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Combinatorial drug delivery approaches for immunomodulation☆

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ABSTRACT

Immunotherapy has been widely explored for applications to both augment and suppress intrinsic host immunity. Clinical achievements have seen a number of immunotherapeutic drugs displace established strategies like chemotherapy in treating immune-associated diseases. However, single drug approaches modulating an individual arm of the immune system are often incompletely effective. Imperfect mechanistic understanding and heterogeneity within disease pathology have seen monotherapies inadequately equipped to mediate complete disease remission. Recent success in applications of combinatorial immunotherapy has suggested that targeting multiple biological pathways simultaneously may be critical in treating complex immune pathologies. Drug delivery approaches through engineered biomaterials offer the potential to augment desired immune responses while mitigating toxic side-effects by localizing immunotherapy. This review discusses recent advances in immunotherapy and highlights newly explored combinatorial drug delivery approaches. Furthermore, prospective future directions for immunomodulatory drug delivery to exploit are provided.

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1. Introduction

The complexity of the immune system affords ample opportunities for pathologies to develop, both from aberrant immune activation and misguided immunosuppression. Recent advances delineating immunobiological mechanisms in infectious disease, cancer, and autoimmunity have helped inform novel therapeutic approaches. Immunotherapy, an increasingly popular methodology, attempts to modulate specific arms of the immune system by interfacing with host biology to augment or suppress natural immune responses. Since Edward Jenner first developed a vaccine for smallpox in the late 18th century, immunotherapy has played a prominent role in improving human health

Abbreviations: CAR, chimeric antigen receptor; *Treg*, regulatory T cell; *PD-1*, programmed death-1; *CTLA-4*, cytotoxic T-lymphocyte-associated protein 4; *PD-L1*, programmed death ligand 1; *APC*, antigen-presenting cell; *DC*, dendritic cell; *TLR*, toll-like receptor; *OVA*, ovalbumin; *PLGA*, poly(lactide-*co*-glycolide); MPLA, monophosphoryl lipid A; poly(I:C), poly(inosinic:cytidylic acid); SB, SB505124; *NK*, natural killer; siRNA, small interfering RNA; GM-CSF, granulocyte-macrophage colony-stimulating factor.

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and quality of life. Similarly, allergy immunotherapy has been used clinically for more than a century, yielding positive outcomes for patients with asthma, dietary, and seasonal allergies [1]. Today, immunotherapies are supplanting several well-established clinical treatment paradigms. For example, cancer immunotherapy has emerged in recent decades as an attractive alternative to chemotherapy, as administration of broadly cytotoxic drugs has dangerous and potentially fatal side effects. By contrast, controlled modulation of innate and adaptive immunity can generate robust anti-tumor responses while minimizing systemic toxicity. Recently, a number of innovative immunotherapeutic strategies have garnered attention. Enthusiasm for immunotherapies such as Sipuleucel-T dendritic cell therapy, chimeric antigen receptor (CAR) T cells, and monoclonal antibodies is buoyed by success in clinical trials. Sipuleucel-T immunotherapy, wherein isolated autologous dendritic cells are exogenously activated, loaded with tumor-specific antigen and are re-administered, was the first FDA-approved therapeutic vaccine for cancer of any kind and showed improved survival in men with metastatic prostate cancer [2]. Similarly, adoptive transfer of $CD19^+$ B cell targeting CAR T cells demonstrated sustained remission of acute lymphoblastic leukemia in children and adults [3]. Overall, immune modulating interventions to harness specific features of the immune system are becoming widespread and multipurpose.

The abundance of immunotherapy strategies being explored is in large part due to the expanding number of therapeutic tools. The increased mechanistic understanding and availability of immunomodulatory drugs including recombinant cytokines (e.g., IL-2, TGF-β, IFNγ), small molecule adjuvants (e.g., CpG, MPLA, Pam3CSK4), and monoclonal antibodies (e.g., anti-PD1, anti-CTLA-4, anti-IL-10) have facilitated development of immunotherapy approaches. In cancer immunotherapy alone, there are over 50 immunotherapy agents currently being used in the clinic or in clinical trials [4]. The targets of these single drug approaches are wide ranging, but similar in that they engage an isolated immune pathway. In one clinical trial, for example, immunotherapy with low-dose administration of IL-2 resulted in a dose-dependent increase of $FoxP3^+$ regulatory T cells (Tregs) in patients with type 1 diabetes, a cellular phenotype critically lacking in many autoimmune conditions [5]. On the other hand, recent work using monoclonal antibodies for checkpoint blockade therapy has potentially revolutionized cancer immunotherapy. Nivolumab, a monoclonal antibody that prevents T cell inhibition by impeding programmed death-1 (PD-1) signaling, dramatically increased survival in metastatic melanoma patients, outperforming a standard first-line chemotherapy regimen [6]. In other clinical trials, monoclonal antibody therapy with ipilimumab, a monoclonal antibody that inhibits cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), improved survival in patients with metastatic melanoma by over 10 months and ~20% exhibited long term survival after five years [7,8]. While clinical achievements from single drug immunotherapies cannot be understated, such approaches are limited by a number of factors. In particular, incomplete understanding of disease pathology and associated immune pathways hinders identification and application of relevant monotherapies. Additionally, heterogeneity within disease pathogenesis and among patient populations can limit the efficacy of drugs that engage individual pathways.

Combinatorial strategies to modulate multiple immune axes in coordination are seen as an attractive strategy to overcome these barriers, the growth of which is well documented [4,9–11]. Combinatorial immunotherapy success is represented by recent clinical trials involving simultaneous administration of nivolumab and ipilimumab [12,13]. This groundbreaking work demonstrated the importance of engaging multiple immune pathways, as metastatic melanoma patients with programmed death ligand 1 (PD-L1) negative tumors displayed significantly reduced survival when administered either agent alone. Conversely, when PD-1 and CTLA-4 monoclonal antibodies were delivered in combination, PD-L1-negative tumor patients had improved survival by over 5 months. While the clinical success of combinatorial immunomodulation has fueled a dramatic increase in such approaches, concerns about toxicity

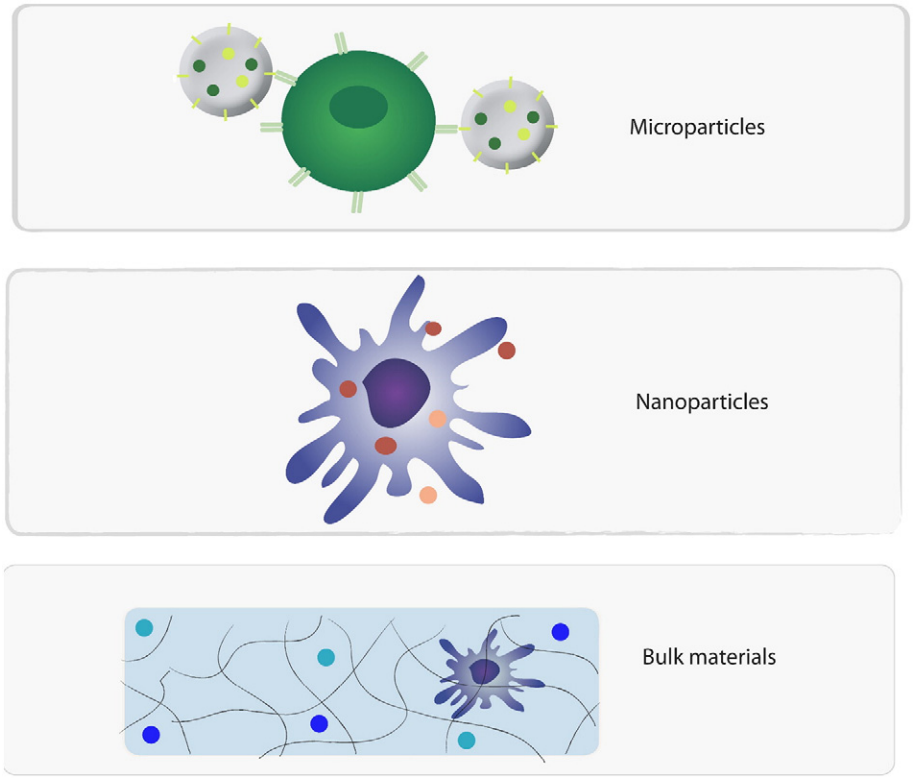

Fig. 1. Various biomaterial platforms have been developed for combinatorial drug delivery to modulate immunity. A few of the most frequently applied systems are depicted here. (Top) Micro- and nanoparticle vehicles have been designed for specific targeting/retention to modulate subpopulations of immune cells (e.g., T cells, DCs). (Bottom) Alternatively, bulk materials have been explored to actively recruit immune populations *in vivo*.