



The Ling Lab: Eliminating HIV Reservoirs

HIV can effectively hide in places that are immunoprivileged, even when individuals are on antiretroviral therapies. Finding ways to target this hidden virus and eliminate it is essential for developing a functional, long-term cure for HIV infection. **Binhua Ling's** lab focuses on studying ways to target the HIV hidden in the central nervous system (CNS) and gut, as well as the basic biology underpinning the ability of HIV to evade clearance in these areas of the body.

Between Acute and Chronic: Stages of HIV

In humans, the transitional period between acute infection with HIV and chronic infection is essential in setting up the pace of HIV disease progression. In order to study this period, the Ling Lab uses a Chinese sub-species of Rhesus Macaques. Unlike rhesus of Indian or other species of macaques, these non-human primates (NHPs) have a relatively longer period between acute and the late-stage chronic infection, more closely mirroring human disease. With a focus on the role of innate immunity in HIV infection, the lab is also interested in the 1/3rd of these NHPs that spontaneously control and slow the development of AIDS-like illness despite being infected with Simian Immunodeficiency Virus (SIV). It is hoped that by studying the genetics and immune systems of these animals that the lab can learn what triggers AIDS and thus prevent the progression of HIV infection in humans.

Hiding in the CNS: Eliminating HIV Infection

The Central Nervous System (CNS) is largely invisible to the immune system. Additionally, the drugs used to treat HIV have a difficult time crossing the blood-brain barrier. This makes the CNS an ideal place for HIV to remain as a reservoir. The resident immune cells in the CNS, like macrophages and microglial cells, can become latently infected with HIV. However, they can become activated and produce virus, meaning that they are an obstacle to a functional HIV cure. The Ling Lab is using genetically "bar-coded" HIV virus that can be tracked using second generation sequencing methods following infection. The lab is using this virus in an NHP model to identify the specific cells within the CNS that can harbor the virus, even during treatment with antiviral drugs. Once identified, these cells can be targeted with CRISPR-based approaches to eliminate the virus.

The Gut as a Reservoir

The CNS is not the only potential source of residual HIV-infected cells. The gut has a lot of resident CD4+ T-Cells, which can readily become infected with HIV. Additionally, antiviral drugs used to treat HIV have poor bioavailability in the gut. The Ling lab is studying the large and small intestines of NHPs infected with SIV to try and determine differences in them that lead to disparate outcomes during the course of disease.

Additionally, the lab is looking at the microbiome of the gut in infected individuals, examining the interplay between the immune system, gut flora, and SIV in progressor and non-progressor NHPs. It is hoped that they will be able to leverage these data to develop new therapies for human patients living with HIV, who often experience gastrointestinal problems and microbiota disruption – even with anti-viral therapy.

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