Modulating T-cell metabolism uncovers new technology for enhancing immunotherapy

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T lymphocytes found in tumors and implicated in killing tumor cells cope with the shortage of oxygen and nutrients in the tumor microenvironment by using fat as the main source of energy. Promoting a switch from glucose to fatty acid to generate energy enhances T cell antitumor activity. These findings from a study conducted at The Wistar Institute were published in the journal *Cancer Cell*.

The presence of tumor infiltrating T lymphocytes (TILs) in solid tumors is often associated with better clinical outcomes and better patient responses to some immunotherapeutic treatments. These cells can be isolated from a cancer patient, manipulated ex vivo, and infused into the same patient to treat her/his own cancer. However, the effectiveness of TILs antitumor responses is limited by their progressive loss of functions. Metabolic stress plays a central role in the exhaustion of T cells as they compete with tumor cells for oxygen and nutrients in the tumor microenvironment. In these unfavorable conditions, the function of TILs is impaired, reducing their potency against the tumor and the efficacy of T cell-based immunotherapy.

"The mechanisms behind TILs exhaustion are poorly understood," said lead author of the study Hildegund C.J. Ertl, M.D., Caspar Wistar Professor in Vaccine Research and member of Wistar's Vaccine & Immunotherapy Center. "Considering the central importance of TILs for cancer immunotherapy, we believe that our findings may have critical implications to boost the efficacy of T cell-based therapies."

This study by Ertl and colleagues shows that low oxygen levels combined with low glucose availability cause TILs to adapt their metabolism and change their source for energy production from glucose to fatty acids, the building blocks of fat. Further inducing this metabolic shift instructs the T cells to increase their use of fatty acids for energy production, thus improving TILs' effector functions and their ability to delay tumor progression.

The Ertl lab studied the effectiveness of metabolic manipulations to improve TIL functions in two melanoma mouse models and in the context of two different immunotherapy approaches. Ertl and colleagues confirmed the clinical relevance of these observations by showing that T cells isolated from metastases of melanoma patients have increased fatty acid metabolism compared with circulating lymphocytes from healthy donors. Furthermore, using fibrates, a class of FDA approved drugs used to lower cholesterol levels, they promoted the breakdown of fatty acids and observed that this enforced metabolic switch is associated with improved T cell functions within tumors. Importantly, these drugs can also synergize with immune checkpoint blockade therapy, improving the efficacy of this melanoma immunotherapy.

"Pharmacological interventions aimed at promoting the metabolic adaptation of TILs towards fatty acid metabolism may have a broad implication for T cell-based immunotherapy for different cancer types," added Ertl.

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