The importance of soluble CD14 and inflammation

Research suggests that one of the body’s sensors to help detect invading bacteria is called soluble CD14, written as sCD14. Levels of this protein are elevated in HIV-negative people who are experiencing severe bacterial infections. Research suggests that sCD14 is released by a group of cells called monocytes. These are cells of the immune system that play multiple roles in helping to detect and fight infections.

Since the 1990s, researchers have found that sCD14 levels are higher than normal in HIV-positive people, including those with severe bacterial infections.

However, interest in sCD14 has resurfaced in recent years as scientists study HIV-related inflammation and its effect on the immune system and survival. Here is a summary of some findings related to sCD14 and HIV:

- Treatment with the HIV integrase inhibitor raltegravir (Isentress) as part of combination therapy can modestly reduce levels of sCD14 in the blood, particularly in HIV-positive women. However, note that levels of sCD14 even in raltegravir users remain relatively high compared to those in healthy HIV-negative people.
- High sCD14 levels in the blood are associated with an increased risk of death among HIV-positive people.
- In one study, HIV-positive women with elevated levels of sCD14 were at increased risk for cardiovascular disease.

Disagreement about lingering inflammation

Some researchers think that bacteria cause elevated levels of sCD14 in the blood. This seems to make sense because the initial work on understanding sCD14 in HIV-negative people linked this protein to bacterial infections.

The gut (or intestines) plays an important role in human health. The intestines not only absorb food but are surrounded by lymphatic tissues and lymph nodes that intercept any germs that get into our intestines. These parts of the immune system also contain many CD4+ cells. When HIV infection occurs, the immune system surrounding the gut loses many of its CD4+ cells. As a result, some scientists say that the intestines become immunologically weaker and are less able to fend off germs. A weakened intestine may allow more germs to pass through and get into the body. The intestines and their surrounding lymphatic tissue and lymph nodes may also produce more chemical signals that favour inflammation.

The leakage of bacteria from the gut into the blood is called “bacterial translocation” by researchers. Clinical trials are planned or underway to test supplements of gut-friendly bacteria (probiotics) to try to reduce HIV-related inflammation.

Beyond bacteria

Researchers in San Francisco have conducted elegant and sophisticated experiments to try to understand why monocytes produce sCD14 even in HIV-positive people who do not have bacterial infections. As part of this work, they took blood samples from both HIV-positive and HIV-negative people for analysis.

They found that monocytes from HIV-positive people seem to be activated because of exposure to interferon-alpha and not bacteria or bacterial proteins. Furthermore, activation of monocytes in their experiments resulted in the release of sCD14. The activation of monocytes in their experiments stemmed from exposure to HIV.

Other researchers in London, UK, have found that persistent activation of another group of cells—natural killer (NK) cells, which can help fight HIV-infected cells and cancers—occurs in people with HIV. This activation did not occur because of bacterial infections.

Back to the lymph nodes
What all of these studies of sCD14 have in common is that they have assessed blood for this protein. Most HIV (and most of the body's CD4+ cells) is not in the blood. Instead, most HIV and CD4+ cells are inside lymph nodes, lymphoid organs (such as the spleen and thymus) and lymphatic tissues around the gut, mouth, nose, anus and rectum.

Recently, researchers in the U.S. found that HIV-infected cells continue to produce HIV in the lymph nodes of ART users who are highly adherent and who had viral loads in their blood less than 50 copies/ml.

This discovery will likely stimulate much research to explore the impact of HIV and related inflammation. Such research may provide more clues about how to reduce HIV-related inflammation, including levels of sCD14.

—Sean R. Hosein

REFERENCES:

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