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Immunotherapy in breast cancer: An overview of modern checkpoint blockade strategies and vaccines

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ABSTRACT

Immune therapy has recently emerged as a standard-of-care strategy for the treatment of melanoma, lung cancer, bladder cancer, among other malignancies. However, the role of immune therapy in the treatment of breast cancer is still being determined. Two current strategies for harnessing the immune system to treat cancer include drugs that modulate key T cell inhibitory checkpoints and vaccines. Specifically, modern immune therapy strategies can facilitate T-cell mediated tumor regression by priming the immune system against specific tumor associated antigens, by modulating immunoregulatory signals, or both. In breast cancer, preliminary data from preclinical and early clinical studies are promising. In fact, clinical data with checkpoint blockade as monotherapy has been reported in multiple breast cancer subtypes to date, with durable responses observed in a significant proportion of women with chemotherapy resistant disease. However, because the number of genetic mutations and thus, the number of neoantigens available

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for immune response are modest in most breast cancers when compared with other cancers, most breast cancers may not be inherently sensitive to immune modulation and therefore may require strategies that enhance tumor associated antigen presentation if immune modulation strategies are to be effective. To that end, studies that combine checkpoint blockade with other strategies including established systemic therapies (including hormone therapy and chemotherapy), radiation therapy, and localized therapy including tumor freezing (cryoablation) are underway in breast cancer. Studies that combine checkpoint blockade with vaccines are also planned. Herein, we provide a brief summary of key components of the immune response against cancer, a rationale for the use of immune therapy in breast cancer, data from early clinical trials of checkpoint blockade and vaccine strategies in breast cancer, and future directions in the field.

Introduction

Immunotherapy, or the use of the body's immune system to fight cancer, is a rapidly evolving field. Cancer-specific immune responses are initiated when the immune system effectively recognizes abnormally expressed proteins from cancer cells, called tumor-associated antigens (TAAs). Immune responses are tightly regulated by a balance of stimulatory and inhibitory mechanisms. Modern immune therapy strategies in cancer aim to prime the immune system toward specific TAAs, to modulate immune-regulatory signals toward a favorable inflammatory state, or both. To achieve these aims, investigators are exploring several therapeutic strategies including immune checkpoint antibodies which block inhibitory signals to exploit existing immunity, antibodies to other immune targets, tumor vaccines which prime the immune system against TAAs, intratumoral oncolytic viruses, and chimeric antigen receptor CAR T cell therapies. To date, immune checkpoint blockade antibodies and vaccines have been most extensively studied in breast cancer. Emerging data suggest, however, that efficacy can be maximized by combining multiple immunotherapy strategies, for example, immune checkpoint blockade antibodies plus cancer vaccines. Herein, we describe the rationale for immune checkpoint antibodies and vaccines in the treatment of breast cancer, summarize the relevant literature, and highlight future approaches.

An overview of immunotherapy principles

T-lymphocyte activation

The adaptive immune response against cancer depends on antigen-specific T cell activation. In this process, T cells survey tissues for TAAs that are presented in peptide complexes bound to a cellular surface protein called major histocompatibility complex-1 (MHC-1). The T cell receptor (TCR) binds the antigen-MHC complex and, in turn, induces activation of T cell. Although MHC-1 molecules are present on many cell types, including normal and tumor cells, specialized cells called antigen presenting cells (APCs) have costimulatory molecules and are highly effective in presenting peptides and activating T cells. Classical examples of APCs include dendritic cells