

...the *Missing Microbes* theory

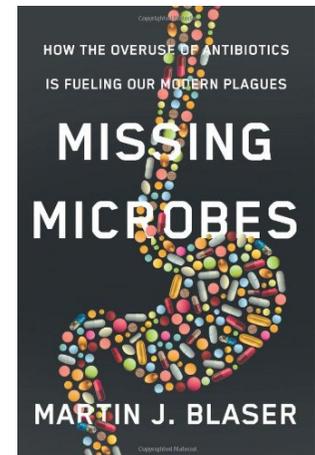
how the Overuse of Antibiotics Is Fueling Our Modern Plagues

“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 similarly 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 combat disease. In short, it is your microbiome that keeps you healthy. And parts of it are disappearing.**

**Early life exposure to
Antibiotic treatments**

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graph TD; A[Early life exposure to Antibiotic treatments] --> B["modern plagues"]; B --- C[obesity, childhood diabetes, asthma, hay fever, food allergies, esophageal reflux and cancer, celiac disease, Crohn's disease, ulcerative colitis, autism, eczema.];
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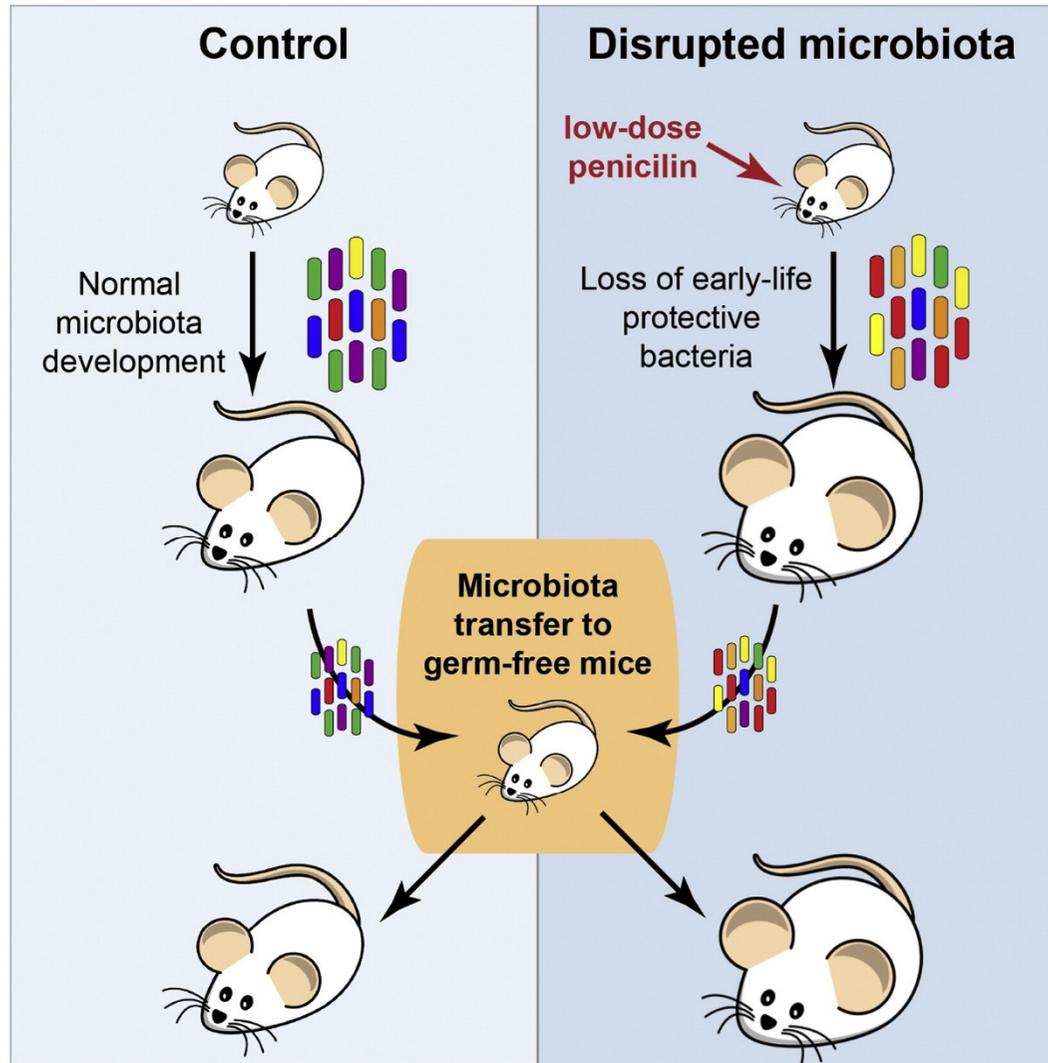
“modern plagues”

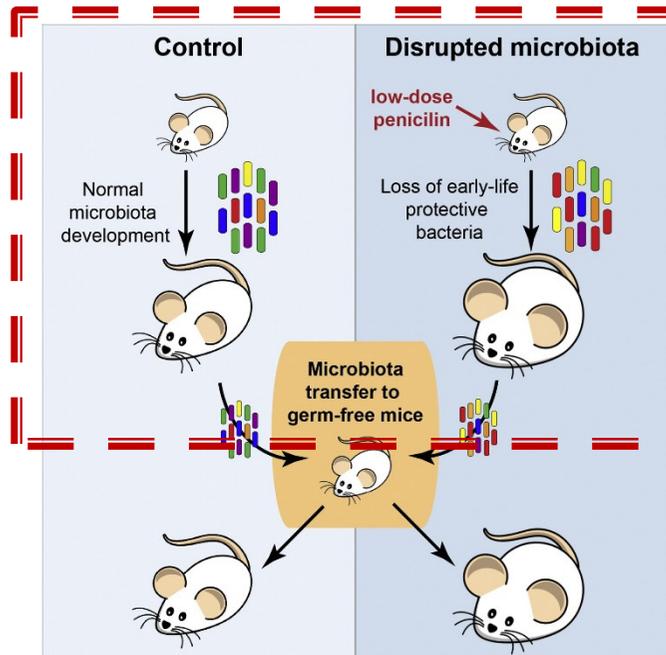
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Altering the Intestinal Microbiota during a Critical Developmental Window Has Lasting Metabolic Consequences

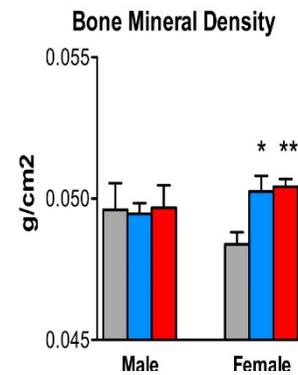
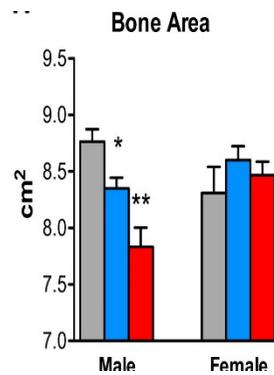
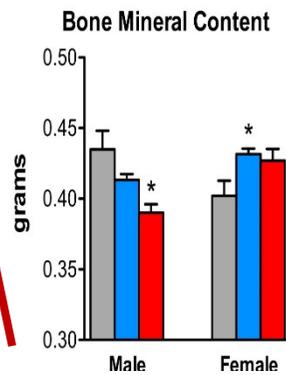
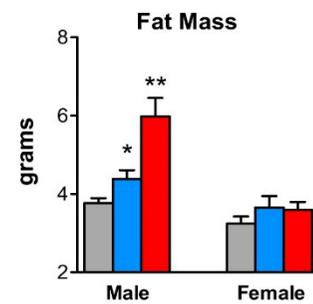
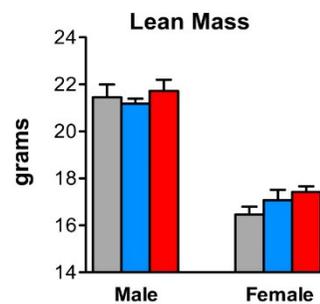
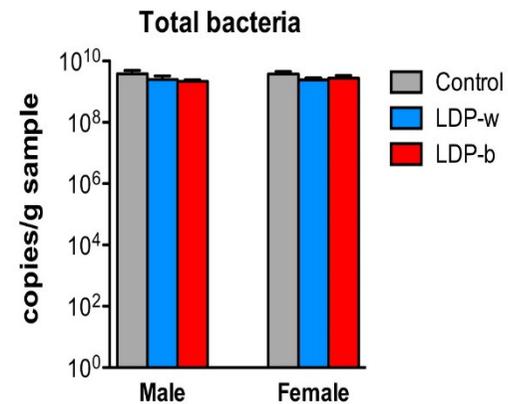
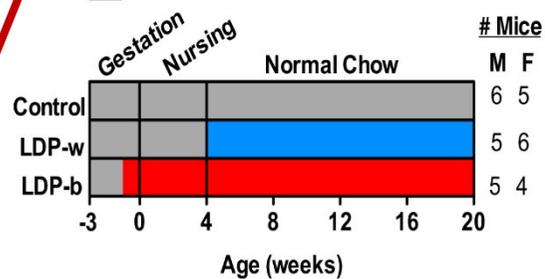
August 2014
Cell

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. Zárata Rodríguez,⁷ Arlin B. Rogers,⁶ Nicolas Robine,⁸ P'ng Loke,¹ and Martin J. Blaser^{1,2,9,*}



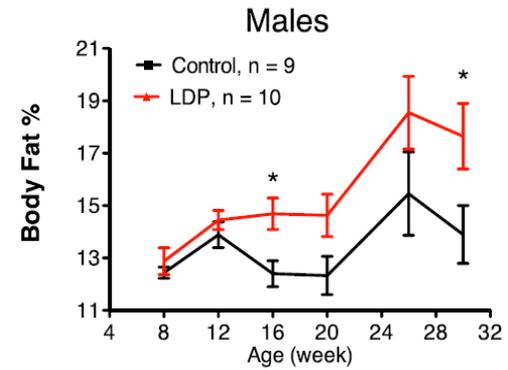
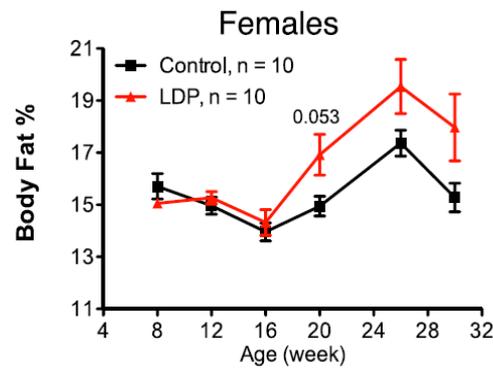
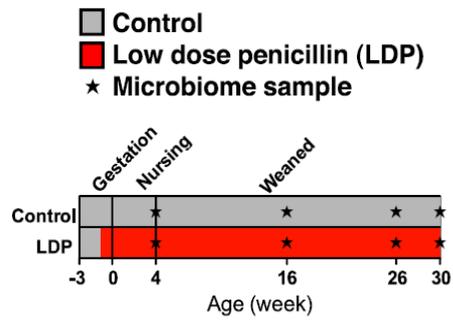
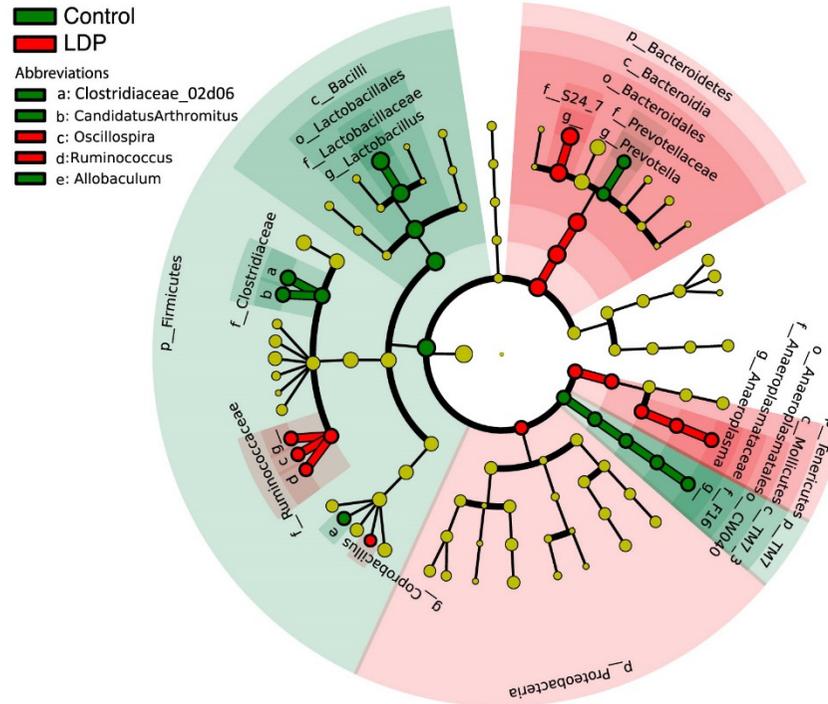


- No Antibiotics
- Low-dose penicillin at weaning
- Low-dose penicillin at birth

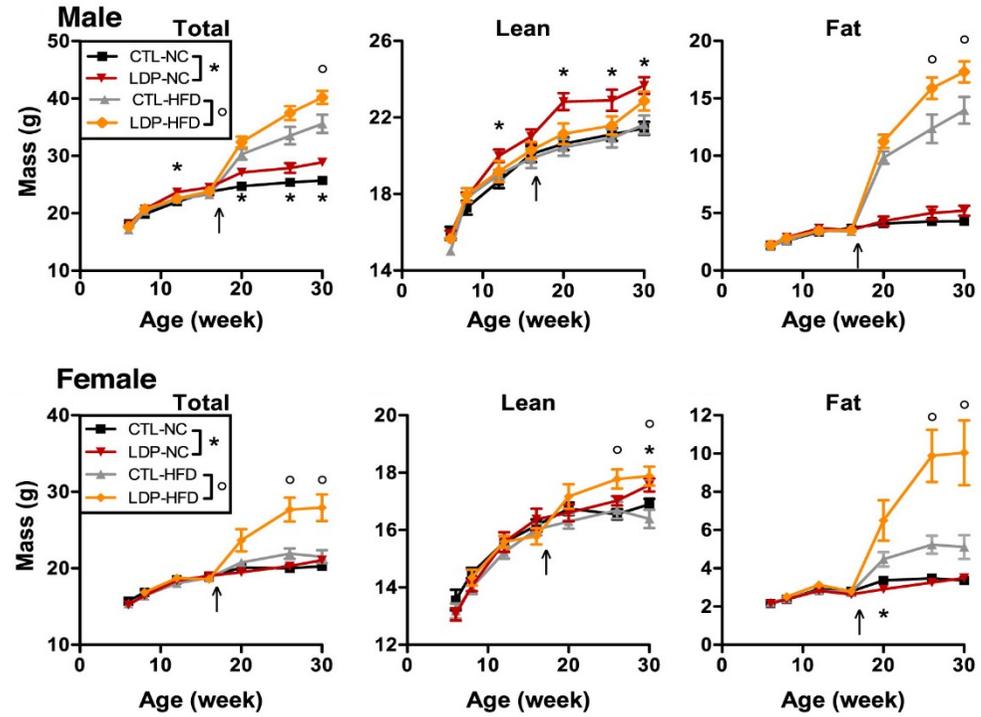
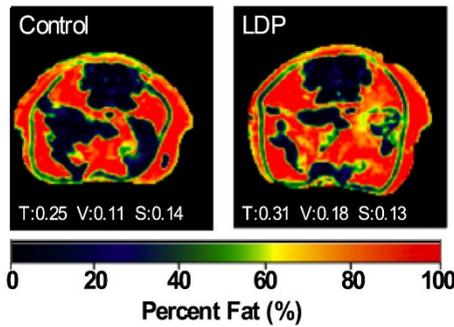
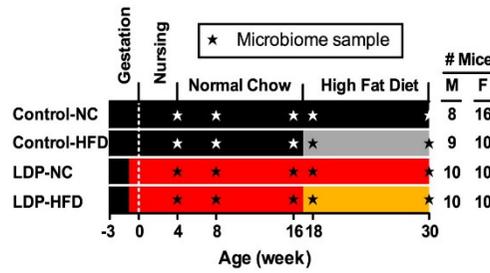


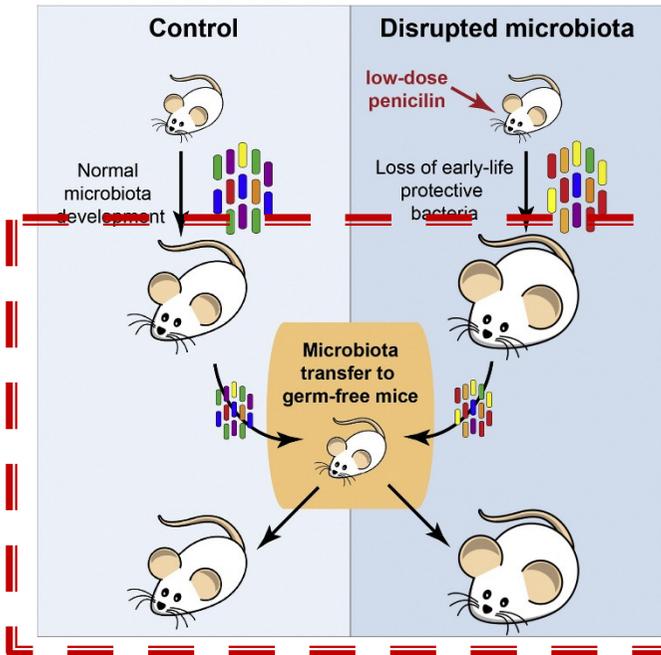
Dynamics of Microbiota and Adiposity Changes over 30 Weeks of Life

Enriched taxa in 4-week fecal samples

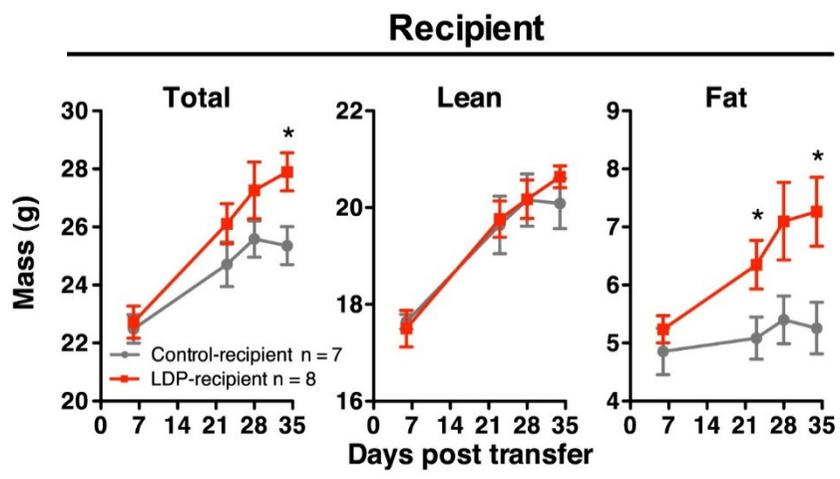
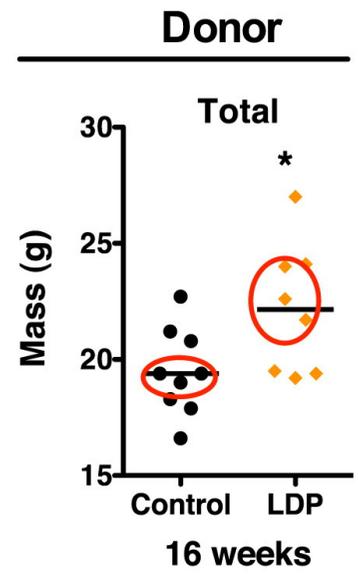


Interaction between Low-Dose Penicillin and Dietary Excess





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.

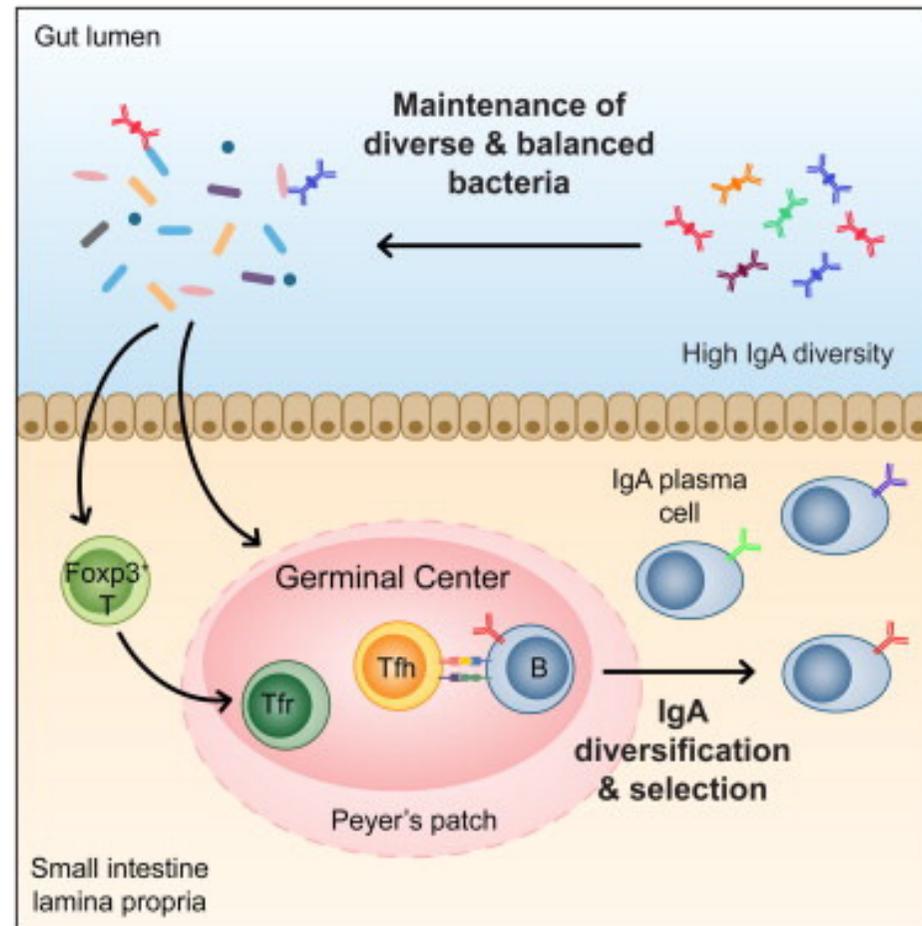


Foxp3⁺ T Cells Regulate Immunoglobulin A Selection and Facilitate Diversification of Bacterial Species Responsible for Immune Homeostasis

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,*}

¹Department 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



July 2014

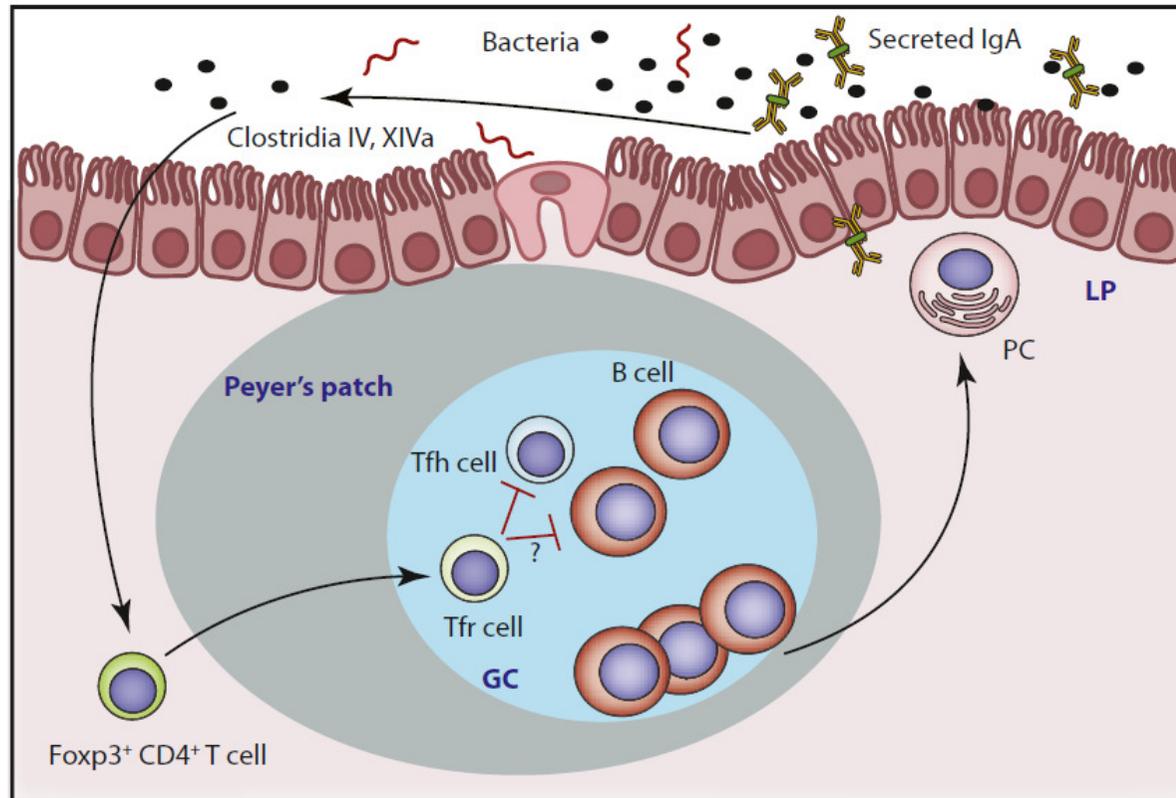


Figure 1. Symbiotic Feedback Loop of IgA Selection and Microbiota Diversification

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