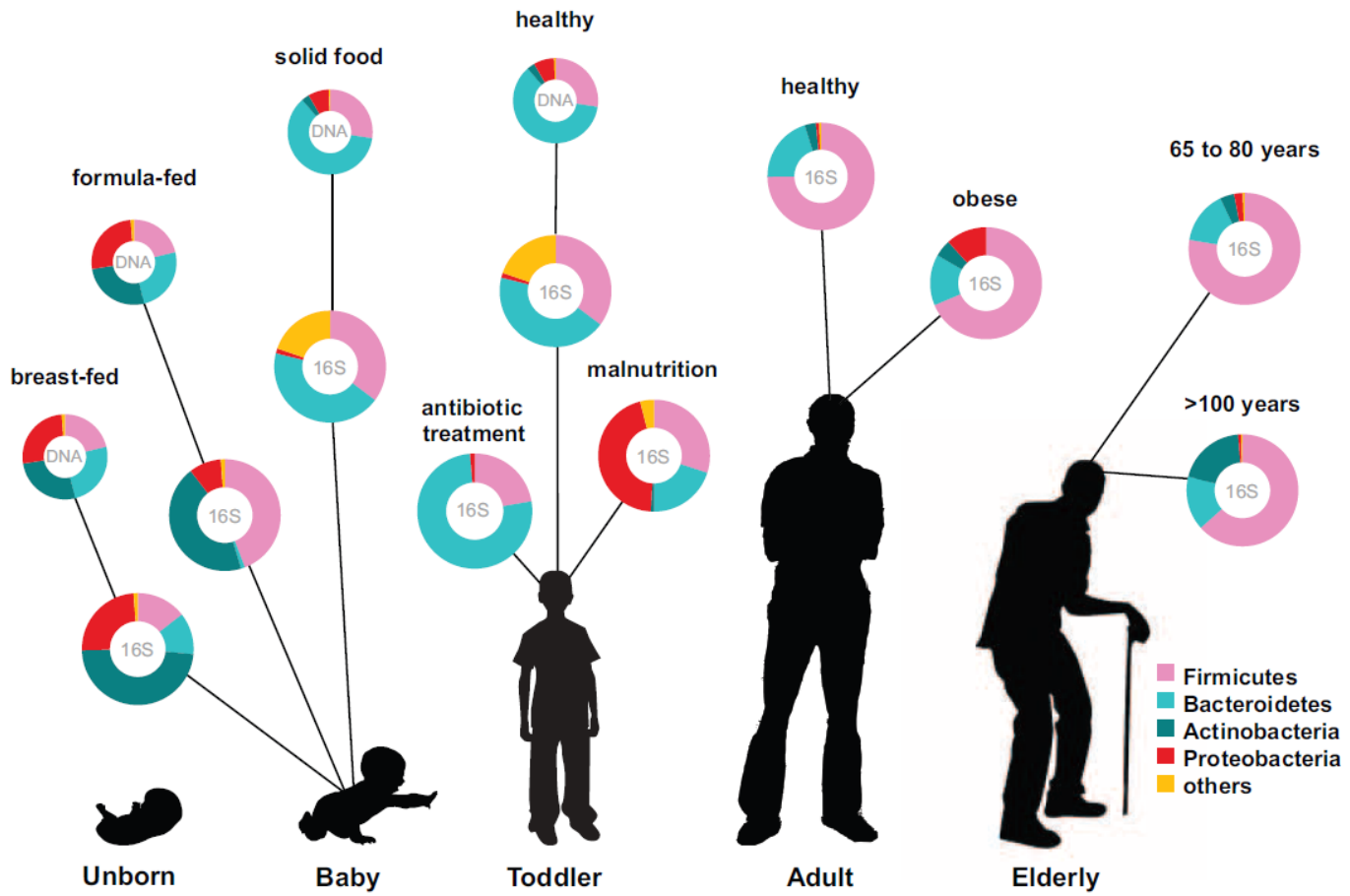


FIGURE 1 | Human microbiota: onset and shaping through life stages and perturbations. The graph provides a global overview of the relative abundance of key phyla of the human microbiota composition in different stages of life. Measured by either 16S RNA or metagenomic approaches (DNA). Data arriving from: Babies breast- and formula-fed (Schwartz et al., 2012), baby solid food (Koenig et al., 2011), toddler antibiotic treatment (Koenig et al., 2011), toddler healthy or malnourished (Monira et al., 2011), adult, elderly, and centenarian healthy (Biagi et al., 2010), and adult obese (Zhang et al., 2009).

frontiers in
CELLULAR AND INFECTION MICROBIOLOGY

REVIEW ARTICLE
published: 09 August 2012
doi: 10.3389/fcimb.2012.00104

The function of our microbiota: who is out there and what do they do?

*Noora Ottman[1], Hauke Smidt[1], Willem M. de Vos[1,2] and Clara Belzer[1]**

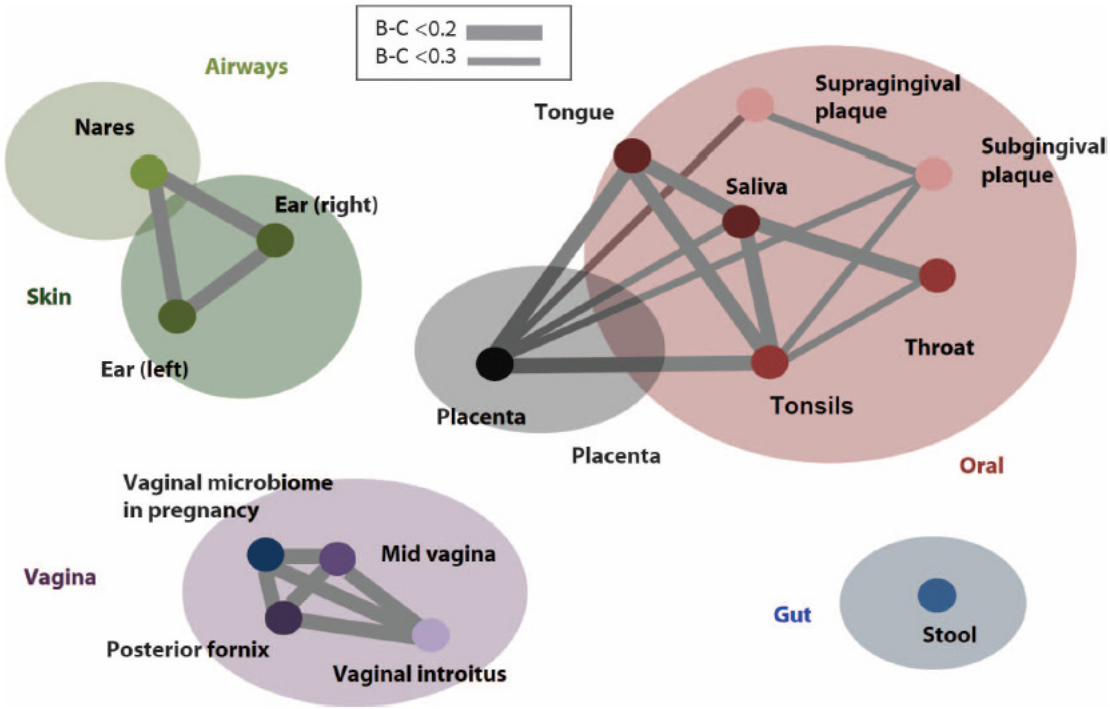
RESEARCH ARTICLE

MICROBIOME

The Placenta Harbors a Unique Microbiome

Kjersti Aagaard,[1,2,3]* Jun Ma,[1,2] Kathleen M. Antony,[1] Radhika Ganu,[1] Joseph Petrosino,[4] James Versalovic[5]

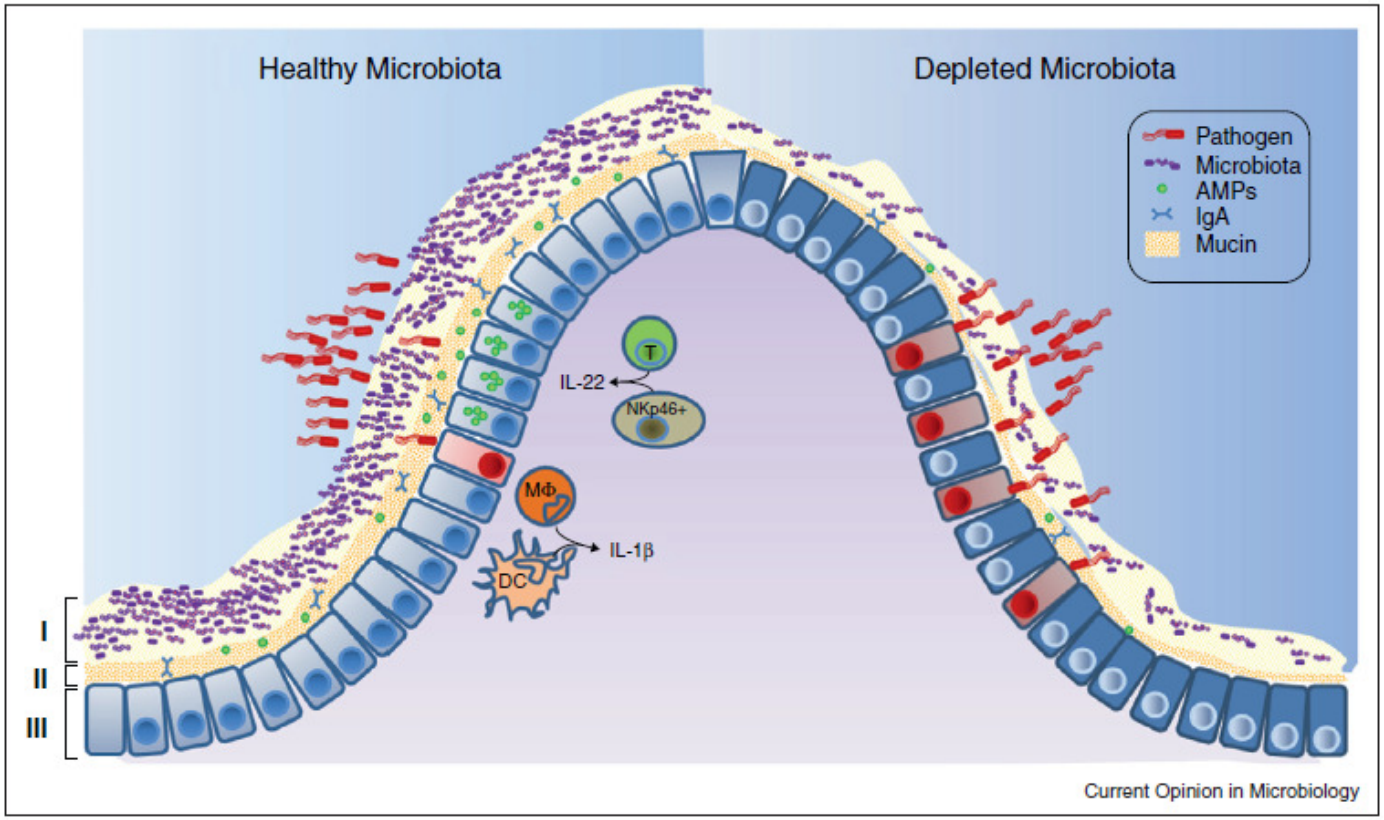
A population-based cohort of placental specimens collected under sterile conditions from **320 subjects** with extensive clinical data was established for comparative 16S ribosomal DNA–based and whole-genome shotgun (WGS) metagenomic studies. **Identified taxa and their gene carriage patterns were compared to other human body site niches, including the oral, skin, airway (nasal), vaginal, and gut microbiomes from nonpregnant controls**.



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

Bray-Curtis (B-C) dissimilarity was calculated using WGS-generated phylum-level abundance of bacteria from each body site, including placental data from this study; gut, vagina, posterior auricular skin, and nasal airways data from the HMP; and vaginal data from previously published gravidae (1–4). The thicker the connecting line, the greater the similarity of the taxonomic profile (Bray-Curtis <0.2). Strong phylumlevel similarity was observed between the placenta and tongue, tonsils, saliva, and subgingival plaque taxonomic profiles. The colors of dots reflect the vicinity of the body sites.

Microbiota and human health



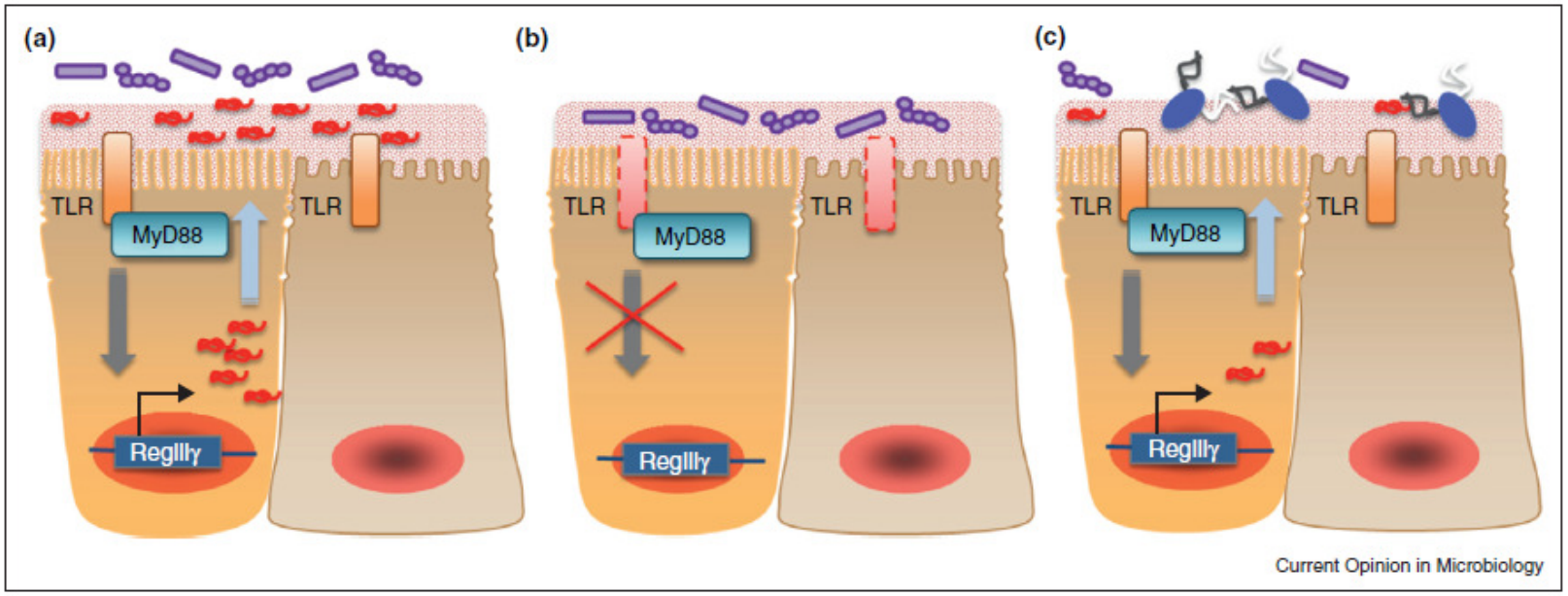
The intestinal microbiota promotes three levels of protection against enteric infection. **(I)** Saturation of colonization sites and competition for nutrients by the microbiota limit pathogen association with host tissue. **(II)** Commensal microbes prime barrier immunity by driving expression of mucin, immunoglobulin A (IgA) and antimicrobial peptides (AMPs) that further prevents pathogen contact with host mucosa. **(III)** Finally, the microbiota enhances immune responses to invading pathogens. This is achieve by promoting IL-22 expression by T cells and NKp46+ cells, which increases epithelial resistance against infection, as well as priming secretion of IL-1β by intestinal monocytes (MΦ) and dendritic cells (DCs), which promotes recruitment of inflammatory cells into the site of infection. In conditions in which the microbiota is absent, such as following antibiotic treatment, there is reduced competition, barrier resistance and immune defense against pathogen invasion.

… certain enteric pathogens are able to outcompete commensal microbes by actively triggering host inflammation which favors pathogen invasion and dissemination.

C. rodentium, *Campylobacter jejuni*, and *Salmonella enterica* serovar Typhimurium (STm) appear to induce inflammation as part of their infectious process, and increasing intestinal inflammation actually promotes disease.

Further, these reports surprisingly demonstrate that **pathogen-induced inflammation** adversely affects the microbiota, **reducing the numbers of beneficial bacteria**, which protect us from infections.

Collectively, there is growing evidence for the notion that pathogens and symbiotic bacteria are engaged in an 'evolutionary combat', with the host serving as the battlefield.



The commensal microbiota primes barrier immunity. Direct stimulation of epithelial Toll-like receptors (TLRs) by commensal MAMPs primes expression of RegIIIγ **(a)**. Production of RegIIIγ is essential to limit microbial contact with host mucosa. As such, defects in TLR function results in deficient RegIIIγ expression resulting in an increased association of commensal microbes with host tissue as well as a heighten risk of infection with enteric pathogens **(b)**. Additionally, reduced TLR stimulation as a consequence of the depletion of the microbiota is sufficient to reduce RegIIIγ expression and render the host susceptible to infection (c).

RegIIIɣ
is a C-type lectin that possesses antimicrobial activity against Gram-positive microbes.

MAMPs
Microbial associated molecular patterns

TLRs
pathogen recognition receptors

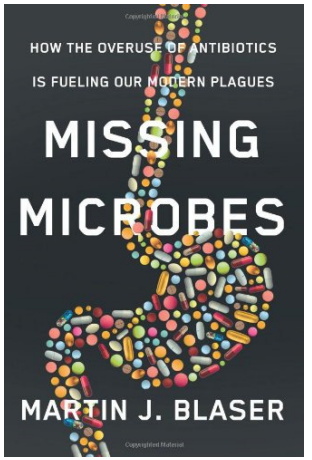
…*the **Missing Microbes*** theory

how the Overuse of Antibiotics Is Fueling Our Modern Plagues

“modern plagues”: obesity, childhood diabetes, asthma, hay fever, food allergies, esophageal reflux and cancer, celiac disease, Crohn’s disease, ulcerative colitis, autism, eczema.

Unlike most lethal plagues of the past that struck relatively fast and hard, these are chronic conditions that diminish and degrade their victims’ quality of life for decades.

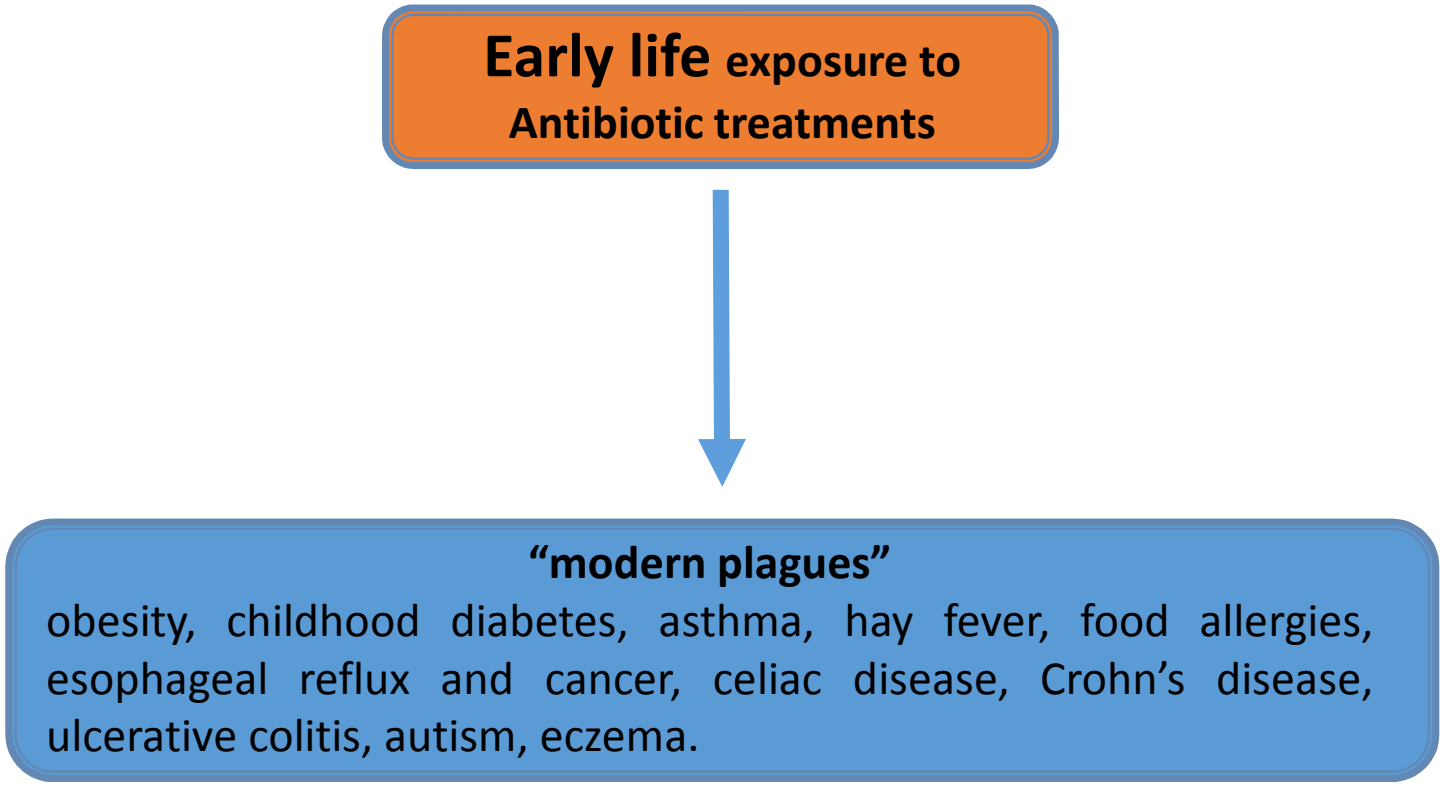
Missing Microbes
Martin J. Blaser (2014)



In US over a million pregnant women are Group B strep-positive and all will get intravenous penicillin during labor to prevent their babies from acquiring Group B strep. **But only 1 in 200 babies actually gets ill from Group B strep acquired from his or her mother. To protect 1 child, we are exposing 199 others to antibiotics. There must be a better way.**
When penicillin had no perceived cost other than occasional allergies, massive overtreatment did not seem like a problem. **But what if changing microbial compositions affect the baby's metabolic, immunologic, and/or cognitive development? … such fears have a real basis.**

In ecology , *biome* refers to the sets of plants and animals in a community such as a jungle, forest, or coral reef. An enormous diversity of species … interact to form complex webs of mutual support. When a keystone species disappears or goes extinct the ecology suffers. It can even collapse.

Each of us host a similarity diverse ecology of microbes that has **coevolved with our species** over millennia./…/ The microbes that constitute your microbiome are generally acquired early in life; surprisingly, by the age of three, the populations within children resemble those of adults. **Together, they play a critical role in your immunity as well as your ability to combact disease. In short, it is your microbiome that keeps you healty. And parts of it are disappearing.**

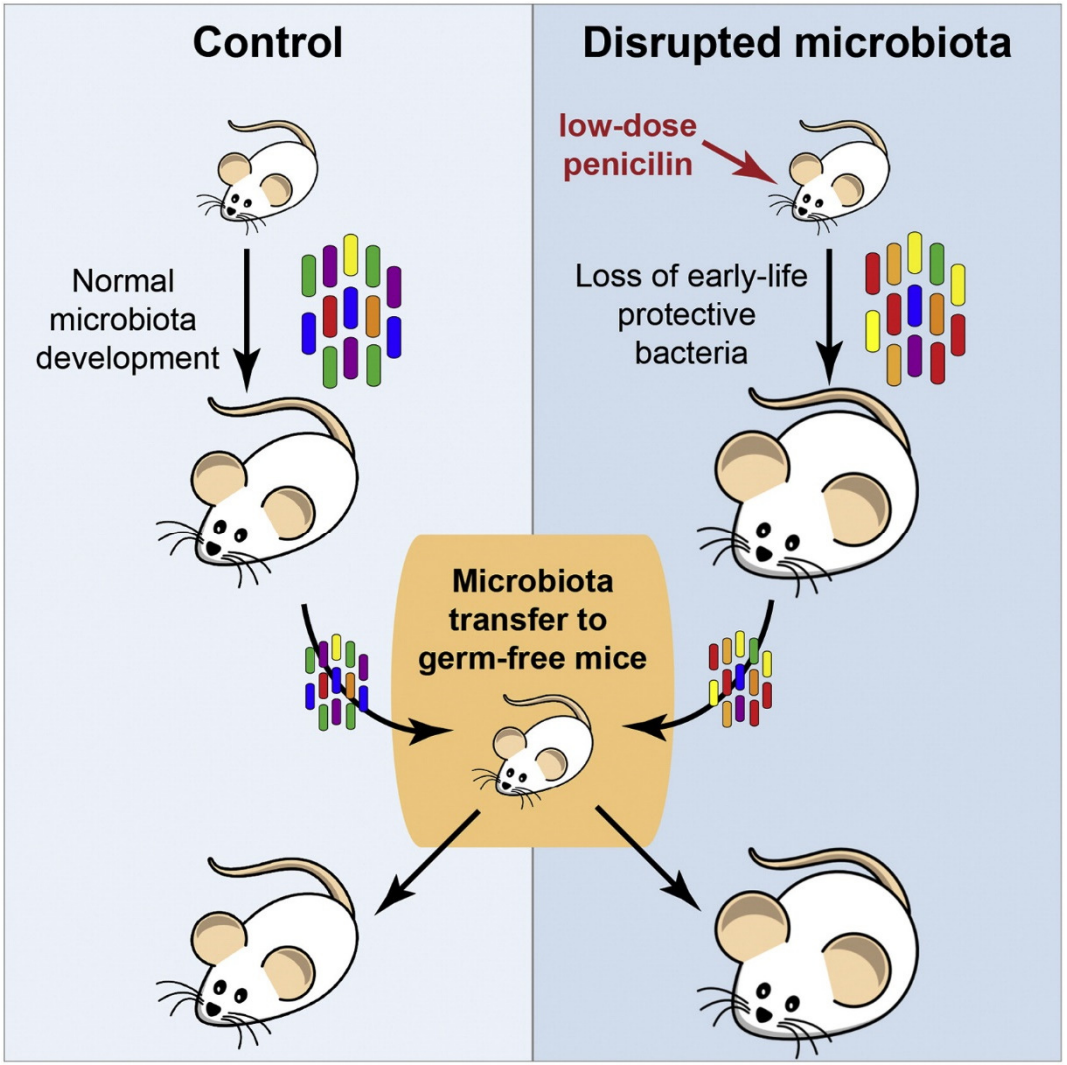

Early life exposure to
Antibiotic treatments
“modern plagues”
obesity, childhood diabetes, asthma, hay fever, food allergies, esophageal reflux and cancer, celiac disease, Crohn’s disease, ulcerative colitis, autism, eczema.

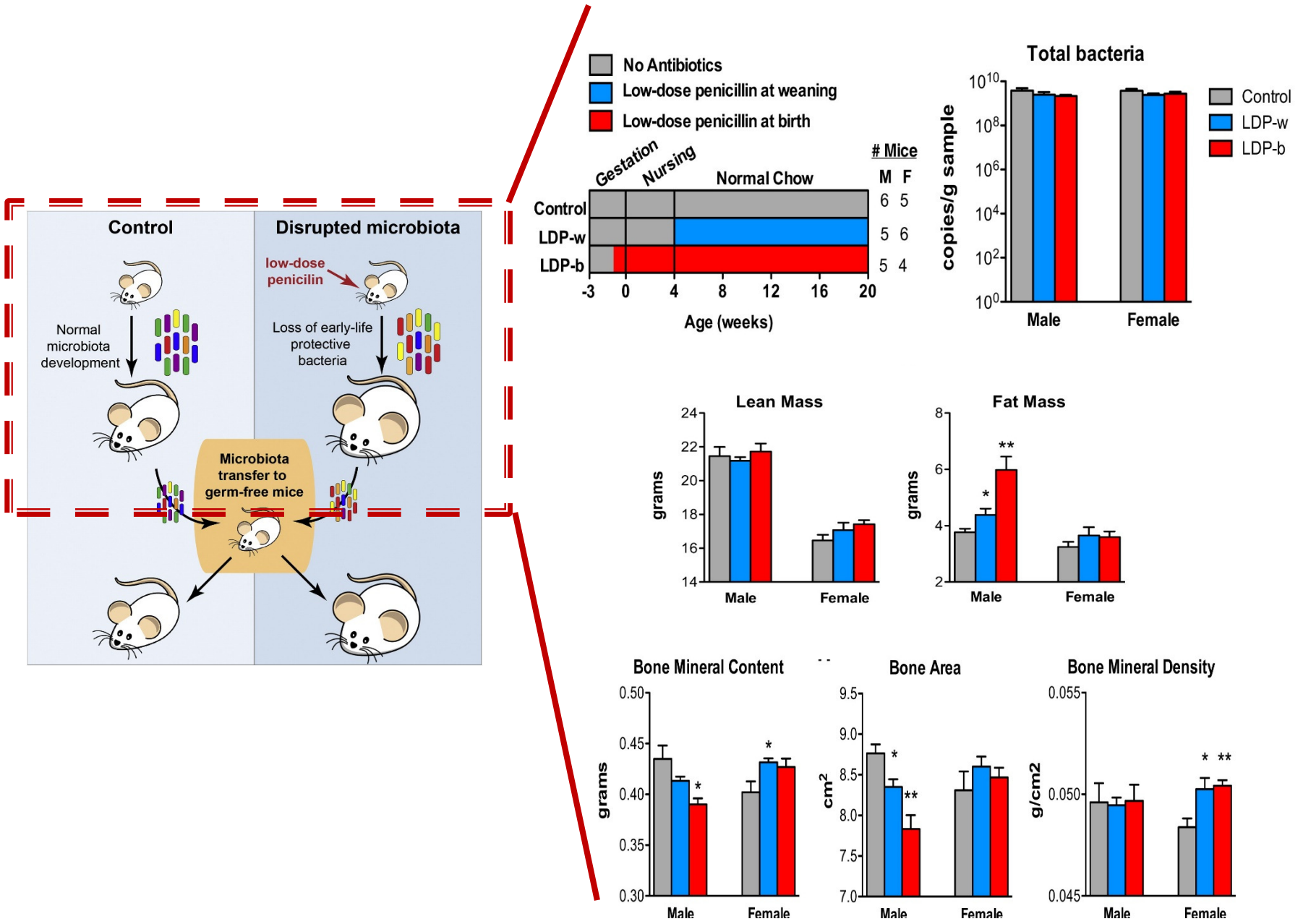
Altering the Intestinal Microbiota during a Critical Developmental Window Has Lasting Metabolic Consequences

Laura M. Cox,[1,2] Shingo Yamanishi,[2] Jiho Sohn,[2] Alexander V. Alekseyenko,[2,3] Jacqueline M. Leung,[1] Ilseung Cho,[2] Sungheon G. Kim,[4] Huilin Li,[5] Zhan Gao,[2] Douglas Mahana,[1] Jorge G. Zárate Rodriguez,[7] Arlin B. Rogers,[6] Nicolas Robine,[8] P'ng Loke,[1] and Martin J. Blaser[1,2,9,*]

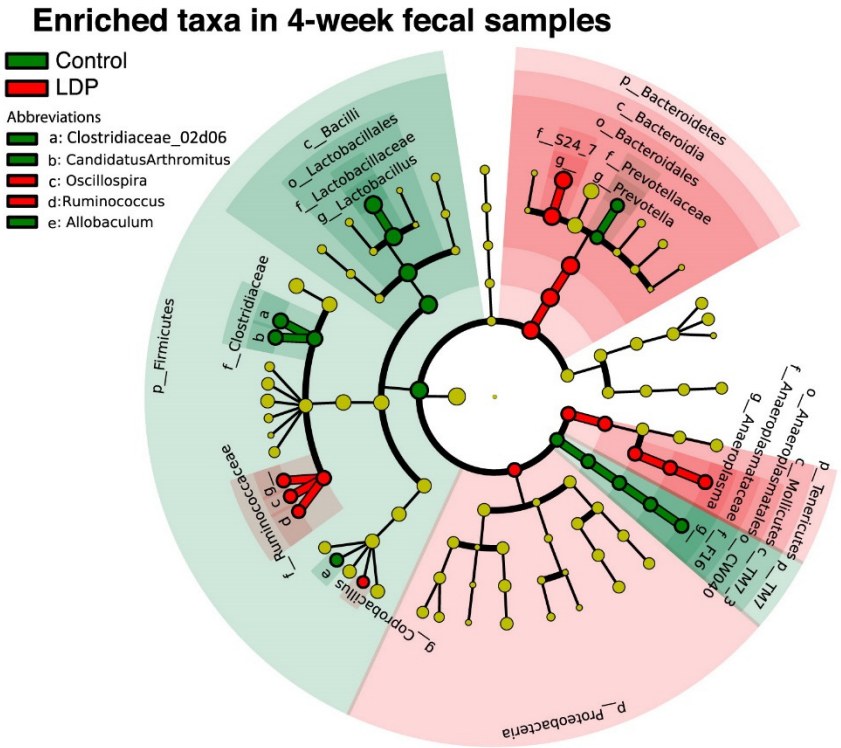
August 2014

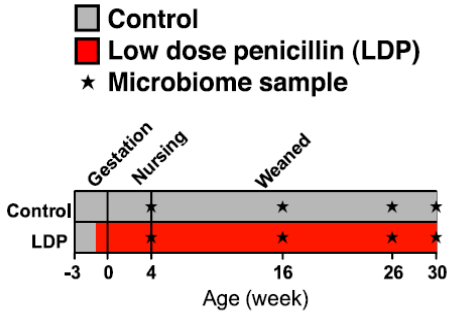
Cell

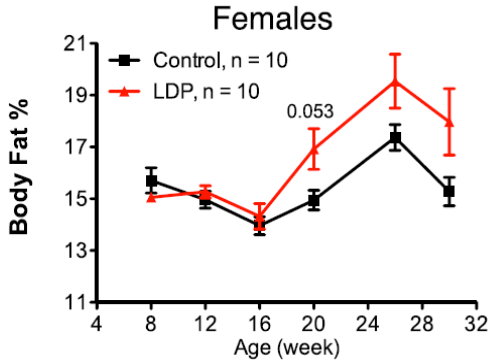


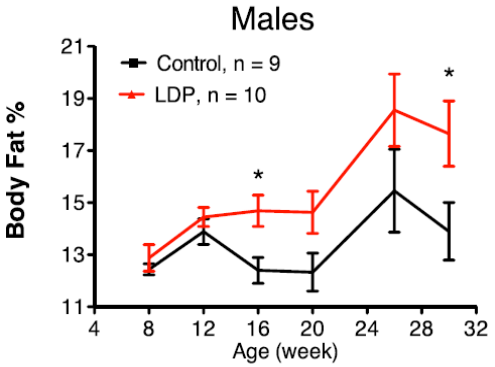

Control
Disrupted microbiota
low-dose penicilin
Normal microbiota development
Loss of early-life protective bacteria
Microbiota transfer to germ-free mice
No Antibiotics
Low-dose penicillin at weaning
Low-dose penicillin at birth
Gestation
Nursing
Normal Chow
Mice
M F
Control 6 5
LDP-w 5 6
LDP-b 5 4
-3 0 4 8 12 16 20
Age (weeks)
Total bacteria
copies/g sample
Control
LDP-w
LDP-b
Male
Female
Lean Mass
grams
Fat Mass
Bone Mineral Content
Bone Area
Bone Mineral Density
cm2
g/cm2

Dynamics of Microbiota and Adiposity Changes over 30 Weeks of Life

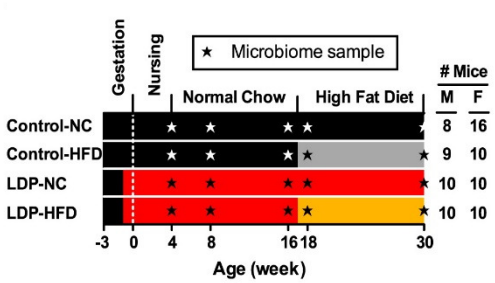


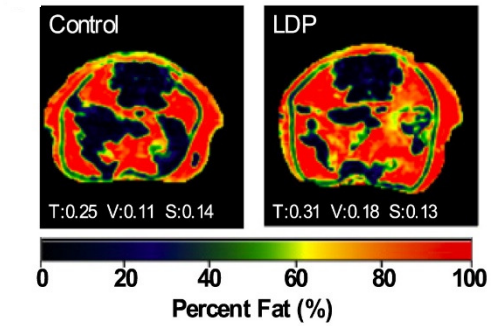


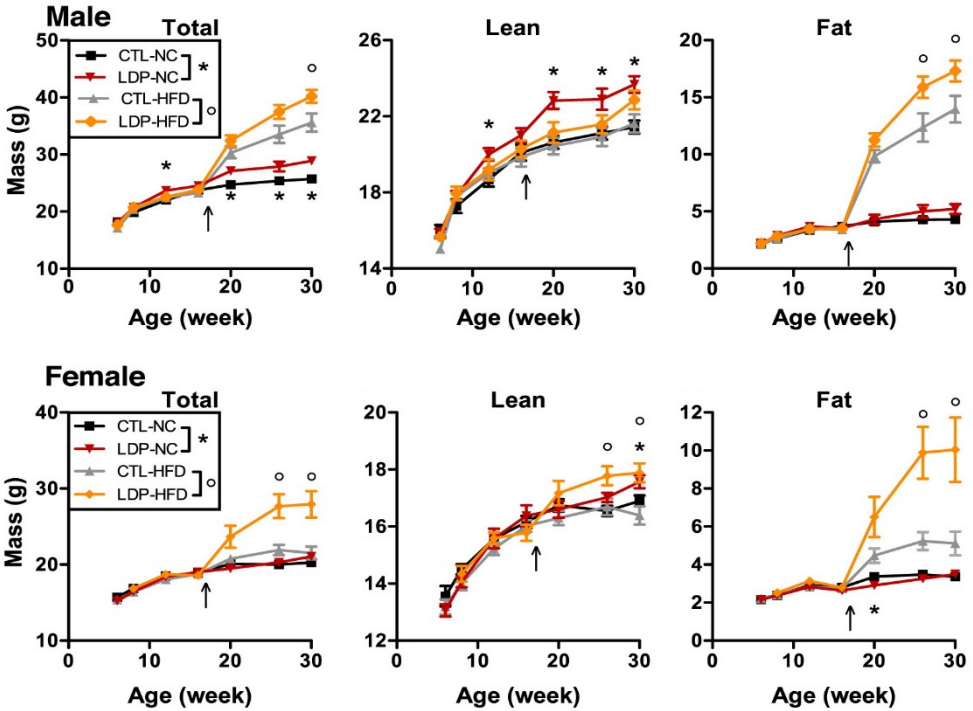


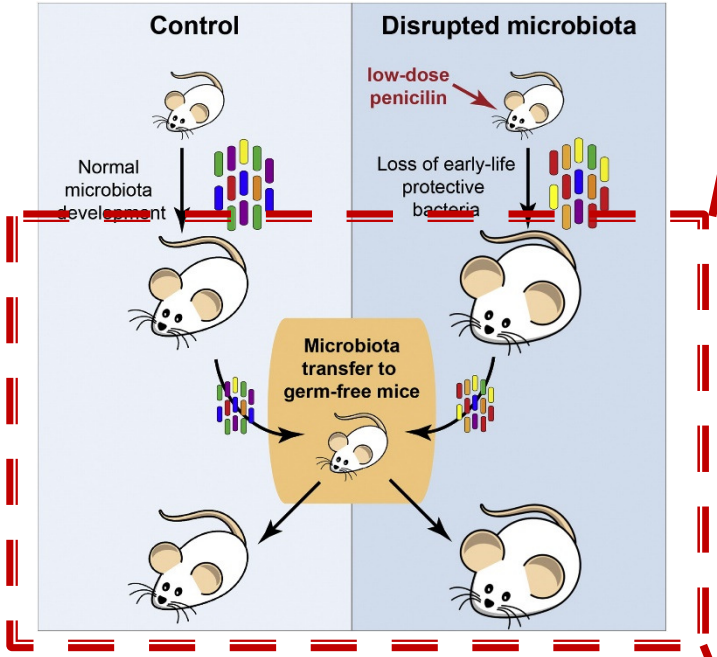


Interaction between Low-Dose Penicillin and Dietary Excess

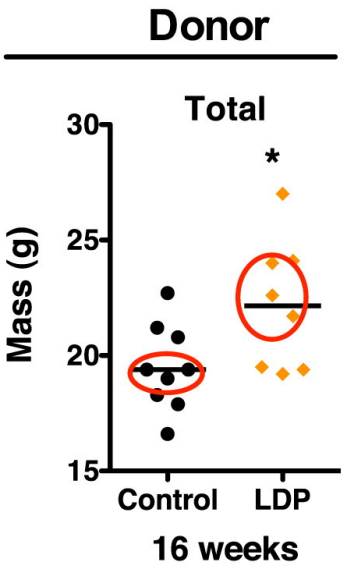


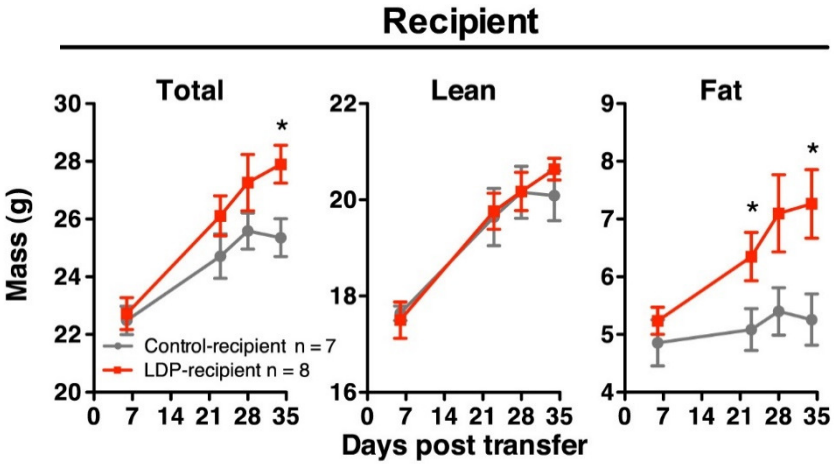






To eliminate the direct effects of penicillin, we transferred cecal microbiota from 18-week-old female control or LDP mice to 3-week-old female germ-free mice.



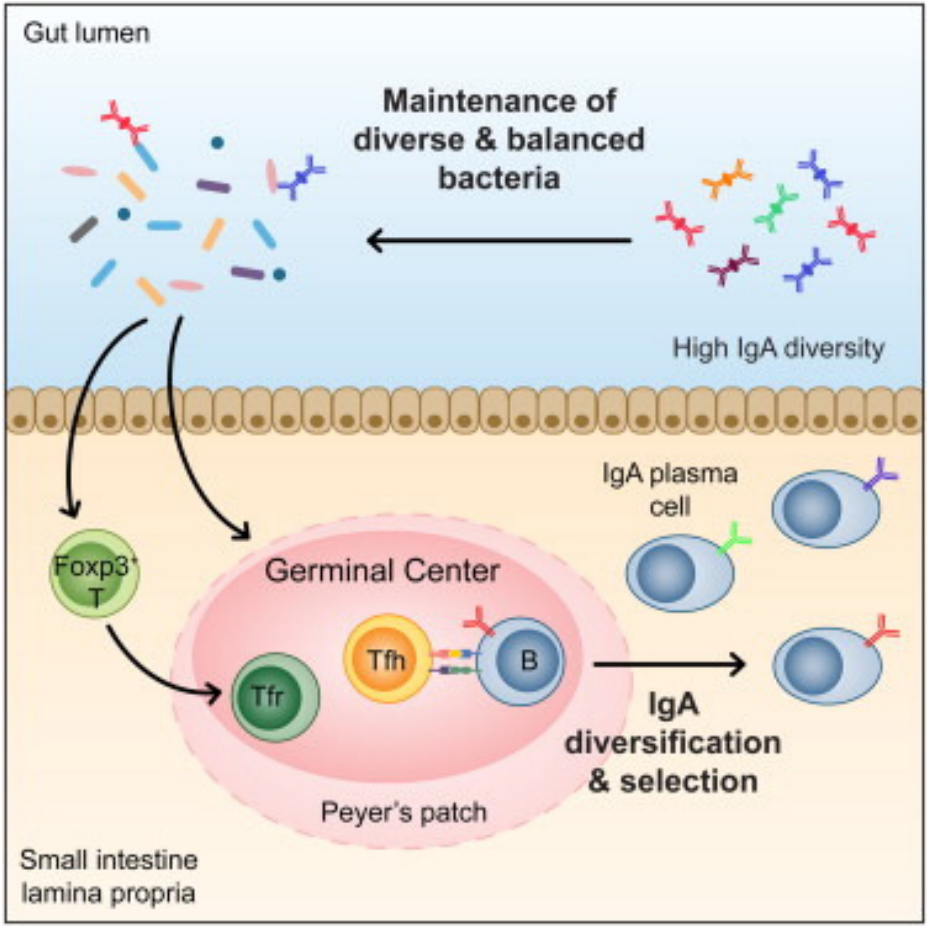


Foxp3^{+} T Cells Regulate Immunoglobulin A Selection and Facilitate Diversification of Bacterial Species Responsible for Immune Homeostasis

Shimpei Kawamoto,[1,6] Mikako Maruya,[1,6] Lucia M. Kato,[1,6] Wataru Suda,[4] Koji Atarashi,[2] Yasuko Doi,[1] Yumi Tsutsui,[1] Hongyan Qin,[1,5] Kenya Honda,[2] Takaharu Okada,[3] Masahira Hattori,[4] and Sidonia Fagarasan[1,*]

Immunity
CellPress
July 2014

The differentiation of Foxp3+ T cells into Tfr cells is required for the IgA's selection in GCs; the amount and quality of IgAs directly influence the diversity and phylogenetic structure of bacterial communities; **rich and balanced Mb induce maturation of the gut immune system** by promoting Foxp3+ T cells and IgAs; and in turn, the Foxp3+ T cells and IgAs, through controlled diversification of stimulatory bacterial species, establish a **self-regulatory loop mediating host-bacterial mutualism**. Thus, it appears that **the adaptive immune system contributes to the maintenance, rather than elimination, of complex microbial communities** that probably enrich the genomic and metabolic capacity of the host, which is required for **gut homeostasis and health**.



Tfr Cells and IgA Join Forces to Diversify the Microbiota

Maria Rescigno[1,*]
[1]Department of Experimental Oncology, European Institute of Oncology, 20139 Milan, Italy
*Correspondence: maria.rescigno@ieo.eu
http://dx.doi.org/10.1016/j.immuni.2014.06.012

Immunity
CellPress
July 2014

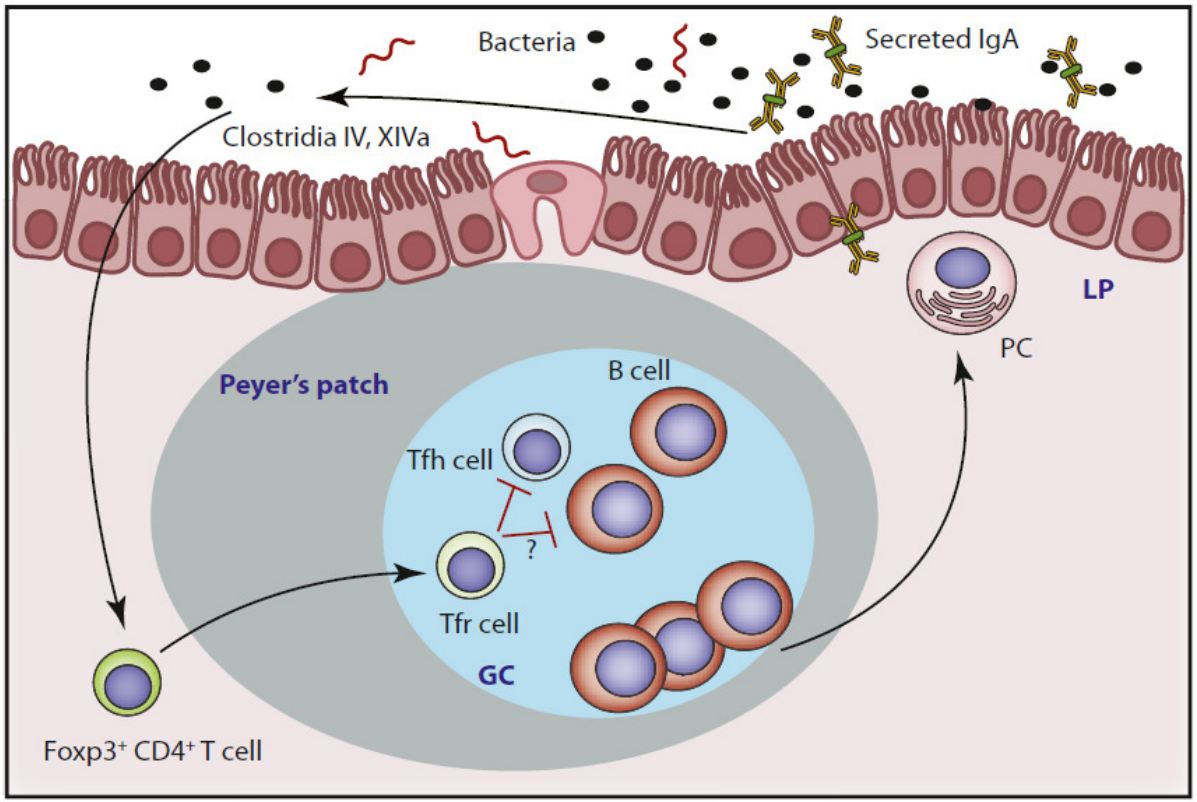
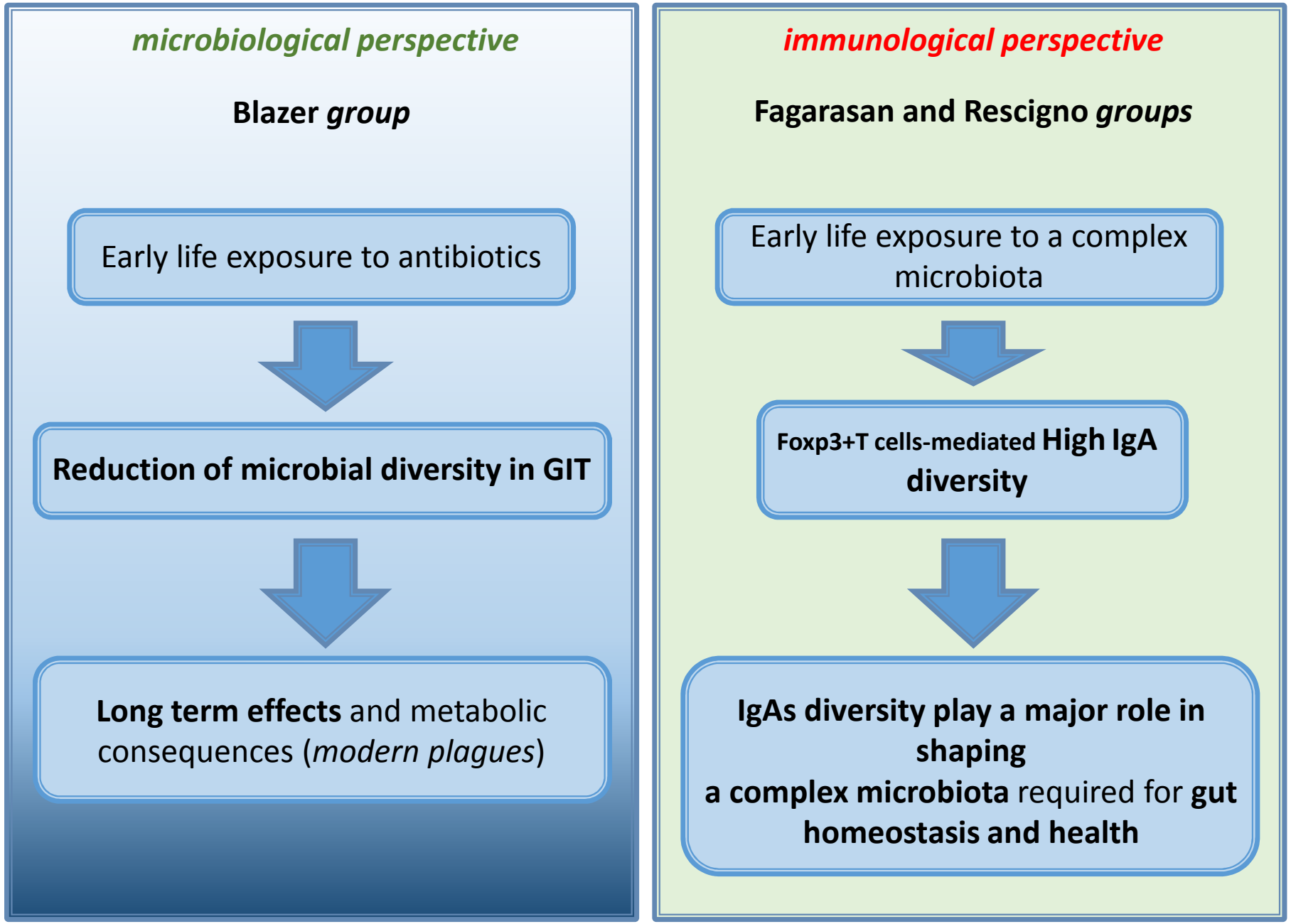


Figure 1. Symbiotic Feedback Loop of IgA Selection and Microbiota Diversification

Foxp3$^+$CD4$^+$ T cells (lower left) give rise to T follicular regulatory (Tfr) cells that control Tfh cell proliferation and the germinal center (GC) reaction. Tfh cells mediate class switch recombination and somatic hypermutation. In the absence of Tfr cells, Tfh cells are uncontrolled and can also induce the proliferation of B cells carrying polyreactive IgA. IgA-B cells proliferate and migrate to the lamina propria (LP) of intestinal villi where they become plasma cells (PCs). Plasma cells release dimeric IgAs that are translocated across epithelial cells through the pIgR. Affinity-matured IgAs foster microbiota diversity, and in particular the expansion of firmicutes (Clostridia cluster IV and XIVa) that in turn drive the development of Foxp3$^+$ T cells, thus initiating a mutualistic feedback loop.

It remains
to be established how
IgAs are
selecting the microbiota.
One speculation
is that **IgAs allow the microbiota to attach to the mucus layer, thus avoiding bacterial wash out in the intestinal bolus and allowing access to the nutrients released by the epithelium**.
Hence, IgAs play a major role in shaping rather than in eliminating the microbiota.


microbiological perspective
Blazer group
Early life exposure to antibiotics
Reduction of microbial diversity in GIT
Long term effects and metabolic consequences (modern plagues)
immunological perspective
Fagarasan and Rescigno groups
Early life exposure to a complex microbiota
Foxp3+T cells-mediated High IgA diversity
IgAs diversity play a major role in shaping
a complex microbiota required for gut homeostasis and health