Scientists unveil mechanisms of immune reconstitution inflammatory syndrome

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Newly published research by scientists at the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, sheds light on a poorly understood, acute illness called Immune Reconstitution Inflammatory Syndrome (IRIS) that develops in some HIV-infected individuals soon after they begin antiretroviral therapy.

IRIS affects certain HIV-infected individuals whose immune systems are heavily damaged by the virus and who have a treated or undiagnosed AIDS-associated infection. When these individuals start antiretroviral therapy and their immune cells begin to regenerate, the immune system unexpectedly produces an exaggerated response that unmasks or worsens the symptoms of the co-infection. IRIS has become a notable challenge in treating HIV disease, particularly in resource-limited settings. The scientists hope that better understanding how and why the syndrome occurs will lead to targeted prevention or therapy.

To find immunologic patterns that distinguish individuals who develop IRIS from those who do not, the researchers analyzed blood samples from HIV-infected individuals, focusing their analysis on a group of immune cells called T lymphocytes. Most of the studied patients had an AIDS-associated fungal, viral or bacterial infection before they started antiretroviral therapy.

The analysis showed that the individuals who developed IRIS had a higher proportion of activated T cells before starting antiretroviral therapy compared with those who did not develop IRIS. These activated

T cells had the propensity to make a key infection-fighting molecule called interferon gamma both before therapy began and during IRIS episodes, suggesting that the cells may participate in the exaggerated immune response seen during IRIS. In addition, the surface markers expressed by the T cells—some with a stimulatory effect and some restraining in nature—suggested they were highly activated as a result of an encounter with the microbes co-infecting the HIV-infected individuals.

A companion study describes a new animal model that can be used to directly analyze the immunologic mechanisms that cause IRIS. This model employs mice infected with Mycobacterium avium, a pathogen frequently seen in HIV-infected individuals who develop IRIS. To mimic the immunologic condition of IRIS-susceptible HIV-infected individuals, the researchers began with mycobacterium-infected mice that had extremely low numbers of T cells. The scientists found that rebuilding the population of T cells in these mice, as usually occurs during antiretroviral therapy in humans, triggered an IRIS-like disease. In addition, the researchers observed that interferon-gamma production by the repopulating T cells in the mice clearly facilitated the development of experimentally induced IRIS. The study also implicated a type of immune cell known as a macrophage in sparking IRIS in the mice.

More information: LRV Antonelli et al. Elevated frequencies of highly activated CD4+ T cells in HIV+ patients developing immune reconstitution inflammatory syndrome. *Blood* DOI:10.1182/blood-2010-05-285080 (2010).

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