Targeting T cells to Eliminate Tumors

By Meghan Delmastro Greenwood, Ph.D.

The body's immune system is charged with controlling threats and removing cells that could be hazardous to survival. However, as tumors grow, their proliferation exceeds the ability of the immune system to protect the body, resulting in the immune system tolerating the cancer. In particular, cytotoxic T cells – a type of white blood cell that triggers other cells to die off – become ineffective at killing tumor cells. The tumor is also able to evade the immune response through various mechanisms of its own, including producing signaling proteins that inhibit cytotoxic T cells, inducing regulatory T cells (Tregs, another type of immune cell that shuts down cytotoxic T cells), and stimulating the growth of blood vessels. All of these efforts promote the survival and eventual metastasis of tumor cells throughout the body. T cells are oftentimes targeted for activation in immune therapy because of their leading role promoting pathogen or tumor clearance as well as their ability to activate other immune cells.

T cells themselves are activated when they recognize an antigen and are also costimulated through CD28, a protein on their surface. Normally, once an immune response ends, the number of T cells is drastically reduced. This process is known as contraction and prevents hyperresponsiveness and subsequent bystander damage. CTLA-4, another surface protein that serves as the antagonist to CD28, is expressed on the surface of contracting T cells. This protein prevents any further costimulatory-mediated activation of the T cell and returns the immune system to base level. Similarly, Tregs constitutively express CTLA-4, which prevents them from becoming cytotoxic and promoting inflammation. In the context of cancer, when T cells are less responsive, blocking CTLA-4 may promote an anti-tumor T cell response, thus improving clinical outcomes.

Some of the first successful studies blocked CTLA-4 with an antibody – a specialized protein that binds a target and neutralizes it – in rodent cancer models. Treating mice with CTLA-4 targeting antibodies (anti-CTLA-4) resulted in complete prostate cancer rejection in 42% of the tested animals[1]. Beyond tumor rejection, anti-CTLA-4 treatment also induced long-lasting tumor immunity[2]. This long-lasting immunity would be able to stop the formation of new cancers, preventing recurrence. In 2011, over a decade after the first successful anti-CTLA-4 antibody study, Ipilumab (the pharmaceutical anti-CTLA-4) was approved by the FDA for the treatment of melanoma. This approval came after a number of promising clinical studies in metastatic melanoma patients. By itself, Ipilumab treatment gave a 10.9% patient response rate[3], but combining it with an FDA-approved IL-2 cytokine treatment raised the response rate 25% [4]. Combinatorial therapy is typical in cancer treatment, with chemotherapy and radiation frequently administered together. Combining anti-CTLA-4 antibody with other therapies may not only result in better tumor rejection but may also lead to increased immune responses. For example, anti-CTLA-4 treatment in conjunction with tumor removal was able to enhance cytotoxic T cell responses in mice[5]. Likewise, combining anti-CTLA-4 with tumor cell vac-

cines in mice[6] can instigate stronger cytotoxic T cell responses, reduce the number of Tregs and sustain survival[7]. Even when the immune system tolerates tumor growth, the T cells may still be attempting to protect against the cancer; however, their response is inhibited in the cancerous area. A recent study by Sundstedt et al. showed that anti-CTLA-4 was able to alleviate a blocked T cell anti-tumor response and reduce Treg numbers, leading to better tumor clearance[8]. Moreover, anti-CTLA-4 therapy given during the intervals between chemotherapy sessions increased the number of cytotoxic T cells. These effects blocked the repopulation of tumor cells after each cycle of chemotherapy[9], which could be important in sustaining long-term remission.

Taken together, the results of these studies show that anti-CTLA-4 treatment can enhance tumor rejection, boost T cell immune responses, and decrease Treg-mediated suppression of the immune system. Promising results in metastatic melanoma give hope to using such a treatment in a variety of cancers. However, the clinical research using Ipilumab – especially for combinatorial therapies – is only in its infancy, and the possibilities for it as an effective overall cancer treatment require more in-depth studies.

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