Supplemental methods

Isolation and primary culture of murine lung fibroblasts

The protocol was adapted from Corti et al ["Isolation and primary culture of murine alveolar type II cells". *Am J Respir Cell Mol Biol* 1996 ; 14: 309-315]. Crude cell suspensions were prepared from two females, 10-12 weeks old C57BL/6 mice (WT or DUOX1-deficient (DUOX1-/- and DUOX1-/+). The peritoneum was opened and the ventral rib cage was removed. The left atrium of the heart was then opened and the lungs were perfused with 2% HBSS (Life Technologies) containing antibiotics, using a 50-ml syringe fitted with a 22-gauge needle, through the right ventricle of the heart until they were visually free of blood. A 20-gauge intravenous catheter was inserted into the trachea and secured tightly with a suture. The lungs were filled with 1 ml Dispase II (2.35 U/ml, Roche). Low melt agarose (1%, in 0.5 ml, stored in a 45°C water bath) was then infused slowly via the catheter. The lungs were immediately cooled by rinsing several times with cold HBSS during 2 min. The lungs were then covered with 2 ml Dispase in a 50-ml propylene culture tube and incubated for 45 min at room temperature. The lungs were transferred to 7 ml DMEM/F12 with 0.01% DNase I (Sigma-Aldrich) in a 100-mm petri glass dish. The digested tissue was carefully teased from the airways with curved edge of curved fine-tipped forceps and chopped by a cutter. The resulting suspension was successively filtered through 70-µm and 40-µm Falcon cell strainers and then through a 20-µm nylon mesh. The filtered suspension was centrifuged at 350 x g for 8 min at 4°C and re-suspended in 15 ml of culture media (DMEM/12, 25% Foetal Bovine Serum (FBS)). The fibroblasts were isolated by adhesion on 150 cm2 flasks for 45 min and the medium was replaced by a new one. The primary cultures were maintained in a humidified incubator (37°C, 5% CO2).

Flow cytometry and fluorescence-activated cell sorting

CD45-BUV 395 (Biolegend) and Ly6G-PE-Texas Red (Biolegend) were used to identify neutrophils ($CD45^{+}$ and $Ly6G^{high}$). The samples were analyzed using FlowJo 10.0.7 (FlowJo, Ashland, OR, USA)

Treatment with Inhibitors and Cytokines

Primary lung fibroblasts from wild type and DUOX1-deficient mice were cultured no more than passage two. The cells were grown in phenol red-free DMEM/F12 medium supplemented with 1% (vol/vol) antibiotics/antimycotics (Life Technologies), 1% Glutamax (Life Technologies), 10% (vol/vol) FBS (Life Technologies). Cells were shifted in DMEM/F12 medium containing 1 or 5% FBS for 24h according the experiments before treatment with TGF-β1 (Peprotech) in the presence or in the absence of SB431542 (Calbiochem)

diphenylene iododium (DPI) (Sigma-Aldrich) Catalase (Roche) as described in figures legends.

Transfection of siRNA by electroporation

5 x 10^5 fibroblasts were resuspended in 100 µl of transfection buffer (*buffer 3P*: 5 mM KCl, 15 mM $MgCl_2$, 90 mM NaCl, 10 mM Glucose, 40 mM Na_2HPO_4/NaH_2PO_4, pH 7.2). 50 pmoles of siRNA against DUOX1 (stealth RNAi duplex HSS182411, as previously described [19]), scrambled siRNA control (Invitrogen), or siRNA against NEDD4L (smart pool, from Dharmacon) were then added to the cell suspension. The mixtures, in 2 mm Gap cuvettes (BTX), were nucleoporated according a specific predefined program (T016) using the AMAXA nucleofector. Following the electroporation, the cells (250 000 per well in 12-wells plates) were then seeded into DMEM/F12 medium with 25% FBS. Four hours later the medium was changed with DMEM/F12 containing 5% FBS and, according the experiments, TGF-β1 was added for 48h.

Transient expression of DUOX1 in fibroblasts

In the electroporation (nucleofection) experiments, 2 x 10^6 DUOX1-deficient fibroblasts were resuspended in 100 µl of transfection buffer (3P). The NH2-terminal hemagglutinin epitope tagged human DUOX1 (HA-DUOX1 pcDNA3) (3.5 µg/transfection sample), kindly provided by Dr. Xavier de Deken (Université libre de Bruxelles, Belgium), was added with or without the plasmid pcDNA3.1-HA-Ubiquitin (encoding HA tagged ubiquitin, 1.5 µg/transfection sample) according the experiments. The plasmid pcDNA3.1-HA-Ubiquitin was a gift from Edward Yeh (Addgene plasmid # 18712; http://n2t.net/addgene:18712; RRID: Addgene_18712). The plasmid pcDNA3.1-GFP (encoding the Green Fluorescent Protein) was used as control (3.5 µg/transfection sample). The mixtures, in 2 mm Gap cuvettes (BTX), were nucleoporated according a specific predefined program (T016) using the AMAXA nucleofector. Following the electroporation, the cells (1 x 10^6 cells per well in 6-well plates) were then seeded into DMEM/F12 medium with 25% FBS. Four hours later the medium was changed with DMEM/F12 containing 5% FBS and, according to the experiments, TGF-β1 was added for 48h.

RNA extraction, cDNA synthesis and Real time PCR

Total RNA from lung tissues and cell samples were purified with the Nucleospin RNA II kit (Machery Nagel). 500-1000ng of RNA was reverse-transcribed using Maxima reverse transcriptase (Thermo Fisher Scientific) and oligodT in a total reaction volume of 20 µl of PCR buffer according to the manufacturer's protocol for 60 min at 55°C, which are the

optimal conditions to detect DUOX1/2 mRNAs. Quantitative PCR (qPCR) was performed on an ABI 7500 system (Applied Biosystems) using Taqman gene expression assays (Thermo Fisher Scientific): mDuox1 (Mm01328685_m1 ; Invitrogen); macta2 (Mm00725412_s1; Invitrogen); mColla1 (Mm00801666_g1; Invitrogen); mTgfβ1 (Mm01178820_m1; Invitrogen); mDuox2 (Mm01326247_m1; Invitrogen); mDuoxa1 (Mm01269313_m1; Invitrogen); mIL6 (Mm00446190_m1; Invitrogen); mIL10 (Mm00439614_m1; Invitrogen); mIL13 (Mm00434204_m1; Invitrogen); mcxcl15 (Mm04208136_m1); mRn18s (Mm03928990_g1; Invitrogen); hActa2 (Hs00426835_g1; Invitrogen); hDuox1, hDuox2 and hPPIA have been previously described [16]. The cDNA was amplified as follow: 50 °C for 2min, 42 cycles of 95 °C for 15 s, and 60 °C for 1min. The fold change in mRNA expression for targeted gene was expressed relative to respectively 18S and PPIA for mice and human samples.

H_2O_2 production in particulate fractions

For particulate fraction preparation, the lung was homogenized using a motor- driven Teflon pestle homogenizer in 2ml of 50mM sodium phosphate buffer containing 0.25M sucrose, 1mM EGTA (pH 7.2), and the mixture of protease inhibitors cocktail (Roche). After centrifuging at 3000 g for 30 min at 4°C, the pellet was resuspended in 0.5 ml of 50mM sodium phosphate buffer (pH 7.2) containing 0.25M sucrose, 1mM $MgCl_2$, and the mixture of protease inhibitors. This particulate fractions (20 µg) were incubated in 50mM sodium phosphate buffer (pH 7.2) containing sucrose (150mM), EGTA (1mM), CaCl2 (1.5mM), SOD (Sigma-Aldrich) (200 U/ml), horseradish peroxidase (0.5 U/ml, Roche), and Amplex red (50 µM, Sigma-Aldrich). The reaction was started by adding 0.1mM NADPH and the fluorescence was measured in a microplate reader (Victor3; PerkinElmer) at 30°C for 40 min using excitation at 530 nm and emission at 595 nm. H_2O_2 production was quantified using standard calibration curves. The specific enzymatic activity was expressed as nanomoles of H_2O_2 per hour per milligram of protein.

For extracellular H_2O_2 generation (1×10^5) cells in Dulbecco's phosphate-buffered saline (D-PBS) with $CaCl_2$ and $MgCl_2$ were incubated with D-glucose (1 mg/ ml), horseradish peroxidase (0.5 U/ml), and Amplex red (50 µM), and the fluorescence was immediately measured as described above. H2O2 release was quantified (nanomoles H_2O_2 per hour per 10^5 cells) using standard calibration curves

Western Blot

For total cell lysates, cells were solubilized in 100 mM Tris·HCl pH 7.0 containing 2.5% (wt/vol) SDS, 1 mM EDTA, 1 mM EGTA, 4 M urea, and a mixture of phosphatase and

protease inhibitors (Calbiochem). Western blot was performed as described previously [19]. For lung tissues, the homogenous tissue was solubilized in RIPA buffer supplemented with phosphatase and protease inhibitors. After solubilization, the homogenate was centrifuged at 100 000 x g at 4°C for 30 minutes. The protein concentration was measured (BCA, Pierce). Electrophoresis was performed in 8% Tris-HCl SDS-PAGE and transferred to nitrocellulose membranes (GE-Healthcare). Membranes were blocked with TBS-0.1% Tween 5% BSA (Sigma) or Dry-Milk (Cell-Signaling) for 1h and incubated overnight with primary antibodies, including Anti-αSMA (42 kDa) (1:2000; Abcam); Anti-Fibronectin (263 kDa) (1:5000; Abcam); Anti-Duox1 (180 kda) (1:1000; home-made previously described [19]); Anti-pSmad2 (60 kDa) (1:2000; Millipore); Anti-pSmad3 (48 kDa) (1:6000; Abcam); Anti-Smad3 (1:2000; Abcam); Anti-Smad2 (1:2000; Cell-Signaling); Anti-Vinculin (130 kDa) (1:4000; Abcam); Anti-Vimentin (51 kDa) (1:2000; BETHYL); Anti-HA (1:2000; ROCHE); Anti-NEDD4L (130 kDa) (1:3000; Abcam). Membranes were then incubated with corresponding secondary antibody HRP/AP conjugate, including Goat Anti-Rabbit Alkaline phosphatase (1:5000; Promega); Goat Anti Mouse HRP (1:10000; DAKO); Goat Anti Mouse Alkaline Phosphatase (1:5000; SouthernBiotech); Goat Anti-Rabbit HRP (1:10000; SouthernBiotech); Anti-Rat Alkaline Phosphatase (1:5000; Promega).

The reactive proteins were visualized using chemiluminescence detection on Hyperfilm-ECL (GE-Healthcare) or alkalin phosphatase substrate NBT/BCIP (Sigma) directly to the membranes. The images were quantified using ImageJ plot plugin.

Cell surface biotinylation

Membrane-associated proteins were prepared using the Cell Surface Protein Isolation Kit (Pierce, Life Technologies) according to the manufacturer's protocol.

Histochemistry and Immunofluorescence

Sections of embedded lung were deparaffinized in xylene, rehydrated, and stained with hematoxylin-eosin-saffran (HES) or Sirius Red. Mounted slides were examined on an Ariol Leica microscope. Digital micrographs were captured at 20x magnification using a QImaging Micropublisher Camera. The Sirius quantification was performed using ImageJ software with the colour deconvolution plugin as following

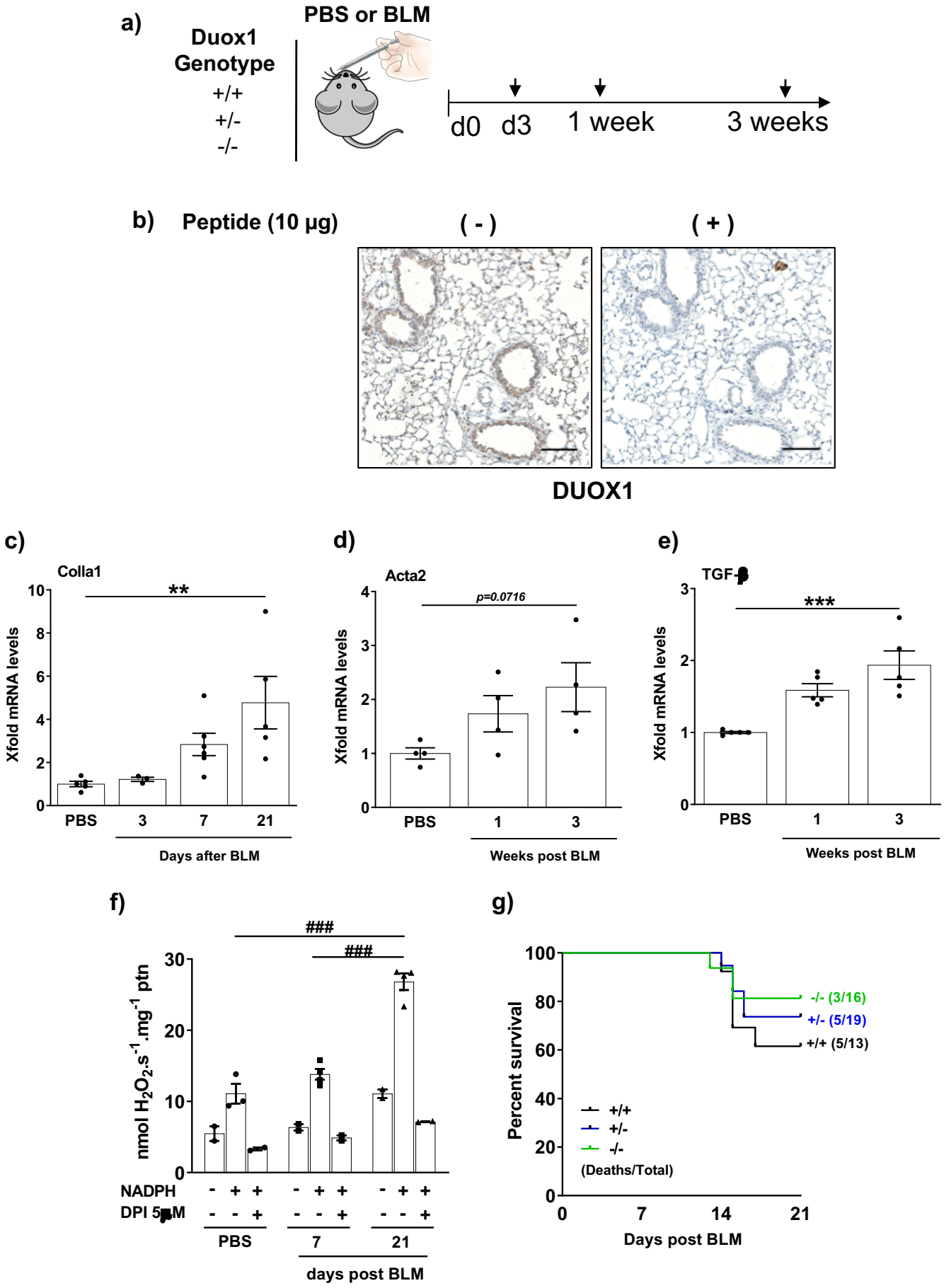
```
requires("1.32f");
dir = getDirectory("Choose a Directory "); // Select input folder
count = 1;
listFiles(dir);
function listFiles(dir) {
  list = getFileList(dir);
  for (i=0; i<list.length; i++) { //Start loops for each image in the folder
     if (endsWith(list[i], "/"))
        listFiles(""+dir+list[i]);
     else if (endsWith(toLowerCase(list[i]), ".jpg") || //You can change the input image file format
        endsWith(toLowerCase(list[i]), ".jpg"))          //You can change the input image file format
     {
        print((count++) + ": " + dir + list[i]);
setBatchMode(true); // If true, process is starting without showing the image and save processor charge
open(dir+list[i]);
ID = getTitle();
run("Set Measurements...", "area min shape median skewness kurtosis area_fraction limit redirect=None decimal=3"); // Measure configuration
run("Copy"); // make a copy to save the original image
run("8-bit"); // Convert the image in 8Bit gray colour
setThreshold(0, 240); // You can change this value for different staining intensity
run("Create Selection"); // Selection on the "TISSUE" zone
roiManager("Add");//Save the selection
close();
run("Internal Clipboard"); //Get the original picture back and put the selection we saved
run("Colour Deconvolution", "vectors=[User values] [r1]=3.545225 [g1]=39.964756 [b1]=10.6514 [r2]=58.504524 [g2]=93.680756 [b2]=36.459515 [r3]=6.7574778 [g3]=50.31245 [b3]=53.275555");  // Split in three colours
//Closing windows we don't need one-by-one
selectWindow("Clipboard"); close();
selectWindow("Clipboard-(Colour_3)"); close();
selectWindow("Clipboard-(Colour_2)"); close();
selectWindow("Colour Deconvolution"); close();

selectWindow("Clipboard-(Colour_1)");// Image corresponding to the colour we want to quantify
setThreshold(160, 200); // You can change this value for different staining intensity
roiManager("Measure"); //measurement in the selection "TISSUE"
        saveAs("jpg", dir + list[i]+" Collagen.jpg"); //Save the image
close();
selectWindow("Results");
saveAs("Results", dir + list[i]+" Collagen.xls"); //Save the results
//Delete results for the next image
run("Clear Results");
roiManager("Delete");
     c = 1;
     while (nImages > 0) {

     }
  }
}
```

```
}
//End of loops
```

The program automatically makes a selection of the cells and matrix tissue by contrast and uses colour deconvolution to calculate the %Area of the specific red signal over the tissue according to a threshold (160-200), allowing to discriminate between pre-existing strong red peri-bronchial collagen from fibrotic collagen with a middle intensity.

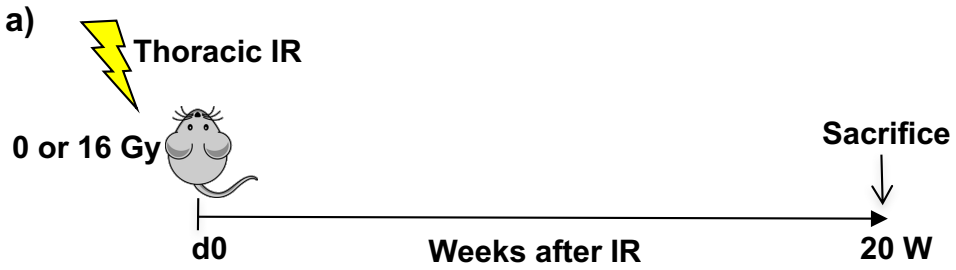
For immunohistochemistry staining, sections were blocked with Dako protein block serum-free 30 minutes and incubated with primary antibodies at 4 °C overnight. Endogenous peroxidase was quenched with 3% H_2O_2 for 10 minutes. Primary immunoreactivity was detected with a polymeric peroxidase-conjugated secondary antibody (DAKO) and visualized by 3,3′-diaminobenzidine histochemistry (DAKO). Sections were counterstained with Mayer Hematoxylin (MERCK), dehydrated, and mounted with Shandon mount (Thermo Fisher Scientific). Images were captured as above at 20X magnification. For quantitative assessments, the number of stained cells per high power field (HPF, 40x) was scored in 6 fields per mouse, 3 mice per condition. For quantitation of immunofluorescence, ten images (40x) were captured from 3-5 lungs for each condition and analysed with ImageJ. Fluorescent intensity was determined for each channel in each image. The means for intensity for each condition was calculated, and the intensity for each condition was normalized to that of the control.

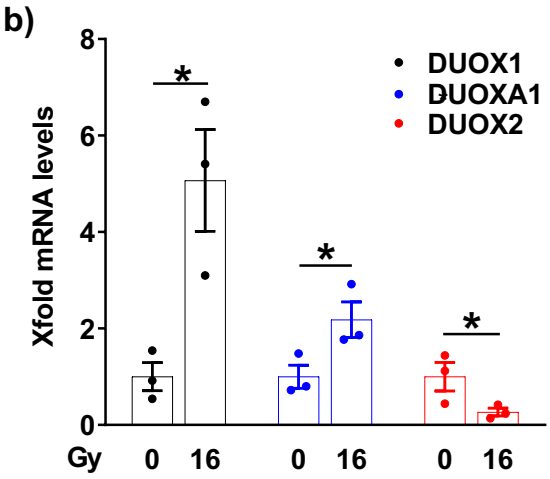
Supplementary Figure S1

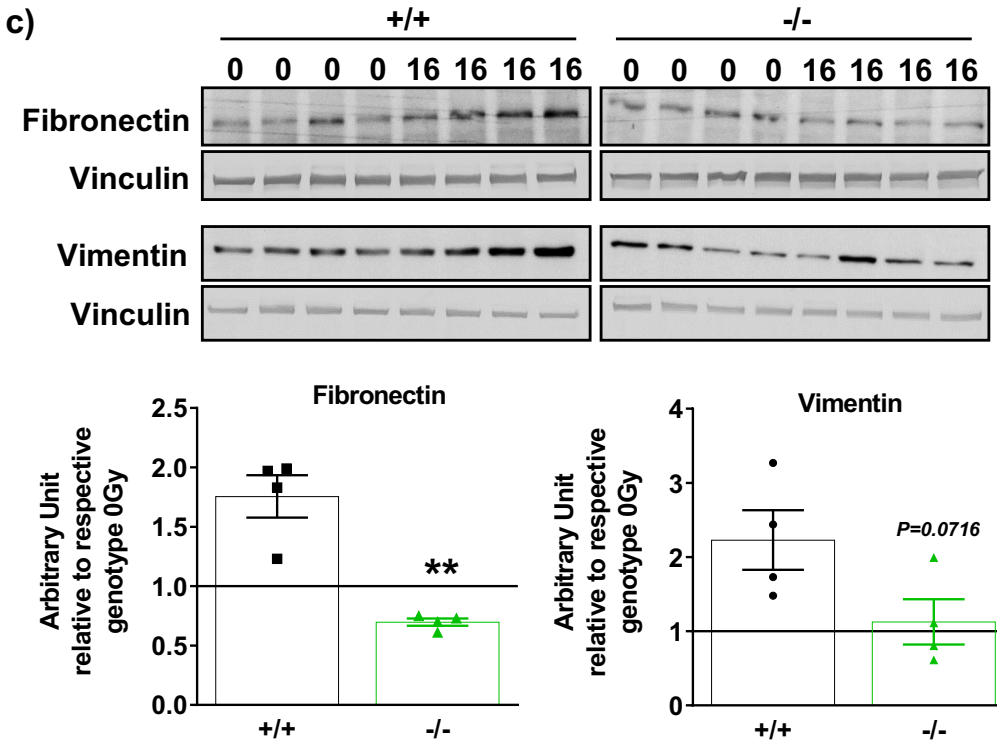


Supplementary Figure 1. Role of DUOX1 in bleomycin-induced lung fibrosis. a) Experimental protocol; b) Immunohistochemical analysis of DUOX1 in lung tissue. Scale bars = 200 µm. Negative controls were obtained by analysing mouse lung tissues incubated with immune sera preabsorbed with an excess of the corresponding peptide (10 µg). The staining of airway epithelial cells was negative in the presence of the peptide indicating that the staining was specific; c-e) qRT-PCR analysis of Collagene1, Acta2 and TGF-β1 mRNA expression in bleomycin-treated lung tissues from wild-type mice at the indicated time points, mouse R18S mRNA was used as internal control **p<0.01 and ***p<0.001 compared with PBS values [Kruskal-Wallis, Dunn test]; f) NADPH-dependent H_2O_2 production was measured in particulate fractions from mouse lung tissues (*n=4* per group) for DPI (Diphenylene iodonium) *n=2*;. ###p<0.001 compared within NADPH stimulated group over experimental conditions [two-way ANOVA, Tukey test] g) Percentages of surviving mice were plotted over a 21-day period after bleomycin treatment (BLM). There is no statistically significant difference between the different groups. Values are expressed as mean±SEM.

Supplementary Figure S2

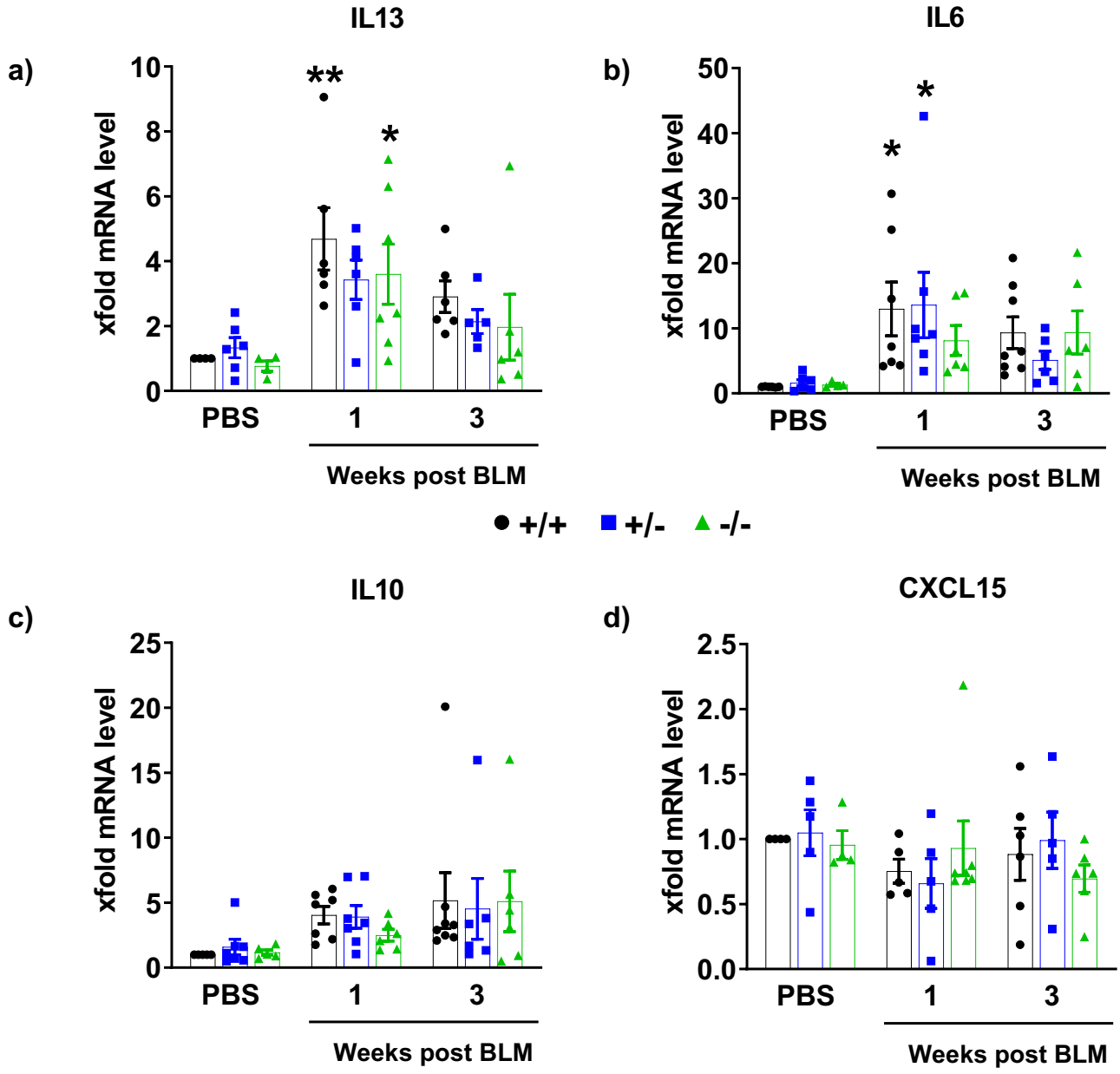






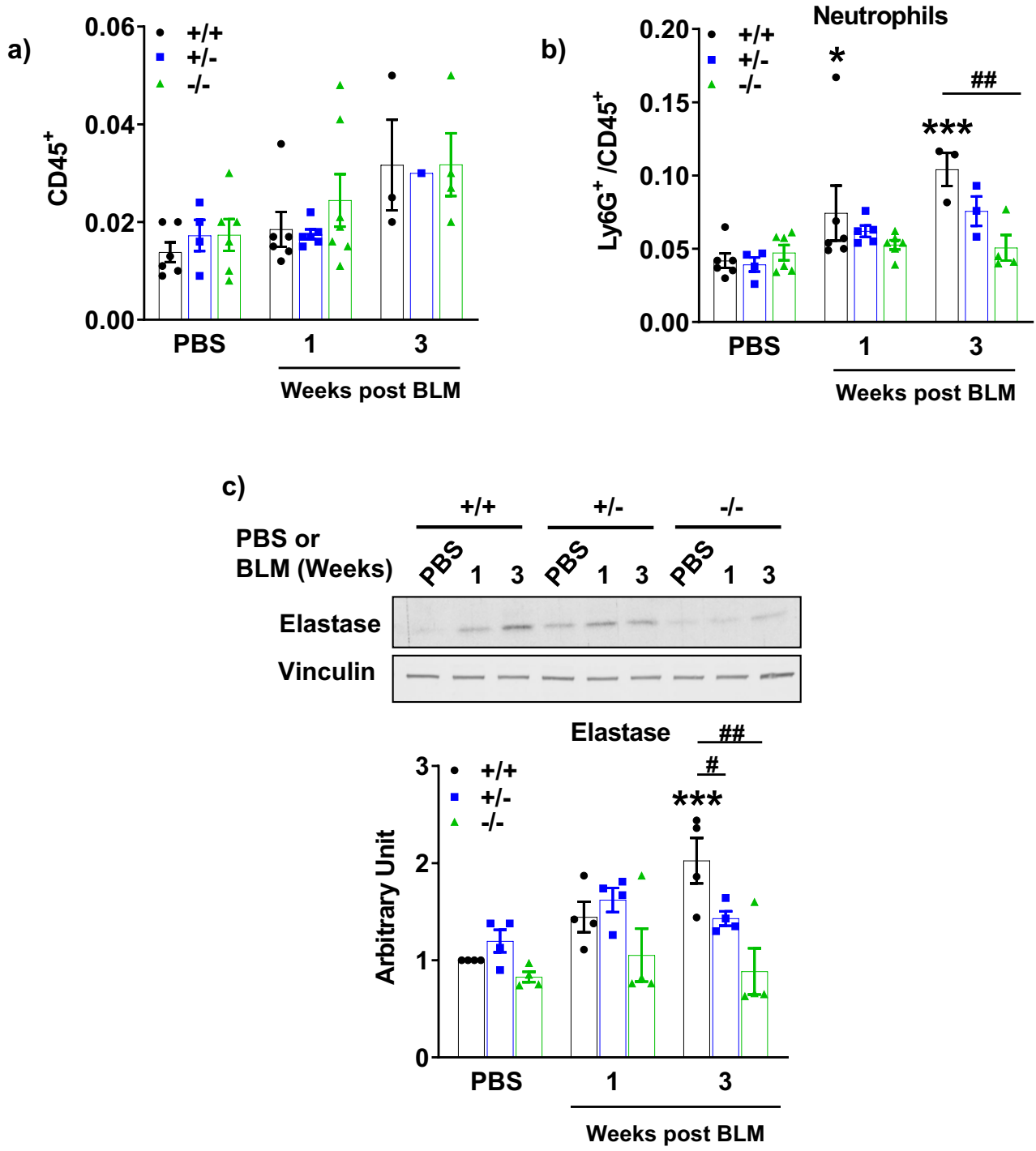
Supplementary Figure 2. Role of DUOX1 in radiation-induced lung fibrosis. a) Experimental protocol; b) Comparative expression of *DUOX1*, *DUOXA1* and *DUOX2* genes in irradiated mouse lung tissues (*n=3 per* group), mouse R18S mRNA was used as internal control; *p<0.05 [unpaired Student's t-test] c) Western blot analysis of Fibronectin and Vimentin in lung tissue of non- and irradiated WT and DUOX1-deficient mice (*n=4* per group). **p<0.01 compared with WT [Mann-Whitney test]. Values are expressed as mean±SEM.

Supplementary Figure S3



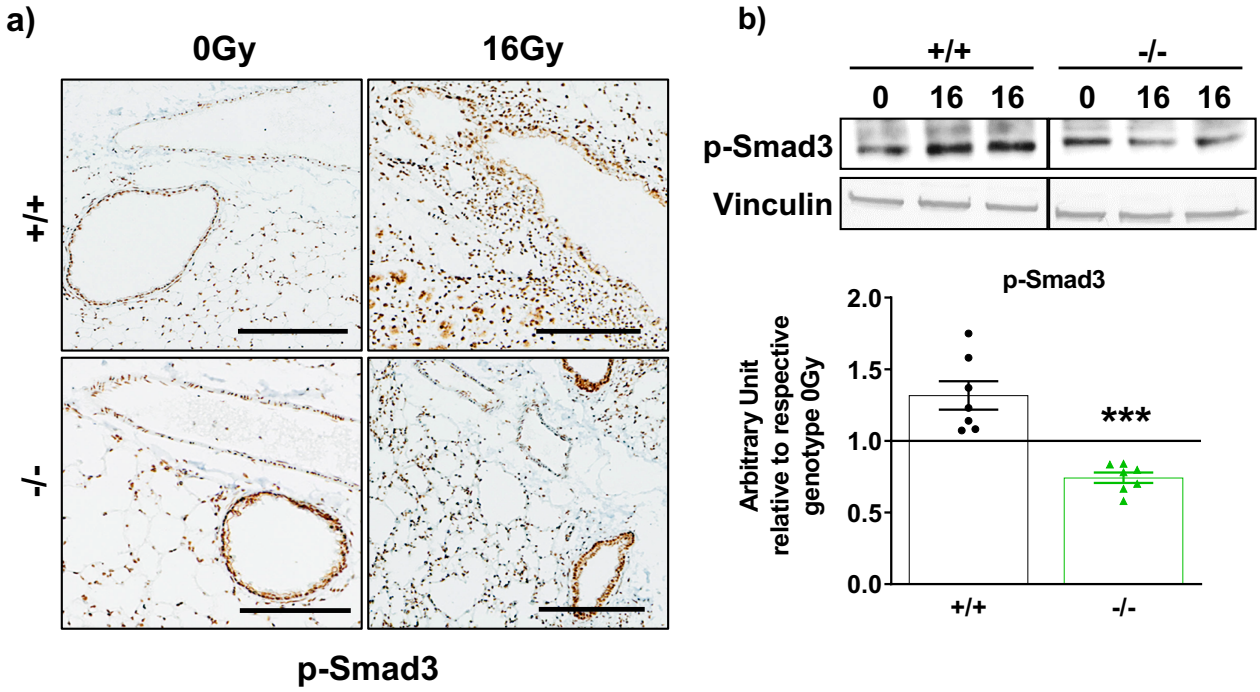
Supplementary Figure 3. Similar inflammatory response in WT and DUOX1-deficient mice after bleomycin treatment. a) to d) qRT-PCR analysis of IL-13, IL-6, IL-10 and CXCL15 mRNA expression in lung tissues of mice at the indicated time points after bleomycin treatment, mouse R18S mRNA was used as internal control (*n=4-8* per group). For all analysis, *p<0.05 and ***p<0.001 compared with PBS values within genotypes [two-way ANOVA, Tukey test]. Values are expressed as mean±SEM.

Supplementary Figure S4



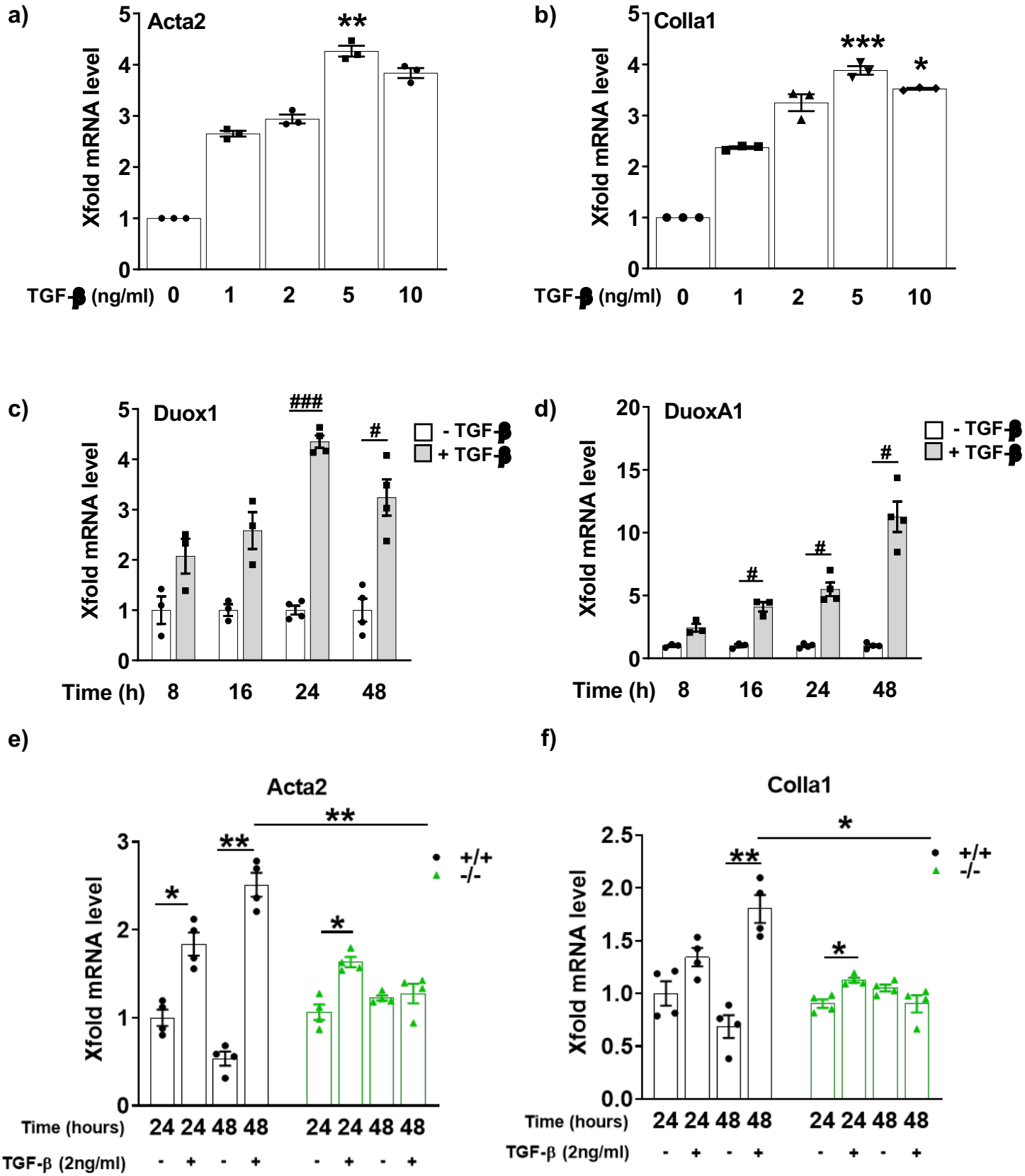
Supplementary Figure 4. DUOX1 regulates neutrophil recruitment in bleomycin-injured mice. a) Total inflammatory cells (CD45+) in lung tissues of mice after treatment with bleomycin at the indicated time points; b) neutrophil (CD45+, Ly6G+) in lung tissues of mice after treatment with bleomycin at the indicated time points (*n=3-6* per group); c) Western blot analysis of elastase expression in lung tissue of mice after treatment with bleomycin at the indicated time points. Vinculin was used as a loading control. (*n=4* for group). For all analysis, *p<0.05 and ***p<0.001 compared with PBS values within genotypes. #P<0.05 and ##P<0.01 between genotypes [two-way ANOVA, Tukey test]. Values are expressed as mean±SEM.

Supplementary Figure S5



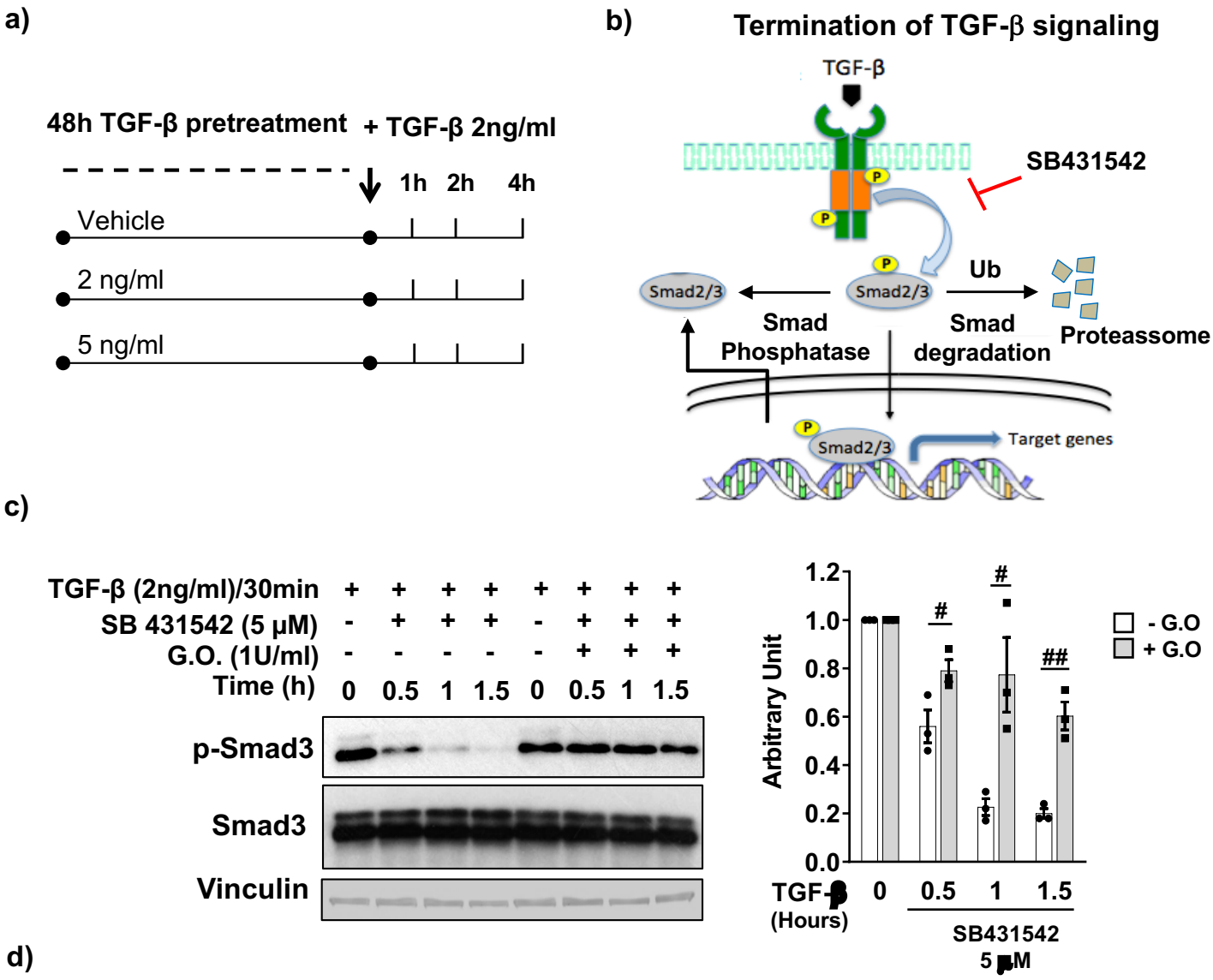
Supplementary Figure 5. DUOX1-deficient mice display decreased Smad3 phosphorylation in lung tissues 20 weeks after a thoracic irradiation of 16 Gy. a) Immunohistochemical analysis of phospho-Smad3 in lung tissue 20 weeks post-irradiation. Scale bars = 500 µm; b) Western blot analysis of phospho-Smad3 in lung tissue (*n=3-5* per group). ***p<0.001 compared with WT [Mann-Whitney test]. Values are expressed as mean±SEM.

Supplementary Figure S6



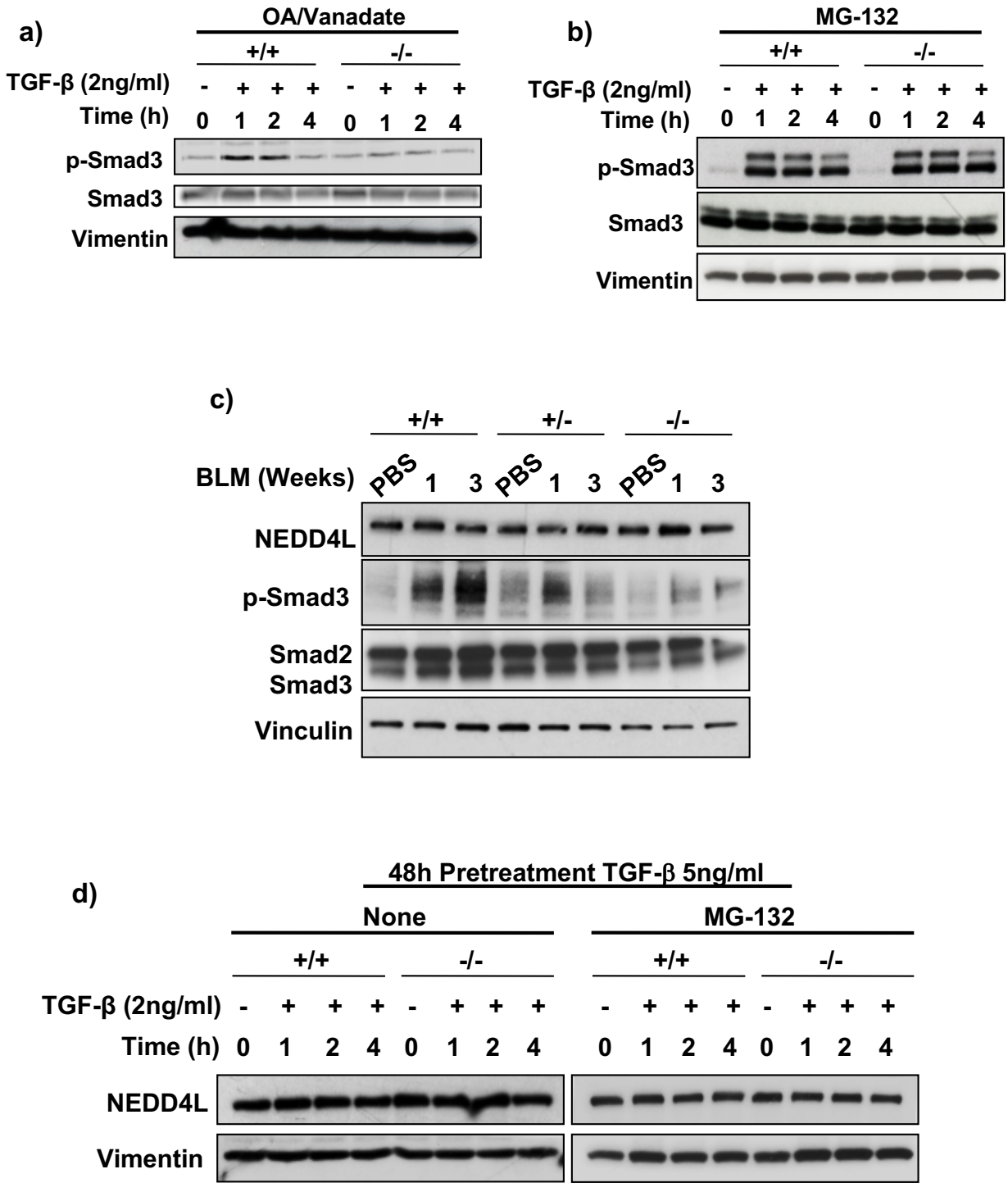
Supplementary Figure 6. DUOX1 is upregulated by TGF-β1 in fibroblasts. a) and b) Dose-dependent increases in Acta2 and Col1a1 mRNA expression in fibroblasts treated with TGF-β1 and analysed at 48 h by qRT-PCR (*n=3*); *p<0.05, **p<0.01 and ***p<0.01 compared with PBS [Kruskal-Wallis, Dunn test]; c) and d) Time-dependent increase of DUOX1 and DUOXA1 after TGF-β1 treatment of wild-type mouse fibroblasts as analysed by qRT-PCR (*n=4*); $^{\#}$p<0.05 and $^{\#\#\#}$p<0.001 compared with vehicle [two-way ANOVA, Sidak test] e) and f) Comparative expression of Acta2 and Col1a1 in wild-type and DUOX1-deficient fibroblasts after treatment with TGF-β1 for 24 and 48 h as analysed by qRT-PCR (*n=4*). Mouse R18S mRNA was used as internal control, *p<0.05 and **p<0.01 [Mann-Whitney test]. Values are expressed as mean±SEM.

Supplementary Figure S7



Supplementary Figure 7. H_2O_2 sustains TGF-β1 signalling in fibroblasts. a) Experimental protocol of sequential treatment with TGF-β1; b) schematic model of TGF-β1 termination signalling. Both dephosphorylation of phospho-Smad3 by phosphatases and its proteasomal degradation participate in TGF-β1 signalling termination; c) extracellular H_2O_2, generated from glucose oxidase-catalysed glucose oxidation sustained TGF-β1-induced phospho-Smad2/3 expression in mouse fibroblasts as analysed by western blot. Vinculin was used as a loading control (*n=3*) $^{\#}p<0.05$ and $^{\#\#}p<0.01$ [unpaired Student's t-test]; d) addition of catalase with glucose oxidase suppressed the effect. Values are expressed as mean±SEM.

Supplementary Figure S8



Supplementary Figure 8. DUOX1 deficiency does not affect NEDDL4 expression in bleomycin-treated lungs or in TGF-β-treated fibroblasts. a) and b) Western blot analysis of TGF-β1-induced Smad3 phosphorylation in primary mouse lung fibroblasts isolated from DUOX1+/+ and DUOX1-/- mice that were pre-treated with TGF-β1 (5 ng/ml) for 48 h, followed with a pre-treatment for 1 hour with okadaïc acid (100 nM) and orthovanadate (1 mM) or MG132 (20 μM) before stimulation with TGF-β1 (2 ng/ml) (*n*=2); c) Western blot analysis of NEDD4L and phospho-Smad3 expression in lung tissues of mice treated with bleomycin for the indicated times. Vinculin was used as a loading control; b) Western blot analysis of NEDD4L expression in wild-type and DUOX1-deficient fibroblasts that were pre-treated for 48 h with TGF-β1(5 ng/ml) and stimulated with TGF-β1(2 ng/ml) for the indicated times. Vimentin was used as a loading control.

Supplementary Figure S9

Tests for normal distribution

Figures		Tests for normal distribution		Statistical test used
numbers	**Parameters**	**Shapiro-Wilk**	**Kolmogorov-Smirnov**	
Figure 1a	DUOX1	no	no	Mann-Whitney
	DUOX2	no	yes	
	ACTA2	no	no	
Figure 1b	DUOX1	no	no	Mann-Whitney
	DUOX2	yes	yes	
	ACTA2	no	no	
Figure 1d	DUOX1	no	yes	Kruskal-Wallis, Dunn test
	DUOXA1	no	yes	
	DUOX2	no	yes	
Figure 2a	H_2O_2	no	no	Two-way ANOVA Turkey test
Figure 2b	Colla1	no	no	Two-way ANOVA Turkey test
Figure 2d	Fibrotic Area	no	yes	Two-way ANOVA Turkey test
Figure 2f	Fibronectin	no	no	Two-way ANOVA Turkey test
Figure 3a	TGFβ	no	yes	Two-way ANOVA Turkey test
Figure 3b	p-SMAD2	no	yes	Two-way ANOVA Turkey test
	p-SMAD3	no	no	Two-way ANOVA Turkey test
Figure 3d	αSMA	no	no	Two-way ANOVA Turkey test
Figure 4a	H_2O_2	yes	yes	Kruskal-Wallis, Dunn test
Figure 4b	DUOX1	yes	yes	Unpaired Student's t-test
	DUOXA1	yes	yes	
Figure 6a	ACTA2	no	no	Two-way ANOVA Sidak test
Figure 6b	DUOX1	yes	yes	Mann-Whitney
Figure 6c	H_2O_2	no	no	Two-way ANOVA Tukey test
Figure 6d	p-SMAD3	yes	yes	Unpaired Student's t-test
Figure 6e	p-Smad2	no	no	Two-way ANOVA Sidak test
	p-Smad3	no	no	
Figure 7b	H_2O_2	yes	yes	Unpaired Student's t-test
				Two-way ANOVA

Figure 7c	p-Smad3	no	yes	Sidak test and Unpaired Student's t-test
Figure 7d	NEDD4L	yes	no	Kruskal-Wallis, Dunn test
	p-Smad3	yes	yes	
Figure S1c	Colla1	no	yes	Kruskal-Wallis, Dunn test
Figure S1d	ACTA2	yes	yes	Kruskal-Wallis, Dunn test
Figure S1e	TGF-β	yes	yes	Kruskal-Wallis, Dunn test
Figure S1f	H_2O_2	no	yes	Two-way ANOVA Turkey test
Figure S2b	DUOX1	yes	yes	Unpaired Student's t-test
	DUOXA1	yes	yes	
	DUOX2	yes	yes	
Figure S2c	Fibronectin	no	yes	Mann-Whitney
	Vimentin	yes	yes	
Figure S3a	IL13	yes	no	Two-way ANOVA Tukey test
Figure S3b	IL6	no	no	Two-way ANOVA Tukey test
Figure S3c	IL10	no	no	Two-way ANOVA Tukey test
Figure S3d	CXCL15	yes	yes	Two-way ANOVA Tukey test
Figures S4a	CD45+	no	no	Two-way ANOVA Tukey test
Figure S4b	Neutrophils	no	no	Two-way ANOVA Tukey test
Figure S4c	Elastase	yes	yes	Two-way ANOVA Tukey test
Figure S5b	p-Smad3	yes	yes	Mann-Whitney
Figure S6a	ACTA2	yes	yes	Kruskal-Wallis, Dunn test
Figure S6b	Colla1	no	no	Kruskal-Wallis, Dunn test
Figure S6c	DUOX1	no	no	Two-way ANOVA Sidak test
Figure S6d	DUOXA1	no	no	Two-way ANOVA Sidak test
Figure S6e	ACTA2	yes	yes	Mann-Whitney
Figure S6f	Colla1	no	no	Mann-Whitney
Figure S7c	p-Smad3	no	yes	Unpaired Student's t-test