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Review

Clinical deployment of antibodies for treatment of melanoma☆

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ABSTRACT

The concept of using immunotherapy to treat melanoma has existed for decades. The rationale comes from the knowledge that many patients with melanoma have endogenous immune responses against their tumor cells and clinically meaningful tumor regression can be achieved in a minority of patients using cytokines such as interleukin-2 and adoptive cellular therapy. In the last 5 years there has been a revolution in the clinical management of melanoma in large measure based on the development of antibodies that influence T cell regulatory pathways by overcoming checkpoint inhibition and providing co-stimulation, either of which results in significantly more effective immune-mediated tumor destruction. This review will describe the pre-clinical and clinical application of antagonistic antibodies targeting the T-cell checkpoints cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death 1 (PD-1), and agonistic antibodies targeting the costimulatory pathways OX40 and 4-1BB. Recent progress and opportunities for future investigation of combination antibody therapy will be described.

1. Introduction

The humoral immune system is capable of making antibodies diverse enough to recognize over 10 billion foreign antigens with targets as diverse as microbial pathogens and tumor cells. After binding to antigen, antibody effector function is mediated by the following: complement fixation, Fc receptor binding leading to degranulation of neutrophils, engagement of other immune cells with cytotoxic function, antibody-dependent cellular cytotoxicity (ADCC) or prevention of binding of the antigen to adhesion or signaling molecules. These events in turn can promote a variety of regulatory functions that modulate the immune response including immunoglobulin class switching, cytokine release, B-cell memory and feedback regulation that influences immune enhancement or suppression. The adaptability and diversity of this system is carefully regulated, and B cells that produce antibodies that bind to self-antigen are eliminated. Autoimmune disease with significant clinical consequences can occur in patients where there is failure to eliminate or regulate self-reactive B cells. One could conjecture that allo-antibodies with the ability to promote immunologic memory or cytotoxic function in the setting of chronic infection or malignancy by engaging stimulatory T-cell receptors or inhibiting T-cell check-point proteins might confer some evolutionary benefit, but no naturally occurring antibody has been described with these properties.

Therapeutic antibodies have been used in medical care and research for decades, but in the last 15 years they have become commonplace in oncologic management. The majority of these monoclonal antibodies are antagonistic, and were engineered to block a protein antigen of interest or to induce ADCC. The value of this approach has been translated numerous times in clinical medicine. Some examples from the last 15 years in medical oncology include rituximab (used in CD20+ B-cell malignancies) (Davis et al., 2000), trastuzumab (erb-b2-overexpressing breast cancer) (Slamon et al., 2001) and cetuximab (tumors that have mutated EGFR, such as colon cancer and head and neck cancer) (Baselga et al., 2005; Cunningham et al., 2004). The mechanism of tumor elimination with these therapeutic agents is complex and likely includes antibody-dependent cellular cytotoxicity (ADCC) as well as inhibition of growth pathways salient to tumor growth (Arnould et al., 2006; Ferris et al., 2010).

Another area of therapeutic investigation has been the use of antibodies as immunomodulators. Anti-CD3, an antibody that binds the CD3 component of the T-cell receptor (TCR), administered at high doses causes immunosuppression and can be used to treat allograft rejection in patients who have received solid organ or bone marrow transplants (Bluestone et al., 1993). Anti-CD3 at low doses has immune stimulating effects and can trigger T-cell activation through the zeta chain of the TCR (Urba et al., 1992). Although

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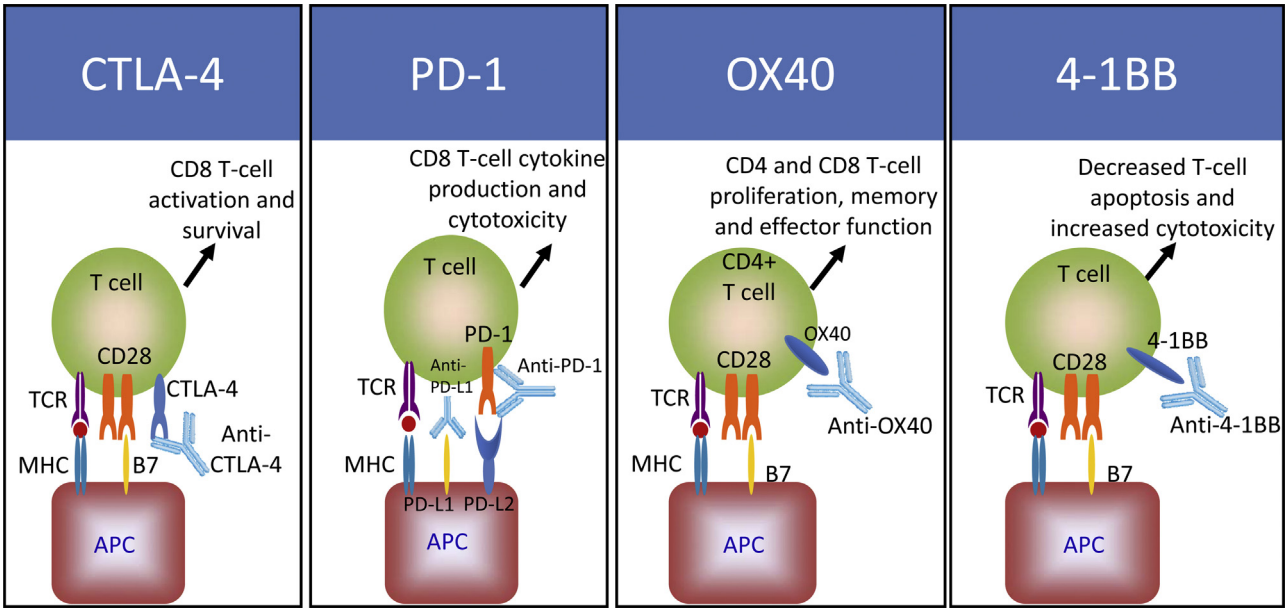

Fig. 1. Summary of major T-cell regulatory pathways and therapeutic targets. Antagonists of the T-cell checkpoints CTLA-4 and PD-1 or PD-L1 increase T cell activation and have antitumor activity in melanoma as well as other solid tumors. Agonists of the co-stimulatory OX40 and 4-1BB pathways also increase T-cell proliferation, effector function and memory.

anti-CD3 is not currently used as an anti-cancer agent, the observation that a T-cell-directed antibody could trigger T-cell cytotoxicity was an important conceptual insight that has lead to a proliferation of research on antibodies that influence the activation state and behavior of T cells resulting in enhanced anti-tumor immune responses. The CD3-zeta chain component has been used as a component of chimeric antigen receptors (CARs) to target tumor antigens with remarkable clinical activity in acute myelogenous leukemia and may have application in a wide variety of malignancies (Mardiros et al., 2013). Bispecific antibodies that link V_H and V_L for CD3 binding with the V_H and V_L that binds a tumor-associated antigen (e.g. CD19) have been used to redirect T cells to kill tumor cells. This approach has been studied in hematological malignancy and has recently garnered FDA approval, (Topp et al., 2014) but could also be applied to other solid tumors including melanoma.

A rapidly expanding knowledge of the receptors and pathways that regulate T cells, natural killer (NK) cells and antigen-presenting cells (APC) has identified the targets to which the current generation of melanoma therapeutic antibodies has been engineered. The T-cell pathways that have been most extensively studied to develop therapeutic antibodies in cancer are the T-cell checkpoints known as cytotoxic T lymphocyte antigen-4 (CTLA-4 designated CD152) and programmed death-1 (PD1 designated CD279). In addition, the study of the costimulatory pathways OX40 (CD134) and 4-1BB (CD137) may also yield therapeutic advances (Fig. 1). This review will describe the T-cell pathways and therapeutic antibodies that are transforming the care of patients with melanoma and other cancers, the rationale for combination antibody therapies currently undergoing clinical investigation and future questions that need to be answered to optimize antibody-based cancer therapy. Although the pathways will be presented individually, it is important to recognize that they function concurrently and that the final effect on T-cell activation is the result of the integration of the multiple coinhibitory and costimulatory signals.

2. CTLA-4: Pre-clinical observations

The steps that lead to T-cell activation include peptide antigen presentation by an antigen presenting cell (APC) to the TCR in the context of the appropriate major histocompatibility complex (MHC) class molecule (signal 1) and engagement of a co-stimulatory receptor (signal 2), the most important of which is mediated through the interaction of CD28 on T cells and CD80/CD86 on APC. Other cytokine signals from APC or regulatory T cells can amplify or diminish immune responses (signal 3). T-cell activation also triggers pathways that eventually dampen the immune response. The chief regulatory pathway that shuts down a T-cell response after activation is CTLA-4, which is normally stored in vesicles in the cytosol of T cells and is released to the surface after antigen presentation (Alegre et al., 1996), where it out-competes CD28 for the binding of CD80/CD86. The net effect is to diminish signaling from the T-cell receptor to the nucleus.

The observation that CTLA-4 mediates suppression of T cells led to the hypothesis that blocking its interaction with CD80 would increase T-cell activation and enhance anti-tumor immune responses, a hypothesis that was first investigated in the laboratory of Dr. James Allison (Leach et al., 1996). His group tested antagonistic antibodies to CTLA-4 in a variety of murine tumor models and demonstrated tumor regression and cures in some mice after anti-CTLA-4 administration. It is interesting to note that prolonged stability of some murine tumors and measurable but slow growth of others were described in this manuscript, an observation that is relevant given the clinical results that will be detailed below. These pre-clinical results illustrated a novel approach to cancer immunotherapy, which was robust and appeared simpler to administer in comparison with other immunotherapies under development at that time including adoptive cellular immunotherapy, vaccines and cytokines to promote an immune response.

3. Anti-CTLA4 clinical results

Two anti-CTLA-4 antibodies, ipilimumab and tremelimumab, have undergone extensive clinical evaluation. Ipilimumab is a fully human IgG1 monoclonal antibody that binds to the CTLA-4 receptor expressed on activated T cells. Phase I and II studies of ipilimumab established a biologically active and tolerable dose; although a new class of immune-related toxicities were observed (see below). These early studies also established that patients with advanced melanoma had more objective tumor regressions, although tumor