REVIEW ARTICLE

Advancing of Cellular Signaling Pathways in Respiratory Diseases Using Nanocarrier Based Drug Delivery Systems

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Abstract: Cell Signaling pathways form an integral part of our existence that allows the cells to comprehend a stimulus and respond back. Such reactions to external cues from the environment are required and are essential to regulate the normal functioning of our body. Abnormalities in the system arise when there are errors developed in these signals, resulting in a complication or a disease. Presently, respiratory diseases contribute to being the third leading cause of morbidity worldwide. According to the current statistics, over 339 million people are asthmatic, 65 million are suffering from COPD, 2.3 million are lung cancer patients and 10 million are tuberculosis patients. This toll of statistics with chronic respiratory diseases leaves a heavy burden on society and the nation's annual health expenditure. Hence, a better understanding of the processes governing these cellular pathways will enable us to treat and manage these deadly respiratory diseases effectively. Moreover, it is important to comprehend the synergy and interplay of the cellular signaling pathways in respiratory diseases, which will enable us to explore and develop suitable strategies for targeted drug delivery. This review, in particular, focuses on the major respiratory diseases and further provides an in-depth discussion on the various cell signaling pathways that are involved in the pathophysiology of respiratory diseases. Moreover, the review also analyses the defining concepts about advanced nano-drug delivery systems involving various nanocarriers and propose newer prospects to minimize the current challenges faced by researchers and formulation scientists.

Keywords: Cell signaling, nanotechnology, drug delivery, respiratory diseases.

1. INTRODUCTION

Cell signaling or communication among the cells is one of the key factors in understanding both cellular mechanisms and system functioning [1–6]. There are various cell signaling pathways that are involved in a myriad of specific mechanisms in the body, ranging from an antigen triggered antibody response to targeted cells responding to particular hormones. The cells in the body are constantly connected to each other in order to maintain the coordination and regulated response throughout [7, 8]. However, any dysfunctionality in such a cellular signaling process leads to abnormality or disease. In most cases, cellular interaction involves the binding of a targeted molecule to a specific receptor that is present on the plasma membrane. This triggers a cascade of reactions to regulate the external stimuli and thereby influence cellular behavior [9]. Cytokine receptors, G protein-coupled receptors (GPCRs), Receptor tyrosine kinase (RTKs) and Transforming growth factor- beta (TGF-β) is the common receptor involved in cell signaling [10]. These receptors involved in cell signaling, generally perceive the on-going information over the cell surface and communicate it to the nearby cells. Standard cascade signaling reactions are usually triggered within the nucleus, which further regulates the transcription factors and amends regulation of genes as well as cellular responses [9].

These cell signaling pathways are the primary regulators of the normal functioning of the cellular system. Hence, any changes in these cell signaling pathways may result in aberrations in the body [11–14]. Approximately, 8.3% of the global population suffers from chronic respiratory diseases (CRDs), due to the aberrant functioning of the respiratory system [15]. These CRDs, namely, asthma, Chronic Obstructive Pulmonary Disease (COPD), tuberculosis (TB) and lung cancer occur because of i) causative environmental factors, ii) microbial infections, iii) genetic make-up and iv) the lifestyle of the individual [16–19]. CRDs demonstrate the involvement of a chemical entity, foreign agent, interleukins, oxidative agent or proteins, which are directly or indirectly associated with these cell-signaling pathways, and therefore, can serve as the active target for treating these CRDs. Targeting cytokines for CRDs can be a potential therapeutic intervention via blocking antibodies or therapeutic proteins. An emerging role of IL-4, IL-5 and IL-13 was found as anti-cytokine therapies for asthma [20]. Anti-IL-5 antibody has been found to be effective in reducing eosinophil numbers in blood and sputum, however, it was found to be substantially less effective at reducing eosinophil numbers in the lung and had a modest impact on lung function [21]. A recent study showed the role of neuroimmune semaphorin 4A in downregulating asthma severity by regulation of IL-13. Several therapeutics targeting the tumour necrosis factor (TNF)-α pathway have been developed and used in clinical trials. Therapeutics such as mouse/human IgG1 antibody against TNF-β, infliximab have been found to be effective in asthma compared to COPD [22].

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The role of NLRP3, caspase-1 and IL-1β responses has been found to be elevated in the lungs of Chlamydia infection-induced experimental severe steroid-resistant asthma [23] and the sputum NLRP3 and IL-1β expression correlate to key clinical parameters of human severe steroid-resistant asthma, including increased numbers of neutrophils in the airways, and reduced lung function. The functional roles and potential for therapeutic targeting of NLRP3, caspase-1 and IL-1β in experimental severe steroid resistant asthma by intranasally administering MCC950 (a potent and highly selective NLRP3 inflammasome inhibitor, ac-YVAD-cho (a selective caspase-1 inhibitor) or neutralising anti-IL-1β monoclonal antibody during Chlamydia and Haemophilus infection-induced severe steroid-resistant asthma. The elevated lung IL-1β response was suppressed by treatments, and this was associated with the suppression of steroid-resistant neutrophilic airway inflammation and airways hyper-responsiveness. Therefore, targeting the exaggerated NLRP3 inflammasome response component in severe steroid-resistant asthma is a novel therapeutic approach and suggests the clinical preference as it allows IL-1β processing through other mechanisms for protection against infections [24].

Furthermore, several known inflammatory target proteins including matrix metalloproteinase-9 (MMP-9), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), cyclooxygenase-2 (COX-2), and cytosolic phospholipase A_2 (cPLA$_2$) have been associated with airway and lung inflammation in response to different stimuli [25]. The environmental insults can reach the lung through airways or pulmonary and systemic circulations. The responses by circulating and resident cells is regulated by different inflammatory signaling pathways, such as Src family kinases (SFKs), protein kinase C (PKC), nicotinamide adenine dinucleotide phosphate (NADPH)/reactive oxygen species (ROS), PI3K/Akt, MAPKs, nuclear factor-kappa B (NF-*k*B), activator protein-1 (AP-1) and activator of transcription proteins (JAK-STAT) [26-28]. These signaling pathways regulate inflammatory signaling pathways and target proteins involved in airway and lung inflammation [29, 30].

Current traditional approaches employed in the treatment and management of these CRDs have become ineffective, as they were originally designed to only adhere and function on the general site [31, 32]. Extensive research on how these respiratory diseases develop under different pathological conditions, along with the various factors that come into play, has uncovered the variability among these diseases and has assisted scientists and researchers in comprehending the role of cell signaling pathways [29, 33, 34]. This review focuses on understanding the function of cell signaling pathways and their synergy with CRDs. Additionally, it will also speculate on various nano-drug delivery systems and nanocarriers currently employed and attempts to propose newer prospects for minimizing the challenges in the near future.

2. GLOBAL PREVALENCE OF MAJOR RESPIRATORY DISEASES

Globally, CRDs are becoming one of the leading causes of morbidity and mortality. Additionally, the rate of CRDs is exponentially increasing and advancing in all socioeconomic classes, as well as regions [35]. According to the World Health Report, the disability, morbidity, and mortality attributed to these CRDs account for up to 8.3% of the global burden. Moreover, most of the deaths caused by these CRDs occur in developing countries [15, 36–38]. The four most prevailing chronic respiratory diseases are pictorially illustrated in Fig.1., and their key features are discussed below:

Asthma is a chronic inflammatory disease of the upper airways, characterised by airway hyper-responsiveness (AHR), airflow obstruction and eosinophilic infiltration [39]. Common symptoms of this disease range from a persistent cough, dyspnea to wheezing. Allergy is reported to be one of the major causes of asthma. Here,

the bronchioles of the upper airways get inflamed, as well as narrowed because of edema. It is further associated with remodeling of the smooth muscles and mucus production [40]. According to the consensus of the Global Burden of Disease-2016 (GBD), there are around 339 million people worldwide, who are suffering from asthma, which is higher by 3.6% from the report published in 2006 [41, 42]. Globally, asthma ranks as the 23rd leading cause of mortality [43].

COPD is a progressive inflammatory lung disease characterized by persistent airflow limitation, caused primarily by inhaling smoke or noxious particles. The primary symptoms of COPD are recurrent incidences of dyspnea, wheezing and cough (with or without mucus) [44]. COPD causes enlargement of air spaces in the bronchioles, disrupting the lung tissues, and eventually resulting in difficulty to breathe. As per the 2016 statistics, around 328 million people suffer from COPD worldwide [45]. It has been reported that COPD accounted for 3.17 million deaths in the year 2015 alone, of which, more than 90% of people belong to developing countries. Globally, COPD holds the 10th position as the leading cause of mortality [46].

Lung Cancer, a chronic respiratory disease, is caused by a mutation in the protective gene or due to DNA damage resulting from persistent smoking or indirect inhalation [47]. Other causes may be air pollution, workplace exposure to certain chemicals such as asbestos, nickel, chromium, radioactive gases like radon etc. [48–51]. The hallmark of lung cancer, like most other cancers, is characterized by abnormal and uncontrolled cell division, which invades nearby tissues, primarily in the lining of air passages [52]. On the basis of histology, they are further classified as non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Moreover, NSCLC is further sub-classified into three sub-groups, namely, Adenocarcinoma (AD), Squamous-cell cancer (SQ) and Large-cell cancer (LC) [53]. The symptoms observed in patients suffering from lung cancer involves loss of appetite, chest pain, cough, compromised immune system, wheezing, and heavy sputum production [54]. As per the available consensus, lung cancer is one of the leading causes of death and accounts for around 1.4 million deaths every year. According to the WHO (2018), there have been 1.76 million deaths worldwide due to lung cancer. The highest prevalence of this disease is recorded in developing countries [55]. Globally, lung cancer holds the 5th position as a leading cause of mortality [42].

Tuberculosis (TB) is a chronic infectious disease caused by the bacterium, *Mycobacterium tuberculosis.* The bacterium usually infects the lungs first, then slowly, they affect the other organs like genito-urinary tract, lymph nodes and the skeletal system [56]. Moreover, it spreads to other people through cough, sneeze or physical interaction. This infectious disease shows symptoms like cough with sputum that contains or stained with blood, fatigue, fever, loss of weight and night sweats [57]. Globally, TB has been accounted for over 1.5 million deaths in 2018 alone, and about 10 million people are still prone to TB. Moreover, the burden of TB is mostly in developing countries. Multi-Drug Resistant TB has evolved as a major threat to public health [58]. Globally, TB holds the 9th position as the leading cause of mortality [59–61].

Interstitial Lung Disease (ILD) is a wide group of pulmonary diseases that include more than 100 disorders which cause scarring and fibrosis of the lung [62]. The characteristic manifestations of ILDs are variable and include respiratory symptoms (cough, dyspnea), reduced pulmonary capacity, chest x-ray abnormalities and pathological fibrosis. ILDs can be categorised into individual disorders according to some of those specific clinical, radiological and histopathological characteristics [63]. For example, granulomatous inflammation is characteristic of sarcoidosis whereas pulmonary fibrosis and lung distortion are unique to idiopathic pulmonary fibrosis (IPF) [64]. The most common ILD is IPF, with an estimation of approximately 3 million people suffering from IPF world-
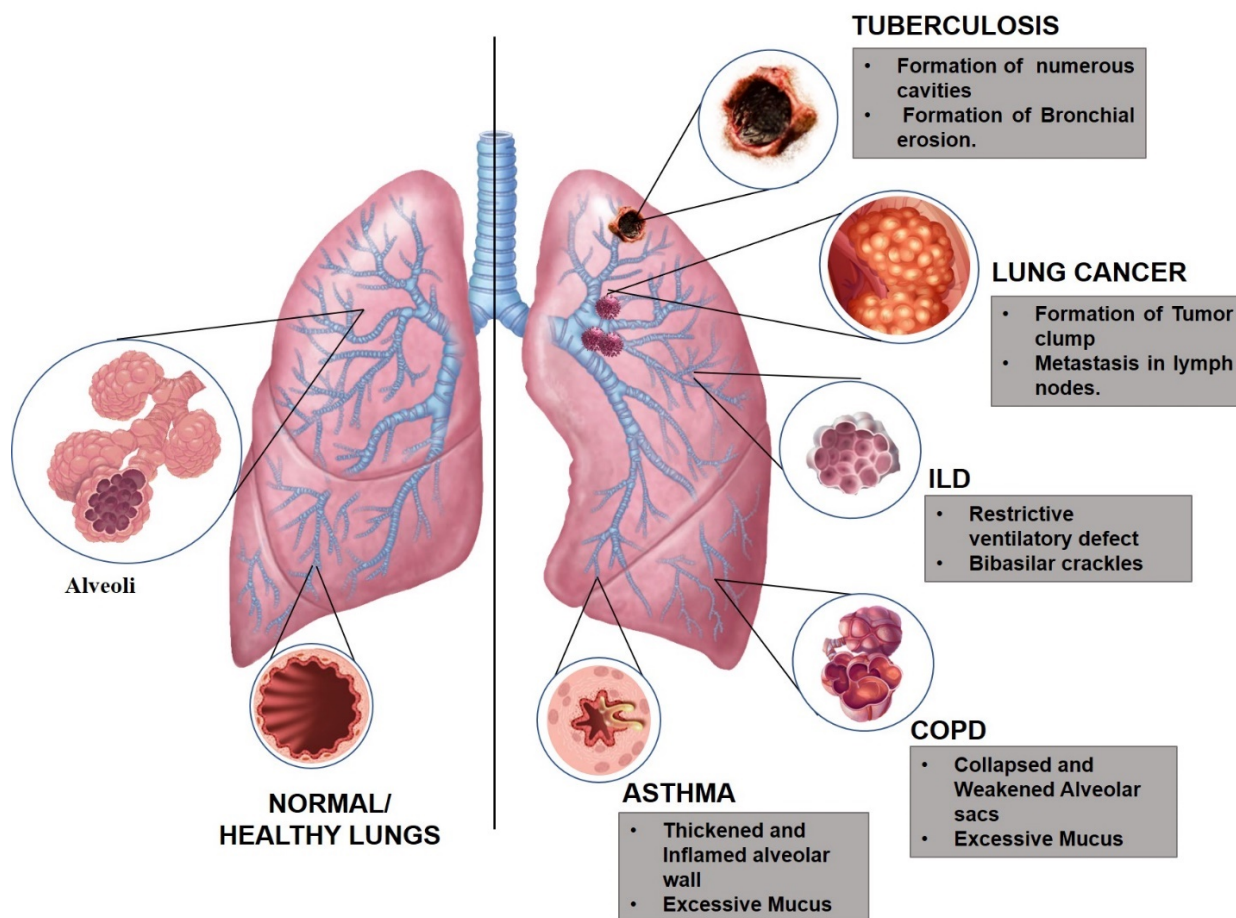
Fig. (1). Overview of the common chronic respiratory diseases. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

wide and 130 000 persons in the United States [65]. ILDs are idiopathic disorders in most cases, meaning the cause of lung damage and resulting fibrosis is unclear [62].

3. TARGETED CELL SIGNALING PATHWAYS INVOLVED IN RESPIRATORY DISEASES

There are numerous cell signaling pathways involved in regulating the normal functioning of the cell. Most of these cell signaling pathways are activated by external signals that transfer information within the cell from its surface to the effector site [66–68]. The focus of this review revolves around the cell signaling pathways that are primarily involved in respiratory diseases. The major cell signaling pathways (Fig. **2**) are summarized below:

4. AKt/PKB/PI3K SIGNALING PATHWAY

Akt/PKB/PI3K signaling pathway is an intracellular signaling pathway having a vital role in regulating the various cellular functions like development, growth, metabolism, proliferation, protein synthesis, survival and transcription [69]. The Akt/PKB/PI3K gets activated either by growth factors, hormones or nutrients [70]. The reaction cascade is triggered by external stimuli on the interaction with any of the receptors, namely, B and T cell receptors, cytokine receptors, G-protein-coupled receptors (GPCR), integrins and tyrosine kinase [71]. This interaction activates PI3K and triggers the generation of phosphatidylinositol-(3,4,5)-trisphosphates (also known as PIP3) *via* phosphorylation. After that, the synthesized PIP3 binds with the pleckstrin homology (PH) domain of Akt for facilitating its transfer to the plasma membrane [72, 73]. In the plasma membrane, Akt gets phosphorylated by Phosphoinositide-

dependent kinase 1 (PDK1) at Thr308, which partially activates the Akt. The phosphorylation of Akt at Ser473 via mTORC2 completely activates the function of the enzyme and regulates the normal functioning of the cellular processes [74, 75].

5. JAK-STAT SIGNALING PATHWAY

JAK-STAT is another intracellular signaling pathway that regulates and controls cellular functions like development and homeostasis [76]. This pathway gets activated by the interaction of cytokines (i.e., interferons) with receptors like epidermal growth factor receptor (EGFR), GPCR, and platelet-derived growth factor receptor (PDGFR) [77]. This interaction phosphorylates the JAKs associated with these receptors on the cytoplasmic side. Hence, these phosphorylated JAKs further phosphorylates the tyrosine residues of the receptor to generate the docking site for Src Homology 2 (SH2) domain of STATs [78]. These docked STATs get phosphorylated by JAKs associated with tyrosine residues located at the C-terminal end. After the phosphorylation of STATs *via* SH2-phosphotyrosine interaction, it dissociates itself from the receptor [79, 80]. Dimerized STATs are then imported into the nucleus with the help of importin-α (i.e., Imp- α). After these events, STATs attach themselves to the promoter region via the DNA-binding domain, which further regulates the transcription of genes essential for cellular processes [81].

6. MAPK SIGNALING PATHWAY

The MAPK signaling pathway is associated with various different pathways and aids in regulating several important cellular processes like apoptosis, metabolism, proliferation and transcription
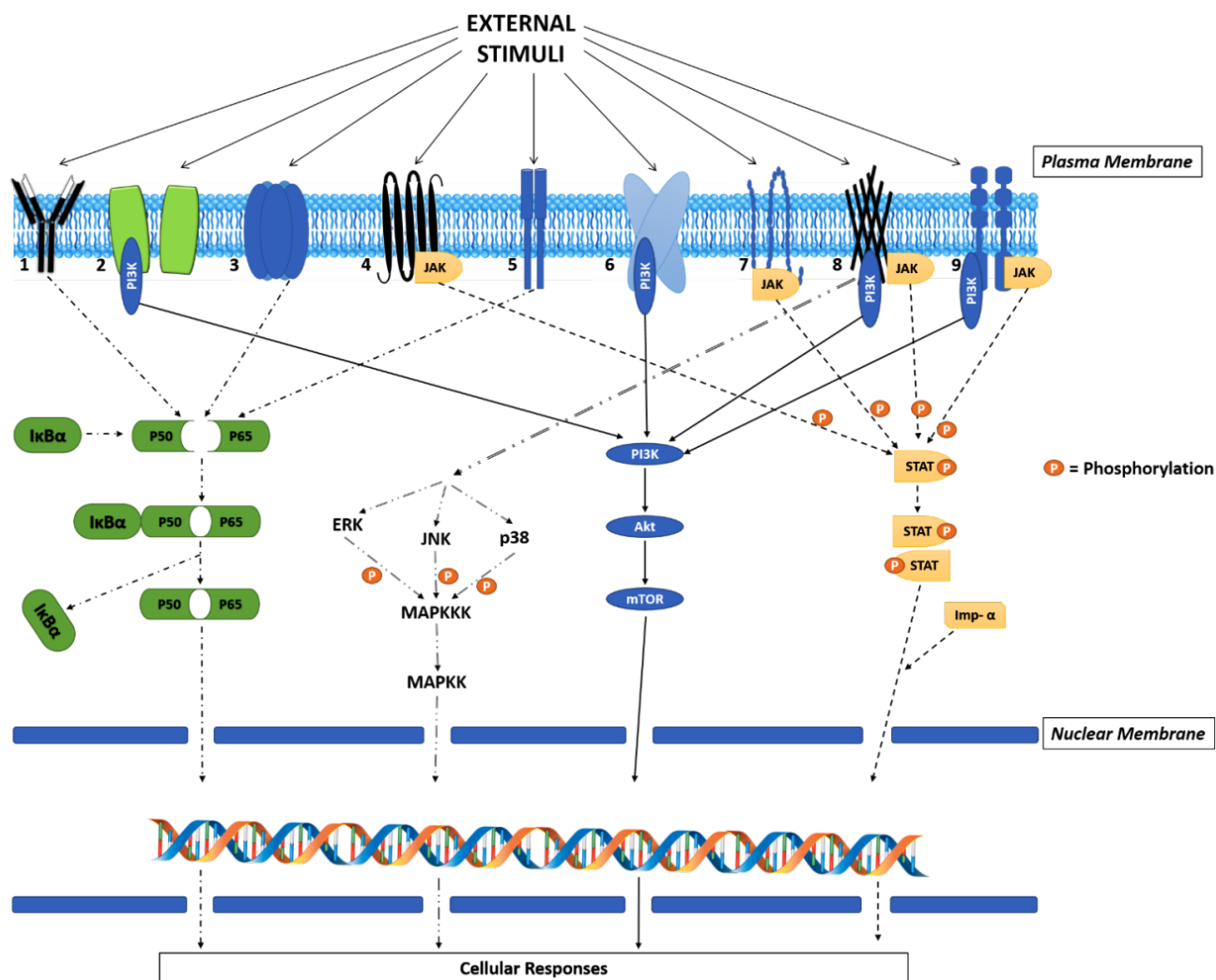
Fig. (2). The classical representation of major cell signaling pathways involved in chronic respiratory diseases. Here, 1- TNF receptor, 2- Integrin receptor, 3-PAMPs receptor, 4- EGF receptor, 5- Interleukin receptor, 6- Tyrosine kinase receptor, 7- PGF receptor, 8- Cytokine receptor, 9- GPC receptor. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

[82, 83]. These different downstream processes get activated by the final MAPK component attached to any of the three signaling pathways like Extracellular-signal regulated kinase (ERK) pathway, c-Jun-N-terminal kinase (JNK) pathway and p38 pathway [84]. External stimuli activate this signaling pathway. The pathway primarily acts on one of the 14 different types of MAPK kinase kinases (MAPKKKs). On activation, these MAPKKKs further phosphorylate one of the 7 types of MAPK kinases (MAPKKs). Sequentially, the phosphorylated MAPKKs further continue to phosphorylate one of the 12 MAPKs for eliciting the cellular responses [82].

7. NF-κB SIGNALING PATHWAY

NF-κB signaling pathway is activated by different external stimuli, namely, interleukin-1 (IL-1), pathogen-associated molecular patterns (PAMPs) and tumor necrosis factor-alpha (TNF-α), responsible for regulating different cellular processes like apoptosis, inflammation and proliferation [85]. This pathway is usually initiated by the interaction of external stimuli with a TNF receptor. On activation, p50 and p65 isoforms of NF-κB form the dimer and recruit the signaling complex on the membrane [86]. The signaling complex comprises the inhibitors of NF-κB (IκB) kinase, i.e., IKKα and IKKβ. These IKKα and IKKβ form the dimer for phosphorylat-

ing the IκBα subunit, which later aids in retaining the p50/p65 isomers within the cytoplasm [87]. Proteasome then acts on it and degrades the phosphorylated IκBα, liberating the homodimer of p50/p65 isomers. The homodimer of p50/p65 isomers is then imported inside the nucleus to regulate the transcription of genes essential for cellular processes [88].

8. ASSOCIATION OF TARGETED CELL SIGNALING PATHWAYS WITH MAJOR RESPIRATORY DISEASES

The cell signaling pathways have the key responsibility to perform important cellular functions. However, any change or alteration in these cell signaling pathways causes a defect, which eventually leads to the development of diseases [11]. There are huge variations in the nature of the pathogenesis, of how each disease gets induced. In a few cases, pathogenic organisms also interfere with these cell-signaling pathways. Thus, tracing the defects in these cell-signaling pathways will also explain the synergism between CRDs and cell signaling pathways [89].

Acute respiratory distress syndrome (ARDS) is a systemic inflammatory disease where lungs and other organ systems are involved [90]. This causes increased inflammatory cytokines such as IL-1β, TNF-α, IL-6, and IL-8 in bronchoalveolar lavage fluid and blood [91]. Development, progression and recovery of ARDS have

been related to TLR signaling pathways. An extracellular matrix glycosaminoglycan, Hyaluronan is produced after tissue injury, which further leads to development of inflammatory response in ARDS via TLR2 and TLR4, and at the same time, promotes recovery from ARDS [91]. TLR3 mediates hyperoxia-induced ARDS and TLR2 mediates hemorrhage induced ARDS [92]. Studies have shown the role of inflammasomes in inflammation during acute lung injury. NLRP3 inflammasome interacts with extracellular histones and leads to the development of hypoxemia-induced ARDS [93]. Once, ARDS results in systemic inflammation; there is a release of mitochondrial components, including mitochondrial DNA, formyl peptides in the circulation, causing cellular damage [94].

Asthma, a chronic inflammatory disease, is triggered by IL, which are found to be involved in cell signaling pathways like Akt/PKB/P13K, JAK-STAT, MAPK, and NF-κB signaling pathways [95]. During the pathogenesis of this disease, IL-4/13 causes the phosphorylation of JAK, which activates the STAT transcription factor and elicit the expression of inflammatory mediator genes. Moreover, there is a production of cyclooxygenase-2 (COX-2) and Inducible Nitric Oxide Synthase (iNOS) in the NF-κB signaling pathway during pulmonary inflammation [96]. Additionally, the upregulation in the levels of IgE and IL-4 is also observed in the MAPK pathway in asthma [97]. Furthermore, miR-107 is found to be indirectly involved in the inflammatory response of asthma [98]. Association of these inflammatory proteins with asthma and their involvement with cell signaling pathways exhibit a wide range of potential therapeutic targets.

COPD, a progressive inflammatory lung disease, is found to involve known inflammatory proteins like COX-2, cytosolic phospholipase A2 (cPLA2), intercellular adhesion molecule-1 (ICAM-1), metalloproteinase-9 (MMP-9) and vascular cell adhesion molecule-1 (VCAM-1) that are associated with cell signaling pathways [99]. An increase in the level of MMP-2/9 serves as the marker for COPD [100]. Protein Kinase C (PKCs) is another intermediate involved in CRD like COPD [101]. ROS development also triggers the inflammatory reaction by activating the NF-κB or Akt/PKB/PI3K. PI3K plays a major role in the expression of multiple inflammation-related genes [102]. The synergism between these inflammatory proteins and cell signaling pathways portrays their association with COPD and allows us to better understand this chronic disease.

Lung cancer, a chronic respiratory disease, is elicited due to a mutation in the tyrosine kinase domain of the cell signaling pathway [103]. Overexpression of EGFR is also found to play a critical role in carcinogenesis, especially in NSCLC [104]. Additionally, the mTOR pathway is reported to be involved in carcinogenesis. MAPK pathway is the major pathway that is found to play a significant role in the pathogenesis of lung cancer [105]. The expression of MAPK phosphatase 1, as well as mutations in phosphoinositide-3-kinase and catalytic alpha polypeptide (PIK3CA), are the determining factors in lung cancer. Moreover, there is significant involvement of Akt/PKB/PI3K and NF-kB signaling pathways [106]. Furthermore, the expression of peroxisome proliferator-activated receptors in lung cancer serves as a biomarker for lung cancer [107]. The involvement of the proteins and receptors plays a significant role in the onset of disease in an individual.

Tuberculosis, an infectious disease, triggers alterations in different inducers involved in cell signaling pathways like Akt/PKB/PI3K, JAK-STAT, MAPK and NF-κB [108, 109]. Pleiotropic cytokine and TNF-α are the chief proinflammatory mediators that are involved in the establishment of TB infection [110]. Additionally, the interaction of *M. tuberculosis* receptors with the host pattern recognition receptors has been understood as the principal reason to elicit the production of cytokines like CXCL2/3(C-X-C motif chemokine ligand 2), CCL2/5 (C-C Motif Chemokine Ligand 2) and interleukins (IL8) [111]. The receptor-interacting

serine/threonine-protein kinase 1 (RIPK1) has also been found to promote the activation of MAPKs and NF-κB signaling pathway. In normal conditions, RIPK1 ubiquitination via cellular inhibitor of apoptosis protein 1 (cIAP1) protein takes place, and it works as an anti-apoptosis effector. However, any alteration in the ubiquitination of RIPK1 causes apoptosis [34]. Therefore, the involvement of different proteins and receptors shows and highlights the role of these signaling pathways in the progression of diseases.

Idiopathic pulmonary fibrosis (IPF) results in alveolar remodelling and loss of pulmonary function, further leading to respiratory failure and death within 5 years of diagnosis [112]. IPF pathogenesis comprises of fibrotic remodelling, inflammation, and loss of lung architecture [113]. Experimental mouse models have shown alveolar remodelling and fibrosis along with activation of TGF-β, TGF-α, and the mTOR/PI3K/AKT pathways [114, 115]. RNA sequencing analysis of IPF shows the activation of Hippo/YAP pathway genes and inhibits the *SAV1* and *MST2* pathway. It also causes activation of mTOR/PI3K/AKT signaling, including increased *MLST8* and decreased phosphatase and tensin homology (PTEN) expression, indicating potential interactions between YAP and mTOR signaling pathways [116].

All CRDs demonstrate the involvement of a chemical entity, foreign agent, interleukins, oxidative agent or proteins, which are directly or indirectly associated with these cell-signaling pathways, and therefore, can serve as the active target for treating these CRDs.

9. NEED FOR DRUG DELIVERY APPROACHES TO TARGET CELL SIGNALING PATHWAYS IN RESPIRATORY DISORDERS

Acute respiratory distress syndrome (ARDS) is characterised by a heterogeneous group of lung diseases along with acute lung injury in critically ill patients, leading to high mortality rates. A number of molecules are associated with the molecular pathology of ARDS. These include Nod-like receptors, Toll-like receptors and downstream signaling molecules such as NF-κB, inflammasomes, and effector molecules like IL-18, IL-1β, and TNF-α. Multiple targets have been identified and evaluated for developing potential therapies for ARDS. Targeting key molecules like NF-κB suppresses inflammation of the lungs but has significant limitations since inhibition of NF-κB is immunosuppressive and affects host immunity [117].

Nanobiotechnology has proved to be the basis of innovative techniques for delivering drugs to the site of inflamed organs, including lungs. Nanoscale drug delivery systems are capable of improving the pharmacokinetics as well as pharmacodynamics of agents, resulting in an increased bio-distribution of therapeutic agents to the site of action and thus improving efficacy of the drug with reduced toxicity [36, 118-128]. MAPK inhibitor ARRY-142886 and the PI3K inhibitor PX-866 is reported to regulate pulmonary fibrosis progression, preserving vital physiological parameters, in a transgenic mice model that overexpressed the 'transforming growth factor' and developed spontaneous pulmonary fibrosis, [129]. Administration of the mTOR (mammalian target of rapamycin) inhibitor rapamycin in this model inhibited the progression of pulmonary fibrosis by preventing the activation of the EGFR signaling pathway [130].

Administration of bio-therapeutic agents systemically allows barely a small amount of drug to reach the targeted site, as the major part of the drug remains distributed in tissues apart from the primary target site. Targeted delivery to a particular organ or tissue may increase the accumulation of drug at the site of action, resulting in improved safety and efficacy [13, 121, 122, 126, 131]. It was reported that targeting plasmalemma vesicle-associated protein (PV1), which is present on the lung endothelial cells, can enhance drug accumulation and thereby improve pulmonary fibrosis state. In a mouse model with idiopathic pulmonary fibrosis (IPF), induced by bleomycin, the fibrosis, as well as collagen content, were found

to be significantly reduced when Prostaglandin E2 (PGE2) conjugated αPV1 was administered, while no such effects were observed with a non-targeted PGE2 antibody conjugate. The results demonstrate that PV1 targeting can be an effective mode for delivering therapeutics to lung tissues, and this approach can be very helpful in the treatment of several lung diseases [16, 132]. Considering all the above preclinical and translational evidences, there is an emerging need for advanced drug delivery systems, which can encapsulate identified biological moieties to target diseases such as ARDS, pulmonary fibrosis, etc. Fig. **3**.
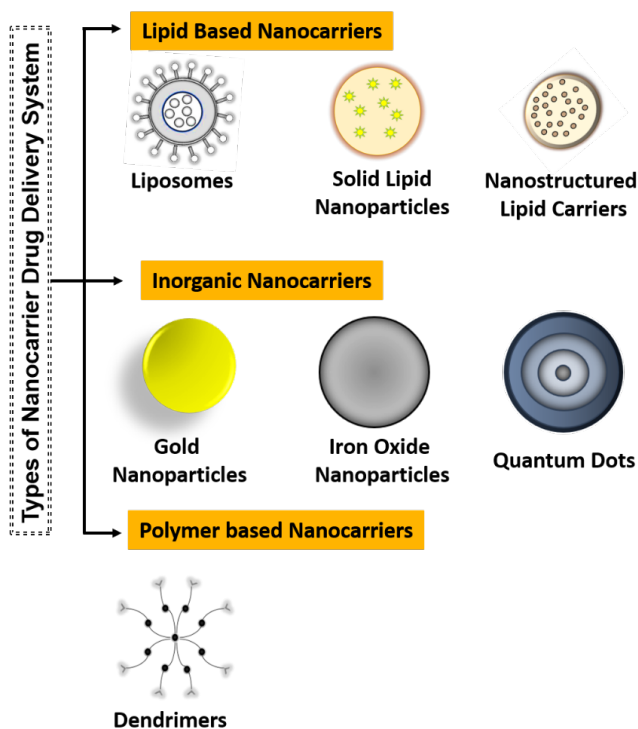

Fig. (3). Pictorial Illustration of Different Types of Nanocarrier Based Drug Delivery Systems. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

10. LIPOSOMES

Liposomes are small artificial amphiphilic structures made of cholesterol and various phospholipids [133, 134]. The amphiphilic characteristics of phospholipids enable them to dissolve in both hydrophobic and hydrophilic drugs. Based on the nature of the drug, these particles can either lodge themselves in the liposome core membrane or in the lipid-aqueous interface [135, 136].

Liposomes have been used as carriers to deliver drugs to treat respiratory infections caused by multi-drug resistant *Pseudomonas aeruginosa*. In one study, transport of colistin and ciprofloxacin liposomes across in Calu-3 cell monolayer indicated that liposomes can prolong the time of drug retention on the lung epithelial surface [137]. Several other studies have also demonstrated the capability of liposomes in prolonging drug retention time and increasing drug concentration in the desired site. Chen *et al.,* reported that the transport rate of liposomal salbutamol into airway epithelial cells was slower than free salbutamol, and *in vivo* studies demonstrated the duration of anti-asthmatic effect of encapsulated salbutamol being prolonged by two times in comparison with free salbutamol solution [61, 138].

Pandolfi *et al.* used liposomes containing hyaluronic acid (HA-liposomes) for inhalation treatment of collagen tissue disease-associated interstitial lung fibrosis (CTD-ILDs) and bronchiolitis

obliterans syndrome (BOS). They prepared two HA-liposomes with different HA molecular weights (MW) and a plain liposome (LIP) to study the effects of HA MW on the targeting efficiency of lung fibrotic cells and inflammatory effectors. Results of real-time qPCR showed that treatment of human THP-1 cells with the above-mentioned liposomes significantly reduced levels of pro-inflammatory cytokines, namely, IL-1β and IL-12, while TGF-β was increased. Furthermore, both LIP and LIP-HA of lower MW increased IL-8 release, while, there was no increase in observed IL-8 levels following the treatment with LIP-HA of higher MW [139].

In another *in vitro* study, quercetin, a natural flavonoid, was encapsulated in T7 surface-functionalized liposomes (T7-QR-lip) to target transferrin receptors of lung tumor cells. The study indicated that a 2% peptide density for T7-QR-lip resulted in a significant inhibition in lung tumor spheroids growth. Inhibition of tumor growth and prolongation of lifespan after T7-QR-lip treatment through pulmonary administration was also confirmed with *in vivo* studies [140].

11. NANOSTRUCTURED LIPID CARRIERS

Nanostructured lipid carriers (NLCs) are the second-generation lipid nanoparticles prepared from a mixture of solid lipids (e.g., Precirol ATO 5) and spatially incompatible liquid lipids (e.g. Squalene) by melt-emulsification. NLCs have been explored as an alternative drug carrier combining the advantages of solid lipid nanoparticles with high encapsulation efficiency and reduced drug leakage [141–149] as a result of their lipophilic and bioadhesive properties. NLCs demonstrate increased residence in the lung and sustained release of the entrapped drug from the lipid matrices [150]. NLCs have been found suitable for the delivery of different drugs and siRNAs. Lipophilic drugs can be loaded into the inner core of NLCs. In addition, the surface of the NLCs can be modified with polyethylene glycol polymer for targeted drug delivery. NLCs containing paclitaxel and siRNA targeted to multidrug resistance protein 1 and B-cell lymphoma 2 mRNAs for inhalation chemotherapy of lung cancer demonstrated therapeutic efficacy. In the treatment of lung cancer with LHRH-targeted NLCs, it was demonstrated that the NLCs predominately accumulated in the lung tumor tissues with a minimal concentration of the NLCs in healthy tissues [151].

Several studies have used NLCs to treat respiratory inflammatory conditions such as asthma and COPD. Montelukast is a leukotriene receptor antagonist used to prevent wheezing and asthma-induced coughing. Inhalable montelukast-loaded NLCs have shown improved systemic bioavailability and therapeutic outcomes when compared to free montelukast *in vivo*. Rosuvastatin, which is used in the management of high LDL and cholesterol has been investigated for the treatment of airway remodeling in COPD. In this study, rosuvastatin has been formulated as an NLC dry powder for inhalation. The study demonstrated that rosuvastatin NLC successfully bypassed the macrophage clearance *in vivo,* leading to a higher concentration of the drug in the lung, highlighting the potential of the formulation for lung targeting and further for COPD treatment [152, 153]. In another *in vitro* study carried out in a bronchial epithelial cell model associated with corticosteroid resistance, NLCs containing fluticasone increased the effectiveness of fluticasone by improving the corticosteroid mediated effects and decreased its side effects [154], which is one of the major problems with the existing treatment options [155].

Metal-based complexes have displayed promising activity against tuberculosis. Specifically, copper and ruthenium complexes have shown excellent antimicrobial potential in tuberculosis. However, the low solubility of metallic compounds makes their application unfeasible. In a study by Sato *et al.*, copper complexes were incorporated into the structure of NLCs. This formulation demonstrated enhanced antimicrobial activity against *M. tuberculosis* [156]. For ruthenium complexes, incorporation into the NLC struc-

ture resulted in increased bioavailability of ruthenium along with reduced toxicity [157].

Rifabutin was studied in another study, where the drug was loaded in NCLs for selective delivery to infected alveolar macrophages *in vitro*. This was achieved by two strategies; optimizing particle size for macrophage uptake and attachment of mannose ligand. The results of this study demonstrated NLCs as a promising strategy for the delivery of rifabutin in TB infection [158].

12. DENDRIMERS

Dendrimers are a family of three-dimensional, nano-sized polymers characterized by a compact spherical structure [159]. The molecular structure of a dendrimer revolves around a central atom or group of atoms known as the core. The branches of other atoms called 'dendrons' expand from this central structure through a range of chemical reactions. Dendrimers can transport molecules by their surface receptors or encapsulate them through cavities between their branches [160]. Several *in vitro* and *in vivo* studies have used dendrimers as carriers to enhance uptake of drugs into cells or synthesized dendrimers with anti-inflammatory properties.

Blattes *et al.,* have developed poly-phosphorhydrazone dendrimers linked with mannose units which mimic *M. tuberculosis* mannose-capped lipoarabinomannan (ManLAMs). ManLAMs inhibit the release of proinflammatory cytokines from LPS-induced human dendritic cells (DCs). This study demonstrated that different dendrimers in terms of size and the number and length of their oligommanoside caps have different potential in reducing TNF-α [161].

In another *in vitro* study, mannose coated 5-glycine ethylene diamine-polypropylimine (5G EDA–PPI) dendrimer was developed as a carrier to transport rifampicin to alveolar macrophages (AM). The findings from this study revealed that the retention amount of rifampicin in AMs from mannosylated dendrimer formulation was significantly higher than the free rifampicin solution [162].

Bohr *et al.* developed two different types of phosphorus-based dendrimers (with either pyrrolidinium or morpholinium) to deliver small interfering RNA (siRNA) to mouse macrophage cell line RAW264.7. Pyrrolidinium dendrimers demonstrated higher anti-inflammatory properties following stimulation of the macrophages with LPS and resulted in a significant reduction in TNF-α expression. The *in vitro* anti-inflammatory observations of this study was further confirmed in an *in vivo* murine model of acute lung injury [163].

A modified polyamidoamine dendrimer has been used as a vector to load AS1411 aptamer and short hairpin RNA plasmid in order to enhance transfection potential on cancer cells and B-cell lymphoma-extra-large (Bcl-xL) protein knockdown. Western blot analysis showed a 55% reduction in Bcl-xL protein expression in human lung adenocarcinoma cell line (A549), however, this finding was not replicated in fibroblasts [164].

13. QUANTUM DOTS

Quantum dots are semiconductor nanocrystals, that exhibit unique optical properties for practical applications such as imaging and drug delivery. Quantum dots exhibit strong light absorbance, bright fluorescence, and photostability [165].

Despite the great potential of quantum dots, their clinical application and translation have been slow due to the role of heavy metals in biological response and induced genotoxicity. The toxic effects of quantum dots in the respiratory system have been reported *in vitro* and *in vivo*. Several studies *in vitro* have reported the reduction in cell viability, genetic material damage and disordered immune cell reactions, while, *in vivo* observations include accumulation of quantum dots, lung injury and inflammation [166]. Interestingly, the toxic effects of quantum dots depend on their type, composition, dose, size, surface chemistry and structure [167].

Recently, a novel formulation of non-cadmium-based quantum dots has been developed where no observable toxicity following long-term exposure in a murine model was observed, indicating the possibility of future clinical applications of quantum dots in the treatment of respiratory diseases. The potential role of miRNAs in the initiation and progression of lung cancers has been demonstrated in several studies. These findings have led to the development of different detection technologies, including qPCR. In this regard, the potential use of quantum dots for cancer cell imaging and detection have been highlighted. The large emission spectrum and surface chemistry of the quantum dots offer long-term stability and a significantly higher sensitivity as bio-probes. Furthermore, as mentioned above, recent advances in non-toxic shells and surface modification has overcome the toxicity issues and increased the ability of quantum dots to quickly identify cancer-associated molecular bio-markers [168].

14. CARBON NANOTUBES

Carbon nanotubes (CNTs) belong to the fullerenes sub-family. They are unique sp2-hybridized hydrophobic-tubular structures synthesized from carbon allotropes, having a C-C distance of about 1.4 A˚ with varying diameters from 4 nm to 100 mm [169]. Structurally, these CNTs have exceptionally high drug loading ability, high surface area and neutral electrostatic potential, which makes them an attractive system for biomedical applications [170, 171]. The insoluble nature of these CNTs in aqueous solutions or organic solvents and the induction of toxicity by these CNTs in biological systems are the foremost challenges that need answers [172]. Chemical modification studies have reported a drastic improvement in their biocompatibility. This has also reduced the toxicity and transformed them into water-soluble nano-systems [173]. Nanotubes have a distinct electrical as well as thermal conductivity, and mechanical strength, which makes them the nanocarrier of interest [174].

Cisplatin (anti-cancerous) was the first drug that was developed with single-walled CNTs (SWCNTs) for targeting the cellular receptor, EGFR. The findings from this study revealed alleviated efficiency against squamous tumor cells that showed a high expression of EGFR [175]. Another study in which functionalized-SWCNTs were used showed the induction of autophagocytosis in both *in vitro* as well as *in vivo* conditions by involving Akt/PKB/ PI3K signaling pathway in A549 cell lines [176]. Other studies using multiwall carbon nanotubes have been found to stimulate ROS production via fibrogenic response mediating the NF-kB signaling pathway [177]. Moreover, comparative studies have also been conducted on normal and mesothelial cells to understand the response of SWCNTs on cell signaling pathways like Akt/PKB/ PI3K, MAPK and NF-kB [178]. The findings from various studies conducted on targeting the cell signaling pathways have elucidated the potential of CNT in treating chronic diseases. These applications of CNTs expand the horizon of this nano-carrier system and directs to explore new potential areas in treating these CRDs by targeting potential cell-signaling pathways.

FUTURE SCOPE AND CONCLUSION

Cell signaling pathways have emerged as effective targets for treating the CRDs. There is an increasing body of evidence related to the inflammatory proteins like COX-2, cPLA$_2$, ICAM, MMP-9, and their involvement in the pathophysiology of CRDs like asthma, COPD, lung cancer and TB. Additionally, the role and function of various cell signaling pathways involving Akt/PKB/ PI3K, JAK-STAT, MAPK and NF-kB in the regulation of these inflammatory proteins, make them possible therapeutic targets. This further prompts for the development of new ligands that can serve as agonists or antagonists adaptor molecules for targeting these cell-signaling pathways and for the treatment of CRDs. Moreover, the development of targeted inhibitors with no or minimal side-effects

remains to be explored. Although, development of inhibitors for targeting cell signaling pathways in the treatment of CRDs seems to be an attractive option, nevertheless, it demands an exploration of the exact roles of such inflammatory proteins, as well as, the cell signaling pathways in these CRDs. Furthermore, appreciating the *in vivo* actions of these drugs and inhibitors in animal models and human patients will highlight the real potential, as well as, the efficacy of these drugs in preventing these CRDs. The overall associations and interactions of these cell signaling pathways with various other signaling pathways should be uncovered in future studies.

LIST OF ABBREVIATIONS

GPCRs	=	G Protein-Coupled Receptors
RTKs	=	Receptor Tyrosine Kinase
TGF- β	=	Transforming Growth Factor- beta
CRDs	=	Chronic respiratory diseases
COPD	=	Chronic Obstructive Pulmonary Disease
TB	=	Tuberculosis
Akt/PKB/PI3K	=	Serine/threonine kinase1/protein kinase B/phosphoinositide 3-kinase
JAK-STAT	=	Janus kinases-signal transducer, and activator of transcription proteins
MAPK	=	Mitogen-activated protein kinase
NF-κB	=	Nuclear factor kappa-B
AHR	=	Airway hyper-responsiveness
NSCLC	=	Non-small cell lung cancer
SCLC	=	Small cell lung cancer
ILD	=	Interstitial lung disease
IPF	=	Idiopathic pulmonary fibrosis
PIP3	=	Phosphatidylinositol-(3,4,5)-trisphosphates
mTORc2	=	Mammalian target of rapamycin complex 2
PDK1	=	Phosphoinositide-dependent kinase 1
EGFR	=	Epidermal growth factor receptor
PDGFR	=	Platelet-derived growth factor receptor
SH2	=	Src Homology 2
ERK	=	Extracellular-signal regulated kinase
JNK	=	c-Jun-N-terminal kinase
MAPKKs	=	MAPK kinases
IL	=	Interleukin
PAMPs	=	Pathogen-associated molecular patterns
IKKα	=	Ik kinase alpha
TLR	=	Toll like receptors
Cox-2	=	Cyclooxygenase-2
cPLA2	=	Cytosolic phospholipase A2
ICAM-1	=	Intercellular adhesion molecule-1
MMP-9	=	Metalloproteinase-9
VCAM-1	=	Vascular cell adhesion molecule-1
PKCs	=	Protein Kinase C
PIK3CA	=	Phosphoinositide-3-kinase and catalytic alpha polypeptide
CXCL2/3	=	C-X-C motif chemokine ligand 2
CCL2/5	=	C-C Motif Chemokine Ligand 2
cIAP1	=	cellular inhibitor of apoptosis protein 1
ARDS	=	Acute respiratory distress syndrome
PV1	=	plasma lemma vesicle-associated protein
PGE2	=	Prostaglandin E2
NLCs	=	Nanostructured lipid carriers
ManLAMs	=	Mannose-capped lipoarabinomannan
DCs	=	dendritic cells
5G EDA-PPI	=	5-glycine ethylene diamine-polypropylimine
AMs	=	alveolar macrophages
Bcl-xL	=	B-cell lymphoma-extra-large
CNTs	=	Carbon nanotubes
SWCNTs	=	Single walled carbon nanotubes

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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