Researchers identify one way T cell function may fail in cancer

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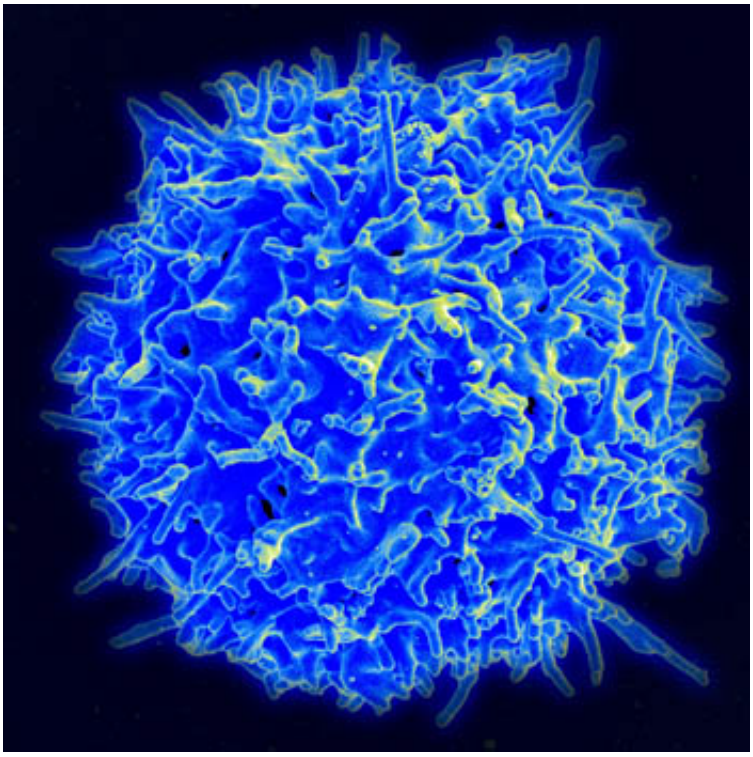

Scanning electron micrograph of human T lymphocyte or T cell. Credit: NIAID/NIH

The immune system is an important defender against cancer. Immune cells continuously search the body for disease and use their anti-tumor cell properties to target and destroy defective cells. However, most cancer patients have an impaired immune system that allows cancer cells to go undetected. Moffitt Cancer Center researchers have discovered a

mechanism by which one type of immune cell, CD8+ T cells, can become dysfunctional, impeding its ability to seek and kill cancer cells.

"The impaired T cell function present in most cancer patients is a primary reason cancer cells can evade protective antitumor immunity, and it represents a major limitation in the development of new immunotherapies," said Paulo Rodriguez, Ph.D., associate member of the Department of Immunology at Moffitt.

In a new study, published in *Nature Communications*, Moffitt scientists investigated how the immune system becomes dysfunctional, with the hope that a better understanding of these mechanisms may lead to improved treatment strategies.

Previous studies have shown that the protein Chop is involved in cellular stress responses and myeloid immune cell responses. The Moffitt team wanted to determine if Chop also plays a role in T cell immunity. They discovered that Chop expression is higher in T cells from ovarian cancer patients than in healthy ovarian tissue. They also found that high nuclear levels of Chop in CD8+ tumor infiltrating T cells in ovarian cancer patients were associated with poor clinical responses. This suggests that Chop may be involved in altered immune responses to cancer.

In order to determine the function of Chop in T cells, the researchers conducted an extensive set of laboratory experiments with mice and primary murine and human T cells. They found that Chop plays an important role in negatively regulating T cell responses, and that Chop levels increase when T cells become activated. This increase is dependent on the protein Perk that is involved in stress responses. When the researchers deleted the Chop gene in T cells, anti-tumor CD8+ T cell immunity was improved and T cell-based immunotherapy treatments were more effective in immunologically relevant mouse models.

These observations suggest that under normal circumstances, Chop plays an important role in helping to balance anti-tumor T cell responses. However, tumors have learned to hijack the normal function of Chop to decrease T cell immunity. A less active immune system permits cancer cells to bypass the anti-tumor immunity function of T cells, resulting in continued cancer cell growth and development.

"Our results demonstrate the primary role of Chop in the impaired activity of CD8+ T cells in tumors and suggest it is possible to overcome tumor-induced CD8+ T cell suppression and increase the efficacy of T cell-based immunotherapy by blocking Chop or ER stress," said Jose Conejo-Garcia, M.D., Ph.D., chair of Moffitt's Department of Immunology.

More information: Yu Cao et al, ER stress-induced mediator C/EBP homologous protein thwarts effector T cell activity in tumors through T-bet repression, *Nature Communications* (2019). DOI: 10.1038/s41467-019-09263-1

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