Toward a More Nuanced Understanding of the Anti-Cancer Immune Response

There is more to cancer immunotherapy than cytotoxic T cells.

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An effective immune system response requires coordination among many types of immune cells, including CD4+ (helper) T cells, CD8+ (cytotoxic) T cells, and B cells. Helper T cells recognize antigens—identifying molecules on the surface of a pathogen—and release warning signals. These signals activate cytotoxic T cells, which kill the infected or cancerous cells, and B cells, which produce antibodies to attack the pathogen directly.

When discussing cancer immunotherapy, we tend to focus on cytotoxic T cells. These are the T cells that immunotherapy drugs target, suppressing their “brakes” to unleash them on cancer cells. But research indicates that helper T cells and B cells play an important role in anti-cancer immunity as well, and a better understanding of their roles could lead to more effective immunotherapy approaches.

At Yale University, former Damon Runyon Fellow Nikhil Joshi, PhD, is investigating the role of a subset of helper T cells known as T follicular helper (TFH) cells. Studies have shown that the presence of TFH and B cells correlate with prolonged survival in cancer patients, but exactly how they contribute to anti-cancer immunity is unclear. To find out, Dr. Joshi’s lab created a mouse model of lung cancer in which some tumor cells presented antigens recognizable to both B cells and T cells, and some presented antigens recognizable to T cells only.

As expected, both types of antigen activate helper T cells. But here the paths diverge, as you can see in the diagram above. In the first scenario, the helper T cell brings the antigen to the B cell, and their interaction stimulates the growth of TFH cells, which release signaling molecules (called IL-21) to activate cytotoxic T cells. Once activated, these cytotoxic T cells infiltrate the tumor and kill cancer cells. In the second scenario, however, the helper T cell bypasses the B cell interaction, does not produce TFH cells, and thus does not activate the cytotoxic T cells.

Dr. Joshi’s findings illuminate the critical and underappreciated role of B cells and TFH cells in the anti-cancer immune response. They open up a world of new therapeutic opportunities, including personalized vaccines containing antigens recognizable to both B and T cells, or engineered versions of IL-21 that can be combined with existing immunotherapies. It appears cytotoxic T cells, the heavy lifters of anti-cancer immunity, can use all “helpers” they can get.

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