Antibodies to intracellular cancer antigens combined with chemotherapy enhance anti-cancer immunity

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An international team of scientists in Japan, Switzerland, and the United States has confirmed that combining chemotherapy and immunotherapy in cancer treatment enhances the immune system's ability to find and eliminate cancer cells, even when the cancer-associated proteins targeted by the immune system are hidden behind the cancer cell membrane. In a study published in *Cancer Research* by Noguchi et al., the scientists show that antibodies, which have been successful in treating certain types of cancers, can effectively reach elusive intracellular targets, delaying tumor growth and prolonging survival when combined with chemotherapy.

"The study provides proof-of-principle for a powerful new strategy that may greatly expand the arsenal of potential targets for cancer drug development and that could be broadly applicable to many different cancer types," said Hiroyoshi Nishikawa, M.D., Ph.D., a Cancer Research Institute (CRI)-funded associate professor in the Department of Experimental Immunology at the Immunology Frontier Research Center, Osaka University, and a senior author on the paper.

The introduction of antibodies against cancer represents one of the biggest successes of cancer therapy over the past 20 years. These treatments work by targeting markers on the surface of cancer cells, and include the blockbuster therapies Herceptin, which targets the HER2/neu marker on breast cancer cells, and Rituxan, which targets the CD20 marker on B cell lymphoma.

The majority of markers that can distinguish cancer cells from normal cells, however, are found exclusively inside cancer cells, where antibodies typically cannot access them. "Therapies that can successfully target cancer antigens found within cancer cells may be able to fight cancer without causing unwanted side effects due to collateral damage to healthy cells," said study co-lead author Gerd Ritter, Ph.D., associate director of the New York Branch of the Ludwig Institute for Cancer Research (LICR), and a leading member of the CRI/LICR Cancer Vaccine Collaborative, which also supported the study.

To assess whether antibody treatment against an intracellular antigen might be successful, the researchers used an antibody against the prototypic cancer antigen NY-ESO-1 and tested it in a model of colon cancer engineered to express NY-ESO-1 within its cancer cells. Alone, the antibody had no effect against the cancer. By using chemotherapy to release NY-ESO-1 from the cancer cells prior to the administration of the antibody, however, they were able to significantly delay cancer progression and prolong survival. The researchers then tested the strategy in another cancer model using a different type of chemotherapy and showed similar results, demonstrating that this approach could be applicable to different tumor types using various standard chemotherapies.

By monitoring the immune responses to these treatments, the researchers on the study found that the anti-tumor effect of the combination was dependent on CD8+, or killer, T cells. Rather than working to kill the cancer cells directly, the antibody worked by binding to the NY-ESO-1 antigen and facilitating its presentation to CD8+ T cells, which then exerted the anti-tumor effects. These findings not only have implications for how scientists understand the mechanisms of current antibody treatments for cancer, but they also shed light on a fundamental question in clinical cancer immunology, which asks how people develop spontaneous antibody and/or CD8+ T cell responses against NY-ESO-1.

"These studies are also representative of a growing trend in immunotherapy treatment, namely the use of chemotherapy and other standard therapies to augment anti-tumor immunity," stated Hiroshi Shiku, M.D., chairman and professor in the Department of Medical Oncology and Immunology, Mie University Graduate School of Medicine, Japan, and a lead investigator on the study. Until very recently, it was thought that these treatments served to uniformly dampen the immune system and would therefore limit the potential efficacy of immunotherapies used in tandem or in sequence. A growing body of literature, however, is suggesting that certain cytotoxic, or "cell-killing," therapies such as chemotherapy and radiation, used in strategic ways, can synergize with immunotherapies to strengthen or expand the anti-tumor immune response.

Based on the success of their preclinical investigations, the study researchers are eager to take the approach into clinical testing. Such a trial would bridge what immunologists refer to as passive immunotherapy and active immunotherapy.

"It's passive because we're using antibodies manufactured outside the body-the body doesn't have to do the work to make these antibodies; but it's also active because these antibodies then mobilize the immune system to actively begin producing potent cells and endogenous molecules like cytokines and complement to attack the tumor. It's a powerful strategy that for the first time capitalizes on the full therapeutic potential of antibodies as mediators of tumor elimination," Ritter said.

More information: Noguchi et al. Intracellular tumor-associated antigens represent effective targets for passive immunotherapy. *Cancer Res.* canres.3072.2011 ; Published OnlineFirst February 8, 2012

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