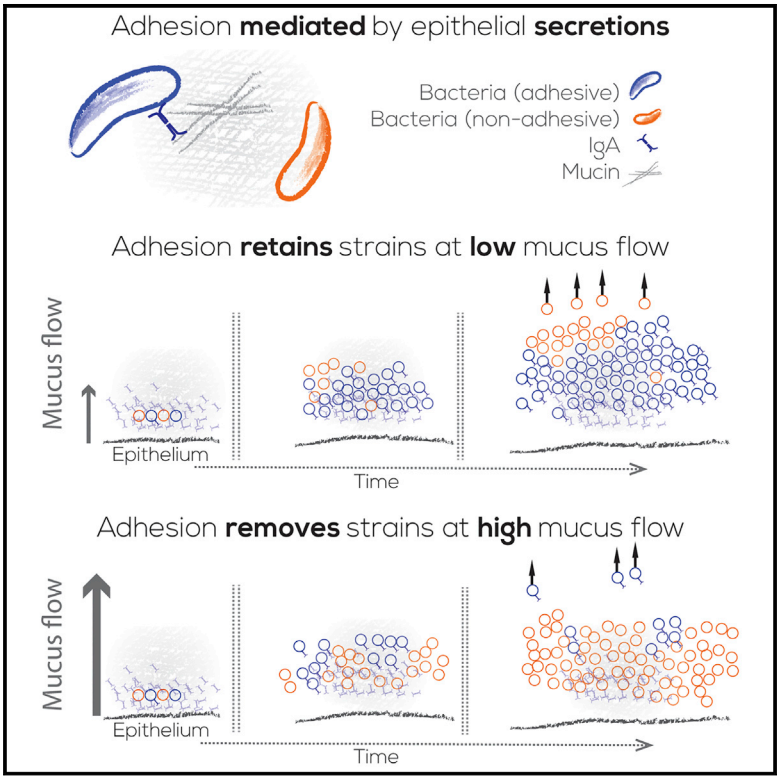
Cell Host & Microbe

Host Selection of Microbiota via Differential Adhesion

Graphical Abstract



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In Brief

Hosts organisms should benefit greatly from controlling microbiota composition, though little is understood of the potential for such control. Here, McLoughlin, Schluter et al. use individual-based modeling to show how a host can select for or against particular microbes by controlling the production and release of adhesive molecules from epithelial surfaces.

Highlights

- Adhesive molecules produced by a host can select for specific microbes
- Selective adhesion can maintain even disadvantaged microbes through refugia creation
- Changes in mucus flow, with adhesion, can select for and against specific microbes
- Candidate molecules for this function are mucus glycans and immunoglobulin A

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Theory

Host Selection of Microbiota via Differential Adhesion

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SUMMARY

The host epithelium is the critical interface with microbial communities, but the mechanisms by which the host regulates these communities are poorly understood. Here we develop the hypothesis that hosts use differential adhesion to select for and against particular members of their microbiota. We use an established computational, individual-based model to study the impact of host factors that regulate adhesion at the epithelial surface. Our simulations predict that host-mediated adhesion can increase the competitive advantage of microbes and create ecological refugia for slow-growing species. We show how positive selection via adhesion can be transformed into negative selection if the host secretes large quantities of a matrix such as mucus. Our work predicts that adhesion is a powerful mechanism for both positive and negative selection within the microbiota. We discuss molecules—mucus glycans and IgA—that affect microbe adhesion and identify testable predictions of the adhesion-as-selection model.

INTRODUCTION

Symbioses with microorganisms are central to the biology of plants and animals. In humans, a healthy microbiota is composed of a complex community of vast numbers of microbes, which predominantly colonizes the lower gastrointestinal tract. The species in these communities are important for normal tissue and immune development (Kamada and Núñez, 2014; Kubinak et al., 2015; Smith et al., 2007), provide metabolic functions (Bäckhed et al., 2004; Stanley et al., 2013), and help prevent pathogen colonization (Kaltenpoth, 2009; Koch and Schmid-Hempel, 2011; van der Waaij et al., 1971). However, the beneficial properties of the microbiota are highly dependent upon its composition (Ivanov et al., 2008; Mendes et al., 2011; Round and Mazmanian, 2009; Stanley et al., 2013; Stecher et al., 2010; Willing et al., 2011). Evolutionary and ecological dynamics continually threaten to disrupt a given community whenever nonbeneficial species can establish themselves (Jarry et al., 2015; Lozupone et al., 2012). This suggests that there is strong natural selection on hosts to control and manage the composition of their microbiota (Schluter and Foster, 2012).

There is extensive evidence that hosts exert some control over their microbiota in humans and other systems (Chu and Mazmanian, 2013; Doornbos et al., 2012; Fraune and Bosch, 2007; Kaltenpoth et al., 2014; Rawls et al., 2006; Suzuki et al., 2004; Weiland-Bräuer et al., 2015). In vertebrates, the typical model of host control is a punitive one, whereby a host suppresses harmful species using the immune system. In the mammalian gut, intestinal epithelial cells act as both a physical barrier between microbes and the host's body, and a mediator of mucosal immune responses through the direct sensing of the microbiota (Goto and Ivanov, 2013; Vaishnava et al., 2008). This includes innate immune responses such as the induction of antimicrobial compounds (including RegIIIγ; Vaishnava et al., 2011; and defensins; Salzman et al., 2010) and mucus secretion (Petersson et al., 2011), as well as adaptive immune responses (specifically immunoglobulin A [IgA] secretion; Hapfelmeier et al., 2010; Peterson et al., 2007).

While punitive host mechanisms have the potential to influence the microbiota, an alternative way for a host to influence its microbiota is via positive control. In positive control, a host acts in a way that promotes beneficial microbes rather than inhibits harmful ones. Theoretical work suggests that positive control can be more effective than negative control because the former encourages growth of beneficial species near the epithelium and thereby pushes harmful species away (Schluter and Foster, 2012). A key candidate mechanism for positive control is the feeding of preferred species via epithelial-derived nutrients, including fucose (Hooper et al., 1999; Pickard and Chervonsky, 2015; Weiss et al., 2014). Consistent with this, a growing body of empirical work suggests that host-secreted nutrients can influence the species composition at the gut epithelium (Kashyap et al., 2013; Peterson et al., 2007; Schluter and Foster, 2012; Weiss et al., 2014).

Our goal here is to introduce and explore a second potentially general mechanism of positive control: adhesion. Adhesion to host epithelial cells and mucus has long been considered a

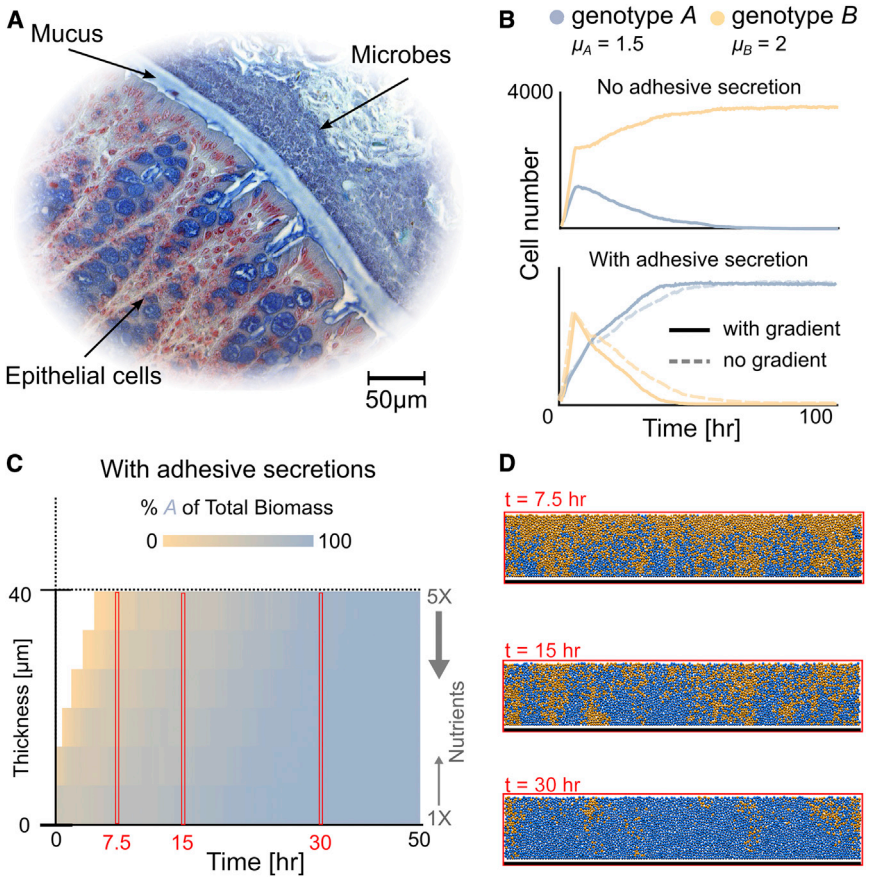

Figure 1. A Host Can Use Adhesion to Select for a Particular Microbial Genotype

We model competition between a slow-growing genotype *A* (blue) and a fast-growing genotype *B* (orange) on the gut epithelium.

(A) Biological scenario of model: micrograph of healthy mouse large intestine (C57Bl/6 mouse, transverse colon stained with Alcian Blue). Photo credit: Lev Lichtenstein and Eugene Chang.

(B) Top: the faster-growing orange genotype *B* (maximum growth rate, $\mu_B = 2$) outcompetes the blue genotype *A* ($\mu_A = 1.5$). Bottom: when the host secretes a factor that increases the relative ability of genotype *A* to resist displacement (adhesion; see Experimental Procedures), *A* can outcompete the faster-growing *B*. This occurs independently of whether or not a gradient for such adhesion-promoting host secretions is implemented (see main text for a discussion).

(C) Average biomass distribution across the entire simulation width shows that when the host secretes a factor that increases the ability of genotype *A* to resist displacement, the two strains separate vertically from each other, and *A* localizes below *B*. The reason for this is that cells of genotype *B* are being pushed up and out of the system more so than genotype *A*.

(D) Snapshots from the simulation at time points corresponding to the red sections in (C). In these simulations, we assume that the concentration of nutrients coming from the lumen is five times the epithelial nutrient concentrations. However, our conclusions are robust to other ratios of nutrient supply (Figure S1).

key property underlying colonization by both pathogenic and beneficial bacteria (Freter, 1981; Hartley et al., 1979). Recent work also suggests that microbes in surface-associated communities can outcompete other genotypes simply by being more adhesive (Schluter et al., 2015). Adhesion allows cells to keep their position better and push other cells up and out of the community. Moreover, many host-secreted factors have the potential to affect adhesion of microbial cells, both to each other and to host factors like mucus. In mammals, these factors include the glycan residues attached to the mucin backbone of mucus and IgA proteins. Both glycans and IgA molecules come in a vast diversity of forms that confer specificity, with particular forms binding certain microbiota species more strongly than others (Naughton et al., 2013; Palm et al., 2014; Robbe et al., 2004; Schroeder and Cavacini, 2010; Tailford et al., 2015).

These observations led us to hypothesize that hosts might not only engage in positive selection by feeding the microbiota but also by affecting their adhesion. We present and develop this hypothesis here using an individual-based model of the epithelial surface (Schluter and Foster, 2012; Schluter et al., 2015). With a vast and rapidly growing body of data on the microbiome, there is a need for complementary theory that both identifies general principles and makes testable predictions to evaluate these principles. By working in silico, we seek to meet this need and evaluate the potential for adhesion as a general host mechanism for positive selection. Our work predicts that adhesion can indeed be used by a host to control the position and abundance of microbial genotypes at the epithelial surface in a way that maintains strain diversity. We also show how host-provided adhesion can act both in positive or negative control, dependent on the rate of mucus flow. Finally, we discuss published data, which are consistent with our model, and outline a number of testable predictions of our hypothesis.

RESULTS

We are interested in how adhesion might be used by a host in order to select for specific strains and species at the epithelial surface. We explore this using an established individual-based model of a multistrain bacterial community that is growing upon a cross section of an epithelial surface of the host (Schluter et al., 2015; Schluter and Foster, 2012). We focus on the epithelial surface as the point where the host and the microbes are in the most intimate contact (Figure 1A). Accordingly, the simulation space is sectioned into host epithelium (bottom boundary), a biofilm domain where microbial cells live, a diffusion layer in which the concentration of solutes is exclusively governed by diffusion (above the biofilm domain), and a bulk phase in the gut lumen where concentrations of solutes are set to a constant value (Schluter and Foster, 2012). Cells are modeled as stiff spheres that grow and divide depending on local nutrient concentrations. Consumption of nutrients then informs a continuum model that is used to update their local concentration. Cells grow

according to this consumption, and upon growth or division, neighboring cells are pushed aside and the community expands. Cells at the top of the community are sloughed off, and we remove them from the simulation.

We follow the fate of different microbial genotypes in the community, which might be different species or different strains of one species. The model is intended to capture known conditions within the gut. Host-ingested compounds will typically provide the majority of the microbiota nutrients, with additional nutrients coming from the host epithelium in the form of compounds such as mucins and fucose (Hooper et al., 1999; Koropatkin et al., 2012; Sonnenburg et al., 2005). While we focus upon a gut system, our model should capture comparable processes whenever microbes grow upon a host epithelial surface, including plant roots (Berendsen et al., 2012), corals (Rosenberg et al., 2007), and other symbioses (Engel et al., 2012; Fraune and Bosch, 2007; Kaltenpoth et al., 2014).

Adhesion as a Mechanism of Host Selection

We first illustrate the problem faced by a host: the microbiome is an ecological and evolutionary system where bacterial populations undergo a continual turnover. The key implication of this is that strains that are faster dividing, or better at surviving, will gradually replace strains that divide more slowly or persist less well (Figure 1B). As a result, whenever the strains and species of microbes that provide the greatest benefit to the host are not the fastest growers, the host has a problem: it will tend to lose its most beneficial strains.

We next recapitulate recent work that suggests adhesion can be used by microbes as a strategy to outcompete other strains (Schluter et al., 2015) (Figure 1B). The process of cell division means that cells will push into each other as numbers increase. In our model, we capture these collisions, and more adhesive cells are better able to resist displacement relative to nonadhesive cells, according to a physical model of viscous drag experienced by cells within a mucus layer. Because adhesion allows cells to resist displacement by other cells, an adhesive strain can better colonize the base of an expanding biofilm community as it is less likely to be pushed away from the epithelial surface by another strain. And so long as there is growth at the base of the biofilm, this positioning will put an adhesive strain in a dominant position to then divide and push all other strains up and out of the system (Figures 1C and 1D). Therefore, adhesiveness may be a bacterial strategy for survival within a nutrient-saturated biofilm that enables commensals to thrive within the gastrointestinal tract (Guzmàn et al., 1997; Grubb et al., 2009; Nowrouzian et al., 2013).

Given the advantages that adhesion can provide to a microbe, we reasoned that differential adhesion might also be employed as a host strategy to positively select for particular strains or species. Specifically, rather than adhesion being a property of the microbes themselves, we wanted to investigate what will happen if, instead, the host secretes factors into the mucus layer that promote adhesion. To capture such host-secreted factors, we model the diffusion of a molecule that is continuously secreted from the epithelial surface, which preferentially sticks to specific strains in the microbial community and limits their movement. In this model, the host-derived adhesiveness decays with greater distance from the source of secretion (Figures 1B and S1, available online).

Does an adhesion gradient function as an effective host selection mechanism? A key distinction for our hypothesis is whether adhesion is a property of the microbes themselves or whether the host provides a factor that influences the adhesion of particular strains or species of microbe. We can compare the effect of a host-secreted molecule that affects microbial adhesion to the case where differential adhesion is a property of the microbes themselves (Figure 1B). Specifically, a host-derived molecule is expected to have the most effect close to the epithelial surface, whereas a microbe-based factor will be a property of the microbial cell that, all else being equal, will have the same effect at any position. In order to compare these two, we set the maximum adhesive effect at the epithelial surface in the host-derived adhesion model to be the same as the effect that occurs throughout the microbial community in the microbial-adhesion model.

Despite the fact that the total adhesive effect is much weaker in the host-derived adhesion model due to the gradual decrease in strength away from the epithelium, we observe a comparable effect on microbial competition in both cases. In fact, the host-secreted case can even perform slightly better than intrinsic microbial adhesion. The reason for this is that an adhesion gradient is maximizing the effect of adhesion at the point where it is most important, at the epithelial surface itself. Thus, cells closest to the surface are the ones that are least likely to be displaced by any other cells in the system. This ensures that the favored cells rapidly conquer the surface and push all others out of the system. In Figure S1, we explore the effectiveness of host adhesion for a range of lumen nutrient concentrations and growth rates of the host-favored strain. These simulations show the intuitive result that the slower a strain grows, the greater the host-supplied adhesion that is required to maintain it. In addition, they show that adhesion-based selection is effective for a wide range of lumen nutrient concentrations.

An important potential feature of microbial selection via adhesive molecules is that it can be both specific and variable. Any one adhesive molecule can have a specific target, and if the host can generate a wide variety of molecules, they can target a diverse set of strains and species. As discussed above, two clear candidates for such specificity in mammalian systems are the glycans of mucus molecules and IgA. Both come in a vast diversity of forms, and, importantly, there is evidence that both preferentially associate with certain microbiome species (Naughton et al., 2013; Palm et al., 2014; Robbe et al., 2004; Schroeder and Cavacini, 2010; Tailford et al., 2015). We next show how such a system can be employed to prevent competitive exclusion of slow-growing strains and thereby maintain a diverse set of strains at the epithelial surface. Without selective adhesive secretions, we again observe the problem faced by the host: starting from a mixed set of species on the epithelial surface typically leads to the loss of diversity during the simulation. This can occur even when all strains have the same growth rate (Figure 2A) through stochastic processes, but it is particularly problematic when different strains have different growth rates (Figure 2B). We next consider the case where the host secretes a range of adhesive molecules at the epithelial surface. Importantly, we assume that the molecules are not all secreted uniformly along the epithelial surface, but each molecule has a unique focus of secretion. This process—secreting different adhesive molecules at different positions—has a powerful stabilizing effect on

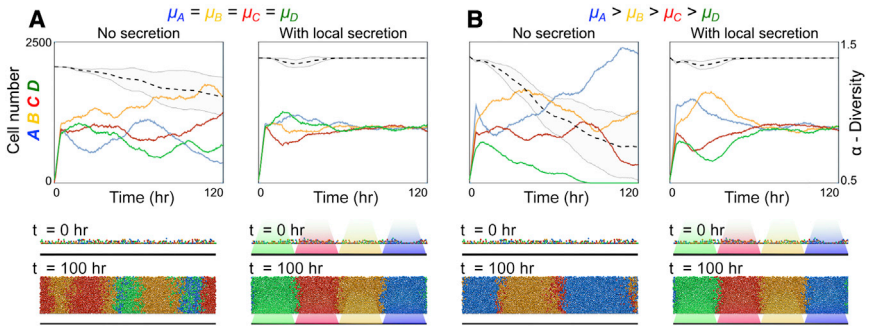

Figure 2. Horizontal Gradients of Host Secretions Maintain Diversity

Here, four genotypes (strains or species) compete, and the host may secrete four different factors in four different horizontal regions. Time-series data show cell number (left y axis) of four genotypes over time for one representative simulation and are accompanied by alpha-diversity data across the whole simulation space from 50 independent simulations (right y axis, black dotted line; the gray lines above and below show the SEM). Snapshots show the simulation at t = 0 hr and t = 100 hr, where adhesion-promoting host secretions form horizontal gradients (for simplicity, vertical gradients are omitted here) and are indicated by shaded areas with the maximum effectiveness of the secretion in the center of each region. Colors of host secretions correspond to colors of genotypes for which they are specific. The x and y axes in the snapshots are distance along and away from the epithelial surface, respectively.

(A) When the four genotypes grow at identical rates, stochastic events can lead to uneven genotype abundances over time. Accordingly, diversity tends to decrease slowly over time. When the host secretes factors that promote the ability of a genotype to resist displacement in a confined horizontal region, this provides a refugium for this genotype and diversity remains high.

(B) When genotypes differ in their maximum growth rates, diversity loss occurs rapidly and dramatically. This can be prevented by host secretions that create ecological refugia for slow-growing strains and species.

diversity (Figure 2). Positive selection by the host is effectively creating a set of niches along the epithelial surface that guarantees that each strain has at least one position where it can establish and thrive.

Adhesion Can Prevent Microbial Extinctions across Feast-Famine Cycles

We have so far assumed that microbial genotypes have a constant growth rate over time. In practice, the growth rate of a particular strain or species will change according to the amount and types of nutrients that are available (David et al., 2014; Kohl et al., 2014). We next explore this scenario by introducing two food types a host may consume. The first food type is only available periodically, and species *A* microbes rely exclusively on this food type. The second food type is always available, and it contains nutrients for a generalist species *B* that can survive on both food types. For example, *Bacteroides thetaiotaomicron* (Sonnenburg et al., 2005) can consume a wide range of complex carbohydrates, some of which are food derived, whereas others may come from host secretions. Modeling these two food sources highlights a problem that variability in diet can cause for a host. Sudden shifts in host diet bring the risk that certain microbial species will be lost if their preferred nutrients are in short supply, resulting in a loss of metabolic potential or other benefits to the host. Specifically, we see in the model that species *A* will often be lost during the fasting periods where the first food type is not available (Figures 3A and S2). These extinction events, however, can be prevented through the use of selective host adhesion (Figures 3B and S2). Adhesion can create a region of the gut where species *A* always persists by providing a large enough competitive benefit despite the lack of growth during a fasting period. In ecological terms, selective adhesion creates an ecological refugium (Stewart et al., 2010) for species *A* that prevents its extinction. The creation of refugia by a host, therefore, may be a way to ensure that a diverse and desirable set of species can be maintained at epithelial surfaces at all times in the face of environmental fluctuations caused by diet and other factors.

Host Matrix Secretion and Selection

Hosts commonly secrete a matrix that surrounds their symbionts at epithelial surfaces. Plants secrete "mucilage" polysaccharides from their roots into the rhizosphere, while animals make mucins, which are heavily glycosylated proteins. In the gut, these mucins form a coat over the epithelium that is broadly divided into two layers. The "inner" layer is formed of dense, interlocking mucins, which progressively unravel farther away from the epithelium to form an "outer" layer that is much more loosely packed (Holm and Phillipson, 2012). The inner layer is largely free from microbes, while the outer layer can contain large numbers of microbes that appear to be both protected from sloughing and fed by the mucins around them (Derrien et al., 2010; Koropatkin et al., 2012; Sonnenburg et al., 2005). The existence of a mucin network is consistent with our model of differential adhesion as different genotypes have differing abilities to aggregate within mucin (Caldara et al., 2012), and some microbial species even attach directly to mucins (Huang et al., 2011). However, mucins are constantly produced by the host, and this creates a continual movement of mucus away from the epithelial surface that our model does not yet capture. Moreover, the rate of mucin production and consequent mucus flow has the potential to vary both within and between individuals. During inflammation and infection, for example, mucin production rates can increase substantially (Boshuizen et al., 2005; Faure et al., 2003; Guilmeau et al., 2008).

Given that many of the processes we observe in our model are due to differential movement of cells away from the epithelium, we wanted to explore what happens when cells move along with the secreted mucus. We incorporated mucus-induced translocation by assuming that cells are contained within a mucus gel that moves upward a fixed distance each time step, where the magnitude of this movement vector increases for an increased rate of mucus flow. Countering this effect, cell division near the epithelial surface will generate new biomass that repopulates the space created by mucus flow. We can then ask whether mucus flow rate influences our predictions on the benefits of adhesion. For low rates of mucus flow, our predictions are

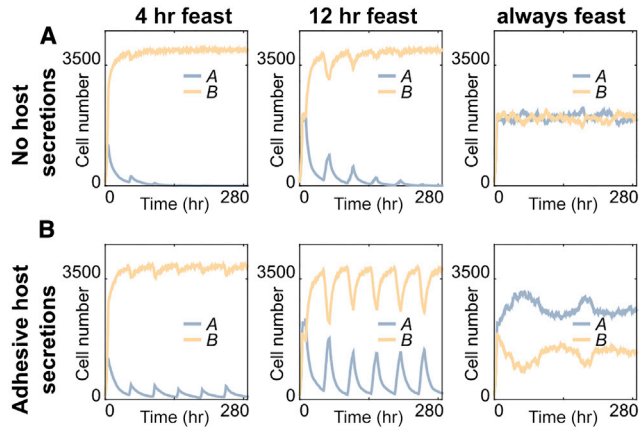

Figure 3. Adhesive Host Secretions Promote Microbiota Stability in Fluctuating Environments

We simulate two genotypes, a generalist species *B* that can consume lumen nutrients, which are available at all times. A second nutrient is only available periodically and is the exclusive nutrient source for a specialist species *A*. We show 4 hr and 12 hr feast durations per 48 hr period; "always feast" is a control where the second nutrient is also available at all times.

(A) Without adhesive host secretions, genotype *A* is lost from the community if "feast" periods are rare and short.

(B) When the host secretes an adhesion-promoting factor that creates a horizontal region in which genotype *A* resists displacement better than genotype *B*, both genotypes can be maintained even when the environment fluctuates. The variability in the "always feast" condition is due to stochastic fluctuations in population size. Our results are robust to changes in duration and periodicity of feasts (Figure S2).

unaffected and adhesiveness provides a competitive advantage to microbes (Figure 4). However, increasing the rate of mucus flow changes the prediction. As flow rates increase, cells are carried more rapidly away from the epithelial surface, and it becomes more and more challenging to repopulate the space created at the epithelial surface. This process is more challenging for adhesive cells that tend to move less within the mucus gel than nonadhesive cells (Figure 4C). The result is that, on average, the adhesive cells are carried more rapidly up and out of the system than nonadhesive cells, and, importantly, this can allow nonadhesive cells to dominate. However, this effect only occurs for a relatively narrow parameter window because with too much mucus flow, no cell type can repopulate the epithelial surface rapidly enough and all microbes are swept away and into the lumen (Figure 4; Experimental Procedures). In sum, increasing the rate of mucus flow can make adhesion shift from a mode of positive selection—keeping strains close to the epithelium—to negative selection, where adhesive strains are flushed out of the system. Too much flow, however, and all strains will be flushed out.

DISCUSSION

The composition of the microbiota associated with a host is central to a host's health and, ultimately, its evolutionary fitness. A host can benefit, therefore, from strategies that allow it to influence which microbes thrive at its epithelial surfaces (McFall-Ngai 2007; Hooper et al., 2012). Here we have presented a series of models that show how host-provided adhesiveness can act as a mechanism to affect the composition of the microbiota (Figures 1 and 2). In particular, our models predict that under certain conditions, a host can use adhesion to favor the colonization and competitiveness of beneficial microbial genotypes. And while we have focused on increasing adhesion here, a corollary of our predictions is that host might also secrete factors that *reduce* adhesion in order limit a strain's colonization. The microbiota associated with a host can shift widely in response to changes in the environment (Faber and Bäumler, 2014; Keeney et al., 2014; Tracy et al., 2015), chiefly host diet in the case of gut communities (David et al., 2014). Host-provided factors that positively select for particular genotypes have the potential to limit the scale of these fluctuations. In particular, the host can provide ecological refugia for symbionts that might otherwise be lost during shifts in composition (Carey et al., 2013; Kohl et al., 2014; Pickard and Chervonsky, 2015) (Figure 3). Along with feeding, adhesion seems a promising mechanism for refugia generation due to the potential for specific binding to target symbionts.

Symbiotic microbes often sit encased in a matrix—mucus in animals and mucilage in plants—that flows outward under host control. The rate of flow of mucus in animals is known to be extremely variable. In particular, during infection or dysbiosis, the inflammatory response is associated with mucus hyperproduction by goblet cells within the epithelial layer (Boshuizen et al., 2005; Guilmeau et al., 2008). Our model predicts that the flow rate away from the epithelial surface is critical to whether increased adhesion acts to benefit or inhibit a particular genotype (Figure 4). Under low flow rates, adhesion helps cells to displace less-adhesive genotypes and stay close to the epithelium. However, adhesive populations are relatively less able to counter the mucus flow by expanding back toward the epithelium. The result is that at high flow rates, adhesive genotypes are more readily carried away from the epithelium than less-adhesive genotypes.

There are multiple host compounds that might enable hosts to affect microbial adhesion. Mucins are heavily glycosylated, and many species of microbes have the ability to attach to these glycans, both as a way to digest them (Koropatkin et al., 2012; Sonnenburg et al., 2005) but also seemingly as way to anchor themselves (Naughton et al., 2013; Derrien et al., 2010; Huang et al., 2011). These diverse moieties can serve as a nutrient source that selects for certain symbionts (Pickard and Chervonsky, 2015), particularly species that have the necessary enzymes to remove glycans from mucins and other macromolecules (Derrien et al., 2010; Koropatkin et al., 2012; Sonnenburg et al., 2005). However, the extreme structural diversity of these glycans also raises the possibility that they act as specific attachment targets for certain symbionts (Naughton et al., 2013; Lee et al., 2013). Glycans may serve then to select for particular strains both by nutrient provision but also by affecting adhesion, and our model suggests that the two can work well together (Figure S3). Consistent with this, there is growing evidence that host-secreted glycans are important for which species occur where in the gut (Donaldson et al., 2016), as well as in providing resistance to infection (Pham et al., 2014).

Another potential candidate for the manipulation of microbial adhesion is IgA, with its well-documented ability to bind to bacterial epitopes and other molecules (Kawamoto et al., 2012; Mantis et al., 2011; Mathias and Corthésy, 2011). Our model

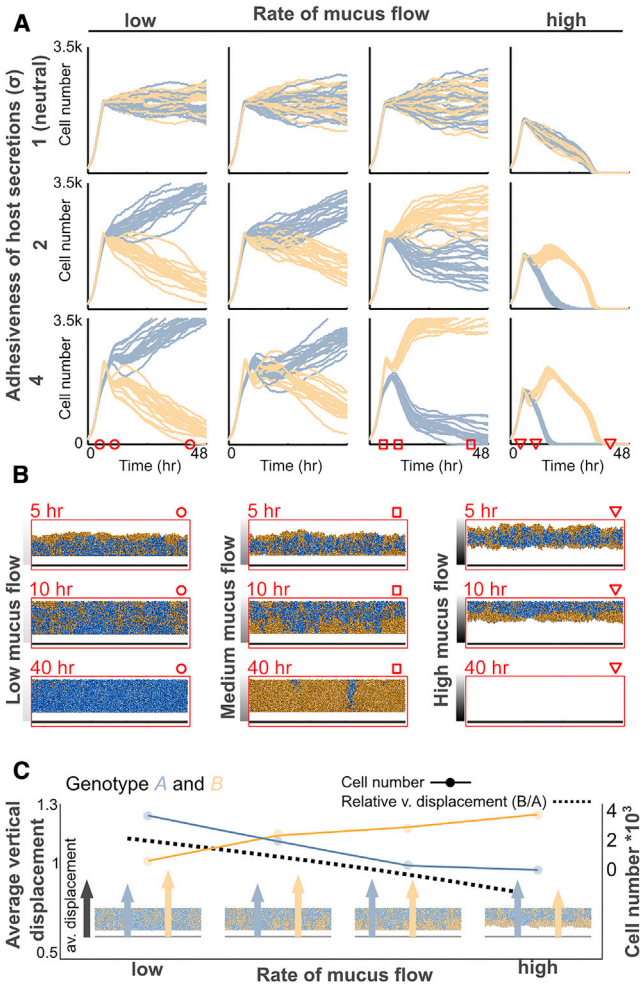

Figure 4. Hosts Can Combine Adhesion and Mucus Flow to Select For or Against a Particular Microbial Genotype

(A) Each plot shows cell numbers of two genotypes, *A* (blue) and *B* (orange), over a 48 hr simulation period for 50 independent simulations. Without adhesion-promoting secretions from the host, both types are equal in all parameters and grow at the same rate (top row). At each time step, cells are moved upward and away from the epithelium, simulating a mucus matrix in which cells are embedded and which pulls them along (Experimental Procedures). If this flow rate is faster than the recolonization of now freed space below, all cells get washed out (top right). When the host secretes a factor that increases the ability to resist displacement of genotype *A*, low flow rates recapitulate the findings from Figure 1 that show how being more adhesive can convey a competitive advantage (two far left columns). However, at higher flow rates that still allow persistence of cells in the mucus layer (third column), the fate of the more adhesive genotype *A* is reversed, and it is preferentially removed from the system relative to the nonadhesive genotype. At even higher flow rates, all genotypes are lost (right hand column).

(B) Snapshots of representative simulations show that less-adhesive cells of genotype *B* are pushed out at low mucus flow rates (left) but tend to persist better at higher mucus flow rates (middle), while both are flushed out at very high flow rates (right).

(C) High fitness is associated with the ability to resist vertical displacement. Quantification of relative vertical displacement (dotted black line) between the genotypes and the resulting effects on fitness (solid lines). The arrows indicate average vertical movement rates of the two genotypes in μm/hr. At low mucus flow rates, cells of genotype *A* experience less vertical movement relative to cells of genotype *B*. This effect is reversed at higher flow rates, as the less-adhesive *B* cells can more easily repopulate the void space created through translocation of the whole community with mucus flow. The result is higher fitness (measured as cell number at t = 22 hr) of the adhesive genotype *A* at low mucus flow, and lower fitness at high flow.

raises the possibility for a positive effect of IgA binding on targeted microbes. Under normal conditions, IgA is produced in large amounts at the gut epithelial surface in response to the presence of symbionts (Moreau et al., 1978; Smith et al., 2007), and it appears to coat the majority of bacteria in the gut (D'Auria et al., 2013; Palm et al., 2014; van der Waaij et al., 2004). These immunoglobulins stay close to the epithelial surface by binding mucins within the mucus layer (Biesbrock et al., 1991; Phalipon et al., 2002).

Broadly consistent with our model, IgA has been shown to promote bacterial adhesion and biofilm formation in vitro (Bollinger et al., 2003, 2006). IgA adhesion is driven both by a hypervariable region that enables different IgA forms to target specific microbial epitopes, and a nonspecific binding region that adheres both to microbes (Mathias and Corthésy, 2011; Nowrouzian et al., 2013) and to the host-produced mucins that form the mucus matrix at the epithelial surface (Bergstrom and Xia, 2013; Biesbrock et al., 1991; Phalipon et al., 2002). As a result, IgA colocalizes with epithelial microbes (Rogier et al., 2014) and its capacity for specific binding raises the possibility that hosts can enrich for a particular microbial strain by secreting a particular IgA form into the epithelial mucus. However, under conditions of high mucus flow, particularly during infection, IgA may act in an opposite manner and help to pull strains away from the epithelial surface, leading to their control and clearance (Boullier et al., 2009; Forbes et al., 2012; Lindner et al., 2015).

Our models make a number of testable predictions that can be used to reject our hypothesis that host-derived adhesive molecules are important in determining the composition of the microbiota. Most generally, we predict that the composition of the microbiota, particularly at the epithelial surface, will shift when the abundance of host-derived adhesive molecules is altered. This prediction is supported by studies showing compositional shifts in the microbiota when fucosylation patterns are altered (Kashyap et al., 2013; Weiss et al., 2014), IgA production is inhibited (Kawamoto et al., 2012; Mirpuri et al., 2014; Suzuki et al., 2004), or its specificity changed (Lindner et al., 2012; Mathias and Corthésy, 2011). A related prediction is that a reduction in the abundance or diversity of adhesive molecules should be associated with a loss of diversity in the microbiota.

The above predictions, however, are silent on whether adhesion is functioning as a mode of positive or negative selection. If a particular class of adhesive molecule is functioning in positive selection, then a more specific prediction is that the molecule should be preferentially expressed when the target focal strain is disadvantaged, as might occur during a famine period or diet switch. Consistent with this, there is evidence of upregulation in IgA production and secretion in malnourished individuals (Brandtzaeg, 1998; Beatty et al., 1983), as well as upregulation of glycan production during famine periods (Hooper et al., 1999; Pickard and Chervonsky, 2015). Available data, therefore, do not reject our hypothesis that host-derived adhesive molecules are important for microbiota composition. However, while the

data do not reject our model, the results could also be explained by other effects of the glycans and IgA that are not associated with adhesion, such as their nutritional value to the microbiota.

A more specific test of our model would first identify which species are preferentially bound by a particular adhesive molecule. With this information, our model predicts that removing (or adding) the focal molecule at the epithelial surface will preferentially affect the frequency of the targeted species over other species. In particular, if adhesion is functioning in positive selection, when the adhesive molecule is removed, the targeted symbiont should suffer a loss of abundance. There are currently few data relevant to this prediction. However, it has been observed that anti-*Helicobacter pylori* IgA is associated with increased *H. pylori* colonization of the stomach epithelium (Akhiani et al., 2005). These data are consistent with the effects of increased adhesion but not with alternative models such as IgA functioning to target and destroy members of the microbiota as part of the immune system.

In sum, our models suggest that hosts can use adhesion to select members of their microbiota. We find that adhesive molecules are flexible in the sense that they can act in a positive or negative manner on targets, depending on the mucus flow rate used by a host (Figure 4). Another potential strength of adhesive molecules is their specificity, particularly relative to selection by growth inhibitors, like defensins, or host-epithelial feeding. However, the potential for adhesive molecules like IgA to be used in positive selection is perhaps the most intriguing prediction of our work. Indeed, we find that positive selection can be powerful, as an anchored strain can then divide and push other strains away from the surface. Our work emphasizes how hosts can benefit just as much from helping beneficial strains as harming pathogens.

EXPERIMENTAL PROCEDURES

Our work extends an extensively tested individual-based simulation framework that has been developed and empirically validated over the past 15 years and has successfully predicted interesting biology (Kim et al., 2014; Schluter et al., 2015; Xavier et al., 2005). The model is a hybrid between an individual-based simulation of microbes and a continuum model of solutes. To simulate microbiota communities, the simulation space is sectioned into host epithelium (bottom boundary), a biofilm domain where microbial cells live, a diffusion layer in which the concentration of solutes is exclusively governed by diffusion (above the biofilm domain), and a bulk phase in the gut lumen where other transport processes dominate diffusion and concentrations of solutes are set to a constant value (Schluter and Foster, 2012).

Cells are modeled as stiff spheres that can grow and divide depending on local nutrient concentrations. Consumption of nutrients then informs the continuum model of solutes and is used to update concentration fields. The model implements a multigrid solver for the reaction-diffusion partial differential equations. Here, consumption of nutrients functions as local sinks for the respective solute. It is assumed that diffusion takes place on faster timescales than cell-based events such as growth and division. Therefore, for each time step, steady-state concentration gradients are calculated. Cells grow according to this consumption, and upon growth or division, neighboring cells are pushed aside and the overall biofilm domain expands. We assume that beyond a distance of 40 μm, cells are sloughed off, and we remove them from the simulation in accordance with a previous model of gut-epithelium-attached microbial communities (Schluter and Foster, 2012; Schluter et al., 2015). We here extend the work of Schluter et al. (2015), who have implemented differential adhesion between cells during the growth and pushing phase of the algorithm (for details regarding the implementation and comparison to a physical model of viscous drag, see Schluter et al., 2015). This model accurately predicted behavior of two differentially adhesive strains in biofilm experiments grown in flow chambers.

Implementation of Adhesive Secretions from the Host Epithelium

We here implement different host secretions from the gut epithelium that convey the differential ability of cells to resist displacement. Adhesion strength is simulated as a relative ability to resist displacement, similar to spheres moving through a viscous liquid that experience viscous drag. Initially, we assume that these secretions have the same effect on cells throughout the simulation space ("no gradient" simulations). We next relax that assumption and explicitly model gradients of secreted adhesive factor concentrations (Figures 1B and S1). For this, we assume that such secretions from the epithelium are at equilibrium between the source (epithelial cells) and a sink in a bulk phase deeper in the lumen (vertical gradient simulations; see Table S1 for parameter values). The local concentration then is a linearly decreasing function with its maximum at the source (bottom boundary) and zero in the lumen (bulk phase). Vertical gradient simulations then simulate a scenario where the relative ability of cells to resist displacement gradually decreases farther away from the source. The effect of the vertical gradient on host selection is negligible (Figures 1 and S1), so we return to the simpler model that lacks a vertical gradient for subsequent simulations. We also implement horizontal gradients where we assume that a certain region of the epithelium secretes a specific solute (such as one epithelial cell secreting IgA molecules specific to one surface epitope and therefore specific to one microbial genotype) (Figures 2 and 3). Left and right of this source, concentrations of this secreted product decrease (see Table S1 for parameter values).

Calculation of Diversity

From our simulation data, we calculate the Shannon-Wiener index. This measures the uncertainty associated with predicting the identity of a genotype when an individual is drawn randomly from the population. Therefore, the diversity index is maximized when all genotype frequencies are equal. Specifically, we calculate the Shannon-Wiener index (Whittaker et al., 2001; Shannon, 1948),

$$H' = -\sum_i p_i * \log(p_i),$$

with p_i equal to the proportion of genotype i in the whole population. Whenever one or few genotypes dominate the population, therefore, the diversity index decreases.

Mucus-Flow-Induced Displacement

To model the effect of cells translocating with the mucus that is secreted by the epithelium, we implement a displacement function that has effect at each iteration (see Table S1 for parameter values). This discretizes the translocation effect that occurs continuously in the real gut environment. However, our models rely on discrete time steps; therefore, our parameter values must be viewed as approximations, which carry meaning in relative rather than absolute terms.

Feast-Famine Implementation

We simulate the effect of temporary availabilities of nutrients that are specific nutrients for some microbial species. During periods where the nutrients are available (feast), the system is flushed with nutrients and concentrations are saturating throughout the simulation space. These periods are of various lengths, as indicated, within a 48 hr period (i.e., 4 hr means a 4-hr-long period of feast begins every 48 hr). Outside these periods (famine), the concentrations of these nutrients are set to zero throughout the simulation space.

SUPPLEMENTAL INFORMATION

Supplemental Information includes three figures and two tables and can be found with this article online at http://dx.doi.org/10.1016/j.chom.2016.02.021.

AUTHOR CONTRIBUTIONS

K.M. provided the initial hypothesis. K.M., J.S., and K.R.F. designed analyses. J.S. and K.M. performed preliminary analyses. J.S. implemented the simulations

and prepared the figures presented in the paper. All authors contributed to interpretation and writing.

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