Researchers identify key characteristics of immune cells in ovarian cancer

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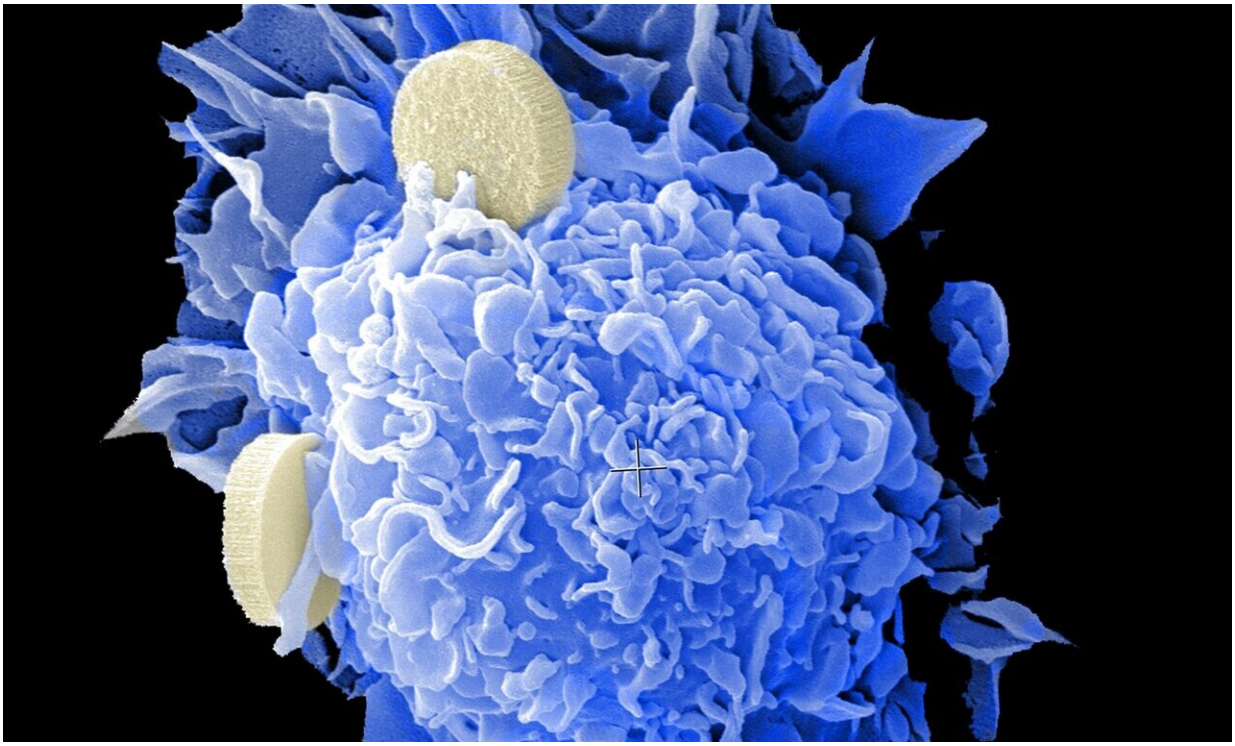

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Ovarian cancer is a difficult to diagnose malignancy that is often caught at a more advanced stage. Treatments for this cancer have changed little over the past few decades, with surgery and chemotherapy being the most common therapeutic approaches. Immunotherapy, a type of treatment that activates a patient's immune system to target cancer cells,

has been successful in many diseases but not ovarian cancer and it is unclear why.

Researchers at Moffitt Cancer Center want to improve their understanding of the immune environment in ovarian cancer in hopes of making immunotherapy an option for these patients. In a new study published in *Cancer Cell*, they report on key characteristics of immune cells in ovarian cancer and identify cell types important for mediating an immune response.

Checkpoint inhibitors are a specific type of immunotherapy that work by activating an immune cell called T cells. In order for checkpoint inhibitors to work, patients must have T cells that are ready to be activated in close proximity to tumor cells. Ovarian cancer is considered a type of tumor that should be impacted by checkpoint inhibitors because of T cell presence; yet clinical studies in ovarian cancer for these drugs have not been successful.

Moffitt researchers, led by Immunology Department Chair Jose Conejo-Garcia, M.D., Ph.D., wanted to determine whether ovarian cancer has the proper T cells to initiate an immune response and characterize the properties of the T cells present within ovarian cancer tumors. They performed a comprehensive analysis of ovarian cancer patient samples at the single-cell and tissue levels. They discovered that ovarian cancer is an immunogenic type of tumor that should be impacted by drugs that activate the immune system; however, immune activity against tumor cells is dependent on a small subset of immune cells.

The researcher team analyzed the types of T cells present in ovarian tumors and discovered that tissue-resident memory like T cells do a better job of recognizing tumor cells than T cells that are circulating and infiltrating the tumor. They also discovered that tissue-resident memory like T cells arise from circulating T cells and undergo a differentiation

process into a tissue-resident memory stem cell that can generate T cells that actively target cancer cells. Some of these active T cells will eventually differentiate into an exhausted, inactivated state. The researchers confirmed that tissue-resident memory stem cells were important for anti-tumor immune activity by demonstrating that high numbers of them were associated with improved patient survival in ovarian cancer.

Interestingly, some of these lymphocytes show features of trogocytosis, a process where T cells take up a chunk of the membrane of target tumor cells. A trajectory of differentiation of tissue-resident memory T cells from stemness to irreversible exhaustion, in addition to evidence of trogocytic activity, identifies the T cells truly relevant to determine ovarian cancer patients' outcome.

These results demonstrate that ovarian cancer, despite resistance to existing immunotherapies, is indeed an immunogenic disease and provide a roadmap for the design of improved immunotherapy options, which could be applicable to other tumors with similar mutational burden.

More information: Carmen M. Anadon et al, Ovarian cancer immunogenicity is governed by a narrow subset of progenitor tissue-resident memory T cells, *Cancer Cell* (2022). DOI: 10.1016/j.ccell.2022.03.008

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