Host-Microbiome Dynamics during SIV Infection

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Chronic inflammation is thought to be one of the principal drivers for the deterioration of the immune system during HIV infection and the progression to AIDS. Such inflammation can weaken antiviral immunity, can allow infection of new cells, and can directly propagate the virus itself. To identify the source of inflammation in HIV, numerous studies have focused on the gut and have observed that the intestinal immune barrier is weakened during HIV infection. This intestinal barrier disruption coincides with the appearance of movement of gut microbial products into the blood and periphery, whereupon recognition by peripheral immune cells is thought to perpetuate the chronic inflammation that is characteristic of HIV infection. However, how and why intestinal immune dysfunction persists during HIV disease remains unclear.

Recent studies in mice have shown that perturbations to immunity similar to those seen in HIV-infected subjects can change the community of bacteria that reside in the gut (i.e., the microbiome). Furthermore, the bacterial communities that arise as a result of such inflammation in mice can themselves cause further immune disruptions throughout the body. We and others have recently reported that the gut microbiome of HIV-infected individuals is substantially different from that found in those who are uninfected, and that this change in gut microbiome composition correlates with inflammatory markers of HIV disease progression. However, further study in controlled models of infection is needed to more precisely identify the bacterial members that are most tightly linked with intestinal immune disruption and disease progression. Furthermore, an understanding of whether and to what extent microbiome shifts occur during non-pathogenic SIV infection, wherein immune deterioration and AIDS do not take place, will provide evidence for the importance of the gut microbiome during HIV/SIV disease.

The proposed study aims to investigate changes in the gut microbiome of the SIV-infected macaque model of HIV infection, which closely recapitulates HIV disease course in humans. The work will take advantage of a separately funded study that will provide measurements of gut immune function in addition to other markers of disease progression from the same animals. We propose to use sophisticated technical and analytical methods developed by our laboratory and that of our collaborators to ask, first, whether changes in the microbiome of SIV-infected macaques are similar to those seen in HIV-infected humans and whether such changes similarly correlate with markers of immune disruption, as was previously observed in humans. Second, we will ask whether such changes in the gut microbiome occur before or after changes in immune parameters, which will provide evidence as to whether they are the cause or the consequence of immune disruptions. Thirdly, we will test the hypothesis that, in non-pathogenic models of SIV infection, the gut microbiome either does not change or eventually returns to the healthy, pre-infection state. The proposed work will gather evidence for the importance of the gut microbiome in HIV/SIV disease and may provide a foundation from which future studies can begin to investigate the relationships between gut-resident bacteria and the human immune system.