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Nano-based approaches in the development of antiviral agents and vaccines

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ABSTRACT

Outbreaks and the rapid transmission of viruses, such as coronaviruses and influenza viruses, are serious threats to human health. A major challenge in combating infectious diseases caused by viruses is the lack of effective methods for prevention and treatment. Nanotechnology has provided a basis for the development of novel antiviral strategies. Owing to their large modifiable surfaces that can be functionalized with multiple molecules to realize sophisticated designs, nanomaterials have been developed as nanodrugs, nanocarriers, and nano-based vaccines to effectively induce sufficient immunologic memory. From this perspective, we introduce various nanomaterials with diverse antiviral mechanisms and summarize how nano-based antiviral agents protect against viral infection at the molecular, cellular, and organismal levels. We summarize the applications of nanomaterials for defense against emerging viruses by trapping and inactivating viruses and inhibiting viral entry and replication. We also discuss recent progress in nano-based vaccines with a focus on the mechanisms by which nanomaterials contribute to immunogenicity. We further describe how nanotechnology may improve vaccine efficacy by delivering large amounts of antigens to target immune cells and enhancing the immune response by mimicking viral structures and activating dendritic cells. Finally, we provide an overview of future prospects for nano-based antiviral agents and vaccines.

1. Introduction

A virus particle is made up of genetic material and a capsid (Fig. 1A). Housed inside the protein-based capsid, the viral genome consists of single-stranded or double-stranded DNA or RNA in linear or circular form. Some viruses, such as human immunodeficiency virus and coronaviruses, have viral envelopes covering capsids. Typically derived from host cell membranes, the envelopes are composed of phospholipids and proteins and may include viral glycoproteins. Infectious diseases caused by viruses have long been serious threats to global public health [1,2]; for example, smallpox and yellow fever have resulted in millions of deaths. In recent years, public health crises have emerged due to epidemics and pandemics of new viruses, including SARS-CoV, MERS-CoV, and H7N9 [3,4]. The recent pandemic of COVID-19 caused by SARS-CoV-2 has become a global health crisis [5,6]. The lack of effective treatments remains a primary challenge in the fight against emerging viral threats [7,8].

The majority of available antiviral agents are synthetic agents, such as nucleoside analogues that prevent viral genome replication and protease inhibitors that selectively bind to viral proteases and block proteolytic cleavage of viral protein precursors [9–11]. Recently, antibodies targeting specific viral proteins have been developed [12,13]. However, novel antiviral agents are urgently needed for newly emerging virus strains. Operating at the nanoscale (1–100 nm), nanotechnology paves a new path for the development of antiviral agents. The unique properties of nanomaterials, such as their small sizes, high surface-to-volume ratios, and modifiable surfaces, are beneficial for contact with viruses and contribute to multiple antiviral effects, such as the inactivation of viruses and blocking viruses from entering host cells [14,15].

Historically, vaccines have been vital against smallpox, polio, hepatitis A, and papilloma [16–18]. However, conventional vaccines are not applicable to some viral infections for two key reasons. First, some viruses are difficult to produce in vitro, which is required for the development of vaccines composed of inactive or attenuated viruses. Second, although vaccines carrying peptide antigens or mRNAs encoding antigens are an alternative, they are limited by low stability and degradation in vivo. Nanomaterials can as act carriers to protect antigens from degradation and improve immune responses, which in turn improves the

effectiveness of nanovaccines. Since the first nanovaccine against hepatitis B virus (HBV) was licensed in 1986, nanotechnology has been applied to develop vaccines against human papillomaviruses (HPV) and hepatitis E virus (HEV), and positive preclinical outcomes have been obtained for HIV and respiratory viruses [19–21]. In light of emerging viruses, such as SARS-CoV-2, nano-based vaccines have received substantial attention [22].

In this review, we focus on nano-based antiviral agents and vaccines, which are among the most promising approaches for countering outbreaks of emerging viral infections. To provide insight into the use of nanotechnology to manage viral threats, the antiviral mechanisms of nanomaterials as well as recent progress in the development of nano-based vaccines are summarized.

2. Antiviral effects of nanomaterials

Viruses invade cells in three steps: (i) contact with the cell membrane and entry into the intracellular space; (ii) amplification of the viral genome and expression of the viral proteome; (iii) assembly of the new virus and release to the extracellular space, inducing infection [23–25]. Nanomaterials have been reported to suppress cell entry and viral replication; moreover, their numerous surface binding sites facilitate interactions with target molecules, consequently trapping and inactivating viruses (Fig. 1B; Table 1) [26,27].

2.1. Trapping effects of nanomaterials

To invade, a virus first attaches itself to the membrane of host cells. This behavior is the basis for broad-spectrum anti-infection nanomaterials based on cell membrane properties, known as nanodecoys. The surface of nanodecoys may be derived from cell membranes, providing cell-surface receptors that are recognized by and trap the virus [28]. Indeed, vesicles derived from CD4$^+$ T cell membranes show effective attachment by HIV-1, thereby preventing HIV-1 from binding to and entering healthy CD4$^+$ T cells [29]. Another artificially engineered membrane-derived vesicle in which the surface is coated with a human sodium taurocholate co-transporting polypeptide effectively blocks HBV infection, spread, and replication in a mouse model [30].

However, cell membrane-derived vesicles are prone to membrane fusion due to the fluid-filled vesicles and cell membranes, thus generating a risk that vesicles bring detained viruses to healthy cells [31]. Therefore, cell membrane-coated nanostructures, in which the membrane is fixed and stabilized by a nano-core, have been developed to avoid unwanted membrane fusion [28,32,33]. Cell membrane-coated nanodecoys effectively trap Zika virus (ZIKV), divert it from healthy cells, and successfully mitigate ZIKV-induced inflammatory responses and fetal microcephaly [34]. In addition to the decreased membrane fusion property, the core-coated structure in which a coated lipid membrane is stabilized by a nanoparticle core also stabilizes cell
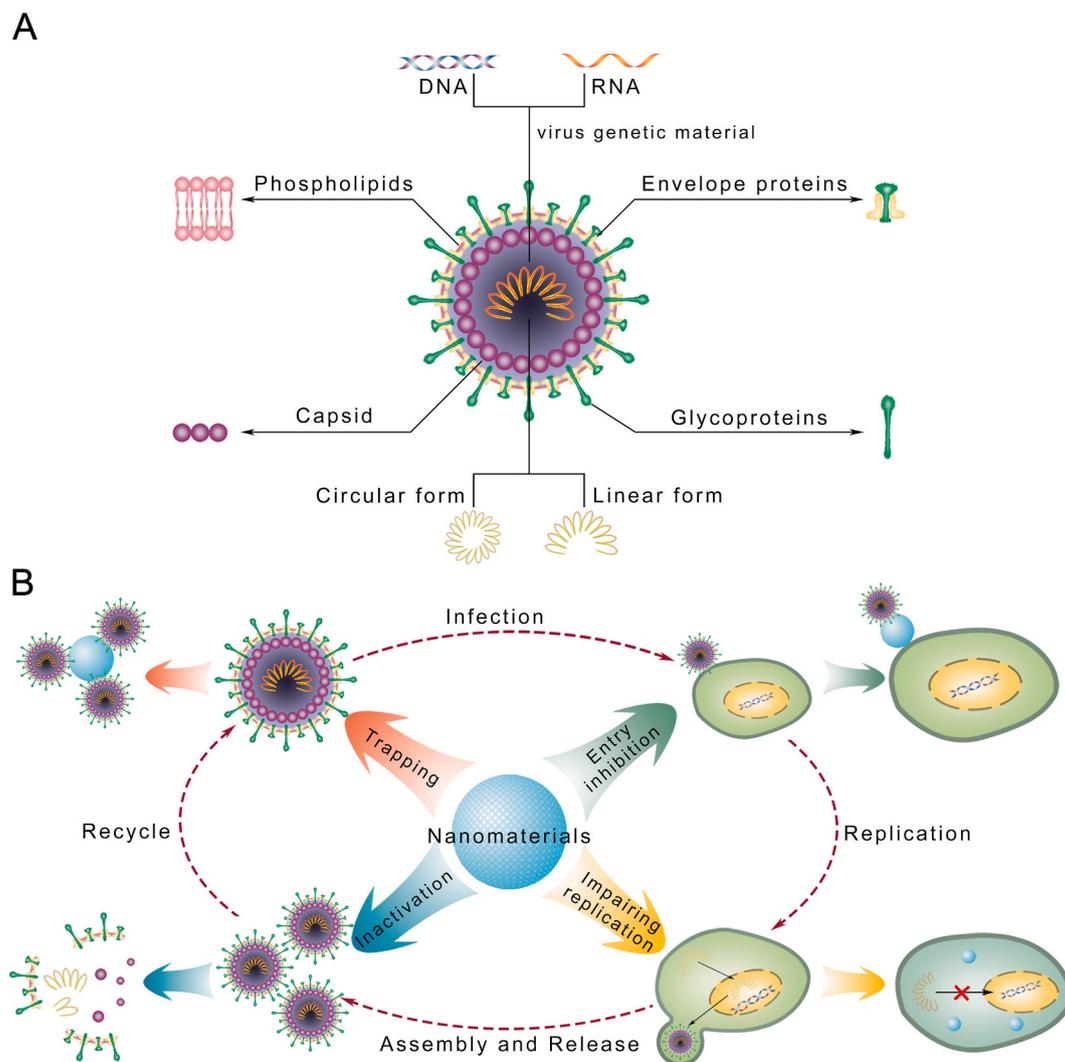
Fig. 1. Schematic representation of how nanomaterials inhibit virus infections. (A) The composition of a virus with envelop. (B) Nano particles could play antiviral effects by mechanisms including: inactivating virus; trapping and detention of virus; inhibiting cellular entry of virus; blocking the replication of virus.

Table 1

Nano-based antiviral agents.

Antiviral effect	Nanomaterial	Virus	Mechanism
Trapping virus	CD4$^+$ T-cell-derived vesicles	HIV-1	Attaching effectively to HIV-1, preventing it from binding to and entering healthy CD4$^+$ T cells [29]
	Membrane vesicle coated with human sodium taurocholate *co*-transporting polypeptide	HBV	Trapping HBV, protecting host cells from viral infection [30]
	Plasma membranes of CD4$^+$ T cells coated on polymeric cores	HIV	Neutralizing HIV and diverting the viruses away from peripheral mononuclear blood cells and human-monocyte-derived macrophages by selectively binding with viral gp120 [32]
	Polymeric core covered by membrane	Zika virus	Trapping Zika virus (ZIKV) and divert it away from its healthy cellular targets [34]
	Polymeric cores coated by the plasma membranes derived from human lung epithelial type II cells or human macrophages	SARS-CoV-2	Neutralizing SARS-CoV-2 and protecting healthy cell from viral infection, as a result of displaying the same protein receptors required by SARS-CoV-2 for cellular entry [36]
Inhibiting viral entry	Polyethylene glycol encapsulated AuNPs	HIV-1	Blocking gp120 attachment with CD4$^+$ cells [38]
	SiNPs with –OH and –NH$_2$ groups	HIV-1	Blocking gp120 attachment with CD4$^+$ cells [39]
	AgNPs	HIV-1	Interacting with viral gp120 in both cell-free and cell-associated virus [40]
	AgNPs	H7N3	Blocking the function of viral hemagglutinin, leading to the hindered viral entry [41]
	AgNPs	HSV-2	Interacting with sulfhydryl group of membrane glycoproteins, thus preventing viral internalization [42]
	Tannic acid functionalized AgNPs	HSV-2	Tannic-acid modification increases biological affinity of AgNPs for viral glycoproteins [44]
	Glycosaminoglycan modified SiNPs	HSV-1, 2	Glycosaminoglycans could bind to the viral glycoproteins [45]
	Nanogels based on dendritic polyglycerol sulfate to mimic cellular membrane heparan sulfate	HSV-1	Multivalently interacting with viral glycoproteins, shielding virus surfaces, and efficiently blocking virus infection [15]
	Polyquaternary phosphonium oligochitosans decorated AgNPs (PQPOCs-AgNPs)	Hepatitis A virus (HAV), norovirus (NoV) and Coxsackievirus B4 (CoxB4)	Binding of AgNPs to the viral active sites and electrostatic interaction between the positive brushes of PQPOCs and negative targets of viruses [47]
	Carbon-based fullerenes	Pseudotyped viral particles (Ebola virus)	Blocking membrane DC-SIGN mediated viral entry [48–50]
	Carbon dots	Human Norovirus virus-like-particles	Blocking membrane HBGAs mediated viral entry [53]
Inhibiting viral replication	AuNPs	Foot- and mouth- disease virus (FMDV)	Binding to FMDV RNA, sub-genomic RNA, or viral replicative proteins [54]
	Fullerene derivatives	Wild-type HIV-1, resistant HIV-1	Affecting viral maturation of wild-type HIV-1 by inhibiting Gag processing, and maturation of resistant HIV-1 viruses by impairing viral polyprotein processing through a protease-independent mechanism [56]
	AgNPs	Peste des petits ruminants' virus (PPRV)	Interacting with virion surface and core protein, impairing viral replication and entry [57]
	AgNPs	dsRNA viruses	Interacting with viral genome [58]
	Carbon dots	PRV, porcine reproductive and respiratory syndrome virus	Inducing antiviral response of interferon-α (IFN-α) production and the expression of IFN-stimulating genes (ISGs) in host cells [59]
	Poly(aniline-*co*-pyrrole) polymerized nanoregulators (PASomes)	H1N1, H3N2, and H9N2	Controlling intracellular ROS levels, resulting in downregulating MEK/ERK pathway-based viral replication [60]
Viral inactivation	Protoporphyrin IX attached acid-functionalized multi-walled carbon nanotubes	H3N2	Binding and destroying viral envelope by photoactivated protoporphyrin IX [62]
	Negatively charged GO	Pseudorabies virus (PRV) and porcine epidemic diarrhea virus	Viral envelop damage due to its single-layer structure and sharp edge [63]
	TiO2 NPs	Influenza virus (H3N2)	Interacting with and destroying the viral envelop [64]
	Graphene oxide (GO) and GO conjugated Ag nanoparticles	Feline Coronavirus (FCoV)	Binding to viral lipid tails, leading to rupture of the envelop [65]
	AgNPs	HSV-1, 2 and HPIV-3	Interacting with and destroying the viral envelop [43]
	TiO2 NPs	MS2	Binding and destroying viral capsid protein through a photocatalytic effect [14,66]
	AgNP-MHCs	Murine norovirus, Adenovirus serotype 2 and Bacteriophage φX174	Binding and damaging thiol group-containing biomolecules embedded in the capsid proteins [68]
	AgNPs	Poliovirus	Interacting with and destroy the viral proteins, leading to damaging the structure of virus particles [69]
	Au/CuS core/shell NPs	Norovirus-Like Particles	Capsid protein degradation and capsid damage [70]

membrane-coated nanomaterials, which is beneficial for in vivo applications with an extended half-life [35]. Recently, cell membrane-coated nanodecoys for SARS-CoV-2 have been established by using plasma membranes derived from human lung epithelial type II cells or human macrophages to coat polymeric cores [36]. Displaying receptors similar to those required by SARS-CoV-2 for cellular entry, these nanodecoys neutralize SARS-CoV-2 and protect mice from infection [36].

2.2. Inhibition of viral entry by nanomaterials

The inhibitory effect of nanomaterials on cell entry by viruses and related mechanisms have been studied extensively. Viral entry usually requires the interaction between viral surface protein(s) and receptor(s) on host cell membranes; thus, nanomaterials that interfere with such interactions are promising antiviral agents.

Some nanomaterials interrupt virus–cell interactions by blocking viral surface proteins. The HIV envelope protein gp120, a glycoprotein

exposed on the surface of the HIV envelope that targets CD4$^+$ cells, is critical for the binding of HIV to CD4$^+$ T cells [37]. Two anti-HIV-1 nanomaterials, gold nanoparticles (AuNPs) encapsulated by poly-ethylene glycol and silicon nanoparticles (SiNPs) modified with -OH and -NH$_2$ groups, function by blocking gp120 on the HIV-1 surface [38,39]. Silver nanoparticles (AgNPs) are able to bind to multiple molecules and have broad-spectrum antiviral effects by inhibiting viral entry. For example, commercially available AgNPs show a strong effect against HIV-1 by interacting with viral gp120 in both cell-free and cell-attached viruses, thus impeding viral binding and entry [40]. AgNPs also hinder the attachment of Avian influenza A virus H7N3 to host cells by blocking influenza hemagglutinin, which plays a critical role in cell entry [41]. Moreover, AgNPs block the entry of herpes simplex virus (HSV)-1, HSV-2, and human parainfluenza virus (HPIV)-3 by interacting with the sulfhydryl group on viral glycoproteins [42,43]. In addition to nano-particles (NPs), dendritic polyglycerol sulfate-based nanogels that mimic the cellular membrane heparan sulfate can actively interact with viral glycoproteins, shield virus surfaces, and efficiently block HSV-1 infection [15].

Modifications to nanomaterials promote their ability to block viral surface proteins. AgNPs modified with TA have an increased affinity for viral glycoproteins and reduce HSV-2 infectivity by blocking viral attachment, penetration, and spread [44]. Similar inhibitory effects against HSV-1 and HSV-2 entry have been observed using SiNPs modified with glycosaminoglycans [45], which bind to the "repeat structure" of viral glycoproteins and amyloids [46]. Polyquaternary phosphonium oligochitosan (PQPOC)-decorated AgNPs can inhibit multiple human enteric viruses, including hepatitis A virus (HAV), norovirus (NoV), and Coxsackievirus B4 (CoxB4), via electrostatic interactions between the positively charged PQPOC brushes and negatively charged viral surface targets [47].

Additionally, nanomaterials may inhibit viral entry by blocking cell membrane receptors. For example, several carbon-based fullerenes inhibit the entry of pseudotyped viral particles by blocking the dendritic cell (DC)-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) on the cell membrane [48–50], which plays a critical role in the internalization of Ebola virus [51]. Carbon dots established from 2,2′-(ethylenedioxy)bis(ethylamine) and 3-ethoxypropylamine suppress the entry of human norovirus-like particles by interacting with the histoblood group antigens (HBGAs) of host cells, a norovirus receptor [52,53].

2.3. Inhibition of viral replication by nanomaterials

Nanomaterials can inhibit viral replication by interacting with the viral protein/genome or inducing a suppressive environment for intra-cellular viral replication. AuNPs arrest foot-and-mouth disease virus (FMDV) replication at the post-entry stage and block viral transcription in the host cell by binding to FMDV RNA, sub-genomic RNA, or viral replicative proteins via electrostatic interactions [54,55]. Moreover, several fullerene derivatives can affect the maturation of both wild-type HIV-1 and drug-resistant HIV-1 by inhibiting Gag polyprotein process-ing, which generates the matrix, capsid, nucleocapsid, and p6 gag pro-teins required for a functional virus, thereby hindering viral replication [56]. AgNPs also inhibit the replication of dsRNA viruses and Peste des petits ruminants virus (PPRV) by interacting with the viral genome or core proteins related to RNA synthesis [57,58].

In addition to direct contact with the viral protein/genome, nano-materials can also inhibit viral replication by producing an unfavorable intracellular environment for viral replication. Carbon dots established from PEG-diamine and ascorbic acid induce interferon-α (IFN-α) pro-duction and the expression of IFN-stimulating genes in host cells, resulting in powerful antiviral responses and the inhibition of the replication of pseudorabies virus (PRV) and porcine reproductive and respiratory syndrome virus (PRRS) [59]. As an organic nanomaterial, poly(aniline-*co*-pyrrole) polymerized nanoregulators (PASomes) control

intracellular reactive oxygen species (ROS) levels in vitro to inhibit viral replication and cell death [60]. Since certain viruses can hijack host cell pathways to cause the biphasic activation of the MEK/ERK cascade, which improves viral replication [61], investigations of the precise regulation of the intracellular response to viral infection are still war-ranted when designing antiviral agents.

2.4. Viral inactivation effects of nanomaterials

Nanomaterials, such as Ag, Ti, and carbon-based nanomaterials, directly contact viruses and induce viral inactivation by different mechanisms depending on the nanomaterial and virus. The destruction of the viral envelope by photocatalytic oxidation or physical damage is a common mechanism by which nanomaterials induce the inactivation of viruses with envelopes. A multi-walled carbon nanotube attached to photoactivating protoporphyrin IX interacts with and destabilizes the envelope of influenza virus H3N2 by ROS [62]. Another interesting viral inactivation effect was observed using negatively charged graphene oxide (GO), which interacts with the viral envelope by electrostatic in-teractions and damages the viral envelope via its sharp-edged single-layer structure [63]. There are also envelope-binding NPs that cause the destruction and disintegration of viruses by unknown mechanisms, including TiO$_2$ NPs on H$_3$N$_2$ [64]. Additionally, GO-conjugated AgNPs bind to the lipid tails of feline coronavirus (FCoV) and lead to envelop rupture [65].

Similar to the envelope-rupture effect, some nanomaterials inacti-vate viruses by destroying the viral capsid via photocatalytic oxidation and protein degradation. TiO$_2$ NPs interact with viral capsid proteins and inactivate viruses, such as influenza virus and MS2 bacteriophage, via photocatalytic oxidation in which catalytic inactivation is mediated by hydroxide radicals [14,66,67]. AgNP-MHCs (aminopropyl-function-alized Fe$_3$O$_4$-SiO$_2$ core-shell magnetic hybrid colloid-decorated AgNPs) bind to and degrade thiol group-containing viral capsid proteins, thus inactivating murine norovirus, adenovirus serotype 2, bacteriophage φX174, and poliovirus [68,69]. Moreover, by interacting with capsid proteins and inducing degradation via copper ions in NPs, an Au/CuS core-shell NP causes the inactivation of human norovirus-like particles [70].

3. Nano-based vaccines

Nano-based vaccines, or nanovaccines, are vaccines that use NPs as carriers. A variety of NPs could be used for nanovaccine construction, such as protein/peptide self-assembled virus-like particles (VLPs), inorganic-based NP-like AuNPs, and organic-based NPs, such as lipid nanoparticles (LNPs) (Table 2). Nanovaccines improve antigen bioavailability in vivo and influence the innate and adaptive immune responses, including the generation of memory cells, which are essential for the efficacy of a vaccine (Fig. 2) [71–75].

3.1. Nanoparticle properties related to the induction of the immunological response

Immunological benefits of nano-based vaccines result from a com-bination of the following properties: the ability to mimic viruses in terms of size and structure (pathogen-mimicking VLPs), the ability to deliver viral antigens to target immune cells, the ability to activate DCs, and the ability to efficiently activate B cells and induce humoral immune re-sponses (Fig. 3).

3.1.1. Pathogen mimicry and virus-like particles
VLPs are self-assembled noninfectious NPs that lack genetic mate-rials [76,77]. They could be formed by antigen peptides or self-assembled proteins, such as ferritin. Antigens on VLPs optimize the activation of specific immune responses, including humoral and cellular immunity [78]. With innate viral structures, VLP vaccines benefit from

their ability to interact with the immune system without causing infections and inducing an immune response without an adjuvant, which improves the immune response of vaccines [79,80].

VLPs are the most widely applied nanosystem for antiviral vaccines. Currently available HPV vaccines, such as Gardasil, Gardasil 9, and Cervarix, which effectively protect women from HPV infection, are all nano-based VLP vaccines [81]. A VLP vaccine against HEV, Hecolin, is also commercially available [82].

3.1.2. Loading and delivery of viral molecules

The targeted delivery of antigen peptides or proteins to specific tissues is a major advantage of nanovaccines [19,20,83]. Moreover, since unprotected peptide antigens are unstable in vivo, nanomaterials provide protection against enzymatic degradation [84–86]. Furthermore, NPs may improve antigen transport to the lymphatic system [87–89], since lymphatic gaps preferentially allow the passage of molecules between 20 and 200 nm [90]. For example, in a mouse intradermal injection study, ultra-small nanoparticles (25 nm) are efficiently transported into the lymphatic system and target a subset of lymph DCs [91].

3.1.3. Activation of dendritic cells

The presentation of exogenous antigens on MHC class I molecules by DCs, known as cross-presentation, is essential for the initiation of the CD8$^+$ T cell response [92]. Conventional antigen peptide-based vaccines are insufficient for cross-presentation, while nanovaccines can activate DCs by adequate cross-presentation [93,94]. In addition, nanovaccines have also been reported to enhance the MHC II pathway, which passes antigens to CD4$^+$ T cells, leading to improved B cell activation [95].

Pattern-recognition receptors (PRRs), such as Toll-like receptors, NOD-like receptors, and RIG-I-like receptors, are expressed on DCs and associated with the recognition of pathogen-associated molecular patterns, DC maturation, and the expression of type I IFN, an antiviral inflammatory cytokine [96–99]. Thus, PRR agonists have been used in nanovaccines as adjuvants, which bind to PRRs and upregulate related pathways, thus activating DCs and enhancing immune responses [100,101].

3.1.4. B cell activation and humoral response

Antibody titers are closely correlated with vaccine effectiveness. Nanovaccines have been shown to induce high antibody titers [102–105], probably due to their superiority in target delivery and DC activation as well as the capacity to carry large amounts of antigens [106]. Nanovaccines can be constructed to carry large quantities of peptides or protein antigens; this provides a high concentration of antigens for efficient B cell receptor (BCR) signaling, consequently improving the B cell response and antibody production (Fig. 3) [107]. For example, despite the relatively low immunogenicity of HIV-1 envelope (Env) trimer antigens, the enhanced induction of neutralizing antibodies against HIV-1 has been observed in animals immunized with nanovaccines loaded with these antigens [108].

3.2. Nanovaccine candidates

Nanotechnology is increasingly used for the development of antiviral vaccines. Since a nanovaccine against hepatitis B virus (HBV) was first licensed in 1986, this approach has been used to develop vaccines against HPV and HEV, which have achieved positive preclinical outcomes against viruses, such as HIV and respiratory viruses [19–21,109].

3.2.1. Coronaviruses

Vaccines for coronaviruses usually use viral surface spike proteins as antigens, which play a critical role in viral attachment to host cells. A VLP vaccine was produced by the co-recombination of SARS-CoV spike protein and the influenza M1 protein; the VLPs induced a strong immune response and had a protective effect in mice [110]. Another AuNP-based

Table 2
Nano-based vaccines.

Virus	Antigen	Nanovaccine	Outcome
HBV	HBsAg	VLPs	In clinical use [109]
HPV	Capsid L1 proteins	VLPs	In clinical use [81]
HEV	HEV p239 (aa 368–606)	VLPs	In clinical use [82]
SARS-CoV	Spike proteins	VLPs formed by SARS-CoV spike protein and influenza M1 protein	Induced strong immune response and protectd mice from death [110]
SARS-CoV	Spike proteins	AuNPs	Increased IgG response [111]
MERS-CoV	Spike proteins	Spike protein NPs	Stimulated significant titers of neutralizing antibody and Th2 immune response [112]
MERS-CoV	Spike proteins	Ferritin assembled VLPs	Stimulated CD4$^+$ T-cells and IFN−/ TNF-responses [113]
MERS-CoV	Spike proteins	Hollow polymeric NPs	Stimulated remarkable levels of humoral responses and IgG2a antibodies [114]
MERS-CoV	Spike proteins	Spike protein NPs with aluminum or Matrix M1 as adjuvant	Produced high titer anti-spike neutralizing antibody and protected mice from MERS-CoV infection in vivo [148,149]
SARS-CoV-2	mRNA encoding a full-length spike protein	Lipid nanoparticles (LNPs)	Passed phase I trial, induced high titer of neutralizing antibodies (NCT04283461); currently under phase III trial (NCT04470427)
SARS-CoV-2	mRNA encoding spike protein or its different fragments	LNPs	In clinical trials (NCT04368728; NCT04449276, ISRCTN1707269 and NCT04480957)
HIV	Envelope protein (Env) trimers	Env trimer of various HIV-1 strains self-assembled VLPs	Stimulated broadly neutralizing antibodies (bNAs) against diverse virus strains in rabbits [108]
HIV	Env gp120/ gp41	Env trimer self-assembled VLPs	Induced high titers of bNAs against diverse virus strains in rabbits [125,126]
HIV	HIV Env antigens	Polystyrene NPs	An increase in both bNAs and antibody-secreting cells in mice [127]
Influenza virus	Influenza whole virus	Mucoadhesive carrier chitosan	Successful nasal mucosa immunization in rabbits, significant levels of anti-hemagglutinin antibody, local anti-influenza-virus IgA, systemic IL-2, and IFN-γ were detected in the serum [131]
Influenza virus	Killed swine influenza virus antigens	Cationic alpha-D-glucan nanoparticles with TLR3 agonist poly(I:C) as adjuvant	Induced high levels of virus neutralizing antibodies in bronchoalveolar lavage fluid and cross-reactive virus-specific secretory IgA

(continued on next page)

Table 2 (*continued*)

Virus	Antigen	Nanovaccine	Outcome
			antibodies in the nasal passage and lungs [132]
H9N2	Formalin-inactivated H9N2 virus	Poly(lactic-co-glycolic acid) (PLGA)	Generating a significantly stronger antibody response in chickens, as indicated by the HI titer, than non-encapsulated forms [133]
Influenza virus	Influenza split vaccine	VLPs	Shaped cellular immune responses toward T helper type 1 responses increasing IgG2a isotype antibodies as well as IFN-γ producing cells in mucosal and systemic sites of mice [150]
Foot-and-mouth virus (FMDV)	FMDV VP1 protein	Calcium mineralized FMDV VP1 VLPs	Improved thermal stability and extend the storage time of the vaccine, accompanied with effectively activating DCs to express high levels of surface MHC-II, costimulatory molecules, and proinflammatory cytokines, leading to enhanced immune response [95]
FMDV	VP1 protein	Polyelectrolyte complexation of chitosan and heparin with tumor necrosis factor α (TNF) or CpG as adjuvants	Induced strong immune activation toward antibody production, elicited strong IgA titers, and conferred effective protection against lethal virus challenge in mice comparable to the traditional vaccine [135]
FMDV	FMDV capsid proteins VP0, VP1, and VP3	Hollow mesoporous silica nanoparticles (HMSNs) loaded the (FMDV) VLPs	Induced persistent humoral immunity with high-level antibody titer for more than three months, accompanied with improved T-lymphocyte proliferation and IFN-γ, and the ideal protection against FMDV challenge in guinea pigs [136]
Dengue virus (DENV)	Dengue EDIII antigens	Bacterial membrane vesicles	Evoking dengue-specific humoral immune responses and confering effective protection against DENV-2 infection in mice [137]
DENV	DENV-2 E protein	PLGA NP	Increased the anti-E IgG titer and improved the neutralizing capacity of the antibodies in mice, compared to free E protein [138]
DENV	UV-inactivated DENV-2	Chitosan with Mycobacterium bovis Bacillus Calmette-Guerin cell	Vaccinated mice exhibited upregulated expression of IFN-γ, IL-2, IL-5, IL-12p40,

Table 2 (*continued*)

Virus	Antigen	Nanovaccine	Outcome
		wall components as an adjuvant	IL-12p70, and IL-17, an increased frequency of CD4+ and IFN+ T cells, and higher levels of IgG antibodies [139,140]
DENV	DENV-3 E protein	Chitosan NP	Taken up more efficiently by nasal epithelial cells than free E protein and resulted in increased secretion of IL-1β, IL-6, and TNF-α [141]
West Nile virus (WNV)	Domain III of the envelope glycoprotein	VLPs	Inducing high titers of virus-neutralizing antibodies, and completely protecting mice from WNV infection [142]
Hepatitis C virus (HCV)	E2 subunit of the envelope glycoprotein	Lipid-based nanovaccines	Eliciting 6- to 20-fold higher E2-specific serum IgG titers in mice, compared to soluble antigens [143]
Respiratory syncytial virus (RSV)	RSV F protein	VLPs	Passed phase III clinical trials (NCT02624947)

vaccine increased the IgG response from B cells by stimulating macrophages, DCs, and lymphocytes, resulting in the induction of proinflammatory cytokine production [111].

Positive results have also been achieved in the development of NP-based vaccines for MERS-CoV. A ferritin fusion protein with a viral antigen receptor-binding domain can self-assemble into VLPs, which stimulate CD4+ T cells and IFN/TNF responses. Loaded with a STING (stimulator of interferon genes) agonist as an adjuvant to increase DC activation, hollow polymeric NPs were able to stimulate remarkable humoral responses and IgG2a production. Another nanovaccine formed by the full-length spike protein of MERS-CoV also stimulated significant titers of neutralizing antibodies [112–114].

In terms of SARS-CoV-2, mRNA-based nanovaccines have been developed using LNPs as carriers to protect mRNAs from degradation by extracellular RNases and to efficiently deliver mRNAs to immune cells and thereby trigger the translation of antigen proteins [115–118]. Moreover, the sustained release of mRNAs from LNPs leads to continuous protein translation, stimulating the production of high antibody titers and enhanced B cell and T cell immune responses [119]. There are currently five LNP-encapsulated mRNA vaccines under clinical trials (NCT04470427, NCT04368728, NCT04449276, ISRCTN1707269, and NCT04480957) using mRNAs encoding the full-length spike protein of SARS-CoV-2 or spike protein fragments as antigens. One of these mRNA-based LNP vaccines was reported to induce a strong immune response in participants, resulting in the production of high titers of neutralizing antibodies against SARS-CoV-2 [22], and is now under a phase III trial (NCT04470427) [120].

3.2.2. HIV

HIV is an RNA virus; owing to its high mutation frequency, it is challenging to develop a successful vaccine capable of inducing antibodies against diverse strains [121–124]. A vaccine assembled from HIV Env trimers from various HIV-1 strains stimulated a broad spectrum of neutralizing antibodies (bNAs) against diverse virus strains [108]. Another Env gp120/gp41 trimer-assembled VLP had similar effects [125,126]. In mice immunized with HIV Env-based polystyrene NPs, which enhance the activation of CD4+ cells and lead to improved B cell responses, increases in both bNAs and antibody-secreting cells were found [127].
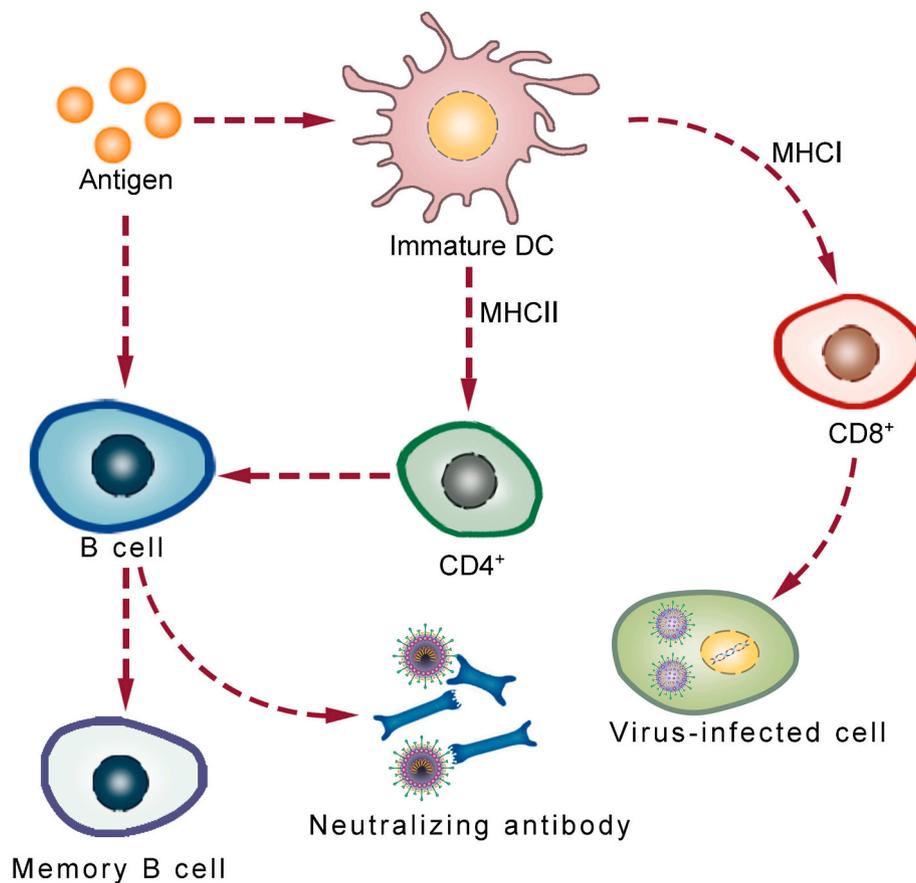
Fig. 2. Schematic representation of the key steps of immune responses induced by nanovaccines. B cell activation is facilitated by directly attached antigens or CD4$^+$ cell-passed antigens that come from DC cells. B cell activation leads to the production of antibodies that neutralize antigens. Moreover, DC cells pass the antigen to CD8$^+$ cells, which activates of CD8+ cells to kill infected cells.
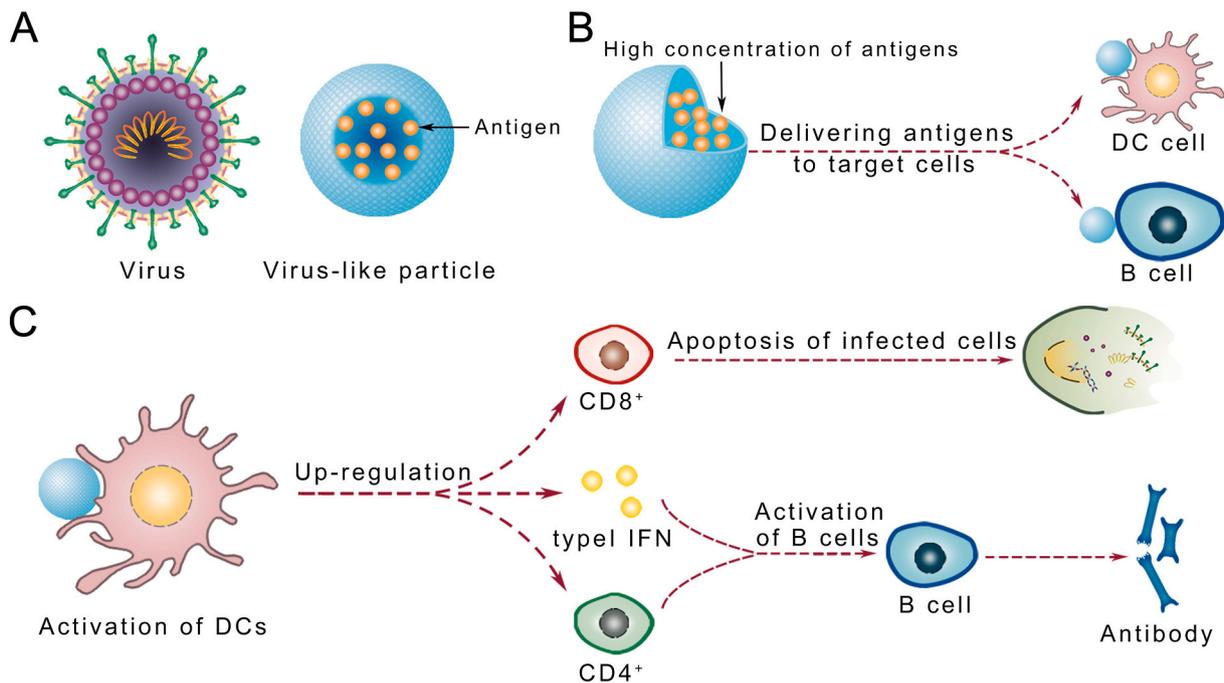
Fig. 3. Schematic representation of the advantages of nano-base vaccines. (A) Model of virus-like particle (VLPs). (B) Nano-based vaccines load a high concentration of antigens and deliver them to targeted immune cells; (C) Nano-based vaccines activate dendritic cells and B cells.

3.2.3. Influenza virus

A conventional method to protect against influenza virus is vaccination with a trivalent inactivated influenza vaccine (TIV), including two influenza A viruses and one influenza B virus [128]. However, the available TIV formulation is insufficient for mucosal protection, since TIV is not able to induce sufficient IgA, which is distributed on and protects the mucous membranes of the lungs, sinuses, stomach, and intestines [129,130]. Nanovaccines have been developed to induce mucosal protection from influenza virus. Successful nasal immunization was achieved in rabbits immunized with whole influenza virus incorporated into a mucoadhesive carrier chitosan; significant levels of anti-hemagglutinin antibody, local anti-influenza virus IgA, systemic IL-2, and IFN-γ were detected in the serum [131]. Another successful nanovaccine was established by adsorbing both inactivated swine influenza virus antigens and TLR3 agonist poly(I:C) onto cationic alpha-D-glucan NPs [132]. The poly(I:C) adjuvant promoted cytokine production; thus, the nanovaccine induced high levels of virus-neutralizing antibodies in bronchoalveolar lavage fluid and IgA antibodies in the nasal passage and lungs of immunized pigs [132]. Beneficial effects of mucosal immunization with NPs were also observed in chickens immunized via the aerosol route. In this study, poly(lactic-*co*-glycolic acid) (PLGA) loaded with formalin-inactivated H9N2 virus and CpG generated a significantly stronger antibody response than that generated by non-encapsulated antigens [133].

3.2.4. FMDV

Foot-and-mouth disease (FMD) caused by FMDV, a picornavirus, and the prototypic member of the genus *Aphthovirus*, is a serious health threat, especially in children [134]. Traditional vaccines against FMDV require multiple injections to confer sufficient immunity. The use of calcium mineralization to fabricate FMDV VLPs is a simple improvement. Such bio-mineralization improves the thermal stability and storage time of the vaccine and effectively activates DCs to express high levels of surface MHC-II, costimulatory molecules, and proinflammatory cytokines, leading to enhanced immune responses [95]. Another vaccine combines the polyelectrolyte complexation of chitosan and heparin to co-encapsulate the VP1 protein antigen from enterovirus 71, which causes FMD, with TNFα or CpG as adjuvants [135]. This nanovaccine induced strong immune activation toward antibody production and conferred effective protection against a lethal virus challenge in mice. Moreover, it elicited strong IgA titers, which may provide unique advantages for mucosal protection [135]. Another FMDV VLP loaded in a hollow mesoporous silica nanoparticle (HMSN) induced persistent humoral immunity with high antibody titers for longer than 3 months in guinea pigs, accompanied by improved T cell proliferation and IFN-γ production [136].

3.2.5. Dengue virus

The applications of a major Dengue virus (DENV) immunogen, the E protein, in NPs has produced promising results in mouse models. Engineered bacterial membrane vesicles carrying dengue EDIII antigens effectively evoke humoral immune responses and confer effective protection against DENV-2 infection in mice [137]. Compared with antigens for free DENV-2 E protein, the combination of PLGA NP with E protein increased the anti-E IgG titer and improved neutralizing antibodies in mice [138]. Another NP vaccine composed of chitosan with UV-inactivated DENV-2 induced high IgG levels in mice [139,140]. An NP nasal vaccine based on chitosan has been tested for the delivery of DENV-3 E protein; it was taken up efficiently by nasal epithelial cells, resulting in increased IL-1β, IL-6, and TNF-α secretion [141].

3.2.6. Hepatitis C virus, respiratory syncytial virus, and West Nile virus

Nano-based vaccines have also been developed against other viruses, such as hepatitis C virus (HCV), respiratory syncytial virus (RSV), and West Nile virus (WNV). HCV and WNV nanovaccines have successfully stimulated the immune system to produce antibodies and protect animal models from viral infection in preclinical tests [142,143]. Vaccines against RSV have been successful in clinical trials (NCT02624947).

4. Conclusions and outlook

Pandemics and epidemics caused by newly emerged viruses, such as SARS-CoV-2, have revealed the urgent need to develop antiviral agents that function by novel mechanisms and various routes to combat viruses. Nanotechnology has a tremendous opportunity to improve the prevention and treatment of viral diseases for several reasons. First, nanomaterials can be flexibly functionalized with multiple molecules to realize sophisticated antiviral designs. Second, nanomaterials inhibit virus infection from multiple directions based on various antiviral effects (Fig. 1B). Third, nanomaterials have broad-spectrum antiviral properties due to common underlying mechanisms. For example, nanodecoys trap diverse viruses prone to attachment to cell membrane-derived or -coated structures [28].

Nanomaterials have many advantages for the development of antiviral drugs. Compared with antibodies, nanomaterials are relatively easy to produce and thus more affordable. Moreover, rational design could be introduced to improve clinical effects [144,145]. Nanomaterials could also be designed to target viral factors, such as antibodies. For example, AuNPs and AgNPs could be designed to target gp120 in HIV and hemagglutinin in influenza virus, respectively [38,41]. Moreover, the combined use of nanomaterials with other antiviral drugs may resulted in enhanced antiviral effects. For example, carbon dots can be used to induce IFN-α production and IFN-stimulating gene expression in host cells, which may increase the inhibitory effects of synthetic agents, such as nucleosides, on viral replication [59].

Vaccination is an efficient intervention to protect against viral infection. Nano-based vaccines have many clinical advantages over conventional vaccines, including their ability to transport high concentrations of antigens to B cells and to induce abundant immune responses (Fig. 3). Although many nano-based vaccines remain in preclinical stages, progress in the application of nanotechnology to vaccines against viruses, such as coronaviruses, HIV, and FMDV, suggests that this approach is promising for the development of vaccines.

Finally, although they have various advantages over other approaches, the safety of antiviral nanomaterials needs to be carefully evaluated before the clinical translation of novel nanotechnologies. Given the lack of knowledge about the risks of exposure to nanomaterials in humans, in-depth studies of nanotoxicity, especially under long-term observation, are needed [146]. Further investigations of the distribution, accumulation, and clearance of nanomaterials in the human body are also warranted. Fortunately, nano-based anti-cancer candidates are already undergoing clinical trials (www.cancer.gov/nano/cancer-nanotechnology) [147], which will provide insight into their safety in humans and extend their use as antiviral agents and vaccines.

List of chemical compounds

polyethylene glycol; polyglycerol sulfate; heparan sulfate; tannic acid; glycosaminoglycans; poly(aniline-*co*-pyrrole); protoporphyrin IX; ascorbic acid; 2,2′-(ethylenedioxy)bis(ethylamine); 3-ethoxypropylamine.

Declaration of competing interest

There are no conflicts to declare.

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