Interactions between the Microbiota and the Immune System

Universitat Autònoma de Barcelona
Faculty of Biosciences
Microbiology
May 2015

Celia Seguí Pérez

Introduction

- Since before birth, humans are colonized by a large number of microorganisms (10^{14} in the adulthood) which surpass the 10^{13} human eukaryotic cells; mostly found in the colon.
- The development of the gut associated lymphoid tissue (GALT) begins in mammals before birth and requires a microbiota for a proper development.
  1) Umbilical cord and amniotic fluid
  2) Mode of delivery
  3) Lactation
  4) Environment and diet exposure
- Intestinal microbiome →
  - 75% Bacteria of the phylum *Firmicutes*, *Bacteroidetes*, *Actinobacteria*
  - Archaea such as *Methanobrevibacter smithii* and *Methanosphaera stadtmanae*
  - Fungi of the genus *Candida* and *Saccharomyces*

Goals

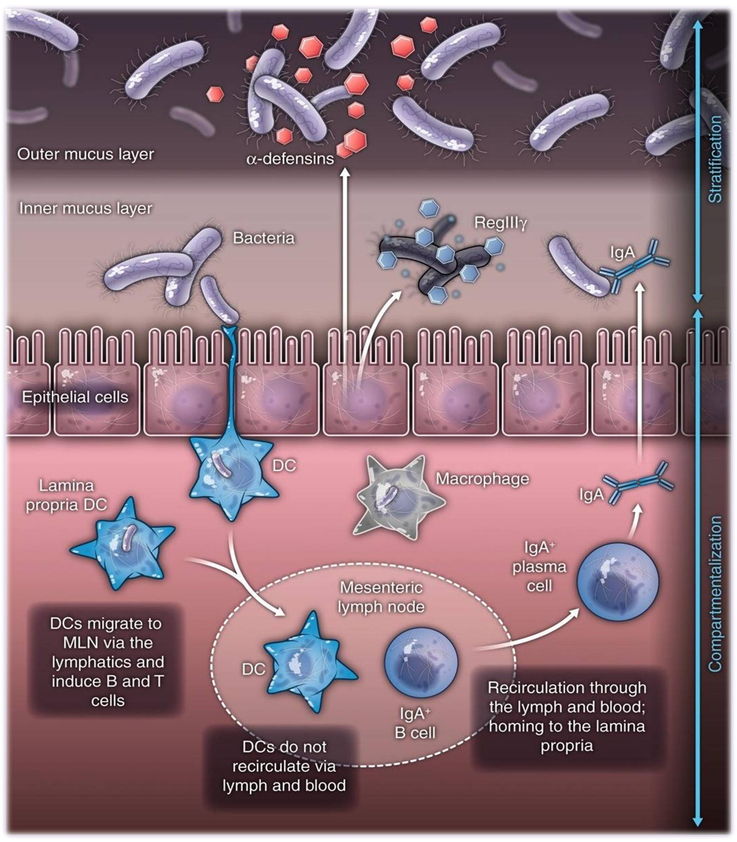
- Comprehension of the microbiota establishment and its affecting factors.
- Mechanisms description by which the immune system interacts with the microbiota and its relationship.
- Discussion about probiotic, prebiotic and symbiotic effects on the health of the host.

Metodology

- Reviews and Scientific Research Publications (NCBI and Google Scholar) with word limitaion: "Immune system, intestinal microbiota, immunomodulatory, maturation, mucosal immune responses, gut, microbiota, probiotic, development", in the last 10 years.
- MOOC Course "Gut Check: Exploring Your Microbiome" by University of Colorado.
- VIII Congress "Societat Catalana d'Immunologia" (SCI).

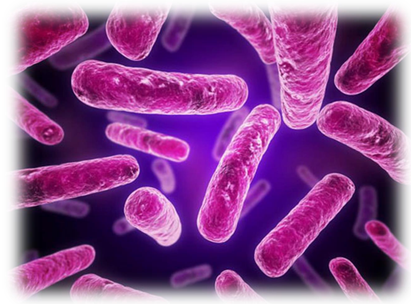
Results

The Immune System Controls the Microbiota



<u>Stratification</u>: minimizing direct contact between intestinal bacteria and the intestinal cell surface

- Mucus layer → by Goblet cells
- Antibacterial proteins →
  - α-defensins by Paneth cells
  - β-defensins by intestinal epithelial cells (IECs)
  - Catelicidins by IECs
  - RegIIIγ by Paneth cells and enterocytes
- Stomach pH
- Lactoferrin
- Phospholipase A2
- Proteins of the complement system
- Immunoregulatory cytokines and chemokines
- sIgA



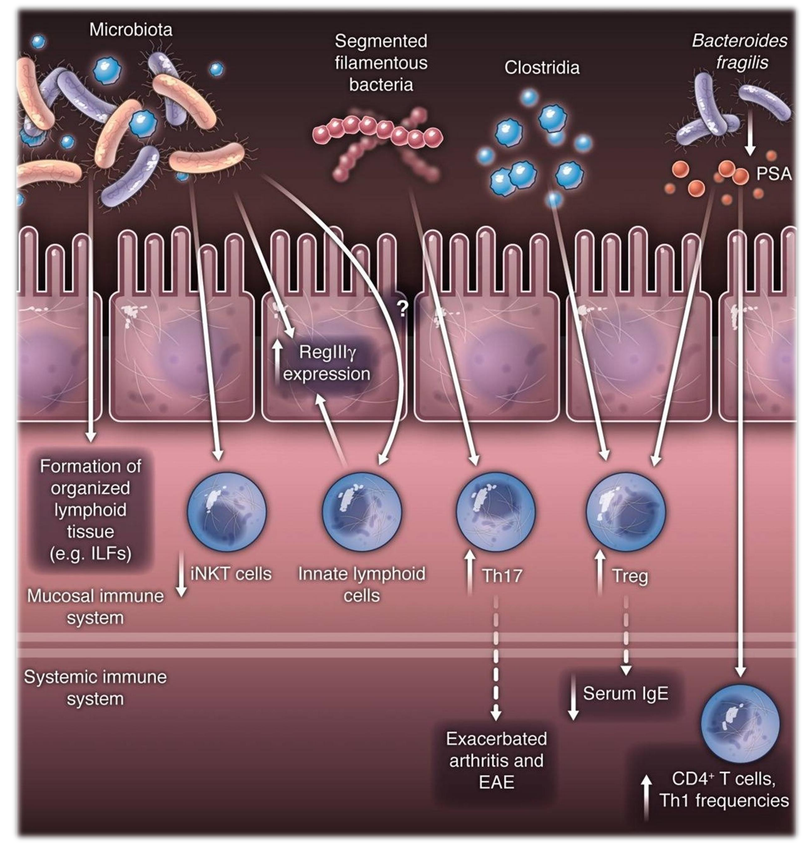
<u>Compartmentalization</u>: confining the bacteria that are able to penetrate and limiting their exposure to systemic immune compartment

- Specific sIgA in the mesenteric lymph node → by B cells activated when antigen presenting cells (APCs) sample microbial antigens
- Differential distribution of TLRs
  - NOD and TLR9: located intracellularly
  - TLR5: basolateral distribution
  - TLR4: internalized into endosomes
- T cell differentiation

Microbiota Modulates the Immunity

Impact on the epithelial function and the lymphoid structure development

- Impact on the epithelial function and the lymphoid structure development
- Germ free animals have a scarce and inactive mucosal immune system
  - undeveloped intestinal lymphoid tissue (ILFs)
  - less production of sIgA
  - reduction of intraepithelial lymphocytes (IELs)
- Affects systemic immunity
- Control of iNKTs and IL-17 and IL-22-producing CD4+ T cells
- Can protect from autoimmune diseases



Segmented filamentous bacteria

- ↑ Th17 and Th1 cells → ↑ inflammatory state
- IELs recruitment
- ↑ IgA and RegIIIγ expression
- IL-10 and IFN-γ- producing CD4+ T cells induction

***Clostridium* clusters IV and XIVa**

- ↓ Systemic serum IgE
- iT_{REG} induction → ↑ anti-inflammatory state

***Bacillus fragilis* polysaccharide A**

- ↑ T CD4+ and Th1 cells
- ↑ IL-10 anti-inflammatory response
- iT_{REG} induction

Prebiotics **Symbiotics**

Indigestible dietary fibers which selectively stimulate growth and bacterial activity, mostly from the genus *Bifidobacterium* and *Lactobacillus*.

V. g. Breast milk → Indigestible oligosaccharides (HMOs) —Saccharolytic fermentation→ Short-chain fatty acids (SCFAs)

Antimicrobial effect by blocking bacterial adhesion to the intestinal barrier
Prevent an excessive permeability
IL-10 lymphocyte production

Probiotics

➢ Live microorganisms, which if administered in appropriate quantities, can benefic the host's health.

- ***Lactobacillus***
- ***Bifidobacterium***
- **Lactic acid bacteria (LAB)**
- ***Streptococcus***
- ***Enterococcus***
- ***Propionibacterium***
- ***Escherichia coli***
- ***Saccharomyces boulardii***

Conclusions

- Deviations from proper microbiota establishment alter the immune system development and may lead to inflammatory disease emergence; such as inflammatory bowel disease (IBD) including Crohn's disease and the ulcerous colitis, NEC as well as atopic and autoimmune diseases.
- Children microbiota is easily modulated as it is not consolidated.
- Probiotic, prebiotic and symbiotic use have led to heterogeneous effects and therefore cannot be a useful tool in this field.
- Further research → Use genetically-modified commensal bacteria as liberation platforms for antimicrobial agents and vaccines

Expectations

- Deeper understanding of microbiota mechanisms through which the immunity controls its composition and the potential members of a healthy microbiota.
- Obtain a standardized microbiota in isogenic mice and "humanized" animal models.
- Determine which microbiota molecules drives Th17 and T_{REG} cell differentiation.

Pictures references

1. Hooper L, *et al*. Interactions Between the Microbiota and the Immune System. *Science* 2012, 336: 1268-1273.