Potential therapy may boost chemoimmunotherapy response in bladder cancer

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Adding an anti-inflammatory medication to immunotherapy and standard chemotherapy drugs may provide long-term suppression of aggressive bladder tumor growth, according to a proof-of-concept study led by Cedars-Sinai Cancerinvestigators. The findings, made in laboratory mice, were published TK in the peer-reviewed journal *Nature Communications*.

The researchers' previous work, led by Cedars-Sinai scientist Keith Syson Chan, Ph.D.—the study's corresponding author—found that the combined use of the chemotherapy drugs gemcitabine and cisplatin is unable to activate a patient's own immune response to cancer. They also found that chemotherapy prompts the overwhelming release of an inhibitory signal, or brake, that suppresses an immune response by counteracting "go" signals. When the investigators added the anti-inflammatory drug celecoxib to gemcitabine to remove the brake, they were able to shift the balance toward the "go" signals, improving the immune response in laboratory mice.

Building on those findings, the researchers discovered a mechanism that may drive the immune-dampening effect of chemotherapy and determined how to counteract it, therefore activating a longer-lasting immune response.

"These results are significant because the novel drug combination of an anti-inflammatory medication like celecoxib, chemotherapy and immunotherapy potentially can increase the chemoimmunotherapy response in patients with muscle-invasive bladder cancer," said Fotis Nikolo, Ph.D., a project scientist at Cedars-Sinai Cancer and first co-author of the study. "We're also hopeful that our findings will be relevant to other cancer types."

Muscle-invasive bladder cancer is aggressive and more likely to spread to other parts of the body, according to the Urology Care Foundation. Each year, more than 83,000 new U.S. cases of bladder cancer are diagnosed in men and women. About one quarter of those newly diagnosed have the muscle-invasive type.

Past and Present Treatments

Since the 1940s, the main treatment for killing cancer cells has involved chemotherapy drugs, which kill the cells directly. But many of the current drugs fail to induce the most efficient form of cell death, known as immunogenic cell death, which activates the release of a protein that instructs the patients' own immune cells to kill the invading cancer cells. This "go" signal prompts immune cells—called dendritic cells—to activate T cells to eradicate tumors. Instead, most current chemotherapies for pancreatic, bladder, breast and ovarian cancers not only are non-immunogenic, they suppress the immune system.

In recent years, immunotherapy drugs have been added to cancer treatment regimens to help a patient's own immune cells attack cancer, but the response rate is low. Currently, about 70% to 80% of patients taking immunotherapy drugs fail to respond to them, Nikolo said.

Unlocking the Puzzle

The researchers may have discovered why the combination of chemotherapy and immunotherapy often fails. In their current study, the investigators found that chemotherapy induced a remarkable release of prostaglandin E_2, a bioactive lipid associated with inflammation and cancer. Called an inhibitory damage-associated molecular pattern, or iDAMP, prostaglandin E_2 blocks dendritic cells from maturing and fighting cancer, explained Kazukuni Hayashi, Ph.D., a study co-author.

To counteract that effect, the researchers added to the chemoimmunotherapy the drug celecoxib. The anti-inflammatory medication targets the protein COX-2, which promotes the release of prostaglandin E_2, Hayashi explained. This drug combination allows killer T cells to infiltrate the tumor core and kill the tumor cells.

"The addition of the celecoxib not only worked well with chemotherapy, it also sensitized bladder tumors toward chemoimmunotherapy, providing a long-lasting response," Hayashi said.

Next, the researchers plan to test the efficacy of the new treatment in randomized, placebo-controlled human trials in collaboration with their Cedars-Sinai Cancer and Mount Sinai clinical colleagues, including those researching new treatments for colon and pancreatic cancer.

"Harnessing the patients' immune system to attack tumor cells has become an important tool for physicians treating cancer," said Dan Theodorescu, MD, Ph.D., director of Cedars-Sinai Cancer and a study co-author. "With these findings, patients who don't respond to chemotherapy and immunotherapy have the potential for better outcomes in the future."

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