



Review

Immune-directed support of rich microbial communities in the gut has ancient roots

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ABSTRACT

The animal gut serves as a primary location for the complex host–microbe interplay that is essential for homeostasis and may also reflect the types of ancient selective pressures that spawned the emergence of immunity in metazoans. In this review, we present a phylogenetic survey of gut host–microbe interactions and suggest that host defense systems arose not only to protect tissue directly from pathogenic attack but also to actively support growth of specific communities of mutualists. This functional dichotomy resulted in the evolution of immune systems much more tuned for harmonious existence with microbes than previously thought, existing as dynamic but primarily cooperative entities in the present day. We further present the protochordate *Ciona intestinalis* as a promising model for studying gut host–bacterial dialogue. The taxonomic position, gut physiology and experimental tractability of *Ciona* offer unique advantages in dissecting host–microbe interplay and can complement studies in other model systems.

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1. Introduction

Complex communities of microbes colonize nearly every epithelial surface of animals, including mucosal epithelial surfaces that become highly valued locales for microbial attachment and growth immediately upon birth (Neish, 2014). The gastrointestinal (GI) system, in particular, has emerged as a prime example of an epithelium-lined organ that sustains an abundant and complex

community of closely associated, generally species-specific microbiota, which can exert enormous physiological influence on animal hosts (Savage, 1977; Falk et al., 1998; Neish, 2009; Lozupone et al., 2012; Yatsunenko et al., 2012). The host–microbe interactions at the surface of the epithelium are benign or beneficial as a whole and generally are tolerated by the host, although pathogenic breach of the epithelium can result in strong host immune responses. Understanding the multiple types of microbe–host interactions in the gut may provide insight as to the types of selective pressures that spawned the emergence and elaboration of the immune systems of metazoan animals.

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From an ecological standpoint, the alimentary canal (or GI system) is an external environment that passes through animals, generally via two openings (i.e., in and out). In the simplest terms, this canal evolved to deliver water and nutritional sustenance to an increasingly complex and generally sterile body. Although this function is essential for life in nearly all animals, such a direct juxtaposition of substances from the external environment inside the body nevertheless poses an enormous challenge for the host. Within the gut tube, the host encounters an essentially continuous microbiological load that can include pathogens as well as a myriad of either beneficial or innocuous species. This complexity is enhanced by the presence of distinctly differentiated compartments within the gut tube, each with potentially distinct and permanent commensal communities (Faust et al., 2012; Koren et al., 2013; Segata et al., 2012). One often studied example is the human colon, which contains several compartments, including the often controversial cecal appendix, and hosts up to 100 trillion (10^{14}) bacterial cells at any given time, in effect generating orders of magnitude greater intraorganismal genetic complexity than that of the host genome itself (Andersson et al., 2008; Costello et al., 2009; Eckburg et al., 2005; Gill et al., 2006; Human Microbiome Project, 2012; Ley et al., 2006; Macfarlane and Macfarlane, 1997; Savage, 1977). Reduced diversity and/or shifts in the composition of microbiota among different epithelial compartments can dramatically affect homeostasis and host health, in some cases promoting infections that endanger host wellbeing (Chan et al., 2013; Fallucca et al., 2014; Luckey et al., 2013; Mondot et al., 2013; Petrof et al., 2013; Power et al., 2014; Shim, 2013). Further, in mammals, the direct epithelial dialogue with bacteria is generally critical for immune maturation (Cebra, 1999; Cebra et al., 1998; Sommer and Backhed, 2013), and often can provide tolerogenic signals to the host (Lee, 2009; McFall-Ngai et al., 2013; Shin et al., 2011). It might seem at the outset that the monumental task of managing the complex microbial milieu of the alimentary canal would be performed by a multilayered system of immune attack that is effectively repelling an ever changing array of invaders intent on circumventing its defenses. Indeed, the gut of animals evolved so that its epithelial surface is fully immunocompetent, serving as a barrier to potential pathogens while simultaneously recognizing and communicating with microbes in both the lumen (inside) of the gut and the intra-organismal tissue that is generally sterile. [e.g., (Bosch et al., 2009; Duerkop et al., 2009; Duerr and Hornef, 2012; Pott and Hornef, 2012)]. This function is carried out in large part by immunocytes, which migrate to tissue spaces adjacent to the epithelial barrier early during development. In some species, these immunocytes form dense communities and produce an outward appearance of a defense system poised to attack, analogous to an army preparing to repel an invasion. In vertebrates, this tissue space is well recognized for the presence of gut-associated lymphoid tissue (GALT), one of the most prominent immune tissues (Pearson et al., 2012; Shields, 2000). Whereas certain aspects of host immunity certainly do involve these aggressive characteristics, an increasing amount of emerging data indicate that the system as a whole may be much more tuned for harmonious existence with the microbes it encounters and may have evolved such relationships in this cooperative manner (Eberl, 2010; Equileor and Ottaviani, 2011; Loker, 2012; Nyholm and Graf, 2012; Thomas and Parker, 2010).

In this review, we use an immune-phylogeny approach (Fig. 1) to argue that host defense systems have met the challenge of managing microbial communities by evolving strategies that not only directly protect the host's tissue from pathogenic infection but also actively support the growth of specific communities of microbes such that the maturation of these barriers becomes as much, if not more so, of a "welcome wagon" for mutualists in the lumen as opposed to a buildup for war against pathogens. This dichotomy

serves to protect against pathogenic invasion, to ensure proper nutritional sustenance to the host and to train the host's immunological systems. The host-microbial dialogue, as part of the metaorganism or holobiont (Bosch and McFall-Ngai, 2011; McFall-Ngai et al., 2013; Rosenberg et al., 2010), has helped shape the evolution of gut immunity and exists as a continually dynamic but primarily cooperative system in the present day. Furthermore, we present the concept that protochordates, such as the tunicate *Ciona intestinalis*, can serve as unique and highly informative models for defining sets of chordate rules for host-bacterial dialogue in the gut. These organisms provide experimental advantages based on both their taxonomic position and specific gut physiology, and, when compared to vertebrates, can offer fascinating insights into the evolution of host-microbe relations in the gut.

2. Simplest epithelium

The most basic and phylogenetically conserved interactions between complex metazoan hosts and the microbial world occur across epithelial barriers (Fig. 2A). *Hydra sp.* are solitary freshwater Cnidarians with a simple body architecture consisting of a thin gelatinous mesoglea separating an internal endoderm and external ectoderm (Fig. 2B). They have become an indispensable model system for defining the origins of the most basic interactions across epithelial barriers (Augustin et al., 2012; Bosch, 2013). Distinct bacterial communities have been shown to colonize the epithelium of two *Hydra* species cultured under identical laboratory conditions; the microbial communities observed are representative of those identified in *Hydra* isolated from the wild (Fraune and Bosch, 2007). These observations constitute the first compelling evidence that even the simplest of animals maintain species-specific microbial communities and give rise to several questions: What regulates these bacterial communities? Could it be that ecological factors at the surface of the epithelium such as nutrient composition and pH create conditions that favor some microbial communities over others? Alternatively, does host immunity play a much more specific and active role in defining the communities, and if so, could genetic factors outweigh environmental influences? Further insight into the mechanisms affecting this unexpectedly high degree of selection can be gained by considering several key observations.

First, in experiments lasting more than 15 weeks, colonization of the epithelial surface of *Hydra* was noted to occur in reproducible stages (Franzenburg et al., 2013a). Both experimental and mathematical concepts were applied to demonstrate that colonization is controlled first by competitive interactions among diverse bacteria for access to the host surface and resources. The initial colonization of the tissue appears to prime the response, which matures over some defined period of time. The result is reduced diversity of bacterial communities as well as a reduction in variation in the abundance of certain groups in a process that is influenced by host-derived factors. A key feature of the *Hydra* system (but unlike some other Cnidarians) is the apparent lack of mobile phagocytic cells. Microbial sensing in this species is mediated exclusively by the epithelium and involves the nuclear factor kappa B (NF- κ B), Toll-like receptor (TLR), and Myd88 signaling cascades (Bosch et al., 2009). Preliminary sorting of bacteria apparently is carried out by diverse antimicrobial peptides (AMPs) that influence composition of the microbiota from the onset of development onwards (Franzenburg et al., 2013a,b; Fraune et al., 2010). The association of stable microbial communities is governed by epithelial homeostasis and is influenced by the physical process of cellular turnover (Boehm et al., 2012; Bosch, 2013; Fraune et al., 2009). In mammals, for comparison, stem-cell guided gut epithelial turnover helps to promote not only healing of injured

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