Promising treatment target found in Hodgkin lymphoma

July 31 2007

Dana-Farber Cancer Institute scientists have identified a protein that prevents the body's immune system from recognizing and attacking Hodgkin lymphoma cells. Based on this finding, the researchers are now investigating targeted therapies to disable this molecular "bodyguard" and boost a patient's ability to fight the blood cancer.

If the strategy proves successful, patients might escape some of the long-term complications -- like heart damage and the threat of a second cancer -- caused by standard treatments that include radiation, said Margaret Shipp, MD, of Dana-Farber, who headed the study. A report will be posted online by the *Proceedings of the National Academy of Sciences* on July 30 and will appear in an upcoming print issue of the journal.

"We're excited about this treatment lead," said Shipp, a medical oncologist. "We are currently generating antibodies that can neutralize the 'bodyguard' protein, and we'd like to fast-track this experimental therapy into clinical trials."

Nearly 8,200 people in the United States -- the great majority of them young adults -- will be diagnosed with Hodgkin lymphoma in 2007, according to the American Cancer Society, with an estimated 1,070 deaths. The cancer begins in the lymph nodes and channels that distribute infection-fighting white blood cells around the body. Its symptoms can include swollen glands in the neck, night sweats and fatigue.

The biological trademark of Hodgkin lymphoma is a type of giant, mutant white blood cell called the Reed-Sternberg cell that is found in the lymph node tumors. While most solid cancers consist almost entirely of tumor cells, says Shipp, Hodgkin tumors, which can reach the size of a basketball, contain only about 5 percent cancerous Reed-Sternberg cells; the rest are different types of immune cells recruited to fight the tumor, but they are ineffective.

"You would expect with all these host immune cells attracted to the area of the tumor cells that they would mount a great antitumor response," Shipp says. "But that's not the case. There are a lot of immune cells, but they're the wrong kind."

The immune army includes different types of T cells, such as T helper 1 (Th1) cells designed to recognize and kill foreign infectious agents and sometimes tumors, T helper 2 (Th2) cells, which normally control allergic responses, and T regulatory (Treg) cells that suppress other T-cell types and shut down an immune response when the job is done. The Hodgkin tumors are overloaded with Th2 and Treg cells that act as bodyguards for the cancer by weakening the Th1 immune response against it.

Przemyslaw Juszczynski, MD, PhD, Jing Ouyang, PhD, and colleagues from the Shipp laboratory, together with collaborators from Brigham and Women's Hospital, the Broad Institute and the University of Buenos Aires, hunted for the source of the cancer cells' protection. Using gene microarray chips, the scientists looked for genes that were active in Reed-Sternberg cells but not in cells of another non-Hodgkin B-cell lymphoma.

The comparison revealed that a gene called Gal1 was up to 30 times more active in the Reed-Sternberg cells, causing them to secrete large quantities of a protein -- Gal1 or Galectin 1 -- that turns down the Th1

immune response. The Shipp team then defined the mechanism for Gal1 overexpression in Hodgkin lymphoma. Next, they demonstrated that Th1 immune cells underwent apoptosis, or cell death, when treated with Gal1, leaving increased numbers of Th2 cells and the suppressive Treg cells. Using a gene-silencing technique, RNA interference or RNAi, they then turned off the Gal1 gene in Hodgkin Reed-Sternberg cells and showed that it blocked the death of infiltrating normal Th1 cells, making them an equal force to the Th2 cells.

"Likely what's happening here is that the tumor cells essentially hijack a normal regulatory program and use it to avoid being knocked off by the immune response," explains Shipp, who is also a professor of medicine at Harvard Medical School. "These observations provide an important explanation for why you have this ineffective immune response in Hodgkin lymphoma."

She adds that this bodyguard strategy may not be limited to Hodgkin lymphoma. One of the collaborating authors, Gabriel Rabinovich, PhD, of the University of Buenos Aires, has blocked Gal1 in mice with a form of the deadly skin cancer melanoma, and the animal's immune system succeeded in eliminating the cancer, Shipp says. "We think it's very possible that this strategy will be applicable to other types of cancer."

Source: Dana-Farber Cancer Institute