



Applications of Nanoparticles in Cancer Immunotherapy: Possibilities and Challenges

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The last decade has witnessed a major change in the paradigm of cancer treatment from a focus on cytotoxic chemotherapies towards strategies to utilize the immune system to generate anti-tumor immunity. A significant surge happened with the recent approval of several immunomodulating agents by the United States Food and Drug Association (US-FDA) for applications in humans [1]. Immunomodulating therapies rely on the fact that among the several functional capabilities attained by cancer cells over time, immune evasion is indeed a rate-limiting step and a core hallmark [2]. Immune surveillance can identify transformed cells and eliminate them from the body, and hence remodeling immune response using exogenously administered agents in the form of vaccines, adoptive immune cell therapies, monoclonal antibodies, interleukins, etc. can pose a significant threat to cancer [3].

Cancer immunotherapy started with 'Coley's toxins' when Dr. William B. Coley, a physician from New York found that spontaneous tumor regression happened among some sarcoma patients treated with heat-inactivated bacterial preparations which were named 'Coley's toxins'. At that time, this study was controversial due to the lack of substantial scientific evidence, difficulties in reproducing similar therapeutic effects, and the fear of infections from bacterial preparations. This happened in 1891, and now in 2024, more than 3000 studies have been registered on Clinicaltrials.gov on either single-agent immunotherapeutics or its combination with conventional cancer therapy regimens. However, harnessing the power of the immune system can come with its disadvantages due to inappropriate dosing and lack of specificity.

Currently, only a subset of patients benefit from immunotherapy, and there is no 'one-size fits all' strategy since different tumor types have varied responses to different immunotherapeutic agents. Some tumors are unresponsive (cold tumors) indicating the presence of an inherent resistance mechanism. Thus, it is dif-

ficult to predict the treatment response and efficacy. Moreover, the way a patient's immune system responds to immunotherapeutics in the long run is a very complex question. Immune-related adverse events (irAEs) such as dermatologic, neurological, gastrointestinal, cardiovascular, pulmonary, and endocrine toxicities have been reported in those who are subjected to ICIs and CAR-T cells. Most importantly, other underlying medical conditions such as autoimmune disorders, chronic infections, etc. can aggravate the severity of symptoms [4]. Most of these limitations are due to the off-target effects, the inability to tune the immune response in a personalized manner, and the failure to hit the desired target by crossing cellular barriers.

It is well-established that nanoparticles, due to their unique tunable architecture and functionalities can overcome some of the core challenges faced by current immunotherapeutics. Lipid nanoparticles (LNPs) have proven their ability to deliver mRNA vaccines in humans during the COVID-19 pandemic. Other nano-delivery agents such as protein nanoparticles, polymeric nanoparticles, dendrimers, liposomes, metal-organic frameworks, etc. are also being investigated for immunotherapy applications. Some of the challenges currently encountered by cancer immunotherapeutics such as off-target biodistribution, undesired subcellular localization, poor transport across cellular barriers, uptake and elimination by phagocytic cells, poor drug loading capacity, undesirable immune activation, and inflammation, etc. can be overcome to a significant extent by rationally designed nanocarriers [5]. The limited understanding of the strong interplay between tumor cells and other components of the tumor immune microenvironment is another reason for the failure to establish sustained disease control. Studies so far show that tumors establish immunosuppressive microenvironments to benefit their invasiveness. Hence, substantial remodeling of the tumor and its microenvironment along with improved surveillance by the systemic immune system is necessary

for long-term disease-free survival [6]. Externally controlled systems such as in the case of ultrasound-mediated microbubbles and nanobubbles and other stimuli-responsive nanocarriers are being investigated for tuning the immune response and remodeling the tumor microenvironment [7,8].

At present, much of the research on applications of nanoparticles in immuno-oncology focuses on the precise delivery of adjuvants by nanoparticles, antigens, and drugs, nanoparticles serving as adjuvants and enhancing antigen-induced immunogenic response, etc. Precise targeting of immunotherapeutics combined with reduced side effects can in turn reduce the cost of the treatment. Taken together, the current studies are indeed promising and will pave the way for improved cancer immunotherapeutics in the near future.

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