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Researchers discover mechanism controlling tertiary lymphoid structure formation in tumors

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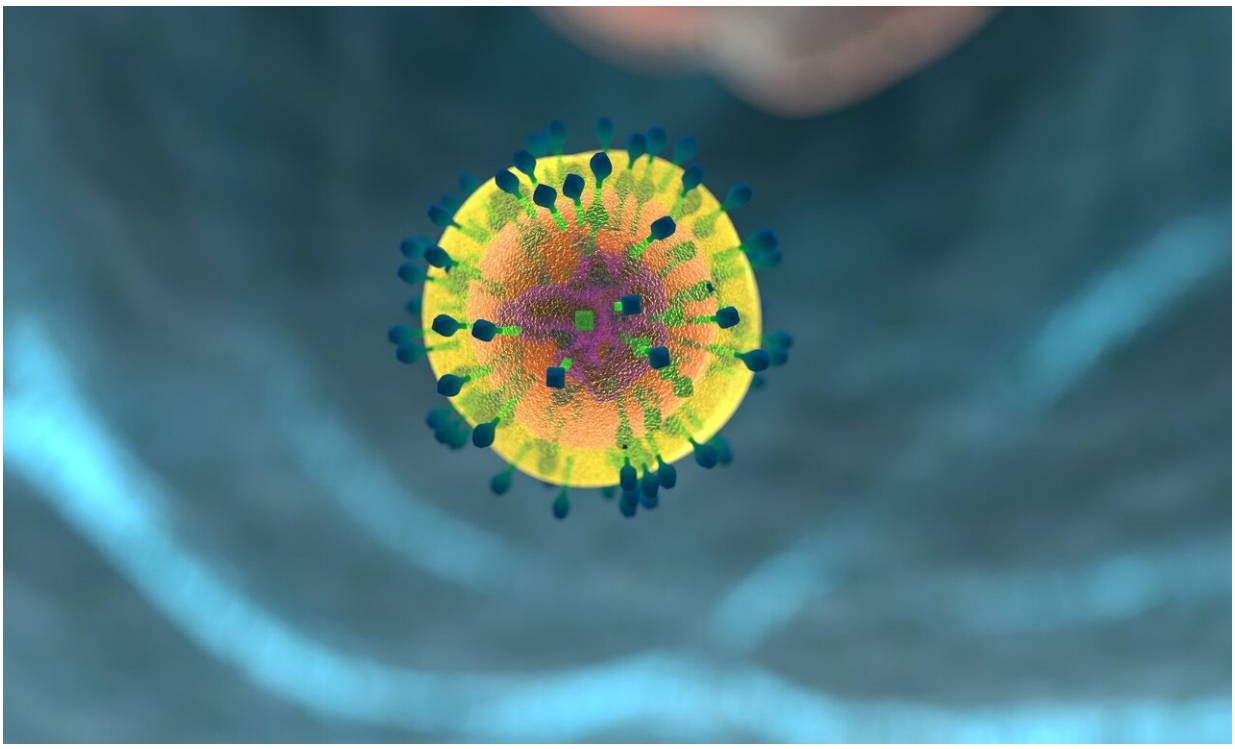

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Tertiary lymphoid structures are formations that occur outside of the lymphatic system. They contain immune cells and are similar in structure and function to lymph nodes and other lymphoid structures. However,

little is known about how tertiary lymphoid structures form. In a new article published in *Immunity,* Moffitt Cancer Center researchers report on the molecular and cellular mechanisms that control tertiary lymphoid structure formation within tumors.

The immune system is composed of different types of cells and their secreted proteins that regulate cancer development, including T cells and B cells. T cells are further categorized according to their function and specific molecules they express, such as T follicular helper (Tfh) and T follicular regulatory (Tfr) cells. Interactions among these different immune cells can either contribute to or inhibit cancer development. Tfh cells stimulate B cells to produce antibodies, while Tfr cells inhibit this activity. Tfh and Tfr cells and other immune cells are found in in the lymph nodes, as well as tertiary lymphoid structures.

Several studies have found better outcomes among patients with tumors that have tertiary lymphoid structures, including superior responses to immunotherapy. It is speculated that the presence of active immune cells within the tertiary lymphoid structures and their secreted proteins contribute to immune activity against tumor cells. However, it is not clear how tertiary lymphoid structures form, particularly since they are rarely found in experimental mouse models.

Moffitt researchers performed a series of laboratory experiments with cells and mouse models to improve their understanding of the molecular and cellular mechanisms that lead to tertiary lymphoid structures formation. They discovered that the protein SATB1 is an important regulator of the differentiation process of Tfh and Tfr cells. SATB1 is a genomic organizing protein that helps to control how tightly DNA is wound and serves as a recruiter for other modifying proteins. The researchers discovered that inhibiting the expression of SATB1 promotes the differentiation process of Tfh cells and prevents the formation of Tfr cells. They also identified some of the key contributing

signaling molecules involved in this process, including ICOS and TGF-β.

The researchers confirmed the importance of SATB1 for this process by showing that mice with T cells lacking SATB1 had a higher proportion of Tfh cells that were able to interact with B cells and form tertiary lymphoid structures within tumors. Importantly, the researchers also showed that tumors grew less in mice that were injected with Tfh cells when compared to control T cells, which was associated with the formation of tertiary lymphoid structures within the tumors.

The researchers hope that their findings will lead to new interventions to orchestrate tertiary lymphoid structures in irresectable tumors, to support anticancer immunotherapies.

"Tertiary lymphoid structures are found in roughly 20% of human cancers. Using the data from our study, we believe intratumoral administration of autologous antigen specific Tfh cells in metastatic cancers or unresectable tumors could promote the generation of tertiary lymphoid structures. The anti-tumor T cells found in those tertiary lymphoid structures could provide a protective niche to exert immune pressure against the progression of advanced malignancies and possibly enhance the success of immunotherapies," said Jose Conejo-Garcia, M.D., Ph.D., chair of the Department of Immunology at Moffitt.

More information: Ricardo A. Chaurio et al, TGF-β-mediated silencing of genomic organizer SATB1 promotes Tfh cell differentiation and formation of intra-tumoral tertiary lymphoid structures, *Immunity* (2022). DOI: 10.1016/j.immuni.2021.12.007

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