Supplemental Table 1

Experiment	
PC naïve 1	FACS sorted, iv *1
PC naïve 2	Unsorted, iv *2
PC naïve 3	Unsorted, ip *2
PC precond 1	In vivo precondition, FACS sorted, iv *3
PC precond 2	In vivo precondition, unsorted, iv, rough LPS *4
PC precond 3	In vivo precondition, adherent, iv *5
PC precond 4	In vivo precondition, unsorted, ip
PC precond 5	In vivo precondition, unsorted, iv
Renal macrophage naïve	FACS sorted, iv *6
Renal macrophage precond 1	In vivo precondition, FACS sorted, iv
Renal macrophage precond 2	In vivo precondition, FACS sorted, ip
BMDM naïve mac	M-CSF *7
BMDM precond mac 1	Ex vivo precondition with 10ng/mL LPS *7, 8
BMDM precond mac 2	Ex vivo precondition with 100 ng/mL LPS + 10ng/mL LPS *7, 9
Monocyte naïve	Peripheral monocyte FACS sorted, iv *6
Monocyte precond	In vivo precondition, peripheral monocyte FACS sorted, iv *6
Serum naïve	Ip *10
Serum precond	In vivo precondition, ip *10

An equal number of cells were infused for a set of experiments and the number of cells infused ranged from $0.5x10^6$ to $2x10^6$ per mouse depending of the type of experiments. In vivo preconditioning was done using 0.25 mg/kg smooth lps ip for 24 h except for the PC precond 1 experiment where rough lps was used. See footnote *4.

*1. Negative selection ($PI^-CD3^-CD19^-$).

*2. A mixture of peritoneal macrophages and other cell types.

*3. Includes both negative selection ($PI^-CD3^-CD19^-$) and forward and side scatter based selection (without adding any antibodies including Fc blockers); no difference was found.

*4. *Salmonella enterica* serotype Minnesota Re 595 (rough strain) and *Escherichia coli* serotype 0111:B4 (smooth strain) were compared. No difference was found on protection and therefore smooth strain LPS was used for the rest of experiments.

*5. Non-adherent cells (peritoneal B cells) were removed with 4 hr incubation which allowed macrophages to settle and adhere.

*6. Renal macrophages and peripheral monocytes were obtained from $CX_3CR1^{GFP/WT}$ mice. We have previously reported that $CX_3CR1^{GFP/WT}$ mice can mount preconditioning comparable to C57BL/6 and BoyJ mice.[1]

*7. M-CSF 10 ng/mL for 7 days, media replaced twice.

*8. 10 ng/mL for 24 h.

*9. 100 ng/mL for 24 h followed by 4 h of 10 ng/mL before cell infusion.

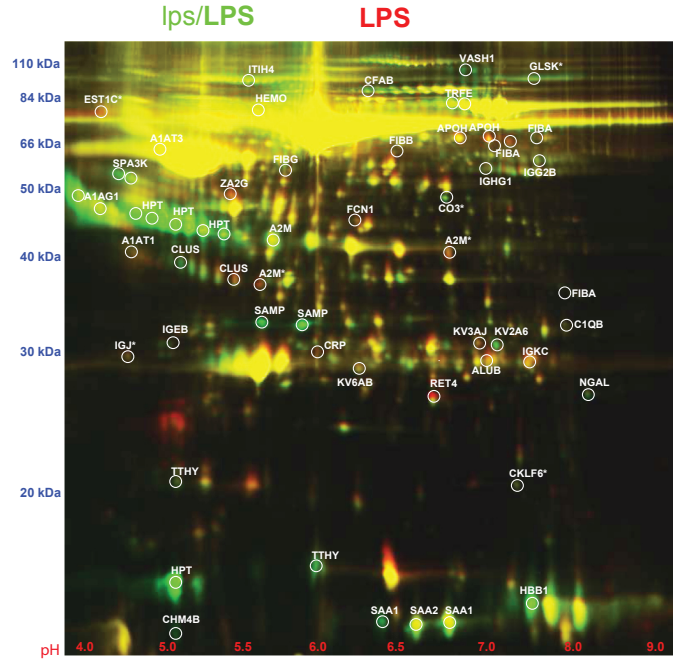
*10. Approximately 200 µL, pooled from 2 animals.

Supplemental Table 2

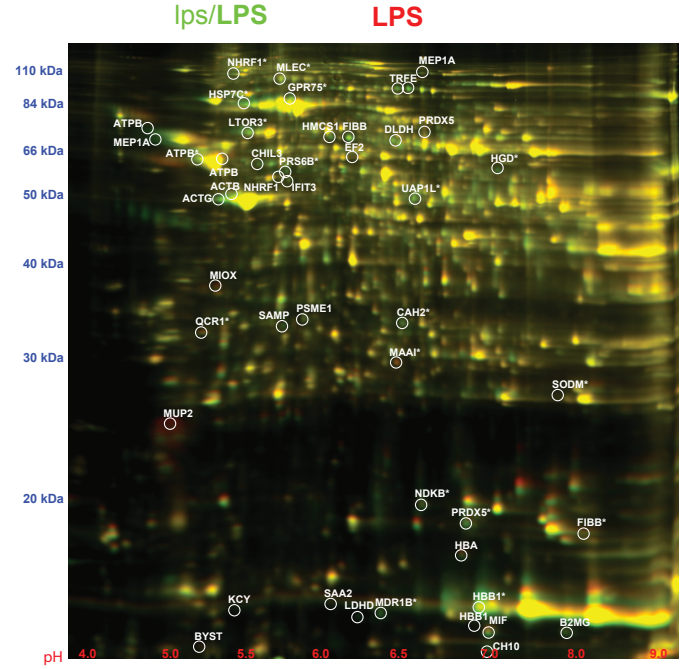
Select target genes, metabolites, and proteins altered in preconditioned animals.

Select candidate target	Our data	Supportive reference
Nicotinamide metabolism	LPS treatment resulted in depletion of nicotinamide and NAD^+ levels and accumulation of downstream metabolite N1-methylnicotinamide amidst deranged expression of genes involved in nicotinamide metabolism (transcriptomics and metabolomics data).	Nicotinamide provides PGC1alpha-dependent renoprotection.[2]
Ketone body metabolism (3-hydroxybutyrate)	3-hydroxybutyrate, Acetyl CoA, and hydroxymethylglutaryl-CoA synthase levels were all increased in lps/LPS compared to LPS (metabolomics and 2DIGE data)	3-hydroxybutyrate inhibits NLRP3 inflammasome-mediated inflammatory disease.[3] Inhibition of ketogenesis worsens mortality in a model of endotoxemia.[4]
Eicosanoids	Proinflammatory eicosanoids including 5-HETE, 9,10-DiHOME levels were increased in LPS but not in lps/LPS (metabolomics data).	These eicosanoids are reported to be cytotoxic.[5, 6]
Glucose metabolism	Glucose-6-phosphate, mannose-6-phosphate and fructose-6-phosphate levels were increased in lps/LPS compared to LPS. These are hub metabolites connecting glycolysis, pentose phosphate, inositol metabolism (G6P), and glycosylation (M6P, F6P). (transcriptomics and metabolomics data).	Metabolic reprogramming and activation of immunity.[4, 7-9] While long-term fructose metabolism could be pathologic,[10] the hypoxia resistant naked mole rat rewires metabolism to fructolysis during acute hypoxic stress.[11]
Tryptophan metabolism	3-indoxyl sulfate, kynurenine, kynurenate, xanthurenate levels were increased in LPS compared to lps/LPS. Aadat, which catalyzes kynurenine to kynurenate and xanthurenate, was also mildly increased in LPS. (transcriptomics and metabolomics data)	3-indoxyl sulfate is a prototype of uremic toxin, produced from gut microbes.[12-14] Kynurenine is a ligand for aryl hydrocarbon receptor which is activated by LPS and involved in disease tolerance.[15]
Inositol metabolism	Myo-inositol and scyllo-inositol levels were increased in lps/LPS as compared to LPS. Mio-inositol oxygenase (Miox), which catalyzes inositol to glucoronate, was decreased in lps/LPS (2DIGE, transcriptomics, and metabolomics data)	Myo-inositol is an important second messenger. Miox is proximal tubule specific, highly enriched in S1.[16] Miox is upregulated in models of diabetic nephropathy.[17]
Carnitine metabolism	Acetylcarnitine, deoxycarnitine (precursor of carnitine), propionylcarnitine levels were increased in lps/LPS compared to LPS (metabolomics data)	Carnitine system is indispensable for beta oxidation, and its deficit has been implicated in various disease models.[18] The last step of carnitine generation is restricted to the liver, kidney and brain.[19]

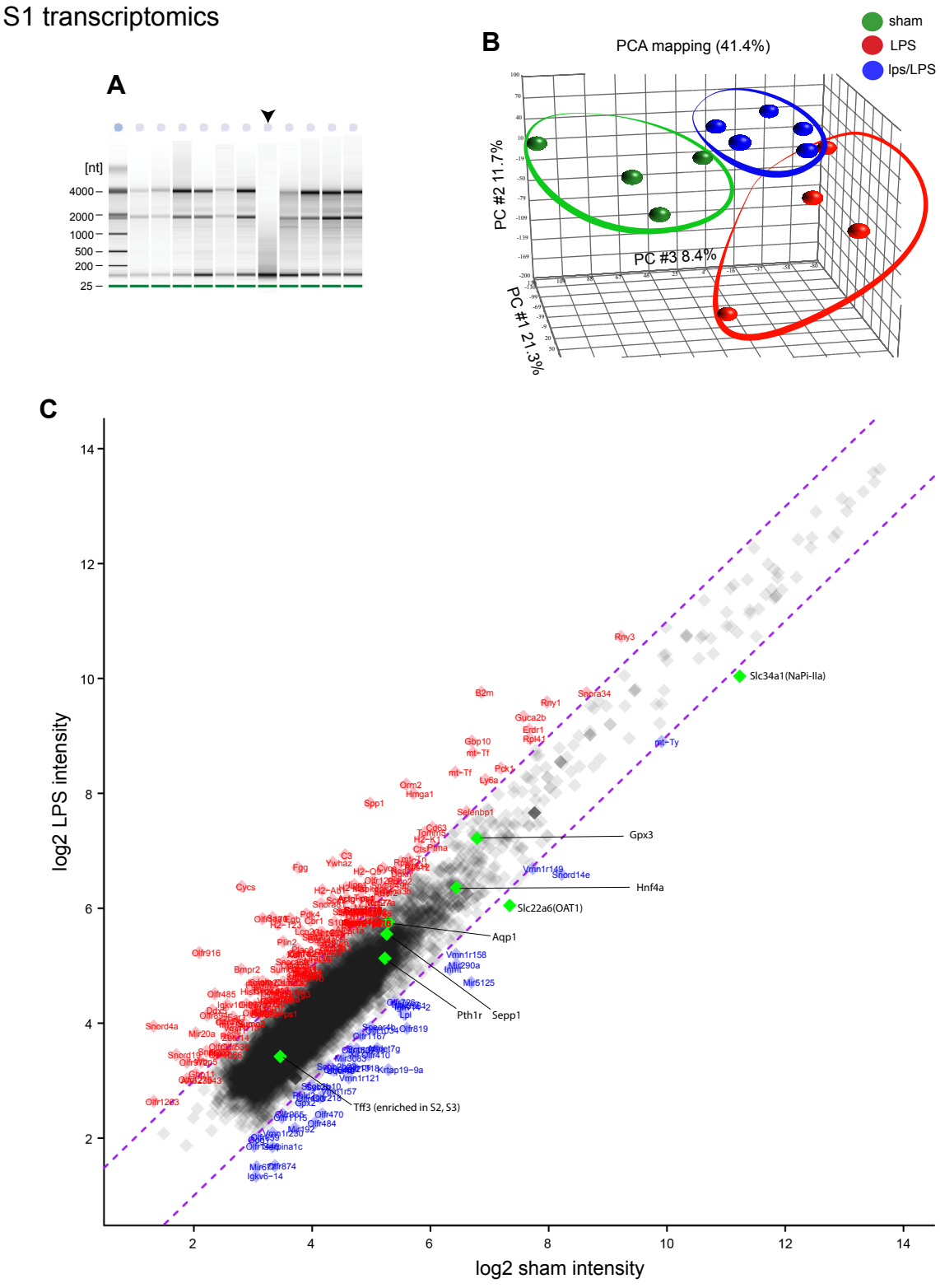
A Serum



B Kidney

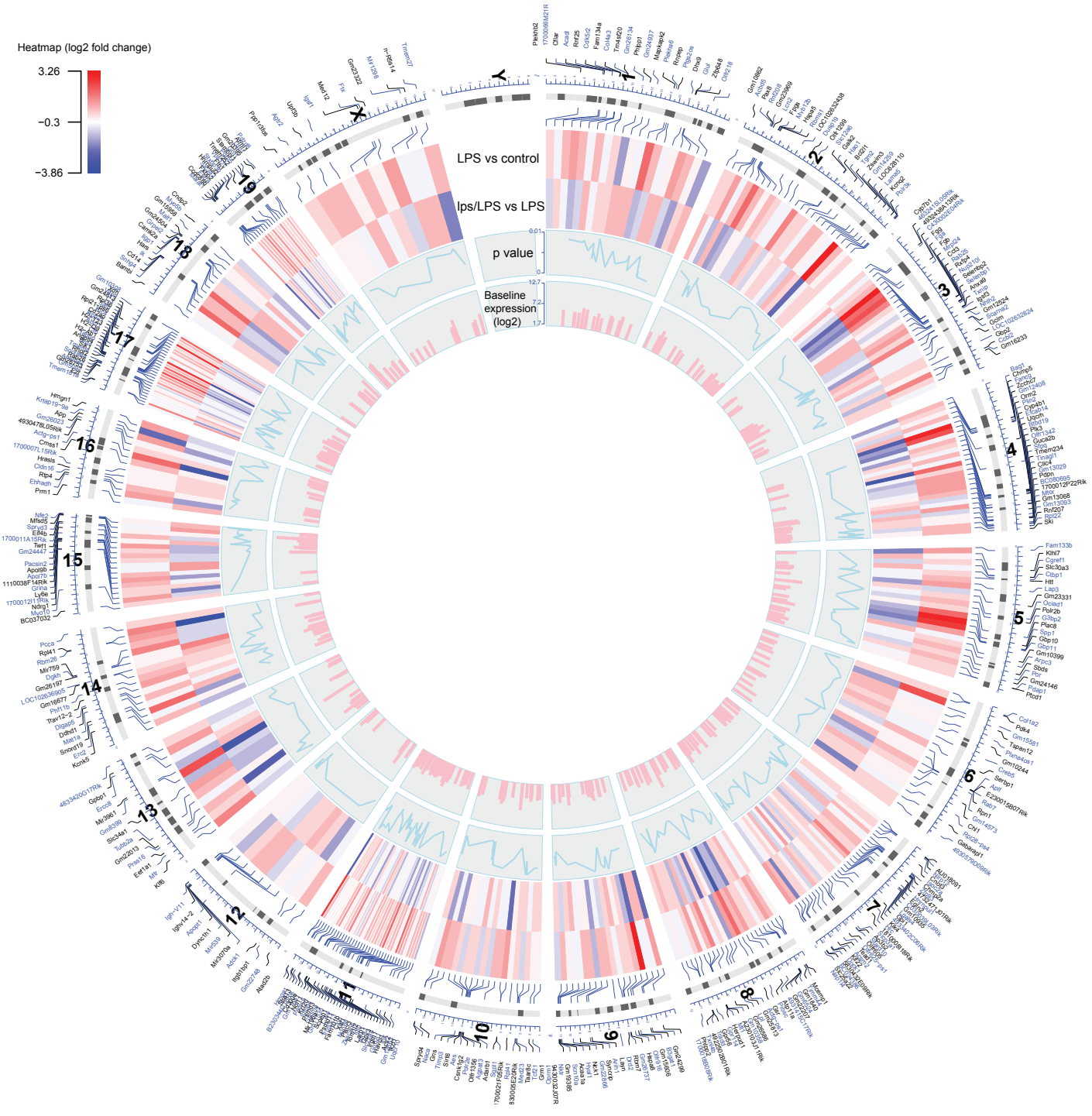


Supplemental Figure 1
(A, B) Serum and kidney two-dimensional difference gel electrophoresis images and identified proteins.
Original gels consist of a mixture of 3 extracts (sham, LPS, and lps/LPS, labeled with Cy2, Cy3, Cy5; each condition is a pool of 3 animals) and only the color-coded comparison between LPS and lps/LPS is shown here for clarity. Spots with fold change > 2.0 in at least one direct comparison among the 3 experimental conditions were used as a cutoff in the DeCyder analysis and those spots were subsequently identified with mass spectrometry (MALDI-TOF). Protein* indicates potential alternative protein with high confidence (protein score C.I.>98%, total ion C.I.>98%).



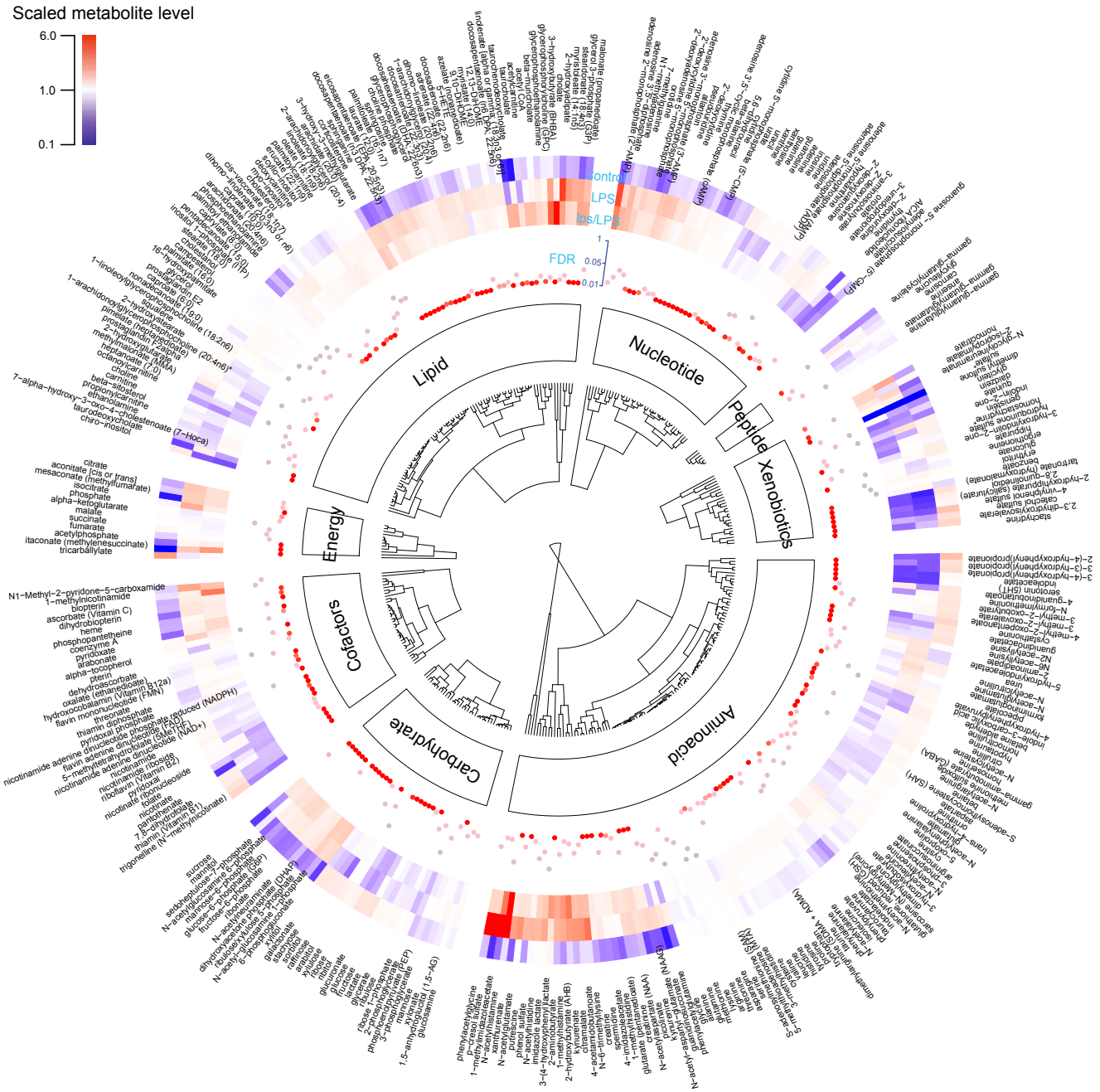
Supplemental Figure 2
(A) Representative integrity of laser microdissected S1 RNA used for microarray (Affymetrix GeneChip WT Pico Kit) is shown. Average RNA integrity number (RIN) was 6.2 with occasional low RIN values (arrowhead). The yield of total RNA was 13.5 ± 10 ng with concentration of 750.6 ± 550 pg/μL after pooling 3 consecutive sections (from the same kidney tissue as one sample). (B) Principal component analysis is shown. (C) Scatter plot of transcriptomics comparing sham and non-preconditioned S1 (x and y axis log2 transformed signal intensity). The dotted lines demarcate ± 2 fold changes and genes above this threshold are annotated. Several genes are highlighted in green to illustrate successful enrichment of S1, and in black (Tff3) as lack of enrichment of S2/S3 (these genes were selected based on NIH Epithelial Systems Biology Lab Database).

S1 Transcriptomics

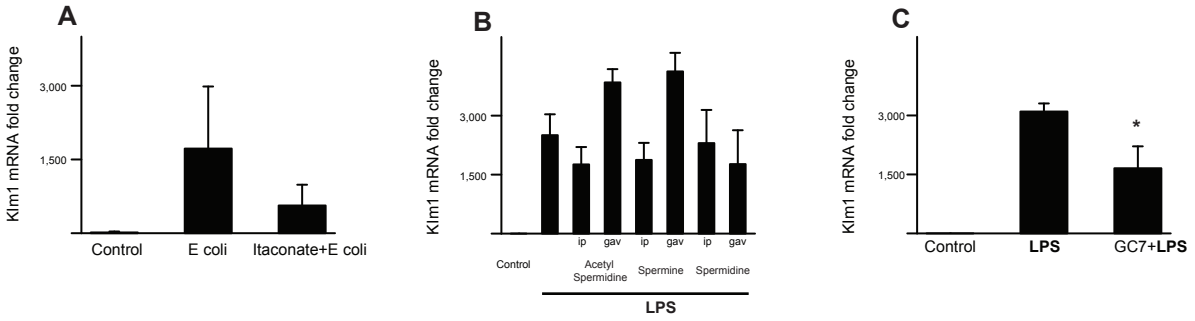


Supplemental Figure 3
S1 genes with ANOVA <0.01 from sham control, LPS, and lps/LPS were selected for generating the circular plot. This annotated plot provides information including gene locus on a chromosome (black lines are cytobands), ANOVA p values, baseline expression levels (log2 fluorescence intensity), and direct comparisons for LPS vs sham and lps/LPS vs LPS (color-coded log2 fold change).

Metabolomics



Supplemental Figure 4
Metabolites that have defined KEGG ID (n=343) were selected for circular visualization under 8 major metabolic pathways. Scaled metabolite levels from sham control, LPS, and lps/LPS are color-coded and displayed in the outer circular tracks. Adjusted ANOVA p values (FDR) and hierarchical clustering as dendrogram are also shown.



Supplemental Figure 5

(A) Each animal was injected with membrane permeant dimethyl itaconate (160 mg/kg body weight) or an equal volume of saline vehicle ip followed 1 hr later by $3.2x10^6$ live E. coli iv. Renal tissue KIM1 mRNA levels were determined 24 hrs after the E coli injection using qPCR, normalized to GAPDH. (B) N1-acetylspermidine (20 mg/kg), spermine (20 mg/kg) or spermidine (20 mg/kg) were administered ip or gavage daily for 3 days. LPS (5 mg/kg iv) was administered 4 hrs after the last dose of metabolite supplementation. (C) Animals were injected with GC7 (deoxyhypusine synthase inhibitor; 4 mg/kg) ip or an equal volume of vehicle (saline and acetic acid) daily for 3 days. Animals were then injected with 5 mg/kg LPS 4 hrs after the last dose of GC7. KIM1 levels were determined using qPCR 24 hrs after LPS and normalized to GAPDH. *$p<0.05$ versus LPS alone group.

References

1. Hato, T, Winfree, S, Kalakeche, R, Dube, S, Kumar, R, Yoshimoto, M, Plotkin, Z, Dagher, PC: The macrophage mediates the renoprotective effects of endotoxin preconditioning. *J Am Soc Nephrol,* 26**:** 1347-1362, 2015.
2. Tran, MT, Zsengeller, ZK, Berg, AH, Khankin, EV, Bhasin, MK, Kim, W, Clish, CB, Stillman, IE, Karumanchi, SA, Rhee, EP, Parikh, SM: PGC1alpha drives NAD biosynthesis linking oxidative metabolism to renal protection. *Nature,* 531**:** 528-532, 2016.
3. Youm, YH, Nguyen, KY, Grant, RW, Goldberg, EL, Bodogai, M, Kim, D, D'Agostino, D, Planavsky, N, Lupfer, C, Kanneganti, TD, Kang, S, Horvath, TL, Fahmy, TM, Crawford, PA, Biragyn, A, Alnemri, E, Dixit, VD: The ketone metabolite beta-hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease. *Nat Med,* 21**:** 263-269, 2015.
4. Wang, A, Huen, SC, Luan, HH, Yu, S, Zhang, C, Gallezot, JD, Booth, CJ, Medzhitov, R: Opposing Effects of Fasting Metabolism on Tissue Tolerance in Bacterial and Viral Inflammation. *Cell,* 166**:** 1512-1525 e1512, 2016.
5. Thompson, DA, Hammock, BD: Dihydroxyoctadecamonoenoate esters inhibit the neutrophil respiratory burst. *J Biosci,* 32**:** 279-291, 2007.
6. Moran, JH, Weise, R, Schnellmann, RG, Freeman, JP, Grant, DF: Cytotoxicity of linoleic acid diols to renal proximal tubular cells. *Toxicol Appl Pharmacol,* 146**:** 53-59, 1997.
7. Jha, AK, Huang, SC, Sergushichev, A, Lampropoulou, V, Ivanova, Y, Loginicheva, E, Chmielewski, K, Stewart, KM, Ashall, J, Everts, B, Pearce, EJ, Driggers, EM, Artyomov, MN: Network integration of parallel metabolic and transcriptional data reveals metabolic modules that regulate macrophage polarization. *Immunity,* 42**:** 419-430, 2015.
8. Ip, WKE, Hoshi, N, Shouval, DS, Snapper, S, Medzhitov, R: Anti-inflammatory effect of IL-10 mediated by metabolic reprogramming of macrophages. *Science,* 356**:** 513-519, 2017.
9. O'Neill, LA, Pearce, EJ: Immunometabolism governs dendritic cell and macrophage function. *J Exp Med,* 213**:** 15-23, 2016.
10. Roncal-Jimenez, CA, Ishimoto, T, Lanaspa, MA, Milagres, T, Hernando, AA, Jensen, T, Miyazaki, M, Doke, T, Hayasaki, T, Nakagawa, T, Marumaya, S, Long, DA, Garcia, GE, Kuwabara, M, Sanchez-Lozada, LG, Kang, DH, Johnson, RJ: Aging-associated renal disease in mice is fructokinase dependent. *Am J Physiol Renal Physiol,* 311**:** F722-F730, 2016.
11. Park, TJ, Reznick, J, Peterson, BL, Blass, G, Omerbasic, D, Bennett, NC, Kuich, P, Zasada, C, Browe, BM, Hamann, W, Applegate, DT, Radke, MH, Kosten, T, Lutermann, H, Gavaghan, V, Eigenbrod, O, Begay, V, Amoroso, VG, Govind, V, Minshall, RD, Smith, ESJ, Larson, J, Gotthardt, M, Kempa, S, Lewin, GR: Fructose-driven glycolysis supports anoxia resistance in the naked mole-rat. *Science,* 356**:** 307-311, 2017.
12. Meijers, BK, Evenepoel, P: The gut-kidney axis: indoxyl sulfate, p-cresyl sulfate and CKD progression. *Nephrol Dial Transplant,* 26**:** 759-761, 2011.
13. Aronov, PA, Luo, FJ, Plummer, NS, Quan, Z, Holmes, S, Hostetter, TH, Meyer, TW: Colonic contribution to uremic solutes. *J Am Soc Nephrol,* 22**:** 1769-1776, 2011.
14. Yang, K, Wang, C, Nie, L, Zhao, X, Gu, J, Guan, X, Wang, S, Xiao, T, Xu, X, He, T, Xia, X, Wang, J, Zhao, J: Klotho Protects Against Indoxyl Sulphate-Induced Myocardial Hypertrophy. *J Am Soc Nephrol,* 26**:** 2434-2446, 2015.
15. Bessede, A, Gargaro, M, Pallotta, MT, Matino, D, Servillo, G, Brunacci, C, Bicciato, S, Mazza, EM, Macchiarulo, A, Vacca, C, Iannitti, R, Tissi, L, Volpi, C, Belladonna, ML, Orabona, C, Bianchi, R, Lanz, TV, Platten, M, Della Fazia, MA, Piobbico, D, Zelante, T, Funakoshi, H, Nakamura, T, Gilot, D, Denison, MS, Guillemin, GJ, DuHadaway, JB, Prendergast, GC, Metz, R, Geffard, M, Boon, L,

Pirro, M, Iorio, A, Veyret, B, Romani, L, Grohmann, U, Fallarino, F, Puccetti, P: Aryl hydrocarbon receptor control of a disease tolerance defence pathway. *Nature,* 511**:** 184-190, 2014.
16. Cheval, L, Pierrat, F, Dossat, C, Genete, M, Imbert-Teboul, M, Duong Van Huyen, JP, Poulain, J, Wincker, P, Weissenbach, J, Piquemal, D, Doucet, A: Atlas of gene expression in the mouse kidney: new features of glomerular parietal cells. *Physiol Genomics,* 43**:** 161-173, 2011.
17. Zhan, M, Usman, IM, Sun, L, Kanwar, YS: Disruption of renal tubular mitochondrial quality control by Myo-inositol oxygenase in diabetic kidney disease. *J Am Soc Nephrol,* 26**:** 1304-1321, 2015.
18. Flanagan, JL, Simmons, PA, Vehige, J, Willcox, MD, Garrett, Q: Role of carnitine in disease. *Nutr Metab (Lond),* 7**:** 30, 2010.
19. Vaz, FM, Wanders, RJ: Carnitine biosynthesis in mammals. *Biochem J,* 361**:** 417-429, 2002.