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The immune response of nano carbon-based photic-driving vaccines to severe acute respiratory syndrome coronavirus 2

Junming Chen[1†], Qiang Wang[2†], Fenfen Zhang[2], Jianshe Yang[2,3*]

[1]Department of Internal Medicine, Minhang Hospital, Fudan University, Shanghai 201199, China
[2]Basical Medicine School, Gansu Medical College, Pingliang 744000, Gansu, China
[3]Department of Nuclear Medicine, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai 200072, China

[†]These authors contributed equally to this work.
***Correspondence:** Jianshe Yang, Department of Nuclear Medicine, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai 200072, China. 2305499@tongji.edu.cn
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Abstract

As the most severe novel infectious disease in this century, coronavirus disease 2019 (COVID-19) faces tremendous challenges due to the hysteresis of drugs and vaccine development. Elucidating the panoramic mechanism of coronavirus-host immune interaction is a strategy for disease surveillance, diagnosis, treatment, prevention, and immunity assessment of COVID-19. A robust carbon nanotube (CNT)-based photic vaccine technology contributes to address the core scientific issues of these challenges. This perspective states the latest prevention and control strategy of CNT-based photic vaccine and its broad-spectrum resistance to high transmissible and pathogenic variants. Furthermore, this perspective covers the potential immune response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) under the CNT-based photic vaccine intervention and finally evaluates its efficacy and the underlying interactive mechanisms. In the future, findings of the highly efficient and conservative T cell epitopes depending on an intelligent chem-physical modulation would provide a promising basis for the development of next generation vaccines. Ideally, these next generation vaccines are prone to be with the function of dynamic allostery responding to the chem-physical changing and present the allosteric epitopes which are affinity to the viral variation.

Keywords

Severe acute respiratory syndrome coronavirus 2, carbon nanotube, photic-driving, vaccines, immune response, allostery, epitope

Introduction

Since the outbreak of coronavirus disease [coronavirus disease 2019 (COVID-19)] in late 2019, it has caused approximately 600 million infections and approximately 6.5 million deaths worldwide [1]. By

means of strict prevention and control policies, the spread of the epidemic has been effectively controlled in China, while the continuous regional spread still seriously affects social and economic development and threatens people's lives and safety [2]. Although the development and application of antiviral drugs and vaccines are in rapid progress, however, a large number of clinical trials reusing the old antiviral drugs or applying emergency authorization of novel antiviral drugs and vaccines showed unsatisfactory effects against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3–6]. Emergent issues have challenged physicians and researchers due to the mechanisms of drugs/vaccines interacting with SARS-CoV-2 remaining unclear. A large population who has sequentially vaccinated or administrated with multiple doses of drugs is still infected by the SARS-CoV-2 and cases of breakthrough infection in the vaccinated population were also reported [7, 8]. Reducing the infectivity, eliminating social panic, and developing effective drugs and vaccines became critical problems related to the national economy and people's livelihood [9, 10]. Currently, the treatment of COVID-19 mainly relies on finding highly specific protease inhibitors, however, the high variability of SARS-CoV-2 and the delay of the drug/vaccine development made this urgent work with unprecedented challenges [11].

Coronaviruses are enveloped single-stranded positive-stranded RNA viruses widely distributed in humans, other mammals, and birds, which can cause respiratory, gastroenterological, and neurological system diseases. To date, it is demonstrated that seven kinds of coronaviruses can infect humans, among which the most highly pathogenic three ones, SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2, having the very higher lethal risk. A relatively higher rate of coronavirus RNA recombination can possibly lead to a persistent variation and the consequent antigenicity alteration, and eventually cause the failure of vaccination and immunity.

The nature of the above processes showed the facts of the extremely strong proliferation and the high frequency of genome mutation of the coronavirus. At present, focusing on specific protease inhibitors, such as heterogeneous recombination and purification of SARS-CoV main protease (M^{pro}), and selection of positive compounds constitute the important basis for the development of anti-SARS virus drugs. Yet the novel drugs and vaccines developed based on this paradigm have not achieved expectant outcomes in COVID-19 clinical trials, which is far from the theoretical prospect. These conditions recall some unconventional methods to be innovated for COVID-19 therapies.

Commonly, coronaviruses have special physicochemical properties, such as acid intolerance and heat sensitivity, so they are easily inactivated at the circumstance of 56°C for 30 min. Carbon nanotubes (CNTs) have been widely used in recent years in the field of applied biology and biomaterials due to their small scale, high efficiency in photothermal conversion, large volume for intracavity storing, and rich fabricated surface of physical and chemical characteristics, consequently resulting in having excellent potential of biological utilization, such as good biocompatibility, high biological barrier permeability, and surface targeted biomolecular modification potential [12]. These characteristics can be applied to developing novel coronavirus drugs. Hence, this perspective proposes a project to conduct the correlation study of acidified functionally modified CNTs for SARS-CoV-2 inhibition using CNTs, to provide theoretical support for new methods and strategies for coronavirus prevention, control, and intervention.

Application, advantages, and disadvantages of photic vaccine in COVID-19 epidemic prevention

At the Tokyo Olympics in 2021, a dark technology device called the "photic vaccine" was widely used against COVID-19. In the end, despite the poor situation in Japan, the Chinese delegation achieved the goal of zero infection. The photic vaccine is not a traditional vaccine. The emission wavelength is 222 nm wavelength irradiation energy. After it is highly absorbed by SARS-CoV-2, its RNA helix link is destroyed, resulting in its loss of replication ability to achieve the elimination effect (elimination rate: 99.99%) [13]. The 254 nm ultraviolet (UV) light, widely used before, has the characteristics of purely physical and high efficiency sterilization, no secondary pollution, high power, and high UV illumination, and it is used in a large area environment [14, 15]. Although this band of UV light can destroy microbial DNA, it can also pass

through the human skin and direct exposure to the human body and the eyes, serious can cause cataracts and cancer. Therefore, UV irradiation has certain conditional limitations [16]. Recently, a study has shown that the 222 nm wavelength is equally effective for many pathogens and that this light does not pose a threat to humans [17]. Hence, low dose rates of far UV exposure can safely and substantially reduce the environmental levels of airborne coronaviruses in occupied public places. The technology highlights the harmless far UV light that allows "man-machine coexistence, real-time disinfection". However, the disadvantages of this technology remain. First, low penetration capacity at such weak energy and short wavelength can only be used for surface contamination and is inapplicable to infected tissues, organs, and cells. Second, cumulative exposure to 99% is a new technology that uses special wavelength UV light for effective sterilization to prevent virus infection, without mounting any immune response.

Application prospect of carbon nanomaterials in new coronavirus control

In any case, by using this 222 nm UV light radiation technology, the simplest measures should be considered to apply to control the pandemic. Coronavirus has the most special physicochemical properties: acid intolerance, heat sensitivity, and easy inactivation at 56°C for 30 min, hence, the thermal effect is undoubtedly the simplest and most effective means to kill the virus [18]. CNTs have been widely studied and used in the field of applied biology in recent years. It has a small scale (10–100 nm), high dimension [two-dimensional (2D), 3D], good photothermal conversion efficiency, great in-tube storage space, and surface load capacity of physical and chemical characteristics, and shows excellent biological properties, such as good biocompatibility, high biological barrier permeability, and surface targeted biomolecular modification potential. These characteristics hold potential for developing novel coronavirus drugs [19, 20]. Numerous studies have shown that CNTs are easily functionalized by surface changes at non-covalent and covalent junctions, and thus, can be used for the transport of small and macromolecules [21–24]. Soluble CNTs functionalized by surface oxidation and coated with a surfactant or amphipathic polymers can phagocytose by cells through an energy-dependent endocytic pathway and are widely used for drug-targeted delivery [25, 26]. However, the nanomaterials are only used as carriers or vaccine adjuvants to improve efficacy, and they have not yet reached their full potential in SARS-CoV-2 treatment.

The application of carbon nanomaterials in virus prevention and control is reflected in the following three aspects: (1) the introduction of new chemical properties (such as strong acidity), by chemically modifying the CNTs' surface and the internal tube for the formation of functional groups or special molecules with special chemical properties. The modified complex can present new chemical properties; (2) targeting (for example, targeting type II alveolar epithelial cells) by grafting biological targeting molecules (that is, sugars, glycolipids, proteins, RNA, DNA, etc.). They act on specific organs or tissues [27]; (3) photodynamic hyperthermia (with an inactivation effect on the coronavirus) using CNTs' superior near infrared (NIR) light absorption characteristics and good photothermal conversion efficiency. The temperature of the local area of CNT aggregation increases sharply (up to 51°C) [28, 29].

Construction and mechanism of action of CNT-based photic vaccine

According to the aforementioned "photic vaccine" and carbon nanomaterials in SARS-CoV-2 prevention effectiveness assessment, this perspective first proposed in the international CNT-based "photic vaccine" design scheme: The modified nanomaterials targeted virus infection of specific areas (for example, lung), and these nanomaterials can be stimulated in biosafety NIR present photothermal conversion effect, leading to local high temperature, and eventually eliminating the virus. Most importantly, this design should initiate the immune response through specialized conjugates, besides regulating or downregulating the competitive binding of angiotensin-converting enzyme 2 (ACE2) receptors on the cell membrane to inhibit novel coronavirus infection [30]. According to the physical and chemical properties of CNTs, which was previously fabricated with the spike (S) protein receptor binding domain (RBD, SARS-CoV-2 S-RBD) [31], which has good potential to target SARS-CoV-2 host cell and can also promote cytoplasm and local cell temperature increase through photothermal conversion [32]. After reaching the target area, the

SARS-CoV-2 S-RBD dissociates from the CNTs' surface and specifically binds to the ACE2 receptor on the host cell membrane, effectively competitively inhibiting the appeal of SARS-CoV-2 to the host cells. Moreover, it has the antibody properties binding to the receptor, inducing the host immune response. Unlike the traditional concept of nano vaccines, neither the nanomaterials coating for the protection of targeted delivery and delivery processes nor nanomaterials are used as vaccine adjuvants to enhance the stability and neutralization of vaccines. Although the previous designed CNT-based photonic vaccine uses the viral core antigen as an immune agonist, it is different from the classical theory of viral immunity [32]. First, the main role of the viral core antigen in this project is immune targeting; contribution immunity is not the main purpose. Next, the nano photic vaccine designed in this study, through its strong acidic microenvironment, effectively exerts a regulatory effect on T cell immunity, including the modification and allostery of T cell epitopes. Though numerous repeated experimental screenings for T cell immune epitopes with effectively improved immunity, the exploration of novel mechanisms of T cell immunity is emergently needed. As a pure carbon skeleton structure, it can effectively prevent the delivery process, immune rejection, and potential signaling interference caused by host cells due to immune heterogeneity [33]; at the same time, the CNT wall modified grafting of SARS-CoV-2 S-RBD and RNA lyase, and can be dissociated under NIR irradiation and the receptor on the host cell membrane, initiating the adaptive immune mechanism of the body. The vaccine can also interact with components of the immune system and soluble plasma proteins to form coronal structures around the CNTs, changing the nature of the interactions between coronary envelope cells and components of the complement system. The opsonins that constitute the coronary structure [including the immunoglobulin G (IgG) and complement proteins] increase the uptake of these nanoparticles by macrophages and other cells in the reticuloendothelial system [34]. Complement protein C1q, mannose-binding lectin (MBL), and C reactive proteins (CRPs) recognize repetitive structures or charge patterns on the CNTs' surface, and natural killer (NK) cells are also stimulated using CNTs [35]. However, the relationship between coronavirus-induced immune activation and CNTs is related to cytokines, such as interleukin-6 (IL-6), IL-12, and interferon alpha (IFN-α) in the C1q pathway. The excellent biofilm penetration of CNTs can achieve rapid and precise vaccine strategies after SARS-CoV-2 S-RBD modification, targeting some antigen and transmembrane serine protease 2 (TMPRSS2) receptor affinity, and this design is equally effective [19]. Because of the high transmission, pathogenicity, and variability of SARS-CoV-2, these CNTs can achieve planned antigenic stimulation through concentration control and NIR source irradiation, and ensure antibody production and efficacy in the necessary stage. Therefore, CNT-based photonic vaccines can fully cover SARS-CoV-2 infection immunity, with broad-spectrum inhibitory effects, and are expected to act as an immunomodulator to combat coronavirus infection.

Feasibility and efficacy of CNT-based photic vaccine treatment against SARS-CoV-2

Because SARS-CoV-2 is heat sensitivity, properties susceptible to degradation by RNA lyases can be combined with the broad applicability of the "photic vaccine" and human innocuity. Using the strong acidity of carbon nanomaterials after chemical modification, excellent photothermal conversion efficiency, and characteristics of targeting the indicated regions of viral infection, a CNT-based "photic vaccine" can be designed. In addition, the functional CNT preparation modified by the SARS-CoV-2 S-RBD of the acidified surface, RNA lyase, and SARS-CoV-2 has been completed (see Figure 1 below). On the basis of the preliminary work, systematic development of molecular, cellular, and small animal experiments, focusing on the body's immune response to SARS-CoV-2 under a CNT-based photic vaccine intervention, the efficacy and action mechanism of CNT-based photonic were evaluated objectively and completely in terms of the aspects of biosafety, vaccine neutralization, virus ability, the interaction between the vaccine and the body immune system, and the promotion of autoimmunity and immune memory. Based on the SARS-CoV-2 inhibition pathways, a novel study was exerted to provide theoretical support for new methods and strategies for coronavirus prevention and control and intervention. This work highlighted that functionalized CNTs play four important roles in inactivating SARS-CoV-2 by identifying the ACE2 receptor

and targeting type II alveolar epithelial cells: (1) high temperature environment: CNTs through NIR irradiation is more than 56°C; (2) cleavage: CNTs release, after NIR irradiation, the RNA lyase group and cleaves SARS-CoV-2; (3) strong acid environment: CNTs release the COOH group after NIR irradiation, which significantly reduces the environmental pH value; (4) epitope allostery: Strong acid environment enrichment and chemotactic T cells for epitope allostery can produce new immunological epitopes.

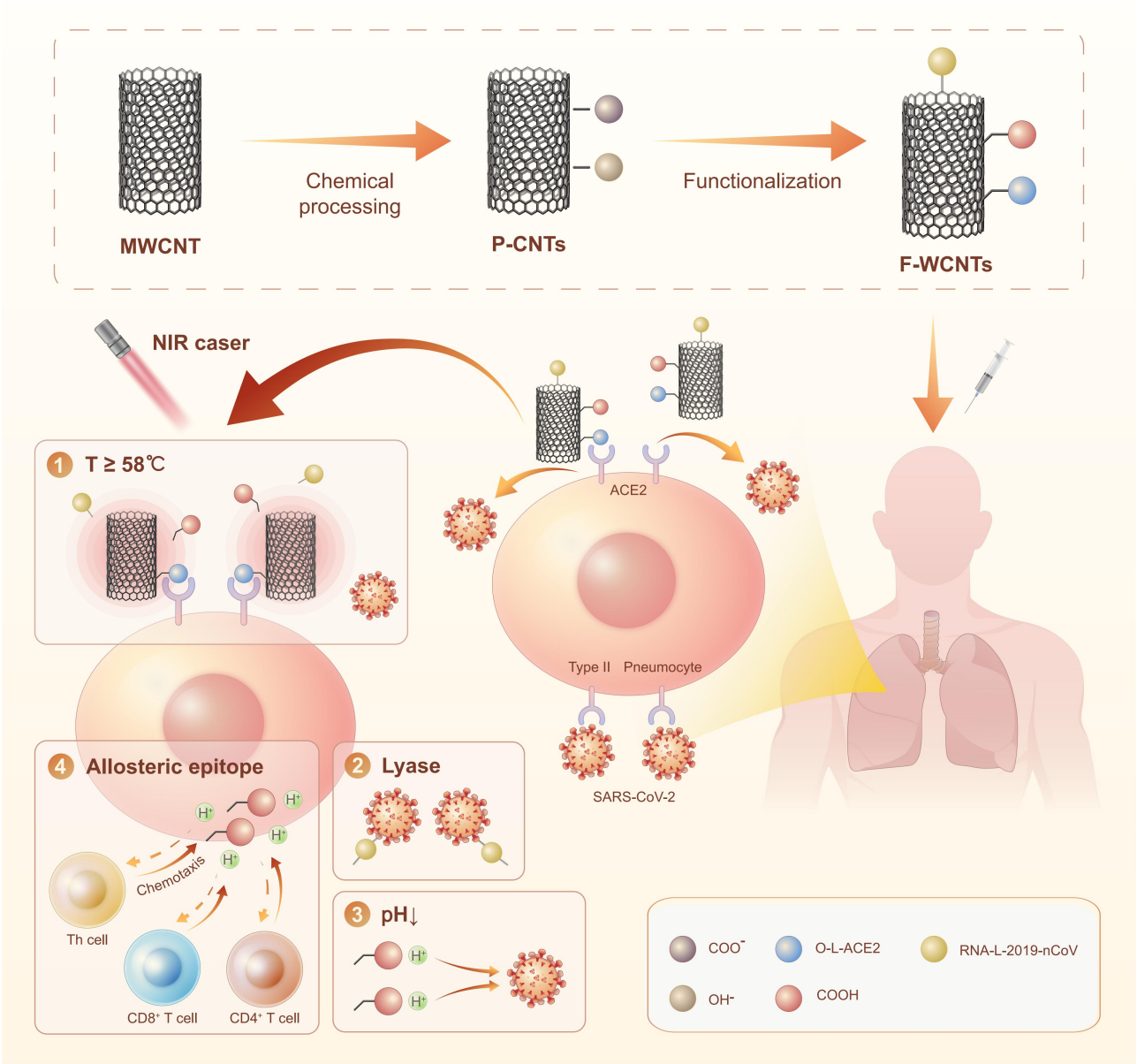

Figure 1. Flowchart and key mechanism of functionalized carbon nanotube (CNT) preparation for anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the promising immunological response presentation with a semiautomatic adaptive modulation of antigen epitopes. The Figure was drawn by the software Illustrator for Biological Sequences (IBS) [36]. MWCNT: multi-walled CNT; P-CNTs: purified CNTs; F-WCNTs: functionalized multi-walled CNTs; NIR: near infrared; T: temperature; ACE2: angiotensin-converting enzyme 2; Th: T helper

Perspective

The effective immune response of CNT-based photic vaccine to SARS-CoV-2 can accelerate the discovery of efficient conserved T cell epitopes, providing a new immunotherapy paradigm for the development of a next generation of T cell vaccine and the continuously variant novel coronavirus-triggered COVID-19. In the future, deepens the discovery of the CNT-based photic vaccines, which are highly and efficiently responding to the conservative T cell epitopes depending on an intelligent chem-physical modulation manner, and

reveals out the real interactive mechanisms between them and viruses would be valuable and emergent. Ideally, these next generation vaccines are prone to be with the capacity of dynamic allostery responding to the chem-physical changing then presenting the allosteric epitopes, which owning the potential to respond the continuous viral variation. Furthermore, this work will surely afford some clues for the vaccination design if the pathogens are sensitive to physic-chemical natures same as coronaviruses, even it can be developed for the cancer vaccines design.

Abbreviations

ACE2: angiotensin-converting enzyme 2

CNT: carbon nanotube

COVID-19: coronavirus disease 2019

NIR: near infrared

RBD: receptor binding domain

S: spike

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

UV: ultraviolet

Declarations

Author contributions

JC and QW equally contributed to: Investigation, Writing—original draft, Visualization, Funding acquisition. FZ: Software, Investigation, Writing—original draft. JY: Conceptualization, Validation, Data curation, Writing—review & editing, Visualization, Supervision, Project administration, Funding acquisition. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

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