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REVIEW

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Mucosal immunotherapy targeting APC in lung disease

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Abstract

Several studies have demonstrated that the pulmonary immune response is primarily facilitated by antigen-presenting cells (APCs), and that both professional and non-professional APCs contribute to overall pulmonary immunity. APCs play unique roles and mechanisms in pathogen elimination and immunomodulation. Mucosal immunity exhibits potential advantages over traditional parenteral immunity in that it stimulates immune defenses in mucosal and systemic tissues, which is important for reducing the burden of lung disease. However, obtaining a comprehensive understanding of the crosstalk between mucosal immunity and APC in the context of various lung diseases remains challenging. This mini-review aimed to elucidate the mechanisms of novel mucosal immunity, targeting APC action during lung infections, allergies, and malignant tumorigenesis. This minreview provides important insights into more effective therapeutic approaches for various lung diseases.

Keywords APC, Lung diseases, Immune, Mucosal vaccine, Adjuvant

Introduction

Specialized APCs are known for their ability to present exogenous antigens to T cells such as dendritic cells (DCs), macrophages (Møs), and B cells. When dendritic cells (DCs) detect and capture proteins that are either immunogenic or linked to activating molecules, they experience a change in their phenotype and move toward the lymph nodes. In these nodes, they display peptides derived from proteins using MHC-I and MHC-II molecules to antigen-specific CD8+and CD4+T cells [1]. After an infection occurs, conventional dendritic cells type 1 (cDC1s) relocate from their intraepithelial origins to the draining mediastinal lymph nodes and are typically recognized as the main subset responsible for cross-presenting antigens to CD8+T cells. Conversely, conventional dendritic cells type 2 (cDC2s) assist in priming CD4+T cells, while plasmacytoid dendritic cells (pDCs) are primarily noted for their synthesis of type I interferons [2]. The process of polarization in lung macrophages is dynamic and influenced by a range of environmental factors. In cases of bacterial infections or inflammatory states, macrophages generally polarize towards the M1 phenotype, leading to the considerable secretion of pro-inflammatory cytokines. In contrast, during chronic infections or heightened inflammatory reactions, these cells might transition to the M2 phenotype, which aids in tissue healing and reduces inflammation by promoting immune tolerance [3, 4]. Alveolar macrophages carry out immunoregulatory tasks by generating soluble mediators that suppress the activity of dendritic cells. Nevertheless, if the macrophage-surfactant-epithelial barrier is compromised, antigens may penetrate to reach deeper sentinel dendritic cells. This can result in modifications to the local cytokine milieu and promote dendritic cell activation, initiating adaptive immune responses. Furthermore, interstitial macrophages have the capability to process antigens into smaller peptides and then present them on the surfaces of adjacent dendritic cells, thereby boosting the immune activity of lung dendritic cells [5]. However, nonspecialized APCs are also capable of antigen

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presentation including endothelial cells (ECs) and epithelial cells, whose mechanisms have recently been investigated [6–8].

Pharmaceuticals aimed at the nasal cavity primarily influence the respiratory mucosa along with the nasal-associated lymphoid tissue (NALT) [9]. The immune mechanisms within the nasal mucosa are divided into inductive and effector locations. Inductive sites are mainly composed of mucosal lymphoid follicles situated in the respiratory zone, commonly known as NALT. Effector sites are responsible for the activation of B cell and T cell immune responses [10]. Surrounding the NALT are epithelial cells and a small quantity of microfold cells. The base of microfold cells is rich in B cells, T cells, macrophages, and dendritic cells (DC). These microfold cells act as multifunctional transporters, facilitating the nonspecific and specific endocytosis of antigens that are displayed on their outer membrane, thereby aiding in the delivery of these antigens to antigen-presenting cells [11]. Immune cells activated by antigens can traverse the bloodstream and participate in both mucosal immunity and systemic immune responses, which are marked by the production of immunoglobulin A (IgA) and immunoglobulin G (IgG), respectively [12]. Mucosal vaccines, including intranasal and intestinal vaccines, not only inhibit infection and prevent the progression of inflammatory diseases but also prevent infection from occurring while targeting tumor cells. Furthermore, mucosal vaccines are advanced by the discovery of safe and effective mucosal adjuvants combined with innovative antigens and exploration of their mechanisms of action [13, 14]. Adjuvants are an integral component of most vaccine formulations, as suitable adjuvants facilitate the promotion of appropriate immune responses against target pathogens at both the innate and adaptive levels [15]. Respiratory immunity offers unique advantages such as the induction of systemic and mucosal responses to prevent respiratory infections. However, the upper respiratory tract is susceptible to infections that endanger the lower respiratory tract due to the invasion of various microorganisms and allergens through the nose and mouth. Therefore, upper respiratory tract-specific defense mechanisms are important [10, 16]. Nasal vaccines can activate immune cells located in the mucosal tissues of the upper and lower respiratory tracts to produce dual stimulation, and this, together with needle-free administration, is conducive to the development of new nasal vaccines to produce long-lasting immunity and improve patient compliance [17]. This mini-review aimed to reveal novel mucosal immunotherapies targeting professional APC versus nonprofessional APC in pulmonary lung diseases, and may contribute to a deeper understanding of the potential immunological role of APC in lung diseases and development of therapeutic directions.

Lung disease treatment: a novel mucosal vaccine that crosstalks APCs

Over time, extensive research has explored the unique role of APC in various diseases. In this study, we review mucosal immunotherapies targeting APC lungs from innocuous to deleterious pathogens and anti-tumors.

Allergic diseases

Asthma is a complex disease that usually occurs during childhood [18]. Epithelial cells serve as natural barriers, while corticosteroids, routinely used to treat asthma, improve epithelial function and enhance the integrity of epithelial tight junctions by inducing pro-calmodulin-1. This reinforces the first line of defense against harmless stimuli, such as allergens [19]. ECs, another type of non-specialized APC, have many innate immune functions performed by Møs, including antigen presentation, and pro- and anti-inflammatory functions, and are important in regulating the differentiation of monocytes into Møs and DCs [20, 21]. Upon exposure to allergens, pulmonary ECs initiate an immune response and coordinate with DCs to induce and enhance adaptive Th2 immunity and type 2 (T2) cytokine production. Steroids not only enhance epithelial integrity, but are also highly sensitive to T2 inflammation, making inhaled corticosteroids the cornerstone of allergic asthma treatment [22–24]. TSLP, a Th2-associated cytokine, is resistant to corticosteroid therapy [25]. The nasal prophylactic vaccine antigen P1 (a conserved region of the HIV-1 gp41 envelope glycoprotein) induces TSLP production when interacting with the nasal epithelium, thus further affecting humoral and cellular antigen-specific responses; caution must be used when utilizing it as an adjuvant to a mucosal vaccine against HIV or tuberculosis in patients with asthma. Caution should be exercised when used as an adjuvant for HIV or TB mucosal vaccines in patients with asthma [26]. For the treatment of corticosteroid-resistant non-allergic asthma, ceramide nanoliposomes are used to treat corticosteroid-resistant non-allergic asthma by limiting cell growth through inactivation of the AKT pathway, which is controlled by a potent epithelial growth factor [27]. Nanoprobes containing an inhibitor of colony-stimulating factor 1 receptor, which targets epithelial cell production, can also be used to eliminate the production of allergen-reactive IgE, thereby preventing new asthma attacks and reversing already present allergic lung inflammation [28].Vaccines formulated with a hydrogel delivery system reduces eosinophilic inflammation and airway remodeling, including that of epithelial cells

[29]. The airway administration of OM-85 targets multiple innate and adaptive immune pathways to suppress allergic asthma, including the *Streptococcus*-dependent airway epithelial/IL-33/ILC2 axis in fungal infections, pulmonary allergeninduced T2 responses, and dendritic cells. It is administered at a lower dose than current oral treatments [30].

Pulmonary infection

A recent study used PVM, the murine equivalent of pneumococcal respiratory syncytial virus (RSV), to develop a novel moues model of RSV coinfection. In this model, PVM infection increases the density of pneumococci in the nasopharyngeal space and accelerates the early stages of pneumococcal transmission. However, there was a reduction in PVM load in the upper respiratory tract of mice with pneumococcal infection [31]. In addition to the observation that flora interacts with each other, fully inactivated influenza, pneumococcal vaccines, and live influenza vaccines combined with recombinant peptides, derived from streptococcal surface factors, enhance pneumococcalspecific responses when co-administered using the nasal cavity. Crosstalk between the pathogen and vaccine influences the immune action of APCs and development of better vaccine strategies for these two pathogens [32, 33].

viral infection

RSV infections during infancy are highly associated with the risk of childhood asthma [34]. Although most acute respiratory viral infections, such as influenza, elicit a longlasting immune response, RSV infections result in relatively short-lived protective immunity and can repeatedly infect the host without antigenic alterations. [35] Conversely, DCs initiate the immune response by first crossing the EC barrier to reach the peripheral tissues, where they uptake antigens through chemokines, and subsequently cross the lymphatic endothelium to enter the T-cell region of the draining lymph nodes [36]. Among them, cDC2s are attracted to and activated by alertin, which is secreted by PAMPstimulated airway epithelial cells and activates T helper cells mainly by presenting viral antigens on MHC II [37]. The combination of DC-targeted therapy with vaccination may have additive or synergistic effects, ultimately treating RSV infections with minimal side effects [38]. The TLR5 ligand flagellin is most potent in activating neonatal lung APCs, inducing a significant elevation in the expression of maturation markers for the cDC1 and cDC2 subpopulations. This unique efficiency suggests its potential use as a potent adjuvant for early mucosal vaccines in infancy for most infections, including those caused by respiratory syncytial and influenza viruses [39]. Interestingly, non-mucosal (intramuscular) inoculation with an IFN-1-inducing adjuvant promotes the release of CXCL9, CXCL10, and CXCL11 from alveolar endothelial and epithelial cells. This leads to the recruitment of CXCR3-expressing pDCs to the lungs and successfully enhances antigen-specific IgA production in intranasally sensitized vaccines [40].

Lung CD8 + memory T cells play a central role in influenza, and in a study where mice were immunized subcutaneously with ovalbumin antigen complexed with complete Fuchs' adjuvant, then boosted by intranasal OVA administration, AM directed the rapid expansion of antigen-specific CD8 + T cells in the lungs whereas cDC1 deficiency had no significant effect [41]. In contrast, intranasal IFN- inhalation was observed in a mouse model of infection, directing the migration and function of cDC1 to develop an optimal anti-viral response consisting of specific CD8 + T cells [42]. This may be due to differences in the pathways that stimulate CD8 + T cell expansion. The intranasal delivery of SIIN-Q11 nanofibers triggers long-lived memory CD8 + T cells in situ in the lungs via cDC1 and cDC2 crossover, precedes the drainage of mediastinal lymph nodes (mLNs) [43]. Intranasal immunisation induces robust systemic and mucosal immune responses with secretory IgA and IgG preventing influenza infection at the site of viral entry. Secretory IgA is produced by subepithelial plasma cells, and is translocated to the apical surface of airway epithelial cells via polymeric immunoglobulin receptors that prevent the adhesion of airborne microorganisms [44]. The chitosan-functionalized iron oxide nano-enzymatic adjuvanted fully inactivated influenza virus, catalyzes DC maturation, and enhances antigen presentation leading to increased IgA mucosal adaptive immunity [45]. Riboflavin, a safe and inexpensive food additive, induces the phenotypic and functional maturation of DCs as an adjuvant for the fully inactivated influenza virus, enhancing the IgA and IgG levels [46]. Adjuvant influenza virus recombinant neuraminidase proteins are much safer as intranasal primary and booster immunization than an intranasal vaccination with live attenuated influenza vaccines [47]. As the primary antibody class in blood and extracellular fluids IgG monomers fuse to influenza virus hemagglutinin antigens in the trimerized structural domains and CpG adjuvants, for intranasal immunization, bind to the receptor and mediate the transport of IgG antibodies across the epithelium, protecting against lethal influenza virus attack. Among them, CpG oligonucleotides are widely used in the laboratory and are recognized as potent mucosal immunomodulators [48, 49]. Graphene oxide nanoparticles have recently been demonstrated to be comparable to CpG, providing a new direction in adjuvant application. However, as secreted

IgA is more broadly reactive than IgG, it is an important component of the protective regimen of graphene oxide nanoparticles against various influenza virus infections [50]. Immunoglobulin G (IgG) shows promise for utilization in influenza virus studies. Sialylated IgG promotes the expression of nuclear REST, dampens NF-κB signaling, and triggers anti-inflammatory reactions, which aids in reducing lung inflammation and alleviating severe cases of influenza. This domain seems to present significant prospects for additional investigation [51].

The alum adjuvant is cytotoxic to the alveoli, causing necrotic apoptosis of alveolar epithelial cells, resulting in the production of IL-33 to induce Th2 immunity and increased expression of MHC class II in antigen-presenting cells in the lungs [52]. Thus, enhancing antigen-specific IgA antibody production. It was observed that alum itself causes lung injury, and that the absence of antibodydependent potentiation effects, which ensures safety, creates new challenges for the use of conventional alum adjuvants. In recent studies, pertussis colonization factor A with alum as an adjuvant for a vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) surfacespiking protein, triggers systemic and mucosal Th1/17-polarized immune responses. The interaction between the two reduced respiratory tract injuries. [53] whereas a shift from the conventional microscale alum adjuvant to a nanoscale reduced the risk of antibody-dependent potentiation, preventing SARS-CoV-2 infection in a highly effective manner [54]. The mechanism of antigen delivery by respirable coronavirus mimetic particles encoded by spiny proteins involves rapid binding to and internalization by alveolar macrophages as immunization in vivo increases mucosal IgA levels [55]. Additionally, mucosal vaccines with C5aR ligand Co1 peptide adjuvanted spicatin acting as antigen target monocyte-derived lysogenic DCs improves vaccination efficiency [56]. The main target for the development of a SARS-CoV-2 vaccine is not only spicatin but also the receptorbinding domain of spicatin that induces potent neutralizing antibodies and contains a major T-cell epitope that is important for viral entry into the target cell [57]. The modified porous silica particulate adjuvant and receptor-binding domain vaccine enhanced the uptake of SARS-CoV-2 antigen by nasal and airway epithelial cells, ultimately triggering a stronger immune response [58]. Furthermore, targeting DCs with a Clec9A-receptor-binding domain antibody construct specifically expressed on cDC1 induced higher specific antibody titers and prolonged the duration of vaccine action in vivo, thus providing robust and sustained systemic and mucosal protective immunity against the rapidly evolving SARS-CoV2 variant [59]. The optimized synthesis of the Shiga toxin B subunit as a protein antigen delivery vehicle targeting DCs was also investigated for its beneficial properties against the new, highly malignant variant [60, 61]. The fusion of a formyl peptide receptor-like 1 inhibitory protein to a spiny protein and an adjuvant with a lipidated formyl peptide receptor-like 1 inhibitory protein promoted the capture of various SARS-CoV-2 variants by DC [62]. Nasal formulations of innovative innate immune stimulators, including Heber-Nasvac, stimulate innate immune markers at sites of viral entry and systemic compartments (HLA class II in monocytes and lymphocytes) and activates DCs. These formulations are suitable for prophylaxis in high-risk groups, particularly the elderly and those at high risk of exposure to new variants with comorbidities. [63] COVID-19 may also cause DC cytopathy, reducing the number and effecting the function of DCs [64]. In this regard, a recently developed intranasal complex consisting of G5-BGG and antigen-expressing plasmid DNA induced antigen expression and dendritic cell maturation in the nasal mucosa exhibits the potential to serve as an effective carrier gene for intranasal vaccines [65]. Basophils can act as APCs and play a protective role against COVID-19. However, its underlying mechanisms and treatments are unknown [66].

Serum IgG and fecal IgA levels were significantly elevated after oral administration of recombinant *Lactobacillus* strains expressing potential antigenic determinants of spiny, membrane, and envelope proteins The carrier *Lactobacillus* also affected macrophage polarization and interacted with DCs for better epitope display [67]. Dendritic cells in the lung, specifically those expressing CD11b + and CD103 +, have the ability to promote the expression of a4b7 and CCR9 in T cells, facilitating T cell homing to the gastrointestinal tract. This mechanism is crucial for the recruitment and maintenance of chronic inflammatory diseases in the intestines. Research into the crosstalk between lung-associated dendritic cells and gut immunity has been explored in further studies [68, 69]. Additionally, DCs from aged mice exhibit reduced tolerance compared with DCs from young mice. In contrast, the tolerogenic function of DCs was successfully restored by introducing *Lactobacillus plantarum* into the intestines of aged mice. Therefore, the development of probiotic intestinal formulations will be helpful in improving immune responses to influenza vaccination and infection in elderly individuals [70].

bacterial infection

Tract infections, particularly lower respiratory tract infections, are a leading cause of death and disability, with *S. pneumoniae* being the major cause of lower respiratory tract infections [71]. There is concern regarding the increasing antibiotic resistance of *S. pneumoniae*.

However, current guidelines indicate that most patients with community-acquired pneumonia can still be successfully treated with antibiotic regimens that have been in-use for decades [72]. However, drugresistant strains and the reduced effectiveness of existing vaccines complicate treatment, thus suggesting the need for continued research focused on new approaches [73]. The recombinant ABC protein SP0148 and its antiserum inhibited *S. pneumoniae* adhesion to human lung epithelial cells in a dose-dependent manner, produced a protective immune response against lethal doses of *S. pneumoniae* infection [74]. A novel lipidated adjuvant, the chitosan derivative OTMC, triggered the release of cytokines from DCs and produced IgG that also potentiated the immune response to the vaccine [75]. Pneumococcal surface protein A was expressed on the surfaces of all *S. pneumoniae* strains. The enzyme polymerized caffeic acid can be used as a serotype-independent universal nasal pneumococcal vaccine formulation, and vaccines constructed with Pneumococcal surface protein A triggers a specific antibody response against pneumococcal infection [76]. However, the detailed mechanisms of this response are poorly understood. It has been demonstrated that targeting the Fc receptor with a fusion protein comprising pneumococcal surface protein A and IgG polarizes alveolar macrophages to an AM1 phenotype and increases the regular DC subpopulation of the lungs while enhancing Th1 cytokines and specific IgG and IgA levels [77]. The lipopolysaccharide bioactive fraction, *Bacillus* alkaloidus-producing lipid A, acts as an adjuvant to a nasal vaccine against pneumococcal surface protein A that stimulates DC to promote the production of the mucosal immune-enhancing cytokines, IL-6 and BAFF, and the formation of germinal centers in the lymph nodes, ultimately resulting in high levels of specific IgA and IgG responses [78]. Lung DC CD103 + and lung DC CD24 + are able to proficiently induce high levels of IgA and B cells to home to the gut [79]. In contrast, the chemical binding of chitosan nanocapsules to *S. pneumoniae* surface protein A promotes DC maturation and antigen presentation, followed by peripheral blood mononuclear cells activation and lymphocyte differentiation [80]. Polysorbate transporter protein adjuvant induces DC and helper T cells responses using the PPAR- pathway, ultimately resulting in a long-term memory response. [81]. Most pathogenic isolates express pneumococcal hemolysin (PLY) and are required for virulence and host-to-host transmission, and immunosuppressive interactions between Ply with MRC-1 expressed on AMs have been demonstrated in an experimental mouse model of lower respiratory tract infection. This mechanism also enables pathogens to penetrate MRC-1-expressing M2-type Møs and DCs within MRC-1-encapsulated endosomes [82, 83]. A146Ply is a mutation in *S. pneumoniae* in which Ply is inactivated and intranasal administration significantly attenuates bacterial-induced iron death in lung tissue and macrophages as well as enhancing macrophage phagocytosis [84]. CDC is an important virulence factor of PLY. A peptide that could bind to the virulence factor was designed, using docking to identify the interaction site with MRC-1.In vitro experiments showed that these peptides blocked the production of inflammatory cytokines by human Møs, inhibited the uptake of bacteria by DCs through MRC-1, and prevented bacterial invasion into the epithelium in a 3D lung tissue model. Calcium phosphate nanoparticles have been developed as peptide nanocarriers in vivo and can be used as an adjunctive therapy alongside antibiotics. [85].

Vaccines formulated with STING-activated cyclic dinucleotide adjuvants induce CD4 + T cells that significantly protect against *Mycobacterium tuberculosis* [86]. The novel therapeutic DNA vaccine, rel Mtb, enhances specific T cell responses by increasing contact with immature DCs and exhibits maximal mycobacteriostatic activity in combination with isoniazid for intranasal administration as well as robust systemic and local Th1 and Th17 responses [87]. BAdv 85C5-infected DCs express a robust transcriptome of genes that regulate antigen processing, ultimately leading to T cell expansion [88]. The transmission of *Mtb* across the alveolar barrier involves the phagocytosis of inhaled bacteria by Ams, which then cross the alveolar barrier by exudation, a process known as the "Trojan horse" mechanism [89]. Møs are the first immune cells to encounter *Mtb* during an infection and serve as its main replicative ecosystem. The entry of *Mtb* into Møs through different receptors can activate different pathways that inhibit or promote bacterial replication; among these, the vitamin D pathway promotes the polarization of *Mtb*-infected human Møs to enhance bacterial killing [90, 91]. Unstructured lipid carrier (NLC)-incorporated linezolid targets macrophages in vitro and in vivo with potent clinical efficacy against drug-resistant tuberculosis [92].

Type 2 diabetes mellitus affects antigen presentation after tuberculosis infection, and the kinetics of Mtb peptide-MHC II complex formation in human monocyte-derived Møs are reduced at high glucose concentrations, thereby decreasing their ability to activate T cells. Nanoparticles containing all-trans retinoic acid in hostdirected therapy are used to treat patients with *M. tuberculosis* or diabetic tuberculosis by targeting macrophages [93–95].

Malignancy

KRAS mutations are targets for immunotherapy in non-small-cell lung cancer, and intranasal immunization with nanoemulsion adjuvants combined with KRAS peptides

enhance KRAS-specific Th1 and Th17 responses as well as reduce tumor incidence [96]. A study using DC therapy to target various tumor-associated antigens for lung cancer treatment was initiated by Kontani et al. In this study, mature DCs loaded with the MUC1 peptide were injected into the supraclavicular region three times at 2-week intervals [97]. The patients experienced a reduction in tumor size or tumor marker levels, suggesting that a DC vaccine targeting MUC1 could be used for cancer immunotherapy. Recently studied MUC -1 PLGA-NA-NPs are being explored as potential candidates for investigating the antitumor effects in NSCLC xenograft models through inhalation [98]. The hr-8-PLGA@Ag/CpG nanovaccine specifically binds to the endocytic receptor DEC-205, which is mainly found on cDC1, promoting dendritic cell maturation and increasing antigen cross-presentation. This process ultimately boosts immune responses against tumors mediated by CD8 + T cells [99]. Squalenebased nanoemulsions at 0.1%, alter mucosal characteristics and induce broad-spectrum antigenspecific cellular immunity after intranasal vaccination. [100] mPLA/mRNA tumor vaccines by stimulating DC maturation, reprogramming of M2 macrophages into M1 macrophages, and crossactivation of innate and adaptive immune responses, ultimately providing ideas and perspectives for mRNA tumor vaccine applications in lung cancer and bone metastases treatment [101]. Intranasal administration of ECF with fucoidan promoted the activation of DCs, natural killer cells, and T cells in mLNs, which is used in immunotherapy to treat metastatic lung cancer [102].

Conclusion

New vaccine developments, adjuvants, and immunization strategies have gradually increased the potential of mucosal vaccines. However, the role of mucosal barriers and vaccine safety has not been effectively identified. Therefore, efforts should still be made to explore effective alternatives. Several factors such as antigens, formulations, routes of administration, adjuvants, animal models, and other factors should be considered for the development of safe and effective mucosal vaccines [103]. Most mucosal immunity is directed against plasma and epithelial cells as well as against crosstalk between DCs and macrophages. In addition, although there are few studies on other APC-based therapies, different classes of APCs elicit different immune responses to pathogens and have distinct mechanisms of action. Understanding their mechanisms of action is beneficial for exploring the potential roles of APCs in lung diseases, which may provide important insights into more effective therapeutic approaches for a wide range of conditions, from chronic to infectious lung diseases. However, APC-based therapies for lung diseases are still in the developmental stage. Most of the vaccination studies have introduced new treatment concepts but have not yet demonstrated significant clinical benefits and low toxicity. Therefore, further research is required to validate these findings.

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Authors' contributions
Conception and design: ZC and WH; Administrative support: WH; Collection and assembly of data: ZC, YL; Data analysis and interpretation: ZC and YL; Drafting the article or revising it critically for important intellectual content: All authors; Final approval of manuscript: All authors; Accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: All authors.

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No datasets were generated or analysed during the current study.

Declarations

Competing interests
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