Update on Immunotherapy in Melanoma

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KEYWORDS

• Immunotherapy • Antitumor immunity • Metastatic melanoma
• Costimulatory blockade • Innate immunity • Adaptive immunity

KEY POINTS

- Immunotherapy agents have been demonstrated to improve survival option for patients with metastatic melanoma.
- The field of immunotherapy now offers treatments with the potential for a long-term cure.
- As the field moves forward, studies will focus on improving the response rates with new immunotherapy agents or novel treatment combinations.

HISTORY OF IMMUNOTHERAPY

The idea of enhancing the immune response to reduce cancer growth can be traced back to Dr William Coley's work at New York Cancer Hospital more than a century ago. Dr Coley initially noted tumor regression in a patient who developed a postoperative infection. The patient had recurrent cheek sarcoma, underwent a partial excision of his tumor, and was cured of the remaining tumor after he developed a wound infection with the bacteria *Streptococcal pyogenes*.[1] Coley concluded that the immune response to the bacteria played an integral role in fighting the cancer. He then inoculated with bacteria his next 10 patients who had tumors that could not be surgically excised successfully. This approach had several problems, given that he saw a range of responses; some patients failed to develop an infection, whereas others developed too strong of an infection that it proved fatal. However, he did find that the patients who had an immune reaction to the bacteria, including fever and inflammation, experienced tumor reduction.[1] He subsequently tested the effect of injecting a vaccine with killed bacteria into the tumors, otherwise known as *Coley's toxin*, to stimulate an immune response without risking fatal infection, and found that he was able to cause complete regression of cancer in some patients.[1] Unfortunately, much of this work

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was abandoned for years after his death as a result of the discovery of radiation and cytotoxic chemotherapy.

However, over the past few decades, the field of immunotherapy has been reborn. Careful preclinical studies have enhanced the understanding of the immune system and ways to promote antitumor immunity, most specifically with the use of adoptive T cells, which are specific for the cancer itself, and immune checkpoint blockade. Prospective randomized trials have demonstrated the efficacy of immune checkpoint blockade in the treatment of melanoma, and the field continues to move forward at a rapid pace. Together these treatments have resulted in a cure for many patients and have changed the way in which metastatic melanoma is treated. This article focuses on the immune system, immunotherapy treatments for melanoma, and the new treatments in development that show potential for improved success.

THE IMMUNE SYSTEM

The human immune system comprises 2 main branches, innate and adaptive immunity, which work together to form a fast and effective response to a pathogen. Innate immunity involves nonspecific mechanisms to fight all foreign invaders. These cells are normally the first responders to an insult because they are always present in individuals and do not need time to develop. The first components of the innate immune response are anatomic barriers, such as the skin, which serves as a barrier to prevent the entry of microbes, and mucous membranes, which trap foreign organisms to remove them from the body; and physiologic barriers, such as the low pH of the stomach, which kills most organisms that are ingested.[2] The main cells involved in the innate immune response are (1) mast cells, which cause blood vessel dilation to increase flow to the injured area, and the release of chemokines, proteins that attract other immune cells to the area; (2) macrophages, which are large cells that phagocytose (engulf and digest) the bacteria and secrete immunostimulatory proteins, also referred to as *cytokines*; (3) neutrophils, which are the most abundant circulating white blood cell (WBC), and phagocytose bacteria or dead cells; (4) basophils and eosinophils, which secrete immunostimulatory proteins; and (5) natural killer cells, which destroy damaged or abnormal cells, including tumor cells, and are recognized by their lack of certain proteins, called *major histocompatibility complex* (MHC) class I, which are on the surface of all normal cells.[2]

On the other hand, the adaptive immune system generates a highly specific response, which depends on the exact pathogen that has invaded. It takes several days after the initial exposure to generate a notable response. Adaptive immunity exhibits memory and, on subsequent exposures to the same antigen, is able to generate a faster and stronger response.[2] The main cells of the adaptive immune response are B and T cells. Each B cell recognizes and binds to a specific antigen, causing the B cell to replicate and differentiate into plasma cells, which secrete antibodies specific for the antigen that then circulate in the blood and bind to the pathogen, leading to its elimination.

There are multiple types of T cells, including helper T cells, cytotoxic T cells, and regulatory T cells (Treg). In general, T cells require an interaction with other cells, called antigen-presenting cells (APCs), to be activated. When activated with antigen, an APC will bind to a T cell with a receptor (TCR) specific for that APC-antigen complex, providing the initial T cell stimulatory signal, or “signal one.” For T cells to be fully activated, a second costimulatory signal is required, which is also known as “signal two.” The best-characterized costimulatory interaction is between CD80 or CD86 on APC and CD28 on the surface of T cells. Once both signals occur simultaneously,