Crucial crossing

A new paper in *PLoS Pathogens* provides the first direct immunohistochemical evidence of the translocation of microbial products from the intestinal lumen during chronic simian immunodeficiency virus (SIV) infection.

Persistent systemic immune activation is a defining characteristic of pathogenic HIV-1 and SIV infections. Despite its central role in disease progression, the precise mechanisms that drive this immune activation remain poorly characterized. Previous work had shown that individuals chronically infected with HIV-1 and rhesus macaques infected with SIV had high levels of circulating lipopolysaccharide (LPS), providing indirect evidence that the translocation of microbial products such as LPS from the intestinal lumen is an important factor in systemic immune activation. However, direct tissue evidence to support this hypothesis was lacking.

Jason Brenchley and colleagues used monoclonal antibodies specific for the core antigen of LPS to stain colon tissue sections obtained from necropsies of SIV-infected rhesus macaques that were euthanized at

different phases of infection, including early acute infection and chronic infection, as well as sections from uninfected controls. In the uninfected animals and during early acute infection there was abundant staining for LPS in the intestinal lumen but little staining in the lamina propria of the large bowel. By contrast, in chronically infected animals there was abundant staining for intracellular and extracellular LPS in the lamina propria. Abundant LPS staining was also seen in the mesenteric and axillary lymph nodes and the livers of chronically infected animals, but not in those of uninfected animals or during early acute infection. Moreover, staining for the tight junction component claudin 3 showed that the integrity of the epithelial barrier was severely compromised in chronically infected animals. This damage began during the late acute phase of infection, and the degree of damage correlated with the degree of LPS translocation.

The authors then investigated whether this translocation was linked to immune activation. Using double-label immunohistochemical staining, they found colocalization of LPS and

the pro-inflammatory mediators interferon- α and interleukin-18 in chronically infected animals. Importantly, both mediators could be observed in close proximity to LPS rather than to sites of local SIV replication. Confocal microscopy also revealed that macrophages were abundant in gastrointestinal tissue during the chronic stage of infection but that a high proportion of these had not taken up any LPS, suggesting that macrophage-based clearance is impaired.

Taken together, these data provide direct evidence to support the hypothesis that the systemic immune activation that occurs during chronic HIV-1 infection is linked to the translocation of microbial products from the intestinal lumen, which in turn is linked to damage to the structural integrity of the gut epithelial layer and impaired clearance by macrophages.

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ORIGINAL RESEARCH PAPER Estes, J. D. *et al.* Damaged intestinal epithelial integrity linked to microbial translocation in pathogenic simian immunodeficiency virus infections. *PLoS Pathog.* **6**, e1001052 (2010)