Host selection of microbiota via differential adhesion

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Summary

The host epithelium is the critical interface with microbiome communities. Despite this, we understand relatively little of how the host regulates the communities at this interface. Here we develop the hypothesis that hosts use differential adhesion to select for, and against, particular members of their microbiota. We use an established individual-based model and study the impact of the host releasing adhesive factors from the epithelial surface. Our computer simulations predict that adhesion can increase the competitive advantage of epithelial 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 like mucus. Our work predicts that adhesion is a powerful mechanism for both positive and negative selection within the microbiome. 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 some 100 trillion microbes, which predominantly colonises the lower gastrointestinal tract. The species in these communities are important for normal tissue and immune development (Bouskra et al. 2008; Pabst et al. 2006; Atarashi et al. 2011; Ivanov et al. 2009; Kamada & Núñez 2014; Kubinak et al. 2015), provide metabolic functions (Stanley et al. 2013; Ramakrishna 2013; Vijay-Kumar et al. 2010; Smith et al. 2007; Bäckhed et al. 2004) and help prevent pathogen colonisation (van der Waaij et al. 1971; Stecher et al. 2010; Stecher & Hardt 2011; Kaltenpoth 2009; Koch & Schmid-hempel 2011; Deshmukh et al. 2014; Pham et al. 2014). However, the beneficial properties of the microbiota are highly dependent upon its composition (Stanley et al. 2013; Khosravi & Mazmanian 2013; Mazmanian et al. 2008; Willing et al. 2011; Round & Mazmanian 2009; Stecher et al. 2010; Maier & Hentges 1972; Ivanov et al. 2008; O'Mahony et al. 2008; Sokol et al. 2008; Mendes et al. 2011). Evolutionary and ecological dynamics continually threatens to disrupt a given community whenever non-beneficial species can establish themselves (Lozupone et al. 2012; Sellon et al. 1998; Round & Mazmanian 2009; Jarry et al. 2014; Barnich et al. 2007). This suggests that there is strong natural selection on hosts to control, and manage, the composition of their microbiota (Schluter & Foster 2012) .

There is extensive evidence that hosts exert some control over their microbiota in humans and other systems (Chu & Mazmanian 2013; Suzuki et al. 2004; Rawls et al. 2006; Fraune & Bosch 2007; Doornbos et al. 2012; Garbeva et al. 2008; Miethling et al. 2000; Yang et al. 2011; Weiland-Bräuer et al. 2015; Kaltenpoth et al. 2014; Seedorf et al. 2014). 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 (Vaishnava et al. 2008; Goto & Ivanov 2013; Maynard et al. 2012; Abreu 2010; Wells et al.

2011). This includes innate immune responses such as the induction of antimicrobial compounds (including RegIIIγ (Cash et al. 2006; Vaishnava et al. 2011), defensins (Salzman et al. 2010), and angiogenins (Salzman 2010; Hooper et al. 2003)) and mucus secretion (Petersson et al. 2011), as well as adaptive immune responses (specifically immunoglobulin A (IgA) secretion (He et al. 2007; 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 their 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 & 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 & 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 (Schluter & Foster 2012; Pickard et al. 2014; Peterson et al. 2007; Weiss et al. 2014; Kashyap et al. 2013).

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 key property underlying colonisation by both pathogenic and beneficial bacteria (Hartley et al. 1979; Fuller & Brooker 1974; Freter 1981). 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, which confer specificity with particular forms binding certain microbiota

species more strongly than others (Tailford et al. 2015; Ann Naughton et al. 2013; Schroeder & Cavacini 2013a; Palm et al. 2014; Patrick et al. 1977; Robbe et al. 2004; Lee et al. 2013).

These observations led us to hypothesise 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 & 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 make 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 works 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. However, we also show how host-provided adhesion can act both in positive or negative control, dependent on the rate of mucus flow. We discuss published data that support 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 multi-strain bacterial community that is growing upon a cross section of an epithelial surface of the host (Schluter et al. 2015; Schluter & 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 & Foster 2012). Cells are modelled 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, neighbouring 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 (Schluter & Foster 2012; Schluter et al. 2015).

The model is intended to capture known conditions within the gut: host-ingested compounds will typically provide the majority of the microbiota nutrients, but various compounds that can feed microbes such as mucins and attached sugars such as fucose are being secreted by the epithelium (Hooper et al. 1999; Derrien et al. 2010; Sonnenburg, Xu, Leip, et al. 2005; Koropatkin et al. 2012). 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; Garbeva et al. 2008), corals (Rosenberg et al. 2007) and other symbioses (Engel et al. 2012; Kaltenpoth 2009; Fraune & Bosch 2007; Kaltenpoth et al. 2014).

Adhesion as a mechanism of host selection

We first illustrate the problem faced by a host (Schluter & Foster 2012). 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 non-adhesive 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 colonise 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 will put an adhesive strain in a dominant position to then divide and push all other strains up and out of the system (Figure 1C, D). 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 by 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 then, 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 then, the host-derived adhesiveness decays with greater distance from the source of secretion (Figures 1B, S1).

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 an intrinsic microbial adhesion. The reason that this occurs is that an adhesion gradient is maximising 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 favoured 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-favoured 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 (Tailford et al. 2015; Robbe et al. 2004; Ann Naughton et al. 2013; Schroeder & Cavacini 2013a; Palm et al. 2014; Patrick et al. 1977; Lee et al. 2013). 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,C) through stochastic processes but it is particularly problematic when different strains have different growth rates (Figures 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 stabilising effect on diversity (Figures 2B, D). 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 species 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 (Lukens et al. 2014; Tachon et al. 2014; Wu et al. 2011; David et al. 2014; Sonnenburg et al. 2005; 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. An example is *Bacteroides thetaiotaomicron* (Sonnenburg et al. 2005), which can consume a wide range of complex carbohydrates, some of which are food-derived whereas others may come from host secretions. Modelling these two food sources highlights a problem that variability in diet can cause for a host. Sudden shifts in host diet brings 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 (Figure 3A, S2). These extinction events, however, can be prevented through the use of selective host adhesion (Figure 3B, 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; Keppel et al. 2012) 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 (Holm & Phillipson 2012; Atuma et al. 2001; Johansson et al. 2011). The "inner" layer is formed of dense, interlocking mucins, which progressively unravel further away from the epithelium to form an "outer" layer that is much more loosely packed (Atuma et al. 2001; Holm & 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 (Sonnenburg et al. 2004; Sonnenburg et al. 2005; Derrien et al. 2010; Koropatkin et al. 2012). 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; Huang et al. 2011) and some microbial species even attach directly to mucins (Kinoshita et al. 2008; 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; Songhet et al. 2011; Guilmeau et al. 2008; Faure et al. 2003; Deplancke & Gaskins 2001).

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 upwards 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 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 non-adhesive cells (Figure 4C). The result is that, on average, the adhesive cells are carried more rapidly up and out of the system than non-adhesive cells and, importantly, this can allow non-adhesive 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, Methods). 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 their microbiota (Figures 1 and 2). In particular, our models predict that, under certain conditions, a host can use adhesion to favour the colonisation 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

colonisation. The microbiota associated with a host can shift widely in response to changes in the environment (Keeney et al. 2014; Tracy et al. 2015; Faber & Bäumler 2014; Moeller et al. 2014), chiefly host diet in the case of gut communities (David et al. 2014; Lukens et al. 2014; Wu et al. 2011; Tachon 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 (Pham et al. 2014; Stevenson et al. 2014; Carey et al. 2013; Pickard & Chervonsky 2015; Kohl et al. 2014; Pickard et al. 2014) (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 outwards 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 hyper-production by goblet cells within the epithelial layer (Boshuizen et al. 2005; Songhet et al. 2011; 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 less able to counter the mucus flow by expanding back towards 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; Derrien et al. 2010) but also seemingly as way to anchor themselves (Bergstrom & Xia 2013; Ann Naughton et al. 2013; Martens et al. 2008; Derrien et al. 2010; Huang et al. 2011; Kinoshita et al. 2008). These diverse moieties then can serve as a nutrient source that selects for particular symbionts (Schluter & Foster

2012; Pickard et al. 2014), particularly species that have the necessary enzymes to remove glycans from mucins and other macromolecules (Koropatkin et al. 2012; Sonnenburg et al. 2005; Derrien et al. 2010). However, the extreme structural diversity of these glycans also raises the possibility that they act as specific attachment targets for certain symbionts (Ann 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 (Kashyap et al. 2013; Donaldson et al. 2015) 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 (Hooper & Macpherson 2010; Wold et al. 1990; Mantis et al. 2011; Macpherson et al. 2001; Kawamoto et al. 2012; Mathias & Corthésy 2011). Our model 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 (Round & Mazmanian 2009; He et al. 2007; Moreau et al. 1978; Round et al. 2010), and it appears to coat the majority of bacteria in the gut (van der Waaij et al. 2004; van der Waaij et al. 1996; D'Auria et al. 2013; Tsuruta et al. 2009; Palm et al. 2014). These immunoglobulins stay close to the epithelial surface by binding mucins within the mucus layer (Olmsted et al. 2001; 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. 2006; Randal Bollinger et al. 2003). IgA adhesion is driven both by a hypervariable region that enables different IgA forms to target specific microbial epitopes, and a non-specific binding region that adhere both to microbes (Friman et al. 1996; Nowrouzian et al. 2013) and to the host-produced mucins that form the mucus matrix at the epithelial surface (Olmsted et al. 2001; Bergstrom & Xia 2013; Biesbrock et al. 1991; Phalipon et al. 2002). As a result IgA co-

localises with epithelial microbes (Rogier et al. 2014) both via its non-specific binding (Mathias & Corthesy 2011; MacKenzie et al. 2009) but also by the classical specific binding that targets certain strains via its hypervariable, complementary determining region-3 (CDR3)(Schroeder & Cavacini 2013b). It is this latter specific binding that 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 a opposite manner and help to pull strains away from the epithelial surface leading to their control and clearance (Forbes et al. 2012; Boullier et al. 2009; Lindner et al. 2015; Mantis & Forbes 2010).

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; Pham et al. 2014; Weiss et al. 2014; Robbe et al. 2004), IgA production is inhibited (Kawamoto et al. 2012; Suzuki et al. 2004; Kaetzel 2014; Mirpuri et al. 2014) or its specificity changed (Lindner et al. 2012; Mathias & Corthesy 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 up-regulation in IgA production and secretion in malnourished individuals (Brandtzaeg 1998; Beatty et al. 1983), as well as up-regulation of glycan production during famine periods (Hooper et al. 1999; Pickard & 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* colonisation of the stomach epithelium in a manner consistent with the effects of increased adhesion (Akhiani et al. 2005). These data are consistent with our adhesion model but not with alternative models such as IgA functioning as a way to target and destroy members of the microbiota via the immune system. Finally, our work suggests that mucus flow rate has the potential to shift the sign of selective effects. For a given adhesive molecule that benefits a symbiont under low mucus flow, we predict that benefit can turn into a cost to the symbiont under conditions of sufficiently high mucus flow.

In sum, we predict that adhesion, along with the secretion of a matrix like mucus, can allow a host to exert control over its microbiota. We find that adhesive molecules are flexible in the sense that they have the potential to act in both a positive and negative manner on targets. Another potential strength of adhesion is its specificity, particularly relative to selection by growth inhibitors, like defensins, or indeed host-epithelial feeding. However, the potential for adhesion to act as a mechanism of positive selection is perhaps the most surprising 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 emphasises then how hosts can benefit just as much from helping beneficial strains as harming pathogens.

Methods

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 novel biology (Picioreanu et al. 1998; Kreft et al. 2001; Xavier et al. 2005; Xavier & Foster 2007; Schluter et al. 2015; Kim et al. 2014). 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 & Foster 2012).

Cells are modelled 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 time-scales 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, neighbouring cells are pushed aside and the overall biofilm domain expands. We assume that beyond a distance of 40um, cells are sloughed off and we remove them from the simulation in accordance with a previous model of gut epithelium attached microbial communities (Schluter & 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 behaviour 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 (Figure 1B, 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 supplementary table 1 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 further away from the source. The effect of the vertical gradient on host selection is negligible (Figure 1, 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 supplementary table 1 for parameter values).

Calculation of diversity.

From our simulation data we calculate the Shannon-Wiener index. This measures the uncertainty to predict the identity of a species 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 species *i* in the whole population. Whenever one or few species 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 supplementary table 1 for parameter values). This discretises the translocation effect which 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 48h period (i.e. 4h means a four hour long period of feast begins every 48h). Outside these periods (famine) the concentrations of these nutrients are set to zero throughout the simulation space.

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Author Contributions

KM provided the initial hypothesis. KM, JS and KRF designed analyses. JS and KM performed preliminary analyses, JS ran those presented in the paper. All authors contributed to interpretation and writing.

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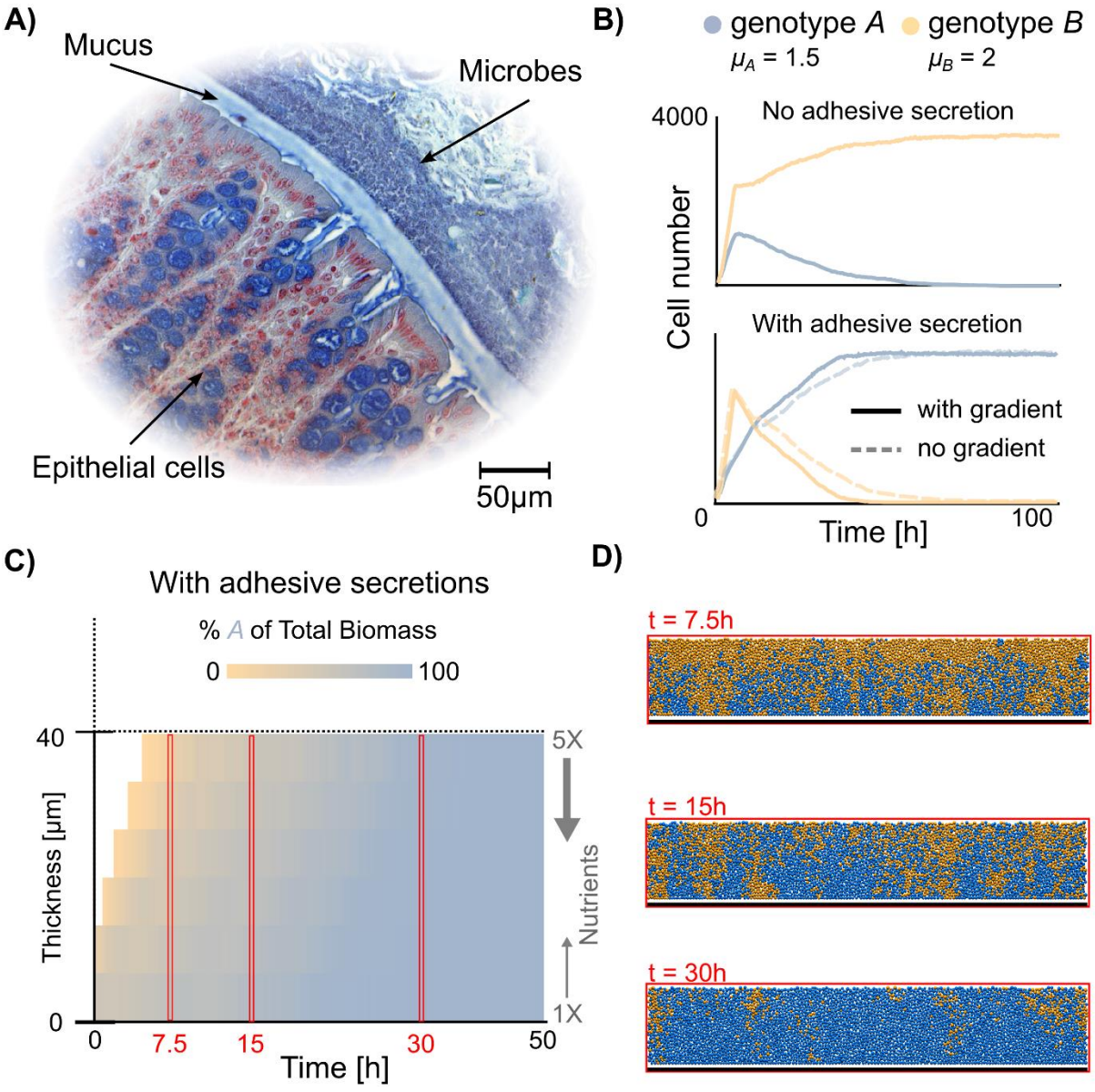

Figure 1. A host can use adhesion to select for a particular microbial genotype. We model competition between a slow-growing genotype *A* (blue) and a fast-growing genotype *B* (brown) on the gut epithelium. A) Biological scenario of model: micrograph of healthy mouse large intestine

(C57Bl/6 mouse, transverse colon stained with Alcian Blue). Photo credit: Lev Lichtenstein and Eugene Chang. B) Top: The faster growing brown genotype *B* (maximum growth rate, $\mu_B = 2$) outcompetes the blue strain *A* ($\mu_A = 1.5$) Bottom: When the host secretes a factor that increases the relative ability of strain *A* to resist displacement (adhesion, see methods), strain *A* can outcompete the faster growing strain *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 strain *A* to resist displacement, the two strains separate vertically from each other and strain *A* localizes below strain *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 are five times the epithelial nutrient concentrations. However, our conclusions are robust to other ratios of nutrient supply (Figure S1).

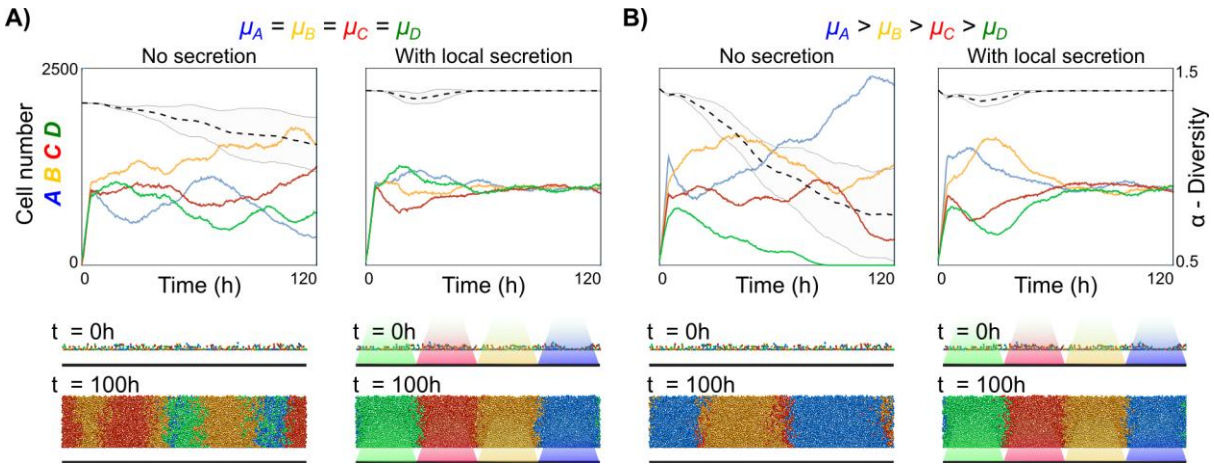

Figure 2. Horizontal gradients of host secretions maintain diversity. Here, four genotypes compete and the host may secrete four different factors in four different horizontal regions. Time-series data show cell number (left y-axis) of four genotypes over time for one representative simulation and are accompanied by alpha-diversity data across the whole simulation space from 50 independent simulations (right y-axis, black dotted line, the grey lines above and below show the standard error of the mean). Snapshots show the simulation at t=0h and t=100h, 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 centre of each region. Colours of host secretions correspond to colours 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. And accordingly, diversity tends to decrease slowly over time. When the host secretes factors that promote the ability of a species to resist displacement in a confined horizontal region, this provides a refugium for this genotype and diversity remains high. B) When species differ in their maximum growth rates, diversity loss occurs rapidly and dramatically. This can be prevented by host secretions that create ecological refugia for the slow growing species.

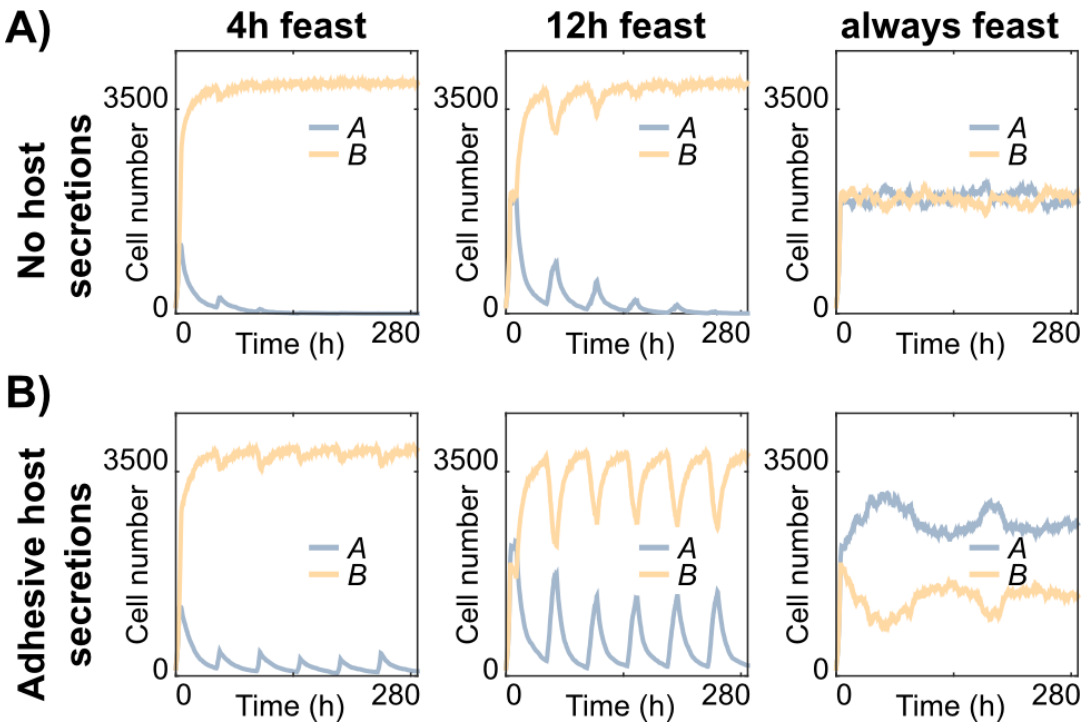

Figure 3: Adhesive host secretions promote microbiota stability in fluctuating environments. We simulate two genotypes, a generalist genotype *B* that can consume lumen nutrients which are available at all times. A second nutrient is only available periodically and the exclusive nutrient source for a specialist genotype *A*. We show 4h, and 12h feast durations per 48h 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).

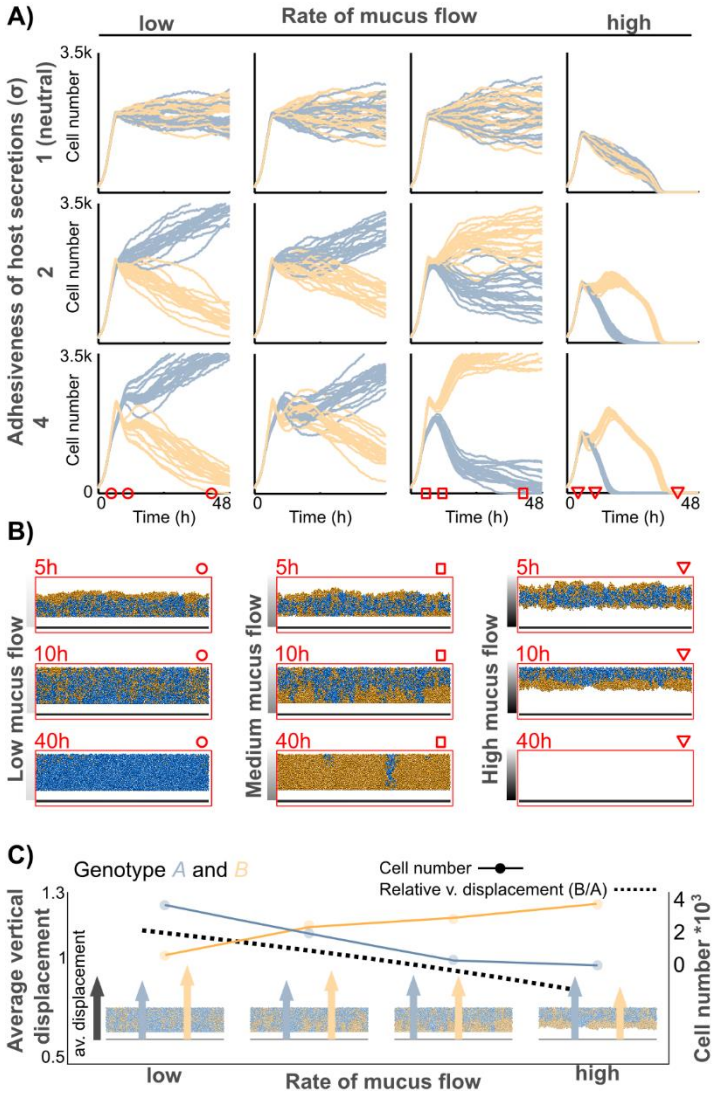

Figure 4. Hosts can combine adhesion and mucus flow to select for, or against, a particular microbial genotype. A) Each plot shows cell numbers of two genotypes, *A* (blue) and *B* (orange) over a 48h simulation period for 50 independent simulations. Without adhesion-promoting secretions from the host, both types are equal in all parameters and grow at the same rate (top row). At each timestep, cells are moved upwards and away from the epithelium simulating a mucus matrix in which cells are embedded and which pulls them along (Methods). 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 in 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 (3rd

column), the fate of the more adhesive genotype *A* is reversed and it is preferentially removed from the system relative to the non-adhesive genotype. 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 with higher 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/h. At low mucus flow rates, cells of genotype *A* experience less vertical movement relative to cells of genotype *B*. This 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. This leads to higher fitness (measured as cell number at t=22h) of the adhesive genotype *A* at low mucus flow, and lower fitness at high flow.