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RESEARCH HIGHLIGHT

Remembering past infections: training exercise for gut microbes

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Colonization resistance is considered a key defense strategy against infection with pathogens. In a recent study published in *Cell*, Stacy et al. identify and dissect a novel, active, microbiome-mediated molecular resistance mechanism; upon pathogenic infection, the "memorizing" microbiome develops a capacity of secreting taurine to restrict pathogen respiration, thereby inducing infection resistance to subsequent exposures.

The microbiota is considered a crucial barrier to infection, by promoting resistance to pathogens in various ways, such as through promotion of host immunity and protective occupation of biological niches.[1] Indeed, disruption of the microbiota with antibiotics can lead to emergence of pathogens such as *Clostridium difficile*, while reintroduction of a healthy microbiota through fecal microbiota transplantation is considered an effective method of cure.[2] Whether a pathogenic encounter by the microbiota induces a differential response to future pathogen insults remains unknown.

In a recent study in *Cell*, Belkaid and colleagues now demonstrate that the microbiota may "remember" past infection, while eliciting an increased resistance to infection with similar pathogens in subsequent invasions, through an intriguing molecular mechanism.[3] The authors exemplify this concept by demonstrating that a pathogenic insult by a transiently infective strain of *Yersinia pseudotuberculosis* leads to compositional and functional changes in the gut microbiota, which, in turn, induce protection from subsequent exposure to the pathobiont *Klebsiella pneumoniae*. Interestingly, the authors show that mice harboring a wild mouse microbiota, characterized by prior exposures to multiple "real-life" bouts of infection, shared similar features to the "trained" microbiota of previously *Y. pseudotuberculosis*-infected SPF mice. They identify taurine-utilizing members of the microbiota, such as *Desulfuvibrio*, as key enriched elements in both microbiota configurations and propose them to constitute major mediators of increased pathogenic resistance in this setting. Indeed, taurine supplementation expands taurine-utilizing bacteria, which utilize taurine to generate sulfides which, in turn, directly inhibit aerobic respiration and growth of *K. Pneumoniae* (Fig. 1). In contrast, sequestration of sulfide by Bismuth leads to increased *K. pneumoniae* respiration and resultant pathogen expansion. These findings highlight the constant arms race between commensals and invading pathogens. While pathogens such as *K. pneumoniae* exploit key environmental niches such as oxygen availability to confer competitive advantage to themselves over the commensal inhabitants, the microbiota has evolved ways to effectively counter these strategies through induction of anti-microbial mechanisms protecting homeostasis and resisting infection.

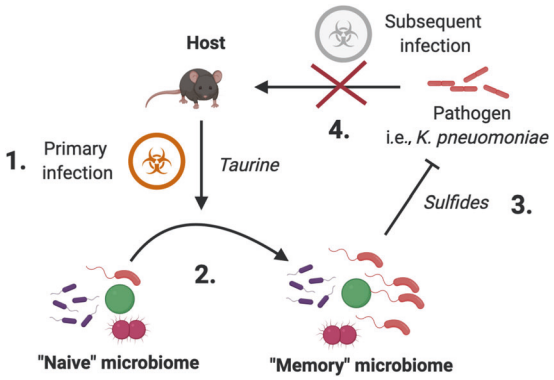

Fig. 1 Key steps by which primary infection modulates the host microbiota crosstalk to promote infection resistance. (1) During primary infection, the host increases production of taurine; (2) increased availability of taurine promotes adaptation of the microbiome to a new functional configuration; (3) exposure to another pathogen leads to production of sulfides by the "memory microbiota"; which, in turn (4), prevents re-infection with pathogens by inhibiting cellular respiration.

Conceptually, the important findings by Belkaid and colleagues have several major implications. In addition to the traditional view of host infectious memory mediated by its adaptive immune arm and the more recently described trained immunity of innate immune cells,[4] the memory of the microbiota adds a new facet of defense mechanism against recurring pathogens. A similar microbiota memory has been described to drive non-communicable diseases such as obesity, through induction of resilient compositional alterations during obesity that drive exaggerated weight regain upon future exposure to obesogenic conditions.[5] This intriguing microbiome training concept highlights the striking complementarity between the host and its microbiota in providing buffering capacities to the holobiont from recurrent metabolic and infectious insults. Metabolites secreted, degraded or modulated by the microbiome are likely to play important roles in contributing to such microbial memory. The elegant roles of taurine and downstream products in inducing direct anti-pathogenic protection may complement its other innate roles in impacting host intestinal gut barrier[6] and innate immune signaling.[7] Of note, infection with helminths can also

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prevent colonization with specific members of the microbiota,[8] while the microbiota plays crucial roles in regulating basic resistance to viral infection via induction of type I interferon reactions.[9] Future studies stemming from the findings introduced by Belkaid and colleagues will likely investigate whether microbiota memory can be observed in infections with other types of bacterial, viral and helminthic pathogens, while elucidating the molecular microbial mechanisms driving memory in these contexts.

In summary, the important findings by Belkaid and colleagues highlight a previously unappreciated microbiota-induced active memory against competing pathogenic gut invaders. These findings convincingly demonstrate that such protective immunity spans far beyond the passive colonization resistance or host immune activation, and involves a complex array of bacteria–bacteria communication. Further decoding of such communication channels, their underlying small-molecule mediators, and downstream impacts on host local and systemic infectious resistance (and possibly other "non-communicable" traits) will likely enable the recognition of therapeutic manipulation of this intriguing "microbial memory" towards induction of infection control and prevention.

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