Exhaustion renders immune cells less effective in cancer treatment

May 9 2012

Rather than stimulating immune cells to more effectively battle cancerous tumors, treatment with the protein interleukin-12 (IL-12) has the opposite effect, driving these intracellular fighters to exhaustion, a Mayo Clinic study has found. The findings appear in the *Journal of Clinical Investigation.*The study helps explain the negative results of clinical trials testing the treatment's ability to ramp up the body's natural immune response to destroy cancer cells. The study also demonstrates that the same "T cell exhaustion" that plagues specialized immune cells during chronic viral infections also affects cells fighting long bouts of cancer.

The results suggest a change in therapeutic tactics for lymphomas and other cancers by dampening, rather than fueling, the effects of cell-signaling molecules such as IL-12.

The study focused on a type of cancer called Follicular B-cell non-Hodgkin's lymphoma (FL), the second most frequent type of non-Hodgkin's lymphoma. Previously, senior author Stephen Ansell, M.D., Ph.D., a Mayo Clinic hematologist, had shown that tumors biopsied from patients with FL and other similar cancers are a 50-50 mixture of cancer cells and immune cells. Although those immune cells are genetically programmed to kill cancer, instead, they seemed content to cohabitate with their deadly neighbors. Dr. Ansell wondered if a phenomenon known as T cell exhaustion may be the cause. The study findings suggest it is.

"It is like beating a dead horse," says Dr. Ansell. "Our study suggests that many immunotherapy approaches are futile, because these cells are already past the point where they can do their job of targeting and killing malignant cells. Before we can stimulate the immune system, we have to reverse this state of exhaustion so the body's T cells can get back to work."

T cell exhaustion was discovered a few years ago in the context of chronic viral infections such as cytomegalovirus (CMV), hepatitis and HIV. Researchers found that constant unrelenting combat with these viruses caused a key contingent of the immune response, known as T cells, to wear out. Even when artificially stimulated, these exhausted cells were unable to proliferate, recruit other members of the immune army, or kill enemy cells. In addition, these T cells began to carry cellular marks of exhaustion, most notably the cell surface proteins PD1 and Tim-3.

In this study, Dr. Ansell and his colleagues tested whether exposing isolated human T cells to IL-12 would induce T cell exhaustion. They found that treatment with IL-12 brought the Tim-3 marker of exhaustion to the cell surface. When they tried experimentally to stimulate those immune cells into action, they discovered that the T cells couldn't proliferate and couldn't make the immune system signaling molecules known as cytokines.

"We think that IL-12 is useful in the short term, but detrimental in the long term," Dr. Ansell says. "Almost like pouring gasoline on a campfire: You get a really big blaze, but then it all burns down to nothing."

The researchers found that the more cells marked with Tim-3 in a given tumor, the worse the patient's prognosis. They also showed that by blocking Tim-3 they could return the T cells to normal function.

"Once we've worked out all factors that are contributing to exhaustion, the next step will be figuring out which of them can we realistically reverse, particularly in the context of patients," Dr. Ansell says. "Some of these cytokines have a critical role in the body, and we wouldn't want to reverse good effects along with the bad."

Provided by Mayo Clinic