Study: Impediment to some cancer immunotherapy involves the free radical peroxynitrite

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Researchers at the Moffitt Cancer Center in Tampa, Fla., and colleagues have found that tumor cell resistance to a specific cancer immunotherapy designed to kill cancer cells can be blamed on a mechanism that involves the production of a free radical peroxynitrite (PNT) that causes resistance to therapeutic cancer-killing cells.

The study, by Moffitt investigators and colleagues at the Dartmouth Medical School, University of Nebraska Medical Center, and the Research Center for Medical Studies, Moscow, Russia, is published in the recent issue of *The* Journal of Clinical Investigation.

According to lead author, Dmitry Gabrilovich, M.D., Ph.D., senior member of the Moffitt Department of Immunology, the researchers found that myeloid cells can infiltrate tumor sites and modify cytotoxic T-cell (CTL) responses in many patients.

"We set out to investigate one possible explanation for the failure of CTLs to eliminate tumors," said Gabrilovich. "We found that therapeutic failure was the result of the presence of the free radical peroyxnitrite, or PNT."

Gabrilovich and his colleagues focus much of their research on gaining a better understanding about how tumors develop ways to avoid recognition by the immune system, as well as how mechanisms of tumor-

associated immunosuppression have an effect on the development and effectiveness of cancer vaccines. In particular, they examine how myeloid cells lose their ability to mature, become functionally defective, and acquire the ability to suppress immune response.

As a further step in their continuing work, in this study the researchers demonstrated that in mouse models of cancer, myeloid-derived suppressor cells (MDSCs) infiltrating the tumor became a source for PNT, the cause of resistance.

"The results suggest that PNT might be affecting the binding of specific peptides," said Gabrilovich. "The data suggests that PNT affects the formation of certain peptide complexes, preventing the CTL's killing of tumor cells."

The researchers next investigated the source of PNT in the tumor microenvironment that could prevent CTL from binding to target tumor cells. They examined tumor tissues from several types of cancers – including lung, breast and pancreatic cancers – and began looking for sites of PNT production in the tumor cells by staining the tissues using nitrotyrosine (NT), known to be a marker for PNT activity.

"In each type of tumor, NT staining was significantly higher in myeloid cells than in tumor cells or epithelial cells," explained Gabrilovich. "The data suggests that these cells are the major source of PNT and tumor cell resistance to CTLs."

According to Gabrilovich, their research suggests that tumors could "escape" immune control even if potent CTL responses against tumor-associated antigens were generated by vaccines, checkpoint inhibitors, or tumor infiltrating or genetically modified T cells.

"This research also suggests that this escape can be diminished by

blocking PNT production by using pharmacological inhibitors," concluded Gabrilovich.

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