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Review

Reversing Gut Damage in HIV Infection: Using Non-Human Primate Models to Instruct Clinical Research

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ABSTRACT

Antiretroviral therapy (ART) has led to dramatic improvements in the lives of HIV-infected persons. However, residual immune activation, which persists despite ART, is associated with increased risk of non-AIDS morbidities. Accumulating evidence shows that disruption of the gut mucosal epithelium during SIV/HIV infections allows translocation of microbial products into the circulation, triggering immune activation. This disruption is due to immune, structural and microbial alterations. In this review, we highlighted the key findings of gut mucosa studies of SIV-infected macaques and HIV-infected humans that have revealed virus-induced changes of intestinal CD4, CD8 T cells, innate lymphoid cells, myeloid cells, and of the local cytokine/chemokine network in addition to epithelial injuries. We review the interplay between the host immune response and the intestinal microbiota, which also impacts disease progression. Collectively, these studies have instructed clinical research on early ART initiation, modifiers of microbiota composition, and recombinant cytokines for restoring gut barrier integrity.

Contents

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1. Introduction

The human gastrointestinal (GI) tract has coevolved with billions of commensal microorganisms that are considered by many immunologists to be an "extended self" (Reynolds et al., 2015). This symbiotic relationship between microorganisms and the host requires efficient barrier and tolerance mechanisms that preserve intestinal immune balance and tissue integrity. HIV infection leads to disruption of both immune balance and epithelial barrier integrity, contributing to residual immune activation (Younas et al., 2015). Such immune activation persists despite ART and is associated with an increased risk of non-AIDS morbidities, such as cardiovascular diseases and neurocognitive disorders. This persistent immune activation is thought to originate from latently infected cells contributing to residual HIV expression, and gut barrier damage. Cumulative evidence indicates that multiple events occur within the GI tract of pathogenically Simian Immunodeficiency Virus (SIV)-infected Asian macaques and HIV-infected individuals (Estes et al., 2010; Brenchley, 2013). These events cause increased intestinal permeability, resulting in the translocation of bacterial products of the GI microflora through the epithelial barrier and into the systemic circulation. This microbial translocation is considered to be a major driver of chronic immune activation and disease progression, even in patients receiving ART (Brenchley et al., 2006; Vyboh et al., 2015).

Our understanding of SIV- and HIV-induced immune gut damage was primarily based on CD4 T cell studies, with changes in CD8 T cells and myeloid populations being relatively less studied. Herein, we highlight the key findings of gut mucosa studies of SIV-infected rhesus macaques (RMs) and HIV-infected subjects that have revealed changes in the distribution of Th17, Treg, Th22, CD8 T cells, innate lymphoid cells and myeloid cells, in addition to the disruption of the local cytokine/chemokine network. We also review studies describing SIV/HIV-induced injuries to the intestinal epithelium, changes in the composition of the gut microbiota, and/or translocation of gut microbial products. Our findings underline the importance of designing novel therapies that target microbial composition and gut barrier integrity to further control immune activation that in turn will improve the quality of life of HIV-infected individuals, while potentially reducing the size of the HIV reservoir.

2. Gut Damage in Conditions Other Than HIV: Learning From "Outside the Box"

Early in the HIV pandemic, GI dysfunctions were reported in patients progressing to AIDS. These dysfunctions included nutrient malabsorption, diarrhea and weight loss, all of which pointed to a link between the disruption of immune homeostasis and gut damage (Kotler et al., 1984). Initial descriptions of the pathological changes observed in patients with advanced HIV infection evoked GI manifestations of Crohn's disease and ulcerative colitis, two major forms of inflammatory bowel disease (IBD), (Ho et al., 2014). Both IBD and HIV infections can be considered as conditions involving a breakage in the mutualism between the host and the gut microbiota. Graft-versus-host disease (GVHD) is also characterized by features of gut damage including immunosuppression, alteration of the composition of the intestinal microbiota, and microbial translocation, all of which lead to systemic inflammation (Jenq et al., 2012).

These findings raise questions regarding the determinants of immune tolerance towards the intestinal microbiota. Due to limitations in assessing mucosal immune responses in patients, non-human primate (NHP) models of SIV-related gut damage have played a critical role in understanding the interplay between microbiota, gut barrier integrity and systemic immune responses. In this review, we synthesize the studies of mucosal immunity in NHP models and discuss their relevance to HIV pathogenesis.

3. Gut Damage in SIV Infection: A Mucosal Tragedy

3.1. Non-human Primate Models of HIV/AIDS

Macaques that develop an AIDS-like disease following experimental SIV infection include rhesus (*Macaca mulatta*), cynomolgus (*Macaca fascicularis*), and pigtail (*Macaca nemestrina*) macaques. The RM model is the most extensively studied and includes the Indian and Chinese subtypes; the Indian subtype experiences faster disease progression compared to the Chinese subspecie (reviewed in Zhou et al., 2013). In contrast to progressive SIV infection of Asian macaques, over 40 known species of African non-human primates are endemically infected (Chahroudi et al., 2012). These natural hosts of SIV, which remain asymptomatic, are characterized by a low level of immune activation despite highly replicating virus. Among these species, sooty mangabeys (SMs) and African green monkeys (AGMs) have been extensively studied as nonpathogenic models. Progressive and nonpathogenic models have contributed to our understanding of mucosal immunity and immune activation during SIV infection.

The gut mucosal immune system of NHP and humans is divided into inducible and effector compartments. The inducible sites are composed of organized lymphoid structures such as Peyer's patches and isolated lymphoid follicles (Brandtzaeg et al., 2008). The effector sites, comprised of the epithelium lining the gut lumen and the subjacent *lamina propria* (LP), contain diffusely distributed myeloid and lymphoid cells.

3.2. CD4 T Cell Depletion: Targeting the "Helpers"

Mucosal CD4 T cell depletion was first reported in AIDS patients; this depletion was predominant in the duodenum (Rodgers et al., 1986), suggesting differential impact of HIV infection along the intestine. CD4 T cell changes in early SIV infection were subsequently investigated in NHP models; key study findings are summarized in Table 1. In Indian RMs, enteropathies were reported by Veazey et al. who observed the depletion of 80% to 90% of activated CD4 T cells in the gut mucosa at day 14 post-infection (Veazey et al., 2000). In Chinese RMs, rectal $CD4^+$ T cells were depleted by 30% at day 14 post-infection, although no changes were observed in the small intestine (Couëdel-Courteille et al., 2003). In these studies, mucosal helper T cell depletion was assessed by measuring CD4 T cell frequencies, which is influenced by the size of other cell populations. Therefore, immunostaining was performed in subsequent studies. The colon of Indian RMs showed up to 50% depletion of CD4 T cells (Li et al., 2005); in newly HIV-infected individuals, CD4 T cell depletion was detected in the effector sites of