4V003 - Interface système immunitaire microorganismes environment

Microbiote et les maladies immunitaires

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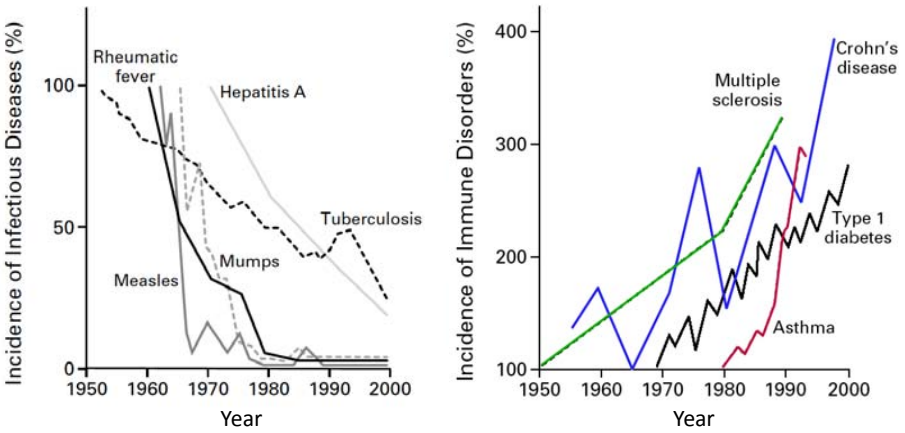
Outline

1. Hygiene theory and environmental factors
2. The gut microbiota and our digestive system
3. Gut microbiota and host immunity
4. Gut microbiota in early life
5. Self-non-self versus the danger model.
6. Gut microbiota and its role in disease
7. Solutions

Hygiene theory and chronic inflammatory diseases

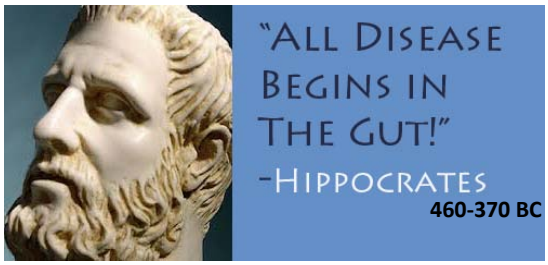


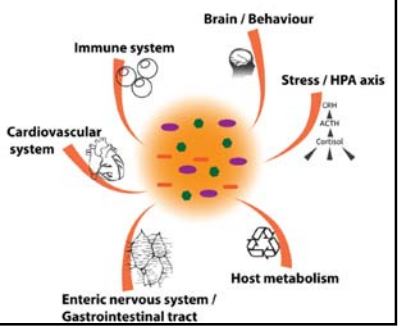
Disappearance of prototypic infectious diseases inversely correlate with occurrence of chronic inflammatory diseases.

Bach *et al.* NEJM 2002

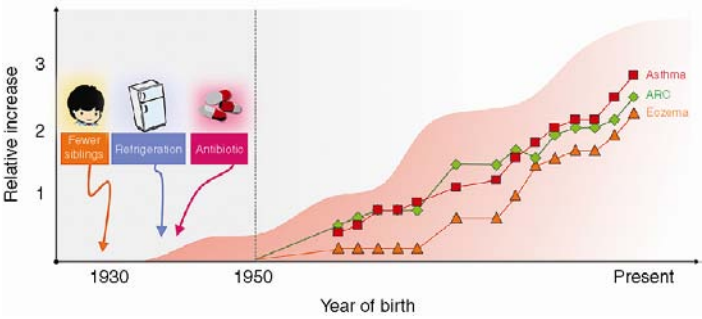
Hygiene theory and chronic inflammatory diseases

- Massive increase in prevalence of chronic inflammatory diseases in Westernized countries.
- Most chronic inflammatory diseases are attributed to both genetic predisposition and environmental factors
- Genetic drift over such a short period of time cannot explain increased incidence of disease
- Westernized life-style has introduced several environmental risk factors, some of which may disturb the homeostatic balance of gut microbiota





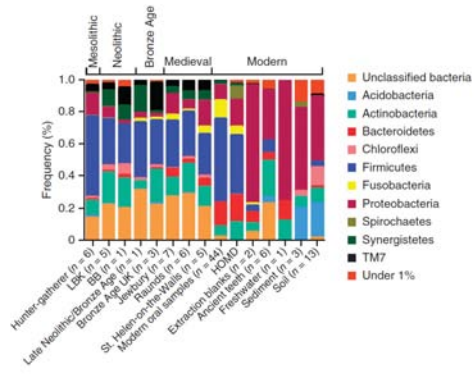
Lifestyle changes affecting Gut Microbiota



- Westernized life-style has introduced several environmental risk factors that disturb the homeostatic balance of gut microbiota
- Excessive antibiotic use, especially during early life (or even during pregnancy)
- Shift towards more formula-fed babies
- Shift towards greater numbers of babies born by Caesarean section
- Western diet

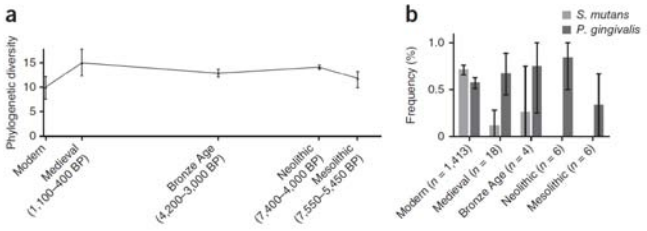
Abrahamsson *et al.* JACI 2015

Oral microbiota shifts through history of mankind



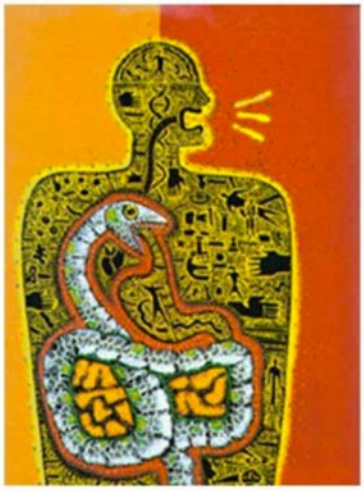
Two of the greatest dietary shifts in human evolution involved :

- Adoption of carbohydrate-rich Neolithic (farming) diets (beginning ~10,000 years before the present)
  - P. gingivalis augments.
- Industrially processed flour and sugar (in ~1850)
  - Streptococcus mutans augments (associated with carries).
- Reduced oral microbiota diversity in the modern human.



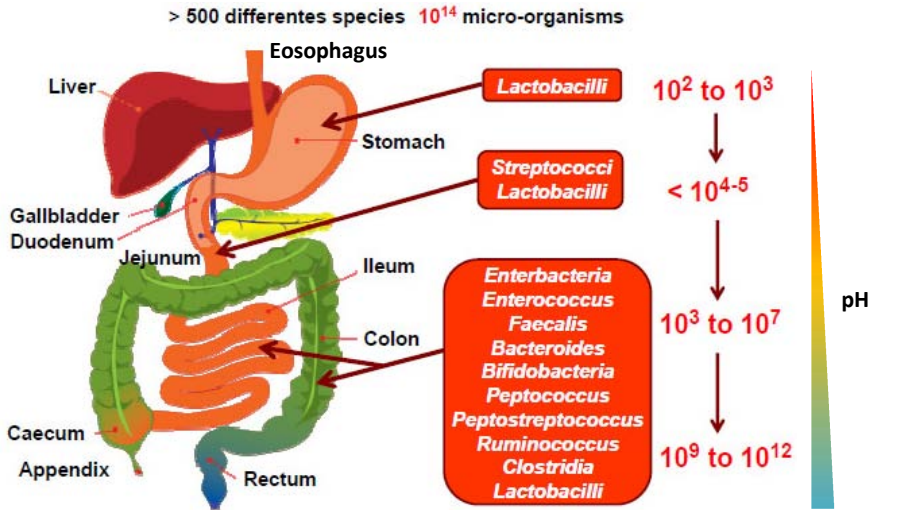
Adler *et al.* Nat Genetics 2013

The human Gut and its inhabitants in numbers



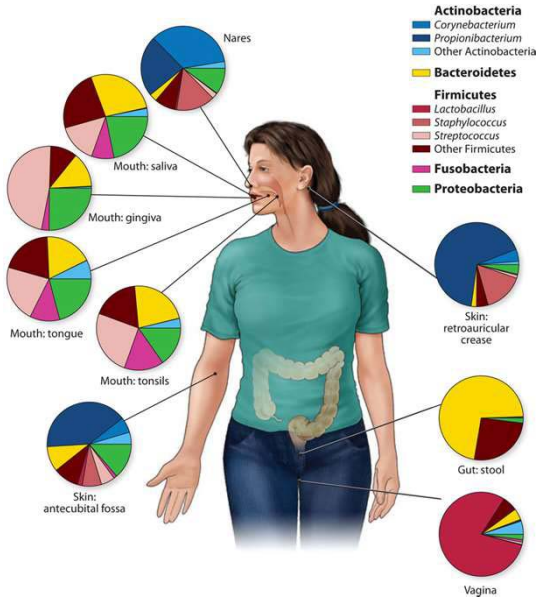
- 30 tons of food and 50.000 L during a lifetime
- Huge mucosal surface:150-200 m^2
- >50 billions of new bacteria every day
- 70-80% of all immune cells are located in the Gut.
- 1-2g secretory IgA per day
- 100 millions of neurons (as many as in the spinal cord).
- $5x10^{13}$ bacteria: 3x number of cells in the entire body, i.e. 1-2 kg.
- 100 times more bacterial genes than human genes.

Spatial distribution of gut microbiota



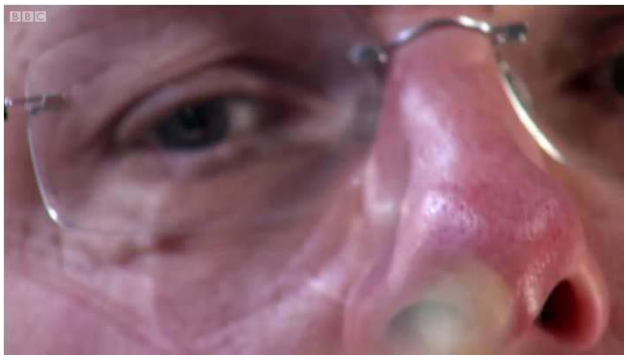
http://www.jpp.krakow.pl/journal/archive/08_15/articles/02_article.html

Human body sites harbor distinct microbiota



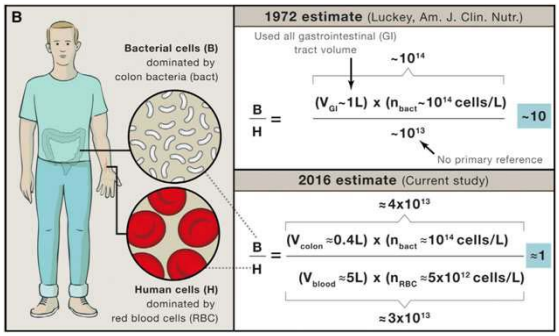
Grice *et al.* Ann Rev Gen Hum Genet 2012

The digestive system - A trip through the GI tract

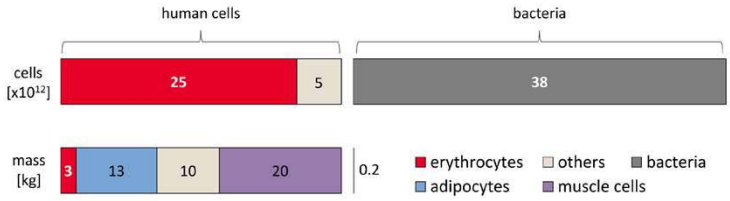


- Mouth (cheewing + saliva containing enzymes)
- Eosophage
- Stomach (very acidic, proteases, few microbes)
- Small intestine (somewhat acidic, microbes (degrade otherwise none-degradable plant fibers).
- Large intestine (Final digestion and return of water to host)
- You all know what happens then……**COLLECTION TIME!**

We are outnumbered and outsmarted



Population	Bacteria:Human
Man	1.3
Woman	2.2
Young Infant	2.3
Infant	1.7
Elder	1.8
Obese	1.4

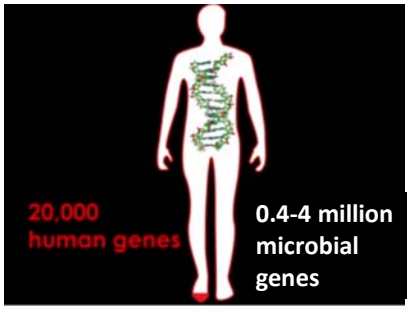


Of note, only takes into account the colon, but demonstrate that the colon contains 98% of all our commensal bacteria.

Sender et al. Cell 2016 & Sender et al. PLoS Biol 2016

We are outnumbered and outsmarted

Outsmarted
(20-200 fold more genes)



Each bacterial species has its own genomic DNA (all human cells have almost identical genomic DNA).

Bacterial genome (2-10x10^6 bps) versus human genome (3x10^9 bps)

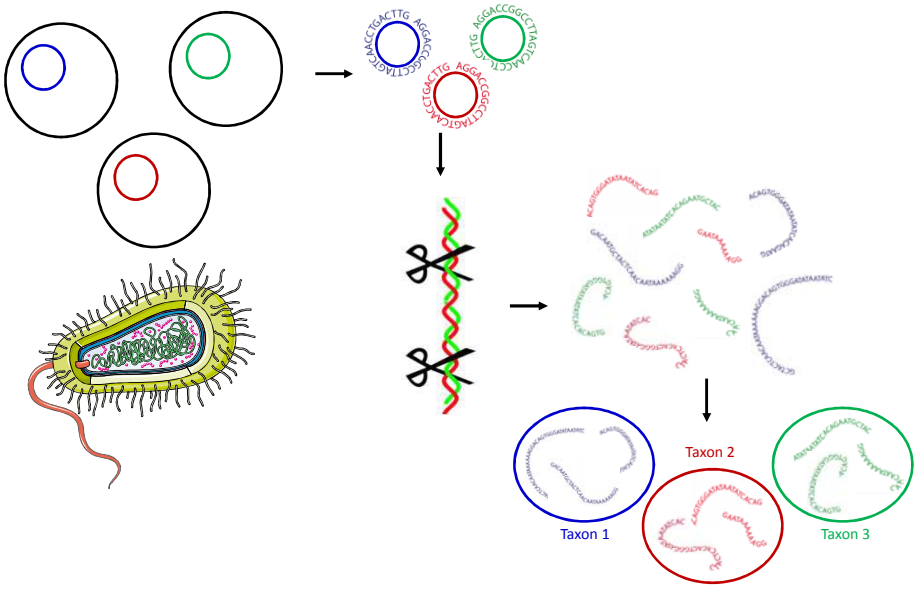
Bacterial DNA is much more compact than human DNA in terms of gene content.

How to study the gut microbiota

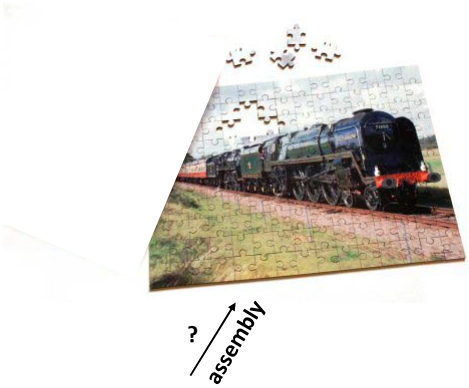
- Culture dependent (classic microbiology – aerobiosis/anaerobiosis, medium)
  - Microscopy
  - Metabolism of substrates
  - Co-culture with host cells (epithelium, immune cells etc.)
  - Genetic modifications
  - Select single-cell culture – strain isolation (FACS)
  - Antibody titers to microbes (ELISA, flow cytometry)

- Culture independent
  - Mass spectrometry
  - Flow cytometry (FISH, immuno-microbiota)
  - Metabolomics
  - Metagenomics (microbiome and immuno-microbiome)
  - Metatranscriptomics

Next Generation Sequencing - like reading a threaded book



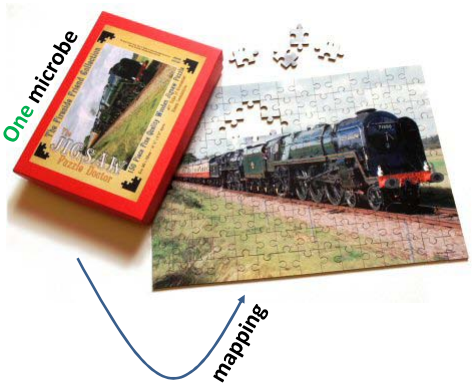
Microbial whole genome sequencing



- One microbe is fully sequenced and assembled.

One microbial genome puzzle

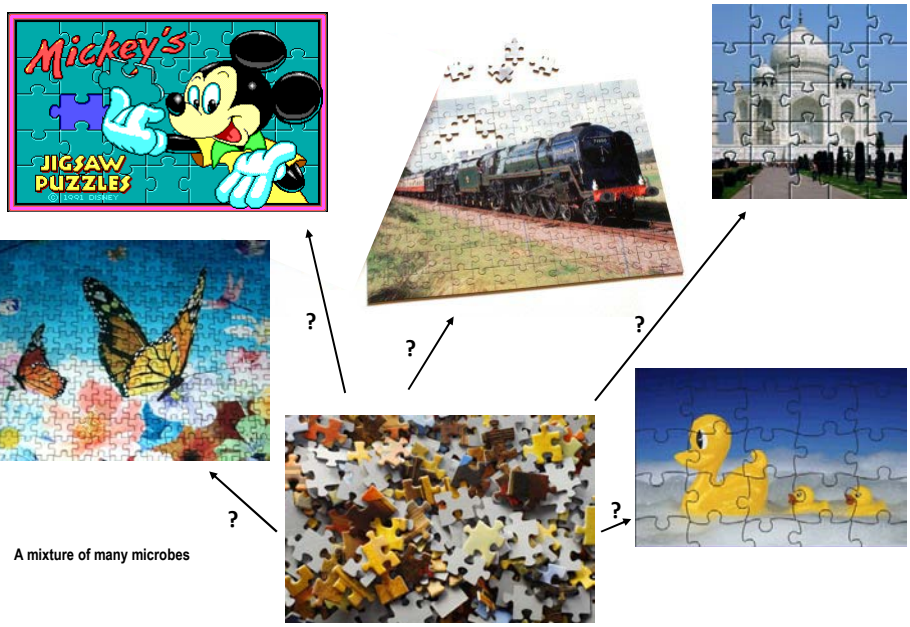
Microbial whole genome sequencing



- Using the reference lid jigsaw genes derived from the reference may be identified.

One microbial genome puzzle

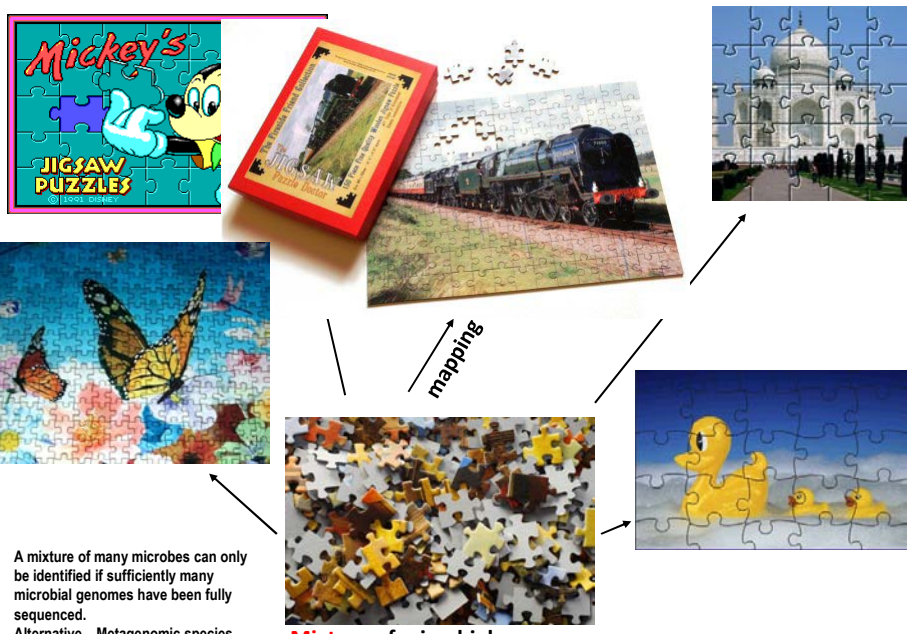
Metagenomic sequencing



- A mixture of many microbes

Mixture of microbial genomes

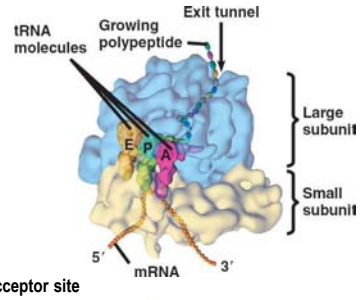
Metagenomic sequencing



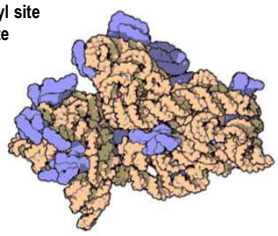
- A mixture of many microbes can only be identified if sufficiently many microbial genomes have been fully sequenced.
- Alternative – Metagenomic species

Mixture of microbial genomes

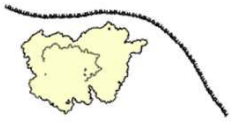
16S rRNA sequencing



A = Acceptor site
P = Peptidyl site
E = Exit site

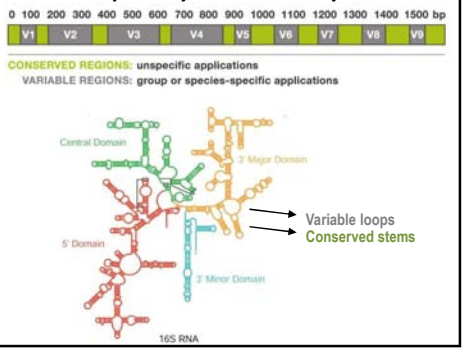


- 16S rRNA in orange
- Associated protein subunits in blue

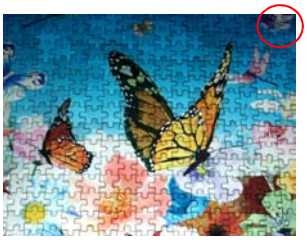


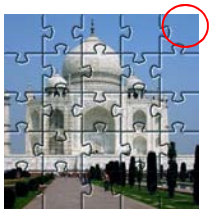
Protein synthesis in the
1. Cytosol
2. Endoplasmic reticulum ER-docking via signal-recognition particle

16S rRNA primary and secondary structures



16S rRNA sequencing





?
assembly

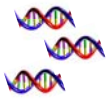
- 16s RNA gene is highly variable and functional as a phylogenetic marker.
- Limitation – species from same genus may be undistinguishable (blue sky jigsaws may be hard to distinguish).

Mixture of microbial 16S rRNA genes

Big data in Microbiology

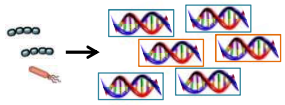
Intestinal tract

Genomic DNA



Next Generation Sequencing

Identification:
1. Ref. genome
2. Co-abundance clustering



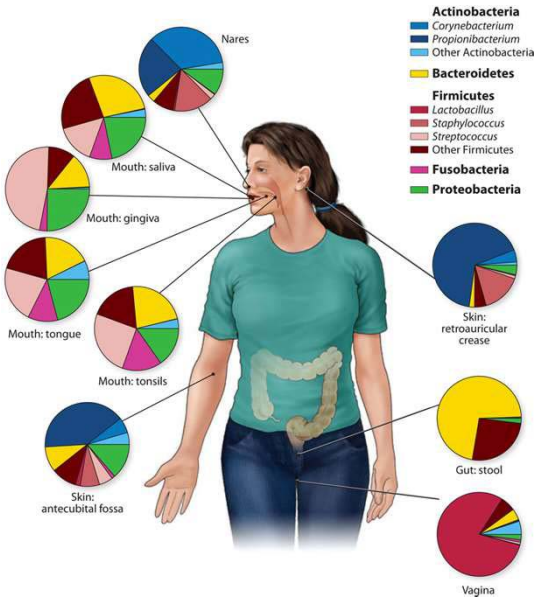
1:2 1:2

MetaGenomic Species (MGS)

16S rRNA: Pruesse et al. NAR 2007 (www.arb-silva.de)
Metagenomics: Qin *et al.* Nature 2010

Nielsen *et al.* Nat Biotech 2014

How to describe and compare complex microbiota compositions



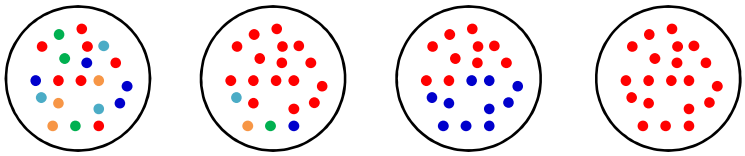
Grice *et al.* Ann Rev Gen Hum Genet 2012

Alpha-diversity

Quantitative
Biomass (g)

- A community's biodiversity correlates with it's size and location
- Ecologists measure biodiversity as heterogeneity, which considers both diversity factors: richness and relative abundance.
- $H = -\sum_{i=1}^{k} p_i log(p_i)$; p=abundance
- $E_H = \frac{H}{log(k)}$; [Normalized]

Qualitative
Richness
Diversity

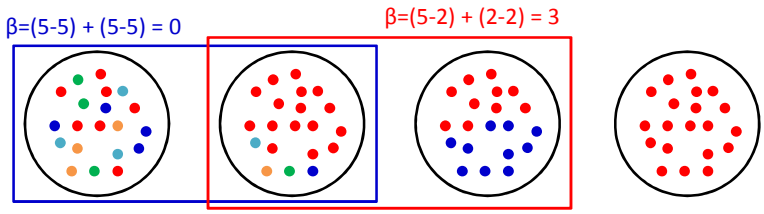


Species richness	5	5	2	1
Shannon entropy [normalized]	p_i=1/5 H=log(5) [E_H=1]	p_{red} ~ 1| $p_{NOT\ red}$ ~ 0 H= ~0 [E_H= ~0]	p_i=1/2 H=log(2) [E_H=1]	p_1=1 H=0 [E_H=0]

- Scores of alpha-diversity: Richness, Shannon, Simpson, Chao1 and Chao2
- Chao1 and Chao2 often used in microbiota research. Used when certain species are rare (based on expected rather than observed number of species in a sample).

Beta-diversity

- Total species diversity (γ) is determined by the mean species diversity of a habitat (α) plus the differentiation among habitats (β). **Robert Whittaker, 1960**
- Pair-wise beta-diversity is measured as similarity or dissimilarity between two samples.
- Beta-diversity is also referred to as species turn-over.
- Absolute species turn-over: $\beta=(R_1-c_{12}) + (R_2-c_{12})$, R=Richness, c=common species



Species richness	5	5	2	1

- Absolute species turn-over is problematic when working with rare species, whose occurrence is associated with random sampling efficiency. Abundance based measures are therefore more appropriate for microbiota work.
- Scores of beta-diversity:
- Occurrence based: Absolute species turn-over, Whittaker species turn-over (special case of Sørensen similarity index) and Proportional species turn-over (Jaccard similarity index).
- Abundance based: Bray–Curtis dissimilarity index, Morisita-Horn overlap index.

Beta-diversity

Occurrence based Beta-diversity

	Habitat 1 (H1)	H2	H3	H4
H1	0			
H2	0	0		
H3	$\beta_{3,1} = 3$	$\beta_{3,2} = 3$	0	
H4	4	4	$\beta_{4,3} = 1$	0

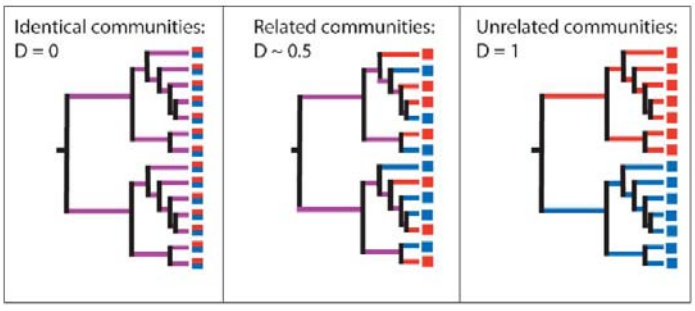
- One could argue that H1 and H3 are more distant ($\beta_{3,1}$) than H2 and H3 ($\beta_{3,2}$), which should be closer to $\beta_{4,3}$. This would be better represented by an abundance based beta diversity.

Beta-diversity

- Classic beta-diversity measures consider all genetically different species equally different (*E. coli* and *K. pneumoniae* (both Proteobacteria) are as different as *E. coli* and *B. longum (Actinobacteria)*).
- Species from same phylum, class, order, family or genus are more phylogenetically similar than unrelated bacteria.
- Solution: UniFrac

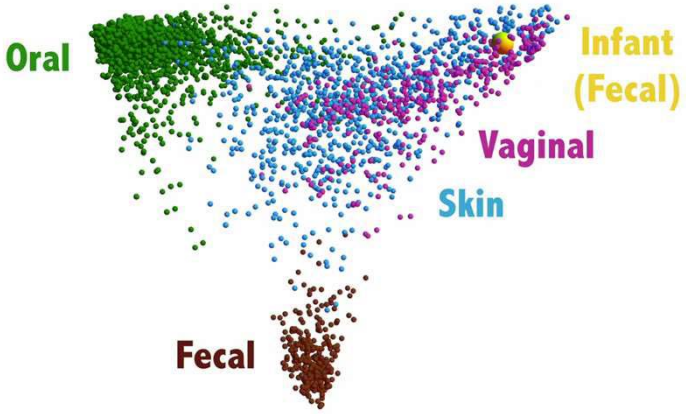
Unique Fraction (UniFrac) metric

- Qualitative phylogenetic β diversity.
- Distance = fraction of the total branch length that is unique to any particular environment.



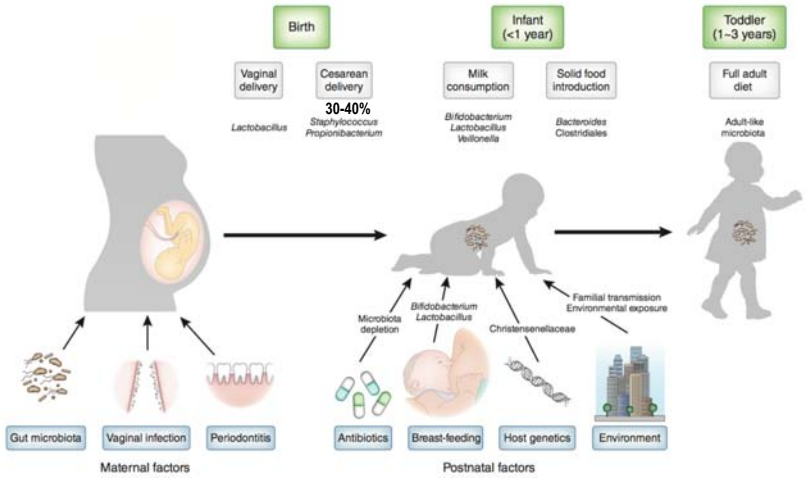
Lozupone and Knight, 2005, Appl Environ Microbiol 71:8228

Gut microbiota maturation during first 2 years of life



Dr. Rob Knight

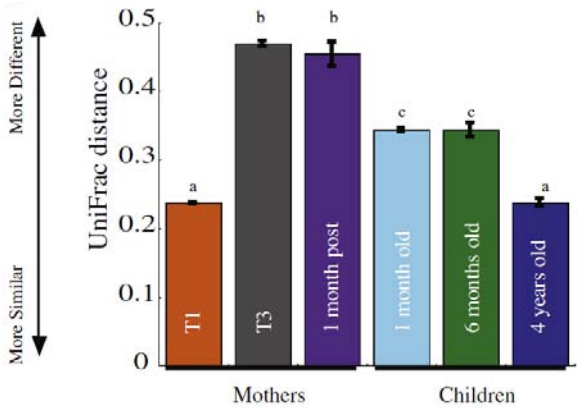
Early-life factors affecting infant gut microbiota



- Both maternal and environmental factors influence early-life gut microbiota colonization.

Tamburini *et al.* Nat Med 2016

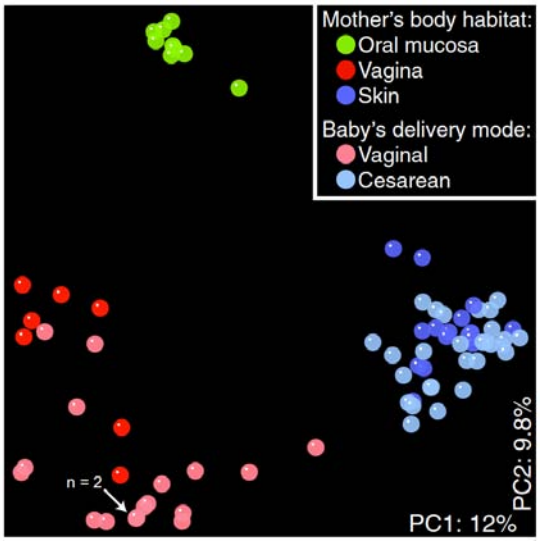
Microbiota alterations during pregnancy and early life



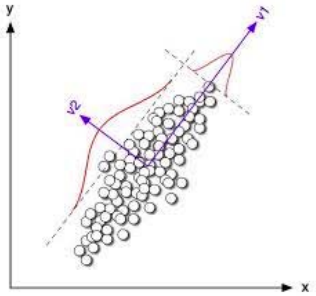
- Maternal microbiota changes between 1st and 3rd trimester and remains altered until at least 1 month post birth.
- Infant microbiota is different from initial T1 maternal gut microbiota.
- Children approaches the maternal microbiota at 4 years of age.

Koren *et al.* Cell 2012

Delivery mode shape early life gut microbiote colonization

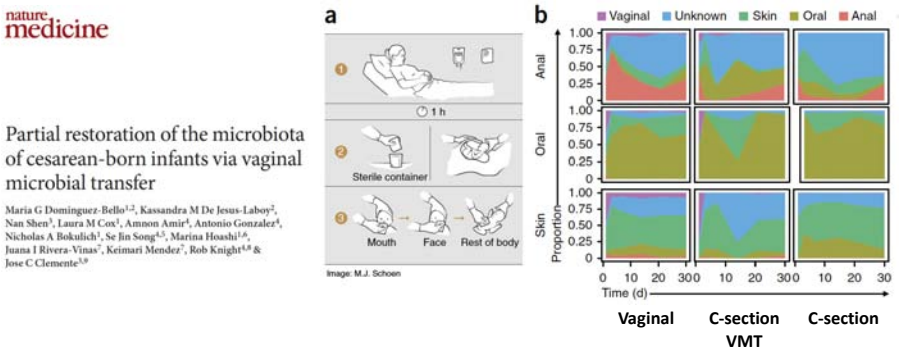


Principal component analysis
Define axis representing maximal data variance!!



Dominguez-Bello *et al* PNAS 2010

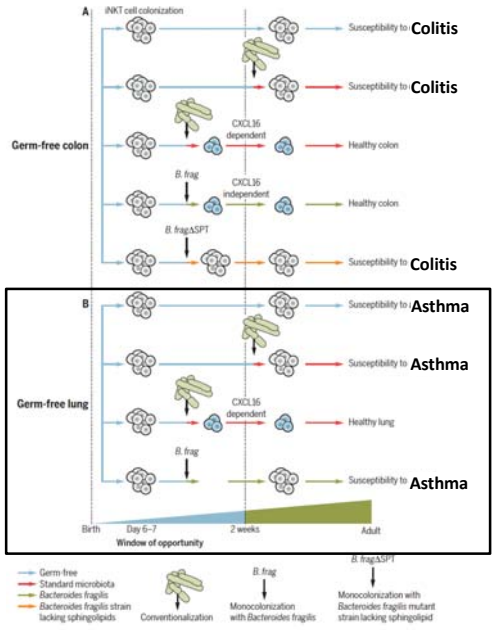
Vaginal Microbial Transfer (VMT) rescue microbiota post c-section.



- Vaginal Microbial Transfer (VMT) partly rescue gut microbiota composition of children born by C-section.
- Would primarily be maternal vaginal microbiota (mother/baby paired).
- However, in the case of mothers treated with antibiotics (such as HIV infected mothers) allogenic microbiota may be of interest – even for children born vaginally.

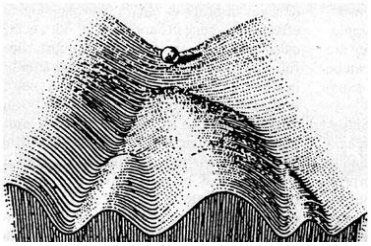
Dominguez-Bello *et al.* Nature Medicine 2015

Primo-colonization - window of opportunity



Gensollen *et al* Science 2016

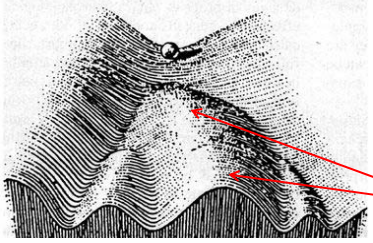
Waddington's landscape & intervention



A B C D

Phenotype

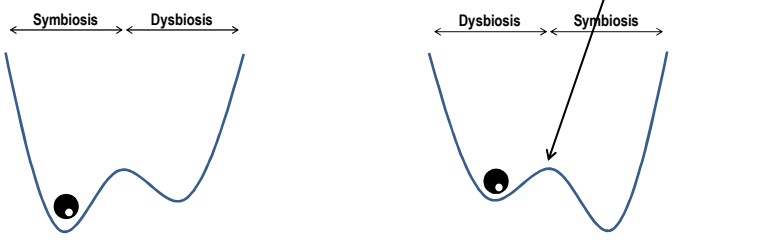
Waddington's landscape & intervention



Early intervention = Less resistance to change

A B C D

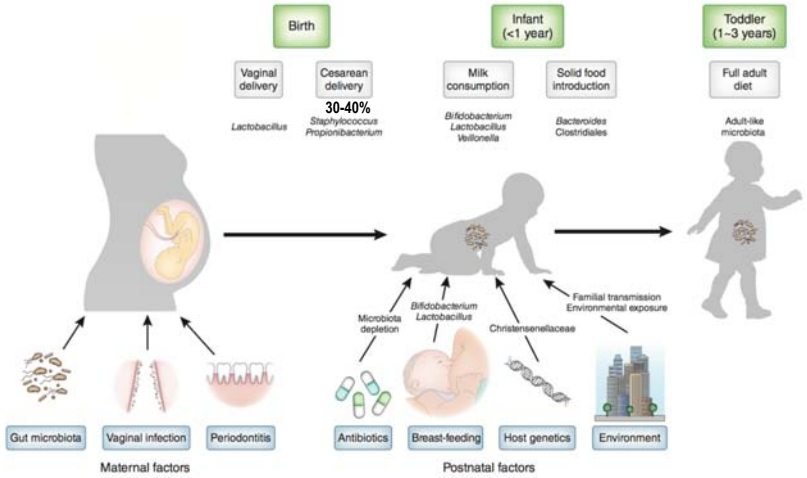
Phenotype



Environmental exposures
Life style
Infectious events
Antibiotics
Dietary habits

Therapy
Alter life style
Fecal transplants
Pro/pre-biotics

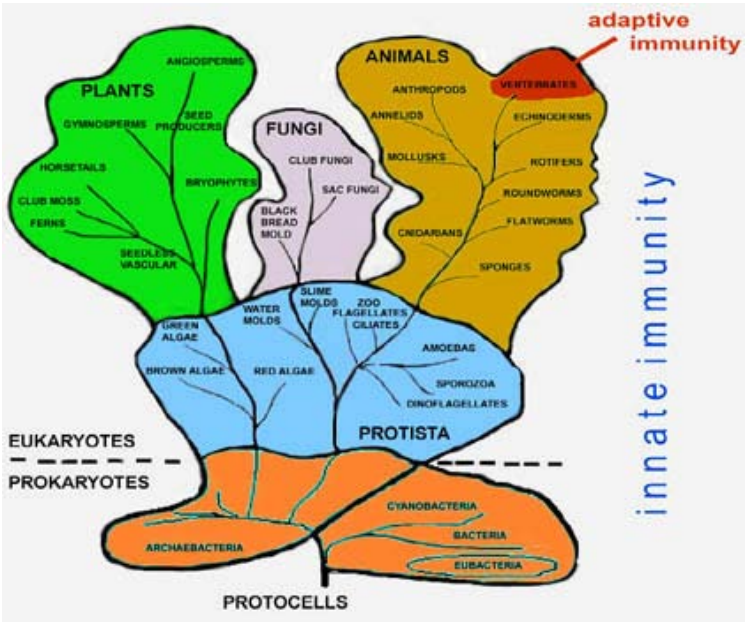
Early-life factors affect infant gut microbiota temporarily



- But at 1-3 years of age the child acquire an adult like gut microbiota, which is identical for all "healthy" children, independent of birth route and breastfeeding.
- If global gut microbiota is unaltered, but disease risk elevated – what can be the cause.
  - Minor persistent alterations in gut microbiota?
  - Long-term immunological memory to gut microbiota? Etc.

Tamburini *et al.* Nat Med 2016

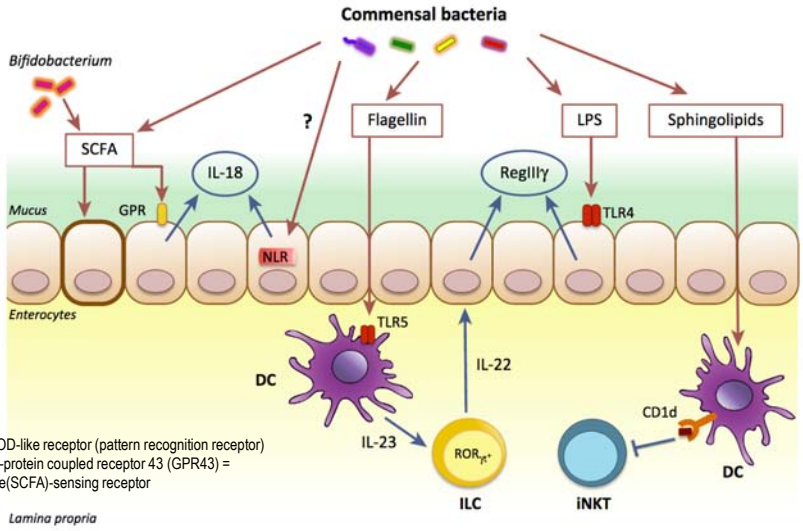
Evolution of Innate and Adaptive immunity



http://bio1510.biology.gatech.edu/module-5-integrative-health/03-adaptive-immunity/

Gut Microbiota in health - Innate immunity

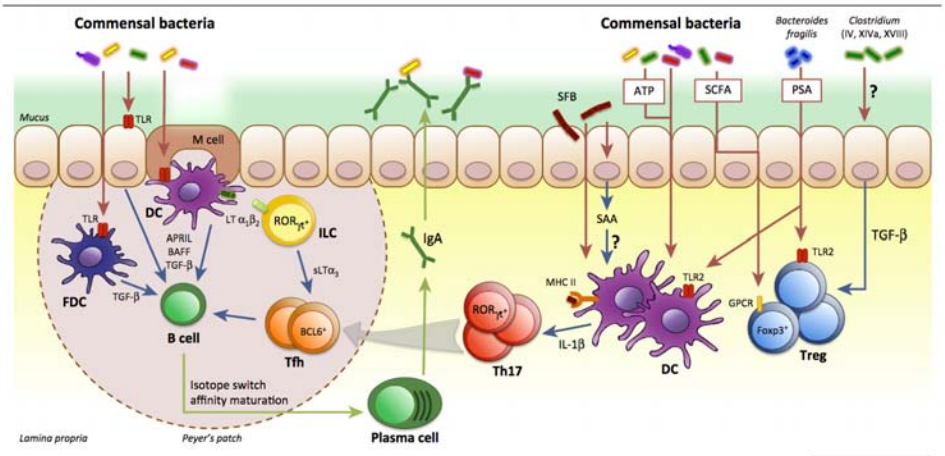
- Microbiota influences intestinal immune responses primarily through the expression of pathogen-associated molecular patterns (PAMPs) and metabolic by-products.



NLR = NOD-like receptor (pattern recognition receptor)
GPR = G-protein coupled receptor 43 (GPR43) = metabolite(SCFA)-sensing receptor

Gut Microbiota in health - adaptive immunity

- Microbiota stimulation leads to B cell switch to IgA, regulatory T cell induction, T cell differentiation to Th17



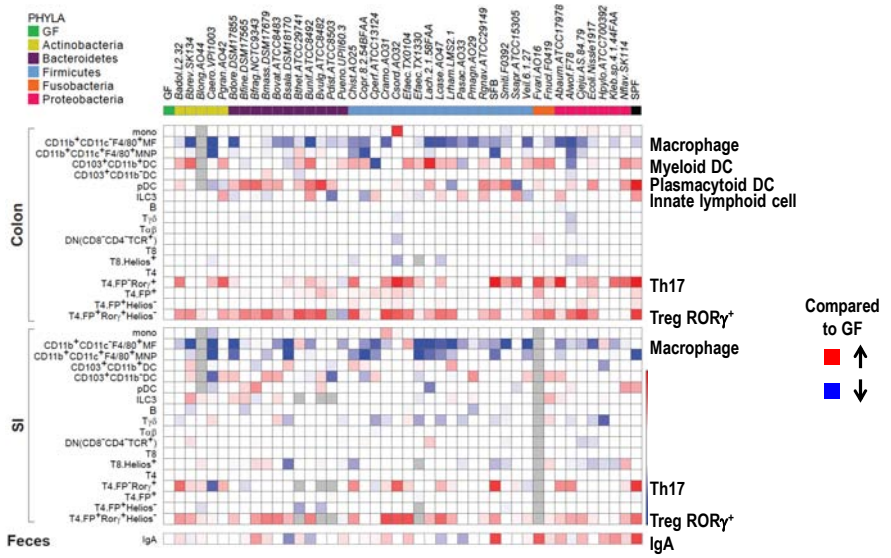
SAA=Serum amyloid A; GPCR=G protein-coupled receptor; PSA=Polysaccharide A; ILC=Innate lymphoid cells

Microbes stimulate cellular immunity

- Monocolonization of GF mice with 53 bacterial strains.
- Extensive immune phenotyping

Geva-Zatorsky *et al.* Cell 2017

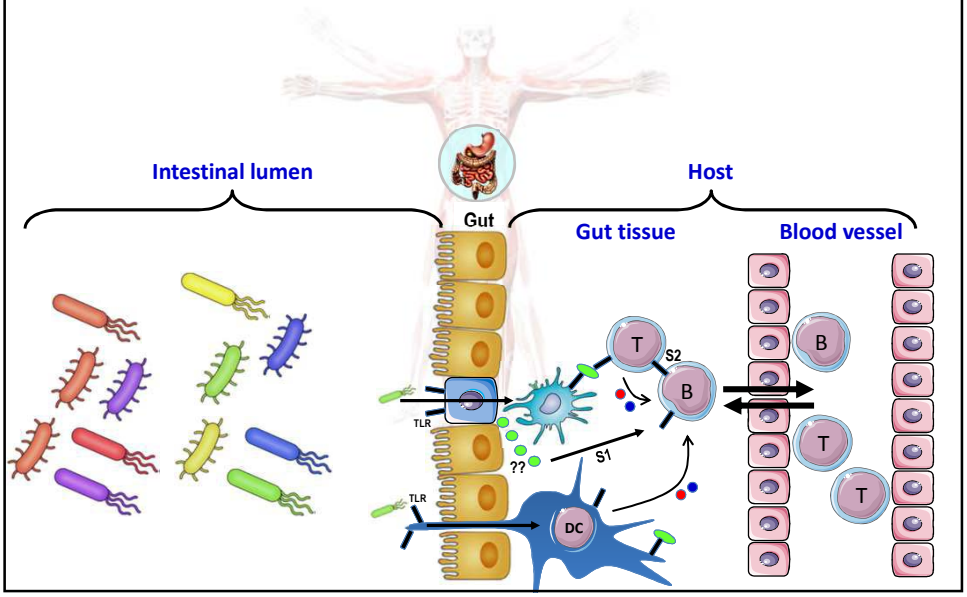
Microbes stimulate cellular immunity



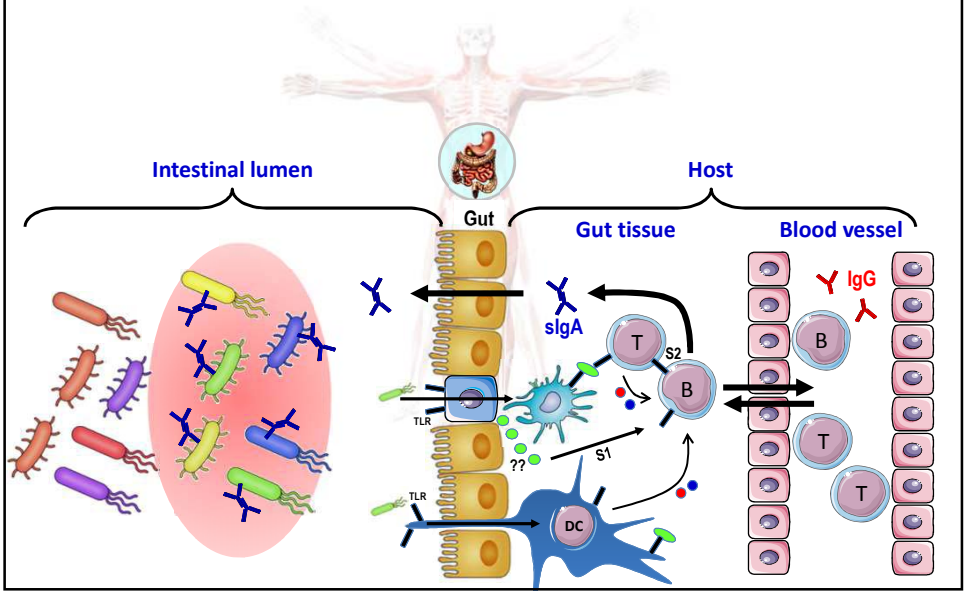
- APCs shifts from macrophages to DCs (more professional antigen presentation)
- Commensals increase gut residing Th17 and Treg cells.
- Phylum independent strain specific effects (e.g. free IgA in feces).

Geva-Zatorsky *et al.* Cell 2017

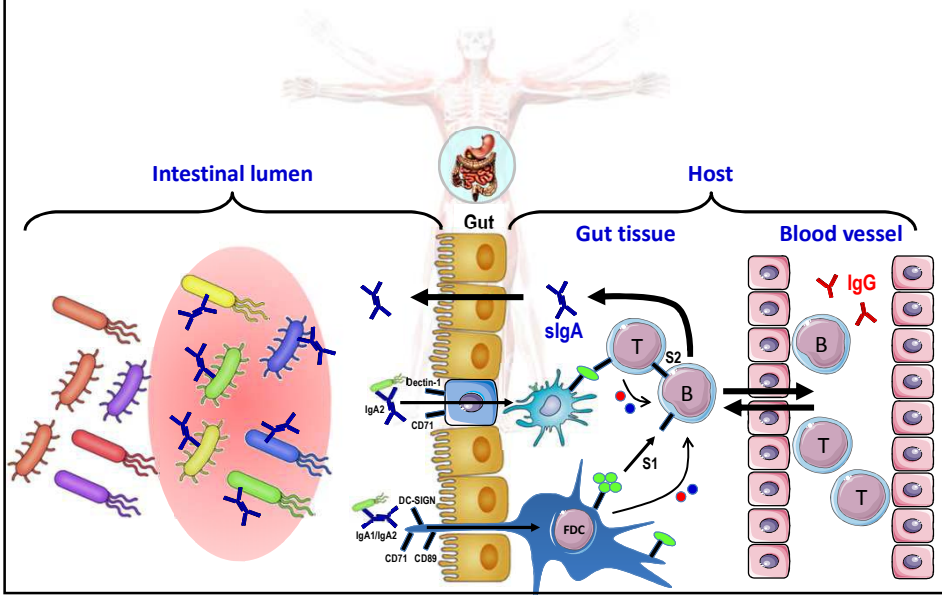
Interactions between host and gut microbiota



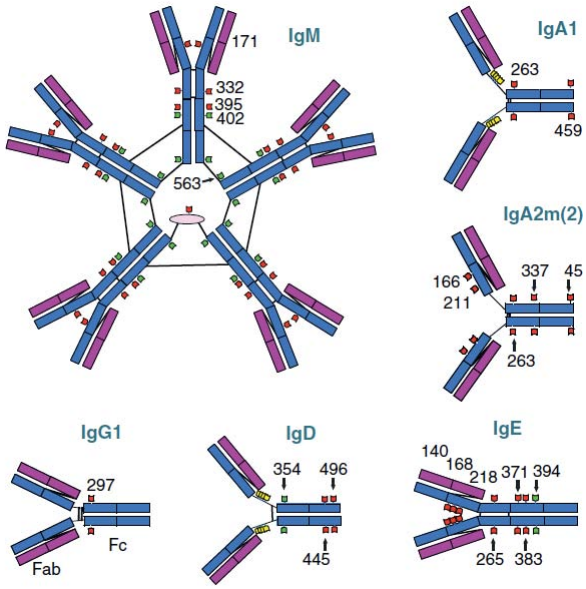
Interactions between host and gut microbiota



Interactions between host and gut microbiota

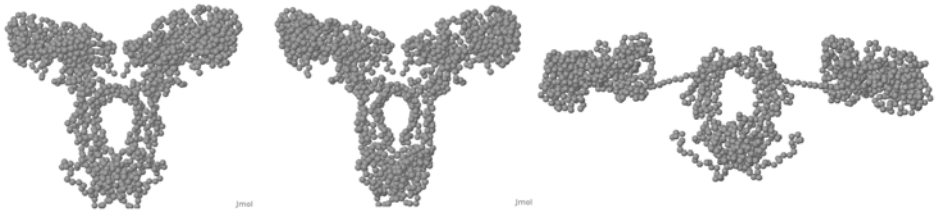


Antibody characteristics



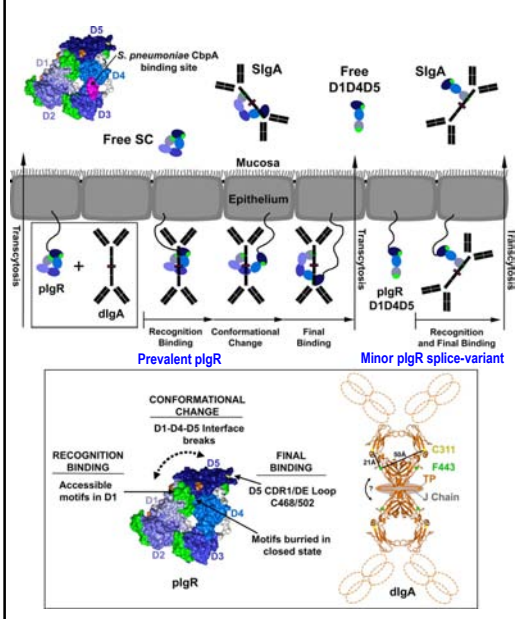
Arnold et al Ann Rev Immunol 2007

Antibody characteristics



IgG	IgA2	IgA1
Small mammals Higher monkeys	Small mammals Higher monkeys	**Not found in** Small mammals Higher monkeys
Y-shape Sensitive to proteases	Y-shape Non-Sensitive to proteases	T-shape Less-Sensitive to proteases
Non-Secretory	Secretory : non-planar (fab fragment not aligned with Fc portion)	Secretory : planar (fab fragments aligned with Fc portion
	Binds to Peyer's Patch M cells to undergo transcytosis thereby delivering antigens to GALT Mantis NJ *et al.* JI 2002	No binding to Peyer's Patch M cells. Warning! Assay used mouse M cells. Rochereau N *et al.* PLoS Biol 2013

Poly Ig Receptor (pIgR), Secretory component (SC) and pIgs



Human pIgR:

- Glycosylated type I membrane protein
- Five tandem immunoglobulin-like (Ig-like) domains (620AA)
- Transmembrane domain (23AA)
- Intracellular domain (103AA)

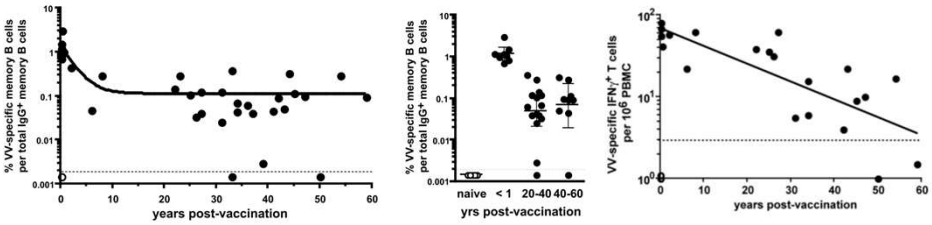
pIgR in evolution

- Oldest identifiable Fc receptor,
- Teleost (bony) fish (2 Ig-like domains)
- Birds, amphibians and reptiles (4 Ig-like domains)
- Mammals (5 Ig-like domains (D1-D5)) plus a splice variant (D1D4D5)

Stadtmueller et al. eLife 2016

Temporal changes of antibody immunity

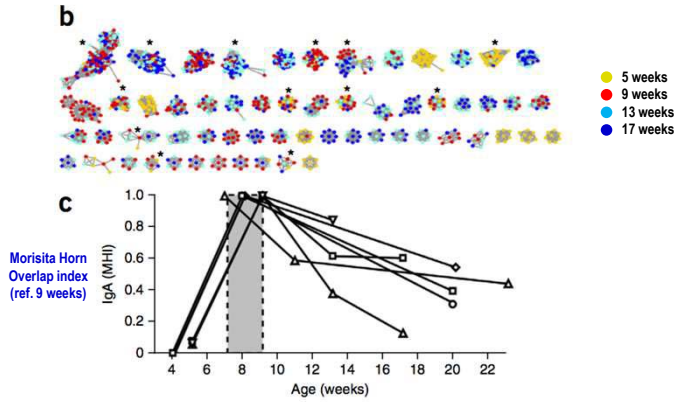
B cells | **T cells**



- B cell retraction phase is followed by long-term (+50 years) stable maintenance of B cell memory.
- T cells continue to retract, but remain detectable for more than 50 years.

Crotty *et al.* JI 2003

Temporal changes of antibody immunity



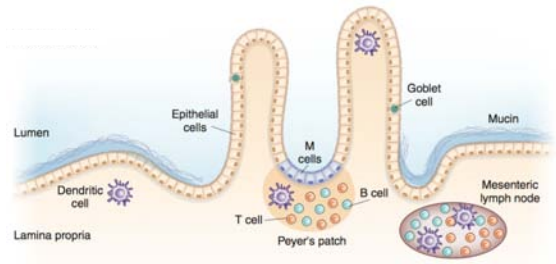
- 5 weeks CDR3 sequences cluster apart from the rest (yellow clusters), but from 9 weeks forward mice tend to have persisting CDR3 sequences in their IgA B cell repertoire (multi-color mixed clusters).
- The Morisita-Horn Overlap Index (MHI) equally shows more overlap between 9 weeks and later time points compared with earlier time points.

Lindner *et al.* Nat Immunol 2015

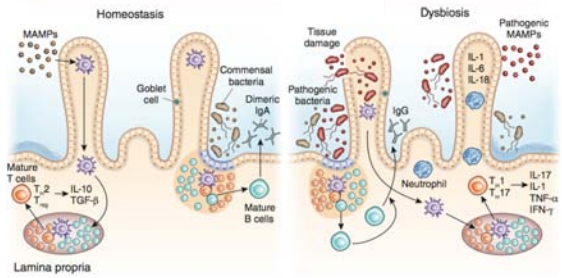
What happens to immunity?

Early-life factors affecting infant gut immunity and health

Pre-natal Small intestine



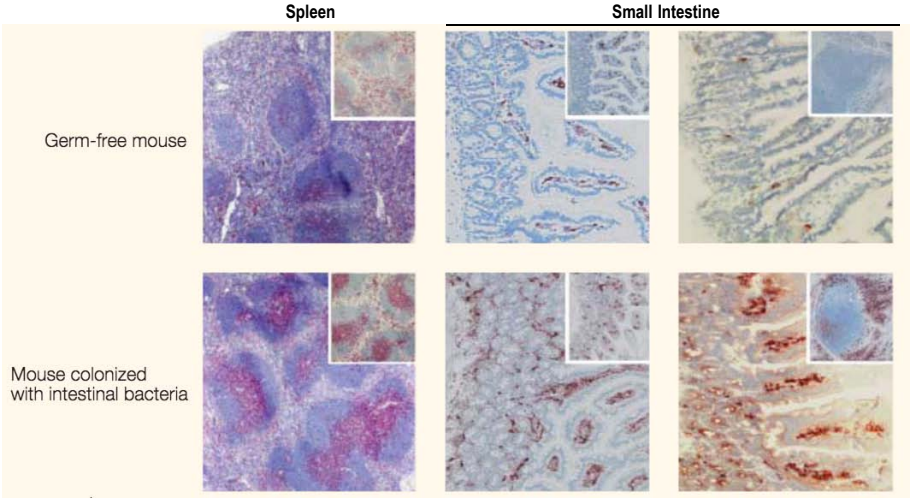
Post-natal Small intestine



- Of note, Pre-natal Peyer's patches are still fairly unstructured with weak definition of B and T cell zones of the lymphoid follicle.

Tamburini *et al.* Nat Med 2016

Lymphoid structures and immune cells in GF mice



- Spleen with few germinal centres and poorly formed T cell (pink) and B cell zones.
- Germ-free mice display hypoplastic Peyer's patches, with reduced T cell numbers and IgA-expressing B cells.

Macpherson et al. Nat Rev. Immunol 2004

Temporal changes of antibody immunity

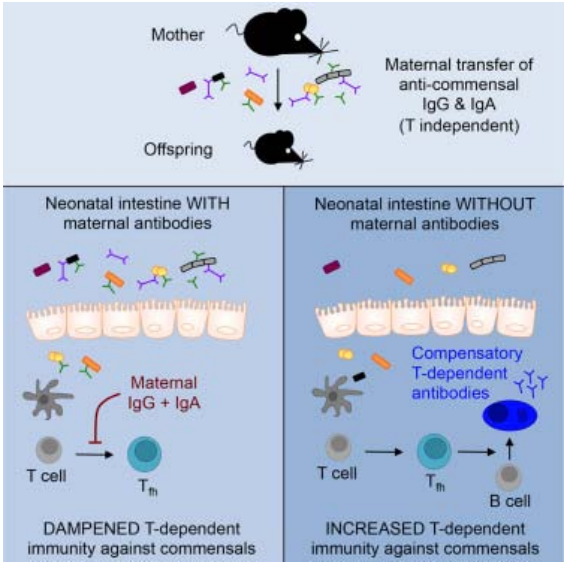
TABLE 12-12 · LEVELS OF IMMUNOGLOBULINS IN SERA OF NORMAL SUBJECTS BY AGE*

	IgG		IgM		IgA		Total Immunoglobulin	
Age	mg/dl	% of Adult Level	mg/dl	% of Adult Level	mg/dl	% of Adult Level	mg/dl	% of Adult Level
Newborn	1031 ± 200†	89 ± 17	11 ± 5	1.1 ± 5	2 ± 3	1 ± 2	1044 ± 201	67 ± 13
1–3 mo	430 ± 119	37 ± 10	30 ± 11	30 ± 11	21 ± 13	11 ± 7	481 ± 127	31 ± 9
4–6 mo	427 ± 186	37 ± 16	43 ± 17	43 ± 17	28 ± 18	14 ± 9	498 ± 204	32 ± 13
7–12 mo	661 ± 219	58 ± 19	54 ± 23	55 ± 23	37 ± 18	19 ± 9	752 ± 242	48 ± 15
13–24 mo	762 ± 209	66 ± 18	58 ± 23	59 ± 23	50 ± 24	25 ± 12	870 ± 258	56 ± 16
25–36 mo	892 ± 183	77 ± 16	61 ± 19	62 ± 19	71 ± 37	36 ± 19	1024 ± 205	65 ± 14
3–5 yr	929 ± 228	80 ± 20	56 ± 18	57 ± 18	93 ± 27	47 ± 14	1078 ± 245	69 ± 17
6–8 yr	923 ± 256	20 ± 22	65 ± 25	66 ± 25	124 ± 45	62 ± 23	1112 ± 293	71 ± 20
9–11 yr	1124 ± 235	97 ± 20	79 ± 33	80 ± 33	131 ± 60	66 ± 30	1334 ± 254	85 ± 17
12–16 yr	946 ± 124	82 ± 11	59 ± 20	60 ± 20	148 ± 63	74 ± 32	1153 ± 169	74 ± 12
Adults	1158 ± 305	100 ± 26	99 ± 27	100 ± 27	200 ± 61	100 ± 31	1457 ± 353	100 ± 24

*The values were divided from measurements made in 296 healthy children and 30 adults. Levels were determined by the radial diffusion technique using specific rabbit antisera to human immunoglobulins.
†One standard deviation.
From Stiehm ER, Fudenberg HH. Serum levels of immune globulins in health and disease. A survey. Pediatrics 37:715, 1966.

- We are born with maternal IgG antibodies circulating our blood stream.
- IgM and IgA **serum** antibodies are virtually absent at birth and slowly increases during childhood.
- Intestinal antibodies are provided through breastfeeding.

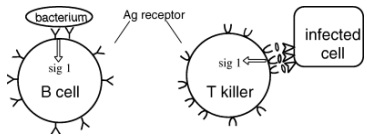
Maternal antibodies dampen offspring immunity

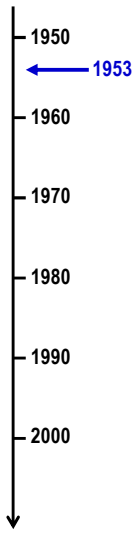


- T-independent production of IgG specific for mucosal bacteria.
- Gut microbes elicit anti-commensal IgG antibodies via TLR signalling on B cells
- Maternal transmission of IgG coordinates with IgA to limit mucosal T cell responses
- Absence of maternal antibodies triggers a compensatory T-dependent immune response in the offspring.

Koch *et al.* Cell 2016

Self/non-self versus Danger model in a historical perspective

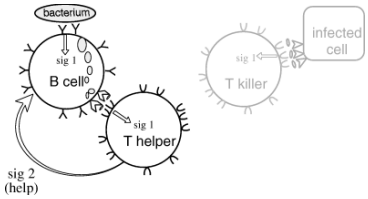




- Burnet and Lederberg propose the antigen receptor (BCR and TCR)
- Antigen stimulation (signal 1) induces immunity including class switch and somatic hyper mutation.

Matzinger *et al.* Scan J Immunol 2003

Self/non-self versus Danger model in a historical perspective



Signal 2: e.g. CD40/CD40L and cytokines

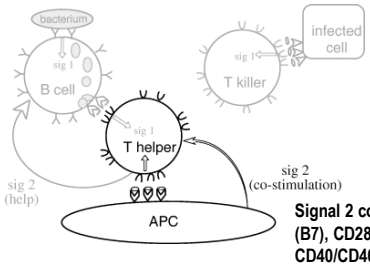
- **Problem:** BCR hypermutation may lead to autoreactive BCRs.
- **Solution:** Cohn add another cell: The T helper cell (only formally proven much later).

- B cells internalize pathogen and present antigens to interact with specific Th cells, which validate that target is non-self.
- Signal 1 alone leads to clonal deletion (both self and non-self reactivity leads to signal 1).
- Signal 1 + 2 lead to activation (non-self rescued by T cells, with TCR which does not hyper mutate).

1950
1960
1969
1970
1980
1990
2000

Matzinger *et al.* Scan J Immunol 2003

Self/non-self versus Danger model in a historical perspective



Signal 2 co-stim: CD80/86 (B7), CD28, CTLA-4, CD40/CD40L

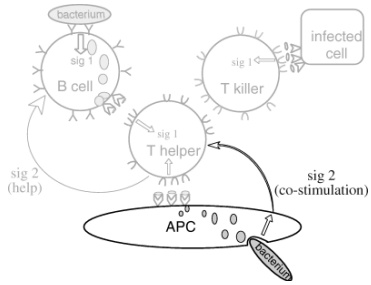
- **Problem:** We need a BCR independent manner to capture and present antigens to prime naïve T cells to become T helper cells.
- **Solution:** Lafferty and Cunningham propose that Th cells are primed and activated through APC antigen presentation and co-stimulation.

- Th cells are not constitutive active – feedback regulation upon antigen removal.
- Heavily criticized because APCs do not explain how the immune system distinguish between self and non/self (which BCR dependent antigen selection provided).

1950
1960
1970
1974
1980
1990
2000

Matzinger *et al.* Scan J Immunol 2003

Self/non-self versus Danger model in a historical perspective



1950
1960
1970
1980
1989
1990
2000

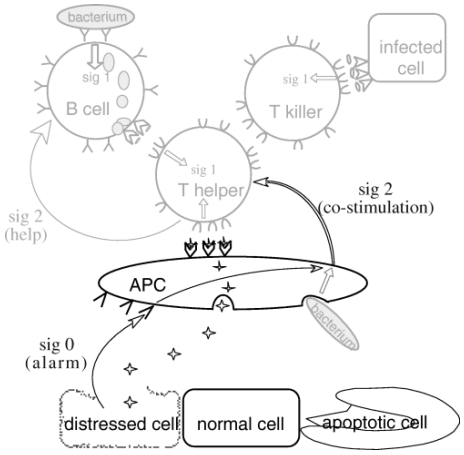
- **Problem:** Contrary to B cells, APCs do not differentiate between self and non-self.
- **Solution:** Charlie Janeway proposes that APCs internalize and present non-self selectively through pattern recognition receptors (PRR), which bind elements from foreign organisms, such as bacteria.

- This model inherently imply that APCs are not constitutively active, but require external stimuli through the PRR signalling pathway.
- Proposes explanation for why vaccines need an adjuvant.

Matzinger *et al.* Scan J Immunol 2003

Self/non-self versus Danger model in a historical perspective

Problem
How to explain:
- Autoimmunity
- Non-reject of tumour with tumour antigen
- DNA therapy versus DNA vaccine
- Why mothers don't reject the fetus.
- Why temporal gene-expression changes doesn't evoke immunity (e.g. breast milk).
- Why can we host tons of microbes?



1950
1960
1970
1980
1990
1996
2000

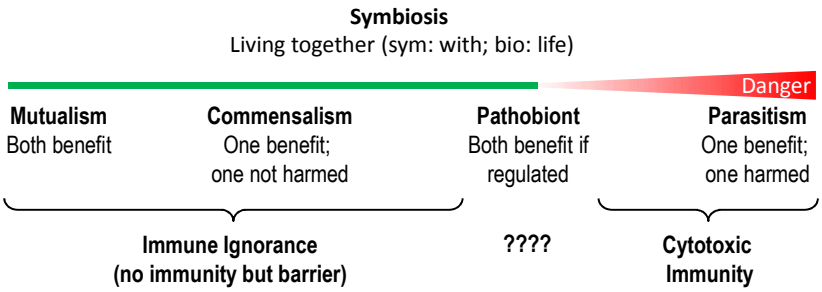
- **Solution:** Polly Matzinger proposes that APCs are activated through danger signals from any distressed tissue (uric acid, heparin sulfate, extracellular ATP and DNA/RNA).

- Advocate that we are a friendly host as long as our visitors are friendly too. Don't push the button first policy.

Matzinger *et al.* Scan J Immunol 2003

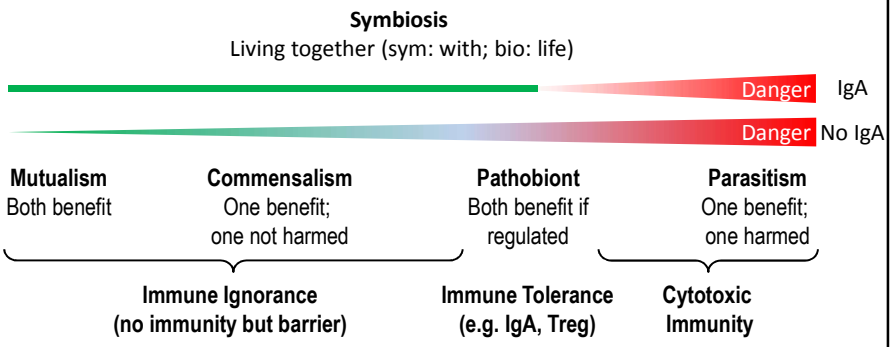
Danger model and gut microbiota symbiosis

- The danger model would suggest that we do not respond to non-harmful bacteria colonizing our gut (Mutualism and Commensalism allowed).



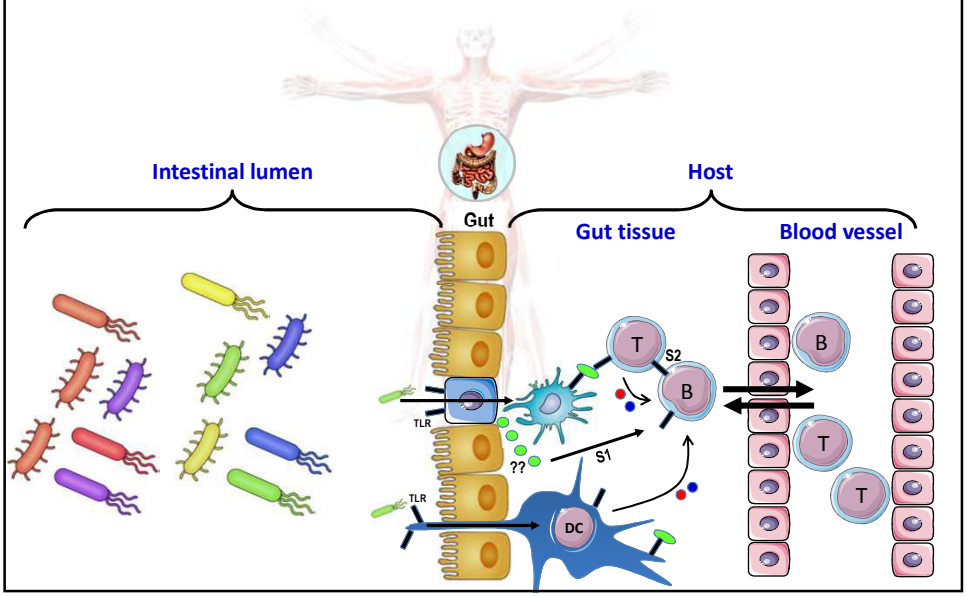
Danger model and IgA responses

- The danger model would suggest that we do not respond to non-harmfull bacteria colonizing our gut (Mutualism and Commensalism allowed).

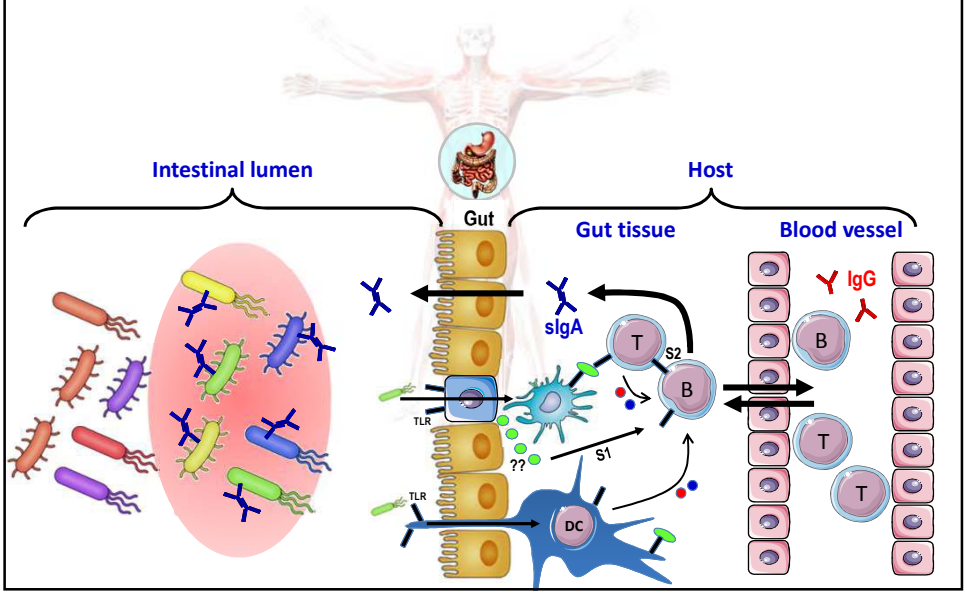


- In reality microbes cannot be categorized discretely, but rather represents a continuum from Mutualism to parasitism.
- How to retain tolerance to commensals, while pathogens are attacked?
- The range of host-microbe interactions evokes ignorance to non-harmful microbes, tolerogenic immunity to beneficial microbes (harmful if not regulated) and cytotoxic immunity to harmful microbes.

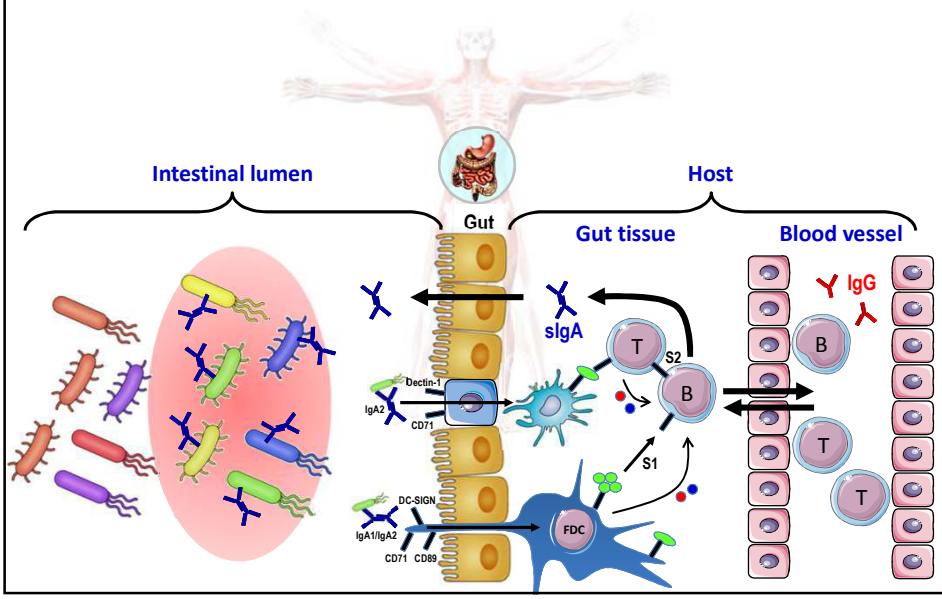
Interactions between host and gut microbiota



Interactions between host and gut microbiota

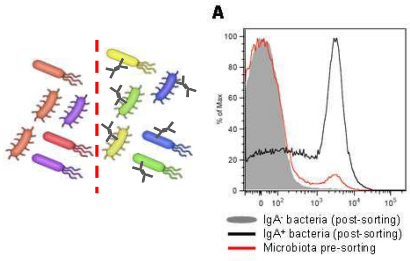


Interactions between host and gut microbiota



Gut microbiota specificity of gut Ig immunity

Gut microbiota sorting (IgA^+ / IgA^-)

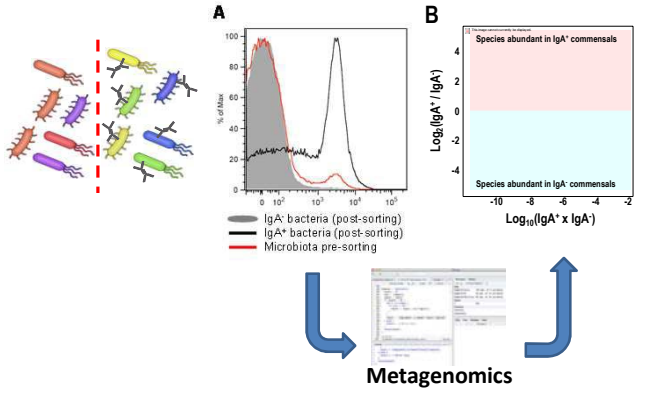


Moor ... Larsen. Nature Prot 2016

Gut microbiota specificity of gut Ig immunity

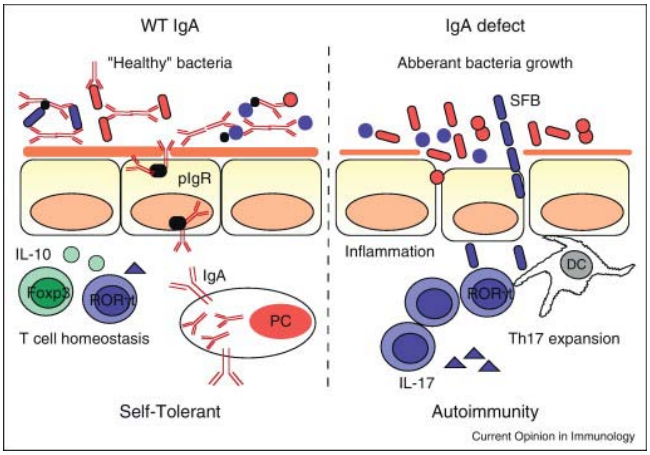
Gut microbiota sorting (IgA$^+$ / IgA$^-$)

Paired metagenomic analysis



Fadlallah, El-Kafsi, ……. Larsen. STM 2018

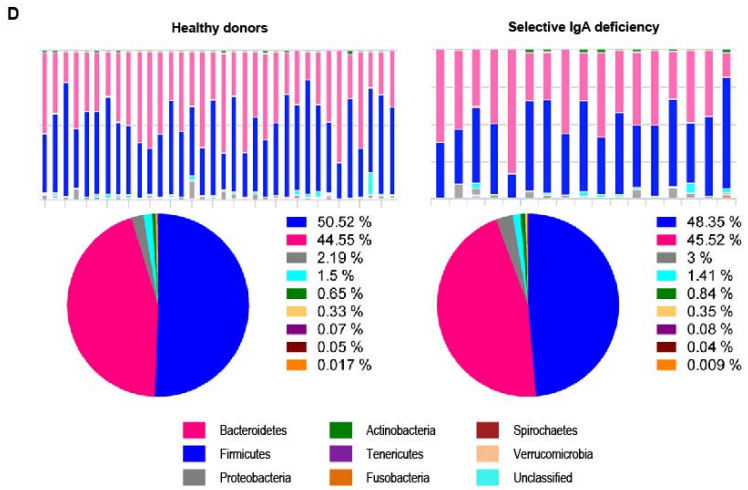
IgA regulates gut microbiota homeostasis



- **Mouse model of IgA deficiency : Dysbiosis and auto-immunity**
- **Human selective IgA deficiency (1 in 500 individuals) :**
  Mild phenotype, but respiratory infections, atopy and autoimmunity (Celiac disease, SLE etc.) are more frequent.

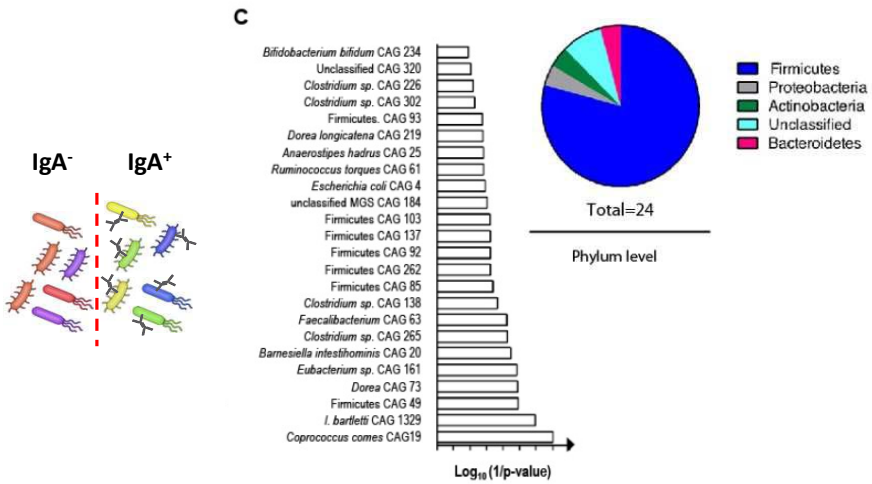
Sutherland and Fagarasan, *Current opinion in Immunology* 2012, Ludvigsson *JCI* 2014

Disease specific gut microbiota composition



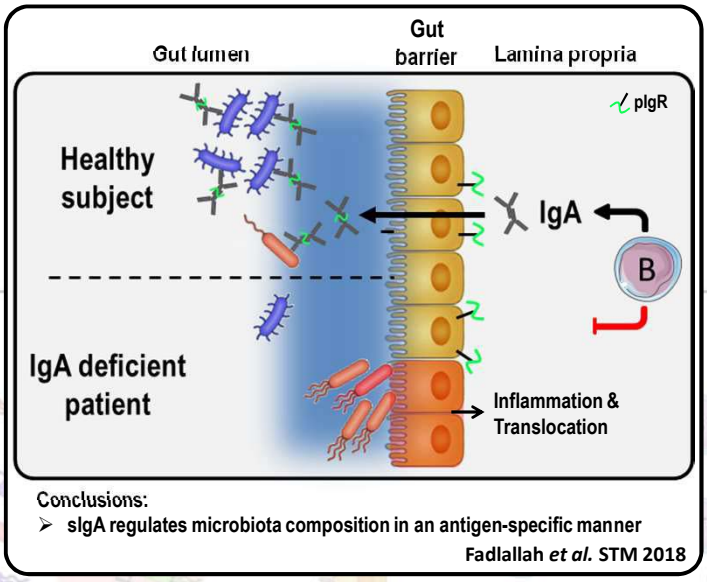
Fadlallah *et al.* STM 2018

Gut microbiota specificity of gut IgA immunity



Fadlallah *et al.* STM 2018

Interactions between host and gut microbiota

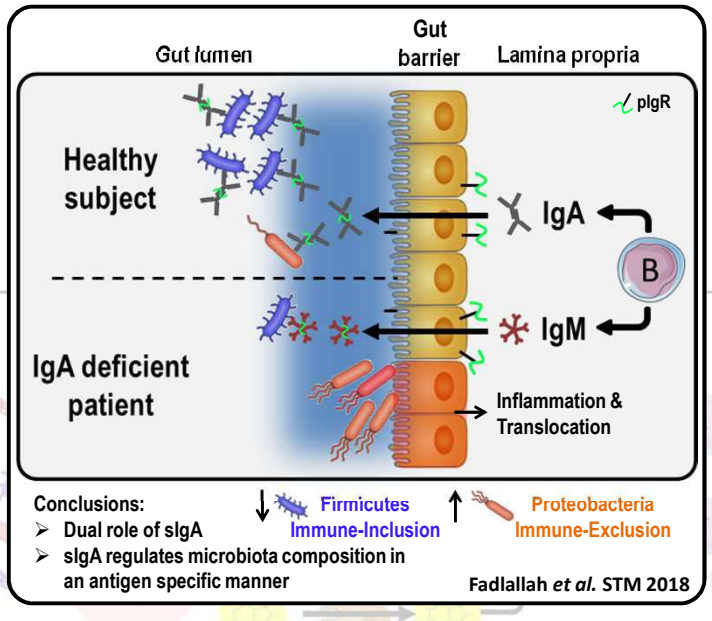


Conclusions:

- sIgA regulates microbiota composition in an antigen-specific manner

Fadlallah *et al.* STM 2018

Interactions between host and gut microbiota



Conclusions:

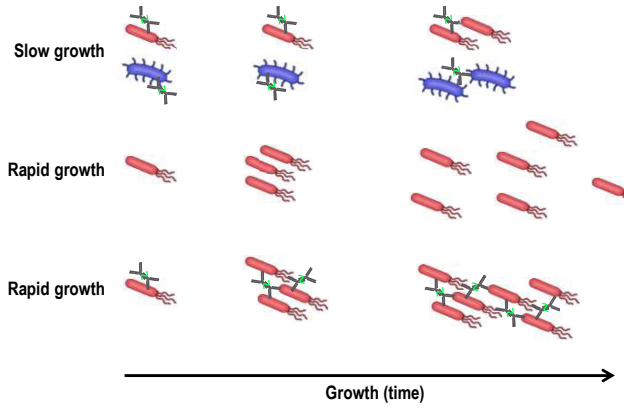
- Dual role of sIgA
- sIgA regulates microbiota composition in an antigen specific manner

Firmicutes
Immune-Inclusion

Proteobacteria
Immune-Exclusion

Fadlallah *et al.* STM 2018

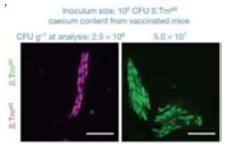
sIgA enchainment of growing bacteria (immune-exclusion)



Small networks of identical bacteria (potential positive effect?). No immune exclusion.

Uncontrolled expansion and unregulated dispersion.

Enchainment of daughter cells leading to exclusion



Dual effect of sIgA – immune exclusion:

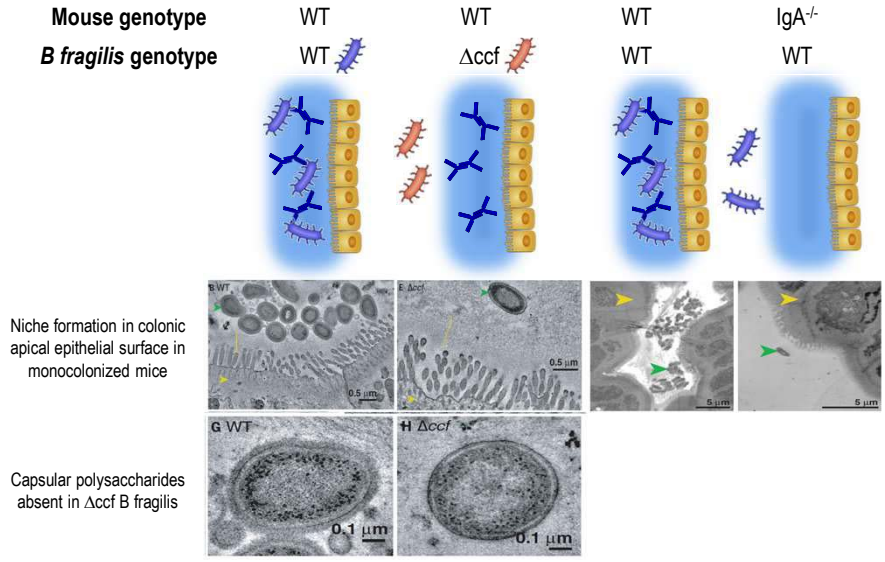
- Pathogenic and commensal microbial strains from the same species/genus (e.g. *E. coli*) could be targeted by the same sIgA, but immune exclusion would be specific to the pathogenic rapidly growing microbe
- Enchainment blocks genetic communication between non-related bacteria, because related bacteria clusterizes.

Moor *et al.* Nature 2017

- Positive effects of microbial communication could be promoted by sIgA for slow growing microbes.

Donaldson *et al.* Science 2018, Fadlallah *et al.* STM 2018

Bacterial niche formation by mucosal sIgA (immune-inclusion)



Dual effect of sIgA – immune inclusion:

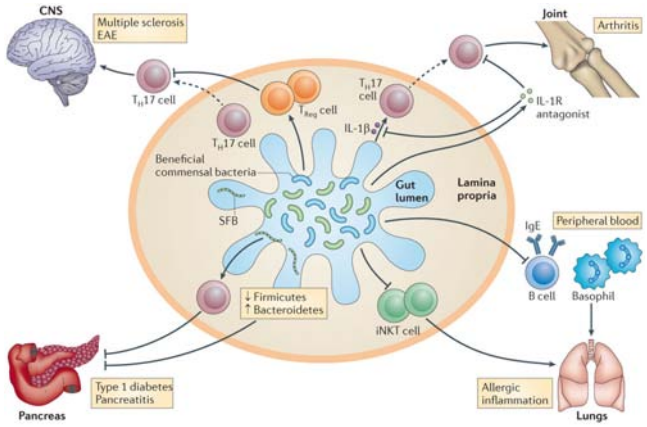
- Gut colonization by *B fragilis* regulated by sIgA : Absence of antibody and/or Absence of the antibody binding site (Capsular Polysaccharides) prohibit colonization.

Donaldson *et al.* Science 2018

Examples of gut microbiota associations with pathology

Gut microbiota and immune pathology

Autoimmune and allergic diseases associated with gut microbiota

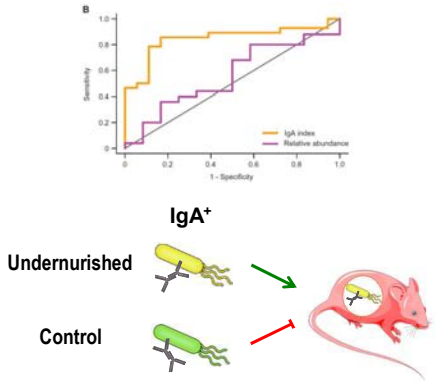


- IBD (Arumugam *et al.* Nature 2011, Juste *et al.* Gut 2014, Palm *et al.* Cell 2014)
- Type-1 Diabetes (Qin *et al.* Nature 2012, Markle *et al.* Science 2013)
- Arthritis (Scher *et al.* Nat Rev Rheumatol 2011, Scher *et al.* eLife 2013)
- Allergy (Russell *et al.* EMBO Rep 2012)
- **EAE / Multiple sclerosis** (Berer *et al.* Nature 2011, Miyake *et al.* PLoS One 2015)

Kamada *et al.* Nat Immunol Rev 2013

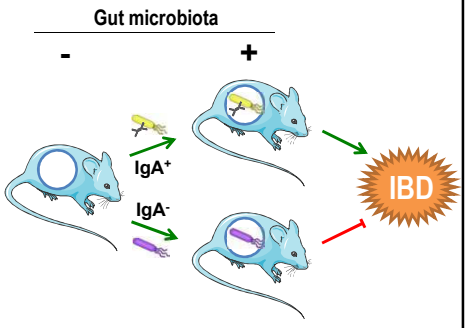
IgA targets bacteria involved in human pathology

- **Undernourished Malawian children produce diet-dependent enteropathy.**
- **IgA coated gut microbiota from children is predictive of nutritional status and enteropathy.**



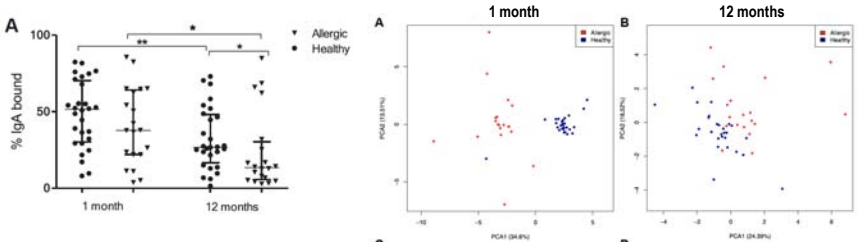
Kau *et al.* STM 2015

- **Mouse model of microbiota-driven colitis.**
- **Human IgA coated gut microbiota from IBD patients confer susceptibility to colitis in germ-free mice.**



Palm *et al.* Cell 2014

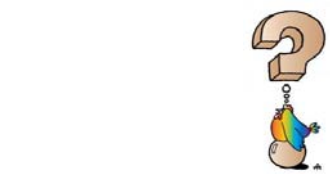
Gut Immuno-Microbiome – allergic disease



- Allergy is associated with reduced sIgA-opsonization levels of gut microbiota in 12 months-old children (tendency already at 1 month).
- Fecal sIgA levels are unaltered.
- Gut bacterial load is reduced at 12 months of age in allergic children
- A unique immuno-microbiome signature precedes allergy already at 1 month of age.
- sIgA-opsonization and immuno-microbiome signature are similar when stratified for birth route and breastfeeding (Of note, breastfeeding is assessed at 12 months – practically all Swedish children are breastfed in the first months of life)

Dzidic *et al.* JACI 2016

Immuno-microbiota – biomarker or causality



Causality ?

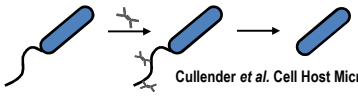
Biomarker

Cross-reactive antibodies (AQP4 and MOG)

Ecological steady-state - pathobionts

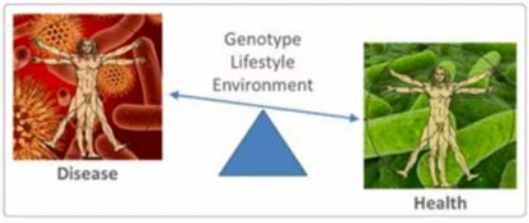
Fadlallah *et al.* STM 2018

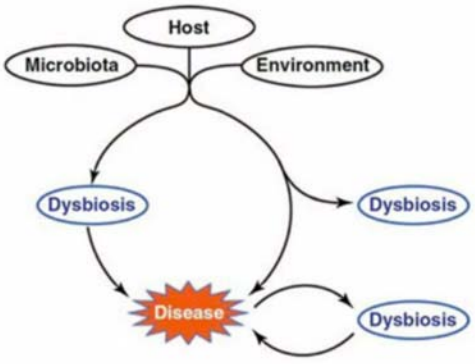
Transcriptional change (fitness and/or metabolism)



Cullender *et al.* Cell Host Microb 2013

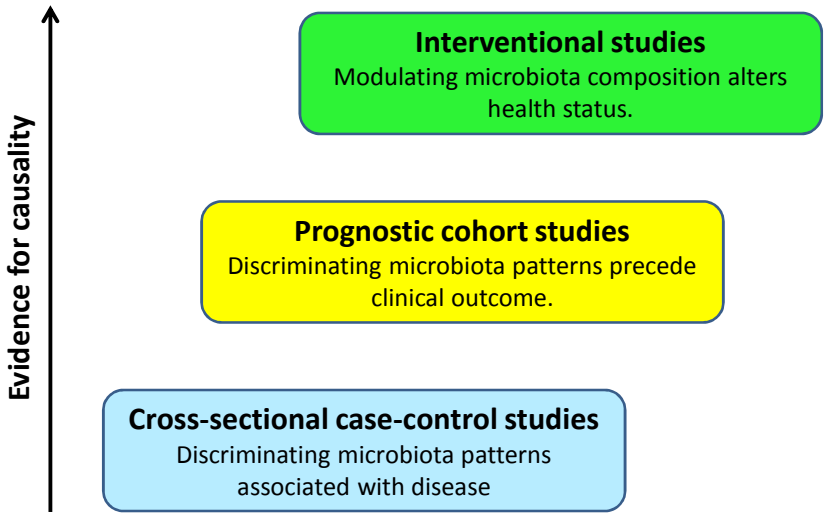
Dysbiosis – cause or consequence of disease?





- Genetic or environmental factors may lead to dysbiosis
- Dysbiosis may lead to disease
- Genetic or environmental factors may lead to disease irrespective of dysbiosis.
- Disease may lead to dysbiosis

Study design defines the ability to determine causality



Take home message

- Gut microbiota influence host immunity (Tolerance versus inflammation)
- Gut microbiota is regulated by host immunity (innate and adaptive (e.g. IgA))
- **Altered lifestyle** influence our gut microbiota composition and is temporally (but maybe not causally) associated with a rapid increase in chronic inflammatory diseases, including allergy (since 1950 forward).
- **Hygiene theory**: Reduced exposure to microbes result in a skewed host immunity, which is insufficiently schooled to regulate inflammatory responses.
- **Save our microbiota:** Vaginal microbiota transplantation (C-section birth), reduce antibiotics use (or use of new treatments, such as DAV132 co-therapy).
- **Save our immunity:** Probiotics (do not colonize), helminths (worms), immune therapy (allergy), promote breast feeding.