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Revolutionizing polymer-based nanoparticle-linked vaccines for targeting respiratory viruses: A perspective

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ABSTRACT

Viral respiratory tract infections have significantly impacted global health as well as socio-economic growth. Respiratory viruses such as the influenza virus, respiratory syncytial virus (RSV), and the recent SARS-CoV-2 infection (COVID-19) typically infect the upper respiratory tract by entry through the respiratory mucosa before reaching the lower respiratory tract, resulting in respiratory disease. Generally, vaccination is the primary method in preventing virus pathogenicity and it has been shown to remarkably reduce the burden of various infectious diseases. Nevertheless, the efficacy of conventional vaccines may be hindered by certain limitations, prompting the need to develop novel vaccine delivery vehicles to immunize against various strains of respiratory viruses and to mitigate the risk of a pandemic. In this review, we provide an insight into how polymer-based nanoparticles can be integrated with the development of vaccines to effectively enhance immune responses for combating viral respiratory tract infections.

1. Background

Respiratory tract infections are among the leading cause of diseases that place a heavy burden on global public health. It has been reported that lower respiratory tract infections (LRTI) and pneumonia have accounted for more than four million deaths annually, killing more people than human immunodeficiency virus (HIV), malaria, and tuberculosis combined, whereby more than 80% of these infections are caused by respiratory viruses [1–3]. Although severe morbidity and mortality associated with respiratory viruses are primarily observed in children, the elderly, those who are immunocompromised, nevertheless healthy adults can be affected as well, especially those in low to middle-income countries [4]. Respiratory viruses such as influenza virus, human parainfluenza virus (HPIV), respiratory syncytial virus (RSV), adenovirus, and coronavirus are generally spread airborne in the form of small droplets or aerosols. These pathogens enter the host via inhalation

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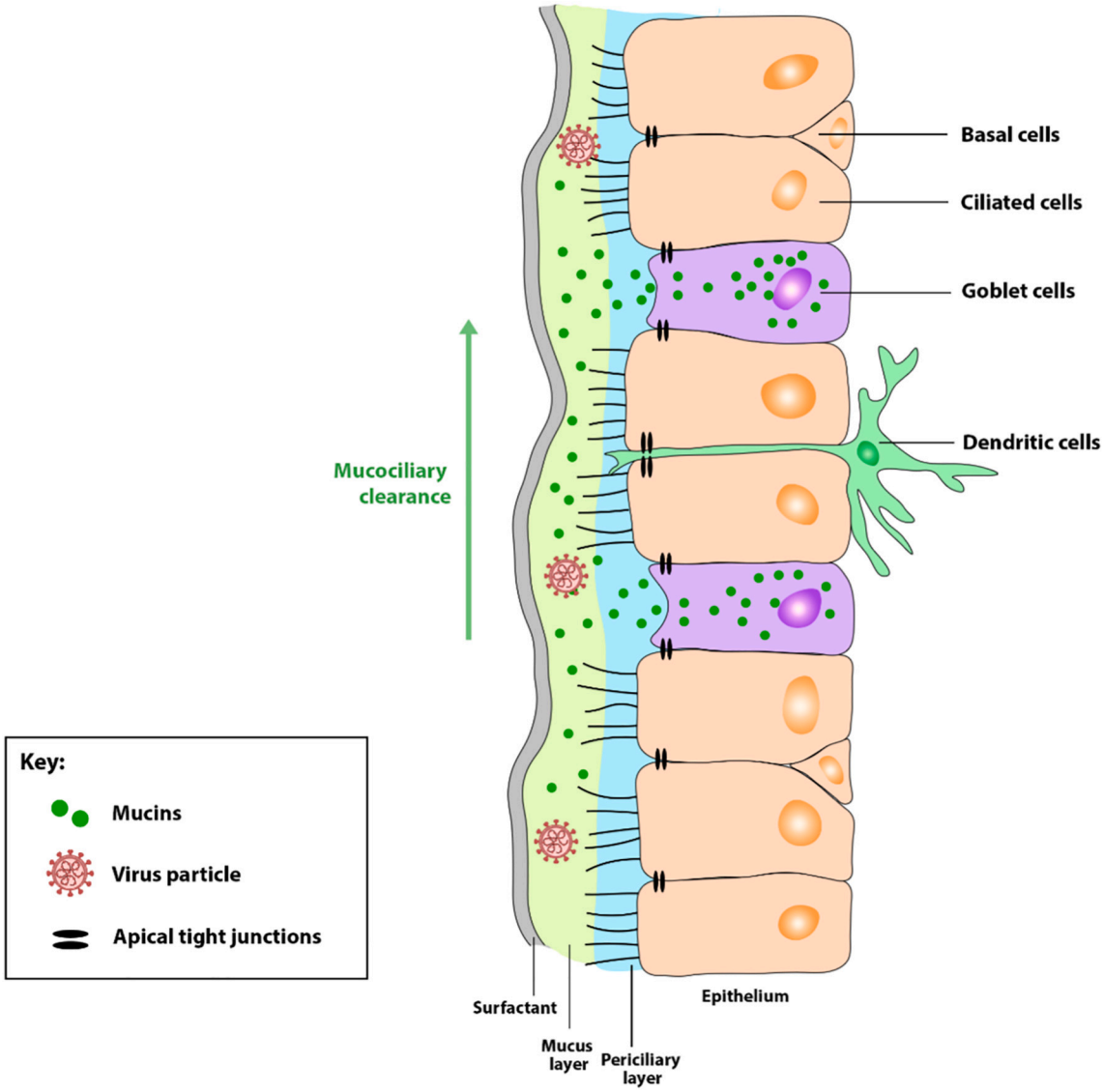

Fig. 1. Mucociliary clearance as the first-line defence mechanism of human respiratory system in the upper respiratory airways.

or surface contact and replicate in the human respiratory tracts, leading to clinical manifestations ranging from mild cold-like symptoms to fever, and further destruction of respiratory cells and tissues resulting in bronchiolitis and severe pneumonia that could be fatal [5,6]. Moreover, the recent global outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19) has proven the potential for zoonotic transmission respiratory viruses, leaving no doubt that effective management strategies are necessary to prevent widespread distribution of these pathogens, as an uncontrolled outbreak could lead to significant socioeconomic loss associated with increased costs of medical care [3,5,7,8].

Currently, vaccination remains as the most cost-effective strategy to combat against respiratory infections. Conventional vaccines typically contain live-attenuated viruses, inactivated or dead viruses, or segments of the virus that could trigger a specific immune response in the human body [9]. While vaccines have been proven useful in tackling viral respiratory infections, there are several drawbacks associated with their application. For instance, live-attenuated vaccines posed safety concerns especially in elderly and immunocompromised individuals due to the nature of the vaccines; whereas virus subunit vaccines and killed pathogen vaccines may induce much weaker immune responses and require an adjuvant to enhance their efficacy [10,11]. Additionally, allergic and hypersensitivity reactions may be triggered by the components of these vaccines, for instance, egg protein [12]. The lack of suitable delivery platform for vaccine antigens to reach targeted site for exerting their intended actions has further hindered the clinical efficacy of conventional vaccines [13,14]. As a result of these challenges, there are no effective vaccines to-date for some of the viral respiratory infections, for instance, RSV and HPIV infections [15]. Hence, modern technologies are explored to overcome these challenges in order to address the increasing concerns regarding global outbreaks of viral respiratory infections. In this article, the novel approach of integrating nanoparticles with the development of respiratory virus vaccines will be discussed, justified by some of the most recent studies performed in the field. Specific focus will be given to polymer-based nanoparticles due to their unique and excellent bio-physicochemical properties, and consequent high potential as vaccine delivery vehicles.

2. Respiratory viruses

Respiratory viruses are viruses that specifically infect the upper or lower respiratory tracts, or both. Examples of respiratory viruses that mainly affect the upper respiratory airways are adenovirus, rhinovirus, and influenza, whereas RSV, HPIV, and coronavirus mainly compromise

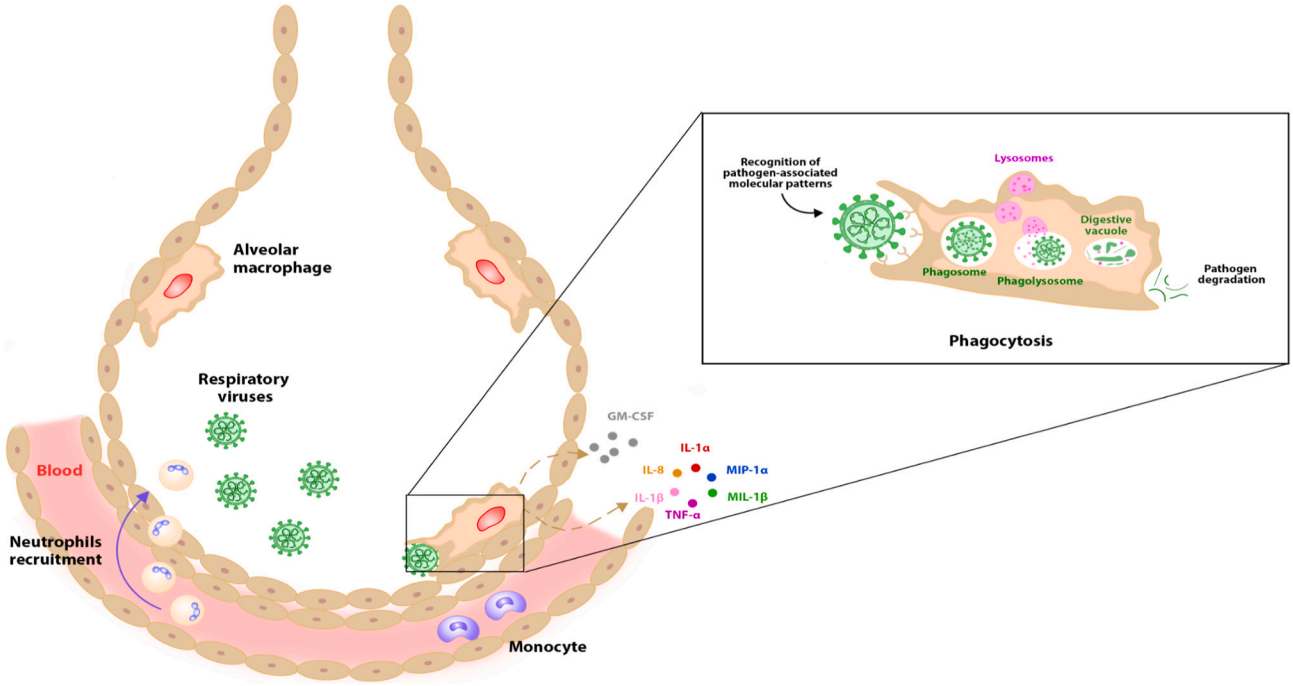

Fig. 2. Alveolar macrophages as the second-line defence of human respiratory system in the alveolar space.

the lower respiratory airways [16]. The human respiratory tract is constantly exposed to various infectious pathogens over a lifetime, but they may not contribute to the development of diseases due to the presence of physical and chemical barriers. However, in certain cases where the pathogens managed to circumvent these defence barriers, a biological competition may be triggered between the early host defences and determinants of viral pathogenicity [17–19]. If these viruses can overcome the first line of defence, the second line of defence involving highly specialized and specific immune response will be activated, at the same time, an immunological memory will be generated, which enables the immune system to respond quickly and effectively upon next contact with the same pathogen [17]. However, if the pathogen managed to circumvent both lines of defence, it will result in a wide range of viral respiratory infections ranging from common cold to life-threatening pneumonia that requires immediate medical intervention [17,20].

2.1. The lung defence mechanisms

Mucociliary clearance is the primary defence mechanism of the upper respiratory airway against inhaled pathogens (Fig. 1) [21]. The upper respiratory tract surface is protected by a blanket of mucus produced by goblet cells, which functions to entrap foreign particulate matter such as dust and pathogens from the external environment. Mucins, such as MUC5AC and MUC5B, are the major components forming the structural framework of mucus barrier by glycoprotein cross-linkages, in which they contribute to the innate immune system via interaction with other components of mucus including IgA, defensins, and collectins [21,22]. The secretion of mucins can be further induced by respiratory viruses, whereby they stimulate the production of mucus for improved efficacy in trapping and clearance of respiratory viruses. In addition, the mucus layer is also kept in continuous flow by the coordinated beating of cilia on ciliated cells, which accounted for approximately 50% of the cell population lining the upper respiratory tract. These are collectively known as the mucociliary escalator [22–24]. Moreover, ciliated cells are also covered by a less viscous periciliary layer, in which along with the thick and viscoelastic mucus blanket, they offer an ideal condition facilitating effective ciliary beating cycle to propel foreign particulate matter from the airways to the oropharynx and are eventually expelled by swallowing or coughing [23,25,26]. Nevertheless, dysregulation and excessive secretion of mucins is a distinctive feature of many chronic respiratory diseases, such as asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis [27].

Due to the requirement for rapid gaseous exchange, the alveoli are not protected by mucociliary escalator as the presence of thick mucus may hinder the diffusion of gases across alveolar membrane. Alveolar macrophages are the most abundant phagocytes in the lower respiratory regions, which function to patrol the alveolar space and clear any foreign particulate matter, including pathogens, that may have evaded the mucociliary escalator in the upper respiratory airways [28–30]. Their primary roles are to neutralize invading pathogens and to recruit neutrophils and other mononuclear cells into the alveolar space (Fig. 2). Phagocytosis is the mechanism involved in the ingestion of pathogens by alveolar macrophages, whereby cytoskeletal rearrangements drive rapid internalization of pathogens in a membrane-bound phagosome. Upon subsequent fusions with endosomes and lysosomes that contain hydrolytic enzymes and reactive oxygen species, the phagosome becomes acidified which facilitates digestion and break down of pathogen [28,31]. The phagocytotic process is mainly initiated through direct recognition of pathogen-associated molecular patterns displayed on the surface of pathogens by phagocytotic receptors. Alveolar macrophages are generally equipped with a wide range of phagocytic receptors, in which some of them can recognize specific molecules expressed on pathogens, such as inflammasome molecules, whereas some receptors bind favourably to phagocytic targets with opsonins coating, such as immunoglobulins (IgG), complement fragments (C3b, C3bi), and surfactant materials. Examples of phagocytic receptors include Fc receptors, which directly promotes pathogen engulfment, as well as Toll-like receptors, which indirectly induce phagocytosis via upregulation of phagocytic receptors and downstream signalling molecules [28,31–33]. In addition to phagocytosis, alveolar macrophages can induce innate immune responses via the production of cytokines and chemokines, such as interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor (TNF)-α, which synergistically interact with other cellular components of the alveolar space to recruit inflammatory neutrophils, monocytes, as well as adaptive immune cells [28,29,31,32]. Apoptotic polymorphonuclear leukocytes (PMN) are also phagocytosed by alveolar macrophages, as

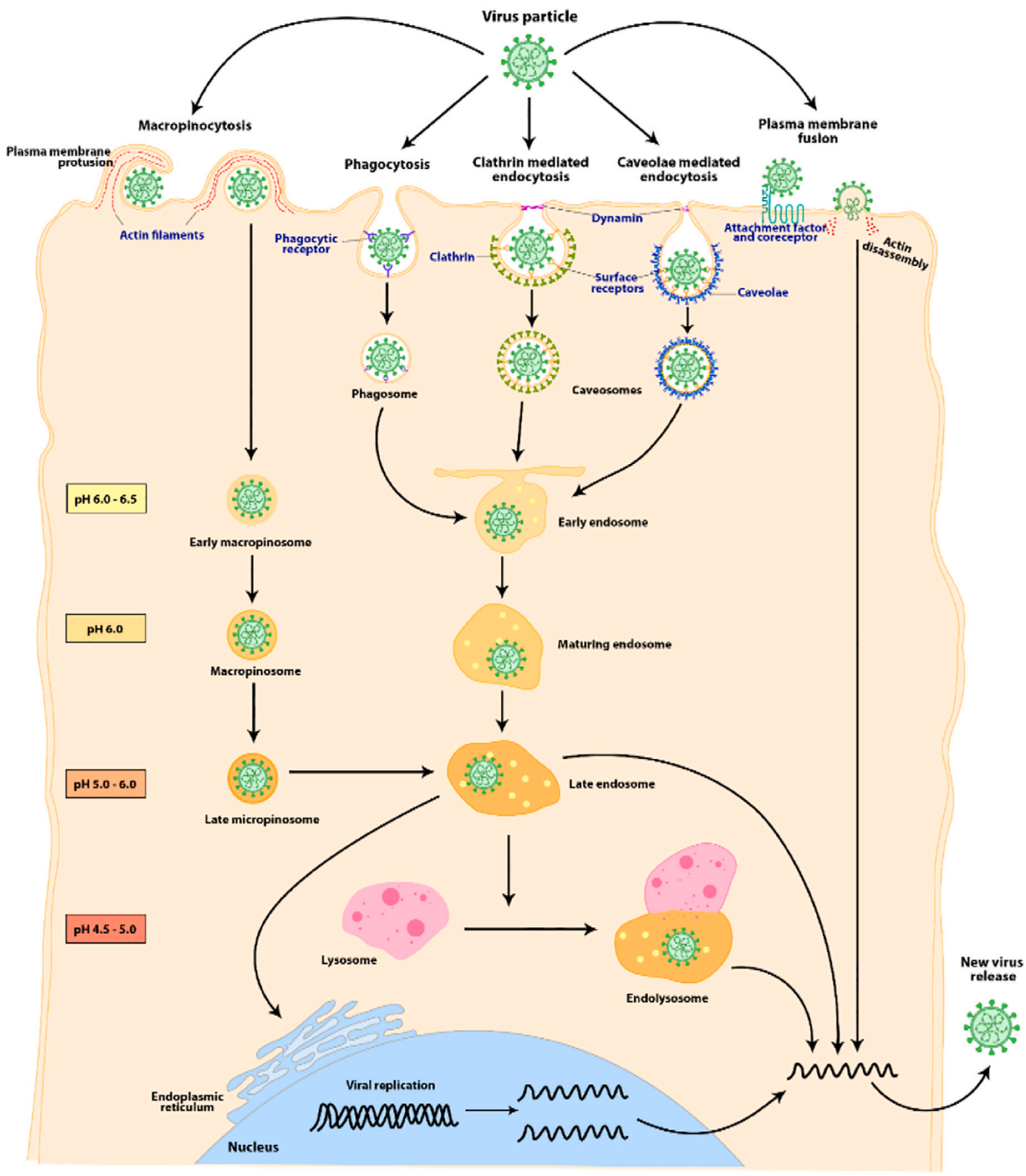

Fig. 3. Various pathways of virus internalization into host cell.

sustained and uncontrolled leakage of intracellular enzymes from the apoptotic PMNs to surrounding tissues can lead to prolonged inflammation and subsequent lung tissue damage [32].

2.2. Virus entry pathways

To successfully establish infection and replicate, viruses must first gain access into the intracellular environment whereby the first physical barrier that viruses must overcome is the host cell plasma membrane (Fig. 3). The first encounter between viruses and host cell mostly takes place via oligosaccharides, proteoglycans, proteins, or glycolipids that are exposed on the cell surface, which can be recognized by cognate viral surface components. Some viruses can enter cells via direct cell-to-cell contacts by utilizing virological synapse, which are structures formed by viral proteins, adhesion molecules, as well as polarized cytoskeleton at the infected cell junction [34,35]. Typically, successful internalization of viral components will lead to alteration of cellular environmental factors including pH and activity of proteolytic enzymes, which eventually result in conformational change of specific proteins responsible for host immune responses [35,36]. There are two main routes of virus internalization, namely the endocytic and non-endocytic routes. Endocytic route refers to transport of viruses via formation of pits or vesicles, whereas non-endocytic route refers to direct transport of viruses across the plasma membrane at neutral pH [36–38]. The choice of entry mechanism is greatly dependent on the type of virus and the cellular receptors that it displays. Its external topology, such as the presence of glycoproteins and/or surface protrusions, can also influence its entry mechanism [39,40]. Nevertheless, it has been found that the entry

mechanisms of viruses are more variable and flexible as compared to the results observed in standard tissue culture cell lines. In fact, viruses can utilize alternative receptors or entry pathways depending on the type of host cell and the strain of virus. For example, the mechanism of entry into non-polarized cells (e.g., fibroblasts, T cells) may differ from the entry mechanism into highly polarized cells (e.g., endothelial cells, neurons), for the same virus [41].

For the non-endocytic route, fusion of the virion with cell plasma membrane is promoted by viral proteins, leading to the formation of a pore. Once the virion becomes uncoated, its genomic cargo will then be delivered into the cytoplasm. This process mainly involves fusogens that can be classified into three different classes, namely, class I fusogens made up of α-helical coils, class II fusogens made up of β-sheets, or class III fusogens made up of both structural types [36,40]. However, most viruses take advantage of multiple endocytic mechanisms over direct fusion with the plasma membrane for entry into host cell as they offer several advantages. Namely, endocytosis allows viruses to bypass the obstacles constituted by plasma membrane and cytoplasmic crowding, as well as the microfilaments meshwork in the actin cortex [39,42]. Upon internalization, viruses will be delivered to endosomal compartments and are transported via actin filaments and microtubules to the subcellular sites for their replication [43,44]. Besides, endocytosis can help viruses to overcome host immune surveillance as there will be minimal evidence left on the cell surface. The changing intracellular pH conditions during the maturation of endocytic vacuoles can also be exploited by viruses to mediate penetration [39,42]. Although the endocytic route is conceptually simple, it is a complex and multistep process, where viruses must overcome several challenges prior to successful hijacking of the host endocytic machinery [36,41]. Viruses must first attach to the cell surface, facilitated by attachment factors that are usually small, charged lipids, proteins, and sugar moieties, which help concentrate virus particles on cell surface via non-specific binding. Some examples of attachment factors include sialic acid, heparin sulfate, and gangliosides. Next, virus particles interact with specific virus receptors to activate cellular signalling pathways and initiate the endocytic process [36,37,40]. Lysosome is a key component of the endocytic route, known as the endolysosomal network. Upon endocytosis, internalized cargos enter the early endosomes in which the cargos can either be recycled to the plasma membrane, or they can be delivered to the late endosomes and fuse with lysosomes for degradation [45]. Throughout the endocytic route, capsids can escape from several locations to penetrate the cytosol, including the early endosomes, late endosomes, lysosomes, macropinosomes, or the endoplasmic reticulum, followed by uncoating of the capsids in the cytosol for viral replication. Some viruses can also move towards the nucleus to deliver their cargo for replication in the nucleus [39,41].

Endocytic route of virus entry can be further divided into several different pathways. These pathways are distinctive in terms of the type of vesicles and particles involved, as well as the molecules that are required for the process [38,40,42,46,47]: (i) Clathrin-mediated endocytosis is the most common endocytic pathway employed by viruses. It is a process where virus is internalized using a clathrin-rich vesicle, which is then delivered into the cytosol via endosomes. This process requires clathrin and cholesterol, and dynamin is required for excision of the pit; (ii) Phagocytosis, also known as cell eating, is facilitated by phagocytic receptors and the formation of large extracellular projections, resulting in internalization of viruses into phagosomes. This process is regulated by actin and RhoA, and it preferentially ingest virus particles larger than 760 nm; (iii) Macropinocytosis is a non-specific process where interactions between cell surface receptors and viral proteins activate intracellular signalling and actin rearrangements. These lead to the formation of filopodia or projection which closes to form macropinosome that carries virus into the cytosol. This pathway is regulated by actin, PI3K, Rho GTPases, and Na^+/H^+ exchange; (iv) Caveolae-mediated endocytosis is a process similar to clathrin-mediated endocytosis, but it involves vesicles containing caveolin instead of clathrin. Caveosomes are responsible for delivering internalized virus to the cytosol in this pathway.

2.3. Management of respiratory viruses

To-date, viral respiratory infections remain as one of the most common reason for medical consultations around the world, and they are known to bring considerable impact on patients' quality of life, productivity, and socioeconomic balance. Therefore, effective control and prevention of viral respiratory infections is crucial for reducing transmission of the viruses, as well as to reduce morbidity and mortality associated with these infections. Although antiviral drugs may be useful in managing viral infections, their development may be hindered by limited understanding on the precise mechanism of how viruses infect and damage cells, as viruses rely on biochemical machinery of host cell to replicate [48]. Antiviral resistance is another possible cause of concern, attributed to errors in base selection during genome replication and mutations [49]. On the other hand, although protective immunity may be generated during a natural infection, such immune responses against respiratory viruses may not be sufficient to provide complete immunity from reinfection, at the same time, they may instead contribute to the pathogenesis of the disease [50]. Thus, vaccination has been presented as the most feasible and cost-effective method in controlling and preventing respiratory viruses, as they are developed to induce immune responses to the pathogen which are more protective and less pathogenic as compared to those of naturally-induced [50–52]. Vaccine antigens, which can be of whole attenuated or inactivated virus, or protein subunits of virus, are taken up by macrophages upon administration, which are then presented to helper T lymphocytes, leading to orchestrated immune responses. As a result, the host immune system is primed in a way that future encounter with wild-type viruses leads to rapid recognition and subsequent elimination from the host [48]. In the following sections, we provide a brief overview to some of the common respiratory viruses and their current management strategies.

2.3.1. Respiratory syncytial virus (RSV)

Human RSV is a single-stranded, enveloped, negative sense RNA virus from the *Pneumoviridae* family. This taxon was formerly a subfamily within *Paramyoviridae* but it has since been reclassified in 2016 as a family consisting of two genera, namely *Orthopneumovirus* and *Metapneumovirus* [53]. The major characteristics of RSV are the number and order of genes, as well as lack of hemagglutinin and neuraminidase activities [54]. Bronchiolitis is the most common clinical manifestation attributed to RSV infection. Besides, RSV is one of the most frequent pathogens that resulted in children's respiratory infections, and it is also the third significant cause of deadly pneumonia in children after *Haemophilus influenza* and *Streptococcus pneumonia* [54,55]. After inoculating the nasopharyngeal or conjunctival mucosa, RSV spreads rapidly through the respiratory airways to terminal bronchioles, preferentially targeting the apical ciliated epithelial cells. Via the RSV-G glycoprotein, RSV binds to cellular receptors and fuses with the host cell membranes through the RSV-F fusion glycoprotein. Its intracellular replication then begins upon insertion of its nucleocapsid into the host cell [56]. This further leads to activation of humoral and host cytotoxic T-cell, in which when combined with viral cytotoxicity, it results in necrosis of respiratory epithelial cells. Initial influx of polymorphonuclear neutrophils into the airways is quickly substituted by primarily lymphomononuclear peribronchiolar tissues infiltration, thereby increasing microvascular permeability resulting in submucosal edema. Moreover, the accumulation of mucus layer and its increased viscosity contributed to widespread mucus plugging, attributed to the loss of ciliated epithelium [56,57]. Overall, this cluster of acute inflammatory responses due to the exponential replication of RSV led to air trapping and airway obstruction, giving rise to the classic clinical triad represented by bilateral hyperinflation, patchy atelectasis, and polyphonic wheezing [57].

Management of RSV infection mainly focuses on supportive care to provide relief from the clinical symptoms. Despite many studies and considerable work conducted in this area, there are currently no approved vaccines available for immunization against RSV [56]. Therefore, development of vaccines for managing RSV remained as the target of great scientific interest over these years. Several agents have been utilized for managing RSV infection. For instance, ribavirin is a nucleoside analogue that has been licensed for management of severe RSV infection in high-risk infants, which acts by suppressing viral replication through inhibition of viral polymerase, mRNA 5' cap formation, as well as IMP dehydrogenase [56,58,59]. Nevertheless, the drug can only reduce the duration of assisted respiratory ventilation without any effects on mortality and pulmonary functions [58]. Another example is palivizumab, which is a monoclonal antibody used to target the RSV fusion glycoprotein. It is mainly utilized as passive immune prophylaxis to prevent serious lower respiratory tract infection associated with RSV [56,58,59].

2.3.2. Human adenovirus (HAdVs)

HAdVs represent a common cause of viral respiratory infections in individuals of all age groups. They are non-enveloped, double-stranded DNA viruses that have been classified into seven different species (A to G) with over 85 genotypes, depending on their biological features, tumorigenicity, as well as DNA homology. HAdV-species B (HAdV-B) (types 3, 7, 14, and 21), HAdV-C (types 1, 2, and 5), as well as HAdV-E (type 4) are frequently linked to outbreaks of symptomatic respiratory infections. Despite most cases being mild or self-limiting, certain individuals such as neonates, elderlies, or immunocompromised patients may be at risk of more severe infection. Typical clinical manifestations of HAdV infections include nasal congestion, cough, and fever, whereas in some rare cases, it may progress to pneumonia and respiratory failure [60,61]. HAdVs are typically spread through droplet inhalation, where lytic infection may occur when the viruses enter epithelial cells and remain until the end of their replication cycle, which then induce further cytokine production and initiation of host inflammatory responses [62]. In most cases, supportive treatment is the mainstay for the management of HAdV infections. Currently, there are no approved therapeutic agents against HAdVs, but certain antivirals have been utilized. Ribavirin and cidofovir are the antivirals used to manage severe HAdV infections in immunocompromised patients, however, they are associated with adverse reactions, such as mild anaemia and nephrotoxicity, respectively [58,62]. In terms of vaccines, live oral adenovirus vaccine developed against HAdV types 4 and 7 has been proven safe and effective in clinical trials, but it is currently not available to the public as it is approved only for use in military personnel [63].

2.3.3. Human parainfluenza virus (HPIV)

HPIV is a single-stranded, enveloped RNA virus of the *Paramyxoviridae* family. Four serotypes of HPIV are known to cause respiratory infections in both adults and children. These are HPIV-1 to -4 serotypes, with HPIV-4 further divided into two genera, known as HPIV-4a and HPIV-4b [54,64]. HPIV infection is usually initiated at the epithelium of upper respiratory tract upon exposure to the pathogen by droplet inhalation, and it rapidly spreads to the larynx and bronchi. It binds and replicates in ciliated epithelial cells in the respiratory tracts, leading to infiltration of inflammatory cells and induced host immune responses that contribute to disease pathogenesis. Although HPIVs are generally associated with similar spectrum of respiratory diseases ranging from common cold to severe pneumonia, certain serotypes of HPIV are associated with certain diseases. For instance, HPIV-1 and -2 are more likely to cause laryngotracheobronchitis, whereas HPIV-3 is more likely to spread to the lower respiratory airways, causing bronchiolitis or pneumonia that resembles RSV infection [64,65]. Presently, HPIV is mainly managed by supportive treatment as there are no antivirals proven for their efficacy in treating HPIV infections, with the except of laryngotracheobronchitis where corticosteroids are found to be useful. There are also no licensed vaccines available to protect against HPIV due to the several challenges, including short-lived cross protection between different HPIV serotypes [58,64]. Nonetheless, a study by Belshe et al. has reported that live-attenuated and recombinant HPIV-3 vaccines when used in conjunction with RSV glycoproteins, can stimulate immune responses, warranting further studies regarding their efficacy in preventing HPIV infections [58,66].

2.3.4. Influenza virus

Influenza viruses are enveloped, single-stranded, negative-sense RNA viruses of the *Orthomyxoviridae* family that can be classified into three different genera, namely influenza A, influenza B, and influenza C viruses [54]. These viruses are transmitted through close contact and droplets inhalation, which can lead to a wide range of clinical manifestations ranging from runny nose, fever, and cough, to more severe viral pneumonia that progresses quickly to death especially in young children, elderlies, and immunocompromised patients [67]. Influenza virus contains hemagglutinin (HA) and neuraminidase (NA), which are the two major surface glycoproteins responsible for viral attachment to host cell receptors and the release of virion from infected cells, respectively. Therefore, such antigenic differences help to further classify influenza viruses into multiple subtypes depending on the combination of HA and NA proteins expressed on virus surface [58,67,68]. Influenza virus primarily replicates in the respiratory epithelium, leading to lung inflammation as immune responses are recruited to combat the spreading of virus [69]. Particularly, influenza A virus can lead to more severe outcome as compared to influenza B and C viruses, as it is a genetically labile virus that is susceptible to a high mutation rates that modify its antigenic and functional proteins [67].

Unlike RSV, HAdV and HPIV infections, licensed vaccines are available in various countries to protect against influenza viruses, such as inactivated virus vaccine (Fluzone®, Fluarix®), live-attenuated vaccine (FluMist®), and recombinant HA vaccine (FluBok®) [70,71]. Generally, these vaccines are mainly focused on the production of antibodies to target HA proteins for neutralizing the virus and preventing infection. However, these vaccines do not induce long-term antibody titers, thereby requiring periodic vaccination to ensure optimal immune responses against influenza viruses. Annual vaccination also helps to match the antigenicity of vaccines to that of circulating viruses at time particular time or season, thus improving vaccine efficacy [70,72,73]. Despite vaccination being the most cost-effective method in reducing influenza associated morbidities and mortalities, there are certain conditions that may warrant the use of antiviral drugs for treating or preventing influenza viruses. For instance, in non-vaccinated individuals or in individuals with inadequate immune response to the vaccine, in times where antigenic mismatch is detected between circulating viruses and vaccine viral strains, or when a new pandemic strain is discovered pending development of a new vaccine [58].

2.3.5. Human coronavirus (HCoV)

HCoVs are enveloped, positive-stranded RNA viruses from the *Coronaviridae* family, and they have the largest known viral RNA genome [74]. Several HCoVs have been identified to cause human diseases and they can be categorized as either low pathogenic CoVs or highly pathogenic CoVs. Low pathogenic CoVs such as HCoV-229E, HCoV-HKU1, HCoV-NL63, and HCoV-OC43 usually cause mild and self-limiting flu-like symptoms and are globally endemic. However, they may cause more severe infections in neonates, elderlies, immunocompromised patients, or in patients with underlying conditions [75,76]. Nevertheless, over the past decades, multiple highly pathogenic CoVs have emerged and had caused huge public concern as they can cause lethal human diseases. For instance, the outbreak of Severe Acute Respiratory Syndrome (SARS) in November 2002 was found to be caused by SARS-CoV, and it was the most severe human disease caused by any HCoVs. Studies showed that SARS-CoV infects lung epithelial cells, and it can enter macrophages and dendritic cells. This induces the secretion

of pro-inflammatory cytokines, contributing to atypical pneumonia manifested by cough, fever, and infiltrates [58,77,78]. Few years later, a novel zoonotic HCoV, the Middle East Respiratory Syndrome-CoV (MERS-CoV) was discovered to cause a series of highly pathogenic respiratory tract infections, with a relatively high mortality rate during its early outbreak [58,76]. Recently, another novel HCoV has emerged as the causative agent of the Coronavirus Disease 2019 (COVID-19) pandemic, which was originally named as 2019-nCoV. As genomic studies have revealed similarities of 2019-nCoV to the SARS-CoV, it is now named as SARS-CoV-2 [58,76–80]. Unlike non-SARS CoV, these highly pathogenic CoVs can encode numerous genes that allow their evasion from host immune system to achieve high intracellular virus titers, causing severe damage to the respiratory system and development of acute respiratory distress syndrome (ARDS) [75,76].

To-date, no approved antiviral therapeutics or monoclonal antibodies that specifically target HCoVs exist, therefore, management is mainly focused on supportive care. There are also no approved vaccines for the prevention of HCoVs [58,81]. Nonetheless, there are promising outcomes in the development of vaccines against COVID-19 infection. The success in COVID-19 vaccine development is most likely attributed to the experience gained by researchers from the vaccine development path of SARS and MERS previously, whereby the prime targets of MERS and SARS vaccines can be exploited as targets for COVID-19 vaccines. As of 7th May 2021, seven COVID-19 vaccines have been listed for emergency use by the World Health Organization (WHO), thereby allowing them to be rolled out globally. These include the vaccines of Pfizer-BioNTech, AstraZeneca-Oxford, AstraZeneca-SK Bio, Serum Institute of India, Janssen, Moderna, and Sinopharm [82]. The production platforms for current COVID-19 vaccines and those under development include live-attenuated vaccines (e.g., Serum Institute of India), inactivated vaccines (e.g., Sinovac, Sinopharm), mRNA vaccines (e.g., Pfizer-BioNTech, Moderna), non-replicating viral vector vaccines (e.g., AstraZeneca-Oxford, Janssen), as well as protein subunit vaccines utilizing Spike (S) protein of SARS-CoV-2 and its receptor-binding domain (RBD) (e.g., Novavax, Sanofi) [81,83–85].

Nevertheless, the initial optimism with regards to the development of COVID-19 vaccines and hopes that vaccination may provide a long-term solution to the COVID-19 pandemic has been perturbed by the discovery of new SARS-CoV-2 variants. For example, the B.1.1.7 variant first identified in Kent, United Kingdom in the December 2020 has eight mutations in the S protein and one mutation (N501Y) in the immunodominant RBD. This variant of concern (VOC) was more transmittable due to its increased binding affinity to the human angiotensin-converting enzyme 2 (hACE2) receptor, thus enhancing its ability to enter human cells [86,87]. Studies conducted on recipients of the AstraZeneca-Oxford, Moderna, Novavax vaccines have shown that the B.1.1.7 VOC is harder to neutralize as compared to the parental virus [88,89]. However, a widespread escape from vaccine-elicited antibody responses and monoclonal antibodies was not observed, indicating that current COVID-19 vaccines may still be effective against B.1.1.7 variant of SARS-CoV-2 [88–91]. Another example of SARS-CoV-2 VOC is the B.1.351 variant first detected in South Africa in December 2020, whereby additional mutations in the RBD at positions E484 and K417 were observed. These RBD mutations resulted in tighter binding of the virus to hACE2 receptor leading to widespread escape from neutralization by monoclonal antibodies [86,87,92]. Studies have shown that the triple mutations of K417N, E484K, and N501Y in the RBD resulted in remarkably reduced susceptibility to vaccine sera in recipients of the AstraZeneca-Oxford, Janssen, and Novartis vaccines, thus offering limited protection against mild to moderate COVID-19 in places where the B.1.351 variant was prevalent [87,93]. As the rapid transmission of SARS-CoV-2 VOCs has sparked concerns on impending cases surge and severe outcome, accelerating the pace of current vaccines rollout and development of next-generation vaccines may be potential strategies to avert the surge in COVID-19 cases throughout the world [87,94].

3. Nanoparticles as alternatives to conventional vaccines

Despite substantial progress, there are rising concerns regarding the application of conventional vaccines in managing viral infections. These include weak immunogenicity, in-vivo intrinsic instability, as well as toxicities and allergic reactions to vaccine components. Complex vaccination schedule is another limitation of conventional vaccines, as the immune protection induced by vaccine antigens may be too slow to achieve its efficacy on time, thereby requiring multiple booster shots to achieve full immunity against specific pathogen [95,96]. On the other hand, difficulty in selecting suitable antigen candidates to protect against the pathogen is among the challenges facing the development of vaccines, as antigens are usually short-lived and easily degraded before they can elicit sufficient immune responses [97,98]. The rapid emergence of mutation strains due to antigenic shift and drift has also made it difficult to confer cross-protection, thereby necessitating the regular development of a new vaccine. However, vaccine development is highly time-consuming, and outbreaks of novel strains may happen before a new vaccine is successfully developed [98,99]. Moreover, there is a lack of an appropriate delivery platform for the vaccines to reach their intended site for enhancing the immune responses. Mucosal delivery of vaccines has great potential as the alternative for parenteral administration, as it can target both the mucosal and systemic immune systems. Ideally, mucosal vaccine delivery can stimulate cytotoxic T cell responses along with secreted IgA, which helps to recognize and delete pathogens prior to their entrance into the human body. Thus, the respiratory mucosa route can be exploited for the delivery of vaccines for combating respiratory viruses [13,14]. Nevertheless, the applications of mucosal vaccines are limited due to low delivery of potentially protective viral epitopes as well as the inability to preserve antigen stability, integrity, and adjuvanticity, attributed to the intrinsic characteristics of the mucosal immune system in inducing tolerance [13,100,101]. Hence, it is crucial that an alternative be sought for the development of next-generation vaccines that can provide superior benefits to those of conventional vaccines in managing respiratory viruses.

Over the recent years, there has been substantial interest in the application of nanoparticles for mucosal vaccine delivery against viral respiratory infections due to their unique physicochemical properties. Multiple types of nanoparticles have been developed as vaccine delivery vehicles and as adjuvants to vaccine antigens, which include inorganic nanoparticles such as gold nanoparticles, iron oxide nanoparticles and carbon-based nanoparticles, virus-like particles, liposomes, as well as polymeric nanoparticles [6,102]. The major advantage of these nanomaterials is attributed to their size, as many biological systems like proteins and viruses are within the nano-sized range. These nanosized materials can also easily penetrate capillaries and mucosal surfaces when delivered intranasally. Besides, nanoparticles-based vaccines can protect the encapsulated antigens from premature degradation, thereby improving their stability and sustained release of antigens can be achieved [103,104]. Nanoparticles-based non-viral vectors can also assist in the encapsulation of genetic payload from those of mRNA and DNA vaccines to protect them from premature degradation due to catalytic hydrolysis by endonucleases, thereby stabilizing the genetic material whilst increasing transfection efficiency of the vaccine [105,106]. In short, nanoparticle-based delivery of vaccines allows the encapsulated antigens or genetic materials to be administered via a suitable route that enhances their cellular uptake, leading to robust innate, cellular, humoral, and mucosal immune responses in comparison with soluble antigens or genes, thus, nanoparticles are highly attractive candidates to revolutionize vaccinology in managing viral respiratory infections.

In terms of immune protection, the primary objective of vaccination is to trigger innate and adaptive responses of the immune system for long-term protective immunity (Fig. 5). Due to the central role of dendritic cells as an antigen presenting cell (APC) in the induction of immune responses, they have been established as the prime target cells for vaccination [107]. The immune pathway of nanoparticle-based vaccines

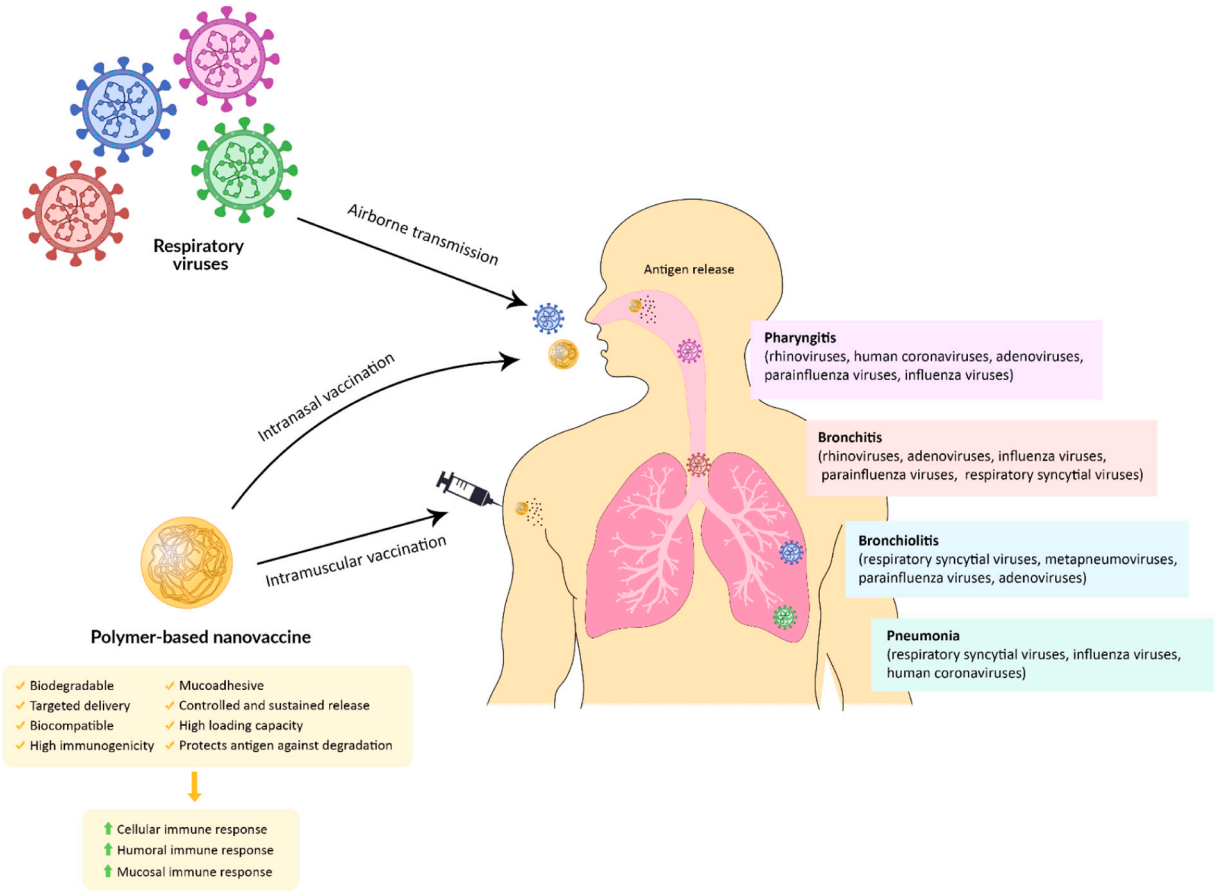

Fig. 4. Application of polymeric nanoparticles as vaccines in the management of respiratory viruses.

begins with the uptake of the nanocarriers encapsulating antigens or genetic materials encoding for an antigen by dendritic cells via the endocytic route [108]. It has been reported that the application of nanoparticles as carriers of the antigens or genetic materials can enhance immunogenicity and impact adaptive immune responses over those of soluble antigens and naked mRNA or DNA by influencing the function of dendritic cells in antigen presentation [108,109]. This can be attributed to nanotechnological advancements which allow nanoparticles to be custom designed with specific size, shape, surface chemistry, solubility, as well as other biological and chemical properties that can be controlled and fine-tuned, thereby influencing the degree of uptake by dendritic cells. For instance, nanoparticles with an approximate size of 100 nm are highly favourable for cellular uptake by dendritic cells [108,110]. Surface functionalization of nanoparticles with ligands for dendritic cells-specific surface receptors such as CD40 and CD11c can also facilitate their cellular uptake by dendritic cells. Besides, the uptake efficiency can be further enhanced by utilizing nanocarriers with a positive surface charge due to the anionic nature of dendritic cell membranes [71,108,110–112]. At the same time, a sustained release profile can be achieved by nanoparticles to remarkably improve the retention of antigens at the site of administration and subsequent antigen presentation by dendritic cells. Furthermore, cytosolic delivery can also be enhanced by utilizing proton sponge effects of nanoparticles by modulating their material properties, in which a positively charged nanocarrier can absorb proton during the acidification of endosomes, leading to osmotic swelling and subsequent vesicle escape of endocytosed nanovaccines [108].

Dendritic cells are also involved in migration towards the lymph node to interact with a large population of T cells, thereby initiating and propagating adaptive immune responses. Therefore, a potent immune response can be achieved by directing antigens to dendritic cells via surface functionalization of nanoparticles whilst increasing likelihood of these nanoparticles to be drained and enriched in lymph nodes, particularly those with sizes ranging between 10 and 100 nm [108,111,113]. Apart from that, as the maturation of dendritic cells can lead to enhanced lymph node migration, nanoparticles can be employed to co-deliver pattern recognition receptor (PRR) agonists such as Toll-like receptor (TLR) ligands to induce maturation of APCs, whereby studies have shown that addition of PRR agonists in nanovaccine formulations significantly enhances immune response and vaccine efficacy [108,114,115]. On the other hand, if a mRNA or DNA vaccine is used, the prerequisite for antigen presentation is their translation to encoded antigens in the cytosol of dendritic cells. An additional step is required for DNA vaccines, in which the DNA must first enter the nucleus of dendritic cells in order to be transcribed into mRNA for subsequent antigen translation. As discussed earlier, the application of nanoparticles can efficiently encapsulate and protect mRNAs and DNAs from quick degradation by endogenous enzymes whilst providing adjuvant properties, as well as to facilitate cellular uptake and receptor interactions of APCs by expanding surface adsorption [113,116]. Once the antigens have been processed by dendritic cells, they will be presented by the major histocompatibility complex (MHC) class I molecules and MHC class II molecules to CD8+ T cells or cytotoxic T lymphocytes, and CD4+ T cells or T helper cells, respectively [107,108]. T helper cells that are specific for the viral antigen then provide help for cytotoxic T lymphocytes and antibody-producing B cells, which work together to eliminate the virus selectively and effectively. In addition, the formation of memory T cells and memory B cells can rapidly trigger an immune response upon a new contact with the viral antigen, thus, they can effectively prevent the survival and proliferation of the viral pathogen in the event of reinfection with the same viral pathogen [107].

To sum up, the application of nanoparticles as a versatile carrier of

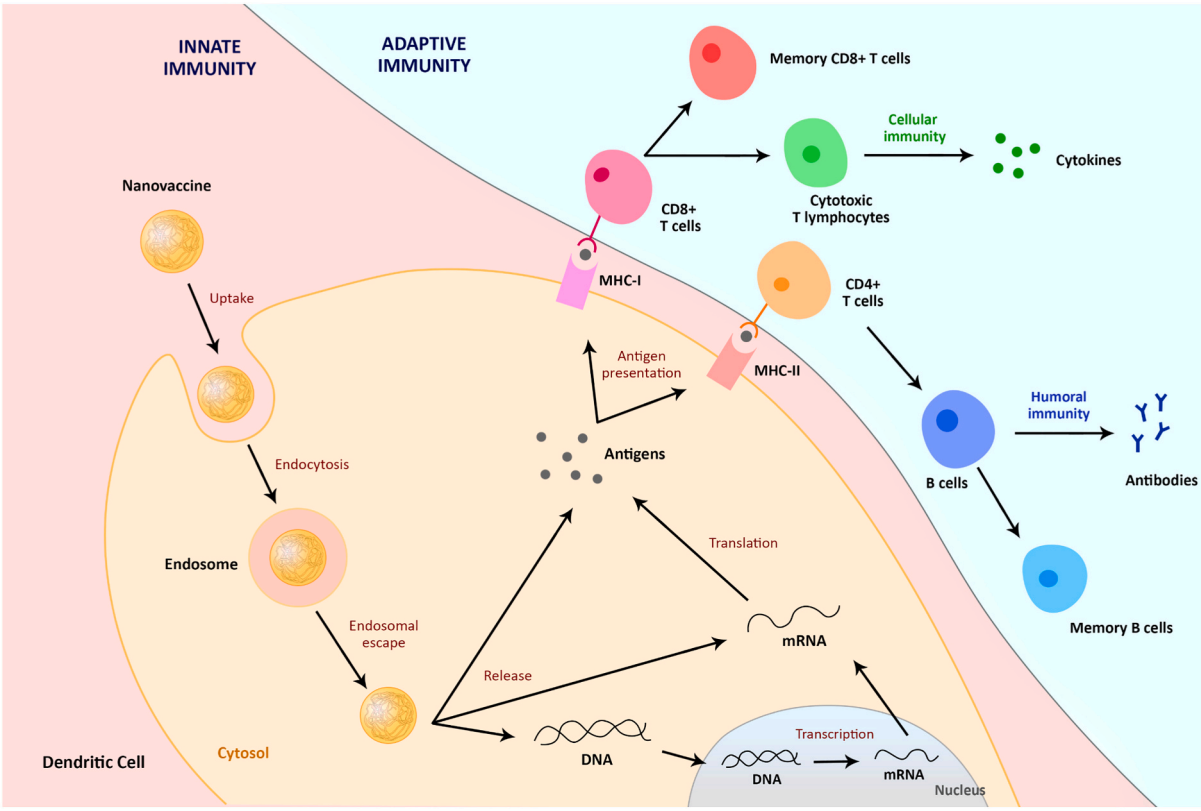

Fig. 5. The mechanisms of the induction of innate and acquired immune systems via the activation of dendritic cells by using nanoparticles-based vaccines.

viral antigens in the prevention of viral respiratory infections can provide various advantages superior to those of conventional vaccination approaches using soluble antigens or naked mRNA and DNA. These include feasibility of intranasal vaccination, enhanced cellular uptake and antigen shielding, improved antigen presentation by APCs, as well as amplified immune responses.

4. Polymer-based nanoparticles

Polymeric nanoparticles are particulate dispersions or solid particles with size ranging from 1 to 1000 nm, which can be composed of either natural, semi-synthetic, or synthetic polymers. Active compounds are typically loaded within or adsorbed onto the core of polymeric nanoparticles [117]. Polymeric nanoparticles are of particular interest in the development of vaccines as they possess higher immunogenicity, better targeting, and are relatively biodegradable as compared to inorganic nanoparticles. The delivery of vaccines using polymeric nanoparticles as the carrier or as an adjuvant facilitates the induction of remarkable anti-inflammatory responses and promotes cross-protective antibody and T cells-mediated immune responses [99,118]. Moreover, polymer-based nanomaterials have excellent biocompatibility and a large surface area that allows the incorporation of antigens with ease, thereby allowing high reactivity for the induction of immune responses [119]. As adjuvants, biopolymers have also been used in conjunction with various antigens for intranasal administration, whereby studies have shown that certain biopolymers when adjuvanted with antigens promote virus-specific antibodies, indicating an augmented immune response. Therefore, safer vaccine formulation strategies using isolated antigens or dead pathogens can be employed, whilst triggering robust immune responses comparable to those of live attenuated vaccines [120]. Hence, the utilization of polymeric nanomaterials is beneficial in the development of vaccines for managing viral respiratory infections (Fig. 4).

Generally, polymeric nanomaterials can be classified as either natural-based polymers or synthetic-based polymers (Fig. 6). Natural polymeric nanomaterials possess more favourable properties such as better biocompatibility in comparison with synthetic-based polymers as they are naturally occurring and fully renewable [121]. Examples of natural polymeric nanomaterials include chitosan, alginate, and cellulose. On the other hand, synthetic polymeric nanomaterials offer certain advantages over natural polymeric nanomaterials in terms of their reproducibility which allows the production of near-exact polymers with negligible batch-to-batch variation [122]. Synthetic-based polymers can also be engineered with tailor-made chemical, biological, mechanical, and interfacial properties [123]. Examples of synthetic polymeric nanomaterials include poly(lactic-glycolic acid) (PLGA), poly (lactic acid) (PLA), poly(glycolic acid) (PGA), and polyethylene glycol (PEG).

In the following sections, we compiled several studies performed by scientists and researchers throughout the recent years on few of the most utilized polymeric nanomaterials in the field of vaccinology, to justify the feasibility of polymeric nanoparticles application in the development of novel vaccines for viral respiratory infections with respect to their intrinsic biological and physicochemical characteristics. We have also selected a few recent studies conducted on other polymeric nanoparticles and summarized their key findings on their potential to be developed as vaccines for respiratory viruses in Table 1.

4.1. Chitosan

Chitosan is a natural polymer obtained via *N*-deacetylation of chitin, which is the most abundant polysaccharide found in fungal cell walls and shellfish exoskeletons [137]. Chitosan has been an attractive candidate for vaccine delivery owing to its good biocompatibility and biodegradability. Its chemical structure also allows binding to plasmid DNA or other negatively charged proteins via electrostatic interaction, forming polymer composites that shield its content from premature degradation. Besides, chitosan possesses mucoadhesive property, which allows it to bypass the mucociliary clearance processes when given

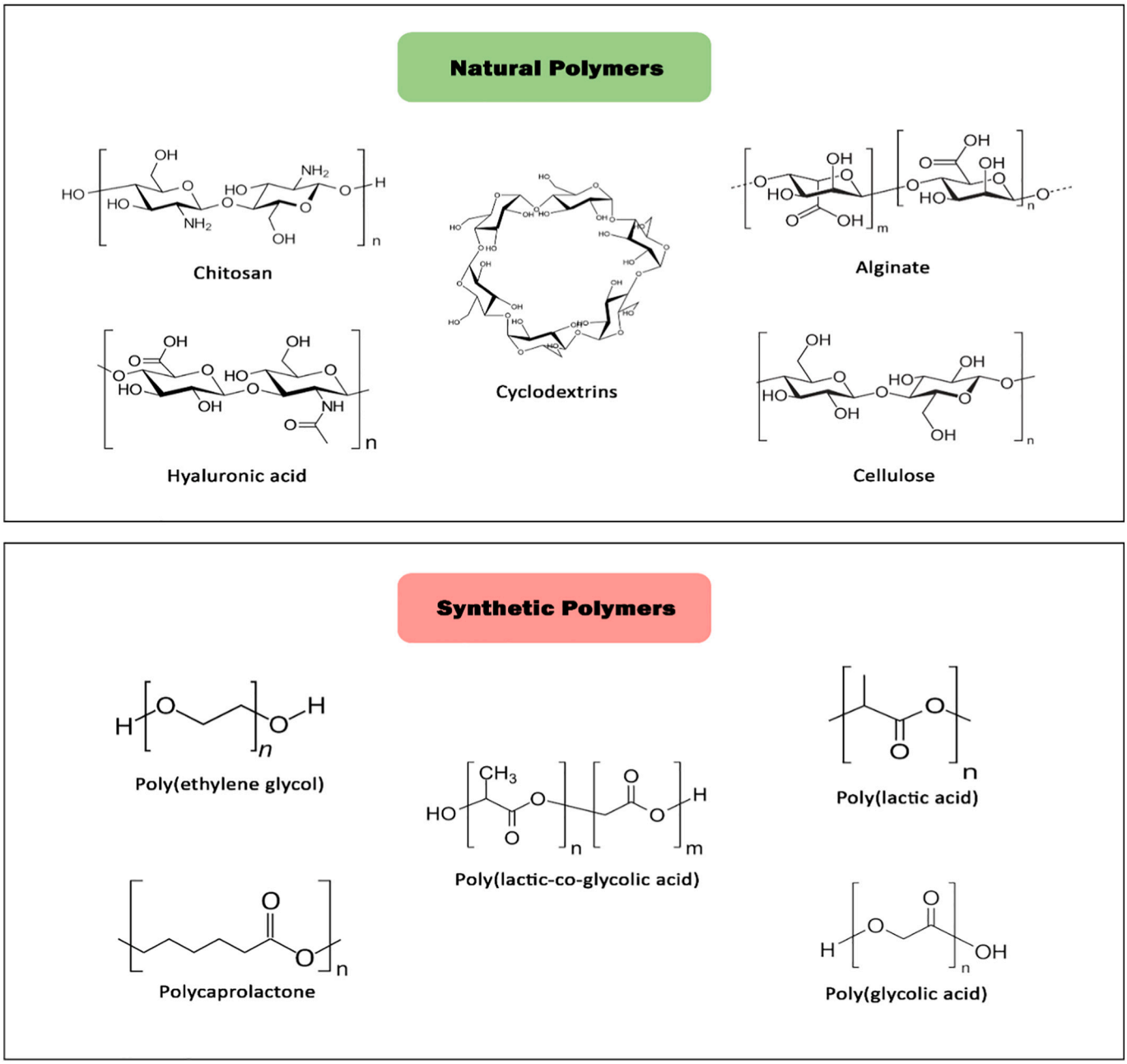

Fig. 6. Examples of various polymeric nanomaterials utilized in the biomedical field.

intranasally, thereby prolonging the resident time of chitosan-based vaccines in the respiratory tract [137–141]. Nevertheless, chitosan is naturally water-insoluble, rending compatibility issues when certain antigens are only stable and soluble within natural pH. In this case, chemical modification and surface charge manipulation of chitosan is possible due to the presence of abundant amino and hydroxyl groups, producing chitosan derivatives with specific performance without compromising its unique biological properties, depending on its intended application [138,139].

Throughout these years, multiple studies have been performed to evaluate the feasibility of chitosan in vaccine development for viral respiratory infections. A study by Muralidharan et al. has investigated the potential of chitosan in altering immune responses when used as an adjuvant with an inactivated RSV vaccine. The results demonstrated that chitosan remarkably suppressed RSV infection when given in conjunction with inactivated RSV vaccine, attributed to enhanced antigen-specific immune responses via induction of regulatory and lung resident T cells, and neutralizing antibodies [142]. In another study, Sawaengsak et al. also evaluated the efficacy of immunogenicity and protective efficacy of a chitosan-tripolyphosphate (CS/TPP) nanoparticles adjuvanted hemagglutinin (HA)-split influenza virus vaccine (CS/TPP-HA) as compared to the antigen alone vaccine in an influenza mouse model. CS/TPP-HA vaccine was found to be safe as it did not induce any adverse reactions when given intranasally. Moreover, chitosan nanoparticles stimulated a cell-mediated immune response, documented by high numbers of interferon-γ-secreting cells in the spleen which is not seen in the HA alone vaccine. Most importantly, chitosan nanoparticles remarkably decreased influenza morbidity and conferred full protection to vaccinated mice when challenged by a lethal influenza virus [143]. Similarly, Sadati et al. formulated influenza whole inactivated virus vaccines with chitosan nanoparticles as a biodegradable delivery system. It was reported that humoral and cellular immune

Table 1
Summary of key findings from studies conducted on polymeric nanoparticles-based vaccines against respiratory viruses.

Respiratory virus	Vaccine platform	Antigen(s)	Adjuvant(s)	Study model	Key findings	Reference
Bovine parainfluenza virus type-3	PLGA nanoparticles	Bovine parainfluenza virus type-3 (BPI3V) peptide	N/A	BALB/c mice	• Intranasal delivery of nanovaccines displayed sustained release of antigens, demonstrated by gradually increasing antigen-specific IgG response for 6 weeks post vaccination. • Stronger IgG antibody response as compared to soluble antigen alone. • Earlier detection of antigen-specific antibodies as compared with soluble antigen alone.	[124]
Bovine RSV	Polyanhydride nanoparticles	Bovine RSV (BRSV) F and G glycoproteins	N/A	Holstein calves	• Nanovaccine reduced viral burden and decreased viral shedding due to enhanced BRSV-specific immune responses. • Encapsulation provided sustained release of antigens and maintained their antigenicity.	[125]
H1N1 influenza virus	*N*-trimethyl chitosan nanoparticles	M2 extracellular domain (M2e)	Heat shock protein 70c (HSP70c)	BALB/c mice	• Increased neutralizing antibody titers by IgA in nasal cavity. • Nanovaccine displayed higher levels of anti-M2e IgG antibody as compared with soluble antigens. • Promoted proliferation of peripheral blood lymphocytes with lower mortality and morbidity against viral challenge.	[126]
H1N1 influenza virus	PEG-PLA nanoparticles hydrogel	Hemagglutinin	TLR 7/8 agonists	C57BL/6 mice	• Nasal vaccination induced long-lasting humoral and cellular immune responses and provided full protection against 90% lethal dose of influenza virus. • PEG-PLA nanoparticles hydrogel allowed co-diffusion of antigen and adjuvant, leading to a sustained co-delivery pattern. • Significantly higher antibody titers 56 days post vaccination.	[127]
H1N1 influenza virus	Protein templated polystyrene nanoball	Hemagglutinin 1	N/A	C57BL/6 mice	• Increased potency, durability, and breadth of antibody responses against future influenza variants. • Nanovaccine upregulated the expression levels of co-stimulatory molecules as well as MHC class I and II, but not observed for soluble antigen. • Increased the mRNA levels of IL-6, IL-12, and TNF-α. • Promoted H1-specific humoral and cellular immune responses, including CD8+ T cell activation and production of IgG, IgG1 and IgG2a, as compared with soluble antigen alone.	[128]
H3N2 influenza virus	Polyethyleneimine-functionalized graphene oxide nanoparticles	Hemagglutinin	CpG oligodeoxynucleotides (CpG ODN)	BALB/c mice	• Protective effect against different types of H1N1 influenza viruses and promoted long-term memory immune responses. • Nanoparticles significantly enhanced antigen-uptake efficiency in dendritic cells and promoted dendritic cell maturation as compared to soluble antigens. • Induced and enhanced cross-reactive immune responses at both systemic sites and mucosal surfaces. • Significantly boosted antigen-specific humoral and cellular immune responses.	[129]
H5N1 influenza virus	PLGA nanoparticles	Hemagglutinin	PLGA-encapsulated TLR ligands MPL and R837	BALB/c and C57BL/6 mice	• Conferred immune protection against challenges by homologous and heterologous viruses. • Nanoparticles containing antigens with dual TLR ligands enhanced antigen specific neutralizing antibodies and T cell responses as compared to soluble antigens.	[130]

(*continued on next page*)

Table 1 (*continued*)

Respiratory virus	Vaccine platform	Antigen(s)	Adjuvant(s)	Study model	Key findings	Reference
H5N1 influenza virus	Polyanhydride nanoparticles	H5 hemagglutinin	Pentablock copolymer-based hydrogels	BALB/c mice	• 5-fold dose sparing effect, as 10 μg of antigen with dual TLR ligands demonstrated much greater response as compared to 50 μg of antigen alone. • Antigen specific memory of T cells was persistent for 1.5 years post vaccination. • Nanovaccine immunization containing antigen and adjuvant enhanced neutralizing antibody titers as compared to soluble antigens. • Sustained virus neutralizing antibody titer for 70 days post immunization. • Lower viral loads in the lung after intranasal challenge of the virus. • Protective hemagglutinin inhibition titer was achieved in the nanoparticles containing both virus and adjuvant.	[131]
Influenza	Alginate nanoparticles	Influenza inactivated whole virus	CpG ODN	Albino rabbits	• Nasally vaccinated groups had higher IgA secretion as compared to parenteral vaccinated groups. • Significantly increased the level of IgG, as well as IL-4 and TNF-α. • Nanovaccines exhibited stronger immune responses as compared to soluble antigens.	[132]
Influenza A viruses	Poly-γ-glutamic acid-chitosan nanoparticles	Matrix protein-2 (sM2) and fusion peptide of hemagglutinin (HA2)	Cholera toxin subunit A1 (CTA1)	BALB/c mice	• Mucosal administration induced systemic immunity by IgG and IgA and increased the levels of sM2 and HA2-specific cell-mediated immune responses as compared to soluble antigens alone. • Nanovaccine provided cross protection against divergent lethal influenza subtypes and was maintained up to 6 months post vaccination. • Reduced viral titers in the lungs post vaccination.	[133]
MERS-CoV	Hollow-core PLGA shell nanoparticles	MERS-CoV RBD protein	Cyclic diguanylate monophosphate	C57BL/6 mice	• Robust and sustained MERS-CoV RBD-specific antibody response was observed. • At an equivalent dosage, antigen-loaded nanoparticles enhanced uptake by APCs as compared to free antigen. • Induced balanced Th1/Th2 immune response and primed both antigen specific CD4+ and CD8+ T cell responses. • Significant reduction of virus load titers in lungs after lethal challenge of MERS-CoV.	[134]
RSV	Thermoresponsive polymer nanoparticles	RSV fusion (F) protein trimers	TLR 7/8 agonists	CB6F1/J mice	• Coupling F trimers to nanoparticles with TLR agonists resulted in approximately 3-fold higher binding and neutralizing antibody titers as compared with soluble F trimers. • Nanovaccine elicited high titers of prefusion-specific Th1 isotype anti-RSV F antibodies post vaccination. • Conferred immune protection against intranasal RSV challenge.	[135]
SARS-CoV-2	Poly(butadiene)-b-poly (ethylene oxide) (PBD-PEO) polymersomes	SARS-CoV-2 spike proteins S1S2 and S2	CpG	C57BL/6 mice	• Elicited robust neutralizing titers that persist 40 days post vaccination. • Induced strong and durable adaptive immune response through increased uptake and processing of nanovaccine by dendritic cells. • Higher spike-specific IgG titers observed for the nanovaccine formulation as compared to free antigen. • Induced functional memory CD4+ and CD8+ T cells that produce Th1 cytokines.	[136]

responses were significantly induced at low-dose, proving that delivery of inactivated influenza virus by chitosan as low-dose can produce the same results as with high-dose vaccines [144]. The potential of chitosan nanoparticles in RSV was also investigated by Zhang et al., whereby siRNA targeting the NS1 gene was complexed with chitosan nanoparticles and administered intranasally to an RSV-challenged mice model. Results showed reduced RSV replication, elevated type 1 interferon, and stimulated T-helper type 1 cell differentiation from CD4+ T cells, suggesting that chitosan nanoparticles can protect against RSV infection in humans [145]. In a nutshell, these studies proved that chitosan nanoparticles are safe and effective, and they can potentially be developed as a novel vaccine delivery vehicle and/or as an adjuvant to existing vaccines of respiratory viruses.

4.2. Alginates

Alginate is another naturally occurring biopolymer obtained from brown algae and bacteria cell walls. It is an anionic polysaccharide that consists of repeating β-D-mannuronate units (M blocks) and α-L-guluronate units (G blocks) linked via 1,4-glycosidic bond [146]. Through the gelation phenomenon, divalent cations such as Ca^{2+} and Ba^{2+} can form complexes with G blocks, producing alginate hydrogels that can be applied in the field of vaccinology to encapsulate proteins and antigens at ease [147]. Some notable properties of alginate hydrogels include non-toxicity, biodegradability, as well as mechanical flexibility. Controlled and sustained release of antigens can also be achieved, which can be customized depending on the type of cross-linker and method used to engineer alginate-based nanoparticles [148]. Typically, the physicochemical properties of alginate are dictated by the M blocks to G blocks ratio and their distribution patterns, block segment length, as well as molecular weight. For instance, alginates containing more M blocks are less mucoadhesive, whereas alginates with more G blocks exhibit tighter ionic cross-linkage, enabling the sustained release of antigens [149,150]. Besides, the release profile of alginate hydrogels is also pH dependent. Namely, the matrix shrinks at low pH, thereby allowing the payload to be preserved, whereas, at high pH, the matrix swells and releases the payload. Along with their mucoadhesive property, the permeability of alginates is enhanced when delivered intranasally, at the same time, premature degradation can be reduced in the acidic biological environment of respiratory mucosa [148,151]. Hence, these advantages of alginate nanoparticles allow them to be an interesting candidate in the development of novel vaccines to combat respiratory viruses.

On the other hand, alginate can also be combined with chitosan to produce more stable vaccines in managing respiratory viruses. The anionic properties of alginate allow it to bind well with chitosan, thereby forming a dense but stable compound. Alginate has also been utilized as a coating for chitosan-based vaccines as it can help to shield encapsulated antigens from premature degradation, thereby enhancing the stability of vaccines [120,152]. This feature is necessary especially for intranasally-delivered vaccines due to the multiple enzymes present in the mucous. Mosafer et al. have prepared alginate-coated chitosan and trimethylchitosan nanoparticles encapsulating inactivated PR8 influenza virus to determine whether alginate coating can enhance transmucosal antigen delivery. The study revealed that alginate-coated nanoparticles can elicit superior immune responses when compared with non-coated nanoparticles, justified by a significantly higher IgG-2a to IgG-1 ratio which is an indication of Th-1 type immune response [153]. Likewise, the advantages of alginate when used in conjunction with chitosan have been documented by McCullough et al., whereby they have investigated the potential of alginate-chitosan nanogel to improve the delivery of self-amplifying replicon RNA (RepRNA) to dendritic cells. It was found that the nanogel promoted the translation of RepRNA in a concentration dependent manner, both in-vitro and in-vivo [154]. Therefore, these results offer future opportunities in mRNA vaccinology using alginate-chitosan nanogels, as they can contribute to an efficient and enhanced cytosolic delivery of mRNA encoding for an antigen, such as those of influenza virus and other respiratory viruses, thereby leading to vaccine epitope synthesis of the transfected cells [105,154]. In a nutshell, it is proven that alginate has an incredible potential to induce robust immune responses when used synergistically with chitosan.

4.3. Poly(lactic-co-glycolic acid) (PLGA)

PLGA is a type of copolymer synthesized from PLA and PGA via ring-opening copolymerization. It is a highly biodegradable and biocompatible polymer as it can undergo hydrolysis that results in the formation of non-toxic degradation products, glycolate, and lactate, which can be safely eliminated from the body [155]. As PLGA possesses the intrinsic properties of both PLA and PGA, its degradation rate is highly dependent on its polymeric content, namely the PLA to PGA ratio. For instance, PLA is less hydrophilic as compared to PGA due to the presence of methyl side chain in PLA, therefore, PLGA with a high content of PLA is more hydrophobic which leads to slower rate of degradation [155,156]. Thus, PLGA nanoparticles can be customized to degrade over a specific period and can act as a reservoir from which the encapsulated antigens can be released in a sustained manner. Another key advantage of PLGA nanoparticles is that unlike PLA and PGA, PLGA can be solubilized in various organic solvents, thereby allowing them to be engineered into various sizes and shapes. At the same time, they can be easily loaded with a wide range of biomolecules and the encapsulated compounds can be shielded from premature degradation [157–159]. The rate of antigen release from PLGA nanoparticles is also affected by the particle size, in which the smaller the particle size, the higher the rate of antigen release due to the larger surface area [160]. In short, PLGA is a versatile polymer that offers scientists opportunity to engineer customized vaccine delivery vehicles with tailor-made physiochemical properties to deliver its payload at the targeted site in a specific manner.

The benefits of PLGA as a vaccine delivery platform have been justified in multiple studies to-date. Dhakal et al. have developed PLGA nanoparticles encapsulating inactivated swine influenza virus H1N2 antigens (KAg) and evaluated their immunogenicity in a pig model. It was found that pigs vaccinated intranasally with PLGA-KAg displayed elevated antigen-specific lymphocyte proliferation with the enhanced frequency of interferon-γ secreting total T cells, T-helper, and cytotoxic T cells in peripheral blood mononuclear cells. Besides, clinical flu symptoms were not present in PLGA-KAg vaccinated pigs, in contrast to the control pigs where fever is present. Decreased viral antigenic mass and clearance of infectious challenge pathogens were also observed. To summarize, these findings indicated that PLGA-KAg vaccine is highly effective in augmenting mucosal immune response and stimulated a cross-protective cell-mediated immune response against both H1N2 and H1N1 influenza [161].

Another similar study by Hiremath et al. have developed PLGA nanoparticle-based vaccine delivery vehicle encapsulated with matrix protein 2 extracellular domain (M2e), highly conserved H1N1 peptides from the 2009 pandemic, and classical human influenza viruses. This study reported that pigs vaccinated with PLGA-nanoparticles did not present any clinical symptoms and the challenged swine influenza H1N1 viruses were not detectable in bronchoalveolar lavage fluid. Moreover, the frequency of antigen-specific interferon-γ secreting T cells response in lung lymphocytes was reportedly increased, indicating that PLGA nanoparticles induced lung immune responses and improved vaccine efficacy [162]. Galloway et al. in their study have also demonstrated that trivalent influenza vaccine-loaded PLGA nanoparticles are safe to use whilst inducing higher responses to influenza HA as compared to standalone soluble antigen vaccine [163]. Hence, all these results suggest that PLGA nanoparticles can potentially be utilized as intranasal vaccine delivery vehicle for combating viral respiratory infections as they can induce remarkable inflammatory responses and trigger robust, cross-protective T cell responses.

4.4. Polyethylene glycols (PEGs)

PEG is a synthetic, hydrophilic polymer that has gained tremendous attention in the biomedical field as they possess multiple favourable characteristics including high solubility, non-toxicity, non-ionic, and great biocompatibility [164]. Besides, PEG also helps to reduce particle aggregations via steric stabilization, thereby increasing the stability of nanoparticles. As PEG is highly soluble in organic solvents, various functional groups can be attached, which could greatly expand their benefits and allow customization of their physicochemical properties depending on their intended applications. Moreover, the low polydispersity index of PEG indicates homogeneity which enables reproducibility in terms of their immunogenicity [164–166]. In terms of vaccine development, PEG is mainly utilized for its 'stealth' behaviour, whereby PEG can be directly conjugated onto vaccine antigens or delivery vehicles, a technique known as PEGylation. Typically, PEGylation facilitates uptake and site-specific targeting of particles, as the polyether backbone of PEG contains high level of hydration that avoids non-specific protein adsorption via steric repulsion. PEGylation also helps to shield vaccine antigens and/or delivery vehicles from rapid degradation, thus prolonging its residence time for achieving a sustained release profile [164,165,167].

Over the years, multiple studies have demonstrated that PEGylation can enhance the action of vaccines. For instance, Sekiya et al. reported that PEGylation of a toll-like receptor 2 vaccine delivery system enhanced its delivery in-vivo, leading to improved immunostimulatory capabilities and augmented cellular and humoral immune responses [168]. Zhang et al. have also shown that moderate vaccine PEGylation led to 2.7-fold increase in IgG titers, indicating that PEGylation can improve immunogenicity of vaccines [169]. Likewise, Zhan et al. showed that PEGylation enhanced trafficking of vaccines in draining lymph nodes and enhanced dendritic cells internalization, which can potentially improve immune responses as a higher level of antigens can be presented to T cells by antigen presenting cells [170]. Recently, PEGylation has been employed in the development of COVID-19 vaccines, namely the Pfizer-BioNTech and Moderna mRNA vaccines, in which PEG facilitates the formation of a hydrophilic protective layer that stabilizes vaccine nanoparticles, thus improving storage stability and decreases non-specific protein adsorption [171]. Nevertheless, PEG has been reported to induce mild to severe allergic reactions in people receiving Pfizer-BioNTech and Moderna vaccines [172–174]. In short, although the advantages of PEG can be exploited for the development of novel vaccines to manage respiratory viruses, careful evaluation of any adverse reactions must be done to formulate a clear safety profile.

5. Conclusions

Polymeric nanoparticles have a great potential to revolutionize vaccination strategies as they are highly biocompatible and mucoadhesive, which can help to shield the loaded antigens or biomolecules from premature degradation. Additionally, they possess unique and modifiable physicochemical properties that allow customization of their biodegradability, release profile, as well as targeting ability. Nonetheless, studies in this area of research remain largely limited, whereby most of the pre-clinical studies are focused on the influenza virus whilst limited attention is given to other respiratory viruses such as the novel coronavirus (SARS-CoV-2), respiratory syncytial virus and human parainfluenza virus. The development of vaccines for combating the rapid emergence of newer strains of respiratory viruses is facing significant challenges, primarily attributed to the rapid degradation of vaccine antigens and the lack of suitable delivery platforms that can elicit sufficient immune responses to combat such viruses. Certain limitations may also be associated with the use of polymeric nanoparticles, for instance, a minor modification to the chemical composition of polymers may drastically affect their toxicity profile, thereby influencing their feasibility for vaccine applications. Thus, detailed preclinical and clinical explorations into polymer-based vaccines must be conducted to elucidate a clear safety profile and the mechanisms involved with the observed immune reactions, and to extrapolate such findings to predict any undesirable chronic adverse reactions [175]. As such, the eventual effective prophylaxis of respiratory viruses could become a reality and widespread transmission of viral respiratory infections, such as the COVID-19 pandemic, can potentially be avoided.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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