Perspective

Yingying Yu, Liangzhu Feng* and Zhuang Liu*

Nanomedicine sheds new light on cancer immunotherapy

https://doi.org/10.1515/mr-2023-0005
Received January 31, 2023; accepted March 17, 2023;
published online April 17, 2023

Abstract: Cancer immunotherapy comprising of immune checkpoint blockade (ICB) therapy, immune cell therapies, cancer vaccines and many others represents a profound arsenal in the fight against different types of cancers. However, their overall clinical objective response rates, particularly against most solid tumors, are still not sufficient owing to a variety of reasons including the heterogenous expression of tumor antigens, limited tumor infiltration of effector immune cells, acquired tumor immunosuppression and some other factors. In recent years, various nanomedicine strategies have been proposed to assist cancer immunotherapy via distinct mechanisms, presenting new promises in many published studies. This perspective will thus provide a brief overview regarding the development of nanomedicine platforms for improving cancer immunotherapy.

Keywords: cancer immunotherapy; *in situ* cancer vaccine; nanomedicine; nanovaccine; tumor microenvironment.

Introduction

Since the first approval of cytotoxic T lymphocyte antigen (CTLA)-4 (Ipilimumab) inhibitor for the treatment of unresectable advanced melanoma, cancer immunotherapy has being intensively explored as a new cancer treatment modality alongside radiotherapy, chemotherapy and targeted therapy [1]. To date, apart from these immune checkpoint blockade (ICB) therapies, immune cell therapies such as chimeric antigen receptor T cells (CAR-T) therapy, cancer vaccines and some others have achieved exciting treatment outcomes toward some specific tumor subtypes in clinical practices or clinical trials [2, 3]. However, due to tumor heterogeneity, immunosuppressive tumor microenvironment (TME) and other limitations, a considerable part of patients, in particular the ones with sloid tumors, do not effectively respond to existing cancer immunotherapies. For instance, the overall objective response rate of ICB therapy toward most solid tumors is roughly 20%–30%. In addition, cancer immunotherapy also suffers from some side effects (e.g., cytokine storm) and therapeutic resistance to some extend. Therefore, a lot of efforts have been recently devoted to improve the therapeutic efficacy and safety of existing cancer immunotherapies [4, 5].

In addition to simply combining cancer immunotherapy with radiotherapy and chemotherapy, nanomedicine derived from the utilization of nanotechnology in medicine holds great promises to potentiate cancer immunotherapy (Figure 1) [6]. Attributing to the versatile molecular encapsulation efficiency and cellular internalization capacity of nanomaterials, they could function as efficient nanocarriers to facilitate the construction of various cancer vaccines. Utilizing nanocarriers as a multifunctional platform, it is possible to use nanomedicine strategies to enhance local tumor treatment and further trigger systemic antitumor immune responses. Furthermore, by utilizing their plenty of physiochemical properties, various rationally customized nanomedicines have found to be potent in potentiating cancer immunotherapy by reprogramming the hostile immunosuppressive TME. In this perspective, we will give a brief summary on the latest progresses on the utilization of nanomedicine to potentiate cancer immunotherapy.

Nanovaccines for cancer immunotherapy

Cancer vaccines through priming tumor-specific T cell responses to selectively attack tumors, are typically rely on the

***Corresponding authors: Liangzhu Feng and Zhuang Liu**, Jiangsu Key Laboratory for Carbon-Based Functional Materials & Devices, Institute of Functional Nano & Soft Materials (FUNSOM), Soochow University, 199 Ren'ai Road, Suzhou 215123, Jiangsu Province, China, E-mail: lzfeng@suda.edu.cn (L. Feng), zliu@suda.edu.cn (Z. Liu). https://orcid.org/0000-0002-1629-1039 (Z. Liu)
Yingying Yu, Jiangsu Key Laboratory for Carbon-Based Functional Materials & Devices, Institute of Functional Nano & Soft Materials (FUNSOM), Soochow University, Suzhou, Jiangsu Province, China

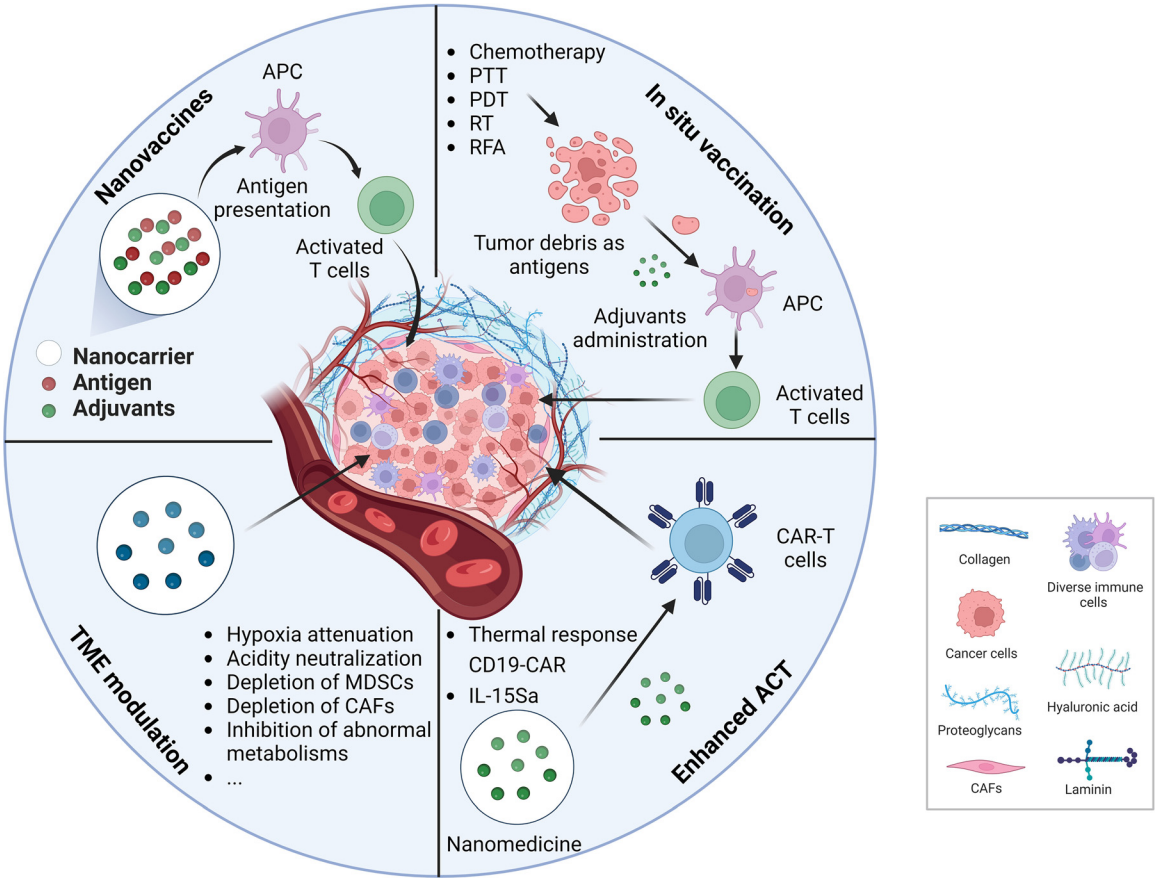

Figure 1: Various nanomedicine strategies for cancer immunotherapy. PTT, photothermal therapy; PDT, photodynamic therapy; RT, radiotherapy; RFA, radiofrequency ablation; APC, antigen-presenting cell; ACT, adoptive cell therapy.

concurrent delivery of tumor-specific antigens and immunostimulatory adjuvants into antigen presenting cells (APCs). Alongside virus-derived antigens and tumor associated antigens (TAAs), neoantigens screened out via gene sequence technology have recently been intensively explored as personalized tumor antigens to enable specific eradication of tumors. In recent years, cancer vaccines especially neoantigen-based cancer vaccines have been tested in many clinical trials, typically used in combination with ICB immunotherapies, presenting encouraging clinicals results.

Nanomedicine tools have shown great potential as vaccine delivery systems. A large variety of nanomaterials ranging from synthetic nanoparticles to bio-derived membrane vesicles have been extensively explored as the delivery nanocarriers to fabricate cancer nanovaccines together with the antigen, the adjuvant. Adjuvant molecules, such as agonists for various toll-like receptors (TLRs) or stimulator of interferon genes (STING), could be loaded inside nanoparticles or anchored on the surface of those nanovaccines. As far as antigens are concerned, in addition to peptide or protein antigens loaded inside those nanoparticles to develop nanovaccines, cancer cell membranes or whole tumor cell lysates based nanovaccines has also attracted tremendous attentions. For instance, in our recent work, we found that fluorinated cationic polymers could form nanoparticles with cancer cell membranes [7]. Such nanovaccines could effectively suppress the tumor growth as they contain the whole repertoire of a patient's tumor antigen epitopes including neoepitopes yet without the demand of a time-consuming neoantigen identification process.

In addition, mRNA cancer vaccine is another promising candidate to endow effective cancer immunotherapy as the high potency of mRNA in encoding multiple neoantigens to trigger tumor-specific immunity. The rapid development and approval of coronavirus disease 2019 (COVID-19) mRNA vaccines was partly resulted from a decade of efforts in the development of mRNA vaccines against cancers, by Moderna and BioNTech. For mRNA vaccines, ionizable lipid

nanoparticles (LNPs) play a critical role as a delivery system to shuttle mRNA into APCs. LNP-based mRNA nanovaccines have indeed demonstrated promising clinical responses to treat last stage melanoma cancer, usually in combination with anti-programmed death 1 (anti-PD1) ICB therapies. Therefore, the rationally developed nanovaccines are a promising class of immunotherapeutic approaches against cancer.

Nanomedicine-based *in situ* vaccination for cancer immunotherapy

One major limitation in cancer vaccine therapy is that personalized screening and vaccine design is required for every patient to be treated, as each individual cancer patient would have different neoantigens in their tumors. As results, developing personalized cancer vaccines would be a rather costly and tedious process. *In situ* vaccination using locally destructed tumor debris as antigens and locally administrated immune stimulating agents as the adjuvant would rather be attractive. Via this strategy, the vaccination could be conducted once the tumor was ablated or treated, without the need of preparation vaccines for each individual patient.

In 2014, our group for the first time proposed that photothermal ablation of tumors using single-walled carbon nanotubes (SWNTs) could result in abscopal effect to inhibit the growth of distant tumor with the help of ICB therapy [8]. In this system, tumor antigens are released once the tumor was ablated, while SWNTs could have immune stimulating function. After this study, our group together with many other research teams have demonstrated that nanomedicine-based local tumor treatment, including photothermal therapy (PTT), photodynamic therapy (PDT), radiation therapy (RT), radiofrequency ablation therapy (RFA) and local chemotherapy, could trigger immunogenic cell death and thus tumor-specific immunity, with the help of locally administrated immune stimulating agents [9–11]. Such local treatment induced *in situ* tumor vaccination with the help of ICB therapy (e.g. anti-CLTA4, anti-PD1/L1) could offer systemic immune responses to attack metastatic tumors, and further result in immune memory effect to prevent tumor relapse. Such a strategy holds great potential in clinical translation.

Nanomedicine for modulation of tumor microenvironment

Different from the physiological environments of parental tissues, solid tumors have a series of unique microenvironmental characteristics of hypoxia, tumor acidity, high levels of reactive oxygen species (ROS), dense extracellular matrix, and infiltration of diverse suppressive immune cells. Such hostile TME characteristics have posed a series of biological barriers to hinder the therapeutic potency of cancer immunotherapy by restricting the tumor infiltration of effector immunes cells such as cytotoxic T lymphocytes (CTLs), and inducing their exhaustion. Recently, intensive studies indicate that effective TME modulation with rationally designed nanomedicine and other formulations is a profound approach to potentiate different cancer treatments, including immunotherapy.

In our recent review article, we have summarized the development of TME-modulating biomaterials and nanomedicine platforms to enhance cancer immunotherapy [12]. In general, the TME of solid tumors can prevent infiltration and negatively affect the activity of immune cells. The immunosuppressive features of the TME including hypoxia, acidity, high levels of reactive oxygen species, a dense extracellular matrix and abnormal vasculature, can be modulated using nanomedicine tools, so as to promote the efficacies of cancer immunotherapies.

As the negative impacts of tumor hypoxia and acidity in promoting the formation of tumor immunosuppression, diverse nanomedicines enabling tumor hypoxia attenuation or tumor acidity neutralization have shown to be capable of reversing tumor immunosuppression (e.g., repolarization of tumor associated macrophages) and thus contributing to augmented cancer immunotherapy. Selective depletion of intratumoral immunosuppressive myeloid-derived suppressor cells and cancer associated fibroblasts with corresponding targeted nanomedicine could also enhance the therapeutic potency of diverse cancer treatments through promoting tumor accumulation of therapeutics and/or boosting the antitumor immune responses. Tumor targeted delivery of nanomedicine enabling ROS scavenging is also potent to remove the negative impacts of elevated ROS on the therapeutic efficacy of immunotherapies. Furthermore, selective inhibition of abnormal metabolisms of cancer cells with well-designed nanomedicine has also shown to be effective in potentiating cancer immunotherapy.

Nanomedicine for enhanced cell therapies

Adoptive cell therapy (ACT) is a widely explored cancer immunotherapeutic modality by harnessing natural or genetically engineered T cells, NK cells and macrophages originally isolated from patients to attack tumor cells. In particular CAR-T cell therapy has exhibited superior therapeutic effectiveness to blood cancers (e.g., acute and chronic B-cell leukemias and B-cell non-Hodgkin lymphomas). However, the potency of CAR-T therapy against solid tumors remains restricted owing to the tumor immunosuppression and conduced extracellular matrix (ECM), all of which would severely restrict the intratumoral infiltration, proliferation and effector functions of perfused CAR-T cells. Therefore, various nanomedicine has also been extensively explored to reinforce the therapeutic effectiveness and accuracy of ACT therapies against solid tumors.

In 2019, Irvine and coworkers prepared a redox-responsive interleukin-15 super-agonist (IL-15Sa)-loaded nanogel, which could release active IL-15Sa in response to the increased surface reduction potential after T cell receptor activation [13]. Intravenous administration of CAR-T cells with such nanogels exhibited 16-fold more expansion in tumors, but remained largely quiescent in the peripheral blood, thereby enabling more effective cancer treatment at reduced side effects. In a recent study, Miller and coworkers reported that tumor localized photothermal treatment with NIR-absorbing nanomedicine can selectively activate the T cells engineered with a thermal response CD19-CAR construct to enable selective tumor suppression [14]. Moreover, it has also been reported that T cells anchored with liposomal avasimibe upon tumor accumulation exhibited rapid T cell receptor clustering and sustained T cell activation for enhanced tumor eradiation [15]. In general, the application of nanomedicine tools to enhance immune cell therapies is a emerging research direction with great promises.

Outlook

It has been demonstrated that nanomedicine is a promising candidate to potentiate cancer immunotherapy through various pathways. Inspired by the clinical applications of lipid nanoparticles based COVID-19 mRNA vaccines, biocompatible nanomaterials hold great promises as delivery nanocarrier of cancer nanovaccines due to their superior capacity in encapsulating diverse molecules, protecting them from enzymatic degradation, promoting their cellular internalization and endo-/lysosome escaping makes them. Various other types of nanomedicine platforms are now being actively explored to assist immunotherapies via different manners. However, chemistry, manufacture and control (CMC) needs to be addressed for the clinical translation of any nanomedicine-based pharmaceuticals with complex formulations. As those nanomedicine strategies are often combined with various existing standard-of-care (SOC) treatments, well-planned clinical trials are needed to eventually verify the benefit of nanomedicine tools in boosts immunotherapies against cancers.

Research funding: None declared.
Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Competing interests: Authors state no conflict of interest.
Informed consent: Not applicable.
Ethical approval: Not applicable.

References

1. Irvine DJ, Dane EL. Enhancing cancer immunotherapy with nanomedicine. Nat Rev Immunol 2020;20:321–34.
2. Tang L, Zheng Y, Melo MB, Mabardi L, Castaño AP, Xie YQ, et al. Enhancing T cell therapy through TCR-signaling-responsive nanoparticle drug delivery. Nat Biotechnol 2018;36:707–16.
3. Jiang W, Wang Y, Wargo JA, Lang FF, Kim BYS. Considerations for designing preclinical cancer immune nanomedicine studies. Nat Nanotechnol 2021;16:6–15.
4. Nam J, Son S, Park KS, Zou W, Shea LD, Moon JJJNRM. Cancer nanomedicine for combination cancer immunotherapy. Nat Rev Mater 2019;4:398–414.
5. Jiang W, Von Roemeling CA, Chen Y, Qie Y, Liu X, Chen J, et al. Designing nanomedicine for immuno-oncology. Nat Biomed Eng 2017;1:1–11.
6. Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an emerging platform for cancer therapy. Nature Nanotechnol 2007;2:751–60.
7. Xu J, Lv J, Zhuang Q, Yang Z, Cao Z, Xu L, et al. A general strategy towards personalized nanovaccines based on fluoropolymers for post-surgical cancer immunotherapy. Nat Nanotechnol 2020;15:1043–52.
8. Wang C, Xu L, Liang C, Xiang J, Peng R, Liu Z. Immunological responses triggered by photothermal therapy with carbon nanotubes in combination with anti-CTLA-4 therapy to inhibit cancer metastasis. Adv Mater 2014;26:8154–62.
9. Yang Z, Zhu Y, Dong Z, Li W, Yang N, Wang X, et al. Tumor-killing nanoreactors fueled by tumor debris can enhance radiofrequency ablation therapy and boost antitumor immune responses. Nat Commun 2021;12:1–12.

10. Chao Y, Liang C, Tao H, Du Y, Wu D, Dong Z, et al. Localized cocktail chemoimmunotherapy after in situ gelation to trigger robust systemic antitumor immune responses. Sci Adv 2020;6:eaaz4204.
11. Chao Y, Xu L, Liang C, Feng L, Xu J, Dong Z, et al. Combined local immunostimulatory radioisotope therapy and systemic immune checkpoint blockade imparts potent antitumour responses. Nat Biomed Eng 2018;2:611–21.
12. Chao Y, Liu Z. Biomaterials tools to modulate the tumour microenvironment in immunotherapy. Nat Rev Bioeng 2023;1: 125–38.
13. Tang L, Zheng Y, Melo MB, Mabardi L, Castaño AP, Xie YQ, et al. Enhancing T cell therapy through TCR-signaling-responsive nanoparticle drug delivery. Nat Biotechnol 2018;36:707–16.
14. Miller IC, Zamat A, Sun LK, Phuengkham H, Harris AM, Gamboa L, et al. Enhanced intratumoural activity of CAR T cells engineered to produce immunomodulators under photothermal control. Nat Biomed Eng 2021;5:1348–59.
15. Yang W, Bai Y, Xiong Y, Zhang J, Chen S, Zheng X, et al. Potentiating the antitumour response of CD8+ T cells by modulating cholesterol metabolism. Nature 2016;531:651–5.