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Immune checkpoint modulation: Rational design of combination strategies

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ABSTRACT

Immune recognition and elimination of malignant cells require a series of steps orchestrated by the innate and the adaptive arms of the immune system. The majority of tumors have evolved mechanisms that allow for successful evasion of these immune responses. Recognition of these evasive processes led to the development of immunotherapeutic antibodies targeting the co-stimulatory and co-inhibitory receptors on T cells, with the goal of enhancement of T cell activation or reversal of tumor-induced T cell inhibition. Several of these agents, such as antibodies targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death receptor 1 (PD-1) have already demonstrated significant promise in clinical trials. Clinical benefit of these antibodies as single agents, however, has been limited to a subset of patients and has not been observed in all tumor types. These limitations call for the development of rational combination strategies aiming to extend therapeutic benefit to a broader range of patients. These include: 1) modalities that enhance antigen presentation, such as radiation, cryotherapy, chemotherapy, targeted agents, vaccines, toll-like receptor (TLR) agonists, type I interferon, and oncolytic viruses; 2) additional agents aiming to reverse T cell dysfunction, such as other immune checkpoint inhibitors; and 3) agents targeting other immune inhibitory mechanisms, such as inhibitors of indoleamine dioxygenase (IDO), regulatory T cells, and myeloid-derived suppressor cells (MDSCs). It is becoming increasingly evident that the efficacy of specific combinations will likely not be universal and that the choice of a treatment modality may need to be tailored to fit the needs of each individual patient.

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Abbreviations: CTLA-4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed death receptor 1; PD-L1, programmed death receptor ligand 1; TLR, toll-like receptor; IDO, indoleamine 2,3-dioxygenase; MDSC, myeloid-derived suppressor cell; IFN, interferon; DAMP, damage-associated molecular pattern; PAMP, pathogen-associated molecular pattern; APC, antigen-presenting cell; DC, dendritic cell; TAA, tumor-associated antigen; TCR, T cell receptor; MHC, major histocompatibility complex; RCC, renal cell carcinoma; NSCLC, non-small cell lung cancer; TIL, tumor-infiltrating lymphocyte; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; STING, stimulator of interferon genes; OV, oncolytic virus; ICOS, inducible costimulator.

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1. Introduction

Malignant transformation of cells triggers activation of innate and adaptive immune responses, which play a critical role in eliminating and controlling early cancer growth. The recognition of these processes led to the development of different immunotherapeutic strategies, many of which have shown significant promise in clinical trials in recent years. Unfortunately therapeutic benefit has not been seen in all cancer types as of yet. Our evolving understanding of the mechanisms of anti-tumor immune response as well as compensatory resistance mechanisms provides the opportunity for the development of rational combination strategies. These combination approaches have the potential to extend therapeutic benefit to a broader population of patients with a variety of tumors. (See Fig. 1.)

The immune recognition of cancer cells typically begins at the cancer site, where fragments of dying cancer cells are taken up and processed by professional antigen presenting cells (APCs) such as dendritic cells (DCs). This process requires specific APC maturation signals (Cavassani et al., 2008), without which APCs can induce immune tolerance rather than activation (Steinman et al., 2000; Lutz & Schuler, 2002; Mahnke et al., 2002). These signals can be provided by certain "danger" molecules released from the dying tumor cells, known as damage-associated molecular patterns (DAMPs) (Kono & Rock, 2008). Some of the characterized DAMPs include intracellular proteins such as high-mobility group box 1 (HMGB1) and heat-shock proteins (HSPs), DNA, ATP, uric acid, heparin sulfate, and mitochondrial components (Krysko et al., 2011). DAMPs are recognized by several classes of pattern-recognition receptors (PRRs), which include the toll-like receptors (TLRs), retinoic acid-inducible gene-1 (RIG-I)-like receptors (RLRs), nucleotide oligodimerization domain (NOD)-like receptors (NLRs), AIM2, and the receptor for advanced glycation end products (RAGE) (Takeuchi & Akira, 2010), which in turn activate signaling cascades required for DC maturation.

Following APC activation and migration to lymph nodes or tertiary lymphoid structures, the peptides from the proteins, some of which may be tumor-associated antigens (TAAs), are then displayed on the surface of APCs in the context of major histocompatibility complex (MHC) classes I and II molecules. This enables antigen recognition by antigen-specific CD4 and CD8 T cells. In addition to the recognition of cognate MHC–peptide complex, the activation of T cells requires

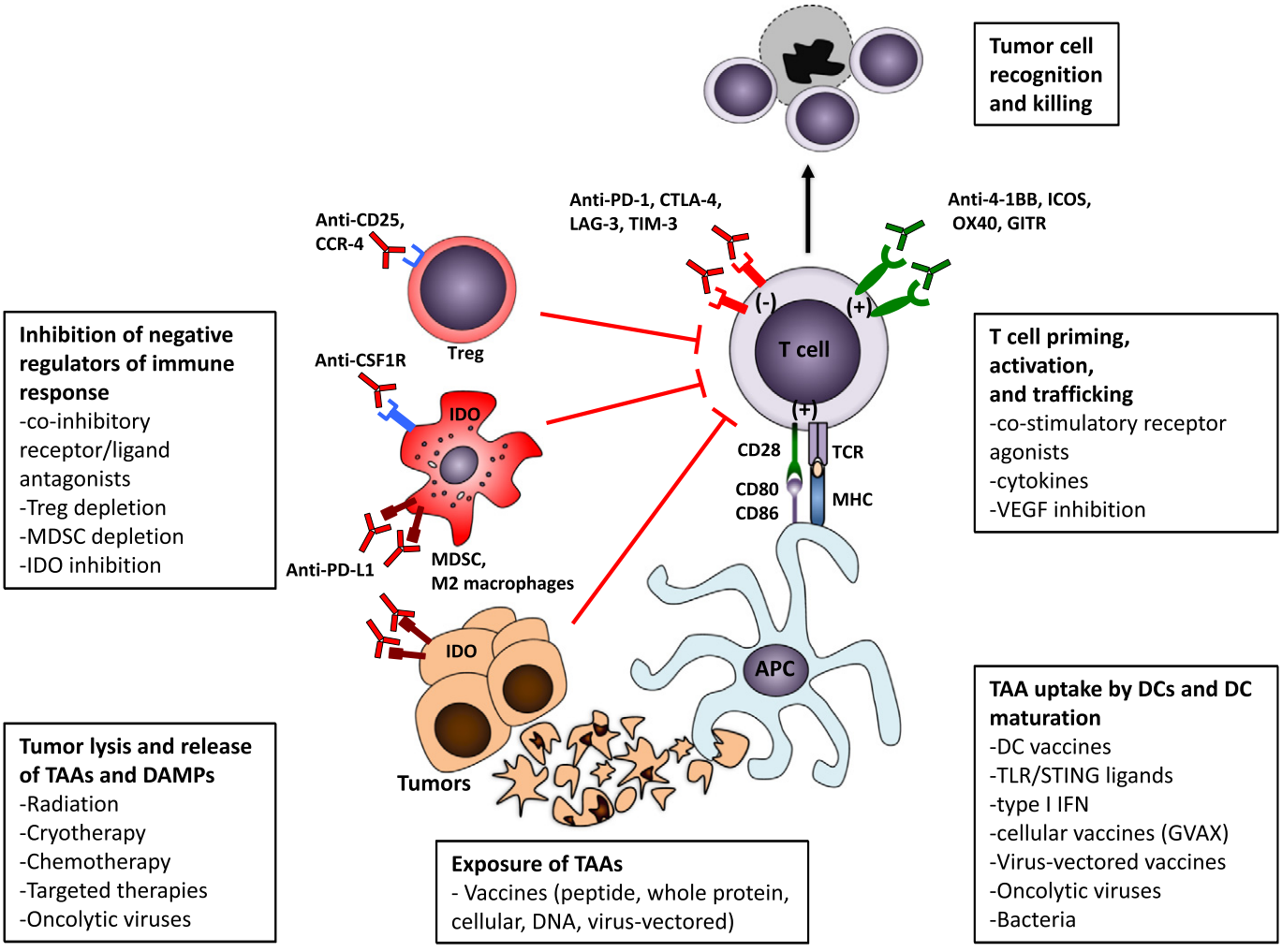

Fig. 1. Mechanism of tumor recognition by the immune system and therapeutic strategies to promote anti-tumor immunity. Activation of anti-tumor immune response is a multi-step process orchestrated by both the innate and the adaptive arms of the immune system. Immunomodulatory antibodies function at the level of T cells, either by enhancing T cell activation or by inhibiting the negative regulators of the immune response. Each of the steps involved in tumor immune recognition can be targeted with various therapeutic approaches, which could be used in combination with immunomodulatory antibody therapy. TAA: tumor associated antigen; DAMP: damage-associated molecular pattern; DC: dendritic cell; APC: antigen-presenting cell; TLR: toll-like receptor; STING: stimulator of interferon genes; IDO: indoleamine dioxygenase; MHC: major histocompatibility complex; TCR: T cell receptor; VEGF: vascular endothelial growth factor; Treg: regulatory T cell; MDSC: myeloid-derived suppressor cell.