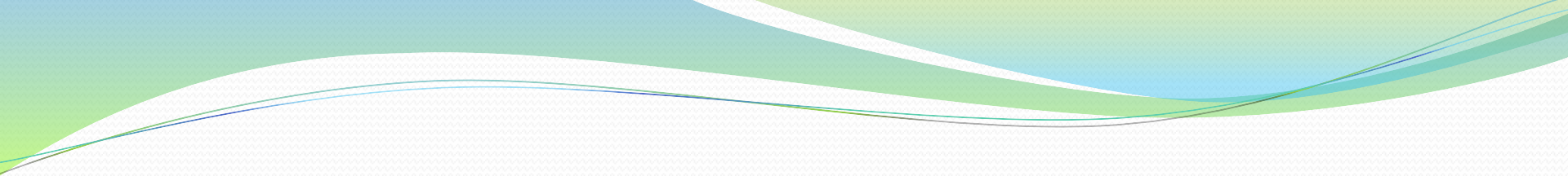


# The Human Microbiome and Autoimmunity

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# Disclosures

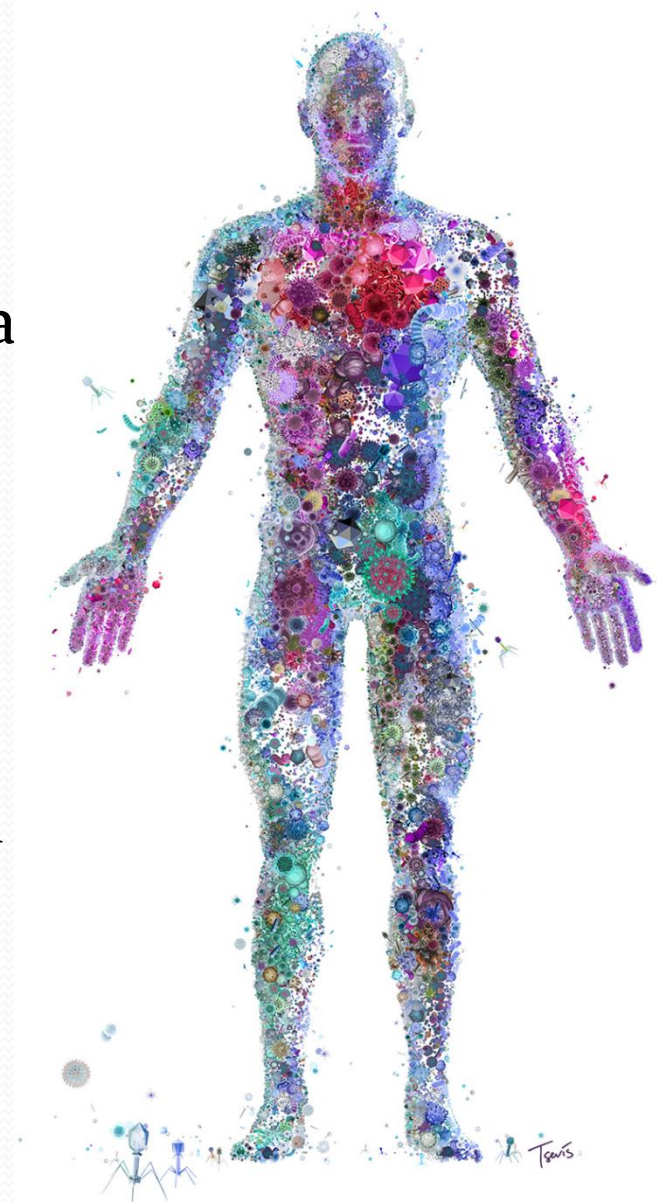
- Celgene speaker's bureau & advisory board member
- Crescendo advisory board
- Genentech speaker's bureau & advisory board, training staff for new hires
- CORRONA
- Mallinckrodt speaker's bureau
- Xcenda research board
  
- There are no off-label references to medications in this particular lecture

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- Basic definitions
  - Microbiome of the oral mucosa and periodontia
  - Microbiome of the GI tract
  - Pulmonary/respiratory microbiome
  - How a change or alteration in microbiome can affect a person's state of having disease or not having disease
  - Are there ways to bring our microbiome back to its natural state of homeostasis?

# Microbiome:

- The community of microorganisms, (bacteria, fungi, viruses) that inhabit a particular environment

\*the totality of microorganisms and their collective genetic material present in or on the human body or in another environment



# NIH Human Microbiome Project

- Collective genomes of the microbes (bacteria, bacteriophage, fungi, protozoa, viruses) that live inside and on the human body (project launched in 2007)





# NIH Human Microbiome Project

- Healthy volunteers with no immunomodulators
- Some were colonized with bacteria & viruses that would normally be pathogenic, but again, these patients were asymptomatic & healthy
- Surprising results, but still need to identify what these may mean

# What does our microbiome do for us?

- Metabolize medications
- Digestion
- Activate and support the immune system
- Help to create a barrier along surfaces to prevent disease



# Toll-Like Receptors

- Important in the innate immune system
- Expressed in cells like macrophages and dendritic cells
- Receptors that recognize key components of microbes that will initiate signal transduction pathway and trigger expression of genes
- The innate immune response is immediate but non-specific, so if it goes on for too long, we can have damage of healthy tissue in addition to the targeted infection





# Inflammasome

- Component of the innate immune system
- Receptors and sensors that regulate activation of caspase-1 and induce inflammation in response to infectious microbes and molecules derived from host proteins
- Detect pathogenic micro-organisms and sterile stressors
- Capable of activating highly pro-inflammatory cytokines

**Microbial Attack**

**PAMPs**

**Sterile Attack**

**DAMPs**

**Inflammasomes**



**Lung**

Asbestosis  
COPD  
Asthma

**Heart**

Hypertension

**Skin**

Psoriasis  
Allergy

**Metabolism**

Arteriosclerosis  
Type II Diabetes

**Brain**

Alzheimer's Disease  
Parkinson  
Multiple Sclerosis  
Prion

**Cancer**

Mesothelioma  
Hepatomas

**Chronic/Acute  
Inflammation**

**Joints**

Rheumatoid Arthritis  
Gout

**Intestine**

Inflammatory Bowel Disease



# Oral microbiome

- Shedding mucosal surfaces vs. non-shedding (teeth)
- Healthy saliva flow is important (provides nutrients, pH, repairs teeth, antimicrobial & antiviral properties)
- Breast fed infants have less Staph, Prevotella, Veillonella suggesting that some of our microbiome can be affected as early as birth
- C-section can affect our oral microbiome as well

# Oral microbiome

- Porphyromonas gingivalis
- Patients with periodontitis present with increased antibodies to this bacteria
- Increased amounts of this bacteria and increased antibodies are found in patients who have rheumatoid arthritis
- P.gingivalis overproduction increases TH17 production
- Produces T cells through TLR 2 activation on APC's



# Oral microbiome

- The most support association in rheumatoid arthritis patients is the presence of oral dysbiosis with periodontitis
- *P.gingivalis* can trigger generation of citrullinated peptides
- Similarities between the erosive appearance of periodontal disease in this situation and the erosive disease of rheumatoid arthritis



# Oral microbiome

- In rheumatoid arthritis
- Decreased *Haemophilus* correlated with increased serum auto-antibodies in patients
- An increase in *Lactobacillus* correlated with very active rheumatoid arthritis
- The dysbiosis in these patients improved with treatment of their underlying rheumatoid arthritis

# Oral microbiome

- Periodontal area; porous/inflamed; rich in microbes
- $\leftrightarrow$  frequent transient bacteremia
- inflammation



# Oral Microbiome

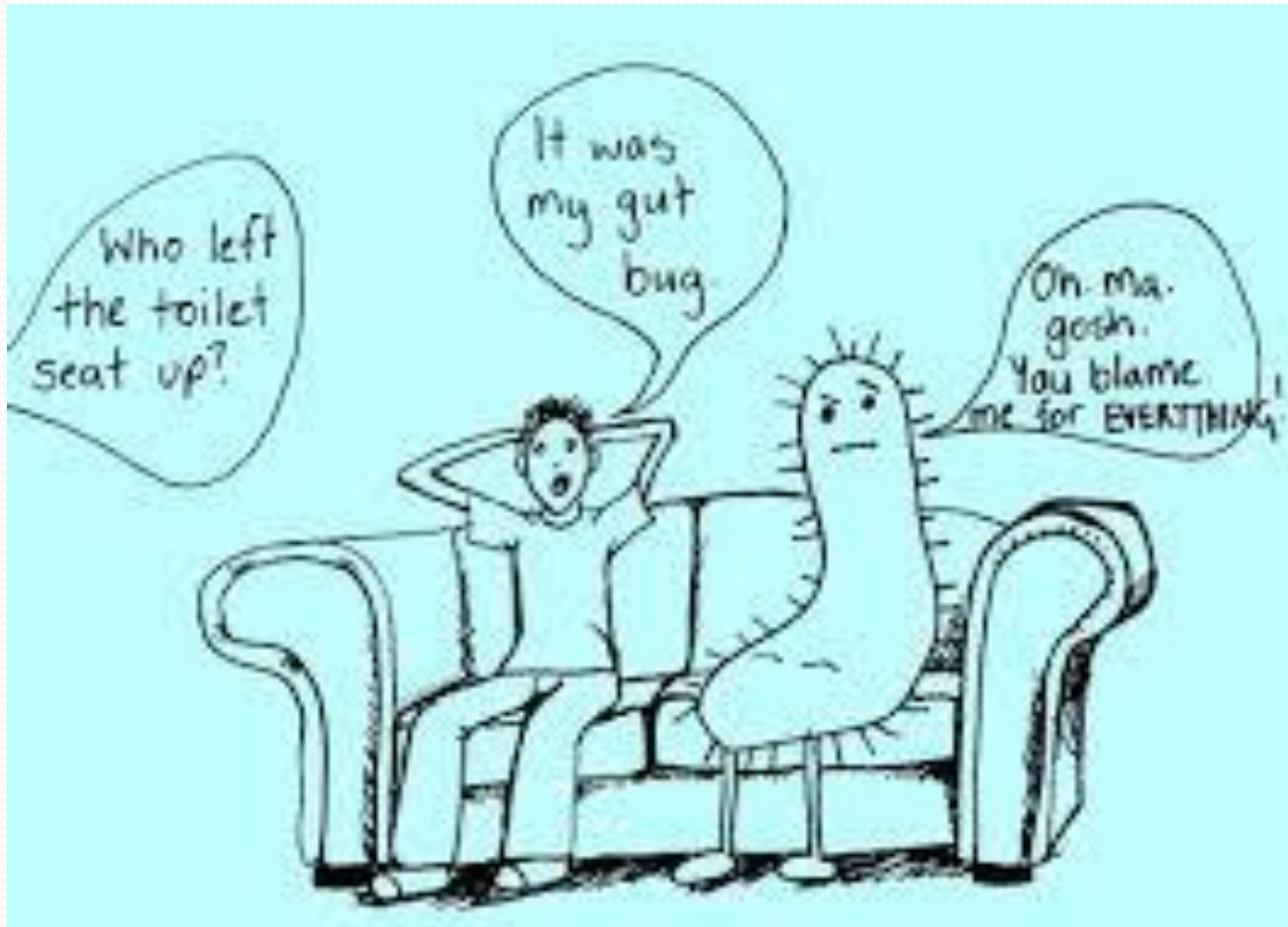
## Rheumatoid Arthritis

- TNF-alpha
  - Interleukins
  - PgE2
  - NFkB
  - MMP
  - RANKL/osteoprotegrin
- 
- RF, ESR, CCP, CRP

## Periodontitis

- TNF-alpha
- Interleukins
- PgE2
- NFkB
- MMP
- RANKL/osteoprotegrin

# GI Microbiome





# GI microbiome

- Our innate immune system performs surveillance that controls how the gut microbiota communicates with the internal environment
- This is how we maintain homeostasis and prevent systemic spread

# Cells in the gut monitor for absorption

- PRRs
  - TLRs
  - NLRs
  - RIG1-like receptors
  - C type lectin family
  - AIM2 like receptors
- 
- These all trigger cascades against the PAMPs and DAMPs

# GI microbiome

- Altered TLR signaling is implicated in rheumatoid arthritis, inflammatory bowel disease, diabetes mellitus, multiple sclerosis
- Concept of molecular mimicry
- Cross reaction between epitopes from microbes and self-proteins causing deregulated immune responses leading to auto-antibody production and activation of effector cells

# Inflammasomes in the gut

- Multimeric protein complexes typically composed of a sensor protein, adaptor protein, pro-inflammatory caspase-1 which can be triggered by a variety of stimuli associated with infection and cellular stress
- Leads to the release of pro-inflammatory cytokines IL-1 $\beta$  and IL-18
- Inflammasomes contain a NLR sensor molecule
- Salmonella, Pseudomonas, Enterobacteriaceae, Proteus mirabilis all can induce IL-1  $\beta$  through NLRP<sub>3</sub>

# GI Microbiome

- IL-1 beta can promote arthritis, particularly of the autoinflammatory subset
- A study of IL-1 receptor antagonist deficient mice develop T cell mediated autoinflammatory arthritis. Germ free mice do not.
- Gut residing segmented filamented bacteria drive IL-1beta, IL6, TH17 development → all of which promote inflammatory arthritis.

# GI Microbiome

- In rheumatoid arthritis studies, we have seen the presence of bacterial cell wall components in the joints of rheumatoid arthritis patients accompanied by changes in their gut microbiota
- IBD & UC patients
  - Increased enterococcus & bacteroides species
  - Decreased bifidobacterium & lactobacillus



# GI Microbiome

- Saccharomyces Cerevisiae Antibodies (ASCA)
  - More likely to be seen in those with inflammatory bowel disease and periodontal disease
- HLAB27
  - Has an amino acid sequence shared with a nitrogenase from Klebsiella and other proteins present in gram negative bacteria

# GI Microbiome

- Gcoup6 protein receptors family “GPR”
- Bind bacterial products and dietary metabolites from gut microbiota
- Caspase recruitment domain containing 9 (CARD 9); important regulatory role in apoptosis through NFKB; defense in pathogens such as yeasts; activates pro-inflammatory cytokines; mutations in this gene associated with AS & IBD

# GI Microbiome

- SpA 50% have subclinical intestinal abnormalities
- C.D.: significant expansion of *Prevotella*, *B. vulgatus*
- Erosive R.A.: fecal samples have higher diversity of bacteria and microbiota, abundance or dominance of *prevotella*

# GI Microbiome

- Prevotella spp.
  - Gram – bacteria
  - Found in oral flora, vaginal flora, recovered from anaerobic respiratory tract infections, periodontal disease
  - Usually a beneficial bacteria associated with plant rich diets (high fiber diet rich in fruits, vegetables, and complex carbohydrates), but also implicated in inflammatory conditions as well
  - Beneficial in glucose metabolism
  - Problematic in inflammatory conditions associated with HIV

# GI microbiome

- Increased animal proteins, simple sugars, saturated fats leads to a less diverse gi microbiome
- Despite what we know thus far, dietary manipulation studies in rheumatoid arthritis patients have been inconclusive, which tells us that there is probably another component that we are not manipulating completely

# Respiratory tract

- Beginning in the nasopharyngeal region, alterations in the microbiota can influence pathology in the lower respiratory tract
- There has been suggested a link between respiratory imbalance and gut imbalance
- Possible implications in neurodegenerative diseases with enhanced response to amyloid proteins and increased inflammation
- Nasopharyngeal imbalance can lead to lower tract diseases like asthma, copd, acute pulmonary diseases

# Respiratory tract microbiota

- Early in being understood
- More is being looked at in the nasopharyngeal microbiome, lower tract microbiome and development of disease
- More is being understood looking at the gut-lung axis of microbiome
- There may be a potential for manipulating the gut microbiome in order to treat lung disease

# Respiratory tract microbiome in Asthma

- In allergic or non-allergic asthma (smoke, environmental pollution, infections, etc.), TH2 cells reside at the center of this process
- Non-atopic, non-IgE asthma tends to show more increased interferon gamma and TH17
- This particular subset also tends to be more steroid resistant
- Since the 1980s, our asthma rates have at least doubled and continued to climb, with unclear reasons/etiologies completely



# Respiratory tract microbiome:

## Asthma

- The “hygiene hypothesis”
- Increasingly clean & sterile environment we live in is producing more of these diseases
- The increased societal emphasis on sterility and cleanliness may have led us to lose many of our so-called “microbial friends”
- Living on a farm actually proved protective in asthma; but as in any circumstance, if patients had extremely high bacterial loads, then they were likely to develop asthma

# Respiratory Tract Microbiome: Asthma

- Some fungi might be protective against asthma, but research efforts are being put towards this currently (cryptococcus was protective)
- Antibiotic exposure early in life was more predictive of developing asthma
- Loss of regulatory T cells in the gut has repeatedly shown development of asthma later
- Research in the lower pulmonary tract has been slower as this was an area previously felt to be “sterile” in the absence of infection for a much longer period of time than the oropharynx & gi tracts

# Stress effects on microbiome

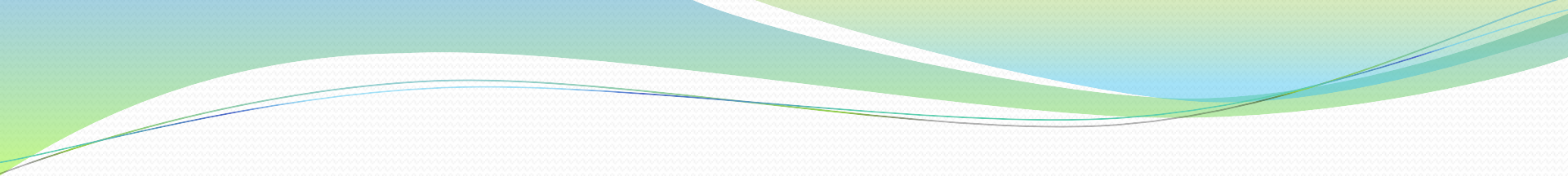
- Stress, smoke, diet
- Can all induce strong bacterial changes
- Exposure of the intestinal epithelium to different metabolites
- Stress can modulate the immune system by inducing a shift away from cellular immunity (TH<sub>1</sub>) to humoral responses (TH<sub>2</sub>)
- Acute stress increases IL-1 and IL-6

# Dietary modifications/Supplements

- Some studies have shown a better response to sulfasalazine if a multi-strain probiotic is co-administered
- Fish-oil (more omega-3 than omega-6)
- Smoking cessation

# General helpful guidelines

- If GI dysbiosis is suspected, don't forget to look for periodontal disease
- “leaky gut”  $\Leftrightarrow$  “leaky mouth”
- Lactobacillus probiotics may treat oral dysbiosis & give some support to these patients
- Avoid antimicrobial mouthwash
- Encourage routine brushing/flossing/dental cleanings
- Probiotics/probiotic toothpaste in those with periodontal disease
- Chewable CoQ10 with possible helpful results

- 
- Our body wants to remain in homeostasis whether on a large scale or on a microscopic scale
  - The innate sensing of our microbiota through TLR's and inflammasomes is an important component of maintaining homeostasis
  - Any disturbance in these areas can lead to local and eventually systemic inflammation along with possible auto-inflammatory syndromes/autoimmunity

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