Intestinal Microbiota in Infants its Impact on Health

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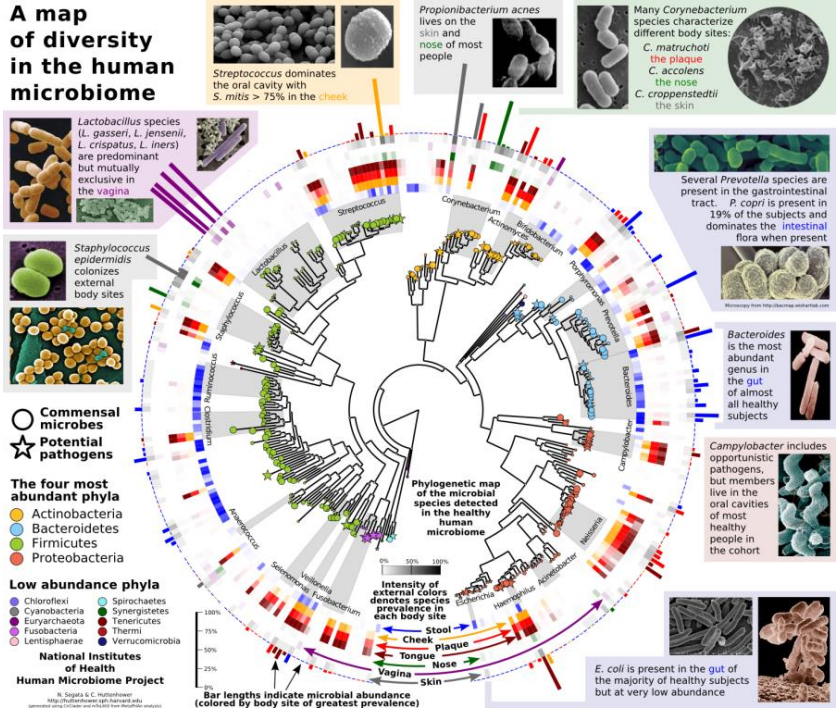
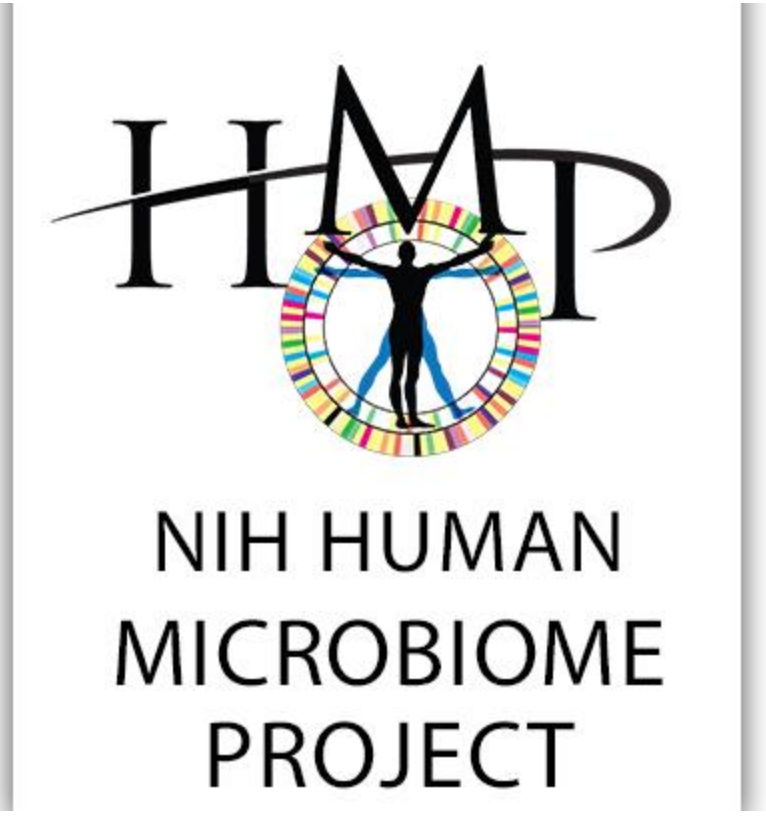
Germ Theory

- At the end of 1800s
- Microbes were discovered as agents of diseases
- Its thought that all microorganisms were bad

- 150 years later…
- Nonculture techniques have been developed
- ***Metagenomics***
- The human body harbors a dynamic and complex microbial population (500- 1000 different species)
- HMP is started in 2008





Intestinal Microbiota

- Consists of more than 1000 seperate species and more cells by 10-fold than cells in the human body
- Contains 100-fold greater number of genes than the human genome
- The metabolic activity of colonizing bacteria is greater than the liver
- Can be considered as an ancillary organ
- Human-microbiota ‘superorganism’

Intestinal Microbiota

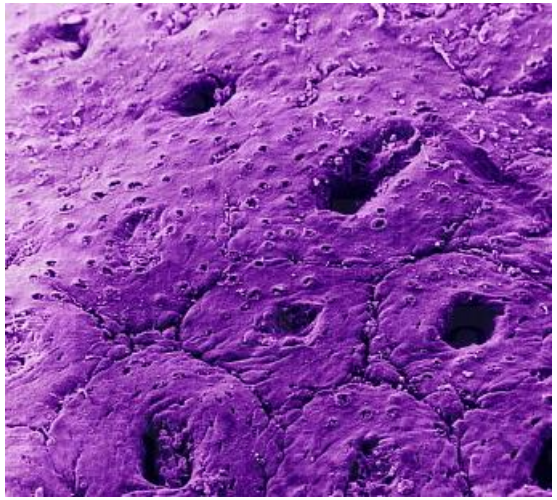
- Digestive functions
  - Metabolizing complex carbohydrates
  - Fermentation into short chain fatty acids
- Synthesis functions:
  - Vitamins

Cross talk between intestine and microbiota

Mucosal cells

Immune cells

Neuronal endings



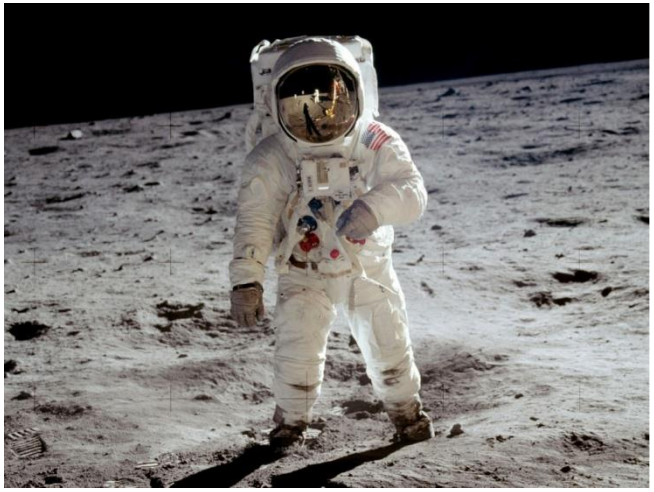
Cross talk between intestine and microbiota

- Interactions between the commensal bacteria and the host in the early postnatal period are important for host metabolism and development of healthy gastrointestinal, immunological and neural systems
- Dysbiosis is linked with a number of gastrointestinal and systemic disorders

Establishment of microbiota in newborns

- At birth, the newborn infant gut is *almost* sterile
- Rapidly colonised in the first days of life
- Dynamic fluctuations in bacterial composition until a relatively stable population is reached similar to an adult around two years old

Establishment of microbiota in newborns: frontiers



Immediately after birth;

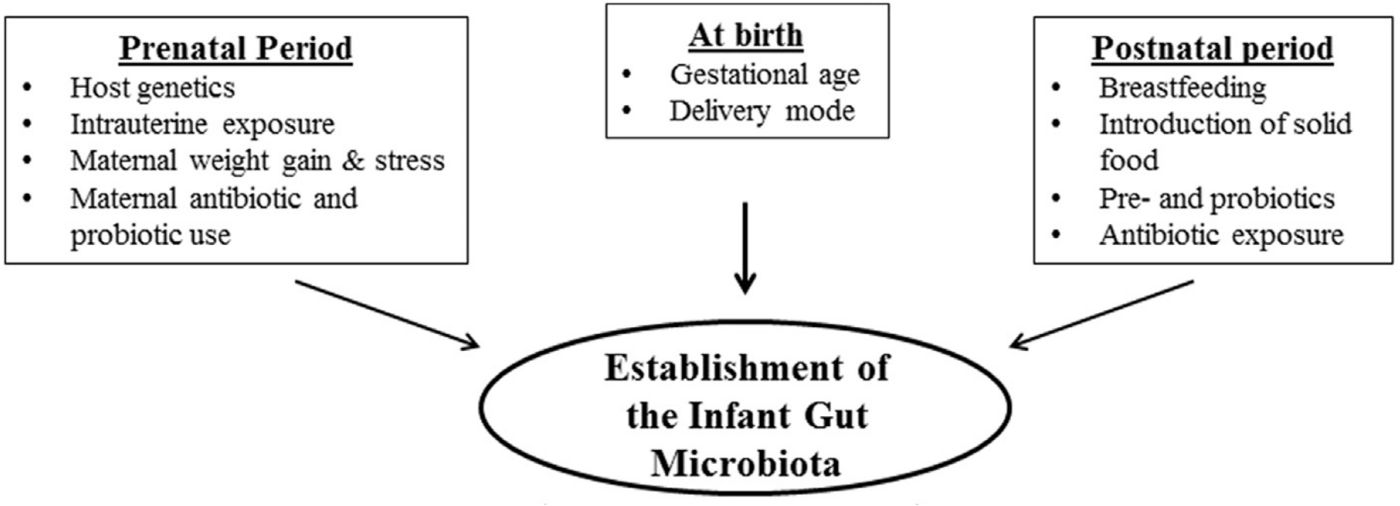
Facultative anaerobic bacteria

- *Enterobacteriacea*
- *Streptococci*
- *Staphilococci*

They consume oxygen and produce new metabolites preparing the intestinal environment for strict anaerobic bacteria

- *Bifidobacteria*
- *Clostridium*
- *Bacteroides*

Establishment of microbiota



Maternal Vaginal Microbiota

- Mostly unculturable microorganisms so can be demonstrated only by nonculture techniques
- Vaginal flora is changed during pregnancy and by gestational age
- Lactobacilli producing lactic acid are increased
- Anaerobics are decreased
- Important for prevention of ascending infections

ORIGINS

Babies are born dirty, with a gutful of bacteria

Far from being sterile, babies come complete with an army of bacteria. The finding could have implications for gut disorders and our health in general

Read more

Fertility Sterility 2015;104:1358

Maternal Microbiota

- Maternal gastrointestinal microbiota is also changed during pregnancy
- Proteobacteria, Actinobacteria ↑
- Bacterial load is increased as pregnancy progressed

ORIGINS

Babies are born dirty, with a gutful of bacteria

Far from being sterile, babies come complete with an army of bacteria. The finding could have implications for gut disorders and our health in general

Read more

Placental Microbiota

- Placenta harbors a low-abundance but metabolically rich microbiota in healthy pregnant women
- Nonpathogenic commensal microbes:
  - Firmicutes, Proteobacteria, Bacteroides, Fusobacteria
- This profile are most akin to the nonpregnant human oral microbiota
- The placental microbiota is probably established by hematogenous spread

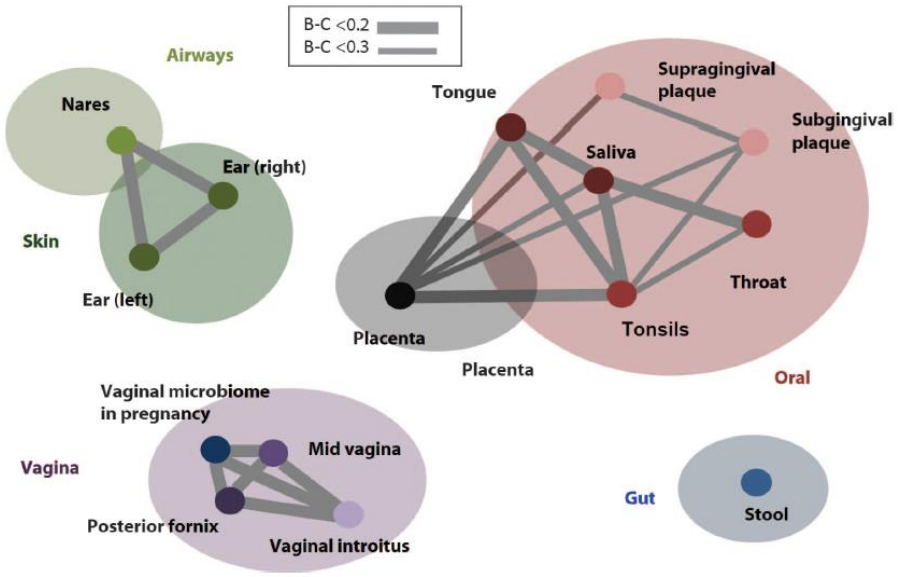


Fig. 1. The placental microbiome has a taxonomic profile that is similar to the oral microbiome.

www. ScienceTranslationalMedicine.org, 2014

Placental Microbiota

- **Are not same with the agents of neonatal sepsis**
- No harm to fetus but no data about its benefits
- Placental dysbiosis→ premature delivery

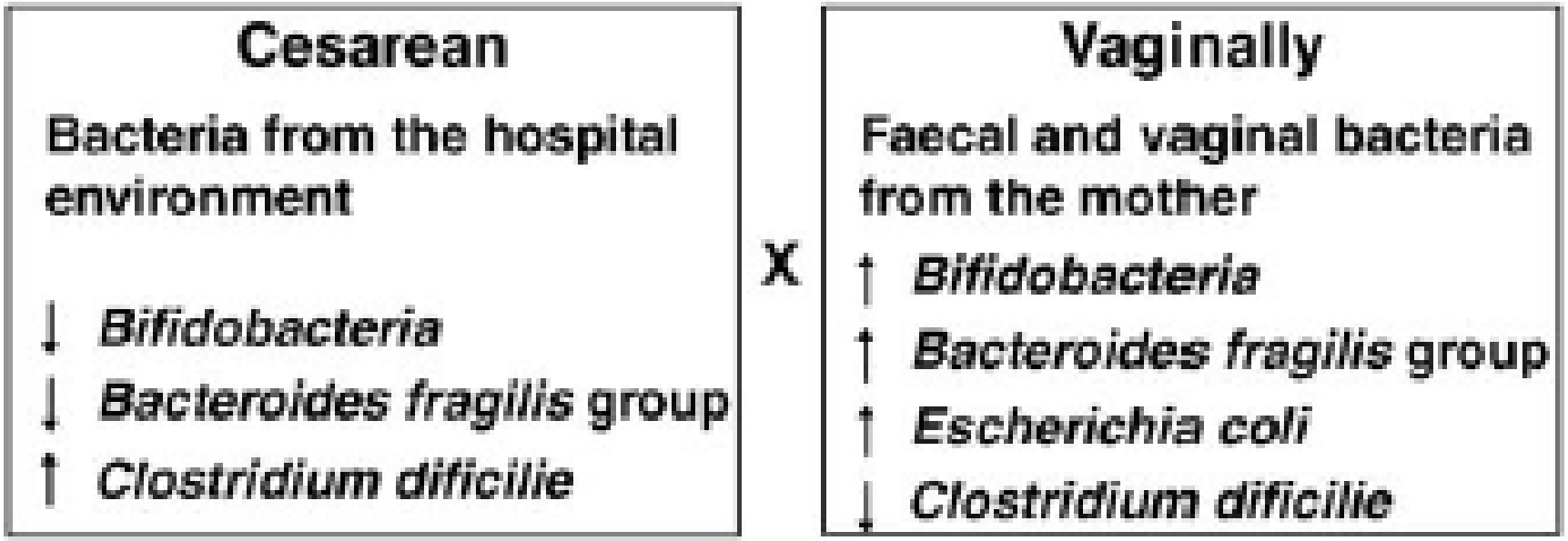
Baby's first gut bacteria may come from mum's mouth

It is thought that babies get their first dose of microbes during birth, but these bugs may arrive in the placenta much earlier, from an unexpected place

Read more

- Therefore, development of the infant gut microbiota is a dynamic process that begins prenatally and continues during the first two to three years of life.

Delivery mode



Gestational age

- 1032 infants
- PCR
- Preterms: C difficile ↑ Bifidobacteria ↓
- Less mo colonization then term infants

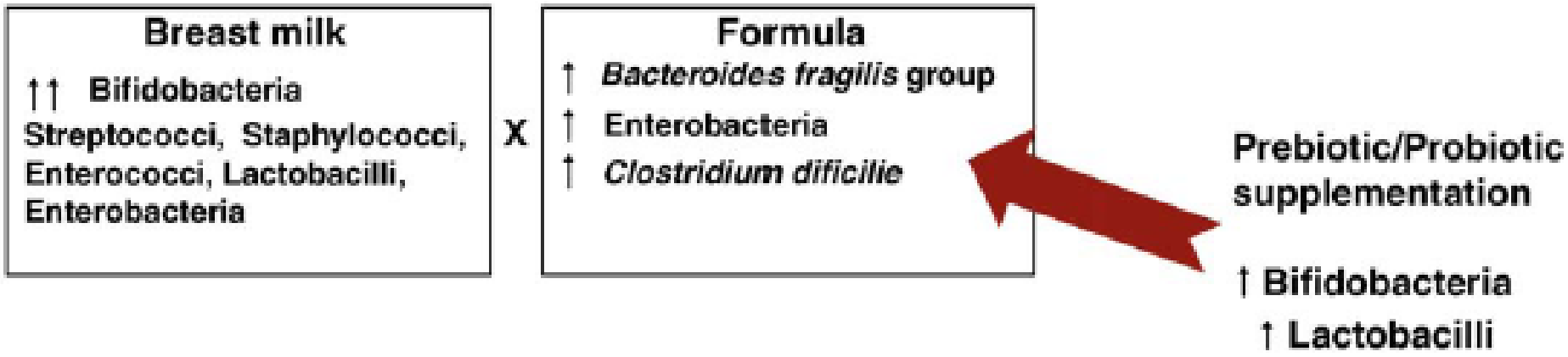
TABLE 3 Median Counts and Prevalence of Colonization With Selected Gut Bacteria in Feces of Infants 1 Month of Age ($n = 1032$)

Characteristics	No.	Bifidobacteria		*E coli*		*C difficile*		*B fragilis* Group		Lactobacilli		Total Counts, Median, $\log_{10}$ CFU/g Feces
		Counts, Median, $\log_{10}$ CFU/g Feces	Prevalence, %	Counts, Median, $\log_{10}$ CFU/g Feces	Prevalence, %	Counts, Median, $\log_{10}$ CFU/g Feces	Prevalence, %	Counts, Median, $\log_{10}$ CFU/g Feces	Prevalence, %	Counts, Median, $\log_{10}$ CFU/g Feces	Prevalence, %	
Gestational age at birth												
<37 wk (premature)	11	10.53	91	9.02	73	7.12	64[c]	8.95	82	8.80	27	10.80
37–41 wk[a]	860	10.68	99	9.30	87	5.06	23	9.27	82	8.61	33	11.12
>41 wk (postmature)	37	10.44	100	9.77	84	6.99	35	9.51	78	8.72	32	11.14
Birth weight												
<2500 g	11	10.45	100	8.67	100	7.12	27	9.31	82	9.12	36	11.28
2500–4500 g[a]	906	10.67	99	9.32	87	5.08	24	9.30	82	8.65	33	11.12
>4500 g	26	10.61	100	9.59	85	6.07	23	9.30	77	8.60	35	11.03

Pediatrics 2006;118(2):511-21

Feeding type

- Especially important in the first days of life
- Human milk contains many bacteria
- 10^9 mo/L in milk in healthy women
- *'Breast milk microflora'*
- Antibacterial properties
- Nondigestable oligosaccharides (prebiotics) stimulate proliferation of Bifidobacteria and Lactobacilli



Jeurink PV, Beneficial Microbes, 2013, 4: 17

Antibiotics

- Antibiotic treatment decreases bifidobacteria & Bacteroides

TABLE 3 Median Counts and Prevalence of Colonization With Selected Gut Bacteria in Feces of Infants 1 Month of Age ($n = 1032$)

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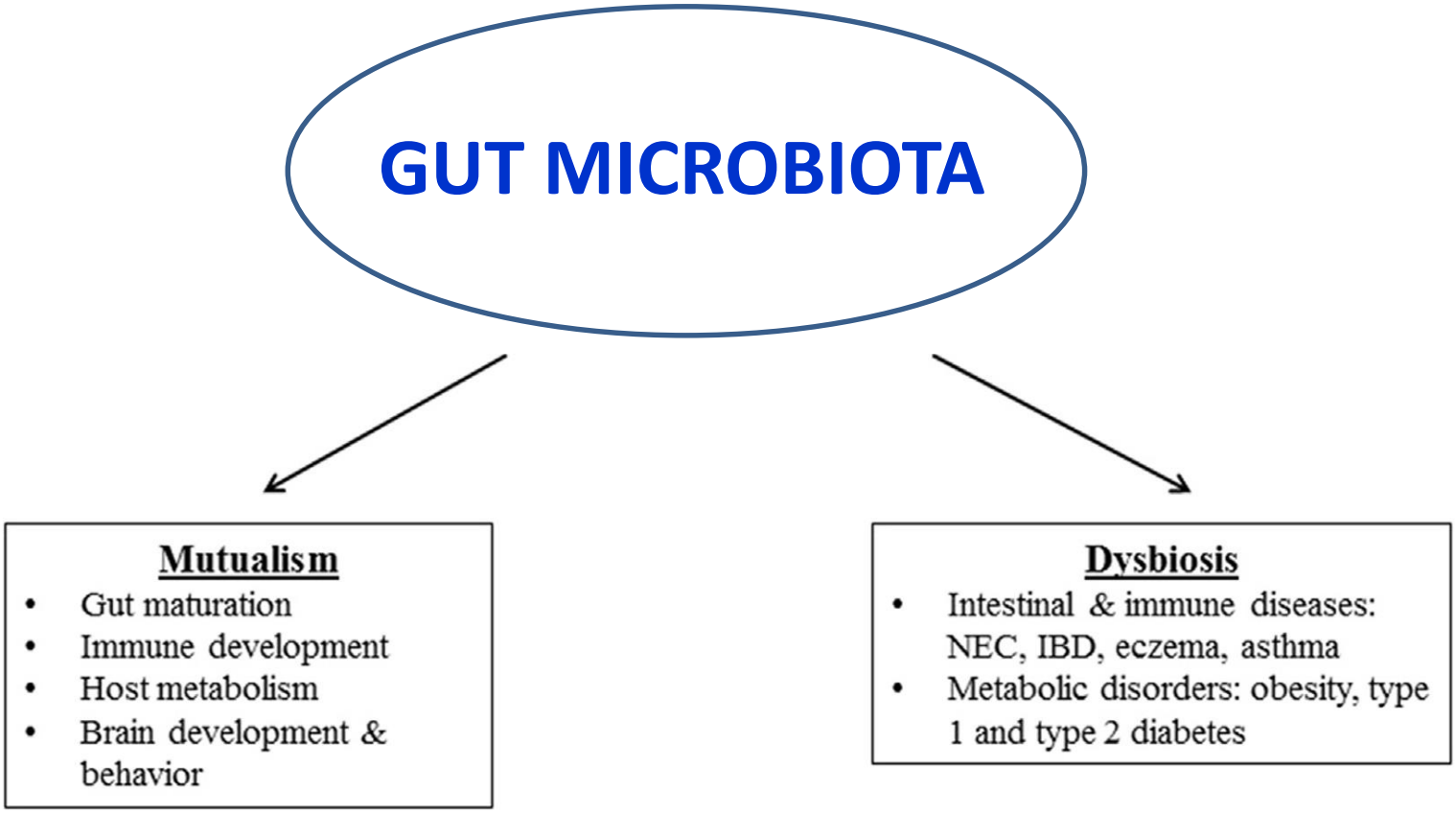
Antibiotic/antimycotic use during first 1 mo												
No[a]	945	10.70	98	9.32	88	5.50	25	9.31	82	8.65	32	11
Oral antibiotic	28	10.29	100[c]	9.45	79	7.12	18	6.39	82[c]	8.62	36	10
Oral miconazole	22	10.18	100[c]	9.57	82	4.47	23	9.35	86	8.68	36	11
Oral nystatin	15	10.77	93	9.67	87	4.81	13	9.33	73	8.64	33	11

Pediatrics 2006;118(2):511-21

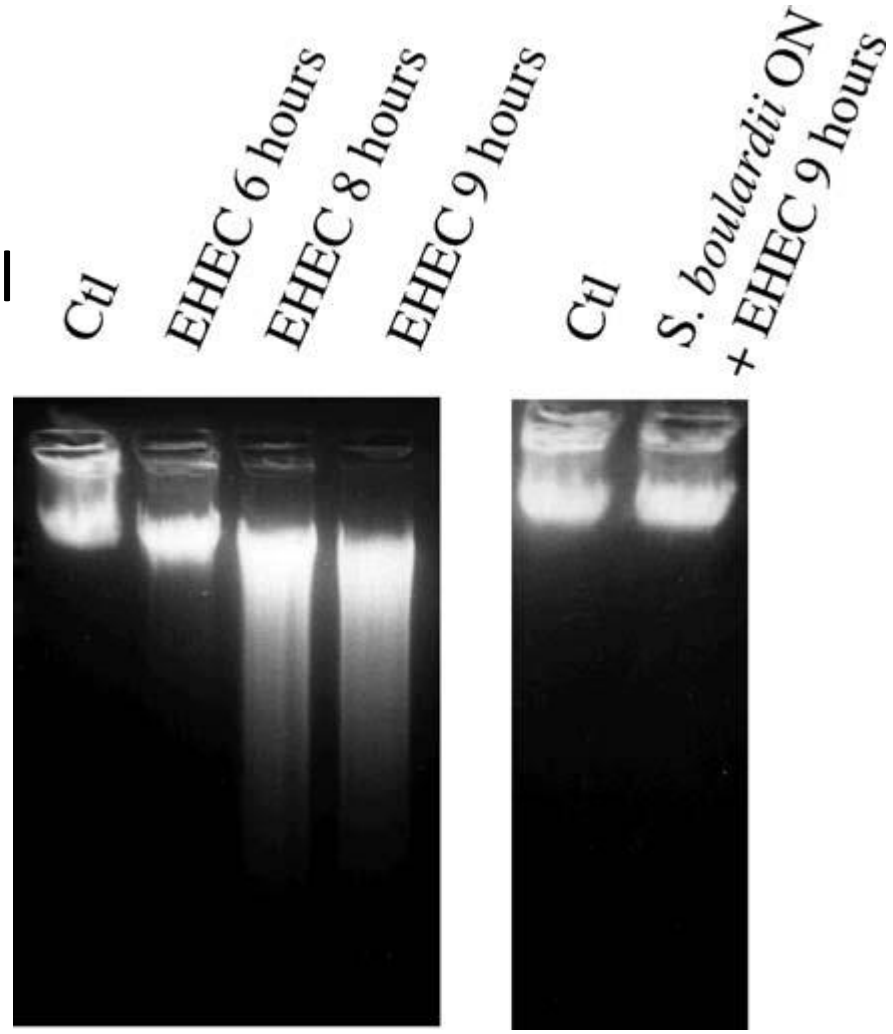

GUT MICROBIOTA
Mutualism
• Gut maturation
• Immune development
• Host metabolism
• Brain development & behavior
Dysbiosis
• Intestinal & immune diseases: NEC, IBD, eczema, asthma
• Metabolic disorders: obesity, type 1 and type 2 diabetes

commensal bacteria

- Epithelial cell proliferation ↑
- Apoptosis ↓
- Intestinal epithelial integrity ↑
- Activation of genes responsible from desmosome functions ↑
- Synthesis of tight junction proteins ↑ (barrier functions)
- Mucus secretion ↑
- Regulation of development of intestinal villus vascular architecture

Intestinal Barrier

- Pathogenic bacteria induced apoptosis of intestinal epithelial cells
- Lactobacillus, bifidobacteria
- commensal bacteria inhibit pathogens induced apoptosis

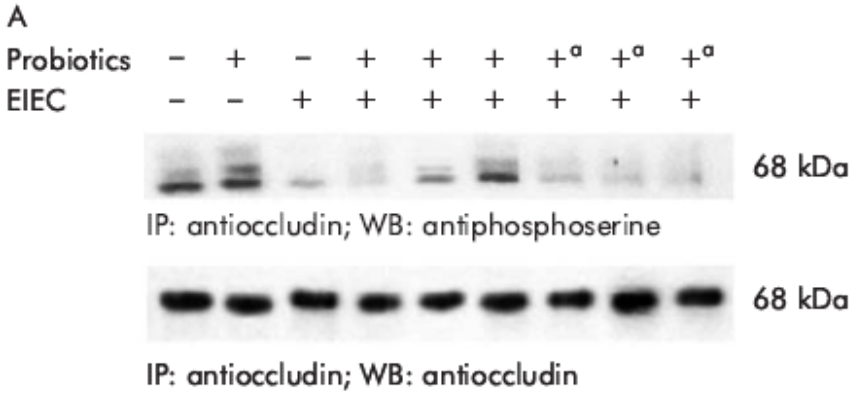


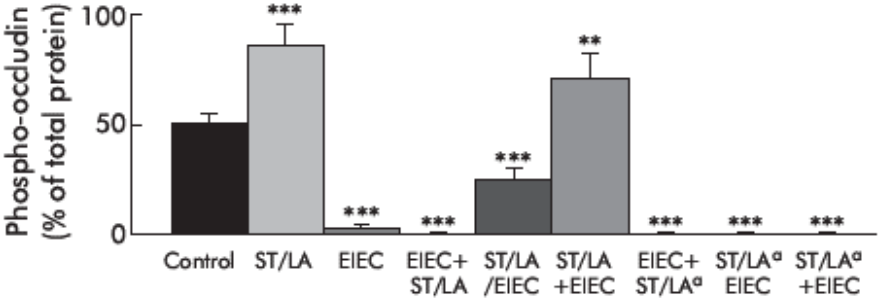
DNA fragmentation in T84 cells infected by EHEC

Res Microbiol 2006;157(5):456-65

Tight Junctions

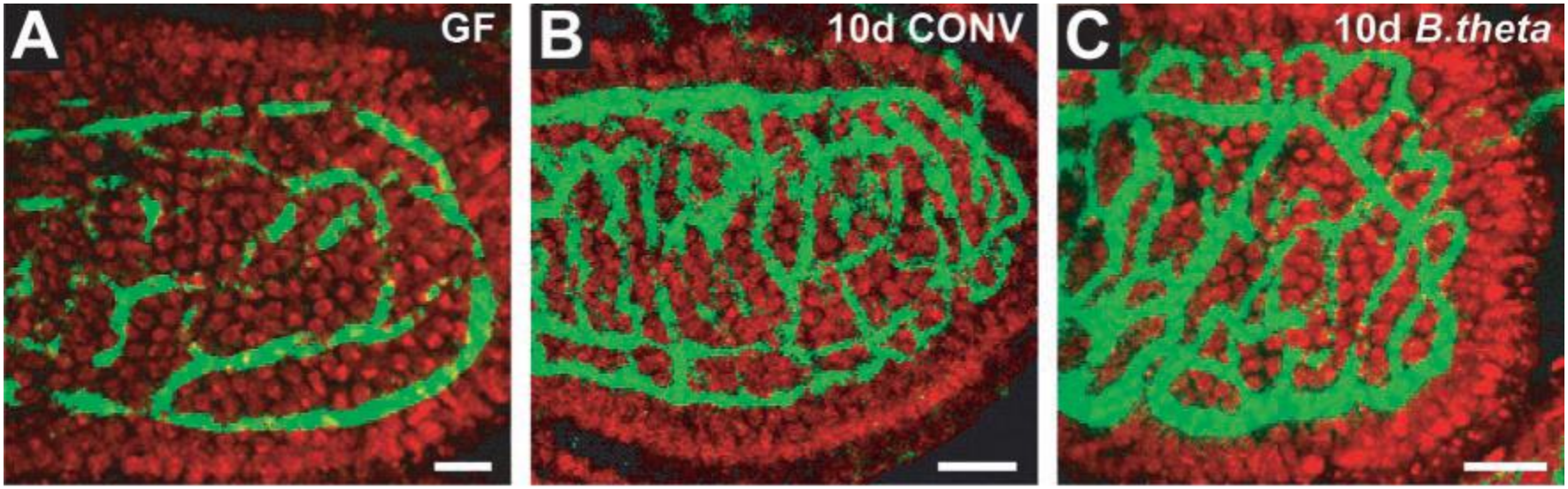
- The most critical part of interstinal barrier is tight junctions
- ‘Occludin’ and ‘Claudin’ proteins
- *L. acidophilus* and *S.thermophilus* are shown to increase the activation of occludin





Gut 2003;52:988–997

Angiogenesis



A: germ free

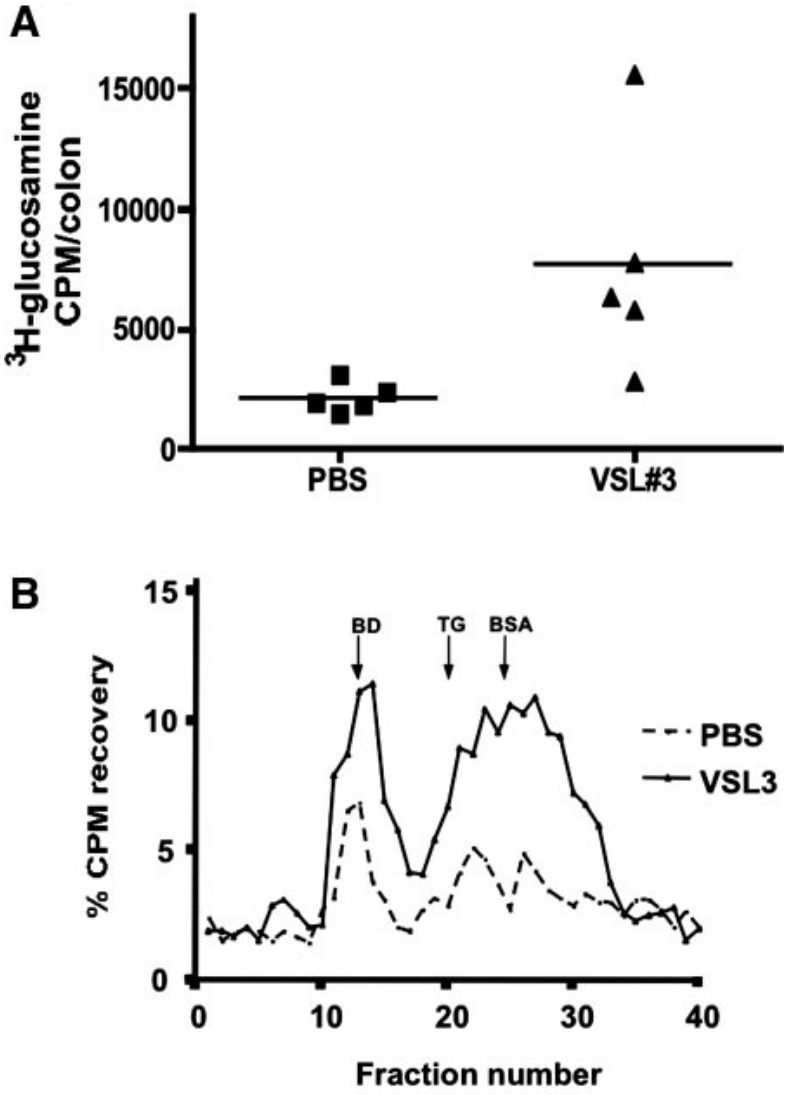
B: 10 days after colonization with conventinal microbioma

C: 10 days after probiotic bacteria colonisation

Proc Natl Acad Sci USA 2002;99(24):15451-5

Mucus Secretion

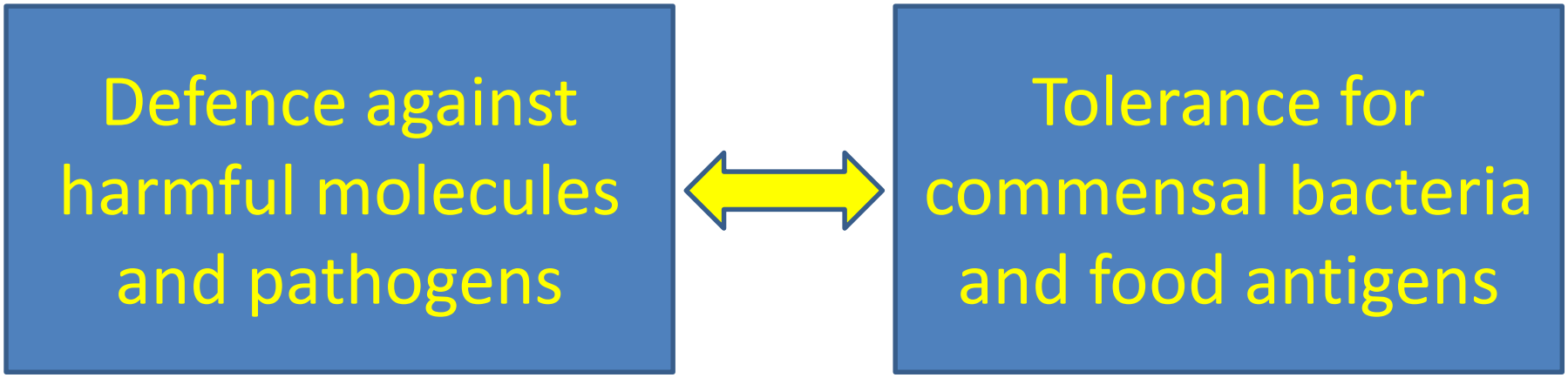
- Lactobacillus species induced MUC2 and MUC3 genes in vitro and in vivo
- Mucus secreton is increased



Am J Physiol Gastrointest Liver Physiol 2007; 292:G315-G322

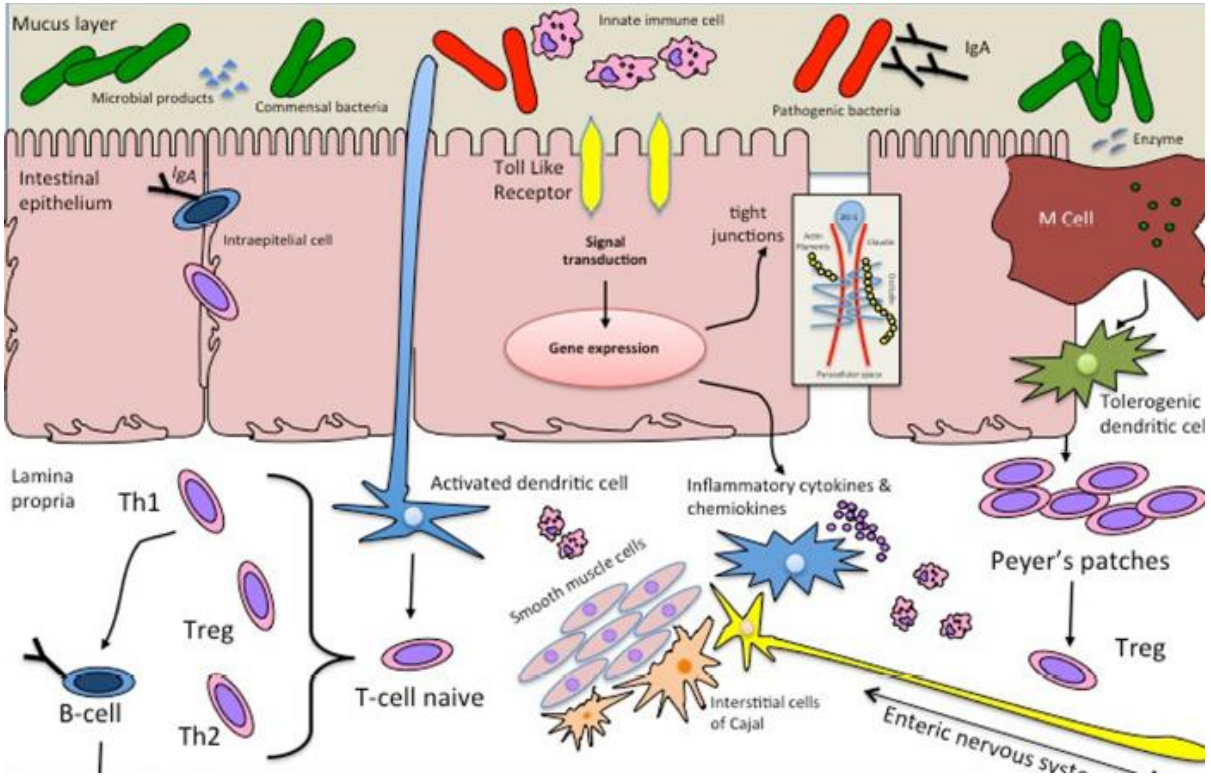
Impact of the microbiota on immune development & functions

- The microbiota is a cental player in the activation and function of the immune system in the early neonatal period and possibily during prenatal life



Impact of the microbiota on immune development & functions

- Commensal bacteria direct dentritic cell differentiation towards to tolerogenic and regulatory T cells
- Inhibit cytokine production and NK T cells



Impact of the microbiota on immune development & functions

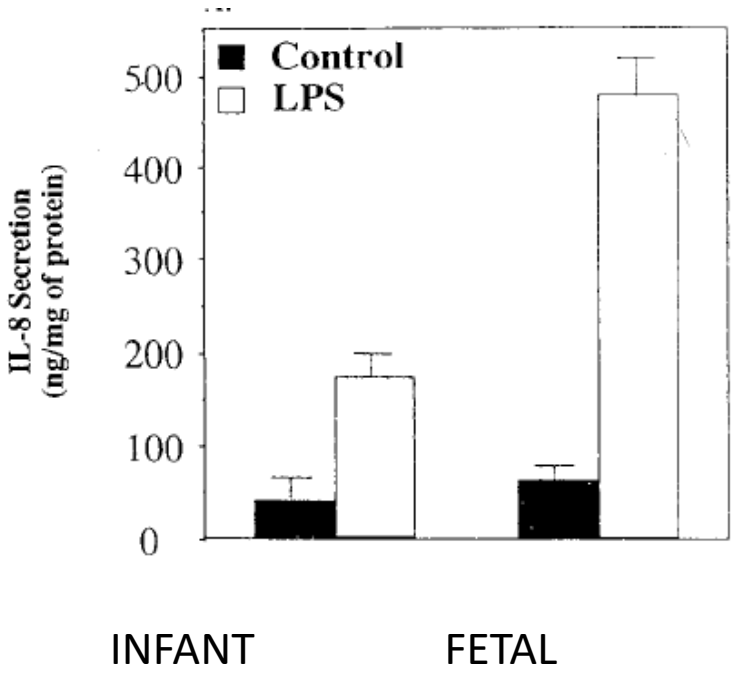
Immature immune cells have a higher sensitivity to microbial stimuli

- <u>fetal intestine:</u>

  LPS'e inflamatory response ↑↑
- <u>mature intestine:</u>

  weak inflamatory response

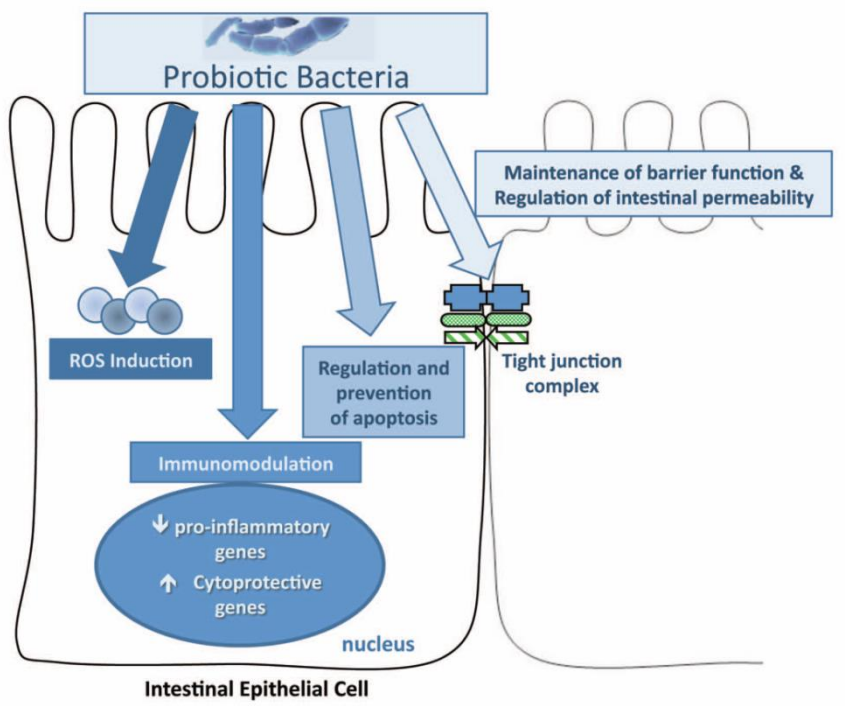
- Postnatal unresponsiveness is related to desensitization due to interaction with commensal bacteria



Proc Natl Acad Sci USA 2000; 97(11): 6043–6048.

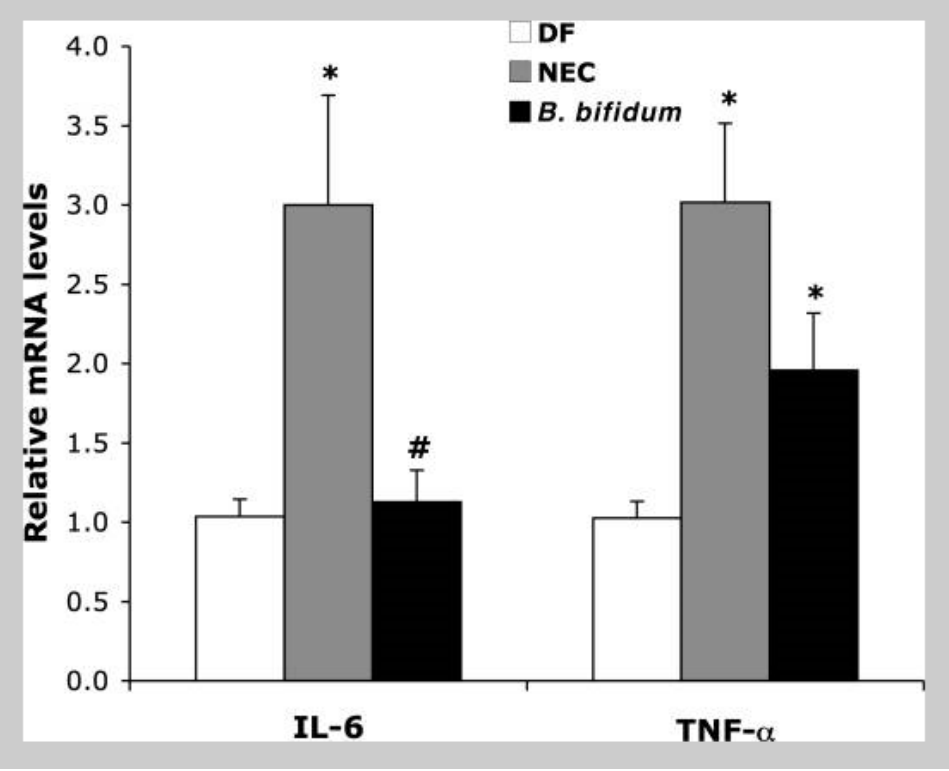
Impact of the microbiota on immune development & functions

- Probiotic bacteria lead to immune tolerance
- In preterm infants
- Bifidobacterium breve → TGF-β1 synthesis ↑
- anti-inflamatory effects ↑



Impact of the microbiota on immune development & functions

Bifidobacterium bifidum decreases synthesis of pro-inflamatory cytokines which are important in the pathogenesis of necrotising enterocolitis

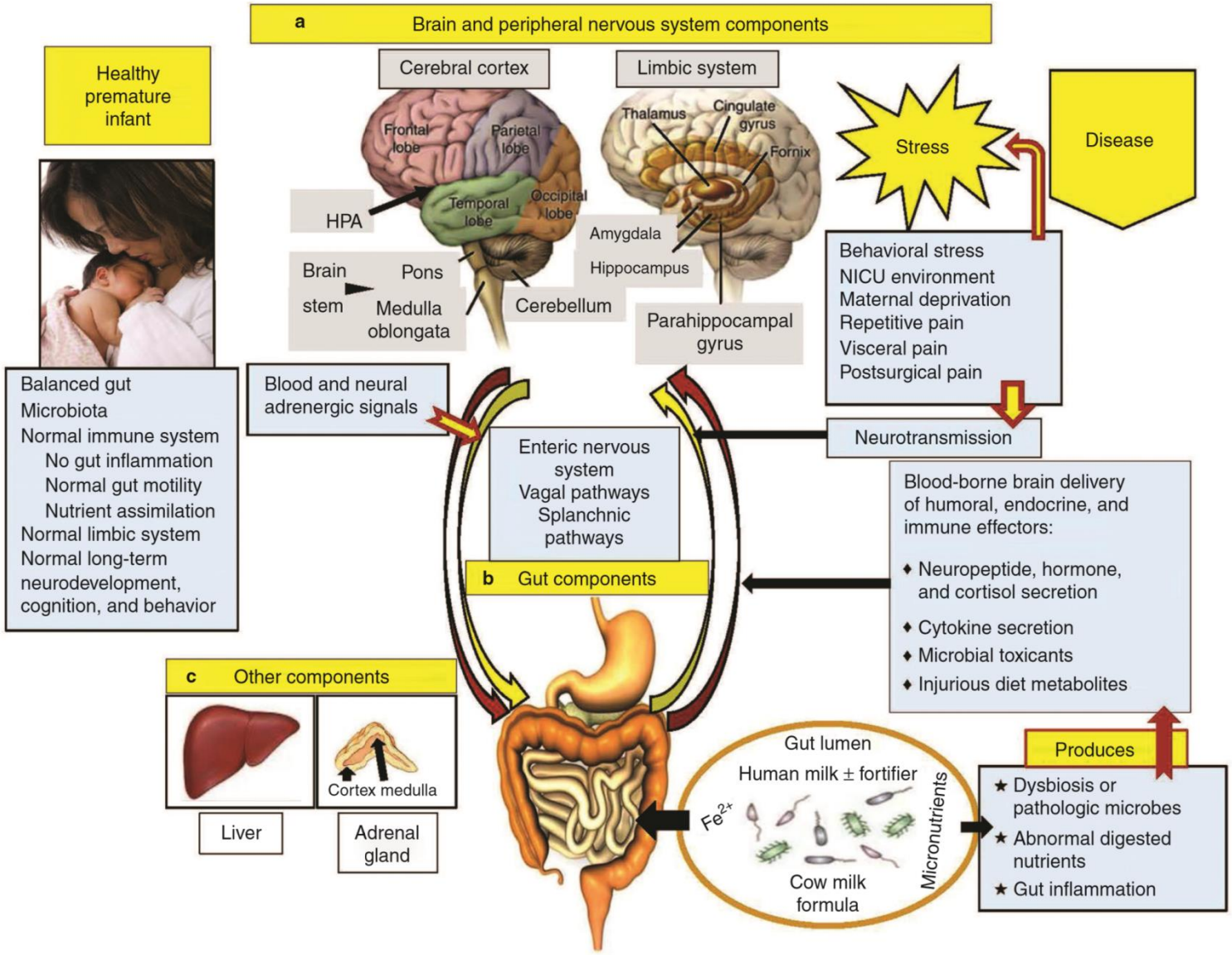


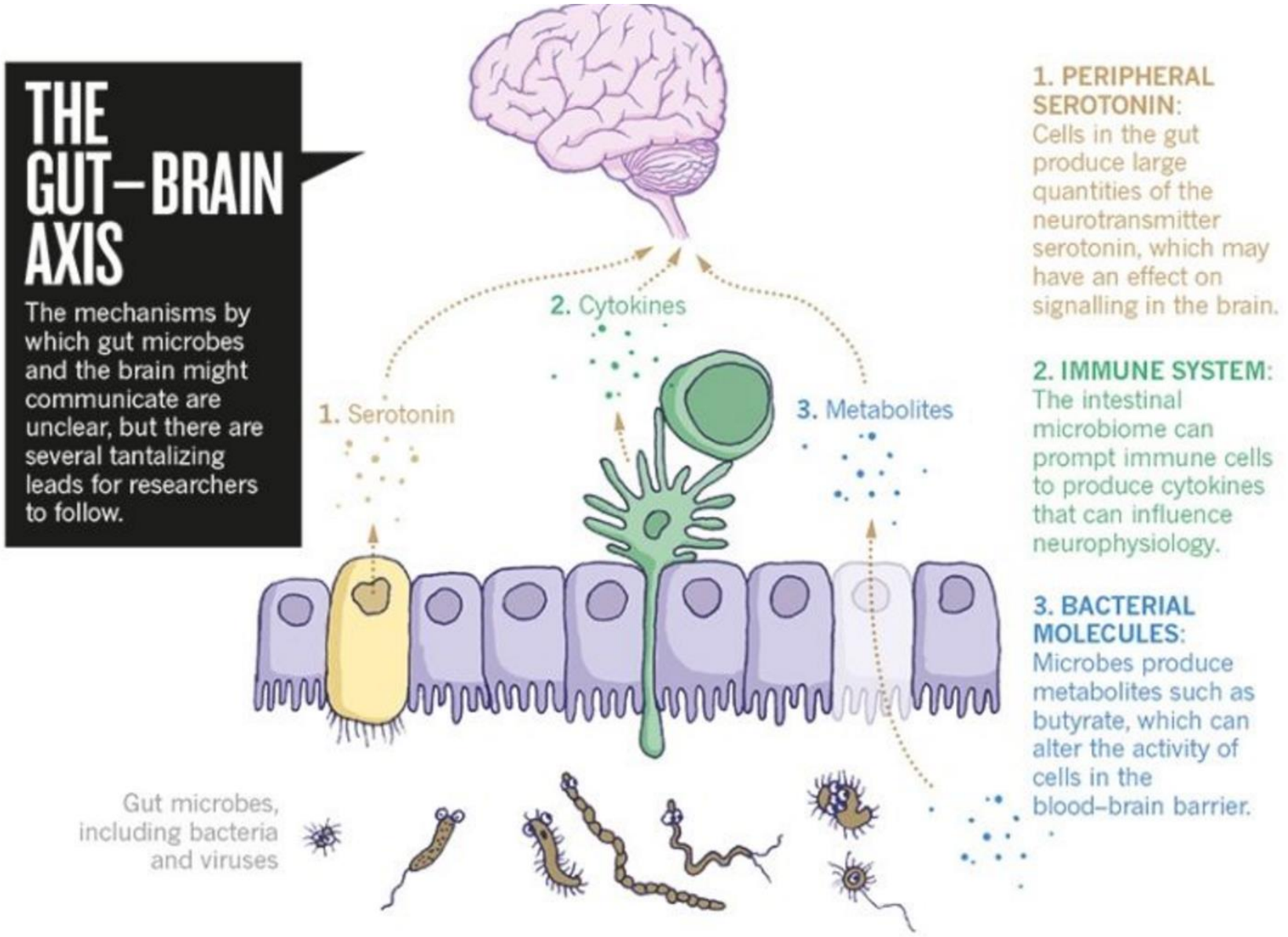
Brain Development & Behaviour

- Several preclinical studies using germ-free mice highlighted the ability of early life microbiota to influence neurodevelopment with long lasting effects on neuronal function

Brain, Behavior, and Immunity 2014; 38: 1–12
Trends Mol Med 2014; 20: 509-18

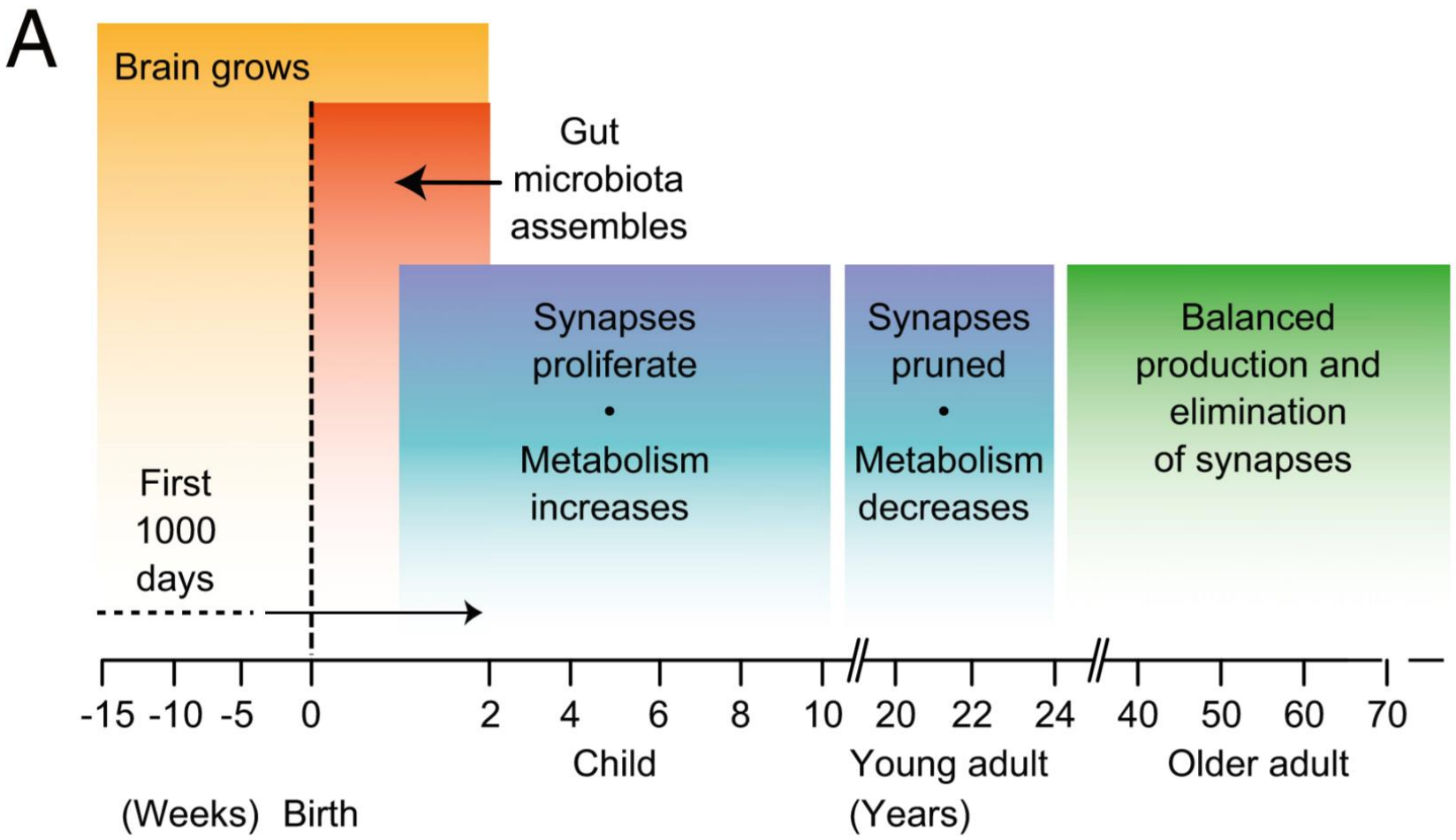
Gut - Brain Axis





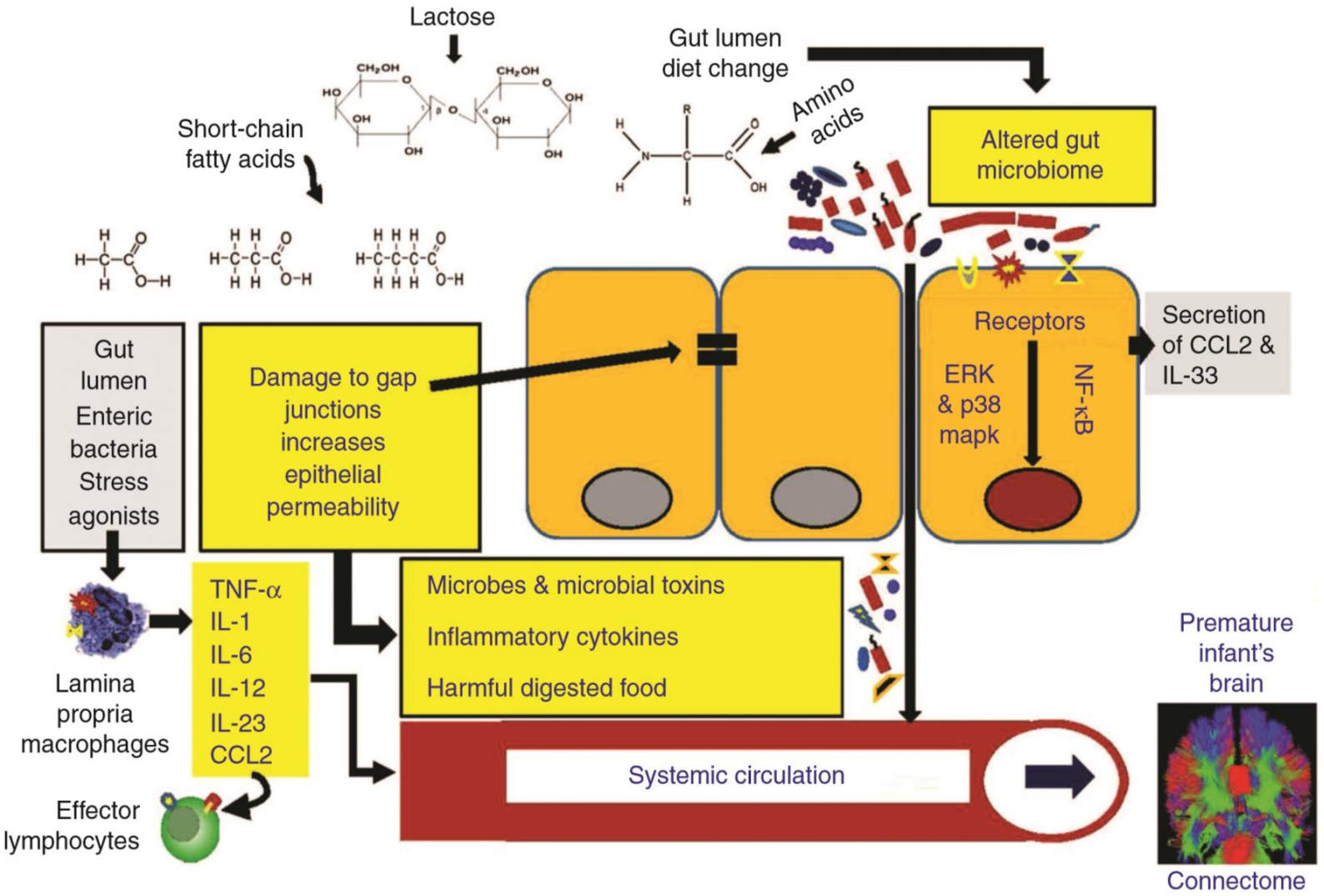
The Gut Brain Axis, as demonstrated by the journal Nature.

The parallel early development of the intestinal microbiota and the nervous system



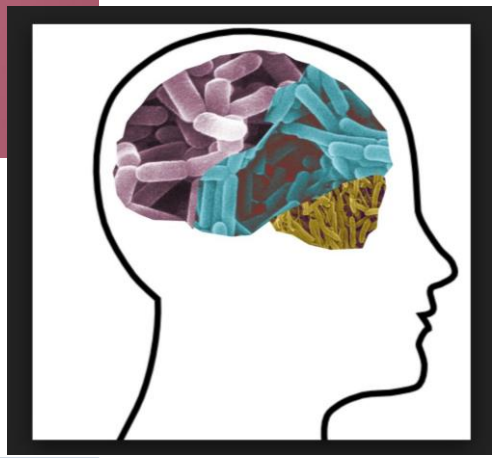
PNAS 2015, 112 ; 46: 14105–14112

Microbiota- Gut- Brain Axis



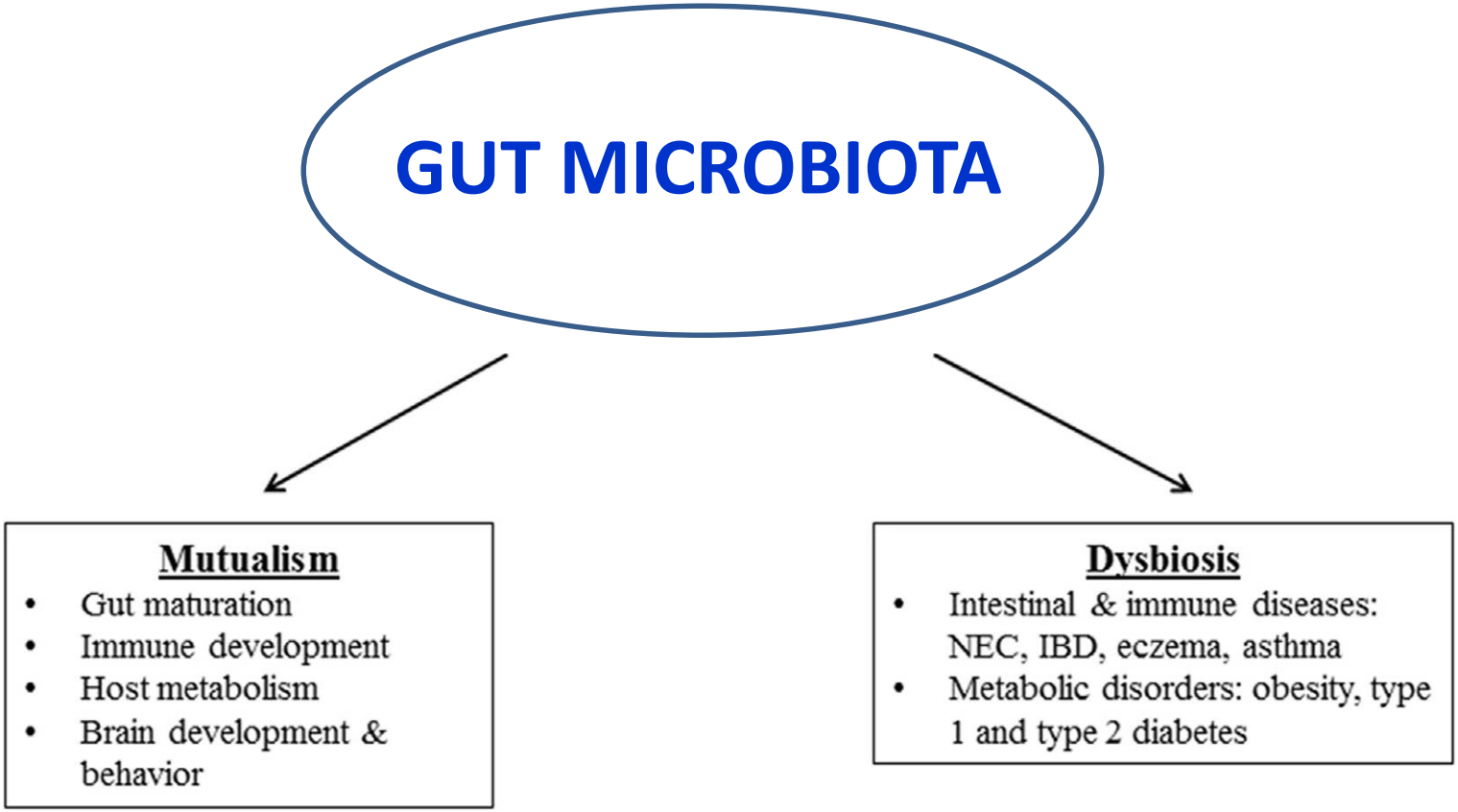
Microbiota- Gut- Brain Axis

psychobiotic

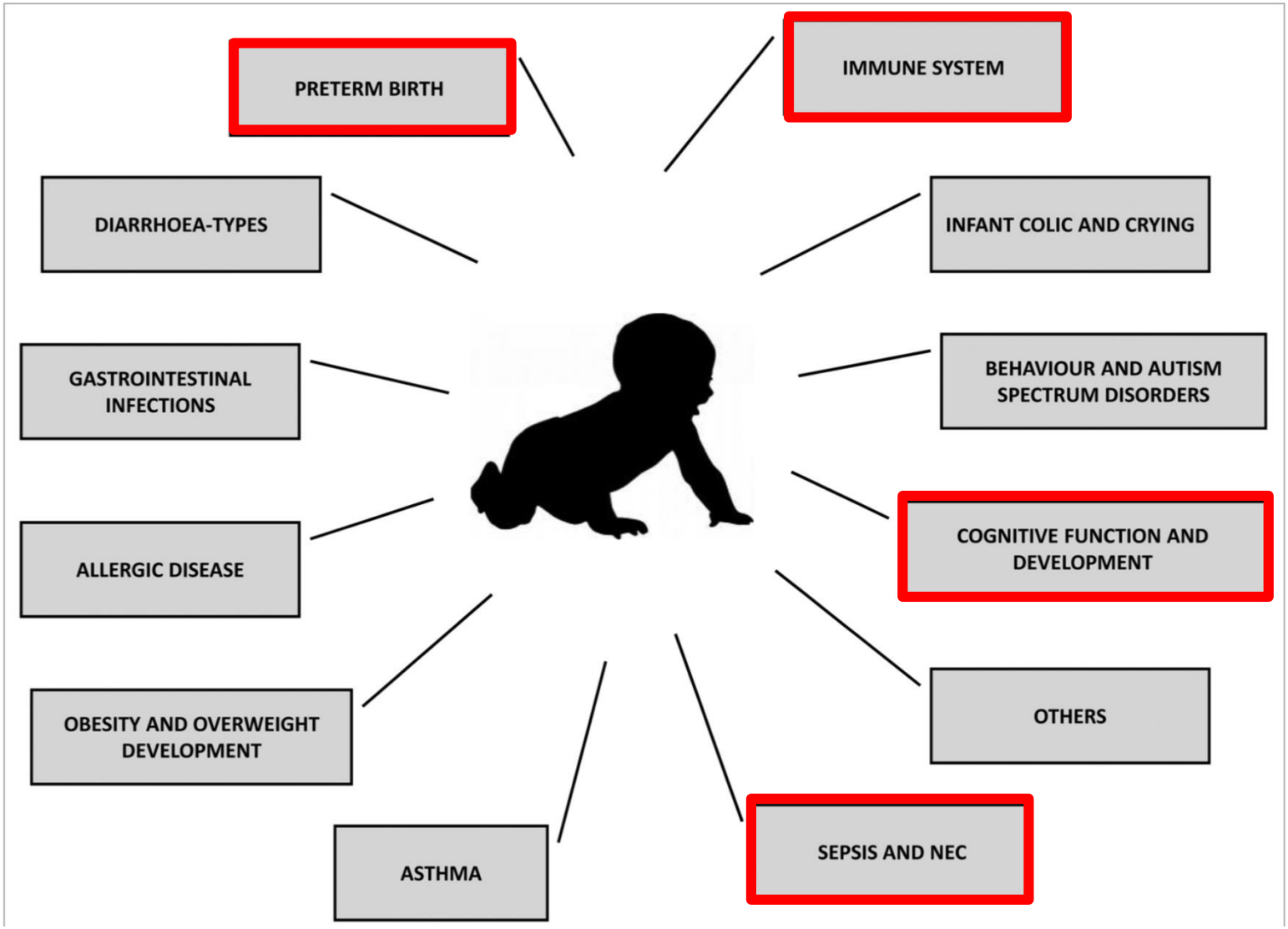


Neurobiotics ?

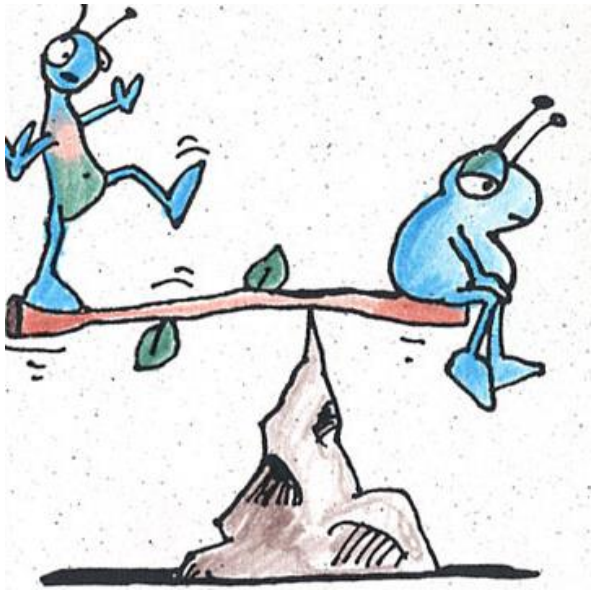
Dysbiosis Related Diseases



Prophylactic and Therapeutic interventions



CONCLUSION



- Symbiotic association between microbiota and host results in a state of ***physiological homeostasis***
- Postnatal gut metabolism, development, immune system development and neurodevelopment are directly influenced by the bacterial community and dysbiosis is associated with several clinical conditions

"FIRST, IT WAS A SYMBIOTIC RELATIONSHIP, THEN PLATONIC, AND NOW, WE'RE HAPPILY MARRIED."