Introduction to Microbiome: Important than Thought

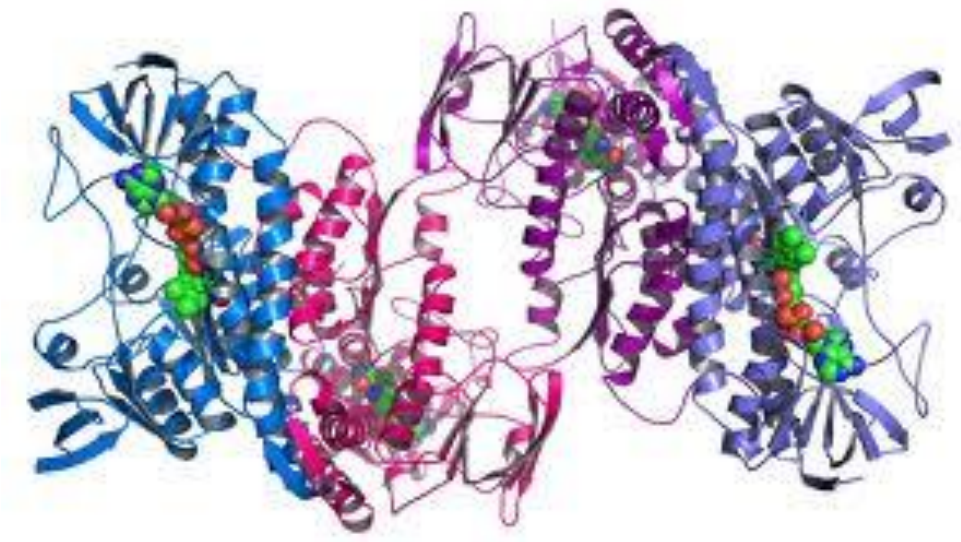
Shahrzad Riazi
NIOC Central Hospital
Tehran, Iran

You Are What You Eat!

- Anthelme Brillat-Savarin, French politician, 1826:
  - "Tell me what you eat and I will tell you what you are"
- Ludwig Andreas Feuerbach, German philosopher, 1863:
  - "Man is what he eats"
- They probably didn't mean their quotations to be taken literally. "the food one eats has a bearing on what one's state of mind and health"
- This appears to be more true than we thought.

How Many Genes do we Have?

- 10 years ago we estimated to have 100,000 genes to explain for all the various proteins and traits.
- Now we have only found about 23,000! slightly more than a mouse or chimpanzee
- Where are the rest? How are the other proteins/traits explained?



Where are the Other Genes?

- There might be none
  - Many genes code for more than one protein
  - Maybe there are not that many proteins/traits
- Other DNA/RNA sources
  - Mitochondria
  - Ribosomes
- Non-human DNA/RNA
  - Flora (gut/skin/mouth/…) – the microbiome

The Microbiome

- Only 200-1400gm (the new organ)
- Outnumber our cells by about 10 to 1
  - 10 trillion (million million) human cells
  - 100 trillion microbes
- Their genes outnumber ours by 100-1000 to 1
  - 23,000 human genes
  - 8 million microbiome genes
- We are more microbe than human!
- Diverse between individuals
  - Human genes are 99.9% identical
  - Microbiome genes are 10% identical (90% different)

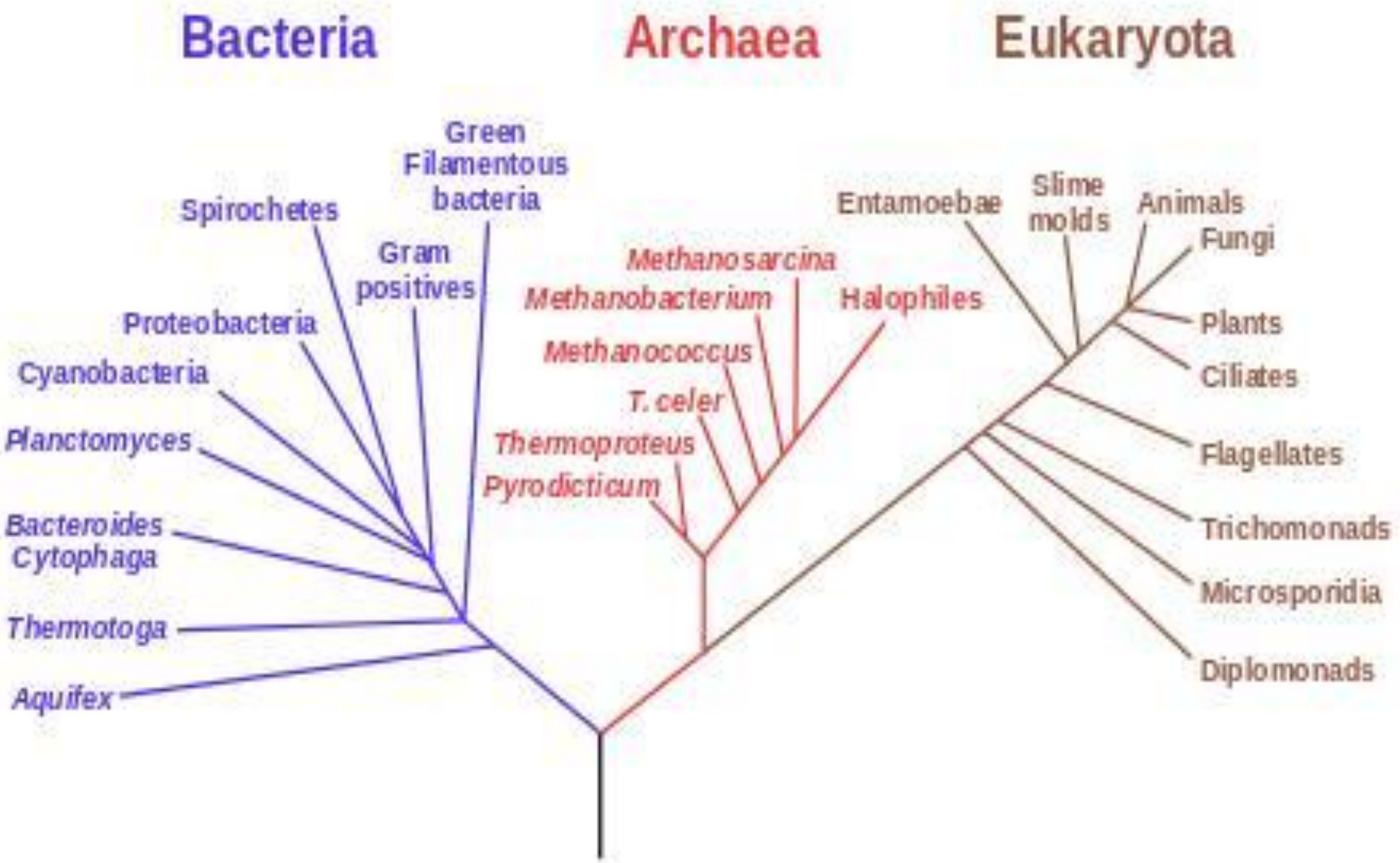
The role of Immune Tolerance

- The immune system becomes less sensitive to an antigen to which it is constantly exposed.
- This tolerance is mediated in part by the gastrointestinal immune system and in part by the liver.
- Many such antigens are produced by gut bacteria
- Diversity in gut bacterial antigens might increase immune tolerance and reduce over-reactive immune responses
  - Such as: allergies, autoimmune disease

Composition

- Bacteria
  - Anaerobes
  - Aerobes
- Archaea
  - Former archaebacteria in the Bacteria domain
  - Prokaryotes (no nucleolus)
  - But their genes and metabolic pathways (especially transcription and translation) is closer to Eukaryotes
  - Something between bacteria and Eukaryotes

Phylogenetic Tree of Life



Where do Microbes Come From?

- It is widely accepted that the amniotic fluid and fetal intestine is sterile.
  - This may not be true for preterm infants
  - It is certainly not true in premature rupture of membrane
    - This "un-sterility" may play a role in the initiation of preterm labor

Where do Microbes Come From?

- At birth
  - Flora from the birth canal
    - There is a difference between NVD and CS, might there be consequences?
  - Mother's skin
  - During breast-feeding (vs. formula?)

Possible Effects of Mode of Delivery

- Mode of delivery is associated with differences in intestinal microbes up to 7 years later
- Intestinal bacteria play an important role in the postnatal development of the immune system
- Babies born vaginally are colonized predominantly by *Lactobacillus*, whereas cesarean delivery babies are colonized by a mixture of potentially pathogenic bacteria typically found on the skin and in hospitals, such as *Staphylococcus* and *Acinetobacter*.
- Epidemiological data show that atopic diseases appear more often in infants after CS than after NVD, especially asthma in females.
- The mechanisms remain poorly understood.

Cesarean Delivery Associated Childhood Diseases[1,2]	
Allergic Rhinitis	
All Cesareans	1.37 (1.14-1.63)
Repeat Cesareans Only	1.78 (1.34-2.37)
Asthma	
All Cesareans	1.24 (1.01-1.53)
Female	1.53 (1.10-2.10)
Female & Repeat Cesarean[3]	1.83 (1.13-2.97)
Celiac Disease	1.80 (1.13-2.88)
Diabetes Mellitus (Type 1)	1.19 (1.04-1.36)
Gastroenteritis[4]	1.31 (1.24-1.38)
Gastroenteritis AND Asthma	1.74 (1.36-2.23)

Microbiome

- Unique set for each human
- The microbiome is usually stabilized by the age of 3
- But they can be changed, at least temporarily:
  - Antibiotics
  - Probiotics
  - Prebiotics
  - Symbiotics
  - Dietary interventions
  - Fecal Transplantation
- Antibiotics given at younger age might have long-term effects on the microbiome

What can the Microbiome Do?

- They metabolize whatever remains from ingested food
- They metabolize secretions from the GI tract
- They produce gas, some of which is absorbed
- They produce metabolites, some of which is absorbed and some effects GI epithelium
- Occasionally, they even enter the blood stream

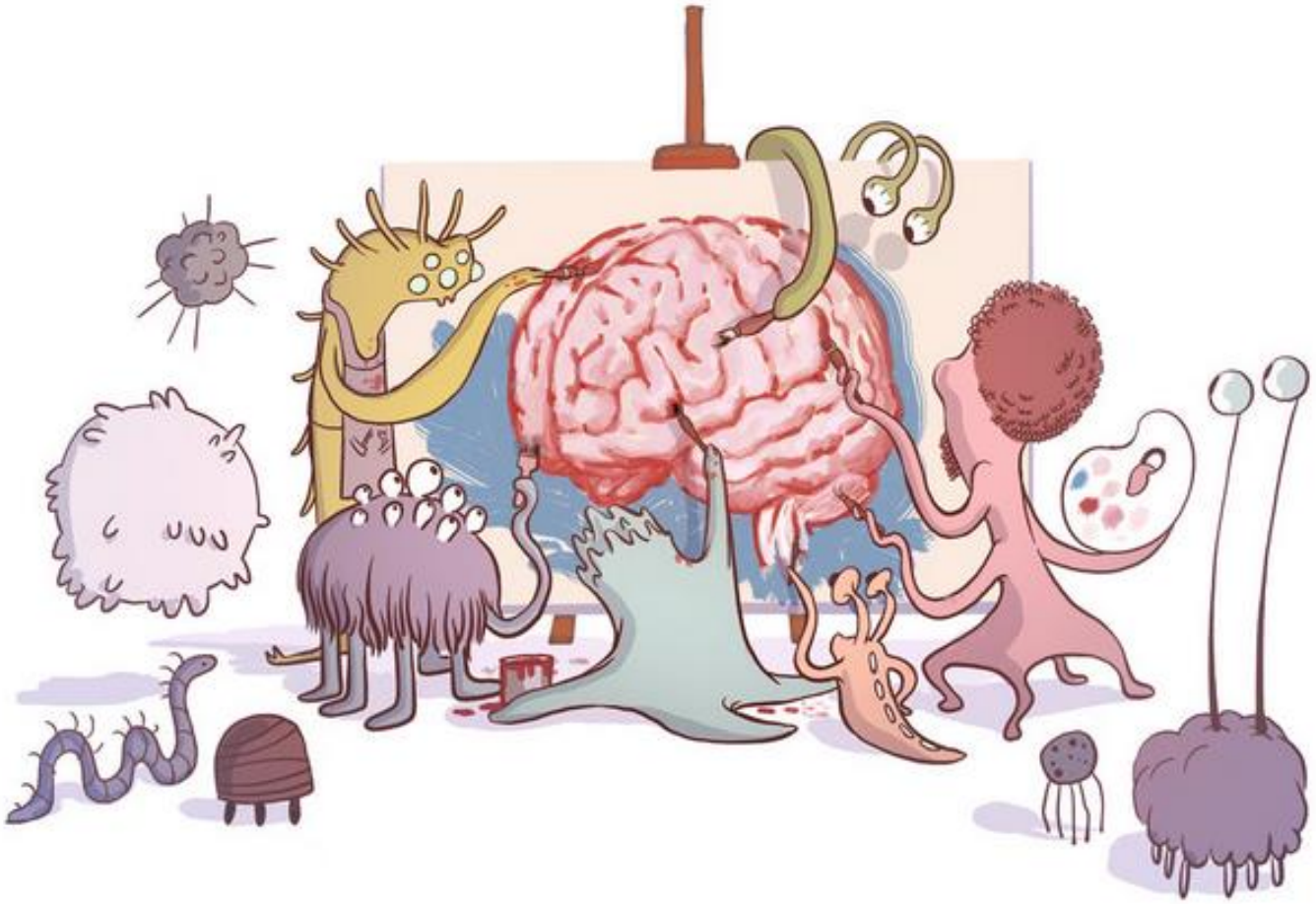
Can it Affect Human Health?

- Appears to be involved in a growing list of human disease:
  - GI tract disease
    - Psudomembranous colitis, food sensitivities, IBD, IBS, BOS
  - Liver disease
    - They determine if acetaminophen is toxic to your liver or not
    - NASH?
  - Auto-immune diseases
    - DM, RA, muscular dystrophy, MS, fibromyalgia
  - Some cancers (eg stomach and colon)
  - Obesity
  - Heart disease
  - Maybe even schizophrenia, depression, bipolar disorder
- They can even drive mosquitos away!

More Specific Mechanism?

- Ingested choline/phosphatidylcholine enters the bowel
- It is metabolized by aerobic bacteria in the gut (with CutC/CutD genes) to trimethylamine (TMA)
- TMA is a small molecule which enters the portal blood and is carried to the liver
- In the liver TMA is metabolized to trimethylamine N-oxide (TMAO)
- TMAO somehow activates macrophages resulting in acceleration of atherosclerosis

The Microbiome can even Modify the production of neurotransmitters



Microbiome and Bad Breath

- One explanation:
  - Gut flora produce gas
    - Varies depending on the substrate they get - what you eat
  - The gas is absorbed to the portal blood
  - Finally expelled through the lungs by respiration
- It's actually from respiration not the stomach and the smell is from the large bowel bacteria not HP
- Constipation aggravates this (more bacteria, more time, more gas)

Role of the Microbiome in Obesity

- Many studies confirm the relation of microbiome and obesity.
- Fat mouse/thin mouse studies
  - Enema of fat mice fecal bacteria to thin mice will make the thin mice fat.
- Correlations of antibiotic use and obesity
  - There is evidence that more antibiotic use in early childhood is correlated with obesity.
- Studies on pregnant women
  - Their gut flora induces obesity and insulin resistance in rats

Role of the Microbiome in Obesity

- Obese individuals have fewer Bacteroidetes and more Firmicutes than lean people.
- The proportion of Bacteroidetes increases when individuals lose weight
- Those with fewer microbiome genes (less diversity) tend to have more body fat and poorer metabolic health
- Microbial genes can differentiate the obese from lean with 90% accuracy, for human genes its 58%

Any Human Experiences?

- In a Chinese experiment a few years ago one subject loss 51 kg with diet + probiotics
- A recent study from China used a mixture of pre/probiotics leading to a mean weight loss of 6 kg in 9 weeks

Can we Treat Obesity with Microbes?

- Probably yes ☺
- Does that mean we don't have to diet?
  - Probably No ☹
  - But who knows? Maybe….Someday….
  - But the diets will definitely be less restrictive

Summary

- Much of human traits might be controlled by the microbiome
- Many disease are related to the microbiome
- Changes in the microbiome affects health
- Microbiome might defer in C/S vs. NVD, in breast vs. formula feeding which might affect future health
- Obesity might be because of the microbiome.