Universitat Autònoma de Barcelona

Therapies to modulate the gut microbiota from a dysbiosis to a homeostasis state

Barragán Laso, Albert

Microbiology, Universitat Autònoma de Barcelona; Tutor: Luquín Fernández, Marina

INTRODUCTION

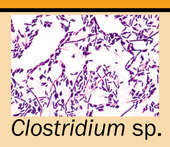
- Up to 10^{14} bacteria can be found in the gut (the largest bacterial population in the body).
- These have multiple functions related to the fermentation of residual foods, modulation of immune response and protection against opportunistic pathogens.
- It is believed that a more diverse microbiota is correlated to a "healthy" person whereas a lower one can bring to a disruption of the homeostasis state.
- An alteration of the gut microbiota has been associated with a phenomenon of "dysbacteriosis" (dysbiosis), which can be accompanied by multiple associated pathologies.

DYSBIOSIS: Change of the structural or functional balance of the microbiota that leads to a failure of the host-microbes homeostasis.

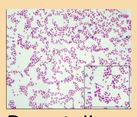
INTESTINAL MICROBIOTA MAINLY PHYLA

- **Firmicutes** (*Clostridium*, *Faecalibacterium*, *Roseburia*, *Ruminococcus*)
- **Bacteroidetes** (*Bacteroides*, *Prevotella*)
- **Proteobacteria** (*Enterobacteriaceae*)
- **Fusobacteria** (*Fusobacterium*)
- **Verrucomicrobia** (*Akkermansia muciniphila*)
- **Cyanobacteria**
- **Actinobacteria** (*Bifidobacterium* spp.)

Ruminococcus sp.



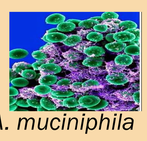
Clostridium sp.



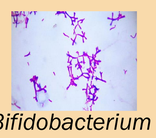
Prevotella sp.

Bacteroides sp.

Firmicutes and Bacteroidetes are the only dominant phyla



A. muciniphila



Bifidobacterium sp.

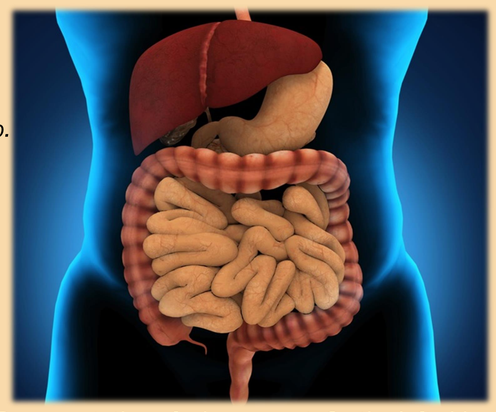


Figure 2. Representation of a human gut. On the left side are detailed the seven phyla that should be present in the yet undescribed "healthy" microbiota.

Figure 1. Mice cecal bacteria with rich (left) and poor (right) bacterial populations (RIKEN; Institute of scientific research, Japan).

Balanced gut microbiota (Homeostasis)

Beneficial/Commensal >> Opportunistic/Pathogens

Antibiotic exposure
High-Fat/High-Sugar Diet
Stress, Hygiene
Infection, Inflammation
Age and Host genetics

High-Fibres Diet
Prebiotics
Probiotics
Bacteriotherapy

Unbalanced gut microbiota (Dysbiosis)

Beneficial/Commensal << Opportunistic/Pathogens

Dysbiosis-associated diseases

Inflammatory Bowel Disease, colorectal cancer, obesity, *Clostridium difficile* colitis, Chron's disease…

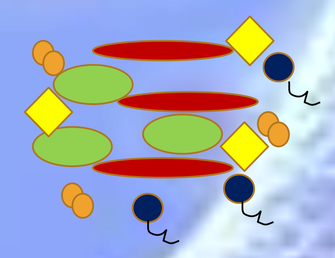


Figure 3. Representation of a balanced microbiota.

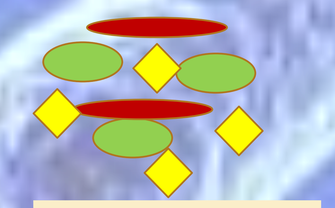


Figure 4. Representation of a less equitable microbiota.

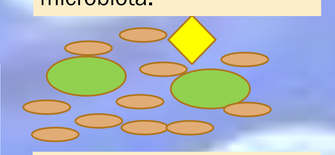


Figure 5. Representation of an overgrowth of one bacterial population.

RESULTS

	PREBIOTICS	PROBIOTICS
Definition	Non-digestible but fermentable substrates (oligosaccharides).	Adequate amounts (10^7) of live microorganisms.
Examples	• **Fructans** (inulin and fructo-oligosaccharides). • **Galacto-oligosaccharides**. • **Lactulose.** • **Resistant starches** and **other oligosaccharides** are under probe.	• **Bifidobacteria** (*Bifidobacterium lactis*). • **Lactobacilli** (*Lactobacillus lactis*). • **Streptococci** (*Streptococcus thermophilus*).
Action	Only <u>some anaerobic bacteria</u> (mainly bifidobacteria) can ferment them → importance of interactive consortia in human gut (production of lactate by bifidobacteria is well-exploited by butirate-producing bacteria).	Multifactorial: • Influencing resident microbiota (replacing a missing part or supplementing endogenous population). • Only stimulating a part of the microbiota.
Effect	Selection of bifidobacteria and other anaerobic bacteria with consequent benefits to the host health.	Changes in enzymatic activity, in the composition of the mucus secreted by colon cells, modulation of immune system and sustaining the tight junctions (reducing the permeability of some pathogens).
Used in a targeted way	• ***Faecalibacterium prausnitzii*:** grows perfectly with fructan supplement → protection against Chron's disease (anti-inflammatory effect). • ***Oxalobacter formigenes*:** uses oxalate for growing → reduces the risk of kidney stone formation.	**Microencapsulation** of bacterial cells to guarantee the survival of the bacteria in a specific part of the gastrointestinal tract and an appropriate diffusion of metabolites and substrates. • ***Lactobacillus acidophilus*:** suppression of colon tumour incidence.
Difficulties	Effects of dietary modulation on the gut microbiota and host response are suggested to be highly individual.	The effect of one probiotic strain cannot be extrapolated to another strain.

BACTERIOTHERAPY

Transplantation of faecal bacteria from a healthy donor.

There are different ways of instilling stool samples

Nasogastric tubes | Nasoduodenal tubes | Through a colonoscopy | Retention enema

Higher cure rates *in* ***C. difficile*** **infection** (CDI) by colonoscopic route (93,2%) than by nasogastric one (85,3%) in Pinn *et al.* review.

Donor selection based on

Medical history :
- Users of illicit drugs, taking antibiotics within preceding 3 months or people with Diabetes Mellitus or Metabolic Syndrome, among others, are excluded from being donors.

Laboratory testing:
- Hepatitis viruses and Abs against them, HIV and stool culture.
- Different Ag/Ab tests: *Cryptosporidium*, *Giardia*, *Helicobacter pylori* and *Rotavirus*.
- Detection of *Cyclospora* and *Isospora* (acid fast stain).
- Stool ova and parasites exam.

First-degree or closer relatives: genetically similarities would represent a great number of microbial species in common.

Pro: CDI cure rate is higher using bacteriotherapy than only using vancomycin or metronidazole (apart from avoiding resistance problems).
Con: Safety → unanswered questions about long-term complications.

CONCLUDING REMARKS

✓Further research (Human Microbiome Project, MetaHIT consortiums) is needed to determine what exactly is a normal "healthy" gut microbiota and if positive effects are caused by the therapies or just by individual characteristics of the patient's microbiota.

✓Lack of knowledge in long-term complications, especially in bacteriotherapy, clinical trials and *in vivo* studies, is retarding the progress of these therapies.

✓Until remains a controversial question: is microbial variation the cause of the disease or is it just an effect of it?

✓Establishment of *stool banks* and a fast standardization and regulation by FDA (Food and Drug Administration) would benefit the future of bacteriotherapy as the first-line therapy for CDI.

✓**FUTURE:** Synthetic stool (knowing the exact bacterial composition) against antibiotic resistant CD colitis (↓ *Proteobacteria*, followed by gradually ↑ in *Bacteroidetes*, *Firmicutes* and *Verrucomicrobia* phyla).

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