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Delivering safer immunotherapies for cancer☆

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ABSTRACT

Cancer immunotherapy is now a powerful clinical reality, with a steady progression of new drug approvals and a massive pipeline of additional treatments in clinical and preclinical development. However, modulation of the immune system can be a double-edged sword: Drugs that activate immune effectors are prone to serious non-specific systemic inflammation and autoimmune side effects. Drug delivery technologies have an important role to play in harnessing the power of immune therapeutics while avoiding on-target/off-tumor toxicities. Here we review mechanisms of toxicity for clinically-relevant immunotherapeutics, and discuss approaches based in drug delivery technology to enhance the safety and potency of these treatments. These include strategies to merge drug delivery with adoptive cellular therapies, targeting immunotherapies to tumors or select immune cells, and localizing therapeutics intratumorally. Rational design employing lessons learned from the drug delivery and nanomedicine fields has the potential to facilitate immunotherapy reaching its full potential.

Contents

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1. Introduction

Immunotherapies, treatments that modulate the immune system, have long been proposed as a potentially powerful approach to "functional" or actual cures of disease, based on the natural function of the immune system in protecting the host and its cardinal features of potency, specificity, and memory [1]. Motivated by these features, immunotherapies are now in preclinical and clinical development for treatment of diverse infectious diseases, autoimmunity, allergies, transplant rejection, graft vs. host disease, and cancer. Among these therapeutic areas, cancer immunotherapy in particular has experienced dramatic recent progress in the clinic [2,3]. For many years, cancer immunotherapies were plagued by high toxicity, low to negligible efficacy, or both. However, steady advances in fundamental cancer immunology and translational immunotherapy have now led to two classes of treatment with significant impact in advanced cancer patients – adoptive cell therapy (ACT), based on the injection of autologous tumor-directed T cells [4,5]; and checkpoint blockade, treatment with antibodies that block the inhibitory receptors cytotoxic T lymphocyte antigen-4 (CTLA-4) or programmed death-1 (PD-1, or its counter-receptors PD-L1/PD-L2) [6,7]. ACT therapy in patients with advanced metastatic melanoma and several hematologic cancers has shown a high proportion of complete responses (complete elimination of detectable tumor burden), some of which are durable responses lasting many years [8]. Treatment with ipilimumab, a fully human anti-CTLA-4 antibody, has led to complete responses in approximately 20% of advanced melanoma patients, with durations lasting >10 years [9]. Treatment with PD-1 blocking antibodies has elicited objective responses in a variety of solid tumors including melanoma, lung cancer, prostate cancer, breast cancer, ovarian cancer, head and neck cancer, and a subset of colorectal cancers [6]. Reflecting their complementary modes of action, combination therapy with anti-CTLA-4 and anti-PD1 has led to even greater response rates in melanoma patients, where a significant fraction of patients exhibit complete tumor regressions in a space of ~10 weeks [10,11].

These findings have energized the field and motivated a massive effort to further explore combination immunotherapies that optimally arm the immune system against metastatic disease, but the power of the immune system creates the potential for not only a dramatic attack on tumors but also a significant danger to healthy tissues. For example, monotherapy with anti-CTLA-4, which both blocks a negative regulatory signal during T cell activation and inhibits the function of regulatory T cells, leads to a series of autoimmune side effects, including gastrointestinal toxicity, pruritis, and fatigue, side effects which become grade 3 or 4 serious adverse events in ~23% of patients [12]. When anti-CTLA-4 is combined with anti-PD-1, enhanced anti-tumor activity comes at the cost of synergistically exacerbated toxicity; ~55% of previously untreated melanoma patients given the combination experienced grade 3 or 4 adverse events [11,12]. As discussed in detail in this review, serious toxicities are characteristic of a broad range of immunomodulatory drugs. Thus, a looming challenge in the field is the development of effective strategies to harness the potential of combination treatments while avoiding debilitating toxicities that prevent immunotherapies from reaching their full curative potential. Clinical studies are already underway seeking to optimize timing and dosing to limit the toxicity of these promising immunotherapy drugs, but in the setting of intravenous administration – believed to be key for systemically modulating the immune response against disseminated tumors – dosing schedules with high safety and high efficacy are often diametrically opposed.

In this review, we discuss the potential for drug delivery technologies spanning a range of approaches to enhance immunotherapies, with a particular emphasis on the potential for enhancing the safety of immunomodulatory drugs. We first review representative mechanisms of immune toxicity from immunotherapy agents of both clinical and preclinical interest, separating systemic and local (i.e. intratumoral) drug administration issues. We then discuss approaches to ameliorate these toxicities based in concepts from the field of drug delivery, employing technologies ranging from nanoparticles to synthetic biology. The immune system as a target for therapy presents several challenges and opportunities relative to somatic tissues: Immune cells circulate through the blood, creating the potential for efficient direct targeting of therapeutics to these cells (relative to, for example, targeting drugs to tumor cells); and immune cells proliferate, providing a source for self-amplification of small doses of appropriately-targeted drugs. However, there is a need to direct immunomodulatory drugs to tumor-specific cells rather than stimulating the entire leukocyte compartment non-specifically, and these cells may be preferentially enriched at tumor sites and tumor-draining lymph nodes. There are thus both challenges and opportunities for the field of drug delivery to impact cancer immunotherapy.

2. Mechanisms of toxicity elicited by immunotherapy drugs

To rationally approach strategies for increasing the safety of systemic immunotherapies, an understanding of mechanisms underlying the toxicity of systemically-administered immunoregulatory drugs is needed. In this section, we review the mechanisms of toxicity underlying several important classes of immunotherapy agents: interleukin-2, representative of several important γ-chain cytokines that promote lymphocyte proliferation and effector function; agonistic antibodies against the costimulatory receptors CD137 (also known as 41BB) and CD28, representative of agonistic antibodies against lymphocyte costimulatory molecules; and the checkpoint blockade agents anti-CTLA-4 and anti-PD-1. A discussion of all immunoregulatory agents in preclinical and clinical testing for cancer immunotherapy is beyond the scope of any single review, but these example biologics represent 3 important distinct mechanisms of immunomodulation relevant to much of the ongoing clinical development of immunotherapy.

2.1. Interleukin-2 as a paradigm for approved but toxic immunotherapy

Systemic high-dose interleukin-2 (IL-2) was one of the first immunotherapy agents to be licensed for cancer therapy, approved by the FDA for metastatic melanoma and renal cell carcinoma (RCC) treatment in 1992. IL-2 was first isolated as a factor promoting the growth of activated T cells, but also stimulates natural killer (NK) cells, both of which motivated its use as a cancer therapeutic. However, it is now also conversely known to also promote activation-induced cell death of stimulated T cells and maintains the survival and function of regulatory T-cells, which restrain the effector arms of the immune system to maintain tolerance and protect healthy tissues from autoimmune attack [13]. Interleukin-2 biology is further complicated by the nature of its tripartite receptor, which is comprised of the IL-2R α chain (CD25), β chain (CD122), and common γ chain (CD132) [13]. Differential expression of the three components of the IL-2R leads to different signaling and functional outcomes on different cell types at different stages of activation.

Based on dosing schedules established clinically in the 1980s, IL-2 is approved as a "high dose" (HD) IL-2 therapy for melanoma and RCC administered intravenously every 8 h for up to 14 total doses [14]. Although much is made in the current renaissance of cancer immunotherapy around the "tail of the curve" effect, where a small proportion of patients treated with checkpoint blockade become long-term survivors [9], such durable increases in survival were already seen in the early 1990s in patients treated with IL-2, where ~12% of patients treated with HDIL-2 at the National Cancer Institute had survival of at least 10 years [14]. Although HDIL-2 elicits objective responses in ~16% of patients, it is also extremely toxic. The very short half-life of IL-2 (~12 min [15]) leads to a requirement for high doses to be administered in order for functional levels to be maintained for a sufficient timespan. High level dosing in turn leads to dose-related toxicities including vascular leak syndrome (VLS) and cytokine release syndrome, a massive systemic cytokine release and inflammatory reaction caused by IL-2 immune stimulation [16]; lethal adverse events were found in 2% of patients [14]. These issues