MedicalXpress

Vitamin E can boost immunotherapy responses by reinvigorating dendritic cells

April 14 2022

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Combining a retrospective analysis of clinical records with in-depth laboratory studies, researchers at The University of Texas MD Anderson Cancer Center have discovered that vitamin E can enhance

immunotherapy responses by stimulating the activity of dendritic cells in the tumor. The findings were published today in *Cancer Discovery*.

The researchers demonstrated that vitamin E directly binds and blocks the activity of the SHP1 checkpoint protein in dendritic cells, which increases antigen presentation and primes T cells for an anti-tumor immune response. The results point to possible new therapeutic approaches to improve immunotherapy outcomes, including combinations with vitamin E as well as directly targeting SHP1 in dendritic cells.

"This study broadens our understanding of factors that can influence responses to immunotherapies," said corresponding author Dihua Yu, M.D., Ph.D., chair ad interim of Molecular & Cellular Oncology. "We demonstrated that vitamin E can reinvigorate dendritic cell antigen presentation via the inhibition of SHP1. These results indicate that vitamin E-treated or SHP1-silenced dendritic cells and dendritic cell-derived extracellular vesicles could be developed as potent immunotherapies for future clinical applications."

Vitamin E connected with improved immunotherapy responses

Immune checkpoint inhibitors, a type of immunotherapy, provide long-lasting responses for many patients with cancer, but not all benefit. There is a need to understand these varied responses in order to improve outcomes for more patients.

Dietary supplements are thought to boost immunity, but little is known about the effects of supplements on immunotherapy activity. To explore the connection, the researchers performed a retrospective analysis of clinical data from MD Anderson patients treated with immunotherapy.

Patients with melanoma who took vitamin E while on anti-PD-1/PD-L1 checkpoint inhibitors had significantly improved survival compared to patients who didn't take vitamin E or multivitamins. This finding was replicated in an independent mixed cohort of patients with breast, colon and kidney cancers. However, patients taking vitamin E while being treated with chemotherapy did not experience the same benefits, suggesting the effects were unique to chemotherapy.

Next, the researchers demonstrated that vitamin E enhanced responses to checkpoint inhibitors in immunogenic mouse models of breast cancer and melanoma. However, models with low levels of tumor-infiltrating dendritic cells did not benefit from vitamin E, suggesting the effects were dependent on these cells.

Deciphering the effects of vitamin E on dendritic cells

Dendritic cells are a specific class of immune cells responsible for presenting abnormal proteins—called antigens—to prime T cells, which is an essential step in the anti-tumor immune response. However, tumor-associated dendritic cells can become dysfunctional due to suppressive signals in the tumor microenvironment.

The researchers demonstrated that the vitamin E treatment led to upregulation of several activation markers on the dendritic cells. Additionally, dendritic cells from tumors treated with vitamin E promoted more T cell proliferation relative to controls, suggesting vitamin E enhanced the priming step.

Through molecular and structural studies, the researchers discovered that vitamin E enters dendritic cells and binds to the SHP1 protein—which acts as a checkpoint to regulate dendritic cell activity—to block its activity and enhance dendritic cells' functionality to prime T cells.

Blocking SHP1 genetically mimicked the results with vitamin E, leading to increased antigen presentation that stimulated T cell anti-tumor responses. Similarly, blocking SHP1 enhanced antigen presentation in extracellular vesicles released by dendritic cells—another important mode of communication between dendritic cells and T cells.

Targeting SHP1 may be a novel therapeutic strategy

As vitamin E appears to improve the antigen presentation of dendritic cells, the researchers investigated whether vitamin E could enhance responses from therapies known to release tumor antigens and recruit dendritic cell infiltration.

Laboratory findings demonstrated that vitamin E treatment could augment the effects of cancer vaccines and immunogenic chemotherapies combined with checkpoint inhibitors, including in a model of immunotherapy-resistant pancreatic cancer.

"SHP1 is an attractive target to effectively activate dendritic cells for the development of potent immunotherapy," said lead author Xiangliang Yuan, Ph.D., research scientist in Molecular & Cellular Oncology. "This work yielded important insights on the interaction between vitamin E and SHP1 that will guide us to develop more specific allosteric SHP1 inhibitors. Compellingly, it appears that unleashing dendritic cells by inhibiting SHP1 may be an advantageous strategy to enhance antitumor immunity."

The research team is now exploring opportunities with clinical collaborators at MD Anderson to prospectively evaluate the effects of vitamin E in combination with checkpoint inhibitors and other immunotherapies. Team members also are exploring opportunities to develop a targeted SHP1 inhibitor as well as SHP1-modified dendritic cells and dendritic cell-derived extracellular vesicles as novel future

therapeutic options.

More information: Xiangliang Yuan et al, Vitamin E Enhances Cancer Immunotherapy by Reinvigorating Dendritic Cells via Targeting Checkpoint SHP1, *Cancer Discovery* (2022). DOI: 10.1158/2159-8290.CD-21-0900