PHYSIOLOGY

Forming a mucus barrier along the colon

Optimal barrier function requires both proximal colon– and distal colon–derived mucus

By **George M. H. Birchenough** and **Malin E. V. Johansson**

The intestine is exposed to numerous hazards and is heavily colonized by microorganisms. This requires a balanced protective system, which includes secreted mucus layers that play an important role in keeping luminal contents, including bacteria, separated from the epithelium (*1*). Intestinal mucus contains many different proteins, and the densely O-glycosylated mucin 2 (MUC2) is the core molecule (*2*, *3*). Colonic mucus defects that allow bacteria to reach the epithelium have been associated with colitis (*4*). On page 467 of this issue, Bergstrom *et al.* (*5*) expand our understanding of the colonic mucus system by showing that mucus from proximal colonic regions contributes extensively to forming the protective barrier in the distal colon. This work highlights the role of the colonic tissue as a whole in driving mucus barrier formation and indicates the potential for regionally targeted therapeutic interventions in intestinal disease.

Mucus coating on distal colonic fecal material has been previously observed (*6*), but Bergstrom *et al.* used glycan-specific lectin staining of fixed whole mouse colons to differentiate between differently O-glycosylated mucus originating from proximal and distal colonic regions. They found that proximal colon–derived mucus primarily encapsulates fecal pellets as they form and is further strengthened by a secondary encapsulation of mucus produced in the distal colon. Thus, mucus from both regions is associated with the excreted pellet. The authors showed that regions between pellets normally harbor relatively low numbers of bacteria compared with mucus-encapsulated pellets. Inducing mucus defects in the proximal or distal colon of mice increased the bacterial load in areas between pellets. This enhanced contact between uncontained bacteria and the epithelium led to inflammation that was most pronounced in the distal colon. Simultaneous disruption of the proximal- and distal-derived mucus resulted in severe loss of barrier function, highlighting the need for cooperation between proximal and distal mucus production in maintaining the protective barrier.

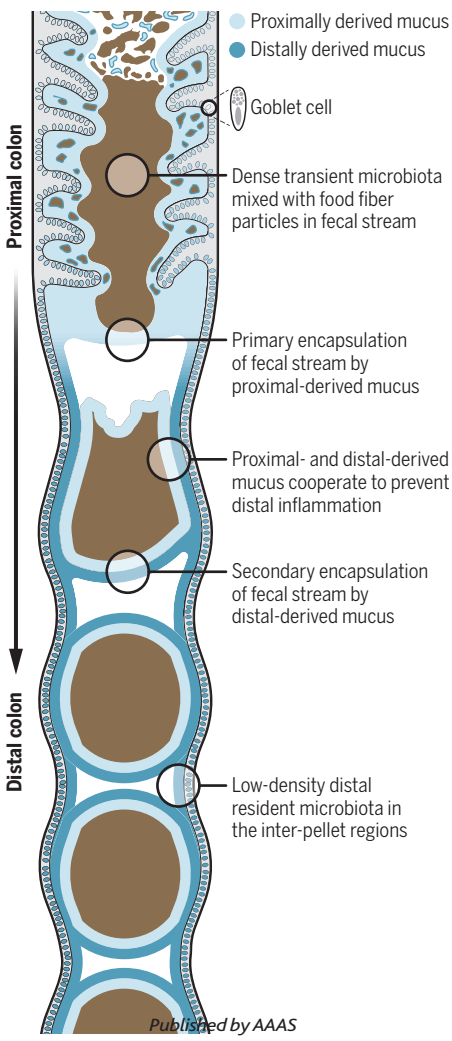
It should be noted that analysis of mucus in fixed tissue sections is challenging because secreted mucus is highly hydrated and shrinks upon exposure to chemical fixatives. In addition, secreted mucus is rarely preserved in fixed intestinal tissue that does not contain fecal material. Indeed, analysis of mucus in live tissue demonstrates that it forms a continuous attached layer on the epithelium throughout the intestine (*7*–*9*). This attached mucus contains several components that restrict direct bacterial contact as part of its protective properties (*9*, *10*). By combining our current understanding of the mucus system with the findings of Bergstrom *et al.*, it is likely that the in vivo mucus barrier comprises an attached mucus layer that covers the epithelium as a local barrier, which is detached gradually and thereby continuously added to the passing fecal pellets (see the figure).

With regard to microbiota-mucus interactions, Bergstrom *et al.* found that formation of the proximal-derived, but not the distal-derived, mucus layer was dependent on bacterial colonization. This effect was not mediated by inflammasomes (innate immune signaling complexes that can play a role in microbe-dependent mucus secretion), suggesting a mechanism different from the fast mucus secretory response to bacteria mediated by microbe-sensing sentinel goblet cells within the colonic epithelium (*11*). The proximal mucus also had marked effects on microbiota composition and metabolism. Mucus alterations in the proximal colon would likely have effects on the mucus niche–associated resident microbiota that are found in the folds of the proximal colon and are thought to have a more intimate relationship with the host than the transient microbiota (*12*). The high load of propagating bacteria in the proximal colon combined with mucus and bacteria from the small intestine and cecum make up the bulk of the fecal pellets in mice. However, there are also mucus-associated bacteria along the length of the intestine that differ in composition from the bulk material found in the fecal stream (*13*).

Bergstrom *et al.* and others (*6*) have noted the paucity of bacteria in the inter-pellet regions in histological sections; however, live imaging and quantitative and qualitative microbiota characterization have indicated the presence of a robust bacterial community that is dominated by mucus specialists (e.g., *Mucispirillum*) (*9*). This mucus-associated community likely represents the distal colonic equivalent of the resident microbiota in the proximal colon, and it probably undergoes interactions with host tissues distinct from those between the encapsulated pellet microbiota and host tissues. Loss of the distinction between mucus-associated and encapsulated bacteria may be associated with disease.

The mucus barrier

Continuous colonic mucus barrier formation along the proximal-distal axis is required for effective barrier function and results in the formation of distinct microbial niche environments.



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The mucus barrier is a critical defensive system that inhibits the interaction of pathogens with the intestinal epithelium. However, many specialized intestinal pathogens have evolved mechanisms that allow them to penetrate the mucus barrier and initiate mucosal infections (*14*). The study of Bergstrom *et al.* raises questions about the spatiotemporal pathogenesis of these infections. For example, does an intestinal pathogen that infects the distal colon first have to escape mucus encapsulation in the proximal colon? Or must separate strategies be employed to penetrate proximally and distally derived mucus barriers that have distinct properties?

Bergstrom *et al.* also detected mucus layer coating of excreted fecal material in both baboons and humans (*5*). The colonic regional origin of the mucus in these samples was not determined; however, it is possible that an analogous continual mucus encapsulation process is active in humans. It is also possible that differences in function, motility, total transit time, and luminal consistency could result in more species-specific solutions to protect the epithelium. In humans, the relatively long exposure to the fecal material and its much higher water content likely give rise to different demands for the mucosal surface. Similarly, mucus secreted in the more proximal elements of the human intestine is exposed to the degradative action of bacteria for a longer period than in mice. In this context, locally produced mucus protection in the human distal colon could be even more crucial for health. Further investigation of how the mucus system works throughout the colon in humans is critical to provide targeted aid to the increasing number of people with intestinal disorders. ■

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SOCIAL PSYCHOLOGY

The upside of aging

Chimpanzees, like humans, place a higher value on positive social relationships as they grow older

By **Joan Silk**

A primary goal of science is to produce robust and generalizable theories of empirical phenomena. For psychologists, the phenomena of interest are the human mind and behavior. Both the robustness and generalizability of psychological theories have come into question over the past decade. Experimental findings from some of the most widely known theories in social psychology could not be reproduced, provoking what is sometimes called the replication crisis (*1*). Moreover, results derived from studies of Western, educated, industrialized, rich, and democratic (WEIRD) societies do not always generalize to a more diverse range of human societies (*2*). Comparative studies of humans and other species can reveal which psychological theories generalize to other species and which apply only to humans. On page 473 of this issue, Rosati *et al.* (*3*) use comparative data to assess the tenets of one prominent theory in social psychology.

Socioemotional selectivity theory (SST) posits that humans become progressively more aware of their mortality, and this awareness prompts us to place a greater priority on positive social relationships as we grow older (*4*). People in several—mainly WEIRD—societies show this pattern (*4*). If these effects are linked to a conscious awareness of the passage of time and knowledge of our own mortality, the pattern should not generalize to other species that do not have a similarly sophisticated concept of time or the capacity to anticipate future events. To test this prediction, Rosati *et al.* examined age-related changes in relationship quality among male chimpanzees (*Pan troglodytes*).

Chimpanzees live in large communities that include multiple adult males, multiple adult females, and immature offspring. Communities regularly split into temporary subgroups (parties) that travel and forage independently within the group's home range (*5*). Throughout their lives, males remain in the communities in which they are born, whereas the majority of females disperse to new communities when they reach sexual maturity. Chimpanzees have very long life spans. Males reach adulthood at about 15 years of age, and some males live into their sixties (*6*). Cooperation among males plays an important role in chimpanzee life. They groom one another, form alliances against rivals, hunt together, share meat, and collectively patrol the boundaries of their territories (*5*). Males rely on strategic alliances to attain and maintain high rank in their groups, and high rank enhances individual fitness (*7*). They also have strong affinities for particular partners, and close bonds among males can last for a decade or more (*8*).

Rosati *et al.* drew on an extraordinary dataset that included behavioral and demographic information collected over a 20-year period on a group of chimpanzees in the Kibale National Park of Uganda. Their sample included 21 males ranging from 15 to 58 years of age. For each year, the authors created an association index that was based on the number of times each male was in close proximity to each of the other males in the community while they were in the same party. A male's "friends" were those for whom the value of the association index exceeded the mean + 0.25 standard deviation of its association indices with all partners. In some cases a male's friendship was not reciprocated. This procedure produced three categories: mutual friends, one-sided friends, and nonfriends.

> **"...the patterns that socioemotional selectivity theory was created to explain...might not depend on...conscious awareness of mortality."**

The authors found that old males have significantly more mutual friendships and fewer one-sided friendships than younger males. Thus, a 40-year-old male has on average three times as many mutual friendships and one-third as many one-sided friendships as a 15-year-old male. Investment of males in their social bonds also changes as they age. Males over the age of 35 selectively groom males with whom they have mutual friendships, and grooming is more equita-

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