Researchers discover mechanism that regulates anti-tumor activity of immune cells

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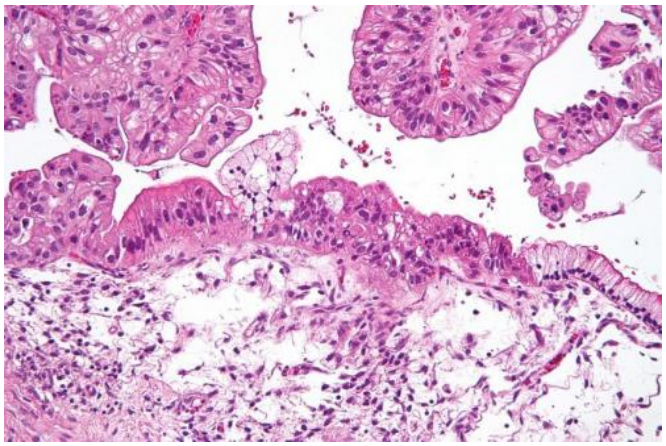

Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. H&E stain. The micrograph shows: Simple mucinous epithelium (right) and mucinous epithelium that pseudo-stratifies (left - diagnostic of a LMP tumour). Epithelium in a frond-like architecture is seen at the top of image. Credit: Nephron /Wikipedia. CC BY-SA 3.0

The prognosis of ovarian cancer is poor, with an estimated five-year survival of only 40% for advanced disease, the stage at which most ovarian carcinomas are diagnosed. These poor outcomes are partly due to the lack of effective therapies for advanced disease and recurrence. Immunotherapies hold promise for many types of cancer; however, studies have shown that patients with ovarian cancer do not have strong responses to existing drugs. In a new article published in *Nature*, Moffitt Cancer Center researchers demonstrate why some ovarian cancer patients evolve better than others and suggest possible approaches to improve patient outcomes.

Immunotherapeutic drugs activate T cells, a type of immune cell, to put up a defense against tumor cells. Immunotherapies are approved to treat several different types of cancer and have greatly changed the standard of care and improved patient outcomes. However, in ovarian cancer, clinical studies using immunotherapies aimed at stimulating T cells resulted in modest response rates. Studies have suggested that cancer patients who have a higher presence of other immune cells, such as plasma and memory B cells, could respond better to immunotherapies, but how these cell types promote better outcomes is unclear. Moffitt researchers wanted to confirm whether antibodies produced by these cells are associated with better outcomes and assess how these cells contribute to the spontaneous anti-tumor immune response against ovarian cancer.

The researchers analyzed a panel of 534 samples from ovarian cancer patients and found that patients who had a higher infiltration of B cells or B cell-derived plasma cells had better outcomes. B cells are a type of immune cell that produce antibodies and express one of five types of B cell receptors on their surface: IgM, IgD, IgG, IgE or IgA. These isotypes regulate different B cell signaling pathways and control B cell processes.

The surprise came when, upon further analysis of the samples, the Moffitt team discovered that the antibodies produced by B and plasma cells were predominantly of the IgA subtype, followed by IgG.

"We found that the presence of IgA regulated downstream signaling pathways of the ovarian cancer cells. Specifically, IgA resulted in inhibition of the RAS signaling pathway, which is known to contribute to ovarian cancer development," said Jose Conejo-Garcia, M.D., Ph.D., chair of Moffitt's Immunology Department.

This inhibition of RAS sensitized the tumor cells to T cell mediated cell killing, produced by both novel CAR T cells and tumor-infiltrating lymphocytes. The team also assessed that IgA and IgG secreted by the B cells recognized specific ovarian tumor cell surface markers and stimulated other immune cells

called myeloid cells to target ovarian cancer cells for destruction.

These data provide new insights into how components of the immune system regulate ovarian cancer progression and offer new opportunities to develop improved targeted agents. This includes a repertoire of tumor-derived antibodies that can be effectively used as novel immunotherapeutic agents. In addition, the study provides a mechanistic rationale for integrated antibody responses in the development of novel immunotherapies, which until now have been based on T cell-centric approaches.

"The findings indicate that immunotherapies that boost both coordinated B and T cell responses against ovarian cancer, an immunogenic disease currently resistant to checkpoint inhibitors, are likely to show superior therapeutic benefit," said Subir Biswas, Ph.D., first author and postdoctoral fellow in the Conejo-Garcia lab.

More information: Subir Biswas et al, IgA transcytosis and antigen recognition govern ovarian cancer immunity, *Nature* (2021). DOI: 10.1038/s41586-020-03144-0

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