GERMAN CANCER RESEARCH CENTER
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50 Years – Research for
A Life Without Cancer

No. 23 June 12, 2015 (Koh)

Call for help to killer cells improves cancer rejection

Many tumors are infiltrated by cells of the innate immune system called eosinophils. Immunologists from the German Cancer Research Center (DKFZ) are now the first to show that eosinophils do, in fact, improve the body's defense against cancer. By releasing special agents, they attract killer T cells into cancerous tissue; the T cells then attack the cancer cells. This finding may help develop more effective cancer immunotherapies.

Sometimes it takes a long time to solve a puzzle: In 1893, German surgeon G. Reinbach discovered that tumor tissue is often infiltrated by special cells of the immune system called eosinophils. Ever since then, scientists have been trying to figure out if and how these cells, which are part of the innate immune system, are involved in cancer rejection.
"There are many studies that link the presence of eosinophils in a tumor with an improved prognosis of the disease. However, even 120 years after Reinbach's discovery, it still remained elusive whether or not eosinophils actively play a role in fighting the tumor," says Prof. Günter Hämmerling from the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ).

Immunologist Hämmerling hypothesized that tumor eosinophils might act as mediators that call for help to other immune cells, thus initiating an immune defense against the tumor. Most prior studies had not taken into account the involvement of other components of the immune system.

Dr. Rafael Carretero from Hämmerling's department has now been able to confirm this hypothesis. Carretero discovered that eosinophils release special agents that attract the immune system's "professional killers" into cancer tissue. These immune cells, called CD8+ T cells, then go ahead and attack the tumor.

Mice whose eosinophils had been incapacitated using antibodies exhibited poor defense mechanisms against tumors and soon succumbed to the disease. In these animals, strikingly low quantities of CD8+ T cells infiltrated the tumor. Carretero also showed that the agents released by the eosinophils are, in fact, responsible for attracting the T cells. To prove this, he used antibodies to catch these attractants. Under these circumstances, hardly any T cells invaded the tumor. Nor was it possible to attract T cells into the tumor when the researchers transplanted non-activated eosinophils, which do not produce attractants, into the mice.

An important approach in advanced cancer medicine is to treat cancer using a patient's immune cells after first arming the cells against the tumor in culture. However, these therapies often fail because insufficient numbers of T cells reach the tumor. Carretero and his colleagues therefore investigated whether the outcomes of these immunotherapies might be improved by adding eosinophils.

While transplantation of T cells alone had only little impact on tumor size in cancerous mice, the researchers achieved substantial regression of the cancer by transplanting both T cells and activated eosinophils. Mice that had received this combination survived significantly longer than animals in the control group that had received only T cells. In subsequent experiments, the investigators showed that eosinophils alone – in the absence of T cells – fail to improve cancer rejection.

Apart from their call for help to killer cells, eosinophils had another impact on the immediate environment of a tumor. They normalized blood vessels in the tumor, thus additionally contributing to tumor rejection.

“We have solved a 100-year-old puzzle here and we have shown that eosinophils initiate cancer rejection by sending out a molecular call for help,” says Hämmerling, the study head. He adds: “This knowledge will enable us to significantly enhance cellular immunotherapies by guiding more T cells into a tumor.” His team is currently studying cases in which cancer patients have been treated by immunotherapy. The researchers want to find out if and how higher levels of eosinophils correlate with better treatment outcomes.

Rafael Carretero, Ibrahim M Sektioglu, Natalio Garbi, Oscar C Salgado, Philipp Beckhove & Günter J Hämmerling: Eosinophils orchestrate cancer rejection by normalizing tumor vessels and enhancing infiltration of CD8+ T cells. Nature Immunology 2015, DOI:10.1038/ni.3159

Contact:

Dr. Stefanie Seltmann
Head of Press and Public Relations
German Cancer Research Center
Im Neuenheimer Feld 280
D-69120 Heidelberg
T: +49 6221 42 2854
F: +49 6221 42 2968
presse@dkfz.de

Dr. Sibylle Kohlstädt
Press and Public Relations
German Cancer Research Center
Im Neuenheimer Feld 280
D-69120 Heidelberg
T: +49 6221 42 2843
F: +49 6221 42 2968
Email: presse@dkfz.de