HHS Public Access

Author manuscript

*Expert Rev Respir Med*. Author manuscript; available in PMC 2019 May 01.

Published in final edited form as:

*Expert Rev Respir Med*. 2018 November ; 12(11): 931–939. doi:10.1080/17476348.2018.1526677.

# Therapeutic Targets For Inflammation-Mediated Airway Remodeling In Chronic Lung Disease

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## Abstract

**Introduction—**Acute exacerbations of chronic lung disease account for substantial morbidity and health costs. Repeated inflammatory episodes and attendant bronchoconstriction cause structural remodeling of the airway. Remodeling is a multicellular response to mucosal injury that results in epithelial cell state changes, enhanced extracellular deposition and expansion of pro-fibrotic myofibroblast populations.

**Areas covered—**This manuscript overviews mechanistic studies identifying key sentinel cell populations in the airway and how pattern recognition signaling induces maladaptive mucosal changes and airway remodeling. Studies elucidating how NFκB couples with an atypical histone acetyltransferase, bromodomain containing protein 4 (BRD4) that reprograms mucosal fibrogenic responses are described. The approaches to development and characterization of selective inhibitors of epigenetic reprogramming on innate inflammation and structural remodeling in pre-clinical models are detailed.

**Expert commentary—**Bronchiolar cells derived from Scgb1a1-expressing progenitors function as major sentinel cells of the airway, responsible for initiating anti-viral and aero-allergen responses. In these sentinel cells, activation of innate inflammation is coupled to neutrophilic recruitment, mesenchymal transition and myofibroblast expansion. Therapeutics targeting the NFkB-BRD4 may be efficacious in reducing pathological effects of acute exacerbations in chronic lung disease.

### Keywords

airway remodeling; bromodomain containing protein 4 (BRD4), mesenchymal transition; myofibroblast; epigenetics

## 1. Introduction

Allergic asthma (AA) and chronic obstructive pulmonary disease (COPD) are chronic inflammatory diseases of the airways. In its classic form, AA is a disease manifested by reversible airway obstruction and Th2 lymphocytic inflammation, characterized by submucosal eosinophil accumulation, IgE production and atopy (1). Asthma affects ~ 8% of the US population, now > 25 million (M) in number (2). Worldwide, the WHO estimates 235 M people suffer from from asthma. By contrast, COPD is manifested by fixed airway obstruction with a neutrophilic inflammation, etiologically associated with environmental exposures, such as smoke or occupational exposure (3). COPD affects ~30 M people in the

US and predicted to be the 4th leading cause of death by 2020 (4). Worldwide, preventable chronic lung disease accounts for 5–6% of deaths (5).

Although distinct in their etiology, both AA and COPD share components of airway inflammation, structural remodeling and their disease course punctuated by intermittent exacerbations (6). The presence of overlapping pathophysiologies and causes of exacerbations has led to a re-examination of the whether both diseases share common origins but are expressed differently through individual variation, a concept known as the 'Dutch' hypothesis (7). Approximately 15–20% of patients with COPD have features of airway reversibility and eosinophilia. Conversely, a subset of asthmatics develop fixed airway obstruction. These common features have led to the acceptance of the Asthma-COPD overlap syndrome (ACOS) as a distinct disease entity (8). Although COPD intervention has focused on reducing environmental smoke exposure, large scale prospective observational studies have identified a potential role of early viral encounters in reduced pulmonary capacity later in life (7). Irrespective of their etiologies, obstructive lung diseases share common triggers, inflammatory responses and some features of remodeling (9), whose mechanism will be examined in this review.

### 1.1 Acute exacerbations (AEs) in chronic lung disease

Exacerbations are intermittent episodes of acute decompensation provoked by mucosal inflammation that are clinically manifested by worsening symptoms due to decreases in expiratory airflow. In AA, AEs are responsible for approximately 15.0 M outpatient visits, 2 M emergency room visits, and 500,000 hospitalizations annually in the US (10). These events diminish the quality of life in patients and their families. Similarly AEs of COPD are associated with enhanced morbidity, mortality and decreases in life quality (11). Patients with COPD experience a median of 1.2–2.4 AEs annually (12), which are more clinically significant with advanced disease (GOLD stage) due to greater degrees of resting lung impairment. Like AA, hospitalizations from AEs in COPD are major drivers of health care costs worldwide (13).

### 1.2 Etiologies of AEs

AEs are provoked by viral and environmental exposures. In adults with AA, viral respiratory tract infections, principally rhinovirus (RV) represents the most common virus isolated during AEs (14). In children with AA, episodes of wheezing are due to both RV and Respiratory Syncytial Virus (RSV) infections (15). COPD AEs are associated with active viral infections, changes in bacterial colonization and/or environmental exposures (smoking, air pollution) (16, 17). Formally, epidemiological studies can only conclude that AEs are associated with active viral replication. Elegant human challenge studies with the common cold virus, RV (18) and RSV (19) have shown that viral infections themselves are *sufficient* to produce AEs in patients with AA or COPD.

### 1.3 Impact of AE on long term airway function

In addition to precipitating acute decompensations in air exchange provoking unscheduled health care visits, large scale prospective observational studies in difficult-to-treat asthma have shown that AEs are associated with accelerated loss of lung function. For example, in

the 3-year prospective observational study of difficult-to-treat asthma (TENOR), a study involving about 4,800 patients, found that the forced expiratory volume ($ppFEV_1$) declined faster in those participants with one or more AE annually (20). This finding was consistent over all age categories. Similarly, frequent AEs in COPD are associated with more rapid loss in airway flow (16). These studies have raised the intriguing possibility that AEs themselves result in structural remodeling of the airway. Loss in pulmonary function probably occurs through multiple mechanisms including the effects of bronchoconstriction and/or innate inflammation (21). Because the effects of inflammation are greater in magnitude than those of bronchoconstriction (21), this review will focus on mechanistic relationship between innate inflammation and remodeling.

### 1.4 Airway remodeling

Airway remodeling is a collective term that refers to structural changes in the airways resulting in enhanced collagen deposition in the subepithelial basement membrane (lamina reticularis), disruption of the epithelial barrier, epithelial cell-state change (mucous metaplasia and/or mesenchymal transition), and smooth muscle hypertrophy (22). Collectively, this process narrows the small airways, producing obstruction and reduced lung compliance accounting for enhanced morbidity and mortality (23). Enhanced mucus production from expansion of submucosal goblet cell population and hypertrophy of airway smooth muscle layers enhances small airway obstruction. These process both contribute to reduce lung compliance and airway hyperreactivity (24). Additionally, remodeling-associated epithelial injury and cell-state change enhance mucosal permeability. This process may account, in part, for defective innate immune response, and enhanced antigen penetration, further predisposing asthmatics to developing non-specific atopy. The reader is referred to an ATS-Research Statement that treats the problem of airway remodeling in some depth (25). This latter analysis emphasizes the progressive, irreversible, nature of airway remodeling.

### 1.5 Mucosal host response is a mediator of AEs

Human challenge models of RNA viruses and allergens have provided unequivocal proof that these agents trigger a robust innate inflammatory response. Subjects with AA challenged intranasally with RV trigger a rapid oxidative response, associated with epithelial-derived chemokine secretion (IL-33), clinical symptoms and Th2 cell inflammation, including delayed eosinophilia (18, 26, 27). Similar studies with RSV challenges have found that viral replication occurs throughout the lower airway epithelium, associated with initial neutrophil response, and activation of CD8 memory T cells (19). RV challenges in subjects with COPD also indicate exaggerated neutrophilic responses, clinical symptomatology followed by CD8+/CD4+ T cell recruitment into the lung (28). Segmental allergen challenges in humans have also provided evidence for epithelial chemokine response coupled with eosinophilia (29). These studies consistently have found that the airways of AA and COPD elicit more robust oxidative response, chemokine expression and clinical symptoms than normal controls.

### 1.6 Pattern recognition receptor (PRR) and toll-like receptor (TLR) signaling in AEs

Airway epithelial cells are a major component of the pulmonary innate defense responsible for forming a semi-impermeabile barrier and inducible secretion of anti-bacterial mucins and inflammatory chemokines (30). Inducible innate defenses are triggered by pathogen-assocated molecular patterns (PAMPS), molecules derived from microbial replication, and danger associated molecular patterns, molecules released by cell stress and/or death. These patterns are recognized via families membrane-associated, endosomal or cytosolic PRRs expressed in respiratory epithelial cells (31, 32). The binding of ligands to their cognate receptors results in the activation of epithelial cell–intrinsic signaling pathways, activating oxidative stress and intracellular signaling pathway including mitogen-associated protein kinases and IκB kinases (30). Viral PAMPs, notably double-stranded (ds) RNA, are bound by membrane-associated TLR3 and intracellular RIG-I (33, 34). These pathways have been extensively reviewed (35, 36) and modeled mathematically (37, 38); only the salient features are elaborated here.

Activation of the innate pathway converges on two primary arms controlling inflammatory and anti-viral response. Of these, NFκB plays a major role in innate inflammation, controlling the expression of inflammatory chemokines as well as the mucosal IFNs. NFκB activation involves a serine phosphorylation of RelA triggered by nuclear oxidative stress, promoting RelA to bind bromodomain-containing protein 4 (BRD4) (39, 40). NFκB mediated recruitment of BRD4 to latent innate genes promotes their rapid expression through a process of transcriptional elongation (41, 42). In this manner, the NFκB-BRD4 complex directly activates immediate-early inflammatory CXC chemokines, and indirectly activates mucosal type I and III interferons (IFNs) via the IFN regulatory factor (IRF)-RIG-I pattern recognition receptor “cross-talk pathway” (37, 43). A characteristic of the innate pathway is the presence of coupled, positive activation loops mediated by chemokines and IFNs that potentiate an anti-viral response (37,38). These cytokines also activate airway dendritic cells, causing their migration to draining pulmonary lymph nodes triggering the pulmonary adaptive immune response (44).

### 1.7 Airway epithelial cells are primary sentinels of virus and aero-allergens

The airway epithelium is an important regulator of airway physiology and homeostasis. Because aero-allergens and pathogens primarily encounter the epithelium, the epithelium plays a major role in sensing the presence of environmental oxidants and invading viruses (30). A number of studies have revealed dynamic responses of airway epithelial cells are initiated via PRRs and TLRs by activated by allergens and respiratory viruses. These receptor-mediated signaling produce acute oxidative injury (35, 45), disruption of cilia function, epithelial apoptosis, disruption of epithelial barrier function (46–49), chemokine production, and neutrophilic inflammation (50, 51). Systems level studies of epithelial responses to viral infection have shown large dynamic genomic responses to viral replication (40), consistent with their prominent innate function.

### 1.8 Unique roles of bronchiolar-derived epithelial cells

For the purposes of this review, the airway epithelium can be divided into three anatomically distinct regions: trachea, bronchioles and alveoli. Comparison of airway epithelial cells

derived from these regions shows marked phenotypic diversity. Epithelium from the large airways are pseudostratified columnar cells, whereas bronchiolar cells are cuboidal, and alveolar cells are simple squamous monolayers (52). Ciliated and secretory airway cells in the trachea trigger innate defenses by muco-ciliary escalator activity and mucin secretion that bind pathogens and facilitate their clearance. By contrast, epitheilial cells of the bronchioles inducibly synthesize and secrete over 400 proteins as free and membrane-bound nanoparticles (exosomes). These include CXC and CC-type chemokines, type I and III IFNs, as well as IFN stimulated genes (ISGs) (53). Interestingly, and of relevance to the pathogenesis of Th2 inflammation and remodeling, bronchiolar-derived airway epithelial cells produce more Th2-polarizing chemokines, such as MIP1α, MCP, TSLP, CCL20 and IL6 than do tracheal epithelial cells (53, 54).

A previously unresolved problem has been identification of the initial innate sentinel cells, e.g., those responsible for triggering innate inflammation. Candidates include alveolar macrophages, intraepithelial lymphocytes, natural killer cells, and the epithelium itself. Recent advances using tissue-specific knockouts have provided new major insights into the identity of airway sentinels in response to luminal virus. An interesting epithelial population found in the bronchiolar alveolar junction expresses both secretoglobin (*Scgb1a1*) and surfactant; these cells function as progenitor cells responsible for populating the distal bronchioles in response to injury (55). Recent work in small animal models selectively depleting NFκB/RelA in these bronchiolar stem cells by Cre recombinase (55) have provided definitive proof that derivatives of these cells (55, 56), are the major functionally important innate sensors of viral infection (Figure 1). Mice with deletion of NFκB/RelA in the *Scgb1a1* progenitor-derived population have significantly reduced inflammation and remodeling in response to RSV infection (56). Similarly, TLR3-driven viral inflammation is also mediated by the same bronchiolar-derived epithelial cells. Like that of RSV, deletion of NFκB/RelA in the *Scgb1a1*+ progenitors mice respond to TLR3 agonism with reduced neutrophilia, epithelial dependent chemokine expression and myofibroblast expansion (57). It is important to note that poly(I:C) mimics acute aspects of RNA virus infections (58), producing inflammatory signatures characteristic of COPD and airway hyper reactivity (59).

Previous work also indicated that the *Scgb1a1* –derived bronchiolar cell mediates inflammation, airway hyperreactivity and remodeling via the canonical NFκB pathway in response to the house dust mite allergen (60). Collectively these data are consistent that this unique bronchiolar progenitor epithelial cell population originating from *Scgb1a1*-expressing progenitors secretes unique Th2 polarizing cytokines and remodeling factors, and activation is required for innate inflammatory response in the airway via chemokine induced neutrophil recruitment.

### 1.9 Epithelial response to oxidative injury

TLR signaling mediates the interface between innate inflammation, cellular injury and adaptive immunity (61). This family of PRRs recognize molecular patterns produced by viral infection, allergen exposure, and smoke/ozone inhalation. Liganded TLRs induce oxidative injury, a second messenger that results in defects in epithelial barrier function and stimulates the release of growth factors and cytokines linked to airway remodeling (35, 62).

The concept that epithelial injury/defective repair is linked to airway fibrosis (63) was directly demonstrated in studies using targeted injury of alveolar epithelial cells via cell type-specific diphtheria receptor expression (64) and in bleomycin-induced pneumonitis, a model that produces a temporal sequence of acute epithelial injury followed by inflammation and remodeling (65). Using novel TLR-induced airway remodeling programs on epithelial-specific gene knockouts, selective small molecule inhibitors and systems levels studies, fundamental insights were generated that the NFκB transcription factor mediates TLR-induced mesenchymal transition, myofibroblast expansion, and extracellular matrix deposition (41, 57, 62, 66). These studies detailed that a prominent epithelial cell-state transcription occurs in the remodeling process.

### 1.10 Linkage of NFκB signaling to mesenchymal transition and airway remodeling

In addition to its central role in inflammation, NFκB plays an essential role in controlling gene regulatory programs driving cell-state change, a process referred to as epithelial mesenchymal transition [EMT, (62, 67, 68)]. High throughput RNA-seq studies of normal human airway cells have discovered that the core regulatory network of TGFβ-induced EMT in normal epithelial cells, the so-called type II EMT (67), substantially overlaps with the NFκB pathway (68). Using selective inducible knockouts in bronchiolar-derived basal cell progenitors, it was found that NFκB signaling drives the transition to a committed mesenchymal phenotype (66). These findings led to the discovery that tonic (or repetitive) NFκB signaling in the airway produces EMT *in vivo* (69). In this latter study, repetitive AEs provoked by exposure to TLR3 agonists activates EMT, remodeling and expansion of myofibroblast population(s).

Previous mechanistic studies *in vitro* showed that the TLR-induced NFκB complexes with the coactivator bromodomain containing (BRD4), a multifunctional protein with intrinsic RNA polymerase kinase (70) and atypical histone acetyltransferase (HAT) (71) activity. Through its sequence specific DNA-binding activity, NFκB redistributes BRD4 to innate inflammatory genes as well as the core EMT regulators SNAI1, ZEB1 and TWIST1 (62, 72). NFκB-dependent activation of the core EMT regulators results in expression of collagen I (COL1) and fibronectin (FN1), a fibrotic response characteristic of airway remodeling and expansion of the subepithelial basement membrane (Figure 2).

Although these fundamental studies were initially developed *in vitro*, evidence that NFκB mediates mesenchymal transition, myofibroblast expansion, and pulmonary fibrosis has been developed in *in vivo* (62). In mice, acute TLR3 activation induces CXCL8/IL-8 expression and neutrophilia, but chronic TLR3 activation produces airway epithelial mesenchymal transition, expansion of the myofibroblast population, and fibrosis (62). Activation of the BRD4 kinase and atypical HAT activity in the airway mucosa has been demonstrated in response to TLR3 activation (69) and viral replication (41, 56). Here, the unique, BRD4-dependent histone acetylation on Lys 122 is induced by virus or allergen, and this induction is NFκB-dependent. Viral and allergen-induced NFκB-BRD4 complex formation was been demonstrated through proximity ligation assays, a technique to detect molecular interactions between the two proteins. Finally, using highly selective BRD4 inhibitors, it was found that inhibition of BRD4 HAT activity interferes with epithelial cell state transition, remodeling,

airway hyperreactivity and myofibroblast expansion (73). These studies validate the central relevant of the NFκB-BRD4 pathway in airway remodeling in a mouse model of AEs.

### 1.11 Linkage of mesenchymal transition to myofibroblast expansion

A central effector cell for airway fibrosis is the myofibroblast, a pleiotropic mesenchymal-derived cell involved in the excessive deposition of extracellular matrix in the *lamina reticularis*. Myofibroblasts are a highly dynamic population distributed throughout the subepithelium and stroma whose number increase in response to viral infections and the active progression of asthma (74). Myofibroblasts originate from a variety of sources, primarily from resident mesenchymal cells, but also from epithelial and endothelial cells undergoing EMT, as well as circulating bone marrow stem cells ("fibrocytes") (75, 76). The myofibroblast population derived from resident fibroblasts and bone marrow-derived fibrocytes increases in refractory asthma (77), acute AEs or actively progressing chronic obstructive pulmonary disease (COPD) (74).

A close bidirectional interrelationship exists between epithelium and myofibroblasts. In response to injury, epithelial cells secrete TGFβ, epidermal growth factor (EGF) connective tissue growth factor (CTGF), and fibrogenic cytokines (IL-6, TSLP, IL-33, IL-25 and others). These are paracrine-acting myofibroblast growth factors whose function is critical for injury-repair processes in airway disease. Fibroblasts from asthmatic biopsies express a more differentiated phenotype and are hyperresponsive to TGFβ1, indicating that these cells have been reprogrammed by the chronic injury (78). In pulmonary fibrosis, fibroblasts upregulate ROS, angiotensin II and trigger EMT through ECM interactions (79, 80); the role of fibroblasts in epithelial cell-state changes in asthma/COPD are under-investigated.

In lung tissues, expansion of the myofibroblast population is demonstrated by quantifying a double-labeled population of COL1+/SMA+ cells underneath the epithelial layer. In a mouse model model of chronic AEs, studies have shown that expansion of the myofibroblast population was dependent on the TLR3-IKK-NFκB pathway, being induced by luminal poly (I:C) and inhibited by the selective IKK inhibitor, BMS345541 (62). These studies have been extended using several strategies to inhibit the NFκB-BRD4 pathway, including RelA mucosal knockout and BRD4 inhibition, have all resulted in the reduction of both mesenchymal transition and expansion of the myofibroblast population (56, 57, 81), indicating linkage of these processes (Figure 3).

### 1.12 Development of highly selective BRD4 inhibitors

In addition to its function as an atypical HAT, BRD4 is also a chromatin organizing protein that connects RelA to CDK9 of the positive transcriptional elongation complex as well as AP2 adapter, SWI/SNF, and DNA directed RNA Pol II complex (57, 82). Within chromatin, BRD4 recognizes acetylated lysine (KAc) residues on transcription factors and histones through its bromodomain (BD). Structure-guided drug design has been used to develop nonselective inhibitors of the BRD family for potential applications in cancer, metabolic and cardiovascular disease (83). Newer, more selective BRD4 inhibitors targeting airway remodeling have been developed using a pharmacophore model. This model involves a polar head that interact with Asn140 in the KAc binding pocket and a tail that forms hydrogen

bonds with Tyr97 in the BD domain (84). These BRD4 inhibitors, ZL-0420 and −0454, display nanomolar binding affinities for BRD4, while exhibiting approximately 30~60-fold selectivity over BRD2 BDs (84). The effect of these selective inhibitors to block formation of H3K122 Ac and inflammation validate BRD4 as a target for treatment of acute lung inflammation mediated by the RIG-I and the TLR3 PRRs (41, 56, 81).

## 2. Expert Commentary

The epithelium has emerged as a major sentinel cell of acute exacerbations in chronic airways disease. The epithelium is dynamically reprogrammed in response to injury to promote innate inflammation, neutrophilic recruitment, mesenchymal transition and subepithelial myofibroblast expansion. Recent work has focused on the unique properties of the bronchiolar cells derived from *Scgb1a1*-expressing progenitors cell as a major viral sentinel cells, responsible for initiating anti-viral and aero-allergen responses. PRR activation induces a temporally coordinated gene program by activation of the NFκB/RelA transcription factor. The activated NFκB complex controls epigenetic reprogramming of innate and fibrogenic gene programs. Systems-level genomic and proteomics studies show epithelial cell-type differences in innate cytokine production in response to RSV infection. Bronchiolar-derived epithelial cells selectively secrete TSLP, CCL20 and IL6, NFκB-dependent proteins that promote Th2 and mucin expression important in the pathogenesis of RSV-induced lower respiratory tract infections. These differences in chemokine expression patterns exhibited by epithelial cells from different regions are immunologically significant and play an important role in airway remodeling. Mesenchymal transition is provoked by repetitive innate stimuli and mediated by NF-κB/RelA. Upon complexing with BRD4, NFκB indirectly induces atypical BRD4 HAT activity. Structure-based drug design has been used to advance the pharmacopeia of BRD4 inhibitors. These compounds are highly selective inhibitors of BRD4 that reduce neutrophilic airway inflammation and prevent epithelial cell state change and myofibroblast expansion in response to viral and aero-allergen exposures.

## 3. Five year view

Recent advances on detailed mechanisms of the activation of the innate immune response have advanced the central role of the NFκB-BRD4 pathway in inflammation-mediated airway remodeling. The unifying conceptual link between innate inflammation, epigenetic changes and triggering the fibrotic pathway represents an important advance. Over the next five years, development of inhibitors of this pathway will be progressing in preclinical space with evaluation in clinical applications. The availability of therapeutics that mitigate AEs and their sequelae in airway remodeling will stimulate work in detection of inflammation/remodeling using advanced imaging and biomarker identification to monitor the effect of these agents.

## Acknowledgments

Funding acknowledgements: NIAID 2P01AI062885, NCATS UL1TR00237

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**4.**

### Key Issues

1. The mucosal NFκB pathway is responsible for acute innate inflammation and anti-viral IFN production.
2. Repetitive or tonic activation of the NFκB pathway results in epigenetic reprogramming of the mucosa resulting in cell state transition, EMT and mucous metaplasia.
3. Chronic activation of NFκB repositions the atypical histone acetyltransferase, BRD4 onto chromatin of fibrogenic genes, resulting in their activation and stimulation of remodeling.
4. An essential role of bronchiolar derived cells from *Scgb1a1*-expressing progenitors in mediating TLR induced neutrophilia, Th2 polarization, extracellular matrix deposition and myofibroblast expansion has been identified.
5. The BRD4 bromodomain is a therapeutic target in AEs mediated by virus or aero-allergens.
6. Structure-based drug design has yielded novel, highly selective inhibitors of BRD4.
7. BRD4 inhibitors are potent anti-inflammatory and anti-remodeling agents.

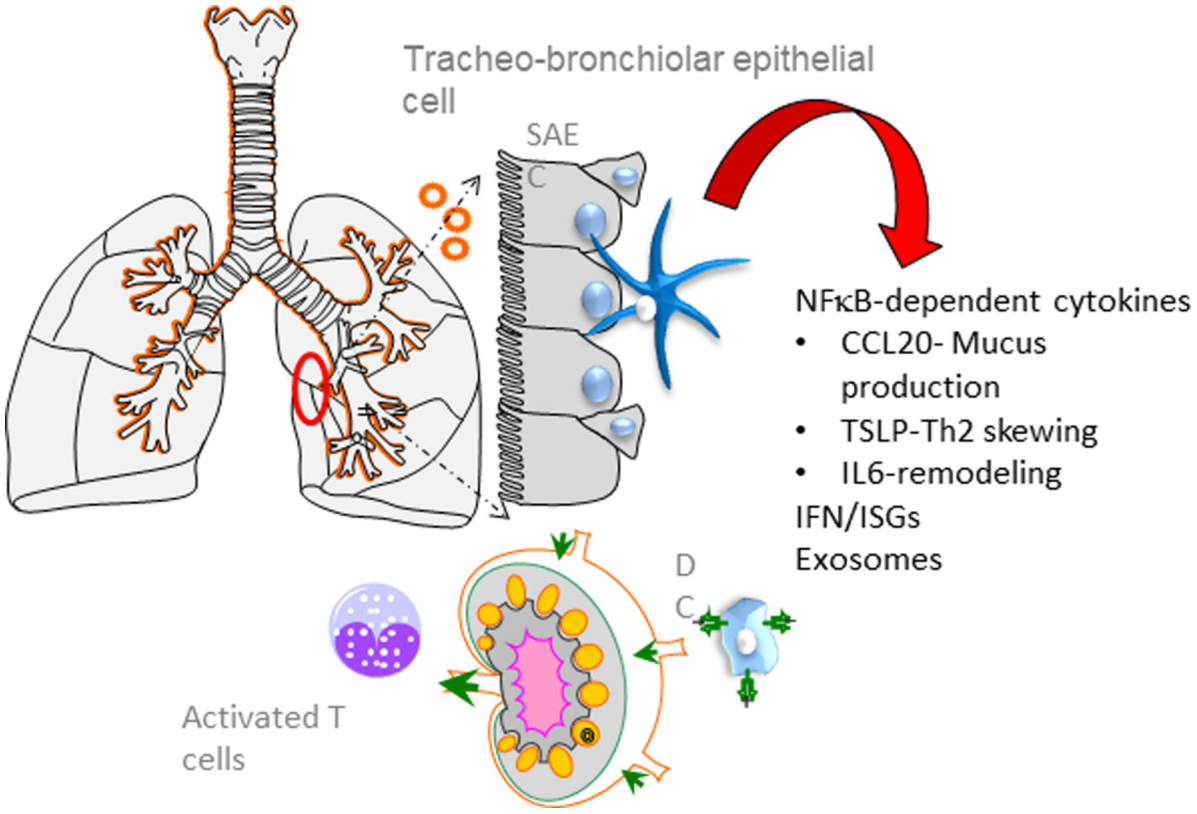


**Figure 1.**

The role of the airway epithelial cell in acute exacerbation. Schematic model of the bronchiolar-derived airway cell in sensing the presence of pathogen associated molecular patterns. Although other epithelial cells express toll like receptors to sense viral patterns, allergens and danger signals, the bronchiolar cells release distinct patterns of fibrogenic cytokines (IL-6), Th2-polarizing cytokines (TSLP), mucogenic cytokines (CCl-20) and exosomal cargo. These factors are responsible for neutrophilic inflammation and shape Th2 polarization and airway remodeling.

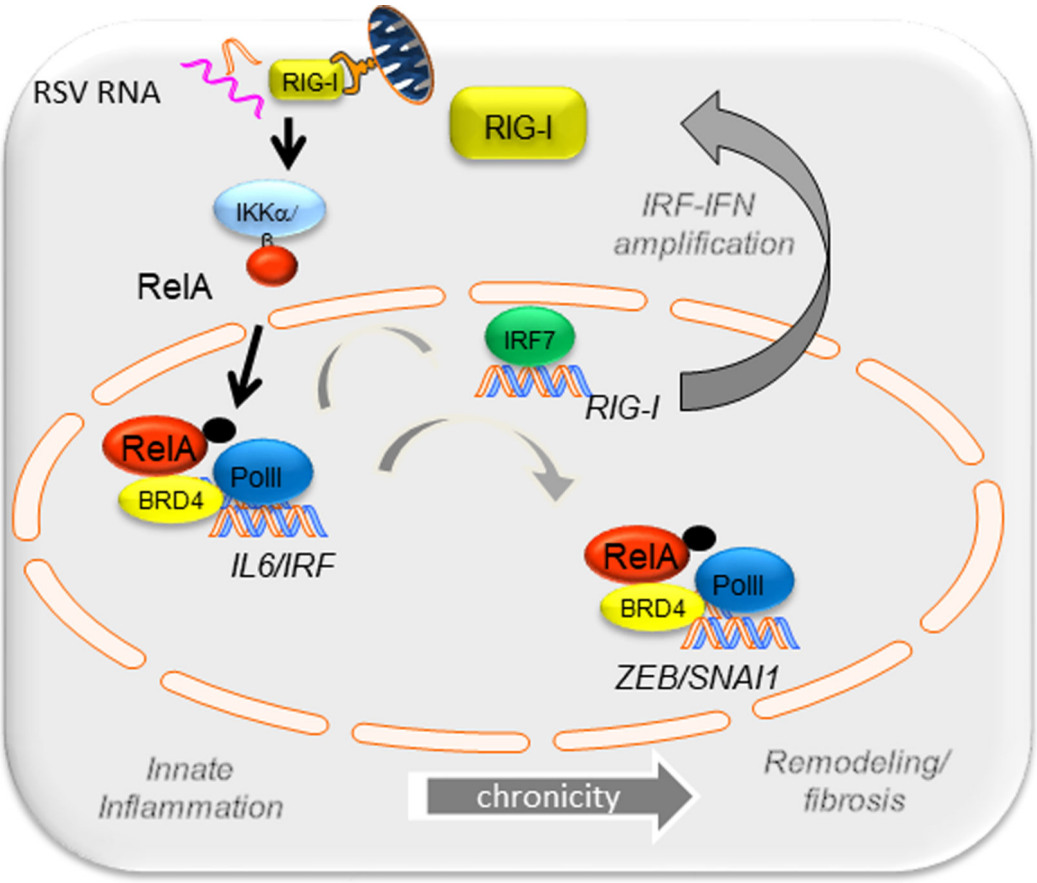


**Figure 2.**

NFκB-BRD4 signaling in innate inflammation and remodeling. Schematic model of mucosal epithelial cell in the bronchiolar epithelium. TLR liberates NFκB from sequestered cytoplasmic stores, in cooperation with oxidative stress generated by activated TLR RelA is phosphorylated on Ser residue 276, a post-translational modification required for binding to BRD4. Transient, short term activation of NFκB results in highly inducible gene expression of innate response genes. By contrast, persistent activation of NFkB signaling results in activation of mesenchymal core regulatory proteins and the fibrotic pathway. NFκB•BRD4 complex links innate inflammation with epigenetic programming and airway remodeling.

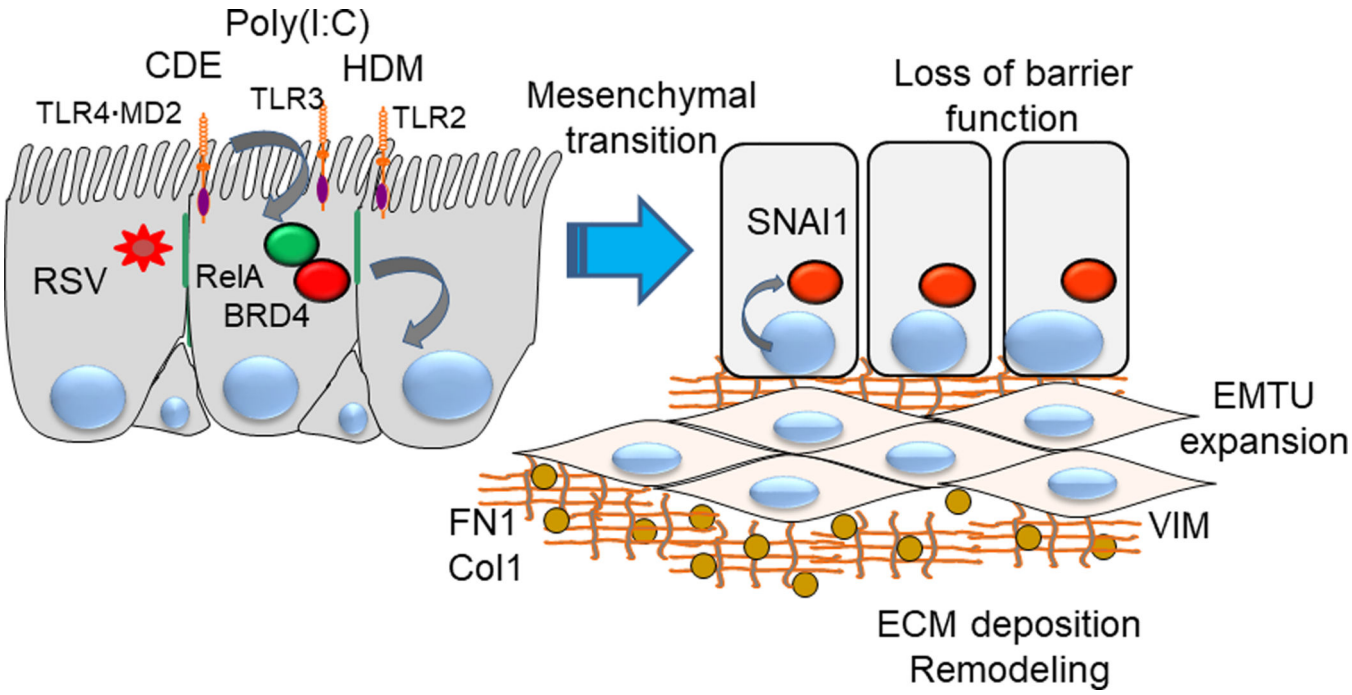


**Figure 3.**

Linkage of innate inflammation with mesenchymal transition. Repetitive oxidative stress mediated by TLR3 agonists (virus), TLR4/2 agonists [aero-allergens, such as cat dander (CD) or house dust mite (HDM)] exposure activates NFκB/RelA to complex with the BRD4 coactivator in the airway epithelial cells and upregulates its atypical histone acetyltransferase (HAT) activity. Subsequently, mesenchymal transition and production of fibrogenic cytokines induces airway remodeling including myofibroblast transdifferentiation, and extracellular matrix formation.