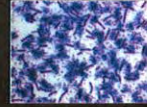


Good Fences Make Good Neighbors: Maintaining Symbiotic Relationships with our Intestinal Bacteria

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The University of Texas Southwestern Medical Center

A Rogues' Gallery of Bacteria



Anthrax



Listeria



Salmonella

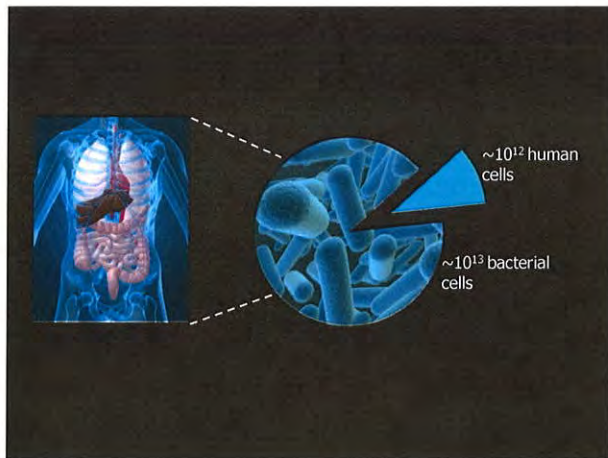
- Public perception:
All bacteria are bad
- Fact: Majority of bacteria
that we are in contact with
every day are beneficial to
human health.




Bacteria and the human body




- Human body contains
about 1 trillion cells
- Approximately 10-100
trillion (!) bacteria reside
in or on the human body
- Most are residents of the
intestine
- Also found on skin, in
nasal passages, etc.




Many animals have beneficial relationships with bacteria



Termite




Gypsy moth




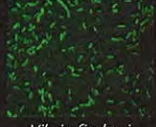
Squid

Euprymna scolopes The Hawaiian bobtail squid



- 1-2 inches long
- Lives off the coast of Hawaii
- Nighttime hunters
- Need stealth in order to capture prey and avoid being eaten themselves
- Since they hunt at night, moon and stars cause them to cast shadows

Vibrio fischeri An ocean bacterium that glows

Vibrio fischeri

- *Vibrio fischeri* is bioluminescent
- Recruited into the squid light organ, where it lives and grows
- Squid is now lit from underneath when out hunting at night....avoids casting a shadow



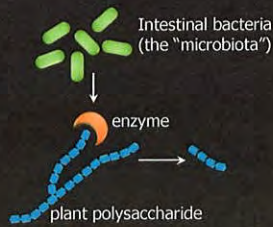
- Humans also harbor symbiotic bacteria, mainly in the intestines
- But we don't glow in the dark, so what are these bacteria doing?



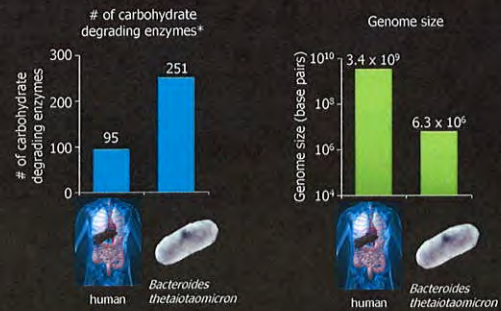
Why do we have 100 trillion intestinal bacteria?

Metabolic functions of the microbiota

- Enhance polysaccharide digestion
- Make an abundance of carbohydrate-degrading enzymes that degrade plant cell wall polysaccharides
- Need many enzymes because of the complexity and variety of structures



Metabolic functions of the microbiota



*Source: The Carbohydrate-Active enZymes (CAZy) Database

Evolution of symbiotic human-bacterial associations

- Mammalian hosts have acquired a readily adaptable, rapidly evolving genome that confers the ability to extract maximum calories from the diet
- Allows flexible adaptations to dietary changes
 - The community is diverse (> 1000 species)

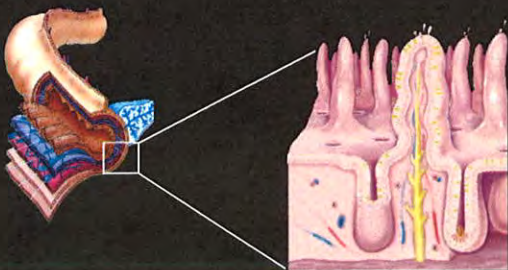


- Metabolic advantages likely drove the evolution of these host-microbial relationships

- Symbiotic relationship
- Still capable of causing disease
 - Inflammation
 - Sepsis

Why don't our intestinal bacteria make us sick?

A thin epithelial layer separates intestinal microbes from our internal tissues



The intestinal epithelium



- Single cell layer
- Primary interface between the microbiota and host tissues
- What molecules protect intestinal surfaces from bacterial invasion?

adapted from T. Ganz (2000), *Nat. Immunol.* 1:99

Germ-free mice



Hooper Lab germ-free mouse colony
UT Southwestern Medical Center

- Microbiologically sterile
- Healthy, breed normally
- Consume 1/3 more calories than conventionally colonized mice

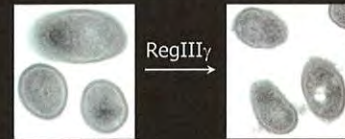
How do intestinal microbiota alter gene expression in the intestinal epithelium?

RegIII γ : a protein antibiotic produced by the intestinal epithelium



Crystal structure of RegIII γ

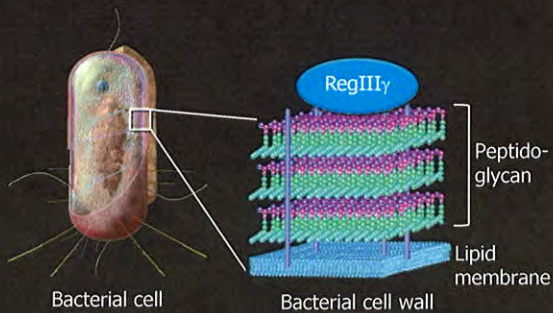
Electron microscopy of *Listeria monocytogenes*, an intestinal bacterium:



How does RegIII γ seek and destroy bacteria?

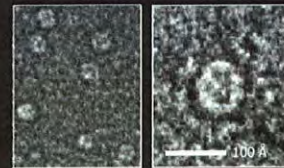
Cash et al., (2006) *Science* 313, 1126-30

RegIII γ seeks out its bacterial targets by binding to peptidoglycan sugars



RegIII γ forms a pore in bacterial membranes

In collaboration with Dr. Qiu-Xing Jiang (Dept. of Cell Biology)



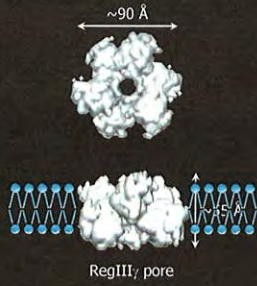
Electron microscopy of RegIII γ in association with artificial liposomes

Pores are RegIII γ hexamers (i.e., 6 RegIII γ molecules per pore)

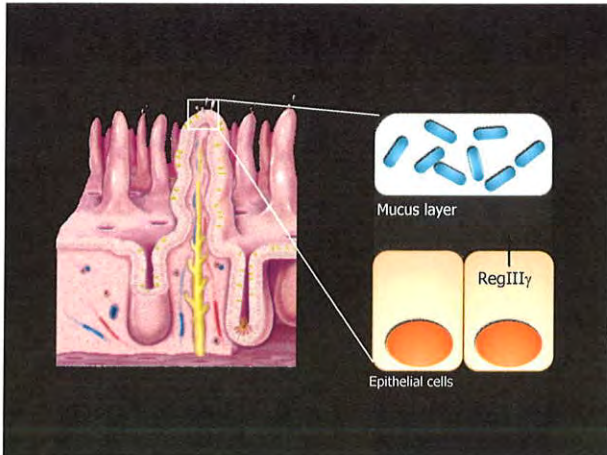
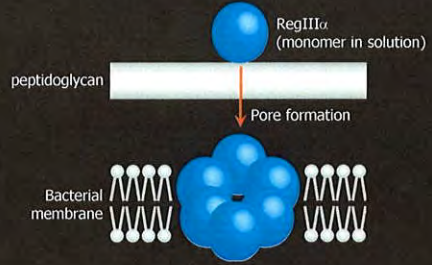
3D model of the RegIII γ pore

In collaboration with Dr. Qiu-Xing Jiang (UTSW Dept. of Cell Biology)

CryoEM
9.2 Å resolution

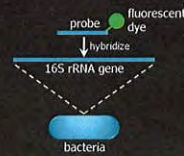


Model of RegIII γ function



Visualizing spatial relationships between the microbiota and the intestinal surface

FISH:
fluorescence in situ hybridization



Bacteria (universal probe)
Intestinal cell nuclei

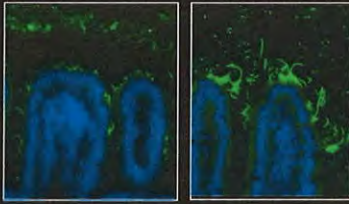
Bacteria are segregated away from the intestinal surface

RegIII γ limits bacterial contact with the intestinal epithelial surface

RegIII γ knockout mouse made in collaboration with Miwako Yamamoto and Ward Wakeland

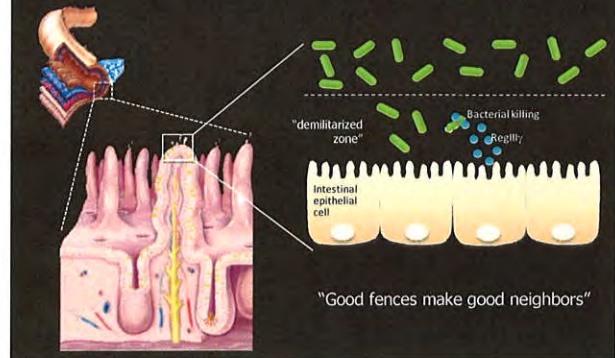
wild-type

RegIII γ ^{-/-}



Vaishnava et al., *Science* 334, 255 (2011)

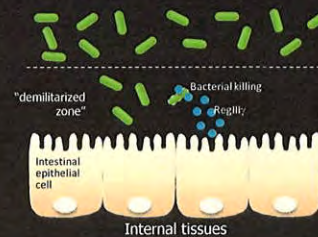
RegIII γ defends intestinal borders



Inflammatory Bowel Disease

- A breakdown in the normally "friendly" host-microbial relationship; results in chronic gut inflammation
 - Ulcerative colitis
 - Crohn's disease
- Afflicts 1 in 600 in the United States
- Root causes are poorly understood
- There is no cure

Can we use RegIII γ as a therapeutic?



- IBD: Increased numbers of bacteria adhering to epithelial cells and possibly invading internal tissues
- Can we deliberately enhance RegIII γ production in IBD patients to reduce the numbers of bacteria that invade tissue and cause inflammation?



Hooper Lab

Collaborators

Ward Wakeland (UTSW Immunology)
Kevin Gardner (UTSW Biochemistry)
Carrie Partch (UTSW Biochemistry)
Jose Rizo-Rey (UTSW Biochemistry)
Qiu-Xing Jiang (UTSW Cell Biology)

Funding

UTSW Endowed Scholars Program
Howard Hughes Medical Inst.
NIH
Burroughs Wellcome
Crohns and Colitis Foundation
Welch Foundation