Neutralizing a tumor's acidic environment improves activity of immune-targeting cancer therapies

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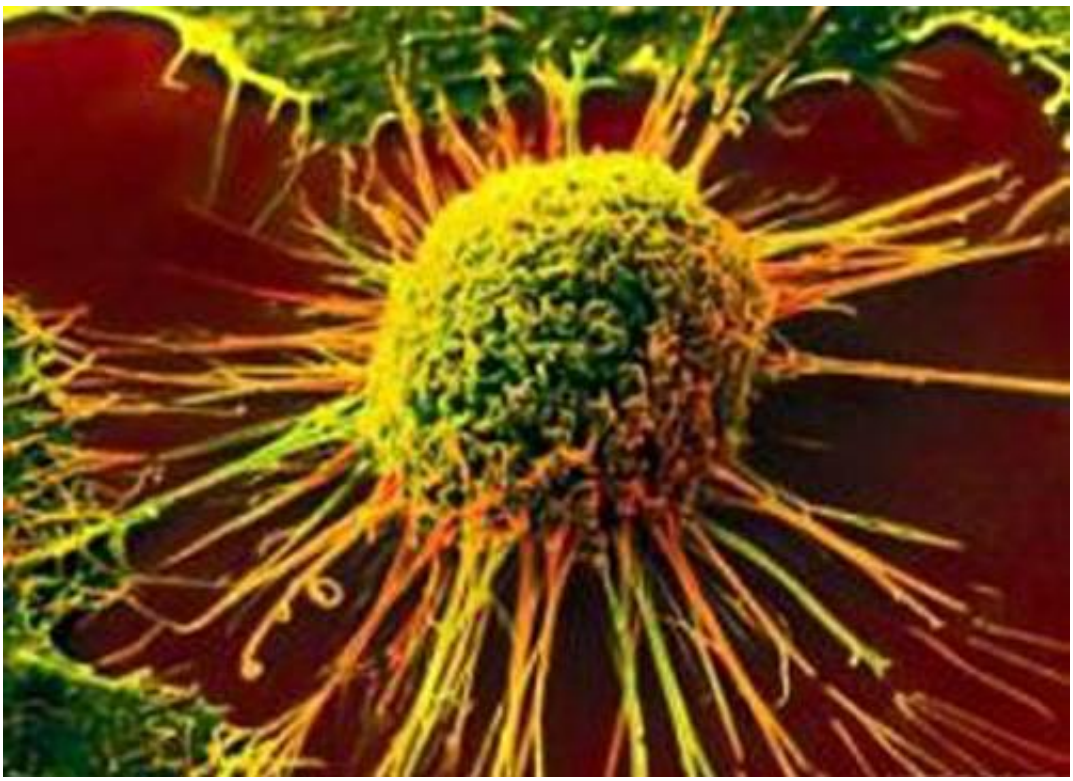

Cancer cells have the ability to grow in an acidic tumor environment that is detrimental to other cells, including immune cells. In a *Cancer Research* cover article published this week, Moffitt Cancer Center reported that neutralizing the acidic tumor environment increases the

efficacy of several immune-targeting cancer therapies.

Solid tumors survive in an acidic environment created by increased tumor cell metabolism and poor vasculature. Increased acidity can reduce the function of several different types of immune cells, leading to improved tumor survival. In addition, tumors avoid detection by the immune system by expressing proteins that block immune cell function.

Several therapies that restimulate the immune system are currently approved or in clinical development, including drugs that target the immune-suppressing proteins PD-1 and CTLA-4. While these agents have shown promising clinical activity, patient response rates still only range from 11 to 27 percent, suggesting that improvements could be made with combination treatments.

Moffitt researchers wanted to assess how an acidic environment affects immune cell function and the activity of PD-1 and CTLA-4-targeting cancer therapies.

They found that an acidic environment reduces the activity of a type of immune cell called a T cell. They hypothesized that neutralizing the acidic environment could affect tumor growth by reactivating T cells that could then target the tumor.

The team treated mice with the neutralizing agent sodium bicarbonate. They observed that, although sodium bicarbonate by itself did not reduce the growth of melanoma tumors in mice, it did increase the levels of T cells within the tumor.

The ability of sodium bicarbonate to increase levels of T cells in the tumor suggests that it could work in conjunction with PD-1 and CTLA-4 inhibitors to further stimulate the immune system. The researchers confirmed this by showing that treatment of mice with sodium

bicarbonate and CTLA-4 or PD-1 inhibitors reduced melanoma and pancreatic tumor growth when compared to each agent alone. Another promising immune therapy is infusing with T cells that are specifically active against a patient's tumor, and this showed much higher efficacy in combination with bicarbonate.

"The acidic pH encountered in a tumor microenvironment has significant immunosuppressive effects. By neutralizing this acid with buffers, we were able to improve the response of melanoma and pancreatic tumors to immunotherapy," said Robert J. Gillies, Ph.D., chair of the Department of Cancer Imaging and Metabolism at Moffitt.

The first author of the work, Shari Pilon-Thomas, Ph.D., assistant member of the Immunology Program at Moffitt, added, "This work adds tumor derived acidity to the list of immunosuppressive factors that are secreted by tumors".

In the future, Moffitt researchers plan to initiate a clinical trial to assess if treatment with sodium bicarbonate increases the efficacy of anti-PD1 therapy in pancreatic cancer and melanoma patients.

Provided by H. Lee Moffitt Cancer Center & Research Institute