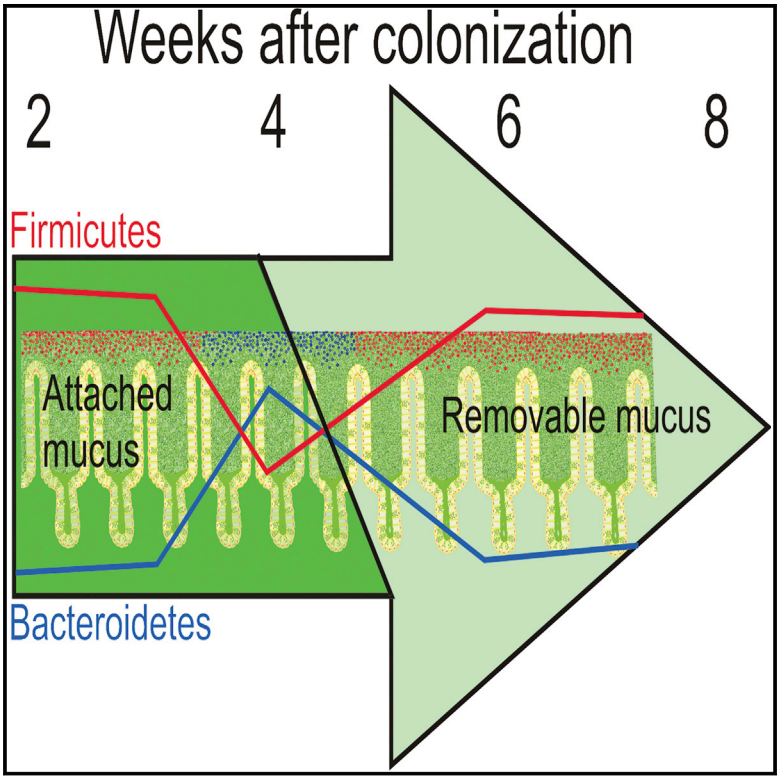
Article

Cell Host & Microbe

Normalization of Host Intestinal Mucus Layers Requires Long-Term Microbial Colonization

Graphical Abstract



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In Brief

The intestinal mucus layer provides a protective barrier and is shaped by microbiota. By examining how microbial colonization modulates gut mucus, Johansson et al. find that it takes 7 weeks for the colonic mucus to normalize and become impenetrable and that the colonizing microbiota undergoes dynamic changes 3 weeks postcolonization.

Highlights

- Impenetrable colon mucus forms 6 weeks after conventionalizing germ-free mice
- Bacterial composition of the small intestine shifts 3–5 weeks postcolonization
- The small intestine mucus layer does not detach until 5 weeks after colonization
- Mucus normalizes after 7 weeks and is not reversed by antibiotics

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Normalization of Host Intestinal Mucus Layers Requires Long-Term Microbial Colonization

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SUMMARY

The intestinal mucus layer provides a barrier limiting bacterial contact with the underlying epithelium. Mucus structure is shaped by intestinal location and the microbiota. To understand how commensals modulate gut mucus, we examined mucus properties under germ-free (GF) conditions and during microbial colonization. Although the colon mucus organization of GF mice was similar to that of conventionally raised (Convr) mice, the GF inner mucus layer was penetrable to bacteria-sized beads. During colonization, in which GF mice were gavaged with Convr microbiota, the small intestine mucus required 5 weeks to be normally detached and colonic inner mucus 6 weeks to become impenetrable. The composition of the small intestinal microbiota during colonization was similar to Convr donors until 3 weeks, when Bacteroides increased, Firmicutes decreased, and segmented filamentous bacteria became undetectable. These findings highlight the dynamics of mucus layer development and indicate that studies of mature microbe-mucus interactions should be conducted weeks after colonization.

INTRODUCTION

The intestine is typically colonized with 10^{13}–10^{14} bacteria residing in the lumen and in the mucus with only limited contact with the epithelium (Bäckhed et al., 2005; Johansson et al., 2013). The MUC2 mucin is the main component of the mucus in mice and humans and responsible for this separation (Johansson et al., 2008). However, the mucus is differently structured in the small and large intestine. In the small intestine, the mucus allows limited diffusion of bacteria and anti-bacterial peptides and keeps the epithelium clean by moving detached mucus with trapped bacteria forward for expulsion in the feces (Ermund et al., 2013; Vaishnava et al., 2011). In the large intestine on the other hand, the inner attached mucus layer acts as a physical barrier that does not allow bacteria to pass due to their size (Johansson et al., 2008). Some bacterial contact with the epithelial cells is tolerated, but massive exposure triggers inflammation as found in inflammatory bowel diseases (IBDs) (Johansson et al., 2014).

Both host and bacteria have adapted to each other and their coevolution has created an intricate symbiotic system that has triggered significant interest during the last 10 years. The main reason has been the capability to identify and characterize the intestinal microbiota by powerful DNA-sequencing methods revealing that a fraction of the bacteria were known using only culture methods (Kuczynski et al., 2012). This development has been further fueled by the understanding that the intestinal microbiota has implications for the development of some of todays' major problems, such as obesity, diabetes, and allergies (Ley et al., 2005). The interdependence of host and bacteria is also obvious from the emerging understanding of mucus and its properties. Germ-free (GF) mucus was observed to be different both in the small and large intestine, and recently the colon mucus was found to be dependent on the bacterial composition (Johansson et al., 2008, 2014; Schütte et al., 2014; Jakobsson et al., 2015). It is today evident that there is a lot of interaction and communication between host and bacteria although they only have limited contact.

Studies of GF rodents have become a necessary tool for the analysis of bacteria-host interactions (Falk et al., 1998; Bäckhed et al., 2005). Adult GF mice can be colonized with limited or full mouse caecal or human fecal flora and studied over a short period usually not exceeding 2 weeks (Lecuit et al., 2007). As we knew that bacteria affect the intestinal mucus system, we undertook a systematic study colonizing GF mice with caecal flora and followed these animals over 8 weeks. The results showed that it takes about 5 weeks until the small intestinal mucus becomes detached and about 6 weeks for the colon inner mucus layer to become fully impenetrable as in conventionally raised (Convr) mice. The microbiota showed dramatic transient alterations during this time and the composition did not reach the conventionalized ones until after 8 weeks. These observations have strong implications on how to perform studies including colonization of GF mice to study host-microbe interactions.

RESULTS

Germ-free Mice Have a Mucus System that Differs from Conventionally Raised Mice

Normal wild-type (WT) mice have mucus that provides protection of the epithelium by creating a diffusion barrier