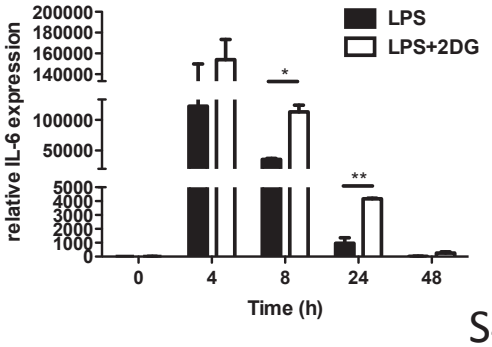
doi:10.1038/nature11986

S1



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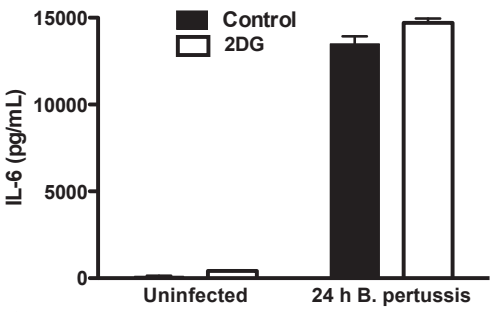

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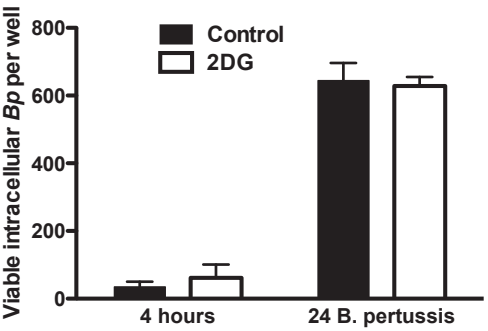

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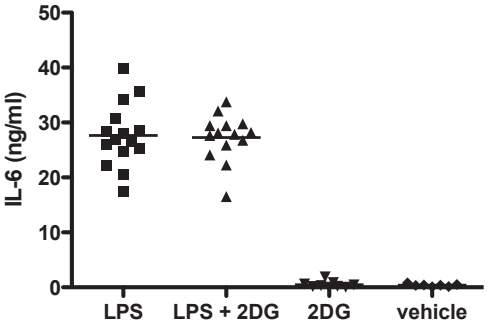
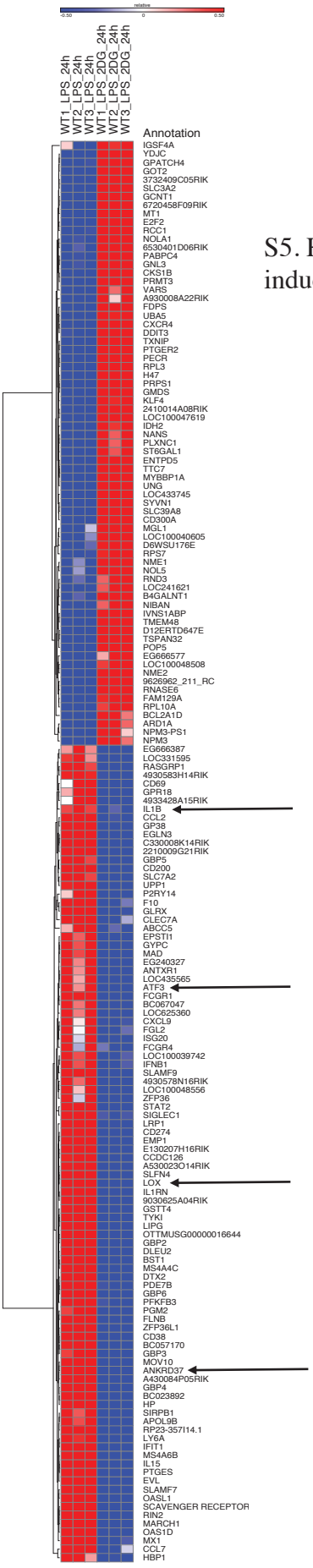
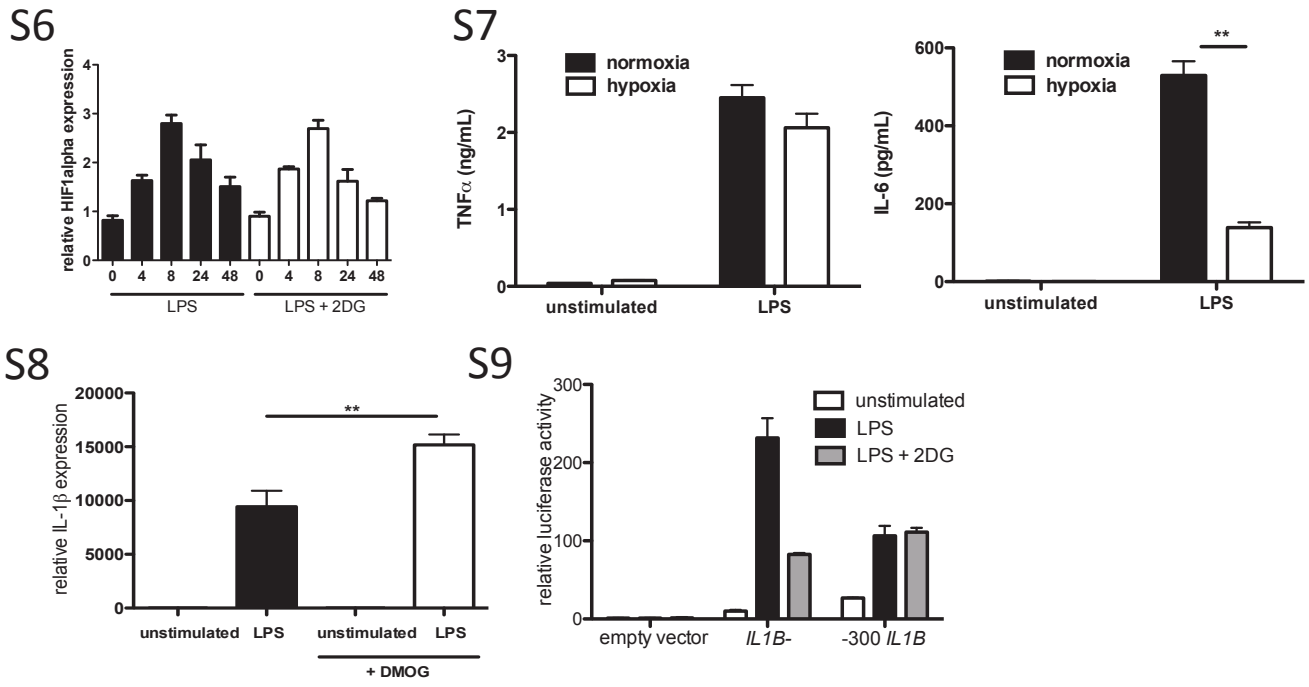


S1. LPS-or S2. *B pertussis*- induced IL-6 in BMDMs pretreated ± 2DG (1mM) for 3 h. S3. Bacterial CFU of *B pertussis* treated BMDMs were calculated following four days incubation at 37^0C . S4. IL-6 in serum of mice i.p. injected ± 2DG (2g/kg) or PBS for 3 h, then LPS or PBS solution for 1.5 h. LPS n=15; LPS+2DG n=14; 2DG n=8; vehicle n=5. Error bars ± s.e.m, * $p < 0.05$.

S5

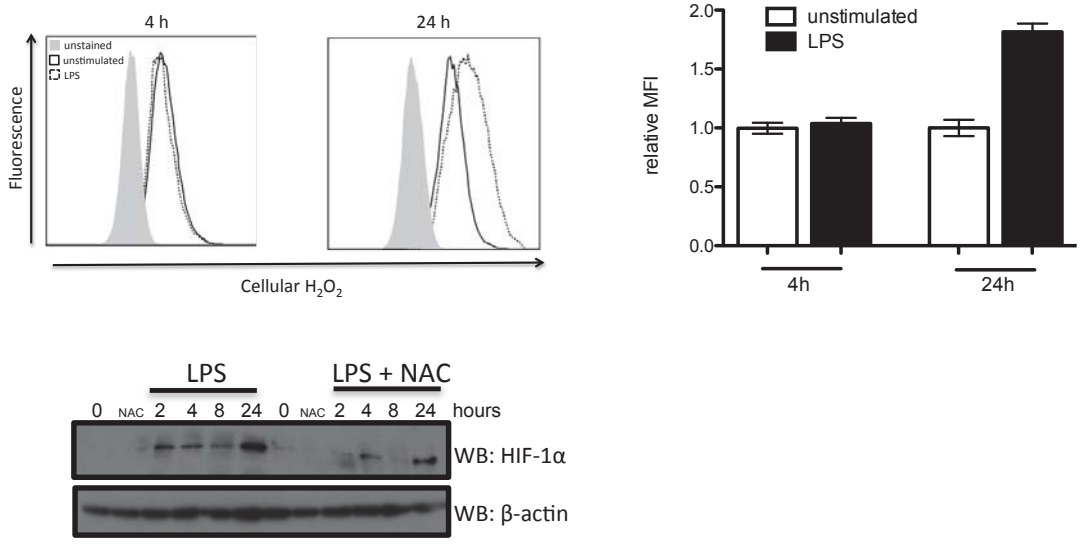


S5. Heat map representing genes regulated at 24 h by LPS that were both induced (red) and repressed (blue) by 2DG in BMDMs. n=3

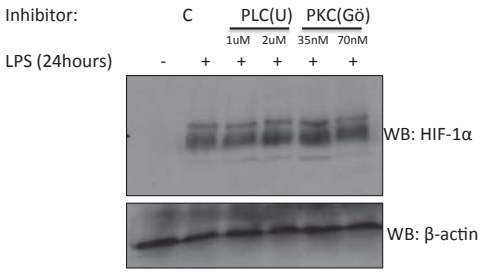


S6. HIF-1α mRNA in LPS-stimulated BMDMs, pretreated ± 2DG. S7. LPS-induced, TNFα (left panel) and IL-6 (right panel) in BMDMs incubated in either normoxia (21% oxygen, black bars) or hypoxia (1% oxygen, white bars) for 24 h and then stimulated with LPS for a further 24 h. S8. IL-1β mRNA levels in LPS-stimulated BMDMs pretreated with DMOG (200μM). Error bars ± s.e.m, * $p < 0.05$; ** $p < 0.01$. S9. RAW-264 cells transfected with the promoter region of human *IL1B* (*IL1B*-) or it's variant (-300 *IL1B)*. Promoter activity was measured by luciferase assay as relative expression over the unstimulated empty vector control (mean ±s.d.). Representative of 3 independent experiments

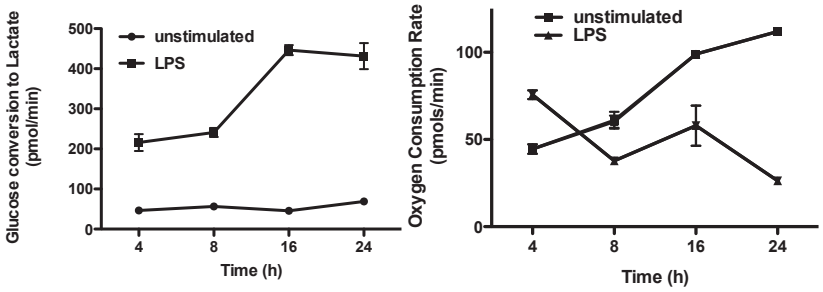
S10



S11

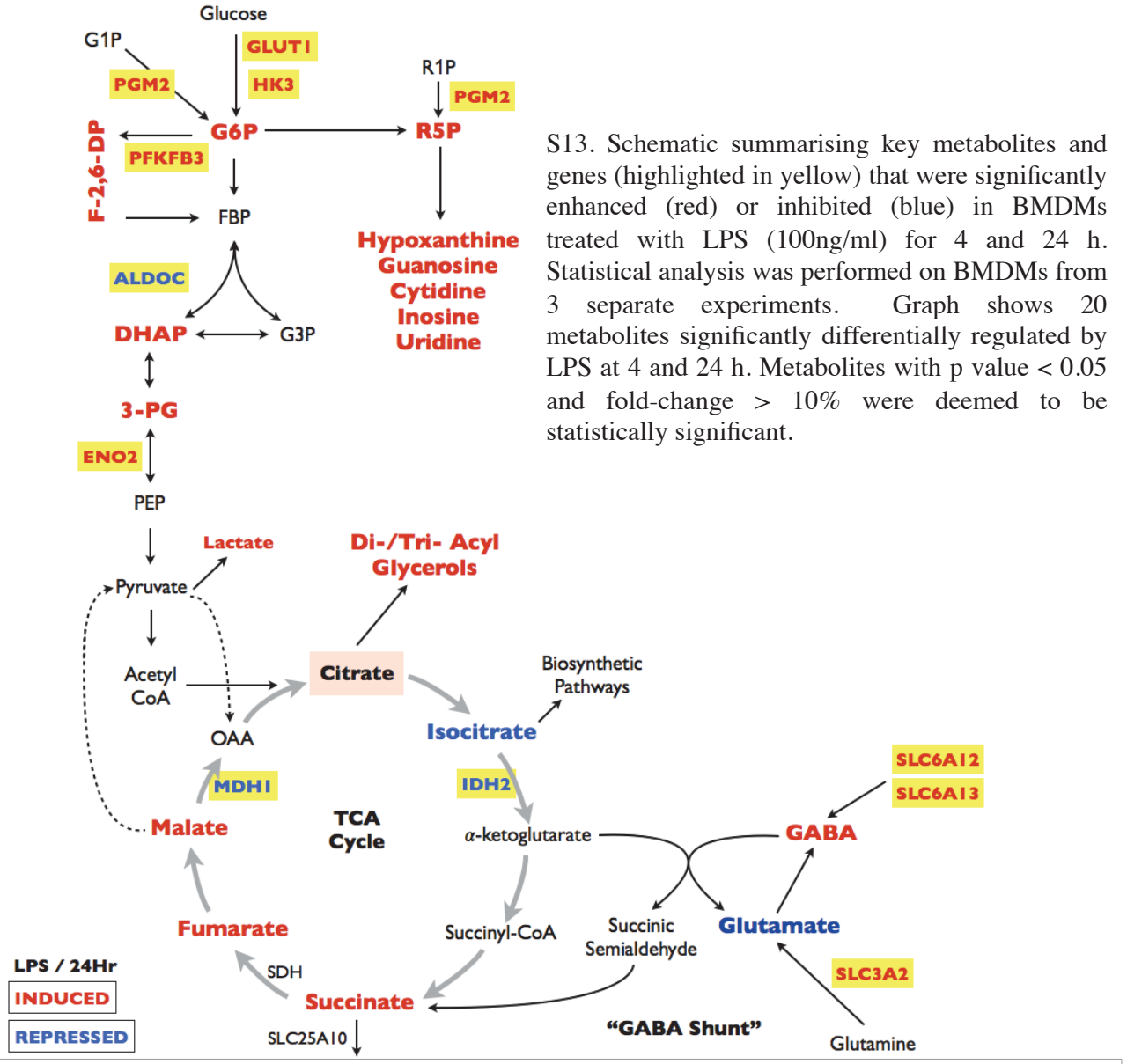


S12

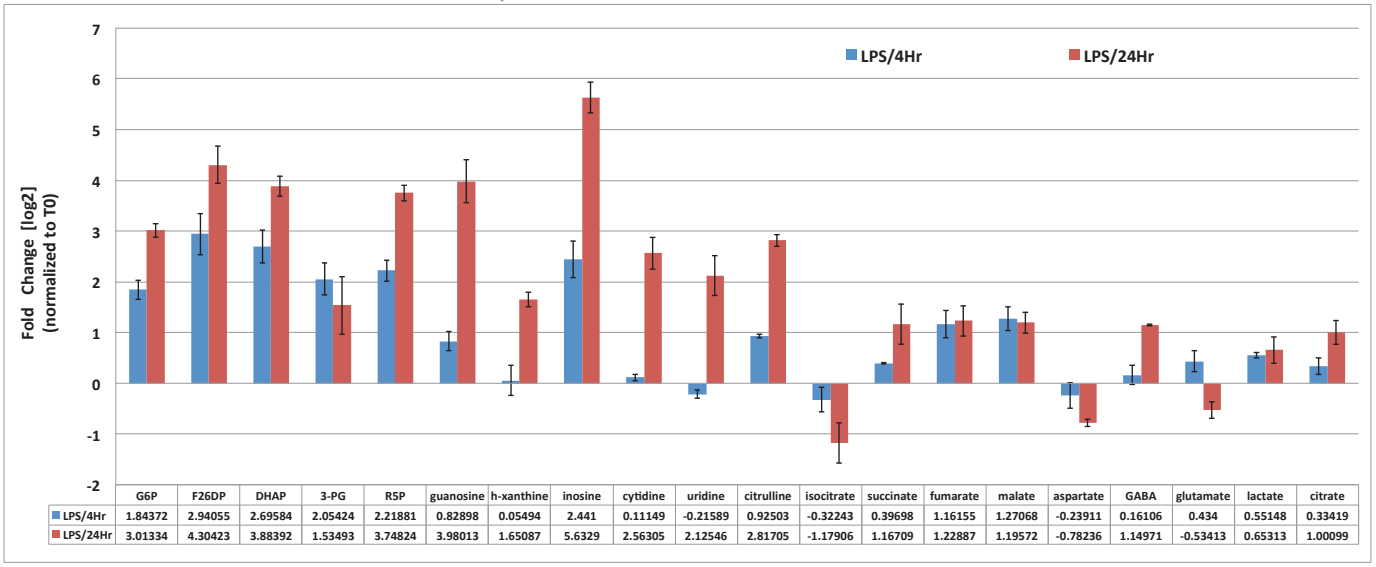


S10. BMDMs stimulated with LPS for 4 and 24 h then stained with CM-H2DCFDA and analysed by fluorescence-activated cell sorting (left panel). Quantification of three separate experiments displayed as relative mean fluorescence intensity (MFI) (right panel). HIF-1α expression in BMDMs pretreated with the antioxidant N-acetyl cysteine (NAC) (2.5mM) then LPS for up to 24 h (lower panel). S11. HIF-1α expression in LPS-stimulated BMDMs pretreated with PLC inhibitor (1 or 2μM) and PKC inhibitor (35 or 70nM). S12. BMDMs stimulated with LPS for 24 h were analysed on the Seahorse XF-24 for ECAR and OCR.

S13

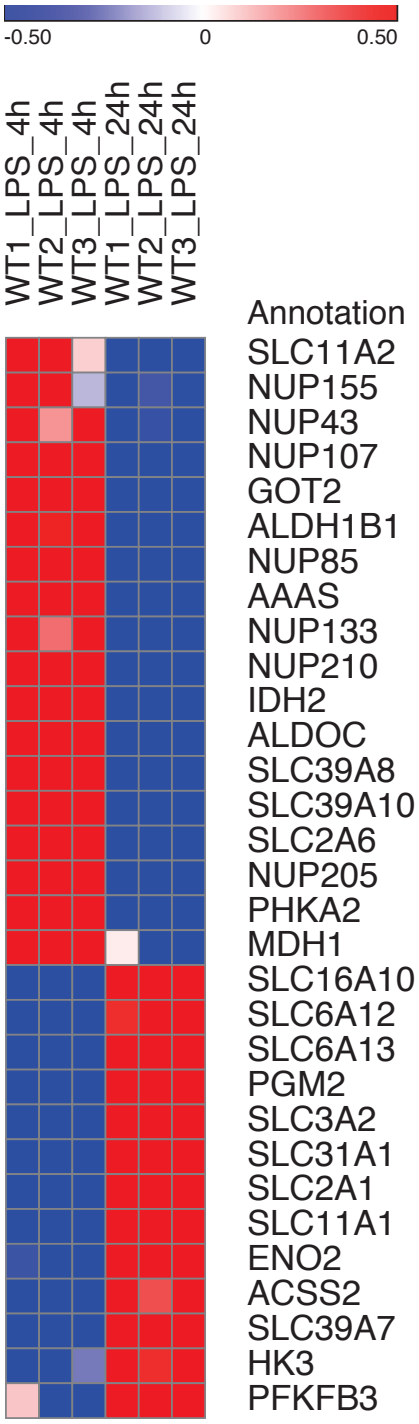


S13. Schematic summarising key metabolites and genes (highlighted in yellow) that were significantly enhanced (red) or inhibited (blue) in BMDMs treated with LPS (100ng/ml) for 4 and 24 h. Statistical analysis was performed on BMDMs from 3 separate experiments. Graph shows 20 metabolites significantly differentially regulated by LPS at 4 and 24 h. Metabolites with p value < 0.05 and fold-change > 10% were deemed to be statistically significant.

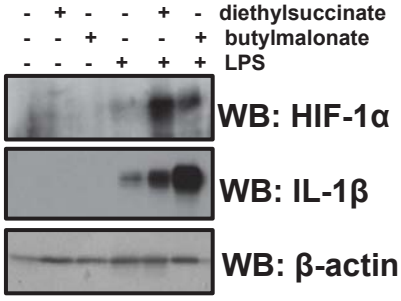


	G6P	F26DP	DHAP	3-PG	R5P	guanosine	h-xanthine	inosine	cytidine	uridine	citrulline	isocitrate	succinate	fumarate	malate	aspartate	GABA	glutamate	lactate	citrate
LPS/4Hr	1.84372	2.94055	2.69584	2.05424	2.21881	0.82898	0.05494	2.441	0.11149	-0.21589	0.92503	-0.32243	0.39698	1.16155	1.27068	-0.23911	0.16106	0.434	0.55148	0.33419
LPS/24Hr	3.01334	4.30423	3.88392	1.53493	3.74824	3.98013	1.65087	5.6329	2.56305	2.12546	2.81705	-1.17906	1.16709	1.22887	1.19572	-0.78236	1.14971	-0.53413	0.65313	1.00099

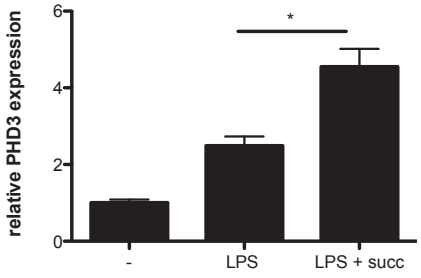
S14



S15

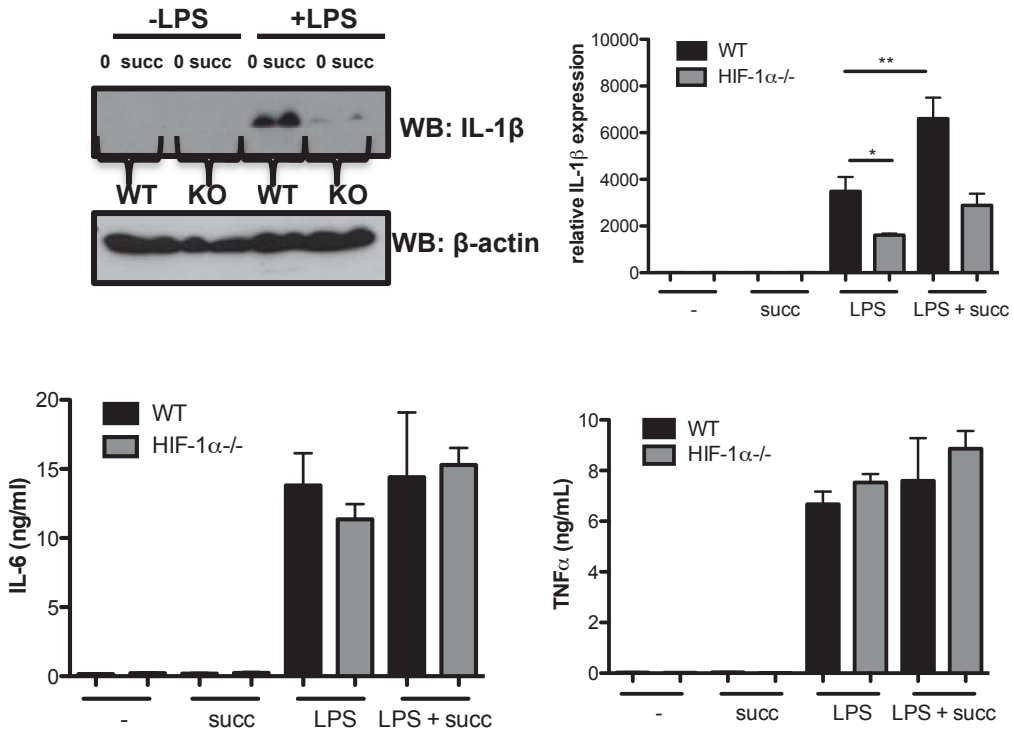


S16



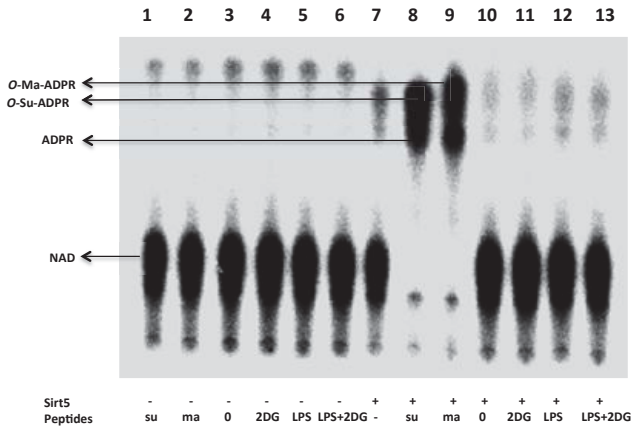
S14. Heat map representing metabolic genes regulated at 4 and 24 h by LPS that were both induced (red) and repressed (blue) in BMDMs. n=3. S15. HIF-1α and IL-1β expression in BMDMs pretreated ± diethylsuccinate (5mM) or ± butylmalonate for 3 h and LPS for 24 h. S16. PHD3 mRNA expression in BMDMs pretreated with diethylsuccinate (succ) (5mM) for 3 h and LPS for 24 h. Error ± s.e.m * $p < 0.05$.

S17

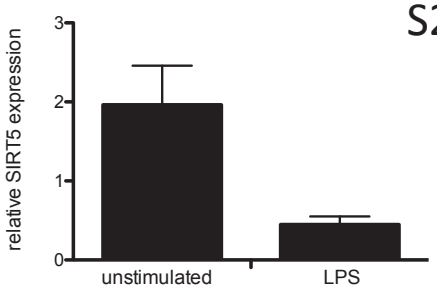


S17. IL-1β protein and mRNA (upper left and right panel) and IL-6 and TNFα (lower left and right panel) expression in WT and HIF-1α-deficient BMDMs treated ± diethyl succinate then LPS stimulated for 24 h. Error bars ± s.e.m, * $p < 0.05$; ** $p < 0.01$.

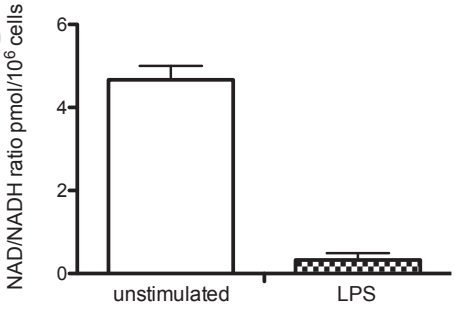
S18



S19

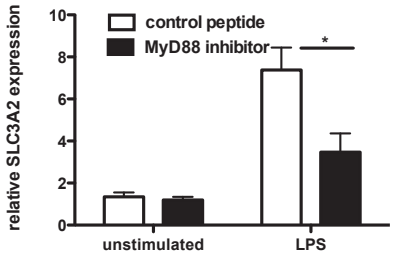


S20



S18. ^{32}P-NAD assay detecting SIRT5-catalyzed hydrolysis of succinyl and malonyl peptides, which formed ^{32}P-labeled *O*-Su-ADPR and *O*-Ma-ADPR. Trypsin digested peptides of whole BMDM cell lysates treated with LPS (lane 12) showed higher protein succinylation level compared with control group (lane 10). Synthetic H3K9 succinyl and malonyl peptides were used as positive controls (lane 8 and 9) to indicate the reference positions of *O*-Su-ADPR and *O*-Ma-ADPR. S19. SIRT5 mRNA expression in BMDMs treated with LPS for 4 h.
S20**.** NAD/NADH ratio in BMDMs treated with LPS for 24 h.

S21



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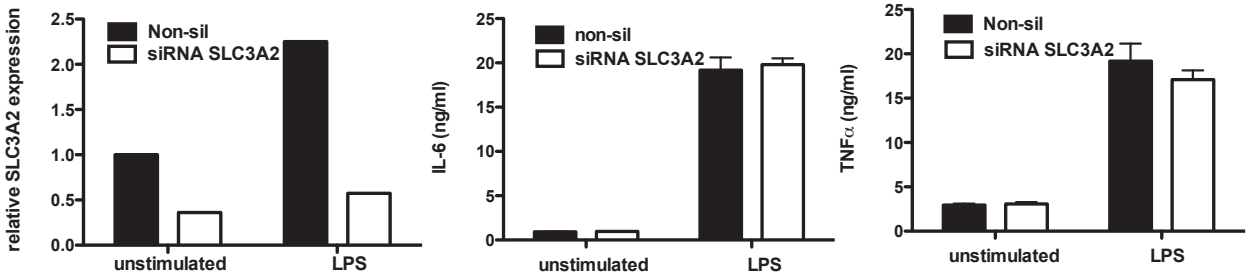

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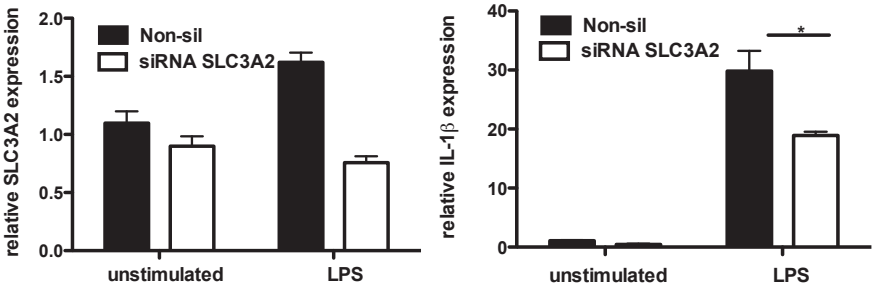
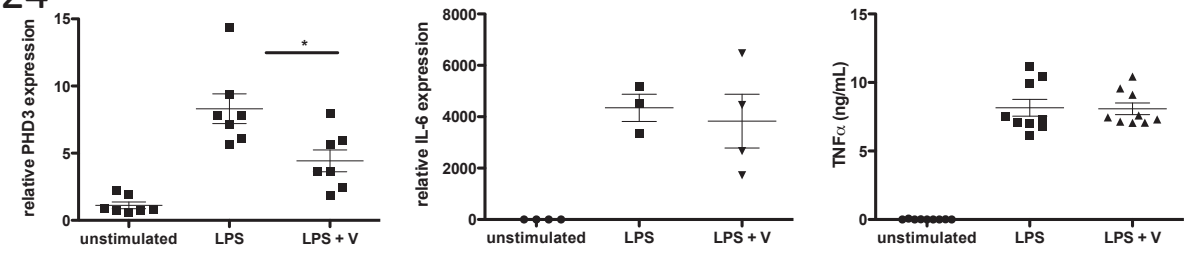
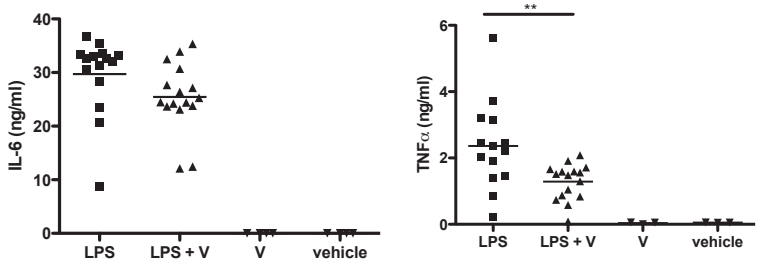


S21. SLC3A2 mRNA in LPS stimulated BMDMs pretreated with control peptide (5μM) or MyD88 inhibitory peptide (5μM) for 5 h. S22. SLC3A2 mRNA, IL-6 and TNFα protein in human PBMCs with SLC3A2 expression knocked down using 100nM siRNA compared to 100nM siRNA of a non-silencing control. Data shown is representative of 3 separate experiments Error bars, ±s.d. S23. SLC3A2 and IL-1β mRNA expression in RAW-264 cells transfected with either 100nM siRNA or 100nM siRNA of a non-silencing control. n=3. Error bars ± s.e.m, * $p < 0.05$.

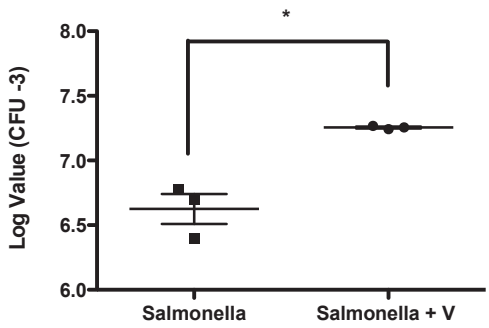
S24



S25



S26



S24. PHD3 mRNA (n=7), TNFα protein (n=9) and IL-6 mRNA (n=4) in serum-deprived LPS-stimulated BMDMs pretreated ± vigabatrin (500μM) for 30 min. S25. Mice i.p. injected ± vigabatrin (400mg/kg) or PBS for 1.5 h, then 15 mg/kg LPS or PBS for 1.5 h. Serum levels of IL-6 and TNFα. LPS n=16; LPS+vigabatrin (LPS + V) n=14; vigabatrin (V) n=3; vehicle n=3. S26. Mice i.p. injected mice ± vigabatrin (400mg/kg) or PBS for 1.5 h then infected with $1x10^6$ *Salmonella* Typhimurium UK1 i.p. for 2 h. Spleens were harvested, homogenised in PBS and following serial dilution plated onto agar plates and left at 37^0C overnight, bacterial load was assessed by colony forming units (CFU). Error bars ± s.e.m, * $p < 0.05$; ** $p < 0.01$.