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Opinion

Not by (Good) Microbes Alone: Towards Immunocommensal Therapies

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Commensal bacteria have been identified as critical drivers of host resilience to pathogen invasion. The resulting 'competitive exclusion' of pathogens by commensals can arise via multiple mechanisms, including direct competition for sites of colonization, production of metabolic products that inhibit pathogen growth, and modulation of host immune responses (including differential targeting of pathogens). Nonetheless, suppression of pathogens through the combined action of commensals and host immunity is far from inevitable. Here, we utilize a simple, within-host ecosystem model to explore the microbiological and immunological conditions that govern the fate of pathogen colonization. Model analysis leads to the hypothesis that robust elimination of pathogens requires a synergy between host immune defense and commensal bacteria. That is, pathogens can proliferate and establish persistent infections if either the state of the microbiota or the host immune defense falls below critical levels. Leveraging these findings, we advocate for improved integration of nonlinear dynamic models in efforts to understand infection dynamics in an immunological context. Doing so may provide new opportunities to establish baseline indicators for healthy microbiomes and to develop improved therapeutics through targeted modification of feedback amongst commensals and between commensals and the immune system.

Highlights

The human microbiota is increasingly recognized as essential for protecting the host from pathogens.

The outcome of an infection is determined by the tripartite interactions between pathogen, the host microbiota, and the host immune system.

Existing mathematical models of human microbiota largely focus on microbial community interactions while the effects of the immune system are represented implicitly.

A modeling framework that explicitly considers immune responses is needed to understand the emergent system dynamics of pathogens, microbiota, and immunity.

An understanding of the microbiota as an integrated immunocommensal system may help to elucidate the role of the immunological context in opportunistic infections and guide host-targeted therapies for infections.

Tripartite Interactions between Pathogens, the Microbiota, and the Host Immune System

In the human body, bacterial pathogens, host microbiota, and the immune system interact and influence one another. For example, a healthy microbiota can suppress pathogen colonization by competitive exclusion [1,2], production of inhibitory products [3,4], modification of virulence expression in pathogens [5,6], and disruption of quorum sensing [7,8]. In addition, the microbiota can stimulate and regulate host immunity to improve defenses against pathogens and limit harmful inflammation [5,9,10]. The host immune system is hypothesized to maintain homeostasis with the microbiota [11,12] and shape the composition of commensal microbial communities [13,14].

The tripartite interactions between pathogen, commensal, and the host immune system change the fate of pathogen colonization and infection. For example, immunosuppressed patients may have disrupted microbiota that facilitate enhanced rates of pathogen colonization and infection [14–16]. It has also been hypothesized that commensal bacteria may exploit innate immune responses to inhibit microbial competitors [17]. However, the combined action of commensals and the immune system is not always beneficial for the human host. For example, probiotic therapies meant to augment baseline levels of commensal microbiota may have strong, negative consequences given immunological context. There are multiple lines of

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evidence that the addition of probiotics, for example, *Lactobacillus*, may cause infections or even sepsis in immunodeficient individuals [18–20]. In addition, evidence from a human gut model system suggested that homeostatic tolerance of the microbiota and probiotics efficacy are contingent on the integrity of the gut mucosal defense [21]. Similarly, a recent study showed that addition of probiotics enhanced susceptibility of immunosuppressed mice to *Cryptosporidium* – a parasite that causes infant diarrhea [22].

We hypothesize that the dynamics of pathogen invasion, or even the dynamics of apparently beneficial microbes, depends critically on interactions with the immune system. As a consequence, we contend that there is a need to adapt a tripartite perspective: considering the emergent dynamics of pathogens, commensals, and the immune system (Figure 1). The emergent dynamics might not be predictable from consideration of pairwise dynamics alone. Here we explore how mathematical models of nonlinear dynamics and feedback provide a potential tool to develop baseline predictions for dynamical outcomes and to shape the effective design of immunocommensal therapies.

Making the Implicit Explicit: Integrating Host Immunity in Microbiota Models

Mathematical modeling is a critical tool in efforts to understand systems-level effects of the human microbiota. In particular, models have generated insights on many aspects of the microbiota, including microbial community interaction networks [3,23,24], digestion [25], evolution of pathogen traits that modulate asymmetric competition [26], and the effects of antibiotics on the microbiota [27]. Yet, previous modeling efforts have largely focused on microbial interspecific interactions [3,23,24] and metabolic reactions of the host and bacteria [25,27,28]. In effect, the immune system's role in microbe–microbe dynamics is often realized implicitly. In an implicit framework, dynamics in distinct immunological states can be modeled given variation in quantitative rates or functional forms of interactions amongst microbes. However, immune populations are critical state variables. Modeling the dynamics of immune responses explicitly provides an opportunity to directly link mechanistic interactions to realized outcomes.

Integrating host immunity into predictive models of the microbiota is essential to elucidate how contributions from the host and microbiota combine to determine the success of commensal

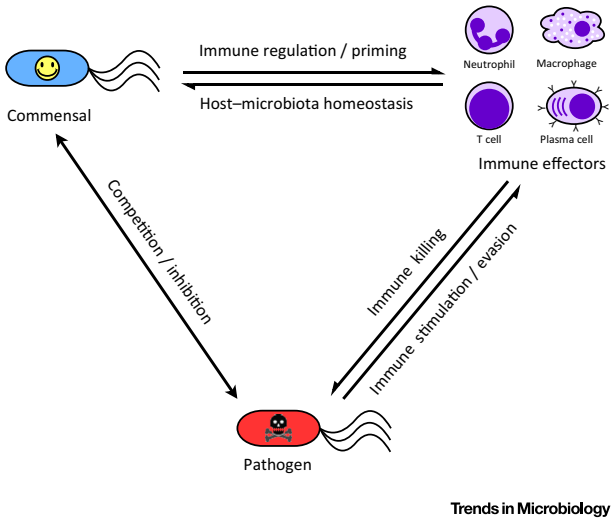

Figure 1. Schematic Showing Potential Interactions between Commensal Bacteria, Pathogenic Bacteria, and Different Components of the Host Immune System.

protection. There is precedent for such an approach in related research problems. For example, Levin and Bull developed a tripartite model of pathogens, a generalized immune response, and a lytic bacteriophage [29]. They hypothesized that inclusion of the lytic bacteriophage could lead to novel outcomes including protection against acute infections. Building upon the seminal work by Levin and Bull, we recently proposed a quantitative model describing synergy between host innate immunity and phage therapeutics to explore the quantitative outcomes of infection dynamics [30]. Our model suggests that the combined action of host immunity and phage may be able to eliminate the pathogen even when neither of them can do so when acting alone. We subsequently adapted our nonlinear population model to murine acute pneumonia involving *Pseudomonas aeruginosa* strain PAK [31]. Both the model and the experiments show that treatment by *P. aeruginosa* phage PAK-P1 led to curative success in immunocompetent mice, but not in mice with deficient innate immune signaling or depleted neutrophils. This work suggests the possibility for a more general set of principles, irrespective of whether the additional biological agent is a phage or another (potentially commensal) microbe.

As an illustrative example, Figure 2 shows a potential mechanism of how host immunity may work synergistically with commensal bacteria in providing resistance to pathogen colonization. Here, we assume that pathogenic bacteria can produce virulence factors that inhibit host

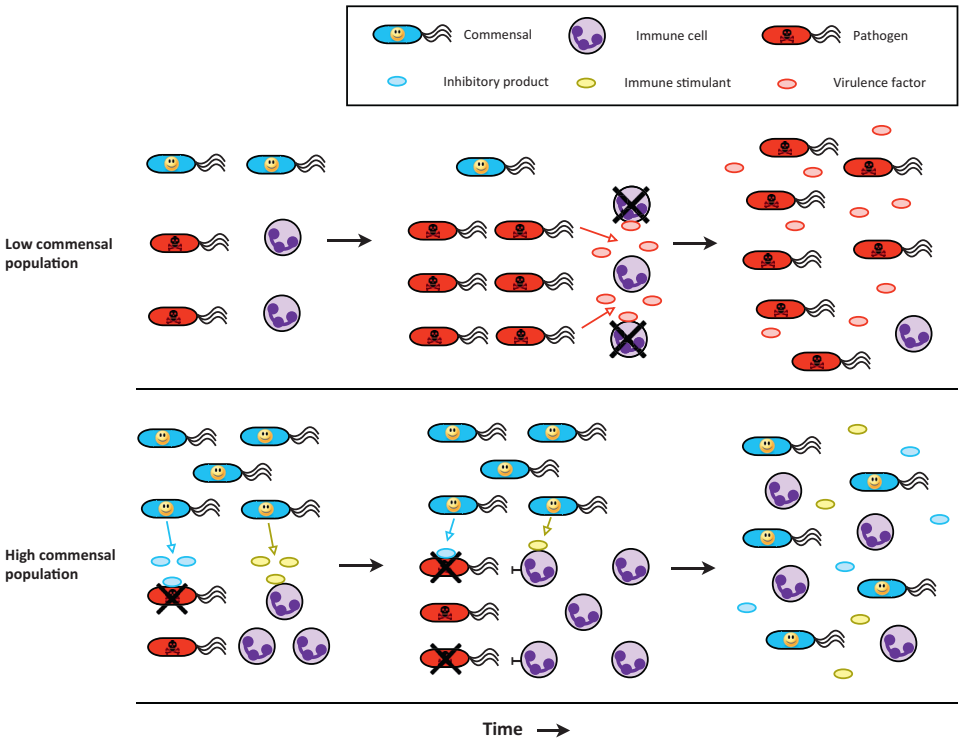

Figure 2. Schematic of a Possible Mechanism of Synergy between Commensal Bacteria and Host Immunity in Providing Protection against Pathogen Invasion. For low levels of initial commensal populations, invading pathogens are able to outcompete the commensal. After reaching a critical population size, the pathogen starts to produce virulence factor against host immune cells, enabling the pathogen to evade the immune response and persist. With a high commensal population, pathogen burden is reduced via competition and immune stimulation by commensals, preventing significant production of virulence factors. In that case, the combined action of commensal and host immunity then eliminates the pathogen.

immune killing [32–34] and that the production is activated at high population density, for example, by quorum sensing [32,35,36]. As such, when the initial commensal level is low, the invading pathogen can displace the commensal and reach a density sufficient to initiate production of virulence factor. The subsequent immune evasion enables the pathogen to persist. Alternatively, when the initial commensal level is high, commensal bacteria inhibit the pathogen and prime the immune response to keep the pathogen level low. This prevents significant production of the virulence factor. As a result, the increased efficiency of host immune defense is able to eliminate the pathogen when combined with commensal protection.

To evaluate the synergistic mechanism proposed in Figure 2, we developed a simple within-host population model that incorporates the nonlinear interactions between pathogen, commensal, and host immune responses (see Box 1 for the model details). In our model, the pathogenic and commensal strains of bacteria grow and compete with each other. The host immune response is activated in the presence of pathogen and primarily targets the pathogen for elimination while tolerating the commensal bacteria. We account for key immunological features including saturation of the immune response and immune evasion by bacteria at high densities.

Synergy between Immune Defense and Commensal Bacteria

To determine how commensal bacteria and host immunity influence the outcome of an infection, we simulated the model while selectively removing and including different model components. Figure 3A shows a comparison of the population dynamics of pathogenic bacteria in the presence of commensal bacteria only, host immune response only, and a combination of commensal competition and immune control. In the absence of host immunity, the inoculation of pathogenic bacteria can outcompete and displace the population of commensal bacteria. The pathogenic bacteria also persist in the presence of an immune response without commensal competition, provided that the bacterial inoculum is sufficiently high to overwhelm the immune response. However, when host immune killing is combined with commensal competition, the pathogenic bacteria are eliminated. This suggests that commensal bacteria and host immunity may be able to act synergistically ('immunocommensal' synergy), such that pathogen elimination is possible when both commensals and the immune response are present and active but not when either of them is absent.

To evaluate the generality and robustness of immunocommensal synergy, we study the effects of different microbiological and immunological parameters on the fate of an invading pathogen population (Figure 3B1,B2). In Figure 3B1, we systematically vary the competition parameters λ_{PC} and λ_{CP} under different host immune killing rates. As a baseline, consider the *in vitro* case with no immune response. In this case, the model reduces to the standard Lotka-Volterra competition model with three different possible outcomes: commensal domination, pathogen domination, and commensal–pathogen coexistence. Importantly, the results show that elimination of pathogen by commensal is possible only when the commensal population can strongly inhibit the pathogen ($\lambda_{PC} > 1$).

With the help of host immunity, the requirement for the strength of commensal competition λ_{PC} to eliminate the pathogen is lowered (elimination possible for $\lambda_{PC} < 1$). As such, there is a parameter regime where pathogen elimination is possible in the presence of both commensal and the immune response but not when host immunity is absent. Further expansion of the regime of pathogen elimination is observed for higher immune killing rate, for example, comparable to an immunocompetent neutrophilic response [38]. In this case, the combination

Box 1. Modeling Commensal–Pathogen–Immune Dynamics

Model Description

The model describes the interactions between pathogenic bacteria (B_P), commensal bacteria (B_C) and host immunity (I) targeting the pathogenic bacteria (see schematic in Figure I). In this model, the pathogenic and commensal bacterial populations grow and inhibit each other through competition. Here the commensal bacteria are assumed to be well tolerated by the host immune system, and the immune response primarily targets the pathogenic bacteria.

This model incorporates two key features of the host immune response. First, the immune response saturates at high intensity as suggested by experimental evidence that the killing capacity of the immune response is finite and can be saturated [37–39]. Second, it is assumed that the bacteria can evade the immune response in a density-dependent manner. For example, pathogenic bacteria can utilize quorum sensing to activate immune evasion strategies such as biofilm formation and production of virulence factors at high population density [32,35,36]. It has been shown previously that these two assumptions together can lead to dose-dependent alternative infection outcomes, including bacterial elimination and long-term bacterial persistence [30], consistent with the empirical observation of an infectious dose required to establish an infection [40].

$$\dot{B}_P = \overbrace{r_P B_P \underbrace{\left(1 - \frac{B_P + \lambda_{PC} B_C}{K_P}\right)}_{\text{Competition}}}^{\text{Growth}} - \overbrace{\frac{\varepsilon I B_P}{1 + B_P/K_D}}^{\text{Immune killing}}, \quad [\text{I}]$$

$$\dot{B}_C = r_C B_C \left(1 - \frac{\lambda_{CP} B_P + B_C}{K_C}\right), \quad [\text{II}]$$

$$\dot{I} = \overbrace{\alpha I \left(1 - \frac{I}{K_I}\right)\left(\frac{B_P}{B_P + K_N}\right)}^{\text{Immune stimulation}} \quad [\text{III}]$$

We propose a system of coupled differential equations (**Equations I–III**) comprising a Lotka-Volterra competition model coupled to an immune component. Here, r_P and r_C are the maximum growth rates of strain B_P and B_C, respectively. K_P and K_C are the respective carrying capacities of strain B_P and B_C in the absence of the competing strain. λ_{PC} is the inhibitory strength of B_C on B_P due to competition, and λ_{CP} is the inhibitory strength of B_P on B_C. The pathogenic bacteria are killed by the immune response with a rate parameter given by ε. However, B_P can overwhelm or evade the immune response when it reaches a high population density, with a half-saturation density of K_D. The immune response is stimulated by the pathogenic bacteria at a maximum rate of α until it saturates at the maximum immune intensity K_I. K_N is the bacterial density at which the rate of immune stimulation is half its maximum.

This model has three qualitatively distinct outcomes, including a commensal-dominated regime (in which pathogens are eliminated), a pathogen-dominated regime (in which commensals are eliminated), and a coexistence regime.

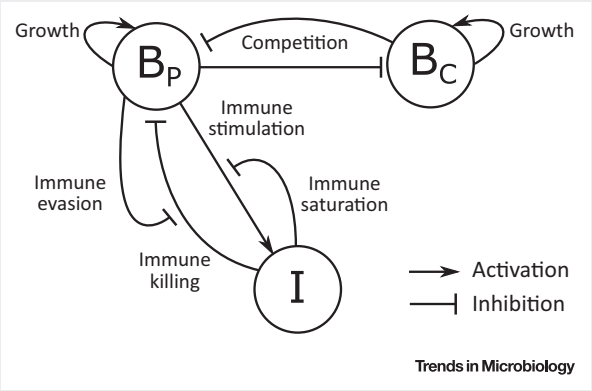

Figure I. Schematic and Equations of the Model with Interactions between Pathogenic Bacteria (B_P), Commensal Bacteria (B_C), and Host Immunity Targeting the Pathogenic Bacteria (I).

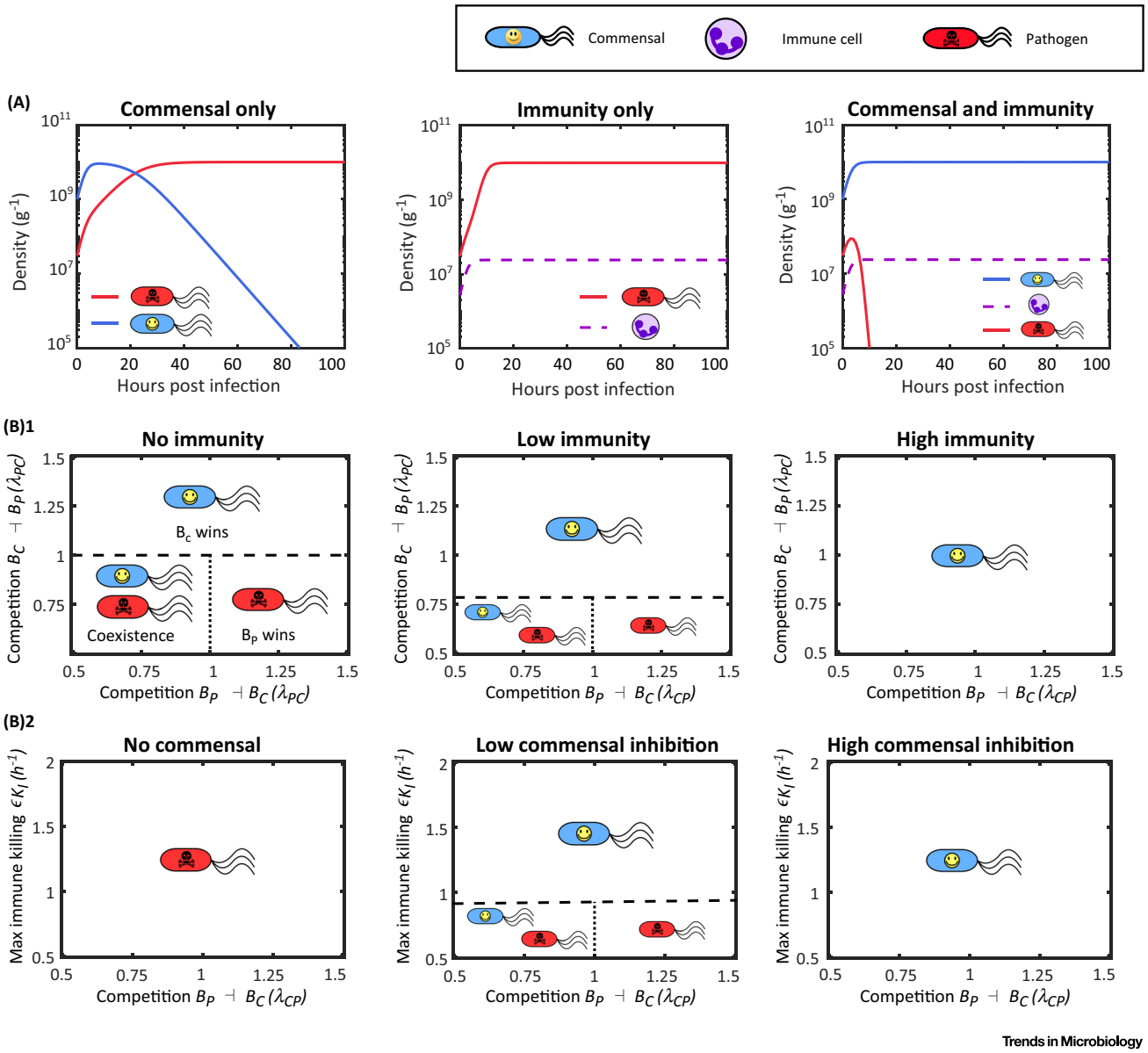

Figure 3. Population Dynamics and Regimes of Steady States from the Model at Different Levels of Host Immunity and Commensal Protection. (A) Commensal competition and host immune response can synergistically eliminate the pathogen even when neither of them can do so alone. The figures show time series of population densities of pathogen B_P, commensal B_C, and host immune effector I. The panels correspond to cases with the pathogen interacting with commensal bacteria only, host immunity only, and a combination of commensal and host immunity. The bacterial competition parameters are given by $\lambda_{PC} = 0.75$ and $\lambda_{CP} = 1.25$. (B1,B2) The combination of commensal competition and host immunity lowers the commensal inhibitory strength and immune killing rate required for pathogen elimination. (B1) Different regimes of infection outcomes as functions of the competition parameters λ_{CP} and λ_{PC} at different levels of immune responses: no immunity, low immune killing ($\varepsilon K_I = 0.82\ h^{-1}$), and high immune killing ($\varepsilon K_I = 1.97\ h^{-1}$). (B2) Different regimes of infection outcomes as functions of λ_{CP} and maximum immune killing rate εK_I at different levels of commensal inhibition: no commensal, low inhibition ($\lambda_{PC} = 0.75$), and high inhibition ($\lambda_{PC} = 1.25$). The black dashed line and dotted line mark the thresholds of the different parameter regimes. The parameters for all simulations are given by $r_P = r_C = 0.75\ h^{-1}$, $K_P = K_C = 10^{10}$ cell/g, $\varepsilon = 8.2 \times 10^{-8}$ g/(h cell), $K_D = 4.1 \times 10^7$ cell/g, $\alpha = 0.97\ h^{-1}$, and $K_N = 10^7$ cell/g. The initial conditions are $B_{P0} = 3 \times 10^7\ (g^{-1})$, $B_{C0} = 10^9\ (g^{-1})$, and $I_0 = 2.7 \times 10^6\ (g^{-1})$.

of commensal competition and host immune killing is sufficient to eliminate the pathogen even when the commensal is expected to be significantly outcompeted on its own.

In Figure 3B2, we investigate the effects of maximum immune killing rate (εK_I) on immunocommensal synergy at different levels of commensal inhibition (λ_{PC}). In the absence of commensal bacteria, pathogen elimination is not observed, even at high immune killing rates. A low commensal inhibitory strength is sufficient for the commensal population to dramatically reduce the immune killing rate required for pathogen elimination. At a high level of commensal inhibition, pathogen elimination becomes more robust and is observed even at maximum immune killing rates that are lower than the maximum pathogen growth rate ($\varepsilon K_I < r_P = 0.75\ h^{-1}$). As such, there is a parameter regime where host immunity alone cannot eliminate the pathogen even at high immune killing rate, but can easily do so when combined with commensal protection. Taken together, these results suggest a robust mechanism for host immunity and the microbiota to synergistically eliminate pathogens. This synergy highlights how nonadditive effects can arise from density-dependent feedback and drive the dynamics of commensal protection.

Concluding Remarks

We have developed a simple model of immunocommensal synergy that suggests that the combined effects of host immunity and commensals may control the outcome of pathogen invasion. We speculate that commensals and the immune response can prevent pathogen proliferation due to nonlinear feedbacks, even in the absence of direct stimulation or regulation of the immune response by the commensal microbiota. As a result, we suggest the need to prioritize studies of emergent system dynamics of pathogens, microbiota, and immunity in addition to examining molecular and cellular mechanisms modulating host–pathogen or commensal–pathogen interactions.

To characterize the immunocommensal interactions in this tripartite system quantitatively, we advocate for a conceptual framework that makes the implicit immune system explicit. Such an approach has the potential to characterize the relative contributions of commensal bacteria and host immunity to protecting against or eliminating bacterial pathogens. Under this framework, the combined action of microbiota and host immunity may be synergistic, additive, or antagonistic. Although our model examines the synergistic regime, we recognize that such benefits need not always occur.

Our proof-of-principle model demonstrates the relevance and potential impact of immunocommensal synergy. Such a synergistic effect can be tested empirically in a way similar to how synergistic drug combinations are identified by comparing the response of the combination to the additive effect of the individual drug components [41]. Likewise, the effect of combining immune and commensal protection can be compared to their individual effects when acting on the pathogen alone. In principle, this can be achieved in animal experiments by studying the protective effects of different doses of commensal bacteria on immunomodulated hosts with varying levels of immunodeficiency. While quantitative control of the host immune response and commensal population may prove challenging, we have employed a similar approach in an earlier study to reveal a synergistic effect between host neutrophils and phage therapeutics [31]. We also advocate for improved monitoring of host immune status in microbiome studies and human clinical trials of probiotics. Integration of host microbiome and immunological data will provide much needed insights into the interplay and potential synergy between the microbiota and host immune system.

Our simple model has a number of limitations and can be extended in different ways. For example, we have assumed that the host immune response preferentially targets the

Outstanding Questions

What are the microbiological and immunological conditions for synergistic elimination of pathogens by host immunity and the microbiota?

To what extent is host immunity driving microbial interactions within the microbiota?

How does host immunity influence the composition and stability of the microbiota?

What is the role of host immune and commensal interactions in shaping opportunistic infections caused by microbes not typically considered as pathogens?

How is it possible to leverage nonlinear dynamics principles to manipulate immune–microbe feedbacks to enhance microbiome resilience?

pathogenic bacteria. We have not yet included other mechanisms such as the detrimental effects of excessive inflammation on mucosal immunity [42,43], the existence of potentially harmful pathobionts in the microbiota [44,45], and immune regulation or priming by commensals [46,47]. In addition, bacterial pathogens can modulate their surface to thwart immune surveillance [48] or promote inflammation to remove competing commensals [49]. These generalized mechanisms may lead to less than synergistic or even antagonistic interactions between host immunity and the microbiota. Future models will need to incorporate these complex interactions as well as more realistic microbial community structure. Our model may also be generalized to consider infections caused by opportunistic pathogens that are not typically associated with infections in healthy individuals, including multiple species in the genera *Pseudomonas*, *Acinetobacter*, and *Campylobacter* [50]. Such opportunistic infections depend crucially on immunological context [51,52], and future extension of this modeling framework may incorporate interactions between pathogenicity and host immune status (see Outstanding Questions).

The understanding of the microbiota as an integrated immunocommensal system also suggests the benefits of therapeutically targeting the host immune system in conjunction with commensal bacteria for improved infection treatments and more effective microbiome engineering. Current methods of microbiome engineering rely on targeting the within-host bacterial community using chemical or biological agents such as antibiotics, probiotics, phage, or microbiome transfer [53,54]. The host immune response exerts strong selective pressures on bacteria within the host [55,56], and is therefore an attractive alternative target for modulating the microbiota. For example, host-targeted therapy such as immune stimulation by drugs or bacterial extracts [57,58] may be administered as an adjuvant to antibiotic and/or probiotic therapy. Characterizing the effects of these interactions in the human microbiota may lead to translationally relevant models and deepen our understanding of the protective functions of the microbiota against invasive pathogens.

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