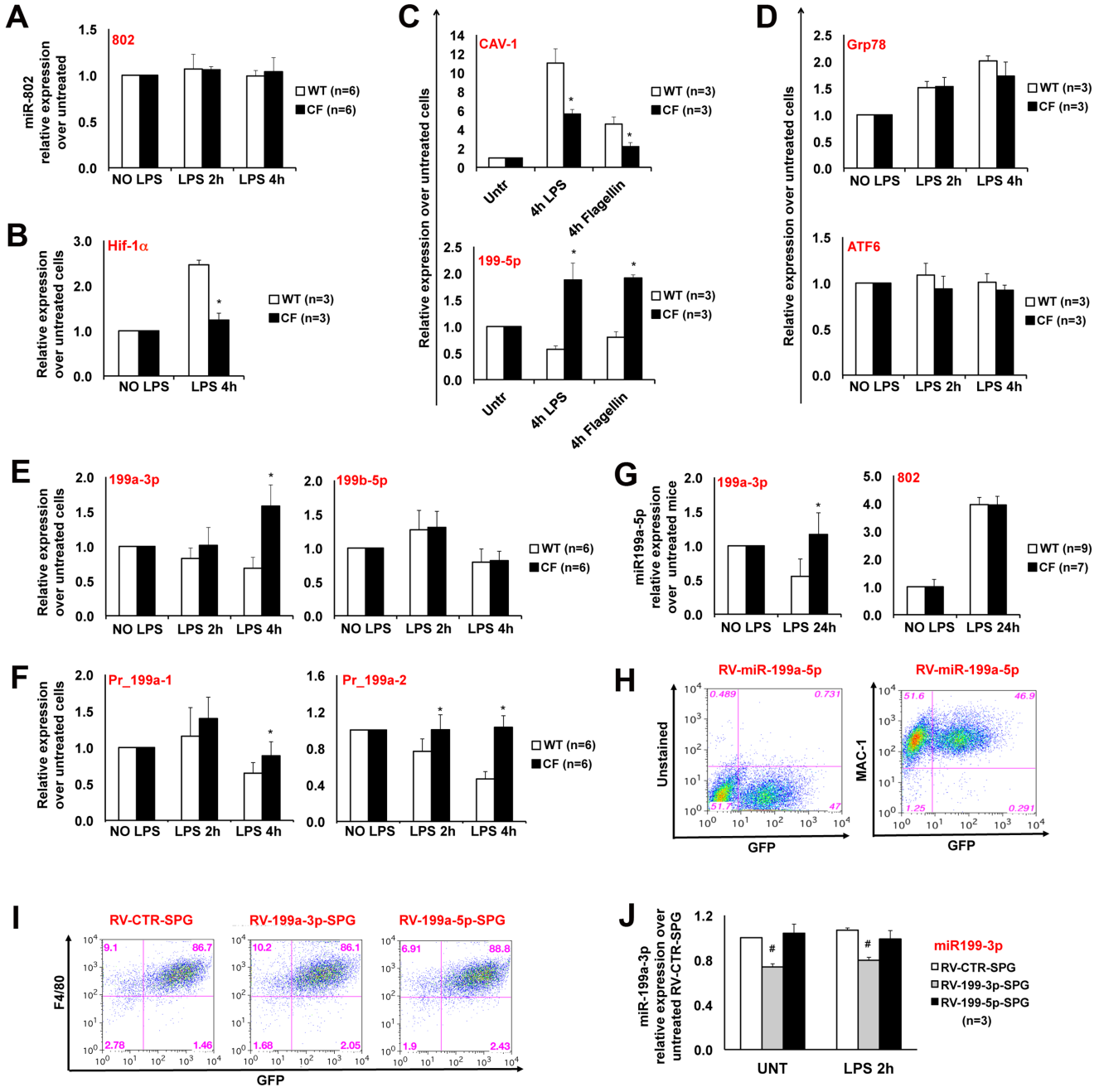
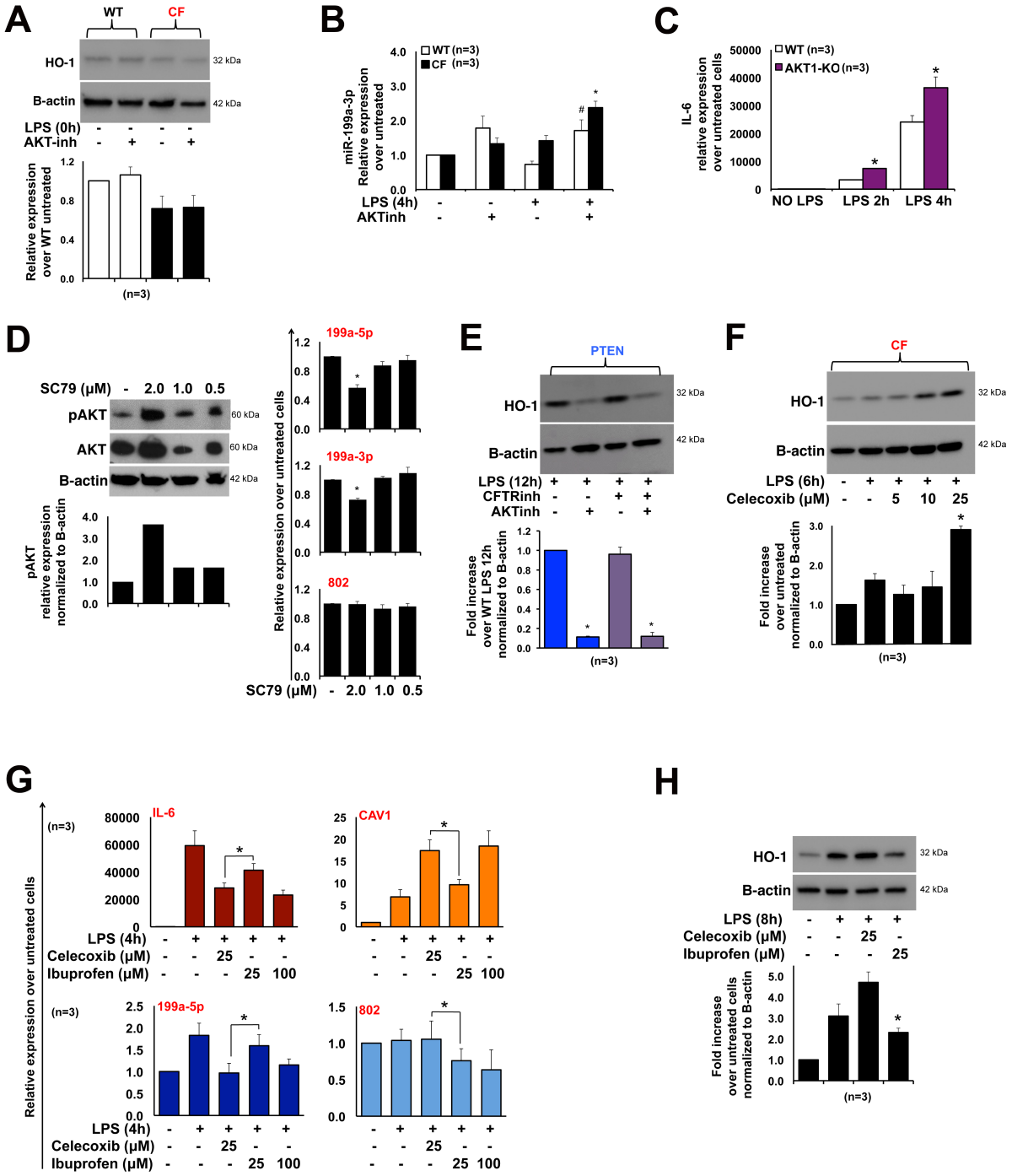
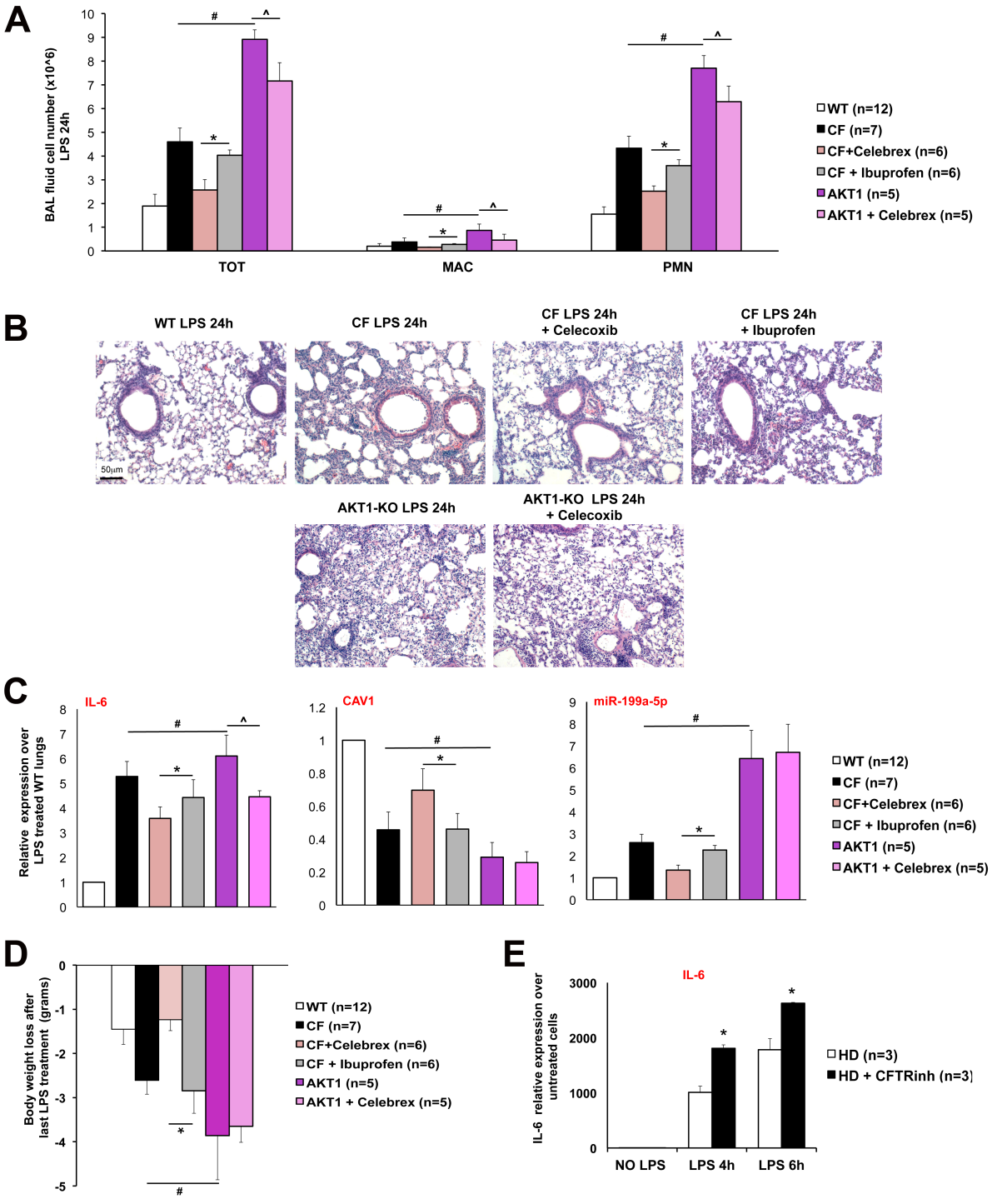


Supplementary Figure 1 MiR-802 **(A)** and Hif-1α **(B)** relative expression (qPCR) in murine WT (white bars) and CF (black bars) BM-derived MΦs, untreated or treated with LPS; **(C)** qPCR for CAV1 (upper panel) and miR-199a-5p (lower panel) in WT and CF murine MΦs treated with LPS or with flagellin at the time indicated; **(D)** RT-qPCR for the unfolded protein response regulator gene Grp78 (upper panel) or for the signal transducer ATF6 (lower panel) in WT and CF murine MΦs challenged with LPS at the time indicated; expression analysis of miR-199a-3p and miR-199b-5p **(E)** and of miR-199a stem loop precursors (Pr) 199a-1 and 199a-2 **(F)** in murine WT (white bars) and CF (black bars) MΦs, untreated or treated with LPS; **(G)** flow cytometry dot-plots of WT murine MΦs infected with RV-miR-199a-5p-GFP, showing that over-expression of miR-199a-5p had no effect on MΦ differentiation; **(H)** flow cytometry dot-plots of CF murine MΦs infected with RV-sponge (SPG)-control, RV-199a-3p-SPG or RV-199a-5p-SPG, showing puromycin-selected-GFP positive population expressing the MΦs marked F4/80; **(I)** qPCR for miR-199a-3pin RV-SPG (control-SPG, 199a-3p-SPG or 199a-5p-SPG) infected and puromycin-selected CF MΦs, untreated or treated with LPS.

For qPCR, miRNAs levels are normalized to RNU6B and Hif-1α/ CAV1/Grp78/ ATF6 expressions to S18. For each experiment, the data are the result of three experimental repeats. Statistical analyses were conducted using one-sided two-sample t-tests. Error bars indicate standard deviation. Symbols * and # indicate a statistically significant difference among the experimental and control groups with a *P* values <0.05. “h” indicates hours.



Supplementary Figure 2 **(A)** WB and densitometric analysis for HO-1 in untreated WT and CF-KO murine MΦs, in absence or presence of the PI3K-AKT inhibitor LY94002; **(B)** qPCR for miR-199a-3p in WT and CF-KO murine MΦs untreated or treated with LPS, in absence or presence of the PI3K-AKT inhibitor LY94002; **(C)** qPCR for IL-6 in WT and AKT1-KO MΦs untreated or treated with LPS; **(D)** WB and densitometric analysis for pAKT/AKT/b-actin (left panel) and qPCR for miRs 199a-5p, 199-3p and 802 (right panel) in untreated or SC79 treated (at the doses indicated) CF-KO murine MΦs; **(E)** WB and densitometric analysis for HO-1 in LPS-stimulated PTEN-KO MΦs untreated or treated with the CFTR inhibitor ($CFTR_{inh}172$), in presence or absence of LY94002. **(F)** WB and densitometric analysis for HO-1 in CF murine MΦs untreated or treated with LPS, in absence or presence of different doses of celecoxib; **(G)** qPCR for IL-6, CAV1, miR-199a-5p and miR-802 in LPS challenged CF-KO murine MΦs untreated or treated with celecoxib or ibuprofen (at the doses indicated); **(H)** WB and densitometric analysis for HO-1 in LPS-stimulated CF MΦs untreated or treated with celecoxib (25μM) or ibuprofen (25μM). For qPCR, miRNAs levels are normalized to RNU6B and IL-6/ CAV1 expressions to S18. For WB, protein fold increase is normalized to B-actin. For each experiment, the data are the result of three experimental repeats. Statistical analyses were conducted using one-sided two-sample t-tests. Error bars indicate standard deviation. Symbols * and # indicate a statistically significant difference among the experimental group and control group with a *P* values <0.05. “h” indicates hours.



Supplementary Figure 3 Total and differential BAL fluid cell number **(A)**, hematoxylin/eosin staining in paraffin embedded lung tissues **(B)**, qPCR for IL-6, CAV1 and miR-199a-5p **(C)**, and body weigh loss **(D)** from WT, CF or AKT1-KO mice treated chronically (10 days) with celecoxib (Celebrex) or ibuprofen (WT and CF mice only) and then challenged with LPS for three days. Mice were sacrificed 24h after last nebulization. **(E)** qPCR for IL-6 in human MΦs differentiated from non-CF CD34-positive mobilized PB cells and conditioned with the CFTR inhibitor $CFTR_{inh}172$ (HD+ CFTRinh) or with vehicle alone (HD). For qPCR, miR-199a-5p levels are normalized to RNU6B and CAV1 and IL-6 expression to S18. For WB, protein fold increase is normalized to B-actin. Statistical analyses were conducted using one-sided two-sample t-tests (q-PCR) or two-sample unequal variance t-tests (BAL fluid cell numbers). The symbol * indicates a statistically significant difference (*P* values <0.05) among CF mice treated with celecoxib or ibuprofen; the symbol # among CF and AKT1-KO mice; the symbol ^ among AKT1-KO mice with or without celecoxib administration. "h" indicates hours. Images were acquired using an Olympus BX51 microscope with a 10x objective; scale bar is 50μm.

FIGURE 1E

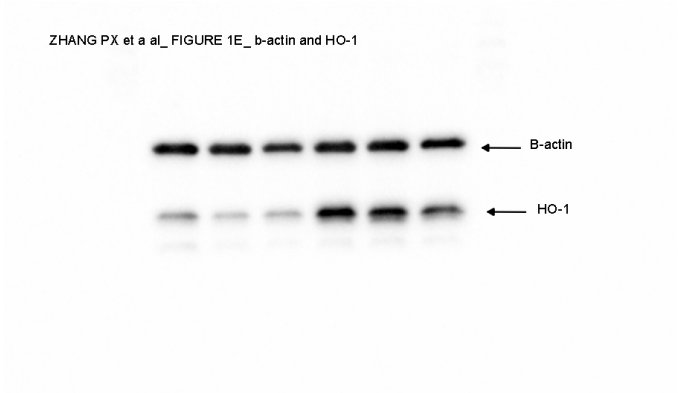


FIGURE 1I

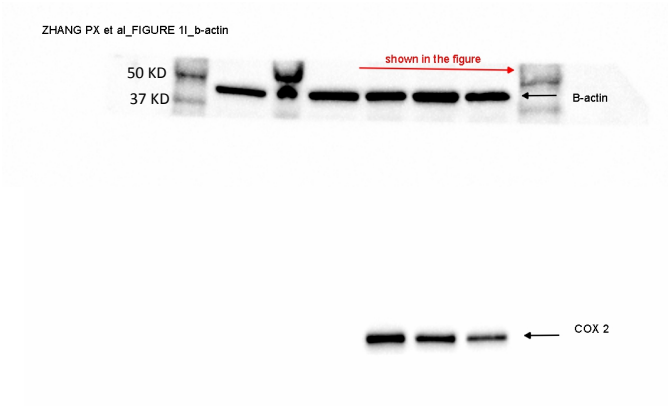


FIGURE 2B

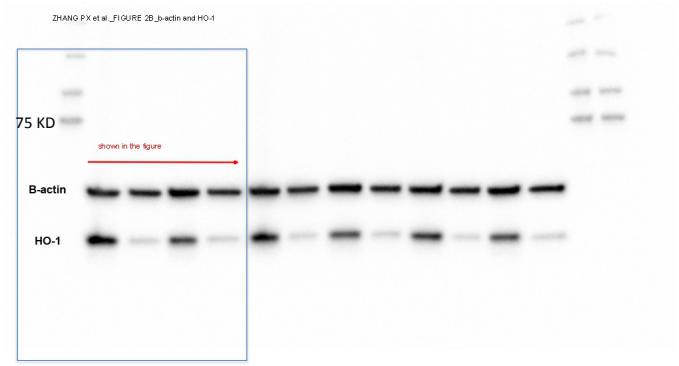


FIGURE 2D

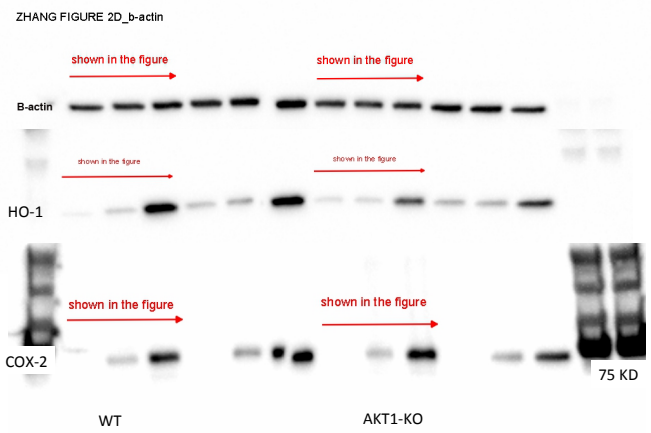


FIGURE 2E

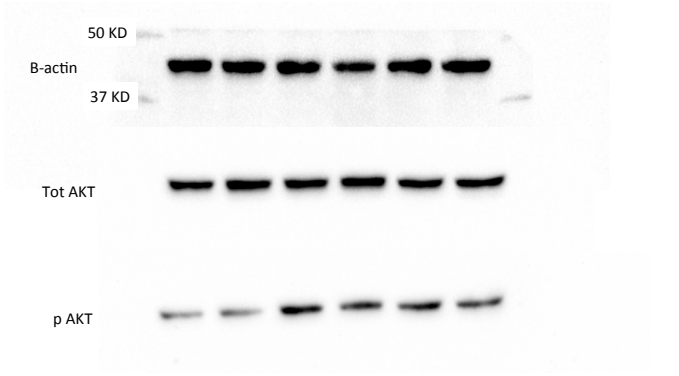


FIGURE 2G

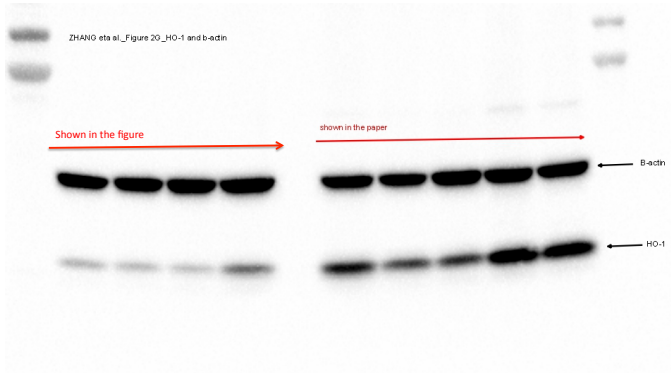


FIGURE 3B

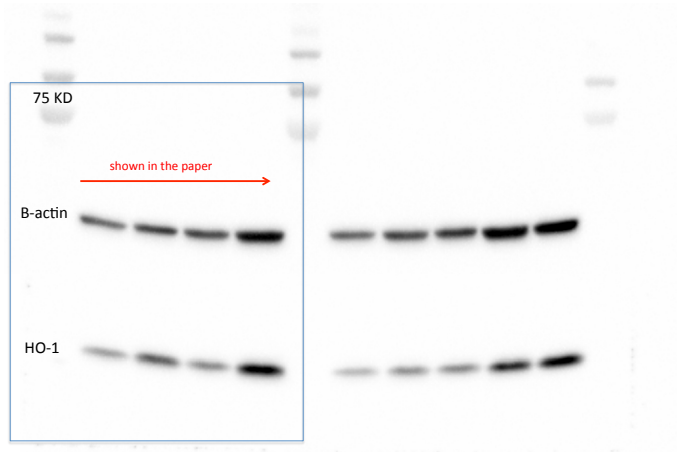
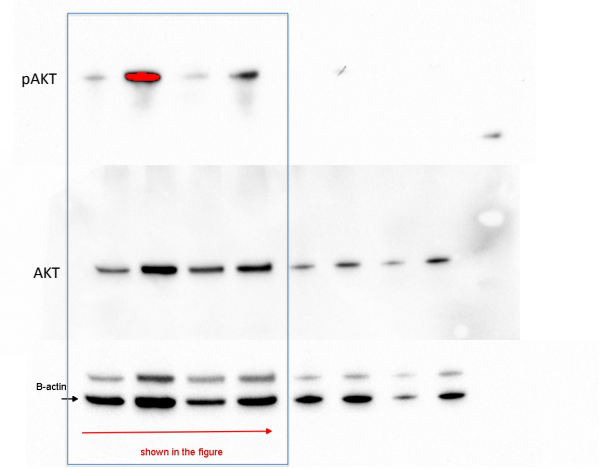
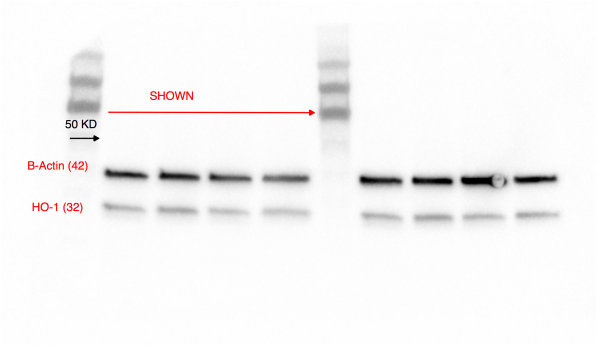


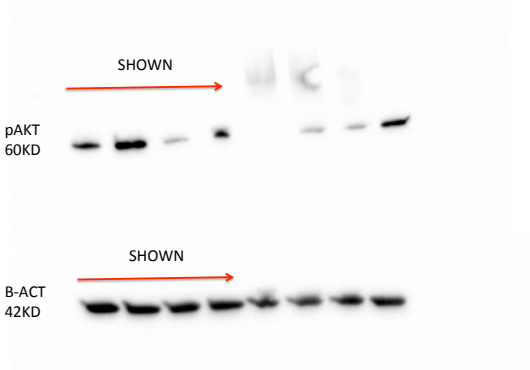
FIGURE 3D



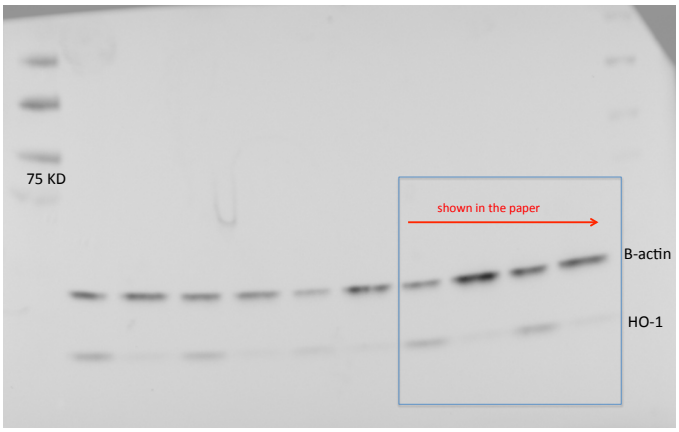
SUPPLEMENTARY FIGURE 2A



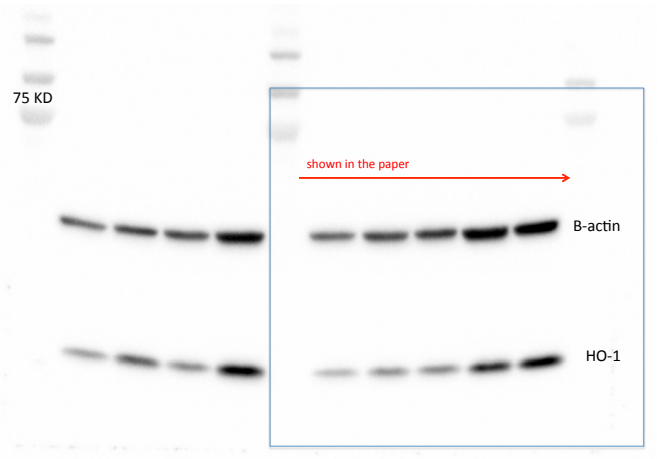
SUPPLEMENTARY FIGURE 2D



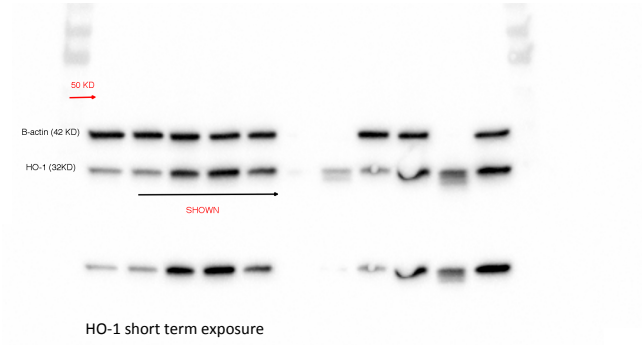
SUPPLEMENTARY FIGURE 2E (PTEN-KO macrophages)



SUPPLEMENTARY FIGURE 2F



SUPPLEMENTARY FIGURE 2H



Supplementary Figure 4 Full western blots

Supplementary Table 1 Mice used for the in vivo study

	Genotype	Gender	Age	Treatment
1	WT	F	2.5 mts	LPS 24h
2	WT	F	2.5 mts	LPS 24h
3	WT	F	2.5 mts	LPS 24h
4	WT	F	3.0 mts	LPS 24h
5	WT	F	3.0 mts	LPS 24h
6	WT	M	3.0 mts	LPS 24h
7	WT	F	2.5 mts	LPS 24h
8	WT	M	2.5 mts	LPS 24h
9	WT	M	2.5 mts	LPS 24h
10	WT	F	5.0 mts	LPS 24h
11	WT	F	5.0 mts	LPS 24h
12	WT	F	5.0 mts	LPS 24h
1	WT	F	2.5 mts	LPS 24h + Celecoxib
2	WT	F	2.5 mts	LPS 24h + Celecoxib
3	WT	M	2.5 mts	LPS 24h + Celecoxib
4	WT	F	3.0 mts	LPS 24h + Celecoxib
5	WT	F	3.0 mts	LPS 24h + Celecoxib
6	WT	M	3.0 mts	LPS 24h + Celecoxib
7	WT	F	5.0 mts	LPS 24h + Celecoxib
8	WT	M	5.0 mts	LPS 24h + Celecoxib
1	CF-KO	F	2.5 mts	LPS 24h
2	CF-KO	F	2.5 mts	LPS 24h
3	CF-KO	M	2.5 mts	LPS 24h
4	CF-KO	F	3.0 mts	LPS 24h
5	CF-KO	F	3.0 mts	LPS 24h
6	CF-KO	M	3.0 mts	LPS 24h
7	CF-KO	M	2.5 mts	LPS 24h
1	CF-KO	F	2.5 mts	LPS 24h + Celecoxib
2	CF-KO	F	2.5 mts	LPS 24h + Celecoxib
3	CF-KO	M	2.5 mts	LPS 24h + Celecoxib
4	CF-KO	F	3.0 mts	LPS 24h + Celecoxib
5	CF-KO	F	3.0 mts	LPS 24h + Celecoxib
6	CF-KO	M	3.0 mts	LPS 24h + Celecoxib
1	CF-KO	F	2.5 mts	LPS 24h + Ibuprofen
2	CF-KO	F	2.5 mts	LPS 24h + Ibuprofen
3	CF-KO	F	2.5 mts	LPS 24h + Ibuprofen
4	CF-KO	M	2.5 mts	LPS 24h + Ibuprofen
5	CF-KO	M	2.5 mts	LPS 24h + Ibuprofen
6	CF-KO	M	3.0 mts	LPS 24h + Ibuprofen
1	AKT1-KO	M	5.0 mts	LPS 24h
2	AKT1-KO	F	6.0 mts	LPS 24h
3	AKT1-KO	F	5.0 mts	LPS 24h
4	AKT1-KO	F	4.0 mts	LPS 24h
5	AKT1-KO	F	4.0 mts	LPS 24h
1	AKT1-KO	M	5.0 mts	LPS 24h + Celecoxib
2	AKT1-KO	F	6.0 mts	LPS 24h + Celecoxib
3	AKT1-KO	F	5.0 mts	LPS 24h + Celecoxib
4	AKT1-KO	F	4.0 mts	LPS 24h + Celecoxib
5	AKT1-KO	F	4.0 mts	LPS 24h + Celecoxib

Supplementary Table 2 CF patients' genetics, baseline demographic and clinical observations

	Genetics	Age	Gender	FEV1 (%pred)
1	F508del/F508del	30	F	1.96 L (65%)
2	F508del/711+1G->T	29	M	2.09 L (47%)
3	F508del/N1303K	22	M	0.80 L (19%)
4	F508del/F508del	38	F	2.69 L (88%)
5	F508del/3849+10kbC->T	37	M	0.58 L (12%)
6	F508del/F508del	25	F	0.87 L (24%)
7	F508del/F508del	24	F	0.96 L (27%)
8	F508del/N1303K	22	M	0.80 L (19%)