Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Microbiology

The rest of the story: the microbiome and gastrointestinal infections

Jhansi L Leslie[1] and Vincent B Young [1,2]

Bacterial infectious diseases are studied primarily as a host–pathogen dyad. However it is increasingly apparent that the gut microbial community is an important participant in these interactions. The gut microbiota influences bacterial infections in a number of ways, including via bacterial metabolism, stimulation of host immunity and direct bacterial antagonism. This review focuses on recent findings highlighting the interplay between the gastrointestinal microbiota, its host and bacterial pathogens; and emphasizes how these interactions ultimately impact our understanding of infectious diseases.

Addresses
[1] Department of Microbiology and Immunology, University of Michigan Medical School, Ann Arbor, MI, USA
[2] Division of Infectious Diseases, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI, USA

Corresponding author: Young, Vincent B (youngvi@umich.edu)

Current Opinion in Microbiology 2015, **23**:121–125

This review comes from a themed issue on **Host-microbe interactions: bacteria**

Edited by **David Holden** and **Dana Philpott**

http://dx.doi.org/10.1016/j.mib.2014.11.010

Introduction

Classically, infectious diseases are viewed as a two-way interaction between a host and an invading pathogen. However, recent studies increasingly demonstrate that this perception is an over simplification. Appreciation that most organisms are colonized with distinct polymicrobial communities, collectively termed the microbiota, has lead to a reexamination of the concept of microbes in the context of health and disease [1]. Experiments in germ-free organisms, which lack a microbiota, show that the acquisition of symbiotic microbes is critical for normal development of the host [2,3]. In addition to host development, there is increasing appreciation that the microbiota plays a role in determining susceptibility and outcome of infections (Table 1).

This review focuses on studies exploring interactions between the microbiota and either a host or a pathogen and endeavors to highlight how integration of the microbiota in to the investigation of host–pathogen interactions can ultimately lead to a more complete understanding of infectious diseases.

Host–microbiota interactions: more than the sum of the parts

While it is becoming evident that few, if any, sites within the human body are truly sterile, the gastrointestinal tract is the most densely colonized site in the human body [4,5]. The adult gastrointestinal tract is primarily colonized by anaerobic bacteria that broadly belong to two phyla; Firmicutes and Bacteroidetes [6]. The presence and composition of the gut microbiota are important determinates of host physiology and health, while 'dysbiosis' or an altered gut microbial community is associated with states of disease [7•,8]. Understanding the interplay between the gut microbiota and the host is an important topic of investigation.

Metabolic interactions

The symbioses between a host and associated communities are integral to the physiology of both. At the core of these interactions is metabolism as the gut bacterial community is important to the metabolic potential of the host. While therapeutic doses of antibiotics are known to alter the microbiome, low doses of antibiotics given early in life lead to lasting effects in composition of the gut microbial community [9]. These changes are associated with long-term alterations in host metabolism, which may predispose the host to diet dependent obesity [10].

Host–microbiota metabolism is tightly linked; disruption of the microbiota shifts the gastrointestinal metabolic profile toward one that supports the growth of bacterial pathogens. In the context of *Clostridium difficile* infection, a study correlating colonization resistance to community structure demonstrates that communities that are drastically different in terms of membership can provide resistance to colonization by *C. difficile* [11••]. Rather than the community structure, the commonality between these resistant communities was their metabolic profile. Specifically, the susceptible community had a significant increase in key metabolites utilized by *C. difficile* such as carbon sources and primary bile acids like taurocholate.

Bile acid metabolism is a process that depends on both the host and the microbiota. The host synthesizes and secretes primary bile acids. Bile acids not actively recovered in the distal ileum are deconjugated by the colonic microbiota into secondary bile acids which are then

Table 1

The effect of the microbiome on infection

Type of interaction	Pathogen	Outcome of infection	Reference
Direct			
Production of bacteriocins	*C. perfringens* *C. difficile*	Decreased colonization	[35,36]
Competition for nutrients	*S.* Typhimurium	Decreased colonization	[37•]
Cross-feeding (e.g. H_2, Salic acid)	*S.* Typhimurium *C. difficile*	Increased colonization	[38,39]
Conversion of host derived metabolites (e.g. Bile acids)	*C. difficile*	Decreased colonization	[11••]
Indirect			
Production of immunomodulatory molecules (e.g. butyrate)	–	–	[16,17,19•]
Stimulation of hematopoiesis	*L. monocytogenes*	Increased myelopoiesis and protection from systemic infection	[21•]

absorbed by the host in the colon (the role microbiota and bile acid metabolism is reviewed here [12]). However, antibiotic mediated alterations of the microbiota disrupts host–microbiota bile acid metabolism leading to increased levels of primary bile acids in the large bowel, setting up an advantageous environment for germination of *C. difficile* spores [13]. The importance of bile acids in the pathogenesis of *C. difficile* is underscored by findings that suggest that *Clostridium scindens*, a bacterium that can convert primary to secondary bile acids, partially restores colonization resistance to *C. difficile* [14,15].

Regulation of host response

Many aspects of host immune function are regulated by signals produced by the microbiome, such as metabolites. Butyrate, one short chain fatty acid produced by members of the microbiota, facilitates the development of localized immunity in the form of populations of peripheral anti-inflammatory T regulatory cells [16,17]. The immunomodulatory aspect of T_{regs} has been shown to play a role in persistent bacterial infections [18]. Since phylogenetically diverse members of the microbial community are able to elicit the differentiation of peripheral T_{regs}, this suggests that there is likely functional redundancy in composition of the gut microbial communities, such that different community structures provide the same function [19•,20].

In addition to altering local immune response, microbiome-derived signals regulate immune function at primary immune sites [21•]. In mice, the presence of a gut microbial community enhances levels of myelopoiesis. Compared to germ-free or antibiotic treated mice, mice with intact microbiota had increased myeloid cells and were protected from systemic infection with the pathogen *Listeria monocytogenes*. Notably in this model, myelopoiesis was only achieved in the context of colonization with live bacteria. Administration of MAMPs or SCFAs was not sufficient to restore myelopoiesis in germ-free mice to levels comparable to mice with intact communities. This suggests that diverse bacterial signals modulate host immunity, tuning the immune system to respond to a given situation such as bacterial or viral infections [22,23].

While microbial products alter the host, changes in host physiology can also alter the microbiota. Due to the abundance of anaerobes in the intestines it has been assumed that the lumen is strictly anaerobic. Characterization of the structure of the GI tract has shown that there are distinct communities associated with the mucosa compared to the lumen [24]. These distinct community structures are arranged in concordance with the radial oxygen gradient that exists within the gut [25,26••]. Microbial communities are not immutable and changes in oxygen maybe a key driver. Notably, exogenous oxygen exposure such as hyperbaric oxygen therapy can shift the composition of the fecal microbiota [26••]. Inflammation can also alter oxygen homeostasis in the gut via the release of reactive oxygen and nitrogen species. While obligate anaerobes are incapable of detoxifying reactive oxygen species, some facultative anaerobes thrive in the inflamed gut [27]. Bacteria from the family Enterobacteriaceae, such as *Escherichia coli* are able to utilize host-derived nitrate as an alternative electron receptor during anaerobic respiration thereby gaining a competitive edge to expand within the gut [28]. Interestingly, antibiotic therapy, a risk factor for infections by non-typhoid *Salmonella*, decreases colonization resistance to *E. coli* by increasing inflammation in the gut [29]. Thus the interplay between a host and its microbiota is central to a host's predisposition to infection.

Pathogen–microbiota interactions: context matters

Another critical function of the microbiota is colonization resistance, or the capacity of the microbes that colonize our body to exclude pathogens. While some aspects of colonization resistance are mediated by bacterial modulation of immune response, bacteria–bacteria interactions also play a role. Unraveling how these direct bacterial