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Mechanism of an effective MEK inhibitor identified

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Understanding the effects of certain targeted therapies on antitumor immunity is necessary to design combined interventions for more effective cancer treatment. In the past, data have shown that trametinib, an FDA-approved MEK inhibitor routinely administered to patients with melanoma and currently being studied to treat a number of other types of cancer, inhibits T cell responses in vitro, but is effective in some tumor models in vivo.

Scientists at The Wistar Institute recently discovered how this drug boosts antitumor activity and slows tumor progression, even if it fails to directly stop tumor cell proliferation. Study results were published in the journal *Cancer Research*.

When small molecule kinase inhibitors—a class of drugs designed to target specific mutations and proteins related to cancer while sparing healthy cells without these mutations—started being approved for different types of cancer, the laboratory of José R. Conejo-Garcia, M.D., Ph.D., professor in the Tumor Microenvironment and Metastasis Program at Wistar, initiated a project to understand the effects of these targeted therapies on immune response.

"We realized that most small kinase inhibitors in the pipeline targeted pathways that are important for the function of immune cells," Conejo-Garcia said. "However, they had been primarily tested in vitro against tumor cells or in immunodeficient animals at best. Very little was known about the consequences of using these interventions on spontaneous or

immunotherapeutically boosted antitumor immunity."

In this study, Conejo-Garcia and colleagues found that trametinib controls tumor progression by halting the mobilization of myeloid-derived suppressor cells (MDSCs), a set of immune cells that have been linked to making tumors resistant to treatment. This reduced the level of immune suppression in the tumor, allowing anti-tumor T cells to target the tumor. In fact, the effectiveness of trametinib is dependent on the activity of these anti-tumor T cells, despite its direct inhibitory effects on this tumor cell compartment, which are largely rescued by certain cytokines present at tumor beds.

Although trametinib failed to directly inhibit tumor cell proliferation, its combined effects on multiple immune and nonimmune compartments boosted antitumor immunity in vivo in tumor-bearing hosts and significantly delayed malignant progression.

"Understanding the effects of trametinib on antitumor immunity is urgently needed to design the sequence of rational combinatorial interventions that include emerging and future anticancer immunotherapies," Conejo-Garcia said. "Our findings demonstrate that trametinib could be combined with existing immunotherapeutic agents in at least tumors that mobilize a significant amount of immunosuppressive myeloid cells."

Provided by The Wistar Institute