MICROBIOLOGY

Keeping Bacteria at a Distance

An antibacterial peptide is essential for restricting contact between the intestinal microbiota and host.

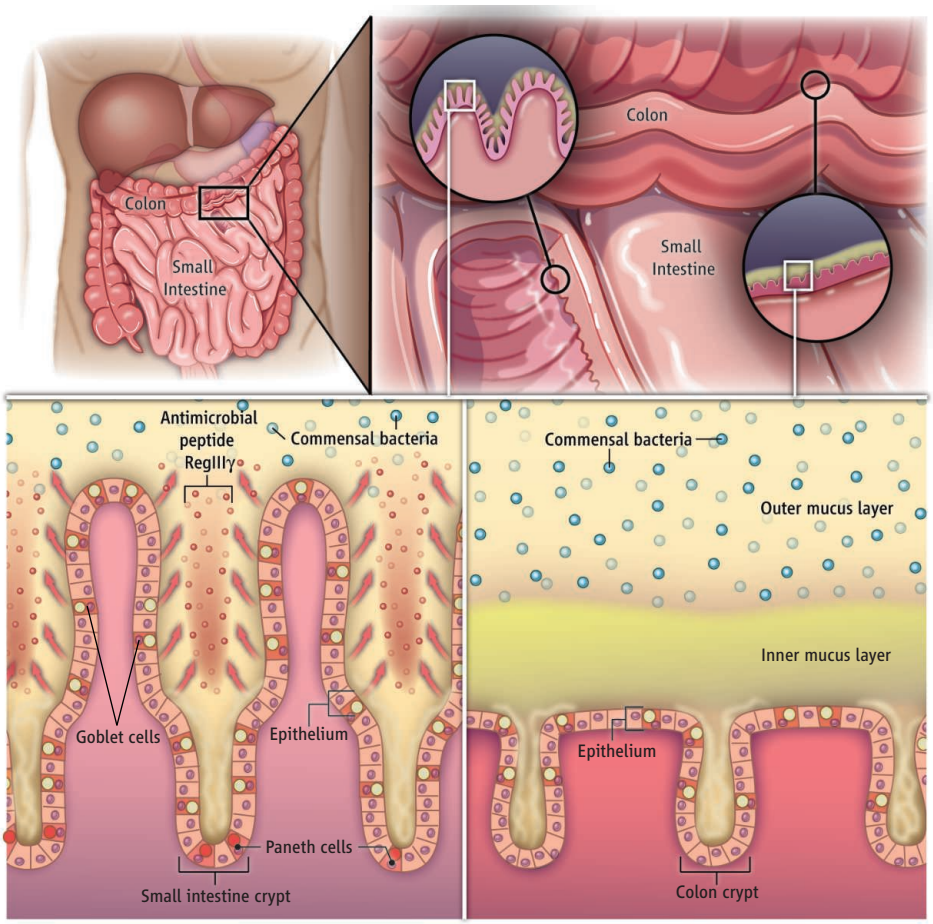
Malin E. V. Johansson and Gunnar C. Hansson

The human intestine harbors enormous amounts of bacteria that have an essential role in host metabolism, but how this mutualistic balance is maintained is unclear. The current understanding has focused on the concept that bacteria continuously interact with the intestinal immune system in a balanced proinflammatory and tolerogenic way. The discovery of a protective inner mucus layer in the colon that separates bacteria from the epithelium has broadened this view (*1*). On page 255 of this issue, Vaishnava *et al*. (*2*) show that the antibacterial protein RegIIIγ secreted by specialized epithelial cells is involved in limiting the epithelial contact with bacteria in the small intestine. This observation further substantiates the role of intestinal epithelial cells and the mucus that covers them as important parts of the innate immune defense.

The small intestine and colon are quite different organs, especially when it comes to the relation between bacteria and host. The colon is protected by an inner mucus layer that is firmly attached to the epithelium and protects it from bacteria and from mechanical stress. This layer is continuously converted to an outer, less dense mucus layer, which is the habitat for the commensal bacteria (see the figure) (*1*, *3*). By contrast, such a compact inner mucus layer in the small intestine would be detrimental as the small intestine must absorb nutrients. Fast peristaltic propulsion in the distal direction, fluid and mucus secretion, and antibacterial proteins instead maintain homeostasis in this intestinal region. The type of mucus that covers the small intestine, unlike that of the colon, is not attached to the epithelium and is permeable to bacteria (*4*). Yet, Vaishnava *et al*. show that bacteria are kept at a distance from the epithelium by the antibacterial protein RegIIIγ, which is secreted into the small intestinal mucus by the enterocytes (*2*).

The mucus of both the small intestine and colon is organized around the net-like polymer formed by the MUC2 mucin (*3*). It is unclear why the same protein gives rise to mucus with different properties in these organs. In the small intestine, the mucus gel acts as a mesh that retains the antibacterial proteins capable of killing the trapped bacteria. The mucus gel is also continuously replenished by secretion from the mucus-secreting goblet cells, providing a rapidly renewable system protecting the small intestine. Vaishnava *et al*. show that in RegIIIγ-deficient mice, more bacteria reach the small intestinal epithelium and trigger the adaptive immune response with increased immunoglobulin A (produced by B cells located beneath the epithelial cells, throughout the intestine) and T helper 1 cells. RegIIIγ is not produced in the colon, where instead the inner mucus layer provides protection. In the absence of the MUC2 mucin in the colon, bacteria reach the epithelium and trigger an overt immune reaction and colitis (*1*, *5*).

In the small intestine, invaginations of the epithelium called crypts contain Paneth cells and the epithelial stem cells (*6*). The Paneth cells constitutively produce high amounts of antibacterial peptides, lysozyme (hydrolyzes bacterial cell wall peptidoglycans), and MUC2 mucin (*7*, *8*). These antibacterial peptides (such as defensins) become trapped in the intestinal mucus. Vaishnava *et al*. show that the more common cells in the intestinal epithelium, the enterocytes, have a regulated feedback system through which bacteria are sensed, probably by Toll-like receptors (TLRs). These receptors signal through the adaptor protein MyD88 and induce RegIIIγ secretion. The enterocytes thereby control



Intestinal protection. The intestinal epithelium is covered by mucus. In the colon, the inner stratified mucus layer acts as a physical barrier separating bacteria from the epithelium. The commensal bacteria are kept at a distance in the penetrable outer mucus layer. The small intestine is only covered with penetrable mucus, where antibacterial molecules such as RegIIIγ generate a bacteria-depleted region close to the epithelium.

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and limit the bacterial load at the epithelial surface. RegIIIγ specifically affects Gram-positive bacteria, and only the mucus-associated bacteria showed reduced numbers as compared to RegIIIγ-deficient mice. How the number of commensal Gram-negative bacteria in the small intestine is controlled is not understood. No RegIIIγ-dependent alterations in the luminal flora were evident in RegIIIγ-deficient mice suggesting that the antibacterial protein was inactivated, degraded, or sufficiently diluted when it reached the intestinal lumen.

The findings of Vaishnava *et al*. emphasize the role of intestinal epithelium and its enterocytes in orchestrating the intestinal defense system (*9*). The epithelium not only senses the intestinal bacterial milieu and responds by secreting RegIIIγ, but also relays information to the host's adaptive immune system about microbial penetration of the mucus (*10*). Reciprocally, the intestinal epithelium also responds to signals from the immune system to alter the mucus properties and turnover as suggested from studies of parasite infections (*8*).

The separation of bacteria and epithelium has emerged as a new concept underlying host-microbiota homeostasis in the small intestine and colon, although by different mechanisms. The different ways these organs solve the challenge of bacterial colonization must have evolved to meet the different physiological needs. However, there is still much to learn about how mucus properties are controlled and how enterocytes sense and coordinate the host response to intestinal bacteria.

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MATERIALS SCIENCE

Self-Assembly Enters the Design Era

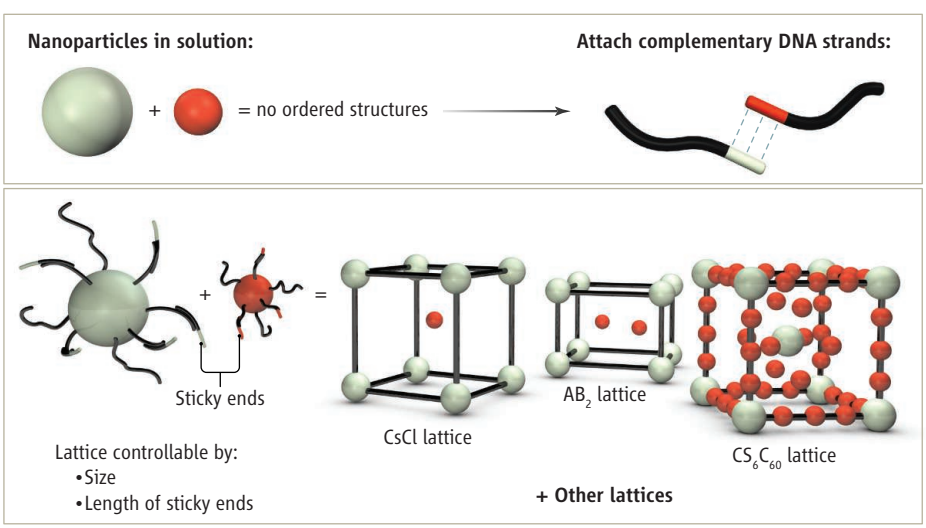
A set of simple rules is used to design and control the self-assembly of nanoparticles into complex structures.

Alex Travesset

Nanotechnology holds the key to the discovery of materials with the electronic, optical, mechanical, or transport properties required to overcome many of today's technological challenges. The past two decades have seen impressive progress in the synthesis of nanoparticles with astonishing properties (*1*). Bringing the potential of nanotechnology to reality requires an in-depth understanding of how to precisely assemble nanoparticles into structures and/or phases over multiple length scales, but this has proven enormously difficult to accomplish. Assembling nanoparticles into periodic structures, for example, has only been achieved for a handful of systems under very specific conditions (*2*). On page 204 of this issue, Macfarlane *et al*. (*3*) show that the use of single-stranded DNA as linkers provides a general strategy to program the self-assembly of almost any nanoparticle into a wide range of different periodic structures and do so with an exquisite control over their properties.

In the mid-1990s the method of using complementary DNA strands as linkers to direct the self-assembly of nanoparticles was pioneered (*4*, *5*). A decade later saw the major breakthrough of programming gold nanoparticles to self-assemble into lattices (*6*, *7*), thus opening the door for a rational design of general periodic structures of nanoparticles. The work of Macfarlane *et al*. is likely to elevate DNA-programmed self-assembly into a technique for the design of nanoparticle structures a la carte. They report nanoparticle crystals with nine different space symmetries, show how to precisely tune the lattice constant to basically any arbitrary value, and provide six simple rules that allow them to predict the lattice structure into which the nanoparticles will self-assemble (see the figure).

There are many open questions as well as exciting opportunities following from this work. For example, the crystalline structures reported are limited in size, typically involving a few thousand nanoparticles. The origin of this limitation is unclear. The authors have gone to impressive lengths to show the reproducibility of the results under a wide range of diverse conditions; hence, there must be a physical effect behind this size limitation. Experimental studies focusing on



Putting it together. Assembling nanoparticles into structures presents extraordinary difficulties. Attaching them with complementary single-stranded DNA linkers (or "sticky ends") overcomes all these difficulties, resulting in the controlled self-assembly of nanoparticles with exquisite control over their properties. AB_2 is a lattice isostructural with aluminum diboride.

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