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REVIEW

Targeting inducible epigenetic reprogramming pathways in chronic airway remodeling

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Abstract

Allergic asthma is a chronic inflammatory airway disease whose clinical course is punctuated by acute exacerbations from aeroallergen exposure or respiratory virus infections. Aeroallergens and respiratory viruses stimulate toll-like receptor (TLR) signaling, producing oxidative injury and inflammation. Repetitive exacerbations produce complex mucosal adaptations, cell-state changes, and structural remodeling. These structural changes produce substantial morbidity, decrease lung capacity, and impair quality of life. We will review recent systems-level studies that provide fundamental new insights into how repetitive activation of innate signaling pathways produce epigenetic 'training' to induce adaptive epithelial responses. Oxidative stress produced downstream of TLR signaling induces transient oxidation of guanine bases in the regulatory regions of inflammatory genes. The epigenetic mark 8-oxoG is bound by a pleiotropic DNA repair enzyme, 8-oxoguanine DNA glycosylase (OGG1), which induces conformational changes in adjacent DNA to recruit the NFκB·bromodomain-containing protein 4 (BRD4) complex. The NFκB·BRD4 complex not only plays a central role in inflammation, but also triggers mesenchymal transition and extracellular matrix remodeling. Small molecule inhibitors of OGG1-8-oxoG binding and BRD4–acetylated histone interaction have been developed. We present studies demonstrating efficacy of these in reducing airway inflammation in preclinical models. Targeting inducible epigenetic reprogramming pathway shows promise for therapeutics in reversing airway remodeling in a variety of chronic airway diseases.

Keywords: 8-oxoguanine DNA glycosylase (OGG1), airway remodeling, bromodomain-containing protein 4 (BRD4), epigenetics, mesenchymal transition, myofibroblast.

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Introduction

Allergic asthma (AA) is a chronic, relapsing disease that affects ~339 million people worldwide.[1] Heterogeneous in nature, AA is typically characterized by Th2- and Th17-polarized lymphocytic inflammation in the airway and variable degrees of bronchial hyperreactivity. The clinical course of AA is punctuated by intercurrent acute exacerbations (AEs). AEs are episodes of obstructive symptoms, including shortness of breath, wheezing, coughing, and mucous production. Mechanistically, these clinical deteriorations are due to inflammation-induced small airway constriction and edema, decreasing expiratory airflow and producing mucous plugging, resulting in ball-valve small airway obstruction.[2] Epidemiological studies show that AEs are provoked by environmental interactions, including aeroallergen exposure, viral upper respiratory tract infections, or environmental oxidants.[3]

AEs produce substantial clinical impact. AEs are responsible for unscheduled visits that produce significant healthcare costs. In the United States alone, AEs account for 15 million outpatient visits, 2 million emergency room (ER) visits, and 500,000 hospitalizations annually.[4] Moreover, AEs diminish the quality of life in patients and their families.[5] In addition to acute worsening of disease, prospective observational studies indicate that AAs with frequent AEs are a distinct phenotype, frequently in association with glucocorticoid resistance.[6] Notably, this phenotype is prone to structural remodeling, producing a functional decline in

lung function.[7] Mechanistically, AEs are the result of toll-like receptor (TLR)-induced inflammation, producing remodeling through complex mucosal adaptions through epigenetic reprogramming. In this review, we will give an overview of the presence of mucosal environmental-inducible epigenetic changes and mechanistic pathways controlling them that influence airway remodeling and inform potential therapeutic strategies. This is a literature review using PubMed searches for allergic asthma, airway remodeling, epigenetics, and innate inflammation.

AEs and airway remodeling

AA is a highly heterogeneous disease in its etiology, triggers, and clinical course. In particular, a subset of 'exacerbation-prone' AAs can be identified that exhibit differences in the course of their disease. Most strikingly, AAs with a history of recent severe exacerbation requiring an ER visit or hospitalization in the past 3 months are at significantly increased risk of having recurrent, future exacerbations. This relationship was confirmed in a 3-year multicenter observational study of difficult-to-treat asthmatics – The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) Study[7] – and a prospective study involving mild–moderate asthmatics presenting to the ER.[8]

Emerging data indicate that the exacerbation-prone phenotype is more likely to have substantial reduction in pulmonary function. For example, in the abovementioned TENOR study, the frequency of exacerbations was linked to reductions in pulmonary function. In the US Severe Asthma Research Program (SARP) study, exacerbation-prone subjects had a greater frequency of irreversible airflow limitation;[9] this association of exacerbations and reduced airflow has been reproduced in the European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA) cohort.[10] Similarly, lower respiratory tract infections in early life are associated with reduced lung function and increased airway reactivity (wheezing) that persists for as much as a decade after the infection.[11–14] A 20-year follow-up study of respiratory syncytial virus-induced lower respiratory tract infection (LRTI) in infancy found that LRTI was an independent risk factor for decreased lung mechanics.[15] These essential findings have been replicated in an independent 18-year follow-up study in a Swedish cohort[16,17] as well as the Dutch Avon Longitudinal Study of Parents and Children (ALSPAC) study.[11] Moreover, the Tucson Children's Respiratory Study identified reduced pulmonary function in children at school age who had respiratory syncytial virus (RSV) bronchiolitis before the age of 3 years.[18] This finding is significant because long-term follow-up studies of reduced lung function in childhood are predictive of adult chronic obstructive pulmonary disease (COPD) and asthma–COPD overlap syndrome.[19] Even repetitive methacholine-induced bronchoconstriction produces enhanced extracellular matrix deposition and remodeling.[20] Collectively, these data indicate AEs of any type trigger airway remodeling.

Reductions in pulmonary function are the consequence of airway remodeling. This term refers to a constellation of structural changes of the cellular components and their supporting extracellular matrix in the pulmonary tree.[21,22] These changes include collagen deposition in the subepithelial basement membrane, disruption of the epithelial barrier, epithelial cell-state change (mucous metaplasia and/or mesenchymal transition), and smooth muscle hypertrophy.[21] Collectively, airway remodeling narrows the small airways, producing obstruction and reducing lung compliance, and is associated with hyperreactivity to nonspecific stimuli.[23]

Epithelial innate inflammation

Epithelial cells represent the initial surface that responds to viruses and aeroallergens in the process of provoking an AE.[24] Not solely a passive barrier, the epithelial cell dynamically responds to environmental exposures, through signal transduction pathways affecting the expression of homeostatic gene- and protein expression programs. These dynamic responses are determined by the type of exposure and location of the cell in the respiratory tree. Of particular focus here, environmental signals trigger innate signaling pathways through families of TLRs. TLRs play a central role in AEs of lung disease by producing mucin, stimulating leukocytic infiltration, and mesenchymal transition that drives fibrosis and remodeling.[25,26] In addition, the epithelial innate response shapes the evolution of downstream Th2- and Th17-type adaptive immunity characteristic of asthma. In AA, aeroallergens induce a robust small airway epithelial transforming growth factor-beta 1 (TGFβ1) response, important in activation of interleukin 13 (IL-13)-producing innate lymphoid type 2 (ILC2) cells and initiating an allergic response.[27]

Epithelial gene expression programs – and consequently secreted chemokines – produced by innate signaling in the upper airway are overlapping, but they are functionally distinct from programs produced by the lower airway epithelium in response to the same stimuli. These cell-type distinctions have been observed in gene expression[28,29] and protein expression[30] studies. In particular, unbiased proteomics studies showed that, compared to proximal (tracheal) epithelial cells, bronchiolar-derived epithelial cells produce over 106 distinct proteins in response to viral infections.[30] These factors include a subset of NF-κB-dependent Th2-polarizing chemokines, including chemokine (C-C motif) ligand 20 (CCL20)/macrophage-inducible protein 3α, thymic stromal lymphopoietin (TSLP), IL6, and CCL3-like 1 that are functionally and immunologically relevant to the pathogenesis of AA.[30] To provide greater insight into the functional role of the small airway epithelial cell in viral-induced inflammation, we examined the response of a conditional knockout of the nuclear factor kappa B (NFκB)/RelA transcription factor subunit in small airway bronchiolar cells. Interestingly, these animals are protected from TLR3-induced leukocytic inflammation[31] and RSV-induced airway obstruction.[32] These findings indicate that a special type of

bronchiolar epithelial cells derived from the secretoglobun expressing-small airway bronchiolar cell progenitor cells are a major sentinel cell responsible for Th2 polarizing and mucogenic cytokine production.

We and others have found that NFκB is activated in upper (nasal and tracheal) airway cells in response to TLR3 stimulation and intracellular viral replication,[33–35] yet these cells produce less CCL20/TSLP/IL6 than lower airway cells. The explanation for the intriguing discrepancy how NFκB activation in bronchiolar epithelial cells produces a distinct expression pattern from that in upper airway cells lies in differences in the chromatin organization of these cells. Small airway epithelial cells are preprogrammed/primed to elaborate unique cytokine expression patterns.

Epigenetic control of gene expression programs through 'innate training'

Epigenetics is a term that refers to heritable changes in gene expression that are controlled independently of primary DNA sequence. These changes are stable and inheritable, influencing environmental susceptibility to airway disease.[36] The mechanisms for epigenetic control can be at several levels, including direct DNA modification (methylation and oxidation), histone post-translational modifications, and changes in micro-RNA (miRNA) expression. Epigenetic changes play important roles in cellular differentiation, cell fate decisions, and cell state transitions that underlie Th2 polarization, dendritic cell (DC) activation, and epithelial cellular adaptation.[37,38] Although epigenetic regulation can be stable, recent work has shown that histone modifications, chromatin accessibility, and miRNA can be dynamically changed in response to innate signaling. This process has been best described in monocyte biology and referred to as 'training innate immunity' resulting in immunological memory.[39] However, epigenetic reprogramming also occurs in the epithelium, affecting extracellular matrix remodeling and inducible type III interferon (IFN) response.[40] In this review, we will focus on the innate training in epithelial cells relevant to coupling AEs with airway remodeling.

Innate-inducible DNA oxidative modifications function as an epigenetic regulator

Liganded TLRs induce reactive oxidative stress (ROS), a second messenger that stimulates the release of growth factors and cytokines linked to airway remodeling. In concert with the second messenger function, inducible ROS produce oxidative DNA damage, an event that alters gene expression programs in addition to its role as a potential mutagen.[41] Among the DNA bases, guanine is the most highly sensitive base to ROS because of its low oxidation potential. Oxidation of guanine results in the formation of 7,8 dihydro-8-oxoguanine (8-oxoG) at guanine-rich promoter regions.[42] 8-oxoG has emerged as dynamic and reversible epigenetic signal in oxidative innate immune responses because this modification is selectively recognized by 8-oxoguanine DNA glycosylate (OGG1). OGG1 is a pleiotropic protein important in DNA damage repair and innate signaling. Of relevance here, OGG1 binding facilitates the recruitment of active transcription factor, NFκB, to promoters of a subset of highly inflammation-inducible genes (Figure 1). These genes control expression of neutrophilic chemokines, including chemokine (C-X-C motif) ligand 2 (CXCL2), a cytokine important in the rapid leukocytic inflammation in response to TNF[43] and pollen allergens.[44]

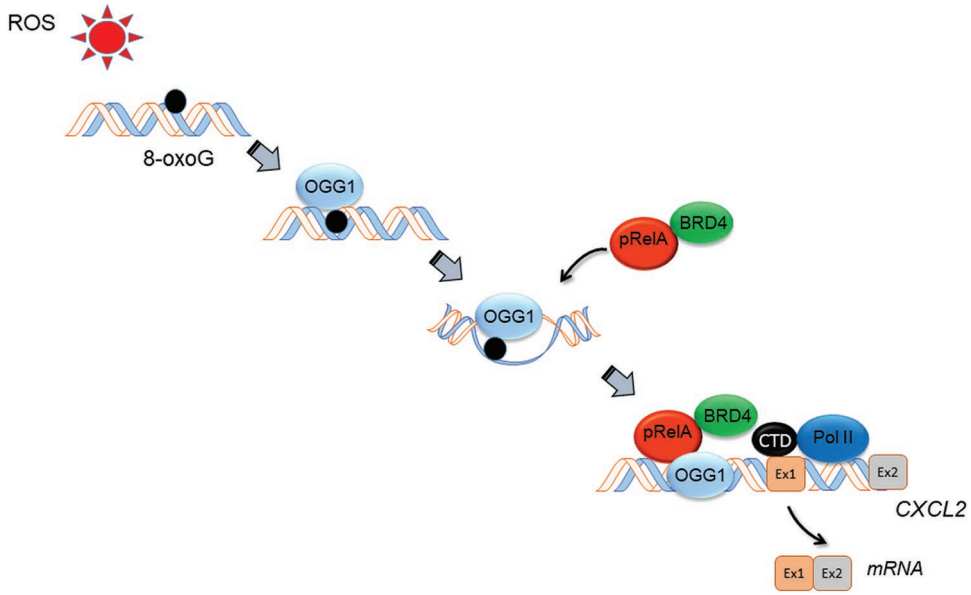
OGG1-induced recruitment of NFκB to regulatory chromatin is associated with rapid and highly inducible gene expression. Mechanistically, activated NFκB is bound to the transcriptional elongation complex (PTEFb), a complex composed of cyclin-dependent kinase (CDK)9 and bromodomain-containing protein 4 (BRD4).[45] BRD4 facilitates phosphorylation of RNA polymerase II,[46] regulating its enzymatic processivity and RNA splicing functions, resulting in the rapid expression of inflammatory genes.[47,48] In addition, we recently found that the association of RelA also induced the atypical histone acetyl transferase (HAT) activity of BRD4, acetylating histone H3 on Lys (K) 122, a modification that destabilizes nucleosomes, enhancing transcription through gene bodies.[49,50] Consequently, the coactivator enzymatic properties of BRD4 mediates cytokine production, neutrophilia, leukocytic infiltration, and clinical manifestations of disease.[26,32,51–53] In this manner, OGG1 nucleates chromatin remodeling complexes to innate genes (Figure 1).

Innate-inducible epigenetic marks affect genomic organization

The core component of chromatin is the nucleosome, a unit consisting of 142 bases of DNA wrapped around a histone octamer. The octamer is composed of two sets of histone H2A, H2B and H3 and H4 molecules with the internucleosome DNA stability H1 monomer. The nucleosomes protect DNA from damage and occlude transcription factors from binding; consequently, highly expressed genes are associated with nucleosome-free upstream control regions. There has been an explosion of the detailed biochemical understanding of histone modifications that affect nucleosomal structure and function.[54] Genes whose regulatory elements are associated with acetylated histones (e.g., the H3K27 acetylation mark) are typically in a configuration accessible to transcription factors and can be constitutively or inducibly expressed. By contrast, genes with methylated histones, for example, H3K27(me)3, are in heterochromatin states and silenced.[55]

Increasingly, it has been recognized that genes involved in innate responses are associated with both activated and inactivated histone marks, so-called 'metastable' genes.[40,56]

Figure 1. Epigenetic control of inducible mucosal inflammation. Schematic view of sequential steps in innate inflammation-induced leukocytic inflammation. Top left, resting cellular DNA is exposed to oxidative stress. Oxidation of guanine produces 7,8 oxoG-dihydro-8-oxoguanine (8-oxoG), an epigenetic signal that is recognized by 8-oxoGuanine DNA glycosylase (OGG1). Local conformational changes and protein–protein interaction results in high affinity binding of NFκB/RelA bromodomain-containing protein 4 (BRD4) complex. RelA–BRD4 activates transcriptional elongation of immediate early genes. Chronic activation of this pathway produces cell-state changes (mesenchymal transition).



Nucleosomes binding metastable genes can be dynamically shifted between active and inactivate states in response to cellular stimuli resulting in the processes of derepression and activation, working in parallel, the process of derepression and activation results in highly dynamic increase in gene expression.

BRD4 is a dynamically responsive chromatin modifying and organizing factor

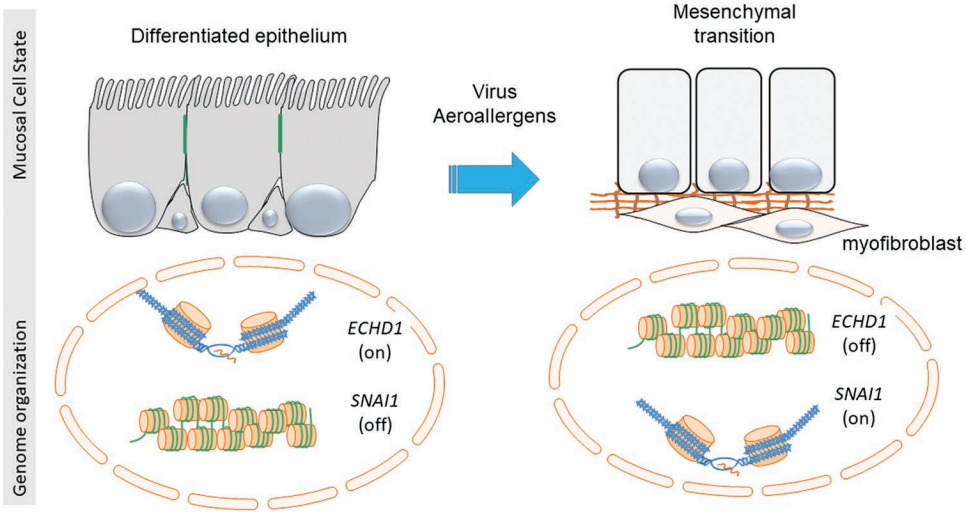
Through its acetyl lysine-binding bromodomains, BRD4 is essential for the maintenance of higher order chromatin configuration.[57] In particular, BRD4 is enriched in enhancer regions (aka 'superenhancers') with other chromatin modifying factors controlling the expression of tissue-specific genes. These superenhancers result in high-level, constitutive gene expression and coordinate with expression of distant gene through looping interactions. These interchromosomal contacts are thought to maintain gene expression programs controlling cell-type identity.[58] In response to inflammatory/TLR signaling, BRD4 superenhancers are repositioned to inflammatory and fibrotic gene expression networks.

Epigenetic mechanisms control cell-state transition

Chronic oxidative stress induced by innate signaling prompt adaptive cell-state transitions of the normal epithelium to a dedifferentiated mesenchymal-like state, called type II epithelial mesenchymal transition (EMT). Type II EMT involves extensive cytosolic restructuring, resulting in the loss of apical-basal polarity, dissolution of adherens junctions, enhanced motility, and expression of fibrotic genes (see Kalluri and Weinberg [2009] and Ijaz, Pazdrak, Kalita, and colleagues [2014] for in-depth reviews).[59,60] As a consequence of this process, epithelial cells acquire stem-cell-like properties, permitting the transitioned mesenchymal cell to repopulate regions of denuded epithelium, promoting tissue repair and extracellular matrix remodeling.[59]

The EMT program involves coordinating epigenetic reprogramming of ~3000 genes mediated by a core group of mesenchymal transcription factors, including SNAI1 and RelA.[60–62] This program inhibits expression of differentiated epithelial cadherin (*CDH1*) and upregulates core EMT transcription factors, mesenchymal intermediate filaments, and extracellular matrix (ECM)-modifying genes (Figure 2). Transition to the mesenchymal state is the product of sequential cell-state changes beginning from the

Figure 2. Epigenetic changes underlying cellular remodeling in the airway. Schematic view of an airway epithelial cell in the normal and allergic state. At left, normal airway epithelium is connected by tight junctions. In these cells, epithelial cadherin (ECDH1) is in an open 30-nm chromatin fiber formation and actively expressed. By contrast, mesenchymal/fibrotic program, Snail Family Transcriptional Repressor 1 (SNAI1), vimentin (VIM), and fibronectin (FN) genes are in inactiveheterochromatin states. In response to viral infection or allergen exposure, injury/repair mechanisms trigger epigenetic reprogramming, silencing ECDH1 and activating SNAI1, VM, and FN genes.



differentiated epithelial state transitioning into uncommitted 'partial EMT (pEMT)' state(s).[63] Chromatin immunoprecipitation and histone-profiling studies have shown that initial responses in type II EMT are mediated predominately by coordinate reversible histone marks in the absence of changes in DNA methylation. Genome-wide ChIP-seq studies found a reduction in the heterochromatin mark H3 Lys9 dimethylation (H3K9Me2), an increase in the euchromatin mark H3 Lys4 trimethylation (H3K4Me3).[64] Other histone profiling focusing on early changes in EMT have found accumulation of the repressive H3K27(me)3 mark,[65] a post-translational modification maintained by the PRC repressor complex, associated with type III IFN silencing.[40]

Activated NFκB·BRD4 drives EMT programs

Our recent unbiased RNA sequencing studies discovered that NFκB is upstream of the 'core' mesenchymal transcription factors SNAI1, zinc finger homeodomain enhancer-binding protein (ZEB), and V-Jun avian sarcoma virus 17 oncogene homolog (JUN) qualifying its consideration as a 'master transcriptional regulator' of EMT. Master regulators of the EMT are a subset of transcription factors engaged in the coordinate regulation of 'cliques' of downstream transcription factors by maintaining their expression by the formation of superenhancers.[58,62] Systems-level studies have shown the essential role of BRD4 in mediating the coordinated gene expression changes underlying EMT.[62] NFκB activation repositions BRD4-enriched superenhancers to inflammation-related genes in a cell type-dependent manner.[58] In the case of type II EMT in airway remodeling, we have shown that NFκB repositions BRD4 to the promoters of mesenchymal regulatory factors, including SNAI, ZEB, and basic helix-loop-helix transcription factor (Twist),[66] activating their expression by the transcriptional elongation.

Targeting therapeutics to the OGG1-8-oxoG and NFκB·BRD4 complexes in airway inflammation/remodeling

Collectively, the studies mentioned earlier provide a rich mechanistic understanding of the mucosal response to innate inflammation. ROS generated by TLR signaling induce site-specific 8-oxoG formation in regions of open chromatin. Binding of OGG1 to its substrate gene regulatory regions and consequential alterations in adjacent DNA sequences facilitates the recruitment of NFκB·BRD4 complex resulting in the rapid expression of innate inflammatory genes. Over time, repetitive NFκB activation of innate inflammation either by aeroallergens,[67] oxidized DNA base products,[68] or viral infections[69] induces innate training as a result of epigenetic

reprogramming and elaboration of the epithelial mesenchymal transition (Figure 1).

These studies inform the development of small molecule inhibitors of OGG1 and BRD4 as first-in-class inhibitors of innate-induced epigenetic reprogramming important in airway remodeling. High throughput screening of inhibitors of OGG1 binding to genomic 8-oxoG resulted in the identification of TH5487, a cell-permeable active-site binding inhibitor.[70] TH5487 prevents OGG1 chromatin binding at nontoxic concentrations suppressing inflammatory gene expression and TNF-induced lung inflammation *in vivo*. These data demonstrated that epigenetic inhibitors targeting oxidative DNA repair can reduce airway inflammation. The effect of the small molecule OGG1 inhibitors recapitulates the earlier discovery that genetic deficiency of OGG1 is associated with resistance to inflammation.[71]

BRD4 inhibitor development

Advancement of small molecule inhibitors directed to BRD4 has been the subject of intense medicinal chemistry work.[72,73] These approaches initially focused on fragment-based ligand design based on the structurally conserved bromodomain (BD) important in low-affinity acetylated-histone recognition, important in chromatin interaction. Consequently, a series of nonselective BD small molecule inhibitors were developed with interesting properties in antiproliferation, anti-inflammation, and antifibrotic activity.[31,51] Because of the structural similarity of the BDs across the entire BET family, the majority of these first generation inhibitors were not BRD4-selective.

Our laboratory's recent development and validation of a highly specific BRD4 inhibitor with nanomolar binding affinity and 30-fold specificity over the closely related BRD2 isoform has advanced the field by providing a useful probe for the testing of the role of BRD4 in pathophysiological conditions *in vivo*.[31,53] These BRD4 inhibitors disrupt BRD4 activity at multiple levels, including disruption of the extensive BRD4 protein–protein interaction complex,[31,74] dissolution BRD4-rich superenhancers,[58] and inhibition of its atypical HAT activity.[26,32,67] Consequently, BRD4 inhibitors show potential to interfere with mucosal inflammation and airway remodeling in response to viruses and allergen challenges. Reduction in airway remodeling has been through reversal of the mesenchymal

Table 1. Active clinical trials of BRD4 inhibitors registered on clinical trials.gov (CT.gov).

Inhibitor	Sponsor	Indication	CT.gov identifier
Apabetalone	Steeve Provencher	Pulmonary artery hypertension	NCT03655704
SF1126	SignalRX Pharmaceuticals, Inc.	Advanced hepatocellular cancer	NCT03059147
AZD9150	AstraZeneca	Relapsed/refractor non-Hodgkin's lymphoma (PRISM)	NCT03527147
AZD5153	AstraZeneca	Refractory solid tumors	NCT03205176
AZD5153	AstraZeneca	Lymphoma	NCT03205176
PLX51107	MDACC/National Cancer Institute	AML/myelodysplastic syndrome	NCT04022785
Olaparib	National Cancer Institute	Metastatic CA with DNA repair defects	NCT03375307
BSM-986158	Dana Farber Cancer Institute	Bromodomain and extraterminal domain (BET) inhibitor BMS-986158 in pediatric cancer	NCT03936465
CPI-0610	Constellation Pharmaceuticals	Peripheral nerve tumors	NCT02986919
CPI-0610	Constellation Pharmaceuticals	Lymphoma	NCT01949883
GSK2820151	GlaxoSmithKline	Metastatic and unresectable solid tumors	NCT02630251
GSK525762	GlaxoSmithKline	Pharmacokinetics, pharmacodynamics, and clinical activity in NUT midline carcinoma and other cancers	NCT01587703. NCT01587703. NCT01943851
INCB057643	Incyte Corporation	Advanced-stage cancer	NCT02711137
ODM-207	Orion	Solid tumors	NCT03035591
CC-90010	Celgene	Lymphoma, solid tumors	NCT03220347
FT-1101	Forma Therapeutics	AML, myelodysplastic syndrome	NCT02543879
ABBV-744	AbbVie	Prostate cancer	NCT03360006
RVX-000222	Resverlogix Corporation	T2DM, CAD	NCT02586155
RVX-000222	Resverlogix Corporation	Chronic kidney failure	NCT03160430

AML, acute myeloid leukemia; CAD, coronary artery disease; DNA, deoxyribonucleic acid; NUT, nuclear carcinoma of the testis; T2DM, type 2 diabetes mellitus.

transition and reduction in the unfolded protein response.[75] A recent demonstration of BRD4 inhibitors in TLR3-induced remodeling has been demonstrated by unbiased optical clearing secondary harmonic generation in a mouse model.[76]

These first-generation inhibitors have been advanced to identify small molecule inhibitors for selective BDs as well as chemistries that degrade the target molecule using proteolysis targeting chimera (PROTAC), promoting ubiquitin-mediated proteolysis of the target molecule (reviewed in Cochran, Conery, and Sims [2019]).[77] BRD4 inhibitors being tested in CT.gov-registered clinical trials in humans are shown in Table 1. The majority of indications are related to the treatment of solid and hematological malignancies.

Advancing BRD4 inhibitors into the clinic for treatment of airway remodeling will require the advancement of biomarkers of BRD4 effect. Biomarkers of BRD4 inhibition in airway disease have been identified recently using systems-level pharmacoproteomics approaches.[78] This latter study discovered that BRD4 inhibitors interfered with vascular permeability and pericyte-myofibroblast transition,[78] indicating that BRD4 inhibitors ameloriate multiple downstream homeostatic components of the coordinate mucosal injury-repair response.

Summary

Inducible mucosal epigenetic responses to mucosal injury underlie a coordinate inflammatory and remodeling response. In this review, we present evidence for guanine residue oxidation as an inflammation-inducible epigenetic mark. This epigenetic change is dynamic and highly reversible. 8-oxoG is recognized by OGG1, recruiting the NFκB transcription factor–BRD4 complex. The evidence that BRD4 is a central nexus in inflammation-mediated remodeling is compelling. Efforts to disrupt the 8-oxoG-OGG1- NFκB·BRD4 epigenetic cascade has been successful with the development of two classes of OGG1 and BRD4 inhibitors. These compounds will find numerous clinical applications in treatment of acute inflammation and chronic remodeling.

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