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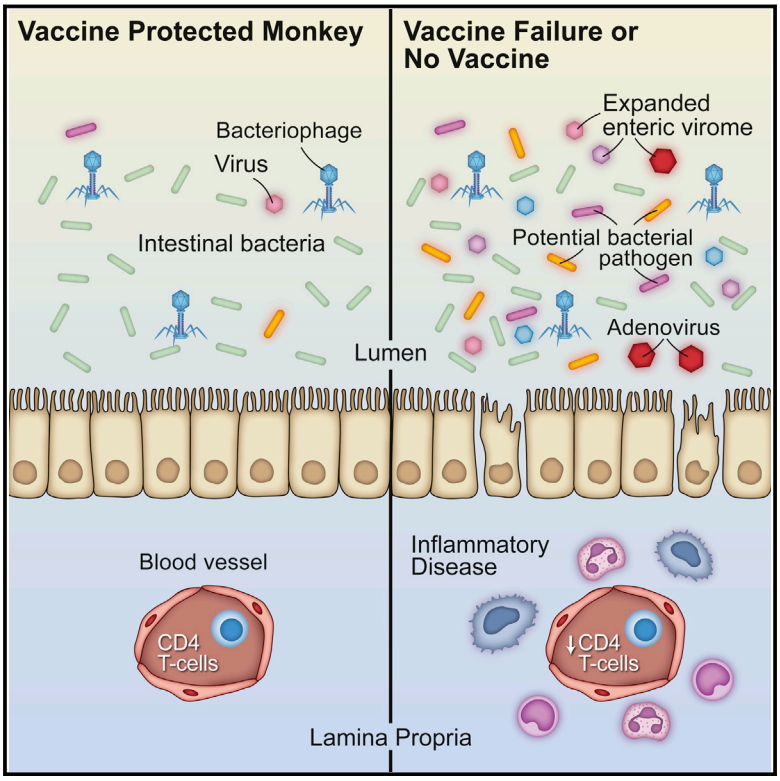
SIV Infection-Mediated Changes in Gastrointestinal Bacterial Microbiome and Virome Are Associated with Immunodeficiency and Prevented by Vaccination

Graphical Abstract



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In Brief

The causes of simian immunodeficiency virus (SIV) associated gastrointestinal disease are not well understood. Handley et al. describe the natural history of gastrointestinal virus and bacteria dynamics during SIV infection and identify associations between enteropathogens and disease. These negative effects were prevented by vaccination against SIV infection.

Highlights

- During SIV infection, enteric virome expansion dynamically changes as disease progresses
- Specific enteropathogenic viruses are associated with enteric disease
- Bacterial enteropathogens are associated with severe disease and immunocompromise
- Prevention of SIV infection using vaccination prevents enteric virome expansion

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SIV Infection-Mediated Changes in Gastrointestinal Bacterial Microbiome and Virome Are Associated with Immunodeficiency and Prevented by Vaccination

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SUMMARY

AIDS caused by simian immunodeficiency virus (SIV) infection is associated with gastrointestinal disease, systemic immune activation, and, in cross-sectional studies, changes in the enteric virome. Here we performed a longitudinal study of a vaccine cohort to define the natural history of changes in the fecal metagenome in SIV-infected monkeys. Matched rhesus macaques were either uninfected or intrarectally challenged with SIV, with a subset receiving the Ad26 vaccine, an adenovirus vector expressing the viral Env/Gag/Pol antigens. Progression of SIV infection to AIDS was associated with increased detection of potentially pathogenic viruses and bacterial enteropathogens. Specifically, adenoviruses were associated with an increased incidence of gastrointestinal disease and AIDS-related mortality. Viral and bacterial enteropathogens were largely absent from animals protected by the vaccine. These data suggest that the SIV-associated gastrointestinal disease is associated with the presence of both viral and bacterial enteropathogens and that protection against SIV infection by vaccination prevents enteropathogen emergence.

INTRODUCTION

Systemic immune activation is associated with progressive infection by the lentiviruses HIV and simian immunodeficiency virus (SIV) and is a strong predictor of progression to AIDS (Deeks et al., 2004; Giorgi et al., 1999; Hunt et al., 2008; Liu et al., 1997). One contributor to systemic immune activation is thought to be damage to the epithelial barrier of the gastrointestinal tract, but the specific mechanisms responsible for this are incompletely defined. Gastrointestinal barrier compromise is concomitant with the detection of bacterial and viral pathogen-associated molecular patterns (PAMPS) and antigens in the blood (Brenchley et al., 2006; Handley et al., 2012; Klase et al., 2015), which most likely contribute to immune activation. SIV infection is associated with depletion of lamina propria CD4 T cells and CD103$^+$ dendritic cells, resulting in limited production of interleukin-17 (IL-17) and IL-22, two cytokines important for epithelial barrier function (Brenchley et al., 2008; Cecchinato et al., 2008; Estes et al., 2008; Klatt et al., 2012; Raffatellu et al., 2008). In addition, expansion of the enteric virome during pathogenic SIV infection is associated with direct damage to the epithelial barrier by adenoviruses and spillage of enteric parvoviruses into the circulation (Handley et al., 2012). Although bacterial lipopolysaccharides (LPSs) and LPS-binding protein can be detected in the serum of SIV-infected macaques or HIV-infected persons, changes in bacterial community structure have not been detected in cross-sectional studies in monkeys (Handley et al., 2012; McKenna et al., 2008). However, recent work has indicated that HIV infection is associated with the emergence of groups of bacteria containing potential enteropathogens (Mutlu et al., 2014).

To better understand the relationship between progressive lentivirus infection and the enteric virome and bacterial microbiome, we performed a longitudinal study to determine how the fecal metagenome changed over the course of infection. Further, to define whether changes in the metagenome are due to SIV exposure itself rather than progressive SIV infection and immunodeficiency, we studied a cohort of animals vaccinated with adenovirus serotype 26 (Ad26) vectors expressing Env/Gag/Pol antigens with or without Env protein boost (Barouch et al., 2015). Vaccine protection in this cohort of animals is associated with strong antibody responses to the Env protein and decreased detection of picornavirus sequences in the feces (Barouch et al., 2015). This cohort allowed us to contrast changes in the fecal metagenome between animals that were intrarectally challenged with SIV, but were or were not protected against establishment of chronic lentivirus infection, and