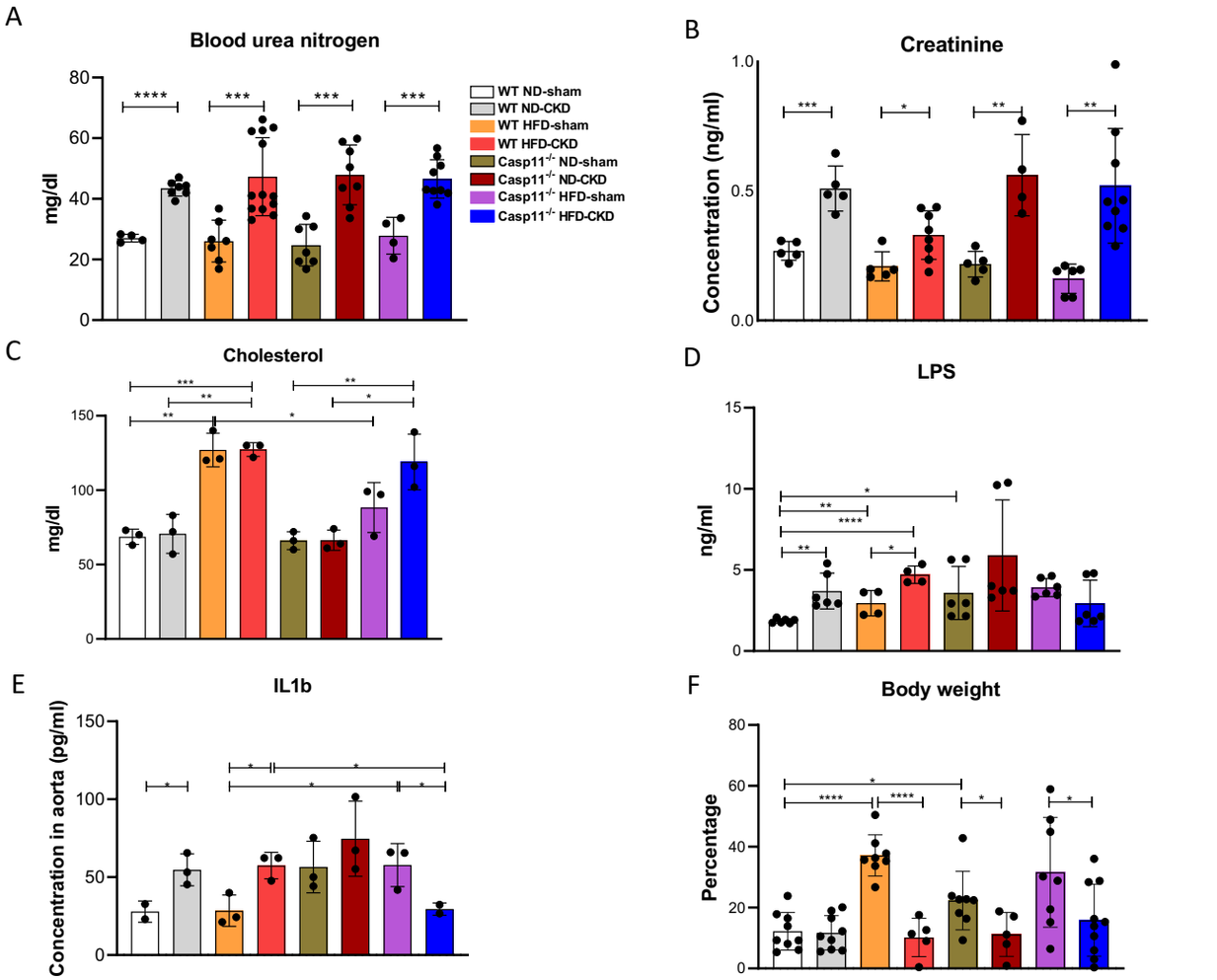
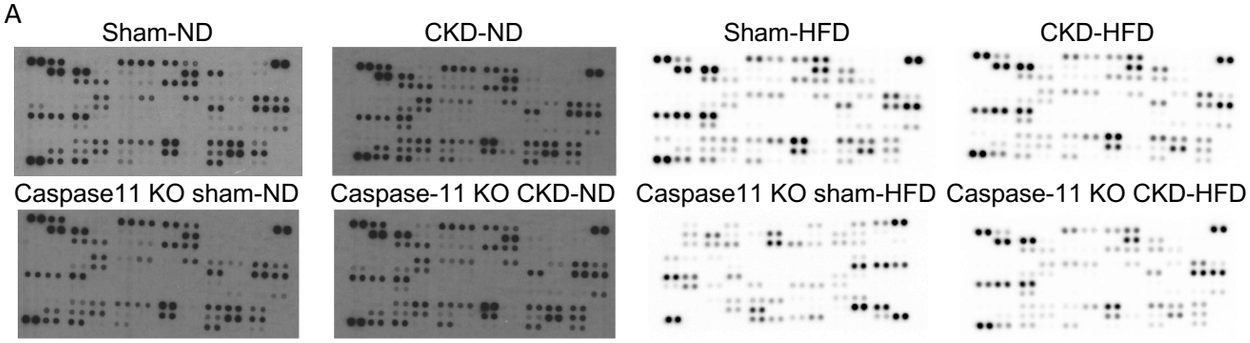


Supplementary Figure 1. A-C. The renal function markers blood urea nitrogen (**A**), creatinine (**B**), and cholesterol (**C**) levels were detected in the plasma of ND and HFD, WT and casp4/11$^{-/-}$, CKD and Sham mice. **D and E**. The LPS levels (**D**) and IL-1β secretion (**E**) were detected in the plasma of ND and HFD, WT and casp4/11$^{-/-}$, CKD and Sham mice using ELISA. **F**. The percentage of increased body weight from 9th week to 18th week versus body weight at 9th week was measured in ND and HFD, WT and casp4/11$^{-/-}$, CKD and Sham mice. *P<0.05, **P<0.01, ***P<0.001

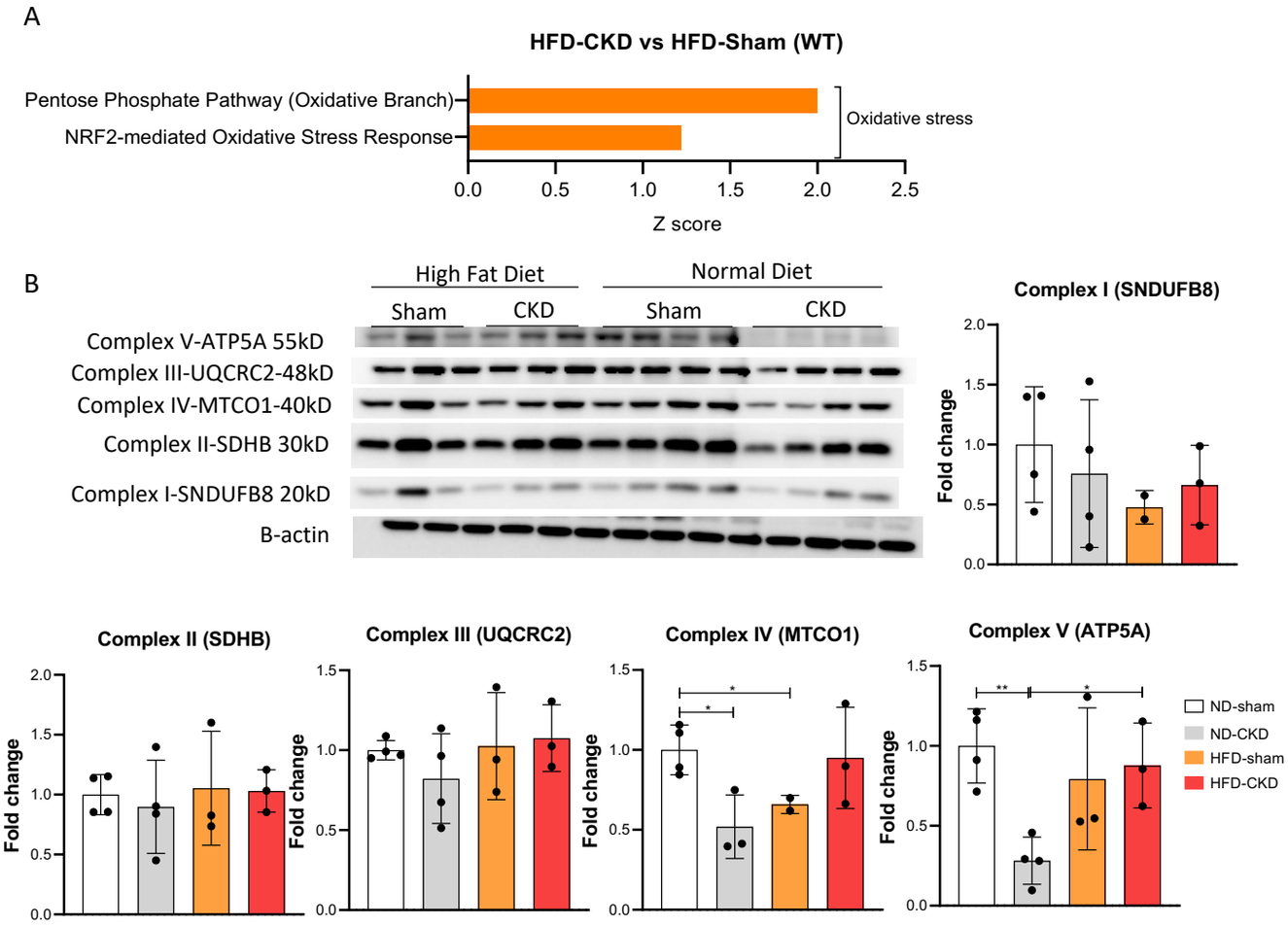
A



	1	2	3	4	5	6	7	8	9	10	11	12
A	RS		Adiponectin/Acrp 30		Amphiregulin		Angiopoietin-1		Angiopoietin-2		Angiopoietin-like 3	
B			CCL6/C10		CCL11/Eotaxin		CCL12/MCP-5		CCL17/TARC		CCL19/MIP-3β	
C			CD160		Chemerin		Chitinase 3-like 1		Coagulation Factor III/Tissue Factor		Complement Component C5/C5a	
D	CXCL9/MIG		CXCL10/IP-10		CXCL11/I-TAC		CXCL13/BLC/BCA-1		CXCL16		Cystatin C	
E	FGF acidic		FGF-21		Flt-3 Ligand		Gas 6		G-CSF		GDF-15	
F	IGFBP-3		IGFBP-5		IGFBP-6		IL-1α/IL-1F1		IL-1β/IL-1F2		IL-1ra/IL-1F3	
G	IL-10		IL-11		IL-12 p40		IL-13		IL-15		IL-17A	
H	Leptin		LIF		Lipocalin-2/NGAL		LIX		M-CSF		MMP-2	
I	PDGF-BB		Pentraxin 2/SAP		Pentraxin 3/TSG-14		Periostin/OSF-2		Pref-1/DLK-1/FA1		Proliferin	
J	RS		E-Selectin/CD62E		P-Selectin/CD62P		Serpin E1/PAI-1		Serpin F1/PEDF		Thrombopoietin	

	13	14	15	16	17	18	19	20	21	22	23	24
A	BAFF/BLyS/TNFSF13B		C1q R1/CD93		CCL2/JE/MCP-1		CCL3/CCL4/MIP-1α/β		CCL5/RANTES		RS	
B	CCL20/MIP-3α		CCL21/6Ckine		CCL22/MDC		CD14		CD40/TNFRSF5			
C	Complement Factor D		C-Reactive Protein/CRP		CX3CL1/Fractalkine		CXCL1/KC		CXCL2/MIP-2			
D	DKK-1		DPPIV/CD26		EGF		Endoglin/CD105		Endostatin		Fetuin A/AHSG	
E	GM-CSF		HGF		ICAM-1/CD54		IFN-γ		IGFBP-1		IGFBP-2	
F	IL-2		IL-3		IL-4		IL-5		IL-6		IL-7	
G	IL-22		IL-23		IL-27 p28		IL-28A/B		IL-33		LDL R	
H	MMP-3		MMP-9		Myeloperoxidase		Osteopontin (OPN)		Osteoprotegerin / TNFRSF11B		PD-ECGF/Thymidine phosphorylase	
I	Proprotein Convertase 9/PCSK9		RAGE		RBP4		Reg3G		Resistin			
J	TIM-1/KIM-1/HAVCR		TNF-α		VCAM-1/CD106		VEGF		WISP-1/CCN4		Negative Control	

Supplementary Figure 2. The expression of pro-inflammatory and anti-inflammatory cytokines and growth factors was examined in the plasma of ND and HFD, WT and caspase-4/11-/-, CKD and Sham mice. The plasma of mice is collected at the 18th week from groups of HFD-CKD, HFD-sham, ND-CKD and ND-sham. After that, the plasma levels of pro-inflammatory, chemokines, anti-inflammatory cytokines and growth factors are detected in these groups using cytokine array. The cytokine array film images of ND-Sham, ND-CKD, HFD-Sham, HFD-CKD in WT mice are indicated. The cytokines, chemokines, and growth factors examined are indicated. Each sample is pooled from 3 mice in each group (n = 3).



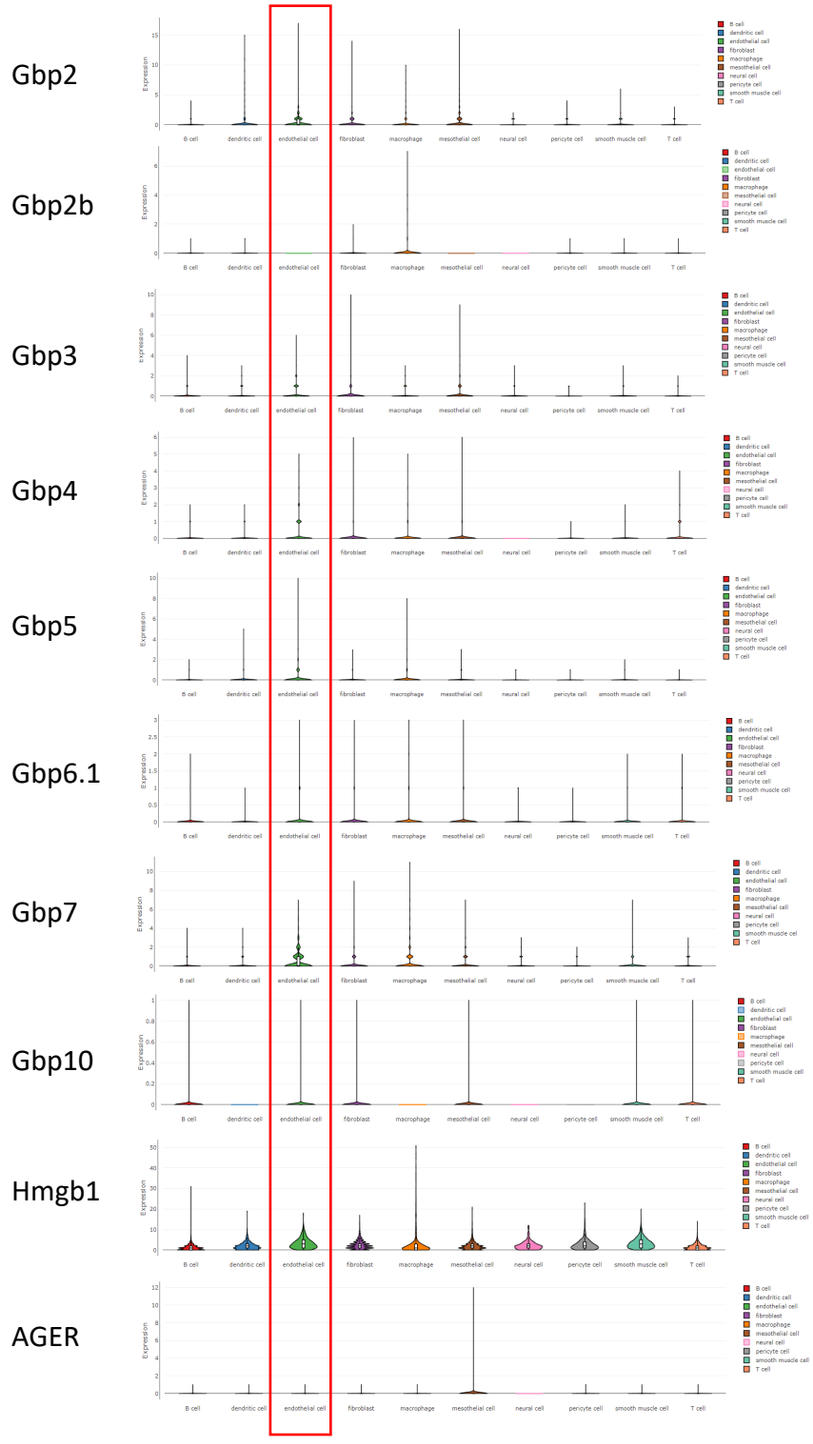
Supplementary Figure 3. ROS signaling is increased in the aorta of HFD+CKD. A. The oxidative stress pathways were analyzed in the aortic RNA-seq data from groups of HFD+CKD vs. HFD-sham. **B**. The expression of mitochondrial complexes was examined in the aortic lysates of HFD+CKD, HFD-sham, ND-CKD and ND-sham, and quantification of the expression of mitochondrial complex I (SNDUFB8), complex II (SDHB), complex III (UQCRC2), complex IV (MTCO1) and complex V (ATP5A) was quantified by ImageJ. * P<0.05, ** P<0.01.

A

GBP family gene

	HFD CKD vs HFD		HFD CKD vs CKD	
Gene	P	LogFC	p	LogFC
GBP2				
GBP3			0.01	0.88
GBP4				
GBP5				
GBP6	0.03	0.57	0.00	1.11
GBP7				
GBP10				
HMGB1	0.02	-0.33		
RAGE				

B



Endothelial cell

C

Canonical and non-canonical inflammasome regulator gene

HFD CKD vs HFD Canonical

Gene	P	LogFC
IL1B	0.03	1.96
ITPR2	0.00	1.07
CYBB	0.04	0.85
NAMPT	0.00	0.73
MAVS	0.00	0.66
TXN2	0.01	0.59

HFD CKD vs CKD Canonical

Gene	P	LogFC
IL1B	0.02	2.10
ITPR2	0.00	1.32
MAVS	0.00	0.67
NAMPT	0.00	0.67
OAS2	0.03	0.66
TXN2	0.01	0.63

Non-canonical

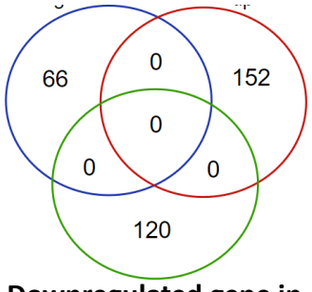
Gene	P	LogFC
IL1B	0.03	1.96
SLC25A22	0.00	1.05
GBP6	0.03	0.57

Non-canonical

Gene	P	LogFC
IL1B	0.02	2.10
SLC25A22	0.00	1.20
GBP6	0.00	1.11
GBP3	0.01	0.88

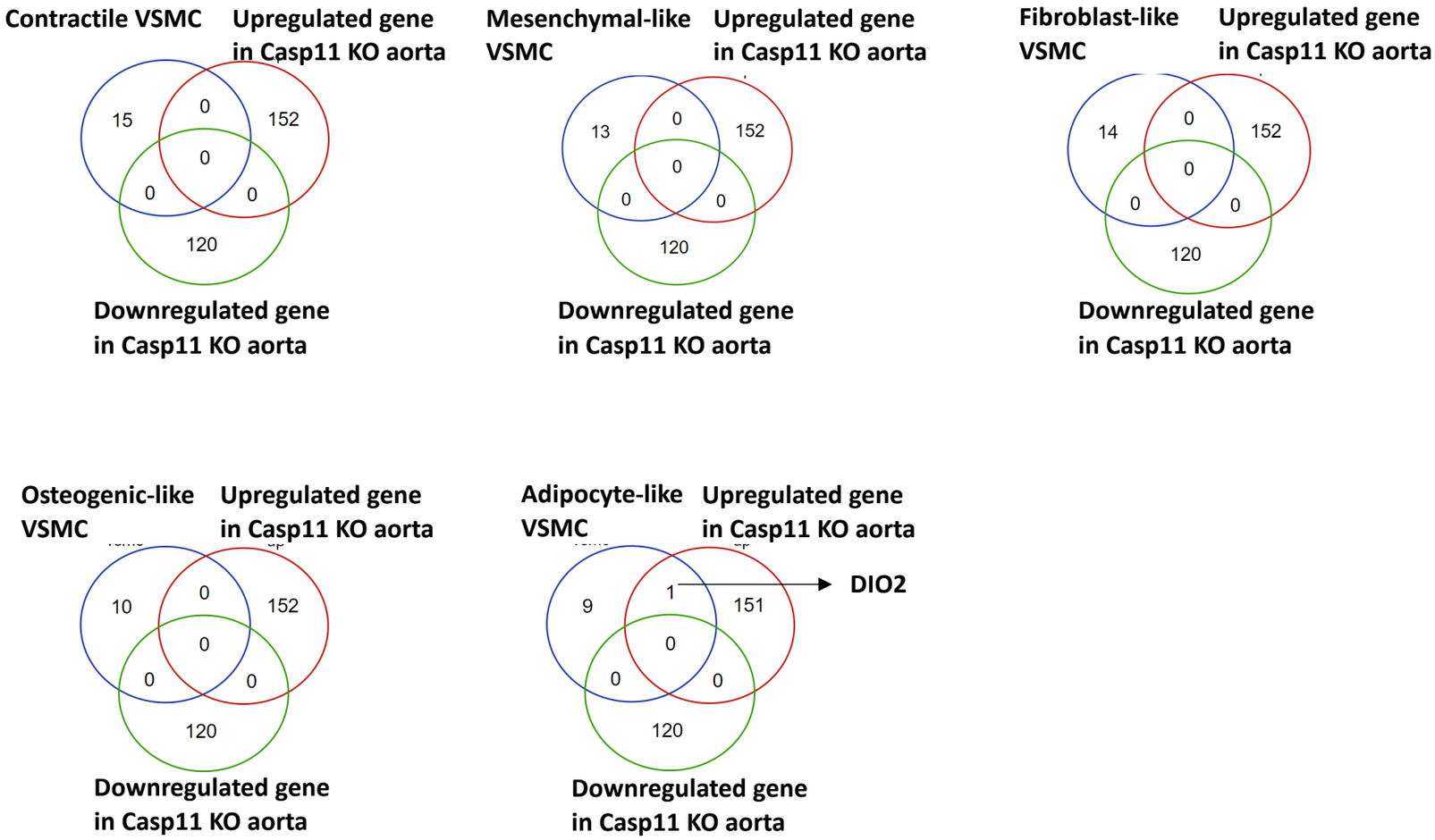
D

EC markers **Upregulated gene in Casp11 KO aorta**



Downregulated gene in Casp11 KO aorta

E

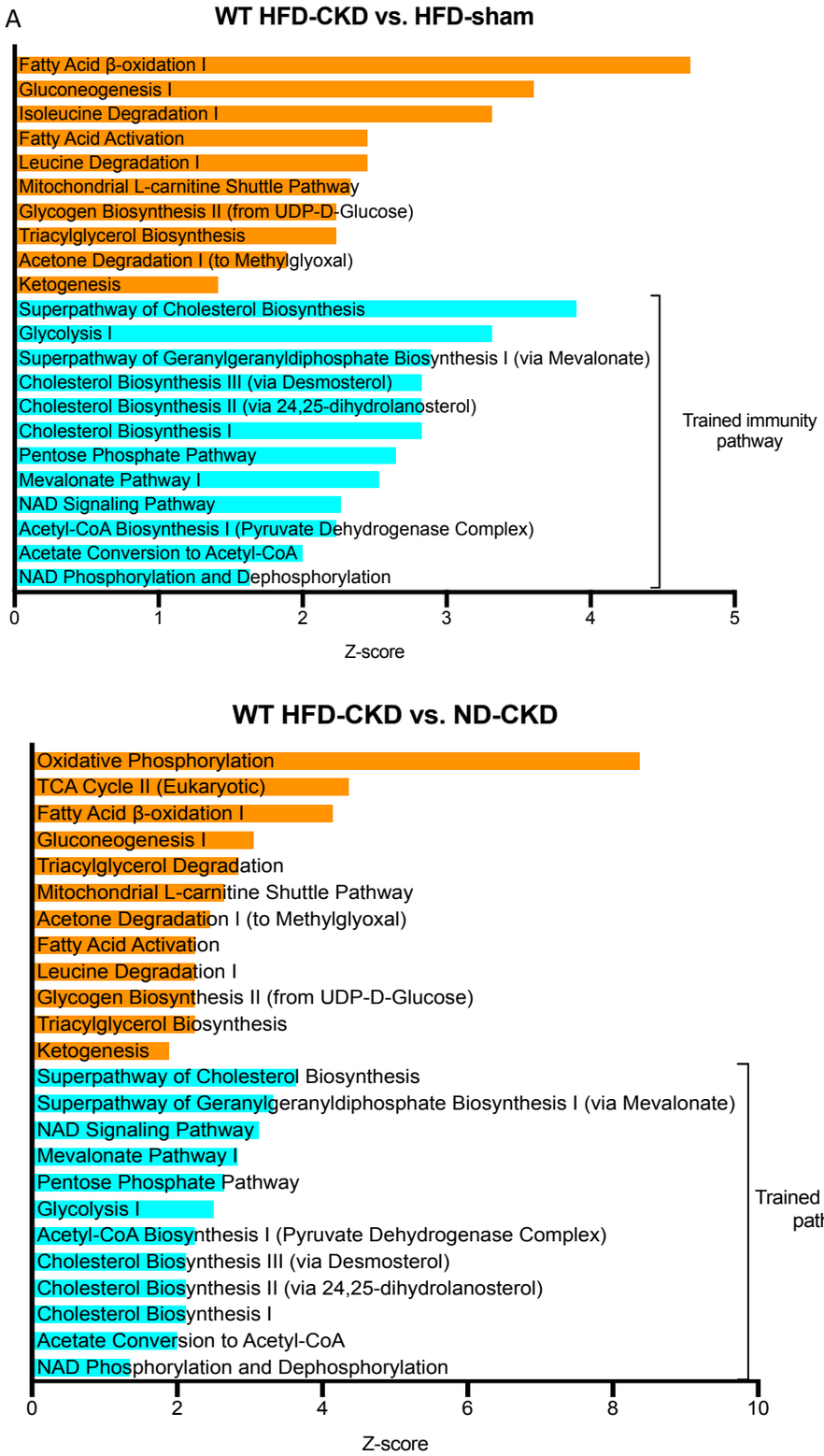


F

Potassium channel gene in CKD HFD vs. Sham ND

Gene	P	LogFC
KCNK2	0.02	2.41
KCNT1	0.04	-1.12
KCNK10	0.01	-2.15

Supplementary Figure 4. RNA-seq analysis in HFD+CKD vs. HFD and HFD+CKD vs. CKD.
A. The expression of GBP family genes in an RNA-Seq dataset. **B**. The single-cell RNA-seq (Single cell portal at the Broad Institute of MIT and Harvard) in the aortas of HFD fed mice showed upregulated LPS endocytic machinery components in endothelial cells . **C.** The expression of canonical and non-canonical inflammasome gene in an RNA-Seq dataset. **D.** EC marker gene list from PMID: 29333215, Upregulated and downregulated gene from Casp11 HFD CKD vs. WT HFD CKD group (P<0.05 and LogFC>1 or <-1) **E.** Vascular smooth muscle cell phenotype marker from PMID: 33324416; 34470477. Upregulated and downregulated gene from Casp11 HFD CKD vs. WT HFD CKD group (P<0.05 and LogFC>1 or <-1) **F.** 79 potassium channel genes collected from HGNC (https://www.genenames.org/data/genegroup/#!/group/183) are screened in RNA-seq of WT CKD HFD vs. WT Sham ND.



Supplementary Figure 5. the ingenuity pathway analysis (IPA) showed that HFD+CKD vs. HFD and HFD+CKD vs. CKD upregulated 12 TI pathways