Anti-CD47 antibody may offer new route to successful cancer vaccination

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(Medical Xpress)—Scientists at the School of Medicine have shown that their previously identified therapeutic approach to fight cancer via immune cells called macrophages also prompts the disease-fighting killer T cells to attack the cancer.

The research, published online May 20 in the *Proceedings of the National Academy of Sciences*, demonstrates that the approach may be a promising strategy for creating custom cancer vaccines.

Various researchers have been working over the years to create vaccines against cancer, but the resulting vaccines have not been highly effective. Current approaches to developing the vaccines rely on using immune cells called dendritic cells to introduce cancer protein fragments to T cells—a process known as antigen presentation. The hope has been that the process would stimulate the body's T cells to identify cancer cells as diseased or damaged and target them for elimination. However, this process often only modestly activates the most potent cancer-fighting kind of T cell, called killer T cells or CD8+ T cells.

The Stanford team discovered that there was another viable vaccine approach, using the macrophage pathway to program killer T cells against cancer. Irving Weissman, MD, professor of pathology and of developmental biology, and his team previously showed that nearly all cancers use the molecule CD47 as a "don't-eat-me" signal to escape from being eaten and eliminated by macrophages. The researchers found that anti-CD47 antibodies, which can block the "don't-eat-me" signal and

enable macrophages to engulf cancer cells, eliminated or inhibited the growth of various blood cancers and solid tumors.

In the new study, the Stanford team showed that after engulfing the cancer cells, the macrophages presented pieces of the cancer to CD8+ T cells, which, in addition to attacking cancer, are also potent attackers of virally infected or damaged cells. As a result, the CD8+ T cells were activated to attack the cancer cells on their own. "It was completely unexpected that CD8+ T cells would be mobilized when macrophages engulfed the cancer cells in the presence of CD47-blocking antibodies," said MD/PhD student Diane Tseng, the lead author of the study. Following engulfment of cancer cells, macrophages activate T cells to mobilize their own immune attack against cancer, she said.

The Stanford group plans to start human clinical trials of the anti-CD47 cancer therapy in 2014. The new research provides hope that the therapy will cause the immune system to wage a two-pronged attack on cancer—through both macrophages and T cells. The approach may also give physicians early indicators of how the treatment is working in patients. "Monitoring T-cell parameters in patients receiving anti-CD47 antibody may help us identify the immunological signatures that tell us whether patients are responding to therapy," said co-author Jens Volkmer, MD, an instructor at the Stanford Institute for Stem Cell Biology and Regenerative Medicine.

The research revives interest in an aspect of macrophages that has been neglected for decades: their role in presenting antigens to T cells. For many years, researchers have focused on the dendritic cell as the main antigen-presenting cell, and have generally believed that macrophages specialize in degrading antigens rather presenting them. This research shows that macrophages can be effective at antigen presentation and are powerful initiators of the CD8+T cell response.

The fact that T cells become involved in fighting cancer as a result of CD47-blocking antibody therapy could have important clinical implications. The antibody might be used as a personalized cancer vaccine allowing T cells to recognize the unique molecular markers on an individual patient's cancer. "Because T cells are sensitized to attack a patient's particular cancer, the administration of CD47-blocking antibodies in a sense could act as a personalized vaccination against that cancer," Tseng added.

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