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Novel immune check point inhibiting antibodies in cancer therapy—Opportunities and challenges

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ABSTRACT

Drug resistance of tumor cells to chemotherapy is limiting the therapeutic efficacy of most anticancer drugs and represents a major obstacle in medical oncology. However, treatment of various human malignancies with biologics, mostly monoclonal antibodies (mAbs), is not limited by such chemoresistance mechanisms. However, other resistance or evasion mechanisms limit the efficacy to anticancer therapeutic mAbs that engage tumor-associated antigens on the surface of the malignant cells. Immune checkpoint blocking monoclonal antibodies are heralded as a promising therapeutic approach in clinical oncology. These mAbs do not directly attack the malignant cells as most anticancer mAbs; rather, they enhance the anti-tumor response of the immune system by targeting immune regulatory pathways. Three mAbs targeting immune checkpoint molecules are currently used in the clinic and new mAbs that target other potential inhibitory targets are being actively investigated. This therapeutic approach, while proving as highly beneficial for many patients, is prone to toxicities and side effects of an autoimmune nature. Defining suitable management algorithms and biomarkers that predict therapeutic effects and adverse toxicity are required to provide survival benefit for larger numbers of cancer patients. Overcoming these challenges, along with opportunities for new agents and combinatorial strategies are the main focus of immune checkpoint blockade research today.

1. Background

One of the main obstacles towards curative cancer therapy is the emergence of multidrug resistance (MDR), where cancer cells evade the cytotoxic effects of conventional chemotherapy drugs which are structurally and functionally unrelated (Wijdeven et al., 2016; Zhitomirsky and Assaraf, 2016). This anticancer drug resistance, which can be innate or acquired as a response to treatment, is a leading cause in of chemotherapeutic treatment failure in both solid tumors as well as hematological malignancies (Kunjachan et al., 2013; Livney and Assaraf, 2013). MDR mechanisms are associated with drug transport alterations (drug uptake or efflux from the cell), qualitative and quantitative alterations in target proteins, drug compartmentalization, and inhibition of apoptosis (Assaraf, 2007, 2006; Gottesman, 2002; Gottesman et al., 2002). The extensive research of MDR mechanisms enabled the development of new approaches to address this problem, for example silencing MDR-related mRNA, targeting MDR efflux pumps, or developing new chemotherapeutic agents able to evade said pumps (Gao et al., 2012; Shapira et al., 2011).

Treatment of cancer with biopharmaceuticals (biologics) is a therapeutic approach not subject to the resistance mechanisms described above. Most anticancer biologics are monoclonal antibodies (mAbs) that target a cell-surface protein on the malignant cell with an aim to inhibit cell growth and cause cell death. To that end, mAbs are applied as “naked” or “unarmed” molecules where their mechanism of action involves, in most cases, recruitment of immune effector mechanisms or effecting cell physiology or metabolism, or mAbs are “armed” and used to deliver lethal cargos to the cancer cells (Shefet-Carasso and Benhar, 2015). Unfortunately, most anticancer mAbs have limited efficacy, and are considered “life-extending” rather than “life-saving” treatments (Scott et al., 2012). A paradigm shift in immune-oncology during the past few years is the introduction of therapeutic mAbs that do not directly attack the malignant cells, but, rather, affect immune regulatory mechanisms that were hijacked by the malignant cells to evade the onslaught of the immune system. Such antibodies are collectively referred to as “immune checkpoint inhibitors” in cancer therapy and can be regarded as a new strategy to overcome the problem of drug resistance.

Following the understanding of the interactions between cancer and the immune system gained in the last three decades of basic and pre-clinical research, the notion that immune checkpoints, regulators designated to maintain self-tolerance, can be blocked and thus

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unleash the immune system to eradicate tumors, has been studied intensively in the last decade. Since the anti-CTLA-4 monoclonal antibody ipilimumab (YERVOY®) was approved by the FDA in 2011 for the treatment of metastatic melanoma and NSCLC, immune checkpoint inhibitors have become the standard of care in cancer therapy, and are now being evaluated for their efficacy in additional malignancies. In 2014, the revenues from cancer immunotherapy drugs reached $41 billion and accounted for ~50% of all oncology drug sales. Remarkably, in 2016, there are over 1000 clinical trials being conducted to test new cancer immunotherapies and combinations. Expert analysts project that the immunotherapy market will attain $35 billion in value by 2023, based on the currently visible drug pipeline (Piros et al., 2016).

At first, immunotherapy agents were evaluated under the established chemotherapy drug-development paradigm. As pre-clinical research progressed, the understanding that immunotherapy entails distinct patterns of response came, rendering the need to re-define clinical efficacy criteria for these novel antitumor biologicals (Hoos 2016). The new criteria are termed immune-related response criteria (irRC), immune-related overall response rate (irORR) immune-related disease control rate (irDCR) and immune-related progression-free survival (irPFS) (Hoos et al., 2010). In addition, immune-related adverse events (irAEs) were defined as side effects and toxicities as a result of immune checkpoint blockade treatment, and their clinical management was defined in treatment algorithms (Topalian et al., 2015).

This review focuses on immune checkpoint inhibitor antibodies – their principle mechanism of actions, pathways targeted successfully and potential opportunities, as well as clinical challenges stemming from their administration.

2. The biology behind blocking immune checkpoints

Knowledge gained in the past three decades regarding the basic principles governing the interactions between cancer and the immune system, provided the rational for the development of agents that activate the immune system for cancer therapy. Tumor cells evade recognition by the immune system via various mechanisms including regulatory immune cells, immunosuppressive cytokines and chemokines, and 'immune checkpoint' pathways that down-modulate immune functions. The notion of using T cells against tumors as a therapeutic approach has several advantages: their capacity for selective recognition of antigens from all cellular compartments, not just proteins and peptides present on the cell surface; their ability to generate a diverse immune response, either by directly eliminating antigen-expressing cells (through CD8+ T cells) or by releasing cytokines which integrate adaptive and innate effector mechanisms (CD4+ helper T cells); the formation of memory T cells for a fast secondary response should an antigen re-occur; and the adaptive nature of the immune response that can accommodate tumor heterogeneity.

The first step of T cell activation is initiated through recognition of an antigen presented by major histocompatibility complex (MHC) molecules by the T cell receptor (TCR). For complete activation, a second signal is required by the binding of CD28 on the T cell surface to B7 costimulatory molecules (such as CD80 or CD86) on the antigen presenting cell (APC) (see Fig. 1) (Greenwald et al., 2005). These two signals allow full T cell response – the cells begin to proliferate, to acquire effector functions and migrate.

The development of checkpoint inhibitory agents is based on this 'two signal model' of T cell activation. These immune checkpoints are negative regulators of the T cell response, aimed to prevent autoimmunity and protect healthy tissue from damage. The expression of immune checkpoint proteins can be disrupted by tumor cells as a resistance mechanism. By the blockade of these negative regulators, T cells can be unleashed to engage in anti-tumor immune response thus being an effective treatment for various types of cancers.

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is one of the most actively studied checkpoint receptors in the context of cancer therapy, together with PD-1 (programed cell death protein 1). CTLA-4 is the 'master regulator' of TCR signaling; it is a homologue of CD28 with a higher binding affinity to B7 proteins, thus competing with CD28 and inhibiting T cell activity (Lenschow

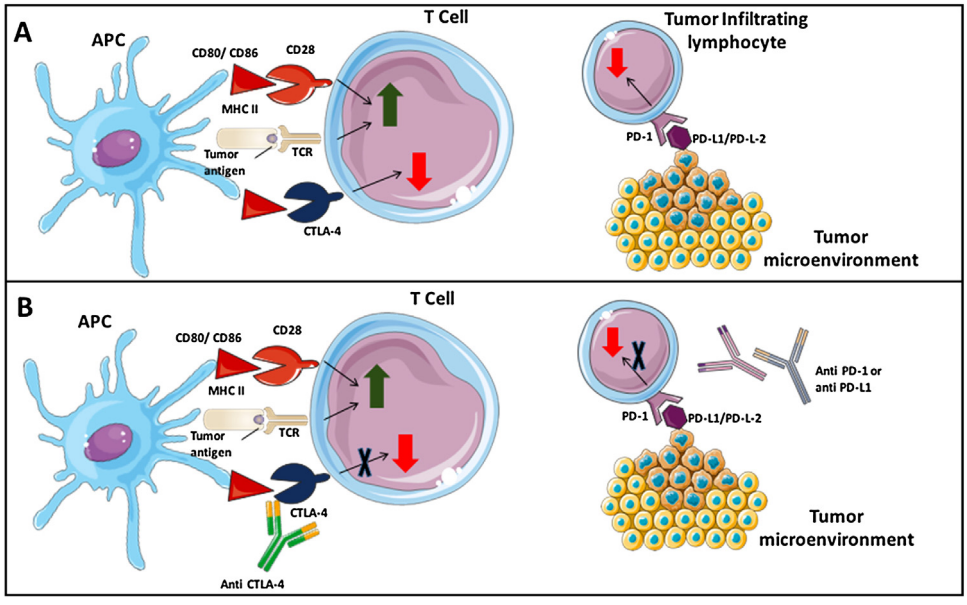

Fig. 1. Schematic representation of immune checkpoint blockade by targeted mAbs.
A 'Two signal mode' of T cell activation. Antigen-presenting cells (APC) display tumor specific antigens on their surface by MHC-II molecules, recognized by T cell receptor (TCR). A second signal, mediated by CD28 binding to B7 costimulatory molecules (such as CD80 or CD86) is required for full activation. CTLA-4 is up-regulated shortly after T-cell activation, down-regulating the immune response to maintain tolerance. PD-1 is expressed by tumor infiltrating lymphocytes (TILs) after antigen exposure, and its interaction with its ligands results in T cells inhibition in the tumor microenvironment. **B.** Antibodies targeting these immune checkpoints, such as ipilimumab (anti CTLA-4) or nivolumab (anti PD-1) block the inhibitory signal, thus markedly enhancing the immune response to the tumor.