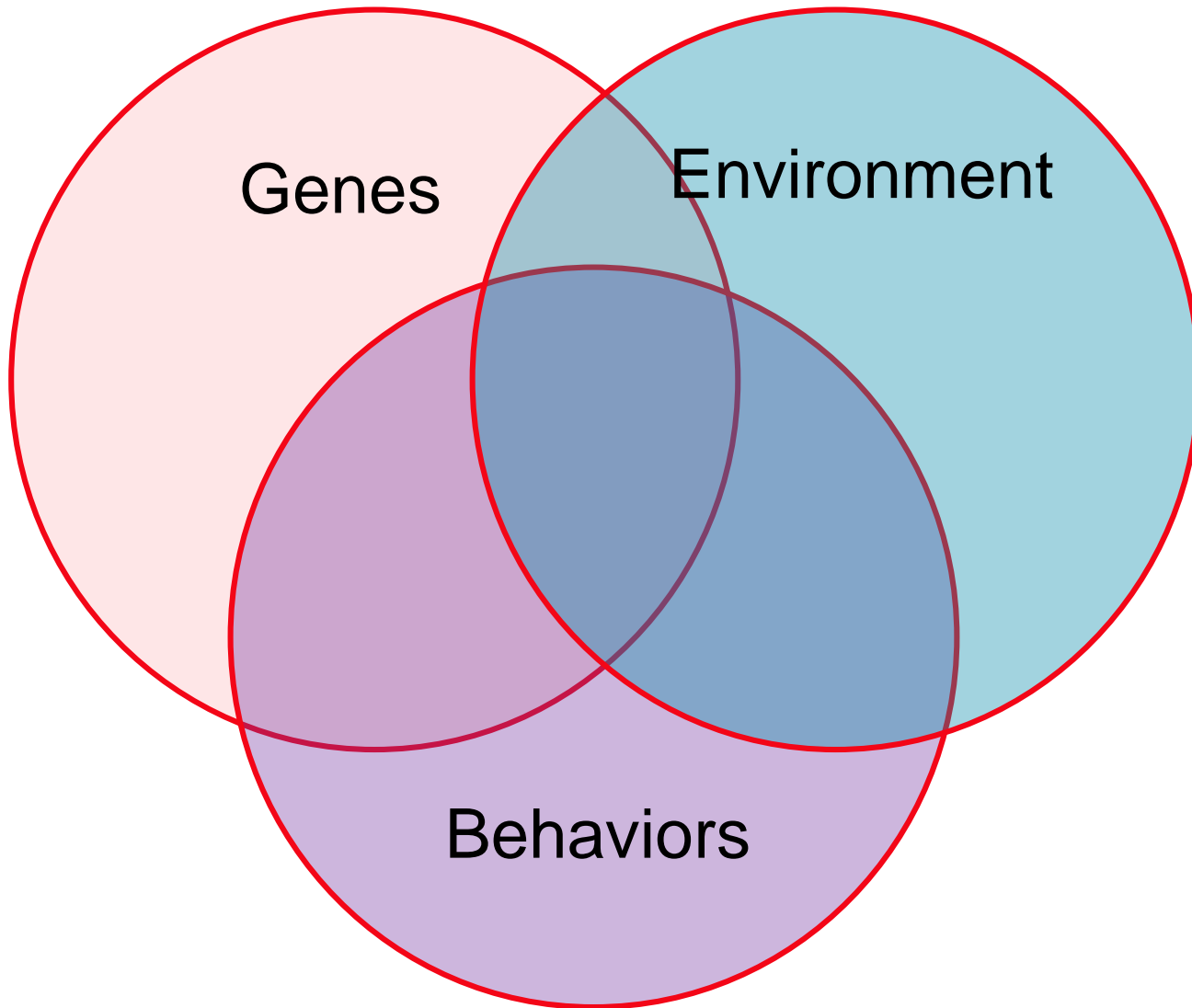
- The gut microbiome
- The role of the gut in immunity
- The role of the gut microbiome in type 1 diabetes
- The role of the gut microbiome in obesity and type 2 diabetes
- Can we affect diabetes development or progression through the microbiome?



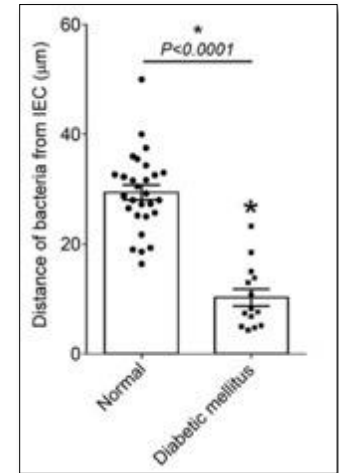
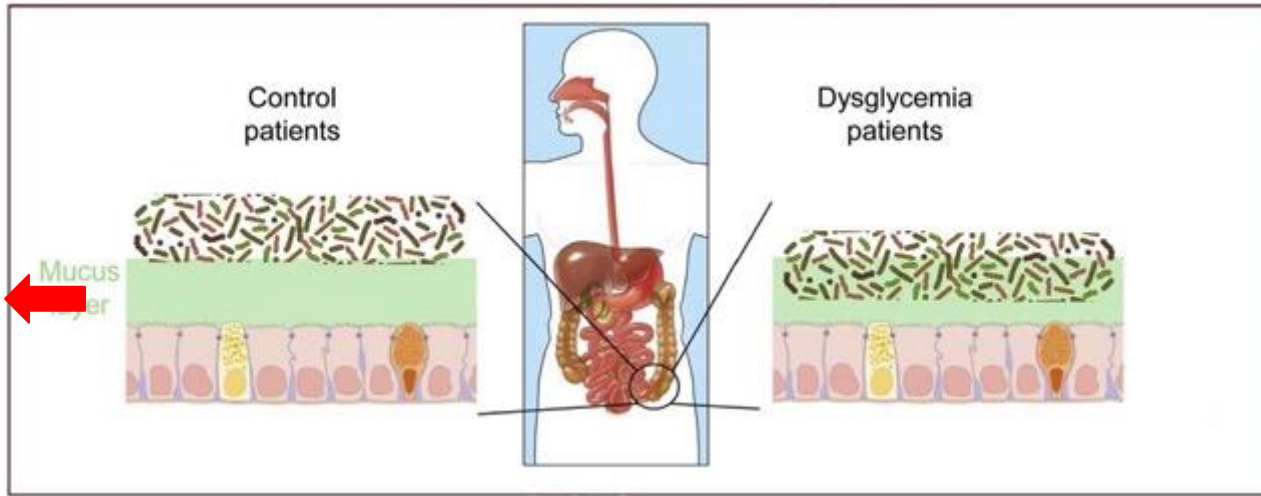
Do gut bacteria have a role in obesity and type 2 diabetes?



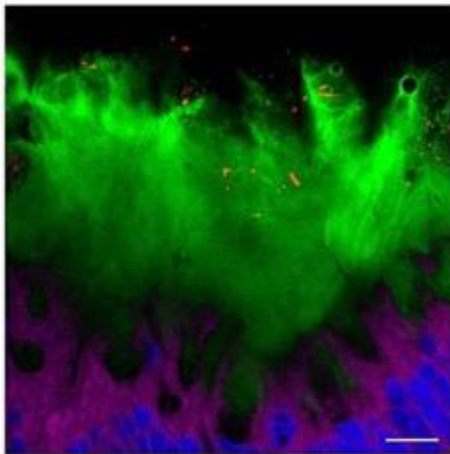
Development of diabetes in humans



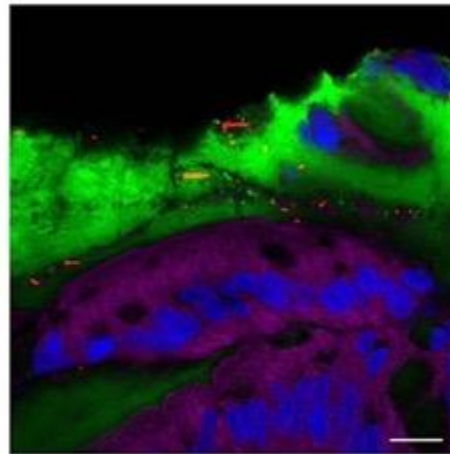
Mechanism for 'leaky gut': ... encroachment!?



Distance from epithelial cell to first bacterium in 5 high powered field pictures of gut biopsy



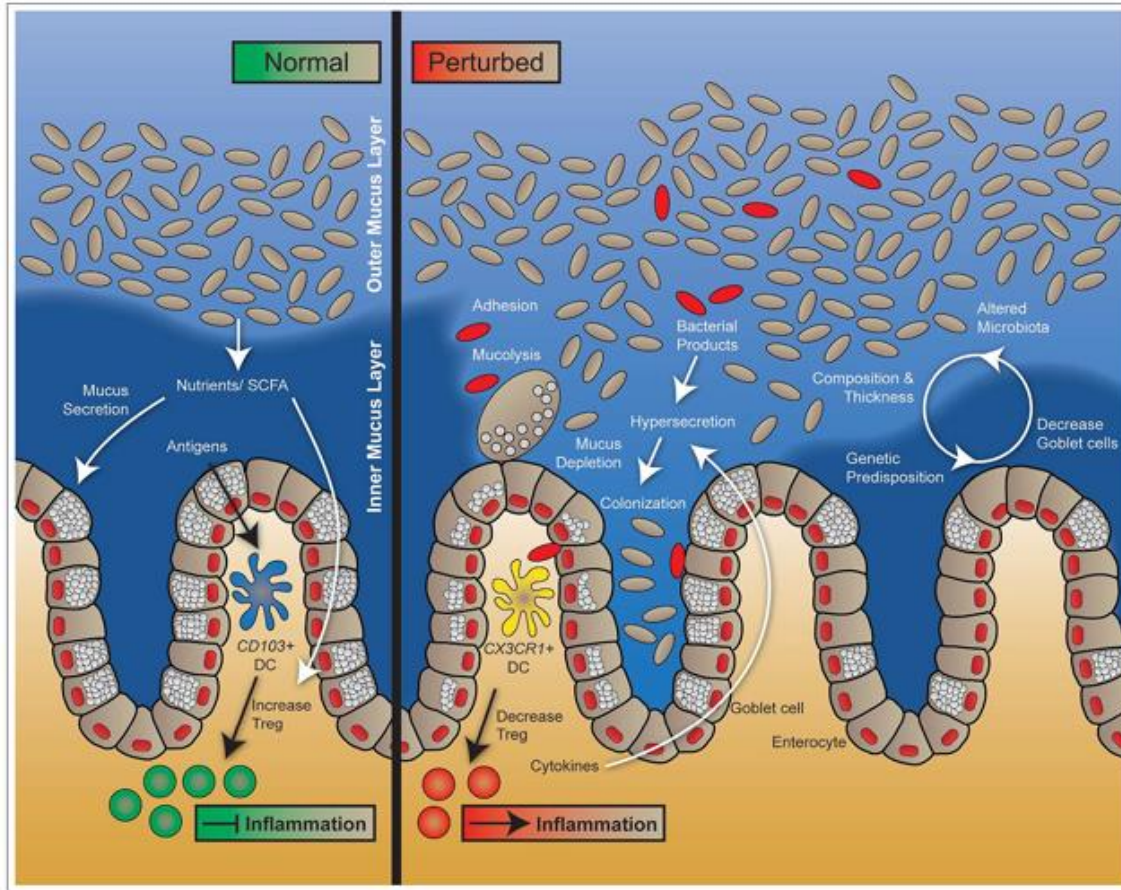
Patient #13 BMI = 28.00, Glucose = 97
HbA1C = 6.1, Diabetes mellitus = No



Patient #8 BMI = 32.02, Glucose = 191
HbA1C = 7.0, Diabetes mellitus = Yes

Microbiota encroachment is a feature of metabolic disease, particularly insulin resistance—associated dysglycemia.

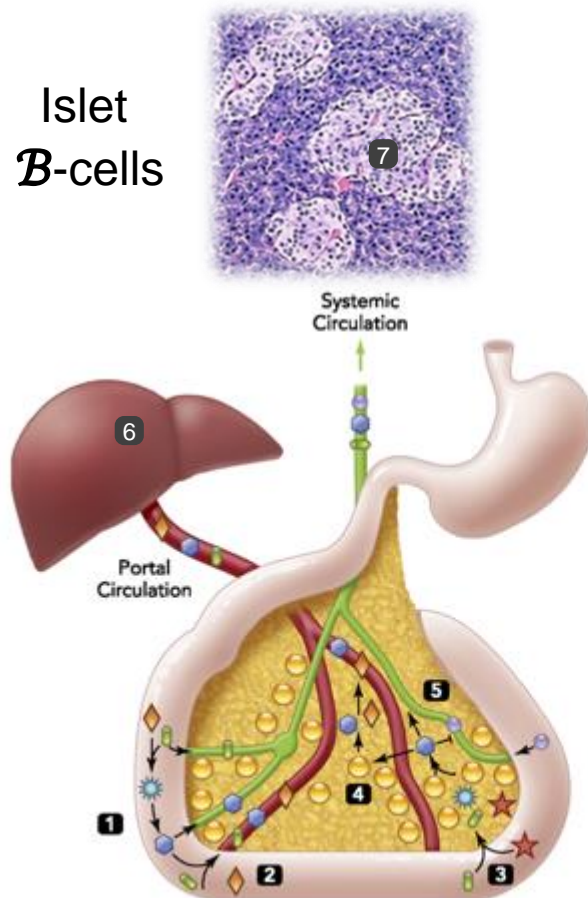
Bacteria encroach on the gut wall, endotoxin and bacteria leak into the circulation



Cornick S, et al Tissue Barriers 2015;3:1-2-e982426

Bacterial products, changes in adipose tissue lead to insulin resistance and ↓ insulin release

- 1) ↑ fat and sugar (Western) diet → ↑ bacterial release of lipopolysaccharide (LPS)
- 2) LPS → inflammatory cytokines into portal system
- 3) ↑ translocation of bacteria and LPS into visceral adipose tissue, ↑ inflammatory cytokines
- 4) Adipocytes release free fatty acids (FFA)
- 5) Reduced clearance of inflammatory mediators from visceral adipose tissue
- 6) ↑ LPS, FFA, and cytokines into portal circulation ↓ liver metabolism and insulin sensitivity
- 7) ↑ delivery of LPS, FFA, cytokines into systemic circulation negatively affect B-cell and systemic insulin sensitivity



What we're going to talk about

- The gut microbiome
- The role of the gut in immunity
- The role of the gut microbiome in type 1 diabetes
- The role of the gut microbiome in obesity and type 2 diabetes
- Can we affect diabetes development or progression through the microbiome?



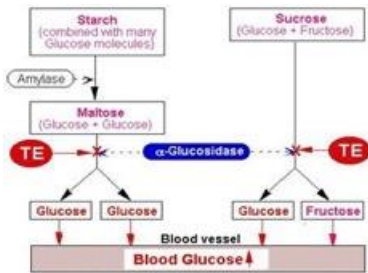


Can we
proactively modify
our gut bacterial
populations?

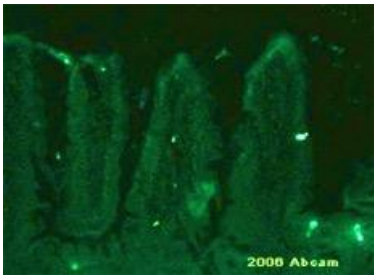
Some things that we know affect the gut/bacteria relationship



- Meformin increases the population of *Akkermansia muciniphila* by 18 fold, enhancing the digestion and of mucin, increasing short chain fatty acids and feeding intestinal cells¹



- Some lactobacilli, and plant principles (e.g. grape extract) inhibit alpha glucosidases in the gut much like acarbose²
- A number of prebiotics feed the microbiome increasing the population of L-cells in the gut which produce increased amounts of GLP-1³



1) Lee H, and Ko GP. Appl. Environ. Microbiol. October 2014 ; 80:19 5935
2) Panwar H, et al. European Journal of Nutrition 2014;53:1465
3) Napolitano A, et al. PLOSone 2014;9:e100778

More on *Akkermansia muciniphila* ...

- A mucin-feeding gram negative organism constituting 3-5% of the intestinal microbiome¹
- Concentrations inversely correlated with obesity and diabetes in many human studies¹
- Pre-biotic consumption (soluble fiber) is metabolically beneficial and increases *A. muciniphila* concentrations¹
- In rodent studies administration of *A. muciniphila* decreases adipose tissue inflammation²
- Dietary polyphenols found in many colored fruits and vegetables (e.g. red wine, cocoa) increase amounts of *A. muciniphila* as well as increasing Lactobacilli and Bifidobacteria³



1) Tilg H. and Moschen AR. Gut 2014;63:1513
2) Roopchand DE, et al. Diabetes 2015;64:2847
3) Marchesi JR, et al. Gut 2016;65:330

Fiber: what it is and why you need it



- Some Raw Vegetables
 - Jicama
 - Jerusalem artichoke
 - Dandelion greens
 - Raw or cooked onions
- Wheat Dextrin
- Inulin

Probiotics in type 2 diabetes: effects on markers of diabetes control, inflammation and oxidative stress

- ↓ Fructosamine
- ↓ Hemoglobin A1C
- ↓ LDL cholesterol
- ↓ Inflammatory cytokines

Randomized, controlled, double blind study; 45 patients with T2DM studied for 6 weeks, comparing fermented milk plus *L. acidophilus* plus *B. animalis* versus plain fermented milk¹

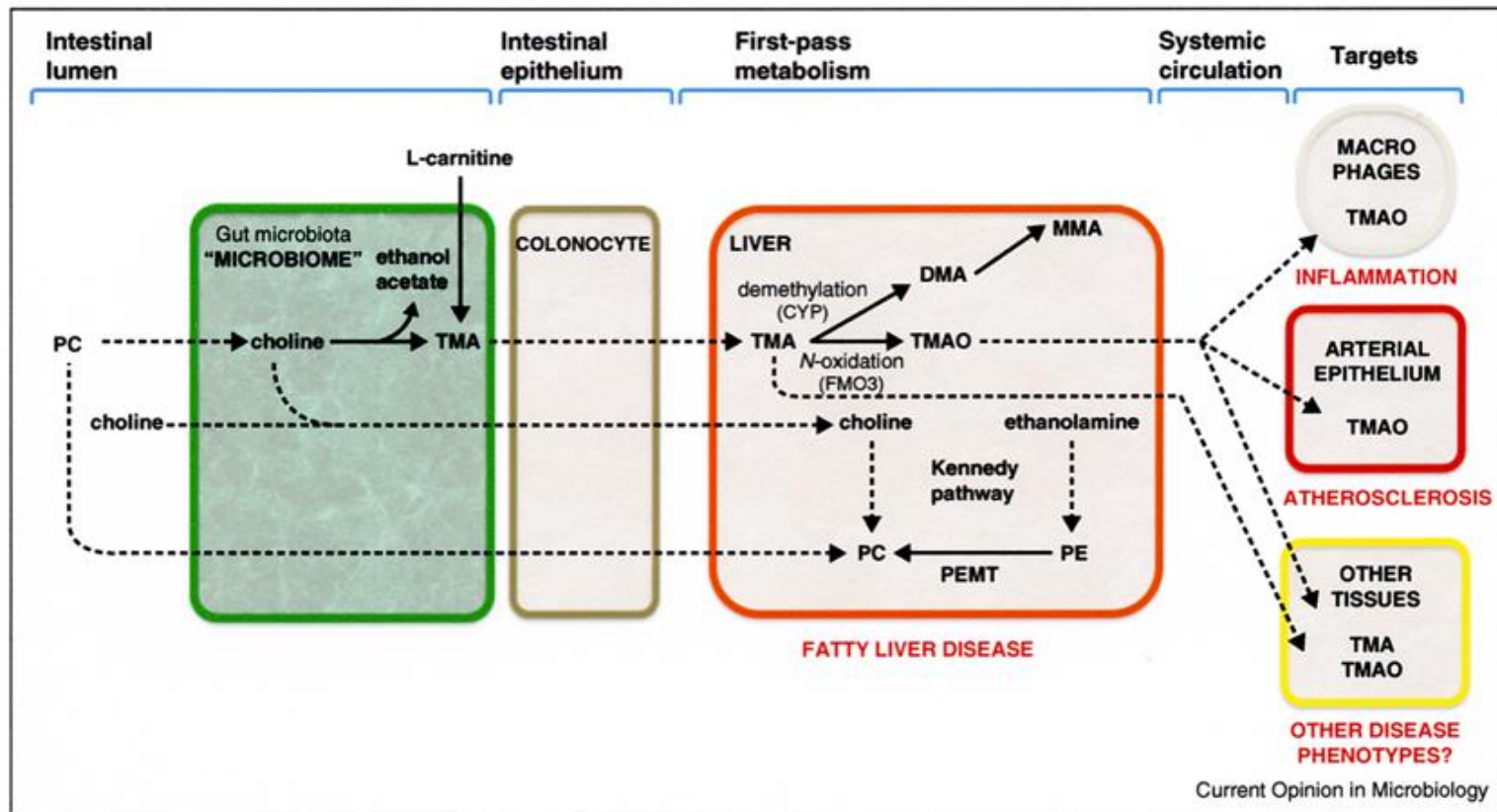
- ↓ Serum insulin
- ↓ Fasting glucose
- ↓ C-reactive protein
- ↑ Reduced glutathione

Randomized, controlled cross-over study; 62 patients with T2DM, 6 weeks exposure to 'Synbiotic' food (*L. sporogenes* plus inulin) versus control food w/o microorganisms or prebiotic²

1) Tonucci LB, et al. Clinical Nutrition 2017;36:85


2) Asemi Z, et al. Clinical Nutrition 2014;33:198

Gut Bacteria and Cardiovascular Risk ...



Recent studies suggest a role of the gut microbiome in the processes of inflammation and atherosclerosis subsequent studies suggest that choline and also carnitine metabolism can result in TMAO

Russel WR, et al. Current Opinion in Microbiology 2013, 16:246–254

A silhouette of a person stands on a dark, rocky outcrop in the lower-left foreground, with their arms raised in a gesture of awe or wonder. The background is a vast, colorful galaxy, likely the Milky Way, featuring a central band of bright, multi-colored dust and stars in shades of blue, purple, pink, and white. The overall scene is set against a deep, dark blue night sky filled with numerous bright, multi-pointed stars.

What we
don't know...

Johnson & Johnson DIABETES CARE COMPANIES

For more information visit www.jjdi.com. **Become a member and opt in** to be notified about our new programs, publications and more!

Follow us on Twitter [@JJDiabetesInst](https://twitter.com/JJDiabetesInst) to receive timely and important updates about diabetes!