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Low levels of DNA repair enzyme NEIL2 May exacerbate inflammation and genomic damage in subjects with stable COPD and during severe exacerbations

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Abstract

Background Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory airway disease that is an independent risk factor for lung cancer. Reduction in NEIL2 function, a DNA glycosylase involved in DNA repair during transcription, has been associated with an increased incidence of malignancies in humans. NEIL2 knockout mouse models have demonstrated increased inflammation and oxidative DNA damage in the lungs after exposure to an inflammatory insult, but data are lacking regarding NEIL2 function in individuals with COPD. We investigated whether NEIL2 levels and oxidative DNA damage to the transcribed genome are reduced in individuals with stable COPD and during severe acute exacerbations of COPD (AECOPD).

Methods The study was conducted at a single center in the US. Eligible subjects underwent a one-time 30 cc venous blood draw. The population consisted of 50 adults: 16 with stable COPD, 11 hospitalized for AECOPD, and 23 individuals without lung disease (controls). We analyzed blood leukocytes for NEIL2 mRNA and DNA damage by RT–qPCR and LA–qPCR, respectively, in all groups. Plasma levels of seven biomarkers, CXCL1, CXCL8, CXCL9, CXCL10, CCL2, CCL11 and IL-6, were analyzed in the COPD groups using a magnetic bead panel (Millipore®).

Results The fold change in NEIL2 mRNA levels were lower in individuals with stable COPD and AECOPD than in controls (0.72 for COPD, $p = 0.029$; 0.407 for AECOPD, $p < 0.001$). The difference in NEIL2 mRNA expression between the stable COPD group and AECOPD group was also statistically significant ($p < 0.001$). The fold change in DNA lesions per 10 kb of DNA was greater in the stable COPD (9.38, $p < 0.001$) and AECOPD (15.81, $p < 0.001$) groups than in the control group. The difference in fold change was also greater in the AECOPD group versus stable COPD $p < 0.024$). Cytokine levels were not significantly different between the COPD groups. NEIL2 levels were correlated with plasma eosinophil levels in the stable COPD group ($r = 0.737$, $p = 0.003$).

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Conclusions NEIL2 mRNA levels are significantly reduced in individuals with COPD and may exacerbate DNA damage and inflammation. These results suggest a possible mechanism that increases inflammation and oxidative genomic damage in COPD.

Clinical trial number Not applicable.

Keywords DNA repair, COPD, Cancer, Genomic damage, Airway inflammation, Eosinophils, NEIL2

Background

Chronic obstructive pulmonary disease (COPD) is a major health burden in the United States. It ranks as the third leading cause of death, claiming 148,000 lives annually and contributed to an estimated $50 billion in healthcare costs each year [1]. COPD is characterized by chronic airway inflammation, fixed airway obstruction, and variable rates of progression [2]. Some patients experience episodic worsening of symptoms including cough, increased sputum production, and breathlessness, described as acute exacerbation of COPD (AECOPD) [2]. Frequent and more severe exacerbations often result in hospitalizations and are associated with more rapid progression of the disease [2].

COPD has been identified as an independent risk factor for the development of lung cancer, with an estimated odds ratio of 1.6 to 2.0 [3, 4]. Additionally, the presence of acute exacerbations is associated with an increased risk of lung malignancy [5]. Lung cancer is the leading cause of death due to malignancy in the United States, with an estimated 127,000 deaths per year, greater than all deaths due to breast, prostate and colon cancer combined [3]. However, the link between COPD and lung cancer has not been fully delineated.

There are a plethora of reports showing that chronic airway inflammation in COPD subjects is also associated with systemic inflammation characterized by leakage of reactive oxygen species (ROS) and cytokines directly into the peripheral blood that further preactivated blood leukocytes [6–9]. Substantially increased systemic inflammatory markers, such as leukocytes, interleukin (IL)-6, IL-8, C-reactive protein, fibrinogen and tumor necrosis factor alpha (TNF-α), have been reported in COPD subjects compared to healthy individuals [9–11]. Additionally, NO and $O2^-$ released from neutrophils or macrophages during inflammation not only increase the number of mutagenic DNA lesions, such as 8-nitroguanine and 8-oxodG but also impair the DNA repair machinery by inhibiting several important DNA repair enzymes [12–14].

In cells, oxidative DNA damage is repaired by base excision repair (BER). The BER pathway involves a multiprotein complex that utilizes one of five DNA glycosylases that recognize single oxidized bases and initiates the process of removal and replacement with the appropriate nucleotide. NEIL2 is a unique DNA glycosylase that removes single oxidized bases during transcription when DNA is in a bubble structure [15]. A reduction in NEIL2 activity has been associated with increased oxidative damage in the transcriptionally active genome in animal models [16]. Reduced or aberrant activity of NEIL2 has also been linked to a variety of human malignancies, including lung cancer [17, 18].

We previously showed a protective anti-inflammatory role of NEIL2 in TNF-α-induced lung inflammation [19]. Additionally, pathogenic bacterial infections, such as *H. pylori* and Fusobacterium, and viral infections such as respiratory syncytial virus (RSV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), significantly downregulate NEIL2, with a consequent increase in the expression of inflammatory cytokines [20–23]. Furthermore, viral or bacterial infections are the most frequent causes of exacerbations in COPD patients. However, the link between COPD and oxidative DNA damage and the role of NEIL2 therein has not been fully explored.

We propose that NEIL2 activity provides a link between airway inflammation and increased DNA damage. We hypothesized that reduced levels of NEIL2 are present in human subjects with COPD and are associated with inflammation and increased oxidative damage to the transcriptionally active genome. To test our hypothesis, we measured NEIL2 mRNA levels and oxidative damage in circulating blood leukocytes in subjects with stable COPD and severe AECOPD.

Methods

Our study is a single-center cross-sectional cohort study that received approval from the University of Texas Medical Board (UTMB) Institutional Review Board (#14–0131). Subjects provided informed verbal consent using an IRB approved script. The study was performed in accordance with the Declaration of Helsinki in 1975 and as revised in 1983.

Inclusion criteria required a confirmed diagnosis of COPD with documented chronic airflow obstruction on spirometry (FEV1/FVC < 80% predicted) within the past year. Participants were divided into two groups. The first group comprised stable COPD patients identified during routine follow-up visits at pulmonary outpatient clinics, with no exacerbations or oral steroid use in the past three months and stable symptoms for over three months. The

second group included COPD patients meeting the same criteria but who were currently hospitalized for a primary diagnosis of AECOPD. Given the lack of consensus on AECOPD diagnostic criteria, we adopted the American Thoracic Society Pulmonary Perspective definition, excluding patients with pneumonia, sepsis, or decompensated heart failure [24]. Demographic and clinical data were extracted from electronic medical records.

Control Group Individuals with no known history of lung disease, acute inflammatory processes, or infections were recruited to serve as controls. These participants provided blood samples for leukocyte analysis, which were used to establish baseline values for DNA glycosylase activity and oxidative damage assays. Demographic data were collected at the time of consent.

Procedures

The subjects underwent venipuncture with one-time removal of 30 ccs of whole blood. Blood was separated into plasma and buffy coats at the UTMB Clinical Research Center, frozen at ⁻80 °C within four hours of sampling and maintained at that temperature until the assays were performed.

Real-time quantitative polymerase chain reaction (RT–qPCR)

Total RNA was isolated from blood samples via the PAXgene Blood RNA Kit (Qiagen) according to the manufacturer's protocol. Up to 2 µg of RNA was used to synthesize cDNA using a PrimeScript™ RT Kit with gDNA Eraser (TaKaRa), and qPCR was carried out using specific primers (NEIL2: Forward primer-CCTGTCTGC TATACACTGC, Reverse primer-CCTGCAGCCAGGC TGTACTG; NEIL3: Forward primer-TACAGCACCCC TCCAAGAAG, Reverse primer-GTTGTGTTTACTGC AGCGAGG and glyceraldehyde 3-phosphate dehydrogenase (GAPDH): Forward primer- CATCACTGCCACCC AGAAGA, Reverse primer- TTCTAGACGGCAGGTCA GGT) and TB Green™ Premix Ex Taq™ II (Tli RNase H Plus; TaKaRa) in an Applied Biosystems™ 7500 Real-Time PCR System. The thermal cycling conditions were 94 °C for 5 min, 94 °C for 10 s and 60 °C for 1 min for 40 cycles and 60 °C for 5 min. The target mRNA levels were normalized to that of the housekeeping gene, GAPDH, and Fold change (FC) was calculated with the $2^{-\Delta\Delta CT}$ method. In each case, qPCR was performed with DNase-treated RNA samples without reverse transcriptase to rule out genomic DNA contamination.

DNA damage: long amplicon quantitative PCR (LA-qPCR)

2 ml of blood was subjected to centrifugation at 2000 × g for 10 min at room temperature, and the buffy coat was collected in a fresh Eppendorf tube. Genomic DNA was extracted using the DNeasy Blood and Tissue Kit (Qiagen) according to the manufacturer's protocol. The DNA was quantified by Pico Green (Molecular Probes) in a black-bottomed 96-well plate, and 20–30 ng of DNA was used for LA-qPCR assays using LongAmp Taq DNA Polymerase (NEB). The transcribed gene HPRT1 (~ 10 kb) was amplified using the appropriate oligos. The final PCR conditions were optimized at 94 °C for 30 s; 24 cycles of 94 °C for 30 s, 58 °C for 30 s, and 65 °C for 10 min; and 65 °C for 10 min.

Since the amplification of a small region is independent of DNA damage, a small DNA fragment (~ 200–400 bp) from HPRT1 was also amplified for normalization of the long amplicon. The amplified products were then visualized on gels using ethidium bromide, and the intensity of the bands was quantified with ImageJ software (NIH). The relative extent of DNA damage was determined by calculating the intensity of bands, and lesion frequencies were derived from the expression $-\ln(A_T/A_C)$, where A_T is the amplification of the test sample (stable COPD or AECOPD), and A_C is the amplification of a nondamaged control [25].

Cytokine testing

Plasma samples were tested using the MILLIPLEX® Human Cytokine/Chemokine/Growth Factor Magnetic Bead Panel A (Millipore®). A seven-point serial dilution standard curve was constructed by reconstituting the lyophilized standards provided in the kit. The plasma samples were tested undiluted and treated as instructed in the kit. A 96-well plate was loaded with the standard curve and positive controls, and samples were then tested for CXCL1, CXCL8, CXCL9, CXCL10, CCL2, CCL11, and Il-6. Bead fluorescence readings were captured using the Bio-Plex 200 System (Bio-Rad®).

Statistical analysis

Demographic variables were analyzed using Fisher's exact test for categorical variables and unpaired t-tests for continuous variables. Two-sided unpaired Student's t-test were used for analysis of the statistical significance between two sets of data for mRNA expression and DNA oxidative damage values. Cytokine levels were assessed using the Mann–Whitney Rank Sum test for nonnormally distributed data. Pearson's correlation was used for analysis of NEIL2 mRNA levels, smoking history, and cytokine and eosinophil levels. Statistical significance was set at $p \leq 0.05$. Statistics were generated using SigmaPlot 15 software (SYSTAT Software, Inc., San Jose, CA).

Results

Sixteen participants were assigned to the stable COPD group, while eleven were included in the severe COPD exacerbation (AECOPD) group. The groups were

Table 1 Baseline characteristics of subjects: individuals with chronic obstructive pulmonary disease (COPD), acute exacerbation of COPD (AECOPD) and controls

Variable	COPD ($n=16$) n (%) or mean (± SD)	AECOPD ($n=11$) n (%) or mean (± SD)	*p*-value	Controls
Age (years)	62.6 (3.5)	66.5 (4.9)	0.376	42.1 (range 29–63)
Sex (n)			0.900	
Male	4(33)	3(27)		13 (56)
Female	12(67)	8(73)		10 (44)
Race (n)			0.080	
White	16 (100)	9 (82)		22 (96)
Black	0	2 (18)		0
Asian	0	0		1 (4)
Current Smokers (n)	4 (25.0)	3 (27.0)	0.900	n/s
Total pack years (mean)	42.929 (9.3)	46.8 (26.4)	0.751	n/s
Forced Vital Capacity (FVC) (L)	2.29 (0.8)	1.96 (0.8)	0.355	n/s
Forced Expiratory Volume in one second (FEV_1) (L)	1.46 (0.7)	0.88 (0.4)	0.029	n/s
FEV_1/FVC (%)	51.5 (12.7)	40.0 (17.92)	0.094	n/s
Diffusing Capacity (DLCO) (ml/min/Hg)	15.87 (5.6); $n=8$	9.66 (4.8); $n=6$	0.050	n/s
Eosinophils (cells/μl)	190.7 (98.6)	*	n/a	n/s

*not included as all AECOPD individuals received steroids, which may reduce eosinophil levels.

n/s not specified

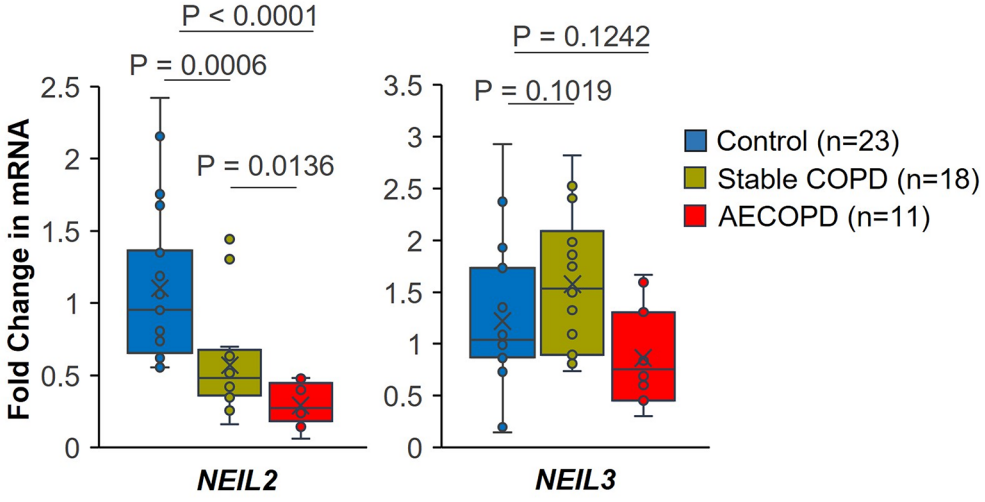

Fig. 1 DNA glycosylase levels by group. Whisker plots displaying the expression levels of DNA glycosylase transcripts in the blood cells of stable COPD ($n=18$) and AECOPD ($n=11$) subjects vs. controls ($n=23$). Boxes represent the interquartile range extending from the first to third quartiles, with the horizontal line representing the median value. Whiskers or error bars represent the maximum and minimum values, respectively; x in the box shows the mean. P values (unpaired two-tailed Student's t test) vs. the control or stable COPD group are indicated

comparable, except for FEV1 and DLCO, which were lower in the AECOPD group ($p=0.029$ and $p=0.050$, respectively) (Table 1).

A total of 23 individuals served as controls for the study. The mean age of the control group was 42.1 years, with ages ranging from 29 to 63 years. A total of 55% of the control participants were male, and the majority of the control group (23 individuals) were of white descent ($n=22$ white, $n=1$ Asian).

DNA glycosylase expression and DNA damage

We tested the mRNA expression of the DNA glycosylases NEIL2 and NEIL3, which are DNA base-specific enzymes that initiate the first step of the BER pathway, in blood cells from COPD subjects ($n=29$), including 11 subjects suffering from AECOPD, compared to those from healthy individuals ($n=23$). We observed an approximately 48% decrease ($p<0.001$) in the NEIL2 mRNA level in the stable COPD group compared to the control cohort (Fig. 1). Furthermore, NEIL2 expression was significantly lower in the AECOPD cohort than in both the control (over 73%; $p<0.001$) and stable COPD (49%; $p=0.014$) cohorts.

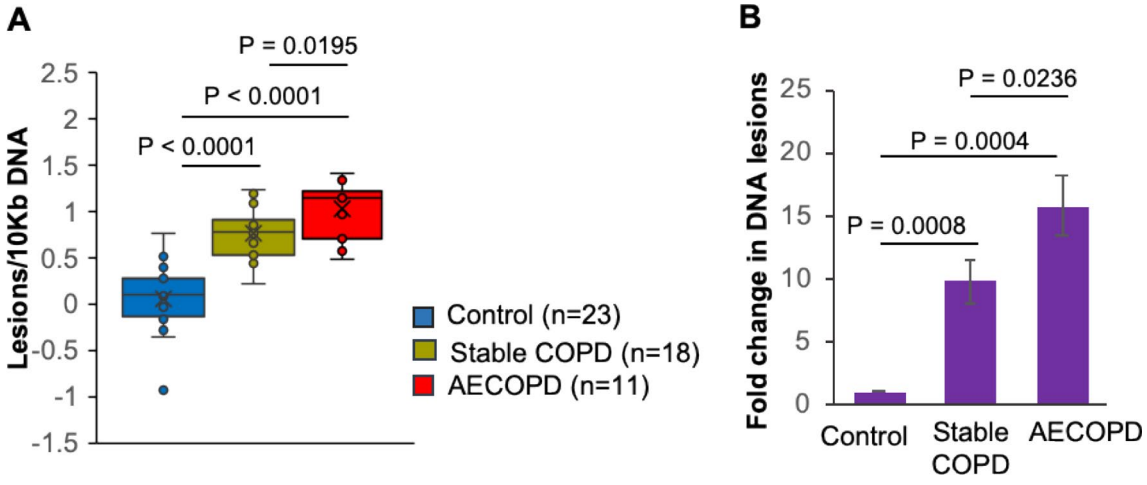

Fig. 2 DNA damage by groups. Whisker plot displaying the levels of DNA lesions per Kb of genomic DNA in blood cells of stable COPD subjects and AECOPD subjects vs. the control group. Boxes represent the interquartile range extending from the first to third quartiles, with the horizontal line representing the median value. Whiskers or error bars represent the maximum and minimum values, respectively; x in the box shows the mean. B. Histogram showing the fold change in DNA lesions in the blood cells of control ($n=23$), stable COPD ($n=18$) and AECOPD ($n=11$) subjects, as analyzed by LA–qPCR. P values (unpaired two-tailed Student's t test) vs. the control or stable COPD group are indicated

Table 2 Pearson product correlation between plasma cytokine levels and NEIL2 mRNA levels

	CXCL1	CXCL8	CXCL9	CXCL10	CCL2	CCL11	IL 6
NEIL2	0.256	0.0678	-0.307	-0.366	-0.287	0.051	-0.0571
P value	0.263	0.742	0.127	0.0661	0.155	0.804	0.791

Conversely, no significant change in NEIL3 was observed among the groups. Overall, the expression of the DNA repair enzyme NEIL2 is significantly decreased in stable COPD subjects and is further decreased in subjects suffering from AECOPD.

NEIL2 has been shown to protect the transcribing genome by participating in transcription-coupled base excision repair (TC-BER) [15, 16]; nonetheless, a decrease in NEIL2 leads to the accumulation of DNA lesions, especially in the transcribing genome. Thus, in light of the diminished NEIL2 levels in COPD subjects, we examined DNA damage in blood cells using the model transcribed gene HPRT1, and indeed, we observed a significant increase in DNA damage in stable COPD and AECOPD subjects compared to that in the control group (Fig. 2A). Compared with those of controls, stable COPD subjects showed a 9.78-fold ($p<0.001$) greater accumulation of DNA lesions, whereas the frequency of DNA lesion accumulation was significantly greater (15.81-fold, $P=0.001$) in AECOPD subjects (Fig. 2B). Notably, compared with stable COPD subjects, AECOPD subjects exhibited ~ 1.6-fold ($p=0.024$) greater oxidative DNA damage, which is in accordance with the significantly lower levels of NEIL2 in AECOPD subjects than in stable COPD subjects or healthy controls (Fig. 1).

There was no statistical difference in NEIL2 levels or DNA damage based on current vs. former smokers ($p=0.649$ and $p=0.793$). Similarly, total pack yrs were not correlated with either NEIL2 levels or DNA damage ($p=0.423$ and $p=0.888$).

Cytokine levels and systemic inflammation

There was no correlation between cytokine levels and NEIL2 mRNA levels across groups (Table 2). Furthermore, there was no significant difference in cytokine levels between the COPD groups (Table 3). There was a significant positive correlation between NEIL2 and blood eosinophil levels ($r=0.737$, $p=0.003$) in stable COPD subjects (Fig. 3). AECOPD subjects who had received parenteral corticosteroids at the time of sampling were excluded.

Discussion

Inadequate DNA repair is implicated in the pathogenesis of chronic obstructive pulmonary disease [26]; however, the mechanisms that underlie inadequate DNA repair in COPD are poorly understood. In the present study, we investigated the expression levels of key enzymes of the base excision repair pathway that initiate the repair of oxidatively damaged bases in cohorts of stable COPD subjects and subjects suffering from AECOPD. The levels of NEIL2 mRNA were significantly decreased in stable COPD subjects and further reduced in the AECOPD group. Reduced levels of NEIL2 were also associated with significantly increased DNA damage in the transcriptionally active genome in both stable COPD and AECOPD

Table 3 Plasma cytokine levels in blood leukocytes (pg/μl) by group

	Median	25th %	75th %	p-value
CXCL1				
COPD	5.63	3.650	9.210	$p=0.481$
AECOPD	6.93	2.560	11.480	
CXCL8				
COPD	1.95	0.857	3.152	$p=0.767$
AECOPD	1.38	0.940	8.490	
CXCL9				
COPD	2061.945	1136.225	3155.440	$p=0.521$
AECOPD	2802.91	1142.130	4386.410	
CXCL10				
COPD	175.25	109.020	309.325	$p=0.167$
AECOPD	255.02	119.810	399.890	
CCL2				
COPD	280.595	183.063	302.445	$p=0.657$
AECOPD	171.3	115.040	371.950	
CCL11				
COPD	64.75	47.990	82.415	$p=0.474$
AECOPD	62.84	35.080	118.190	
IL 6				
COPD	4.015	1.735	5.525	$p=0.257$
AECOPD	4.88	2.448	11.470	

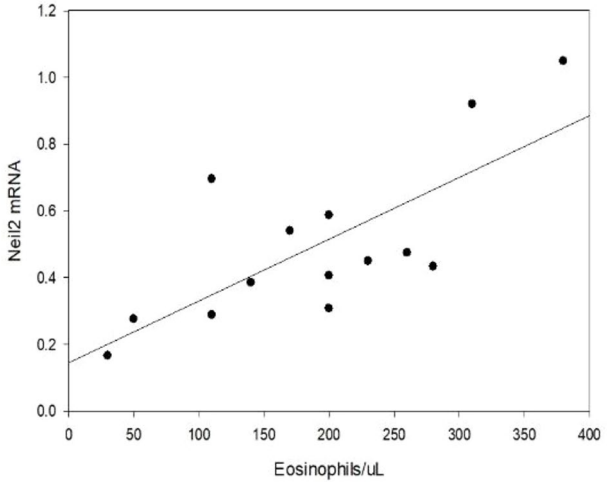

Fig. 3 Correlation between NEIL2 mRNA levels and blood eosinophils in stable COPD subjects. The scatterplot displays the NEIL2 mRNA fold change versus the absolute eosinophil count in subjects with stable COPD. The line denotes Pearson product correlation with $r=0.737$, $p=0.0027$

subjects compared to that in controls, with significantly increased damage in the AECOPD cohort compared to that in stable COPD group.

The cause of the reduction in NEIL2 in stable COPD subjects is unclear. There was no clinical evidence of ongoing infection or a history of lung malignancy in this group. Current smoking status and pack year history were not predictive of NEIL2 levels overall or within groups although the small numbers preclude any definitive conclusion. However, pulmonary fibroblast cell cultures depleted of NEIL2 using silencing RNA technology and exposed to side stream smoke for 24 h demonstrate increased oxidative damage compared to normal cells [27]. Conceivably, recurrent exposures from smoking or other chronic oxidative stresses could suppress/deplete NEIL2 levels. Alternatively, these subjects might have constitutively low levels and are more susceptible to inflammatory stimulation although there is no current data to support this hypothesis.

The increase in oxidative damage in the transcriptional genome paralleled the reduction in NEIL2 levels. A causative link between NEIL2 and oxidative damage is supported in animal studies. NEIL2 knockout mice demonstrate cumulative oxidative damage in the transcriptionally active genome over time while maintaining a normal phenotype [16]. As reported previously, NEIL2 plays an essential role in maintaining immune response homeostasis, where NEIL2 blocks NF-kB-mediated pro-inflammatory gene expression and protects hosts from an uncontrolled inflammatory response and oxidative damage [19, 23]. The administration of exogenous recombinant NEIL2 mitigated these changes.

The most common cause of AECOPD is infection, which is usually viral in origin. Reduced NEIL2 levels and increased inflammation and oxidative damage are demonstrated in RSV- and SARS-CoV-2-infected animal models [22, 23]. Similarly, patients with CoV-2 infection had reduced NEIL2 levels in bronchoalveolar lavage and peripheral blood leukocytes which correlated with severity [23]. While an infection driven reduction in NEIL2 seems most likely, the AECOPD group may have lower chronic depression of NEIL2 levels, which in turn increases their susceptibility to acute exacerbations and increased genomic damage.

Oxidative damage could result in the production of abnormal proteins, impair the healing process and lead to more rapid disease progression. Dysfunctional NEIL2 mRNA from genomic damage could conceivably result in a qualitative defect as well. Although there was no significant correlation between the degree of airflow obstruction and NEIL2 mRNA or oxidative damage, those subjects with AECOPD had a significantly lower FEV1 and reduced DLCO than did those in the stable group. Cumulative oxidative damage could also result in genome instability and contribute to the development of malignancy. A reduction in NEIL2 activity caused by dysfunctional polymorphisms has been associated with an increased risk of malignancy in humans [17, 18]. Acute exacerbations resulting in further reductions in NEIL2 levels and increased oxidative damage suggests that this may be a potential mechanism that contributes to the increased risk of malignancy in COPD subjects with frequent exacerbations.

A recent meta-analysis using two large COPD cohorts did not demonstrate the predictive value of any cytokine for acute exacerbations [28]. Similarly, we examined 7 cytokines, including IL6, CXCL 1, 8, 9, 10, CCL2, and CCL11, in our COPD population and found no significant differences between the COPD groups. The positive relationship between blood eosinophil levels and NEIL2 expression was unexpected. A recent analysis of blood eosinophil levels in the Spiromics COPD cohort revealed that GOLD D subjects with eosinophil counts less than 100/µl who did not receive steroids had more exacerbations and a more rapid decline in lung function [29]. Therefore, blood eosinophils may be an indicator of low NEIL2 expression and potentially worsening lung function. The relationship between NEIL2 and eosinophil levels needs further investigation.

Given the low levels detected, the use of recombinant NEIL2 as a therapeutic intervention is possible. We have previously demonstrated that recombinant NEIL2 modulates the inflammatory response by inhibiting NF-kB-mediated gene expression and decreasing viral replication [19, 22, 23]. Thus, restoring NEIL2 levels could potentially improve therapy for severe exacerbations, slow the progression of COPD in subjects at risk for a more rapid decline in lung function and/or frequent exacerbations and reduce the risk of malignancy in certain subgroups.

Our study is limited by its preliminary cross-sectional nature and use of circulating blood leukocytes. Future directions could include a longitudinal study of AECOPD patients to evaluate whether NEIL2 and oxidative damage levels recover, examine NEIL2 mRNA sequencing to evaluate for potential qualitative dysfunction and examine airway cell populations via bronchoalveolar lavage to correlate with blood leukocyte changes.

Conclusions

Low levels of NEIL2 mRNA may exacerbate inflammation and worsen oxidative damage in COPD patients. Potential consequences may include more frequent severe exacerbations, an increased rate of lung function deterioration and higher risk of lung malignancy.

Abbreviations

COPD	Chronic obstructive pulmonary disease
AECOPD	Acute exacerbation of COPD
GOLD	Global Initiative for Chronic Obstructive Lung Disease
NEIL2	Nei-like 2
RT–qPCR	Real-time quantitative polymerase chain reaction
LA-qPCR	Long amplicon quantitative PCR
CXCL	C-X-C motif chemokine ligand
CCL	C-C motif chemokine ligand
IL	Interleukin
DNA	Deoxynucleic acid
mRNA	Messenger ribonucleic acid
TC-BER	Transcription coupled-base excision repair
RSV	Respiratory Syncytial Virus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
NF-kB	Nuclear factor kappa B
TNF-α	Tumor necrosis factor alpha
Gapdh	Glyceraldehyde 3-phosphate dehydrogenase
FEV1	Forced expiratory volume in 1 s
FVC	Forced vital capacity

Author contributions

VC, TH, JS designed the research study JS, MA and VC obtained the clinical data, consent, and blood samples VC, KS, NT, and RR performed assays and statistical analysis VC, NT, JS, and TH prepared the main manuscript preparation NT, MA, and RR prepared the figures and tables.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

This single-center study was approved by the UTMB Institutional Review Board (#14–0131) for oral consent and performed in accordance with the Declaration of Helsinki in 1975 and as revised in 1983. All patient data were deidentified prior to performing the assays. No individual patient data or identifiers are included in the manuscript. All authors of the manuscript have read and agreed to its content and are accountable for all aspects of the accuracy and integrity of the manuscript in accordance with ICMJE criteria.

Competing interests

The authors declare no competing interests.

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