

Table S1. Medical history of FD Patients When Enrolled

Patients	Age (gender)	Weight (kg)	eGFR	LysoGb3¹	Medical history²	Medications
P1	74 (F)	94	75	1.2	proteinuria, LGE, incidental renal cyst (stable), left shoulder pain	Replagal, coversyl, tylenol, aspirin, vitamin D
P2	64 (F)	64	65	15.2	cardioversion, proteinuria, LGE	Fabrazyme, sotalol, metoprolol, lasix (postconversion), tylenol, coumadin, vitamin D, biotin
P3	49 (M)	59	80	21.4	renal failure, renal transplant 2016, cardiac involvement with mild left ventricular dilation and biatrial enlargement, aortic root dilation, white matter lesions on brain MRI, corneal verticillata, high frequency hearing loss, hypertension, osteoporosis	Fabrazyme, ASA, tylenol, sulfatrim, myfortic, prednisone, tacrolimus, multivit, lasix
P4	44 (F)	66	100	4.9	acroparesthesias, LGE, benign gallbladder polyps, simple right renal cyst of no significance, sternal pain, mild proteinuria, corneal verticillata, first-degree AV block, asthma, reduced tolerance to dilantin, intermittent pain in RUQ	Replagal, gabapentin, salmon oil, motrin, vitamin D, advair, ventolin, domperidone
P5	64 (F)	59	93	10.8	Myocardial infarction	Replagal, lipitor, ASA, tylenol, folic acid, calcium, vitamin D, nitroglycerin spray prn, cold FX
P6	63 (F)	61	57	14.8	hypertension, migraine headaches, D&C for endometrial polyp, cardiac involvement with increased LVMI, hearing loss; renal insufficiency with proteinuria and borderline GFR hypercholesterolemia, bunion, corneal verticillata, acroparesthesias	Replagal, coversyl, crestor, aspirin, folic acid, vitamin D, calcium, nitroglycerin prn

P7	59 (M)	86	44	39.3	LVH, stent replacement, renal insufficiency, hearing loss, neuropathy, hypertension, brain calcification, COPD, iron deficiency	Replagal, cozaar, crestor, dilantin, tylenol, aspirin, brilinta, effexor, pantoprazole, folic acid, Omega-3, vitamin D, multivitamin, Spiriva inhaler, ferrous sulfate, Coenzyme Q10, ativan @ hs, apo-ISMN, potassium
P8	63 (F)	86	50	18.9	LVH with LGE, CKD stage 3, proteinuria, ocular involvement, hearing loss, degenerative c-spine	Replagal, hydrochlorothiazide, losartan, lipitor, ASA, gabapentin, zantac, ropinirole, Omega-3, calcium, Coenzyme Q10, folic acid

Notes:

1. lysoGb3 and Gb3 is detected untargeted mass spectrometry metabolomic approaches
2. LVH is abbreviated from left ventricular hypertrophy; LGE stands for late gadolinium enhancement; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease

Table S2. Cytokine Profile of Plasma from FD Patients versus Normal Donors

Cytokines	Normal donors (n=6) (median[IQR], pg/mL)	ERT-treated FD (n=8) (median[IQR], pg/mL)	<i>p</i>-value (Mann Whitney)	Adjusted <i>p</i>-value (BH)
MCP-1	101.00 [39.42]	244.23 [50.63]	0.0007	0.0062
MDC	334.95 [74.09]	958.42 [525.75]	0.0007	0.0062
PDGF-AA	345.68 [55.64]	952.45 [608.55]	0.0007	0.0062
RANTES	171.67 [100.05]	604.08 [274.67]	0.0007	0.0062
sCD40L	453.81 [131.27]	1466.96 [959.29]	0.0013	0.0099
IP-10	60.94 [15.57]	239.53 [118.41]	0.0027	0.0164
TNF- α	8.45 [4.39]	21.28 [16.83]	0.0047	0.0246
GM-CSF	99.26 [52.32]	33.95 [10.68]	0.0080	0.0370
PDGF-BB	2915.13 [730.19]	5579.99 [3168.83]	0.0200	0.0821
IL-3	0.55 [0.11]	0.68 [0.32]	0.0384	0.1422
IL-15	2.57 [0.44]	4.22 [2.42]	0.0426	0.1434
Fractalkine	69.73 [22.96]	127.72 [37.85]	0.0813	0.2505
MIP-1B	25.79 [23.57]	55.70 [28.66]	0.1419	0.4038
IL-12p70	2.99 [3.19]	6.18 [4.11]	0.1748	0.4619
IL-4	94.23 [120.37]	52.33 [34.20]	0.2284	0.5635
IFN- γ	6.98 [2.96]	6.04 [3.35]	0.2824	0.6146
IL-1 α	15.66 [30.22]	43.94 [65.96]	0.2824	0.6146
IL-17A	4.72 [5.33]	2.38 [1.45]	0.3450	0.6376
VEGF-A	58.63 [38.31]	25.61 [61.68]	0.3450	0.6376
IL-9	0.78 [1.22]	2.44 [2.99]	0.3656	0.6376
IL-13	3.09 [5.33]	2.10 [3.72]	0.3998	0.6376
IL-1 β	2.97 [4.19]	2.16 [1.20]	0.4009	0.6376
FGF-2	133.30 [42.03]	110.31 [21.10]	0.4136	0.6376
IL-1RA	34.17 [41.61]	30.63 [15.46]	0.4136	0.6376
IL-2	0.82 [0.39]	1.41 [0.94]	0.4381	0.6483
IL-12p40	56.54 [29.22]	51.27 [29.62]	0.4772	0.6791

MIP-1 α	7.19 [5.65]	6.22 [2.48]	0.5608	0.7569
TGF- α	1.40 [0.66]	1.00 [1.23]	0.5728	0.7569
IFN α 2	58.67 [30.23]	54.64 [10.96]	0.6507	0.8165
IL-8	7.73 [15.65]	7.71 [4.64]	0.6620	0.8165
EGF	150.23 [98.28]	191.21 [87.95]	0.8518	0.9761
G-CSF	31.21 [18.46]	32.78 [21.84]	0.8518	0.9761
Eotaxin	62.12 [22.76]	64.08 [42.67]	0.9497	0.9761
IL-5	0.58 [0.80]	0.51 [0.33]	0.9497	0.9761
IL-7	2.26 [1.01]	2.72 [1.35]	0.9497	0.9761
MCP-3	15.51 [22.93]	23.25 [33.04]	0.9497	0.9761
IL-10	1.31 [0.92]	1.85 [1.58]	1.0000	1.0000

Table S3. Cytokine Profile of Plasma in FD patients

Cytokines	eGFR>60 (n=4) (Mean ± SD, pg/mL)	eGFR<60 (n=3) (Mean ± SD, pg/mL)	p-value (Mann Whitney)	Adjusted p-value (BH)
FGF-2	123.01 ± 8.04	101.16 ± 10.00	0.06	0.41
IL-10	2.49 ± 1.02	0.76 ± 0.24	0.06	0.41
PDGF-BB	4651.49 ± 327.41	7561.87 ± 1277.41	0.06	0.41
sCD40L	944.49 ± 197.24	2045.00 ± 245.43	0.06	0.41
IL-4	174.73 ± 224.34	36.39 ± 1.36	0.06	0.41
MIP-1a	7.66 ± 1.91	4.67 ± 1.26	0.07	0.41
TGF-α	1.85 ± 1.01	0.69 ± 0.26	0.11	0.41
IL-15	4.70 ± 1.29	3.14 ± 0.66	0.11	0.41
IL-2	1.53 ± 0.46	0.76 ± 0.48	0.11	0.41
IL-5	1.43 ± 1.59	0.37 ± 0.14	0.11	0.41
TNF-β	247.20 ± 411.68	3.12 ± 3.66	0.11	0.41
Eotaxin	78.22 ± 32.54	51.17 ± 32.60	0.23	0.47
G-CSF	39.82 ± 11.86	25.15 ± 5.48	0.23	0.47
Fractalkine	136.04 ± 34.10	101.54 ± 28.11	0.23	0.47
IFN-γ	5.64 ± 1.72	3.68 ± 2.44	0.23	0.47
MCP-3	88.62 ± 112.72	9.88 ± 6.72	0.23	0.47
MDC	1072.20 ± 350.97	762.11 ± 155.40	0.23	0.47
IL-7	2.25 ± 0.57	3.05 ± 0.97	0.23	0.47
RANTES	645.90 ± 221.69	1354.61 ± 1155.24	0.23	0.47
IL-12p70	7.21 ± 2.66	4.65 ± 1.86	0.28	0.53
IL-1β	2.85 ± 1.75	1.68 ± 0.61	0.28	0.53
IL-13	17.58 ± 29.05	0.47 ± 0.42	0.37	0.60
IL-1α	344.94 ± 591.78	26.80 ± 11.53	0.40	0.60
IL-9	10.27 ± 14.99	0.95 ± 0.32	0.40	0.60
IL-6	22.18 ± 36.65	0.79 ± 0.26	0.40	0.60
TNF-α	19.89 ± 11.94	27.94 ± 12.07	0.40	0.60
EGF	179.89 ± 55.68	147.41 ± 82.30	0.63	0.77

IL-17 α	3.58 \pm 3.00	2.05 \pm 1.21	0.63	0.77
IL-3	0.67 \pm 0.17	0.76 \pm 0.17	0.63	0.77
IP-10	180.39 \pm 96.94	230.95 \pm 68.97	0.63	0.77
MCP-1	234.79 \pm 13.09	309.57 \pm 99.29	0.63	0.77
MIP-1 β	43.50 \pm 15.27	59.76 \pm 34.49	0.63	0.77
PDGF-AA	953.30 \pm 340.11	1043.00 \pm 415.49	0.86	0.93
IL-1ra	30.45 \pm 15.25	30.98 \pm 7.96	0.86	0.93
IL-8	21.03 \pm 25.67	7.01 \pm 1.24	0.86	0.93
IL-12p40	46.98 \pm 13.91	37.23 \pm 20.58	0.86	0.93
GM-CSF	31.82 \pm 6.17	37.29 \pm 14.40	1.00	1.00
IFN- α 2	51.65 \pm 7.88	52.63 \pm 8.86	1.00	1.00
VEGF-A	40.54 \pm 43.24	33.94 \pm 31.00	1.00	1.00

Table S4: Changes of Cytokine Production in LPS Stimulated PBMCs from ERT Treated FD Patients by *ex vivo* Apabetalone Treatment

Cytokine	Fold induction by LPS	% Change from LPS+DMSO			
		1 μ M apabetalone	5 μ M apabetalone	20 μ M apabetalone	JQ1 (0.2 μ M)
IL-12p70	83.9	-62.7	-92.3	-97.1	-97.4
IL-12p40	20.2	-51.9	-91.7	-97.3	-97.9
MCP-3	1.6	-67.9	-91.1	-93.9	-93.2
IFN- γ	14.4	-54.4	-88.9	-98.4	-93.7
IP-10	1.3	-46.5	-68.3	-75.0	-73.4
GM-CSF	11.3	-24.6	-66.4	-91.7	-80.8
IL-10	14.3	-24.8	-51.2	-82.7	-74.6
IL-1RA	5.2	-11.5	-42.2	-84.3	-80.6
MDC	3.2	-18.3	-39.7	-49.0	-44.2
IL-13	4.2	-3.1	-39.0	-59.0	-19.2
sCD40L	1.4	-20.8	-26.4	-54.5	-29.6
IL-5	3.9	12.0	-23.0	-52.5	-26.7
PDGF-BB	2.0	-16.4	-9.5	5.8	-9.9
Flt-3L	1.6	-6.2	-9.3	-16.8	-14.7
FGF-2	1.4	-2.4	-6.5	-7.4	4.2
Eotaxin	2.3	-3.8	-5.4	-16.3	-21.8
PDGF-AA	1.2	-2.4	-2.3	-6.5	-4.9
EGF	1.8	-1.1	2.3	-3.2	-2.2
RANTES	3.2	14.4	16.1	7.7	-7.6
IL-2	2.0	26.6	20.9	-37.5	-5.8
IL-1 β	19.2	13.3	22.0	15.6	19.0
Fractalkine	4.6	-45.4	72.4	-50.1	27.4

Notes: Cytokine induction in response to LPS is expressed as mean fold change relative to vehicle(DMSO control). Effect of apabetalone is shown as % change from LPS stimulation (LPS+DMSO). Bold and italic numbers indicate $p < 0.05$ (student paired t test).

Figure S1

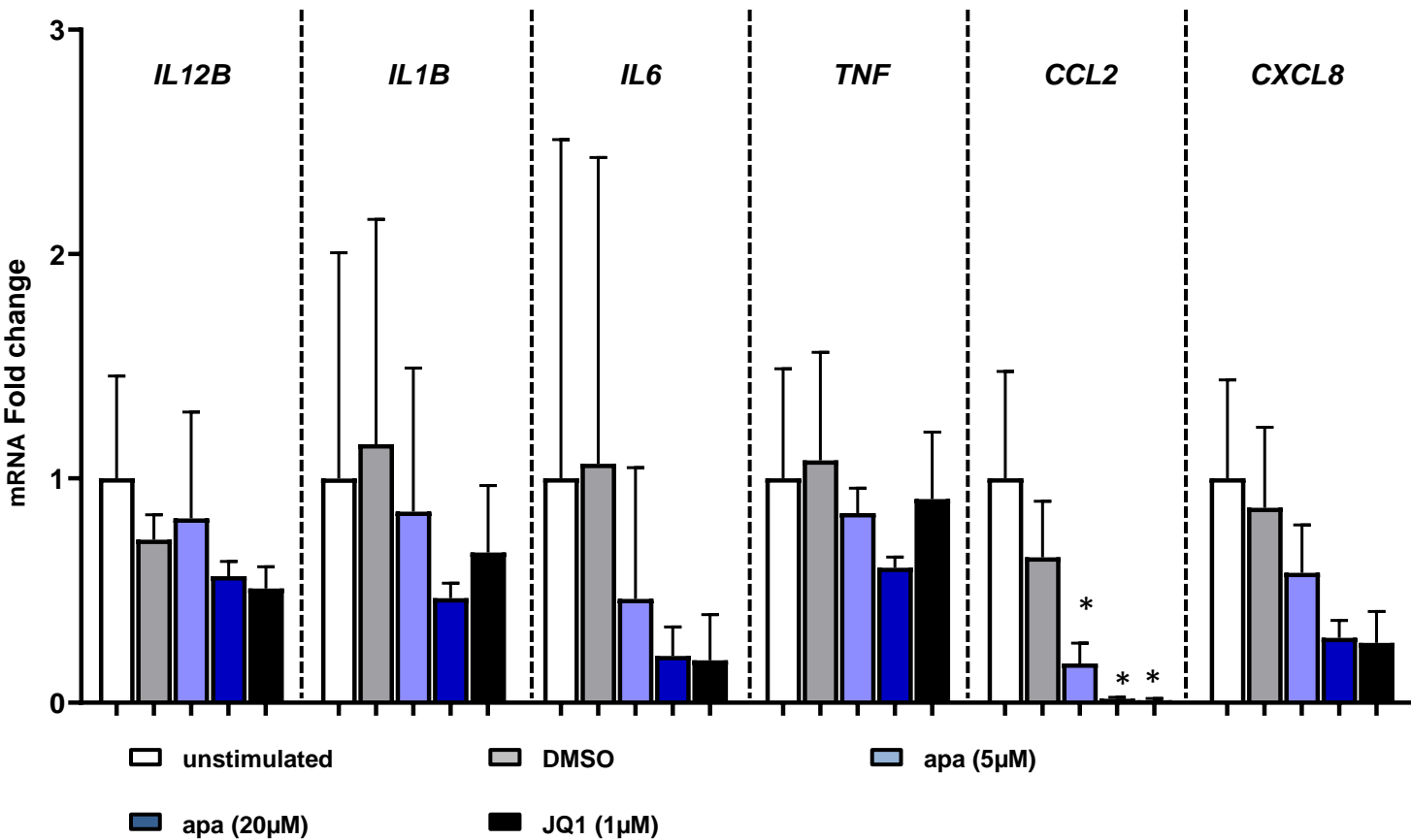


Figure S1. Apabetalone did not induce inflammation in unstimulated PBMCs from ERT treated FD patients (n=4). The data are shown as relative fold changes from the unstimulated baseline. Normalization was calculated as ΔCT values in individual patients divided by the average ΔCT value at the baseline in the tested patients. Bar graphs show the mean \pm SEM. Statistical significance was determined by one-way ANOVA followed by Dunnett's multiple comparison test relative to DMSO. * $p < 0.05$

Figure S2

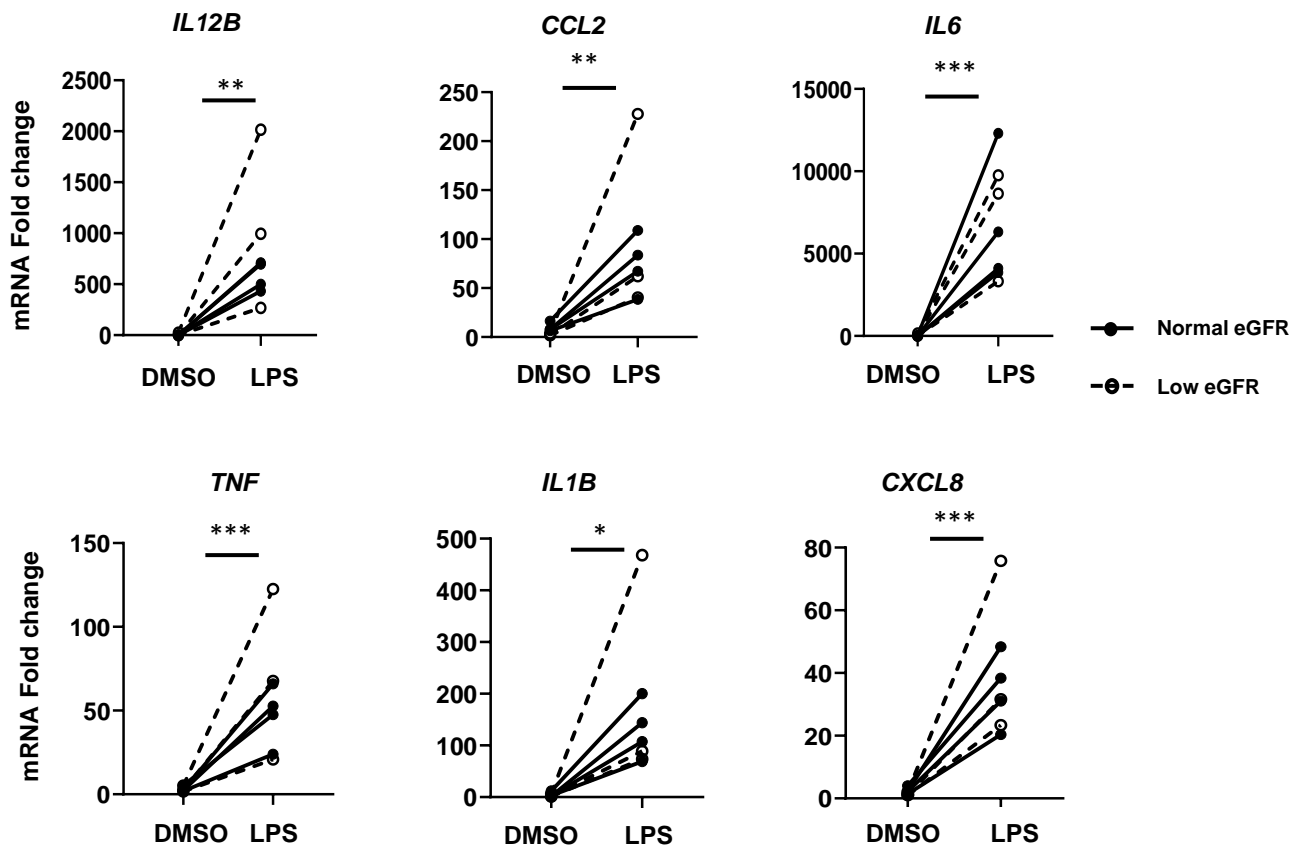


Figure S2. Induction of pro-inflammatory gene transcript levels in response to LPS stimulation in PBMCs from ERT treated FD patients (n=7). The data are shown as relative fold changes from the unstimulated baseline. Statistical significance was determined by the Wilcoxon test. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Figure S3

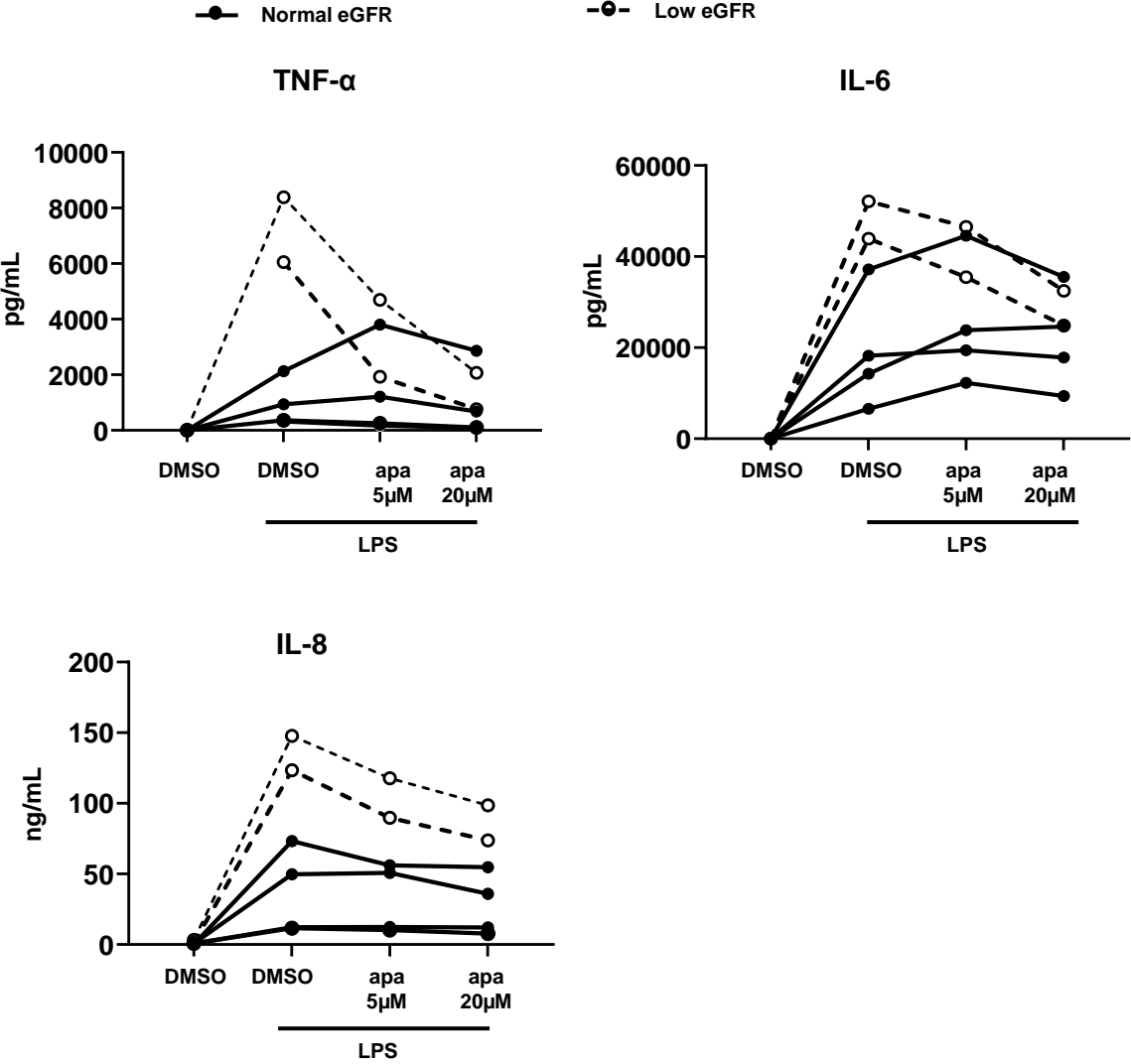


Figure S3. Levels of TNF- α and IL-6 secreted by PBMCs from ERT treated FD patients following 18 hours of LPS stimulation \pm apabetalone co-treatment. The expression was evaluated with bead-based flow cytometry and data was analyzed with FCAP. Each line represents an individual patient.

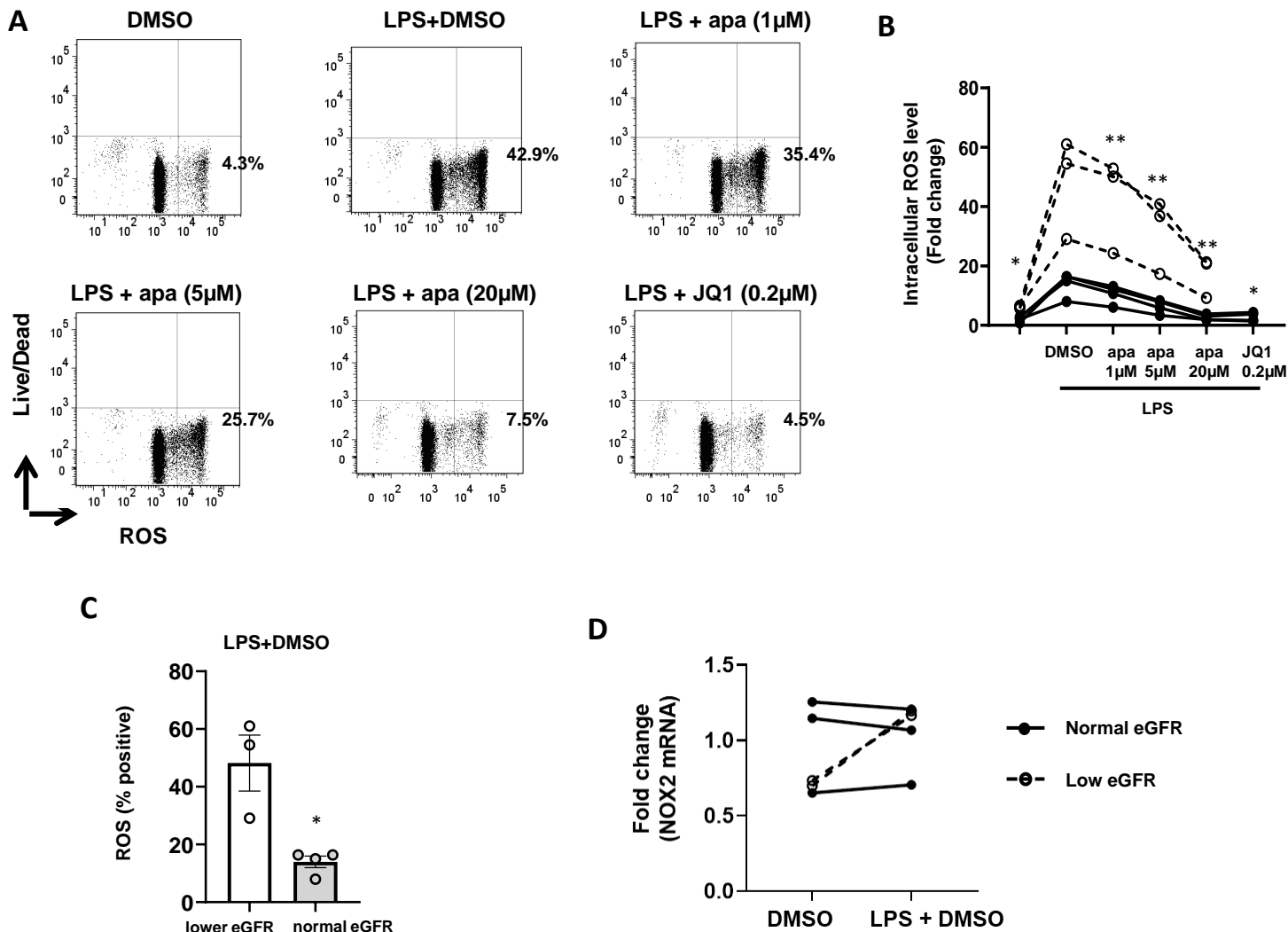
Figure S4

Figure S4. (A) Representative flow cytometric analysis of intracellular ROS production in neutrophils in response to LPS stimulation with 18 hours co-treatment of apabetalone or JQ1. (B) Average ROS levels as a percentage of ROS positive neutrophils from ERT treated FD patients with indicated eGFR levels ($n=7$). (C) LPS-induced ROS levels in neutrophils from ERT treated FD patients with normal or lower eGFR levels. (D) Comparison of NOX2 mRNA levels in resting and activated neutrophils from ERT treated FD patients in response to 4 hours of LPS stimulation. Statistical significance was determined by one-way ANOVA followed by Dunnett's multiple comparison test relative to DMSO in B or Mann Whitney test in C. * $p < 0.05$, ** $p < 0.01$