Role of histone deacetylase 2 in epigenetics and cellular senescence: implications in lung inflammaging and COPD

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THE INFLAMMAGING REFERS to chronic low-grade inflammation with aging, which occurs in chronic inflammatory diseases, such as chronic obstructive pulmonary disease (COPD) (34, 74, 124). The inflammation and cellular senescence (a state of permanent growth arrest) are intertwined in the process of accelerated or premature lung aging. However, the mechanism and causal role of inflammation and premature aging in the development of COPD remain unknown.

Histone deacetylase 2 (HDAC2) belongs to class I histone deacetylases, which catalyze the removal of acetyl groups from ε-amino-terminal lysine tails of core histone proteins. It was first discovered as a mammalian homolog of the yeast transcriptional regulator RPD3 responsible for transcriptional repression (138). HDAC2 itself does not possess a DNA-binding domain; therefore, it requires the presence of corepressor complex proteins including mSin3, NuRD/Mi2, and NCoR to target the substrate DNA. It is tightly regulated by complex protein-protein interaction, subcellular localization, and posttranslational modification (25, 111). HDAC2 functions in regulation of various cellular processes, such as cell cycle, proliferation, differentiation, inflammation, development, and glucocorticoid function. Recently, it has been shown that HDAC2 along with HDAC1 regulates DNA damage response (DDR) and cellular senescence via an epigenetic mechanism (82, 130). The level of HDAC2 and activity is decreased in lung parenchyma, bronchial biopsies, alveolar macrophages, and peripheral blood monocytes from patients with COPD, as well as in macrophages and lungs of mice exposed to cigarette smoke (4, 20, 47, 137). Yang et al. (137) have shown that NF-κB-mediated lung inflammatory response was associated with oxidative posttranslational modifications of HDAC2 in response to cigarette smoke. These modifications led to the ubiquitination and proteosomal degradation of HDAC2 (3, 4). Other studies also showed that HDAC2 is posttranslationally modified by oxidative/carbonyl stress imposed by cigarette smoke, leading to its degradation (75, 80). Interestingly, these modifications and various cellular processes regulated by HDAC2 are shown to be involved in the pathogenesis of COPD. This implicates a pivotal role of HDAC2 in the development of COPD/emphysema. In this perspective review, we have discussed the regulation of HDAC2 in various cellular functions in translational research, particularly in the progression of COPD, and potential for targeting HDAC2 in the intervention of this disease.

**HDAC2 Posttranslational Modifications by Oxidative/Carbonyl Stress**

Several studies have shown that HDAC2 level and activity are closely related to its posttranslational modifications, such as cell cycle, proliferation, differentiation, inflammation, development, and glucocorticoid function. Recently, it has been shown that HDAC2 along with HDAC1 regulates DNA damage response (DDR) and cellular senescence via an epigenetic mechanism (82, 130). The level of HDAC2 and activity is decreased in lung parenchyma, bronchial biopsies, alveolar macrophages, and peripheral blood monocytes from patients with COPD, as well as in macrophages and lungs of mice exposed to cigarette smoke (4, 20, 47, 137). Yang et al. (137) have shown that NF-κB-mediated lung inflammatory response was associated with oxidative posttranslational modifications of HDAC2 in response to cigarette smoke. These modifications led to the ubiquitination and proteosomal degradation of HDAC2 (3, 4). Other studies also showed that HDAC2 is posttranslationally modified by oxidative/carbonyl stress imposed by cigarette smoke, leading to its degradation (75, 80). Interestingly, these modifications and various cellular processes regulated by HDAC2 are shown to be involved in the pathogenesis of COPD. This implicates a pivotal role of HDAC2 in the development of COPD/emphysema. In this perspective review, we have discussed the regulation of HDAC2 in various cellular functions in translational research, particularly in the progression of COPD, and potential for targeting HDAC2 in the intervention of this disease.
Fig. 1. Role of histone deacetylase 2 (HDAC2) in oxidative/carbonyl stress-induced inflammation and steroid resistance. Oxidative/carbonyl stress imposed by cigarette smoke causes HDAC2 phosphorylation, carbonylation, and nitrosylation, thereby leading to the decrease of its level and activity. HDAC2 reduction increases the acetylation of histone, NF-κB, and glucocorticoid (G) receptor (GR), which results in the augmented transcription of proinflammatory genes and steroid resistance. A variety of pharmacological and dietary compounds, such as theophylline, sulforaphane, curcumin, baicalin, and quercetin are under investigation to restore steroid efficacy via regulation HDAC2 posttranslational modifications and activity. P, phosphorylation; 4-HNE, carbonylation; NO-Cys, nitrosylation; Ac, acetylation.
as well as cysteine residues 262 and 274 are at the COOH-terminal end of HDAC2 catalytic domain (57). Indeed, cigarette smoke caused upregulation of inducible NOS and eNOS in mouse lung, despite that the latter effect is transient (110). This may increase NO generation and subsequent HDAC2 nitration and nitrosylation in COPD (75). Because HDAC2 itself does not possess a DNA-binding domain but requires the presence of corepressor complex proteins to target it to substrate DNA (25), it is possible that S-nitrosylation at Cys 262 and Cys 274, as well as nitration on tyrosine 253, affects the ability of HDAC2 to interact with required DNA-binding proteins present in the corepressor complex. HDAC2 nitrosylation occurs at Cys 262 and Cys 274, which is increased in alveolar macrophages from patients with COPD. This leads to inhibition of glucocorticoid receptor (GR)-transrepression activity (75). Interestingly, treatment with Nrf2 activator sulforaphane significantly reduced HDAC2 nitrosylation and degradation, which is in agreement with the findings that reduced HDAC2 abundance is observed in lungs of Nrf2-deficient mice in response to cigarette smoke exposure (2, 75). Thus Nrf2 is an important antioxidant transcription factor that targets HDAC2 via phase II gene induction, thereby reversing corticosteroid resistance in COPD and other corticosteroid-resistant inflammatory diseases. HDAC2 is also regulated by cellular redox GSH status. Intracellular levels of GSH retain HDAC2 in a reducing environment because an increase in intracellular GSH levels can inhibit the oxidatively posttranslational modifications of HDAC2 (4, 75, 137). HDAC2 forms a complex with HDAC1 and HDAC3. Treatment of cigarette smoke extract decreases the protein levels of HDAC1, HDAC2, and HDAC3 in human monocyte/macrophage in cell culture experiments (68, 134, 137), although there is no report regarding the reduction of HDAC1 or HDAC3 in lungs of patients with COPD. Further study is required to determine whether HDAC2 reduction disrupts its complex with HDAC1 and HDAC3, leading to the change of their abundance and activity. Furthermore, it remains unknown whether other antioxidants, such as N-acetyl-L-cysteine, superoxide dismutase, and peroxynitrite scavengers, also can protect against HDAC2 oxidative modifications and nitrosylation.

**HDAC2 in Inflammation and Steroid Resistance**

Corticosteroids suppress inflammation by recruiting HDAC2 to NF-κB-driven proinflammatory gene promoters, thereby inhibiting the transcription of these genes. Furthermore, HDAC2 is required for GR deacetylation, which enables GR binding to the NF-κB complex, leading to the inhibition of NF-κB-dependent proinflammatory gene transcription (38, 48). NF-κB (RelA/p65) itself can also be acetylated and activated by cigarette smoke, which is attenuated by HDAC2 (21, 137, 141). However, HDAC2 level and activity are decreased in lungs of patients with COPD (47). This renders corticosteroids unable to inhibit proinflammatory gene transcription, leading to steroid resistance in COPD (Fig. 1). This is corroborated by the findings that hypoxia-inducible factor-1α activation by hypoxia, which occurs in lung microenvironment of patients with COPD, decreases HDAC2 level, resulting in augmented inflammation and steroid resistance (18). Furthermore, HDAC2-deficient mice are not responsive to budesonide in inhibiting LPS-induced lung inflammation (LPS itself has no effect on HDAC2 level or activity) (2). Hence, the attenuation of HDAC2 posttranslational modification and reduction would restore the effectiveness of steroid in inhibiting inflammation. A variety of pharmacological and dietary compounds can influence HDAC2 activity and level (Fig. 1 and Table 2). For example, treatment of monocytes/macrophages with curcumin (active ingredient in dietary spice turmeric or *Curcuma longa*), a polyphenolic compound, attenuated cigarette smoke extract-induced carboxylation, phosphorylation, and proteosomal degradation of HDAC2, which was associated with the restoration of steroid effectiveness in vitro (80). Nrf2 activator sulforaphane (present in broccoli and cruciferous vegetables) restored dexamethasone sensitivity in alveolar macrophages obtained from patients with COPD and treated with cigarette smoke extract ex vivo (75). Nortriptyline, a tricyclic antidepressant, has been shown to restore corticosteroid sensitivity induced by cigarette smoke-mediated oxidative stress, which is associated with increased HDAC activity (81). Low concentration of theophylline restores corticosteroid responsiveness in rats with smoke-induced airway inflammation and increases HDAC2 activity in alveolar macrophages from patients with COPD (23, 114). A recent clinical trial has demonstrated that a combination therapy with an inhaled corticosteroid and low-dose of theophylline attenuated airway inflammation in patients with COPD (32). Theophylline also suppressed peroxynitrite-induced tissue remodeling via pathways involving NF-κB/TGF-β1 and/or HDAC in the human fibroblast HFL-1 cell line (113). Erythromycin, a macrolide, restored the effect of cigarette smoke-induced decline in HDAC1, HDAC2, and HDAC3 levels associated with inhibition of NF-κB activation (68). Baicalin, a flavonoid compound isolated from the root of *Scutellaria baicalensis Georgi*, can influence cigarette smoke-induced inflammation and overcome steroid resistance via inhibiting HDAC2 phosphorylation in mouse lungs (67). Similarly, long-acting β2-agonists and corticosteroids restore the reduction of HDAC activity and inhibit H₂O₂-induced proinflammatory mediator release from human alveolar macrophages (99). All these findings provide a new avenue for the development of

### Table 2. Regulation of small molecules in HDAC activity and steroid resistance

<table>
<thead>
<tr>
<th>Molecule</th>
<th>HDAC Activity</th>
<th>Steroid Effectiveness and Inflammation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curcumin</td>
<td>Inhibition of HDAC2 phosphorylation and degradation</td>
<td>Restores steroid effectiveness</td>
<td>(80)</td>
</tr>
<tr>
<td>Sulforaphane</td>
<td>Inhibition of HDAC2 nitrosylation and degradation</td>
<td>Restores dexamethasone sensitivity</td>
<td>(75)</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Increases HDAC activity</td>
<td>Restores corticosteroid sensitivity</td>
<td>(81)</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Increases HDAC2 activity</td>
<td>Increases corticosteroid effectiveness in COPD</td>
<td>(23, 32)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Inhibits the reduction of HDAC1, HDAC2 and HDAC3</td>
<td>Inhibits NF-κB activation</td>
<td>(68)</td>
</tr>
<tr>
<td>Baicalin</td>
<td>Inhibits HDAC2 phosphorylation</td>
<td>Overcomes steroid resistance</td>
<td>(67)</td>
</tr>
<tr>
<td>Salmeterol or formoterol</td>
<td>Restores HDAC activity</td>
<td>Inhibits inflammatory response</td>
<td>(99)</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease.
Fig. 2. Epigenetic regulation of HDAC2 in DNA damage response as well as in stress-induced premature senescence (SIPS) and senescence-associated secretory phenotype (SASP) after DNA damage. In response to transient DNA damage, chromatin structure changes, which then allows DNA repair proteins, such as Ku70 and Ku80, and cofactors including heterochromatin protein 1 (HP1) to access the damage sites. Furthermore, HDAC2 is also recruited to damaged sites to promote repair via repressing transcription or to affect the ability of DNA repair factors to bind damaged DNA. However, persistent and sustained oxidative stress induced by cigarette smoke activates the signaling pathways of DNA damage response, thereby causing SIPS. Furthermore, HDAC2 reduction and histone methyltransferase (HMT) activation induce augmented histone acetylation (e.g., H3K9) and abnormal histone methylation (e.g., H3K4) on the promoters of SASP and prosenescent genes, leading to increased transcription of these genes. Me, methylation; NHEJ, nonhomologous end joining; COPD, chronic obstructive pulmonary disease.

Table 3. HDAC2 regulation in histone acetylation and methylation in DDR and cellular senescence

<table>
<thead>
<tr>
<th>Histone Modification</th>
<th>Specific Residue</th>
<th>Effect of HDAC2</th>
<th>Function</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylation</td>
<td>H3K56</td>
<td>Reduce its acetylation</td>
<td>Involved in DDR and DNA repair</td>
<td>(82)</td>
</tr>
<tr>
<td></td>
<td>H4K5</td>
<td>Reduce its acetylation</td>
<td>Involved in DNA repair</td>
<td>(41, 105)</td>
</tr>
<tr>
<td></td>
<td>H4K12</td>
<td>Reduce its acetylation</td>
<td>Regulate telomere function and premature aging</td>
<td>(41, 50, 105, 145)</td>
</tr>
<tr>
<td></td>
<td>H4K16</td>
<td>Reduce its acetylation</td>
<td>Involved in DNA repair and cellular senescence</td>
<td>(59, 82)</td>
</tr>
<tr>
<td>Metylation</td>
<td>H3K4</td>
<td>HDACs inhibit H3K4 methylation via LSD1</td>
<td>Involved in gene activation and DDR</td>
<td>(30, 45, 77, 132)</td>
</tr>
<tr>
<td></td>
<td>H3K9</td>
<td>HDACs increase its methylation via SUV39H1</td>
<td>Involved in replication checkpoint and cellular senescence</td>
<td>(13, 87, 102, 127)</td>
</tr>
<tr>
<td></td>
<td>H4K20</td>
<td>Trichostatin A reduces its methylation</td>
<td>Influence DDR after DSB</td>
<td>(12, 36, 106)</td>
</tr>
</tbody>
</table>

DDR, DNA damage response; DSB, double-strand break.
SASP has been introduced to describe the senescent cells that secrete the senescent-associated secretory phenotype (SASP) (103, 104). HDAC2 Regulation in Cellular Senescence

Recent studies have shown that persistent DNA damage causes stress-induced premature senescence (SIPS) and senescence-associated secretory phenotype (SASP) (103, 104). SASP has been introduced to describe the senescent cells that secrete proinflammatory mediators, such as IL-6, IL-8, and matrix metalloproteinases. This is partially due to NF-κB activation by DDR. Interestingly, NF-κB inhibition in turn delays the DNA damage-induced senescence and aging in mice (118), suggesting the reinforcement of cellular senescence by SASP as well as positive feedback between SIPS and SASP. Replicative senescence occurs as a result of exhaustion of proliferative ability of the cells in concomitance with shortening of telomeres and alteration in telomerase due to organisms/cellular aging independent of environmental stress. This cigarette smoke-mediated DNA damage may be an important contributing factor in initiating and maintaining SIPS and SASP. Indeed, a link between cellular senescence and premature lung aging has been proposed in the pathogenesis of COPD (7, 11, 37, 52, 65, 73, 124). Cigarette smoke induces senescence in lung epithelial cells and fibroblasts in vitro (86, 91, 92, 121–123). Senescence of fibroblasts and myofibroblasts may result in fibrosis in smokers and patients with COPD. It is also likely that carbonyls/oxidants generated or present in cigarette smoke cause immunosenescence of T- and B-cells, leading to abnormal recognition of self-antigens, which is important for the development of COPD (14, 54, 62, 90, 109). The involvement of cellular senescence in the pathogenesis of emphysema is also shown in various studies using genetically altered mouse strains (55, 64, 108, 112, 139). However, the molecular mechanisms that underlie cigarette smoke-induced cellular senescence in vitro in lung cells and in vivo in mouse lung and the precise role of SIPS in the development of COPD/emphysema are unclear. HDAC2 has been shown to protect against cellular senescence via regulating proinflammatory genes (i.e., p21 and p16) (69, 130, 134, 147). In addition, deletion of proinflammatory gene p21 protects against cigarette smoke-induced cellular senescence in lung cells and subsequent emphysema (139). Hence, reduction of HDAC2 may lead to cellular senescence and pulmonary emphysema (83). Hyperoxia occurs during oxygen therapy for patients with COPD with severe resting hypoxemia. However, hyperoxia causes DNA damage and cellular senescence as well as impairs lung development in neonatal rodents via decreasing HDAC2 level and activity (71, 148). This provides a possibility that HDAC2 is an essential factor in regulating premature cellular senescence and the susceptibility to develop COPD. Further study using HDAC2 global and cell-specific knockout mice as well as transgenic animals would identify the role of HDAC2 in cellular senescence during cigarette smoke-induced airspace enlargement/lung destruction (emphysema).

HDAC2 interacts with poly(ADP-ribose) polymerase-1 (PARP-1) and reduces its acetylation that is required for full NF-κB-dependent transcriptional activity (44). PARP-1 is an important molecule that activates DNA repair programs, and PARP-1/NF-κB signaling cascade is activated during cellular senescence (94, 135). Therefore, it is possible that HDAC2 regulates SIPS and SASP via PARP-1-dependent mechanisms on DDR and telomere function in response to cigarette smoking. This contention requires further studies to translate the findings of HDAC2 regulation in replicative senescence in pathogenesis of COPD.

**HDAC2 Regulation in SASP**

The senescent cells are prone to secrete proinflammatory cytokines, which may in turn reinforce cellular senescence, as the deficiency of IL-6, IL-6R, or CXCR2 prevents SIPS (1, 35, 60, 103). Indeed, the percentage of proinflammatory senescent type II cells expressing both p16 and phosphorylated NF-κB (i.e., SASP) was increased in lungs of patients with COPD compared with smokers and nonsmokers (121). Increased proinflammatory gene transcription in senesced cells may be due to abnormal histone acetylation and methylation on these gene promoters. In general, histone acetylation is associated with gene activation. Unlike histone acetylation, histone H3K4 and H3K36 trimethylation activates chromatin (euchromatin), whereas histone H3K9 and H3K27 trimethylation silences gene transcription (heterochromatin) (26, 29, 33, 89). This has been shown to occur by cigarette smoke extract treatment, which increases histone H3K4 and H3K36 methylation but reduces H3K9 and H3K27 methylation in lung epithelial cells (140). It is proposed that histone deacetylation of H3K9 by HDAC2 is a prerequisite for its methylation (87, 102). Moreover, histone H3K4 methylation limits the accumulation of histone H3K4 acetylation at the gene promoter (42). These findings suggest the cross-regulation of histone methylation...
and acetylation, even at the same residue. Hence, the study on the pattern and cross-talk of histone acetylation and methylation at these residues on the promoters of SASP genes will unravel an epigenetic chromatin mechanism underlying abnormal inflammatory response observed in COPD. It also remains to be studied whether HDAC2 regulates histone methylation on the promoters of SASP genes in a residue-specific manner (Fig. 2). Glucocorticoids are shown to suppress selected components of the SASP (61). However, HDAC2-dependent steroid resistance occurs in patients with COPD. Hence, it is possible that steroids may not be able to suppress SASP and thereby SIPS in patients with COPD.

Administration of CXCR2 inhibitor reduces lung mucus production and goblet cell hyperplasia in animal model of pulmonary inflammation (17, 117). Genetic ablation of HDAC2 renders these mice more susceptible to cigarette smoke-induced lung inflammation (2). However, it is unknown whether CXCR2 antagonist can prevent cigarette smoke-induced lung cellular senescence and subsequently the development of emphysema, particularly in HDAC2 knockout-susceptible mice, although NF-κB inhibitor has no effect on premature senescence and airspace enlargement in mice (139).

**HDAC Complex in DDR and SIPS of Lung Stem/Progenitor Cells**

The function of HDAC2 relies on the formation of its corepressor complexes along with HDAC1. Deletion of NuRD complexes including HDAC1 is associated with premature aging and DDR, although ablation of mSin3A or mSin3B does not result in cellular senescence (24, 40, 82, 98). In light of the regulation of cigarette smoke on the interaction of HDAC2 with mSin3, NuRD/Mi2, and HDAC1 (3), it is possible that HDAC complexes are also involved in cigarette smoke-mediated SASP gene transcription, DDR, and SIPS.

Recent studies have demonstrated that HDAC/mSin3A complex regulates the developmental genes, such as Sox-2, Wnt/β-catenin, and bone morphogenetic protein, which are important for branching morphogenesis and epithelial cell differentiation in lungs (10, 39, 43, 53, 85). Apart from lung development, Sox-2 also regulates the maintenance and differentiation of lung progenitor cells, such as Basal and Clara cells, which are senesced in lung of cigarette smoke-exposed mice and patients with COPD (7, 100, 119, 139). Indeed, human lungs contain identifiable stem cells, which are self-renewing, clonogenic, and multipotent (51). Therefore, the study on the regulation of HDAC2 and its complexes in lung development and lung stem cells as well as progenitor cells will unravel the molecular mechanisms and susceptible factors involved in the pathogenesis of COPD. Furthermore, this will provide the potential to repair and regenerate lung tissue in this disease.

**Translational Impact**

HDAC2 is reduced in lungs of patients with COPD. HDAC2 reduction is associated with inflammation, steroid resistance, and DNA damage as well as lung cellular senescence. A variety of pharmacological and dietary compounds/molecules, such as theophylline, sulforaphane nortriptyline, baikalin, quercetin, erythromycin, and curcumin, are shown to target HDAC2 to reverse steroid resistance in COPD. However, all of the above agents have off-target effects. Hence, the development of a specific activator to activate HDAC2 or specific modulator to reduce HDAC2 posttranslational modification and degradation is urgently required to restore steroid efficacy in inhibiting chronic inflammation and premature cellular senescence in patients with COPD.

**Conclusions and Future Directions**

HDAC2 is an important deacetylase in regulating steroid function to inhibit inflammatory response in lungs. Recent studies have demonstrated a novel role of HDAC2 in regulating DNA damage/repair, premature senescence, and SASP. We and others have shown that cigarette smoke reduces the level and activity of HDAC2 in cells in vitro and in mouse lung in vivo, which may contribute to the sustained inflammation, DNA damage, and subsequently cellular senescence in lungs of patients with COPD. However, the roles of DNA damage and cellular senescence as well as their regulation by HDAC2 in the pathogenesis of chronic pulmonary diseases with lung inflammaging are unclear. Specifically, there are obviously multiple questions that remain unanswered. For example, it is unclear whether HDAC2 has a cell-specific effect in terms of steroid resistance (in macrophages, epithelial cells, and fibroblasts) as well as cigarette smoke/oxidants-induced DNA damage and cellular senescence (in lung epithelial cells and fibroblasts). Does HDAC2 protect telomere shortening, which is an important contributing factor in inducing replicative senescence that is observed in COPD (6)? Moreover, it remains to be known whether the clearance of senesced cells (e.g., p16-positive cells) in HDAC2-deficient lungs using recently developed p16-INK strategy delays or halts the progression of emphysema (9, 58, 147). Furthermore, it is not known which cells in the lung are the primary target for reduced HDAC2-mediated lung cellular senescence. Understanding the above aspects would unravel the role of DDR and premature senescence as well as HDAC2 regulation in the pathogenesis of COPD and provide a novel avenue to intervene this disease. COPD has been shown to increase the risk for developing lung cancer (143). Overexpression of HDAC2 confers oncogenic potential to human lung cancer cells (49). Thus further study is required to resolve this controversy by differentiating HDAC2 regulation and its dependent epigenetic changes in senescence during the development of COPD and lung cancer. This will provide translational HDAC2-based therapeutic approaches in lung inflammaging and premature senescence.

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**DISCLOSURES**

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**AUTHOR CONTRIBUTIONS**

Author contributions: H.Y. and I.R. prepared figures; H.Y. and I.R. drafted manuscript; H.Y. and I.R. approved final version of manuscript; I.R. edited and revised manuscript.

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