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Advanced drug delivery systems targeting NF- κ B in respiratory diseases

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“Dysregulation of the NF- κ B pathway serves as the major causative factor in the production of proinflammatory metabolites and dysregulated lung tissue homeostasis, hence causing the onset of the pathophysiology of respiratory disorders.”

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NF- κ B in respiratory diseases

In light of the large number of proinflammatory genes that interact with NF- κ B, it is not surprising that this protein complex plays a central role in the pathogenesis of lung diseases by regulating the pathophysiological transcription of proinflammatory cytokines and chemokines, which may include TNF- α , IL-1 β and IL-6, and proinflammatory enzymes such as cyclooxygenases and nitric oxide synthase [1]. The heightened expression or dysregulation of NF- κ B resulting from physicochemical or physiological stimuli in the lungs manifests as chronic respiratory ailments; namely, asthma, SARS, chronic obstructive pulmonary disease, pulmonary arterial hypertension (PAH), systemic inflammatory response syndrome, acute respiratory distress syndrome, cystic fibrosis and acute lung injury [2].

Advanced nanosystems for targeting NF- κ B in respiratory ailments

Advanced drug delivery nanosystems offer systemic and noninvasive routes of administration of high- and low-molecular-weight nonpolar and polar therapeutics while enabling epithelial or subepithelial absorption of the cargo pharmaceutical agent [3]. Tethering of the advanced delivery vehicles with absorption enhancers and mucolytic agents further improves their transit across the tight junctions of lung epithelia, avoiding the excessive mucous layer that is characteristic of obstructive respiratory diseases. The aerosolized, biocompatible, polysaccharide, nanoparticle-based, advanced drug delivery system ‘Novochizol’, identified as a first-in-class drug delivery vehicle for impending COVID-19 drugs, displays a strong adherence to the lung epithelia. In addition, it exhibits sustained drug release properties and demonstrates remarkable biocompatibility [4]. The nanosystem enables the achievement of an optimal drug concentration in SARS-infected lungs while avoiding undesirable systemic distribution of the cargo

drug molecules, thereby achieving an optimal therapeutic effect by improving the pharmacokinetic properties of the drug. Similarly, polymeric nanoparticles with marked biocompatibility and biodegradability prompt a sustained drug release, thereby maintaining optimum absorption, distribution, bioavailability, metabolism and excretion of the loaded therapeutic. Stimuli responsiveness represents an important feature of polymeric nanoparticles in attaining drug delivery applications by exploiting the local physical, chemical, metabolic or biological environment of the target site [5]. Vesicular drug delivery systems represent a state-of-the-art approach for carrying the cargo pharmaceutical to the target site irrespective of its hydrophilicity or lipophilicity. Specifically, vesicular drug delivery systems that carry a positive surface charge achieve incredible electrostatic adherence to the oppositely charged mucous membrane, which avoids enzymatic degradation of the encapsulated drug molecules and prevents their mucociliary clearance. Importantly, vesicular drug delivery systems prove highly effective in co-delivery of adjuvants with desired pharmaceuticals, achieving an ideal mitigation effect in respiratory diseases [6]. Further advancements have identified metallic, nanoparticle-based drug delivery systems for therapeutic delivery across the respiratory system and the simultaneous imaging of affected tissues or infected sites owing to the characteristic optoelectronic, plasmonic or magnetic properties of the parent metallic nanoparticle. The physical or chemical loading of drug molecules or bioconjugation of antibodies and therapeutic nucleic acids or nucleotides on the surface of physicochemically distinct metal nanoparticles further promotes their drug delivery applications in respiratory ailments [7].

The remarkable profile of advanced drug delivery systems provides a robust candidature in the contemporary respiratory disease management paradigm. However, regulation of the pathogenesis of inflammation-driven disease by these systems represents the cornerstone of concomitant respiratory therapy. Dysregulation of the NF- κ B pathway serves as the major causative factor in the production of proinflammatory metabolites and dysregulated lung tissue homeostasis, hence causing the onset of the pathophysiology of respiratory disorders. The targeting of the NF- κ B pathway by advanced drug delivery systems therefore provides a future path for the effective management of respiratory health.

Metal nanoparticles for the targeting of NF- κ B in respiratory ailments

Ag nanoparticles (AgNPs) are reported to have attenuated allergic airway inflammation and hyperresponsiveness caused by upregulation of the NF- κ B pathway, which resulted in increased levels of IL-4, IL-5 and IL-13, in an ovalbumin-induced murine model of allergic airway disease [8]. The administration of AgNPs caused a marked downregulation in the heightened levels of ovalbumin-triggered intracellular reactive oxygen species in the bronchoalveolar lavage fluid of test animals and demonstrated a significant decrease in NF- κ B-regulated Th2 cell-mediated inflammation, which is the leading immune factor in the induction of asthma. However, *in vitro* and *in vivo* analyses have suggested the contribution of AgNP-induced apoptosis to the onset of cellular senescence in the lung via upregulation of the NF- κ B–COX-2–PGE2 axis, which results in the progression of cystic fibrosis in animal models [9]. By contrast, recent reports concluded that the utilization of AgNP-induced reactive oxygen species generation led to NF- κ B-directed cellular apoptosis, preventing the invasion and malignancy of lung adenocarcinoma A549 cells and suppressing the growth and progression of human lung cancer H1299 cells in a xenograft severe combined immunodeficient mouse model [10,11]. Nevertheless, AgNP-induced alterations in NF- κ B-related genes depend on the cell type, nanoparticle size and basal activity of NF- κ B, further validating NF- κ B-targeted respiratory drug delivery by AgNPs [12].

Biocompatible polymers for targeting NF- κ B in respiratory ailments

Intratracheal instillation of polymeric nanoparticles constituted within bioabsorbable PEG-PLGA in a rat model of monocrotaline-induced PAH for 2 weeks prevented the activation of NF- κ B, thereby discouraging the progression of PAH and remodeling of pulmonary arteries by monocrotaline [13]. The survival rate of the test animals with monocrotaline-induced PAH further improved during the third week of polymeric nanoparticle administration. Glycol chitosan nanoparticles with hyaluronic acid surface fabrication served as a pH-sensitive advanced drug delivery system for co-delivery of doxorubicin and celecoxib in non-small-cell lung cancer, thereby improving drug pharmacokinetics and tissue distribution of the cargo molecules [14]. The drug delivery nanosystem, with an average diameter of 150 nm, displayed stability at a neutral physiological pH of 7.4, whereas drug release using this nanosystem occurred at an acidic pH of 6.0 and 4.0 in response to the tumor microenvironment. Importantly, the drug delivery nanosystem remarkably downregulated the expression of NF- κ B-related genes compared with free doxorubicin and celecoxib. The association of NF- κ B with cancer cell survival, cell proliferation and immune cell

response and its inhibition by the hyaluronic acid-decorated glycol chitosan nanoparticles encourage a novel drug delivery approach in the treatment of respiratory diseases by targeting the NF- κ B pathway with advanced drug delivery vehicles.

Vesicular nanosystems for targeting NF- κ B in respiratory ailments

A liposome drug delivery system loaded with dexamethasone demonstrated marked mitigation of silica-induced pulmonary toxicity by downregulating the expression of NF- κ B and subsequently upregulating the production of anti-inflammatory IL-10 by leukocytes [15]. Histopathological analysis confirmed the attenuation of lung fibrosis and the reduction in silica-induced pulmonary toxicity (based on the ratio of right lung to total body weight) and the reduction in hydroxyproline content in the right lung, which served as the biochemical index for fibrosis. Liposomal curcumin delivery offered similar effects in radiation pneumonitis by inhibiting the expression of NF- κ B in addition to downregulating the expression of IL-6, IL-8, TGF- β and TNF- α instigated during thoracic radiotherapy [16]. The combination of radiotherapy and curcumin liposomes improved intratumoral apoptosis, reduced lung fibrosis and ameliorated the sensitivity of target murine lung carcinoma (LL/2) cells to radiation therapy.

Dry powder inhalers for targeting NF- κ B in respiratory ailments

Dry powder inhalers have proven to be highly beneficial in achieving a higher drug concentration in the lungs while maintaining low systemic exposure to counter the poor solubility and systemic side effects of the drugs. 'Tranilast', which is used for treating airway inflammation, causes these side effects, and this led to the development of a novel powder inhaler that attenuates NF- κ B-triggered inflammation in the airways [17]. The drug delivery powder maintained its therapeutic properties even after 6 months of storage at room temperature. Inhalation of the dry powder formulation remarkably inhibited inflammation in experimental chronic obstructive pulmonary disease models and asthma mainly because of the downregulation of NF- κ B and COX-2 expression. Similarly, liposomal andrographolide dry powder inhalers provided relief upon intratracheal spraying in test animals infected with staphylococcal pneumonia [18]. Andrographolide liposomes displayed a mean diameter of 77.91 nm with a negative zeta potential of -56.13 mV. Rehydration of liposomal andrographolide dry powder inhalers led to the recovery of liposomes that demonstrated suitability for pulmonary delivery of the therapeutic agent, with a fine particle fraction of 23.03% and mean mass aerodynamic diameter of 4.87 μ m. The dry powder formulation proved highly effective compared with the tenfold dose of andrographolide and penicillin. Inhibition of the phosphorylation of NF- κ B provided the principal basis for the downregulation of proinflammatory cytokines as well as the regulation of immune response with regard to the bacterial infection in test animals.

Nanocomposites for targeting NF- κ B in respiratory ailments

Nanocomposites composed of porous chitosan oligosaccharides and SiO₂ nanoparticles displayed a pH-sensitive release of the encapsulated drug while achieving a sustained release pattern and maintaining an optimal concentration of the cargo drug at acute lung injury sites [19]. The nanocomposite significantly downregulated the heightened expression of NF- κ B and related inflammatory cytokines in caerulein-administered animal models. Attenuation of the NF- κ B pathway occurred as a result of the activation of Nrf2 expression in animals treated with the nanocomposite. Similarly, Zn-doped CuO nanocomposites notably inhibited the development of lung adenocarcinoma A549 cells by inhibiting the expression of nucleus NF- κ B p65 [20]. The inhibition of NF- κ B-mediated oxidative stress in cancer cells by nanocomposites encourages their further utilization in the treatment of respiratory diseases.

Conclusion & future perspective

The NF- κ B pathway plays an important role in the instigation of the acute inflammatory response, which is found to be upregulated in most chronic respiratory diseases. The contemporary drug delivery paradigm for treating these disorders, which is broadly based on dry powder inhalers, nebulizers and aerosolized formulations, faces persistent challenges related to several factors; namely, target specificity, preservation of drug pharmacokinetic profile and distribution to infected tissues. Furthermore, the utilization of aerosols enhances the possibility of respiratory infection as a result of accidental inhalation. Advanced drug delivery vehicles respond to the necessity for a new approach by effectively managing the intricacies associated with conventional methods. Metal nanoparticles, vesicular drug delivery systems, polysaccharide-based therapeutic delivery vehicles, polymeric nanoparticles, nanocomposites and respirable powder approaches selectively target the NF- κ B pathway to overcome the acute inflammatory response

and oxidative stress associated with the onset of respiratory pathogenesis. In addition, these tools present themselves as robust candidates for the therapeutic delivery of drugs in the treatment of COVID-19, where the NF- κ B pathway plays a major role in triggering the cytokine storm. These claims further validate their candidacy as the prospective respiratory drug delivery vehicles of the future.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

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