**Extended Data Table 1.** Primers used in Real-Time reverse transcriptase PCR

| GENE | FORWARD SEQUENCE | REVERSE SEQUENCE |
|---|---|---|
| *Gapdh* | 5'- GCC TTC CGT GTT CCT ACC C -3' | 5'- CAG TGG GCC CTC AGA TGC -3' |
| *Ahr* | 5'- CCA CTG ACG GAT GAA GAA GGA -3' | 5'- ATC TCG TAC AAC ACA GCC TCT C -3' |
| *Cyp1a1* | 5'- GAC ACA GTG ATT GGC AGA G -3' | 5'- GAA GGT CTC CAG AAT GAA GG -3' |
| *Ido1* | 5'- TCT GCC TGT GCT GAT TGA -3' | 5'- CTG TAA CCT GTG TCC TCT CA -3' |
| *Ido2* | 5'- CTC AGA CTT CCT CAC TTA ATC G -3' | 5'- GCT GCT CAC GGT AAC TCT -3' |
| *Tdo2* | 5'- GTG AAC GAC GAC TGT CAT ACC G -3' | 5'- GCT GGA AAG GGA CCT GGA AT -3' |
| *Foxp3* | 5' - CCC AGG AAA GAC AGC AAC CTT TT -3' | 5' - TTC TCA CAA CCA GGC CAC TTG - 3' |
| *Rorc* | 5' - ACA ACA GCA GCA AGT GAT GG - 3' | 5' - CCT GGA TTT ATC CCT GCT GA - 3' |
| *Tgfb1* | 5' - CAC AGA GAA GAA CTG CTG TG- 3' | 5' - AGG AGC GCA CAA TCA TGT TG- 3' |
| *Il10* | 5' - ACC AGC TGG ACA ACA TAC TG- 3' | 5' - CGC ATC CTG AGG GTC TTC AG- 3' |

**Extended Data Table 2.** Complete list of datasets used to assess gene expression levels of tyrosine kinases in mouse myeloid dendritic cells.

| GEO accession | Platform | Total samples in series | # of un-stimulated samples | # of LPS stimulated samples | GEO accession of used samples | Reference |
|---|---|---|---|---|---|---|
| GSE28231 | MOE 430 2.0 | 5 | 1 | 1 | GSM698691<br>GSM698692 | 1 |
| GSE28340 | MOE 430 2.0 | 8 | 2 | 2 | GSM700775<br>GSM700776<br>GSM700777<br>GSM700778 | 2 |
| GSE18115 | MOE 430 2.0 | 8 | 1 | 2 | GSM452757<br>GSM452759<br>GSM452761 | 3 |
| GSE23641 | MOE 430 2.0 | 2 | 0 | 1 | GSM579979 | 4 |
| GSE16761 | MOE 430 2.0 | 3 | 1 | 1 | GSM420166<br>GSM420165 | 5 |
| GSE10246 | MOE 430 2.0 | 182 | 2 | 0 | GSM258647<br>GSM258648 | 6 |
| GSE7219 | MOE 430 2.0 | 12 | 3 | 0 | GSM173580<br>GSM173581<br>GSM173582 | 7 |

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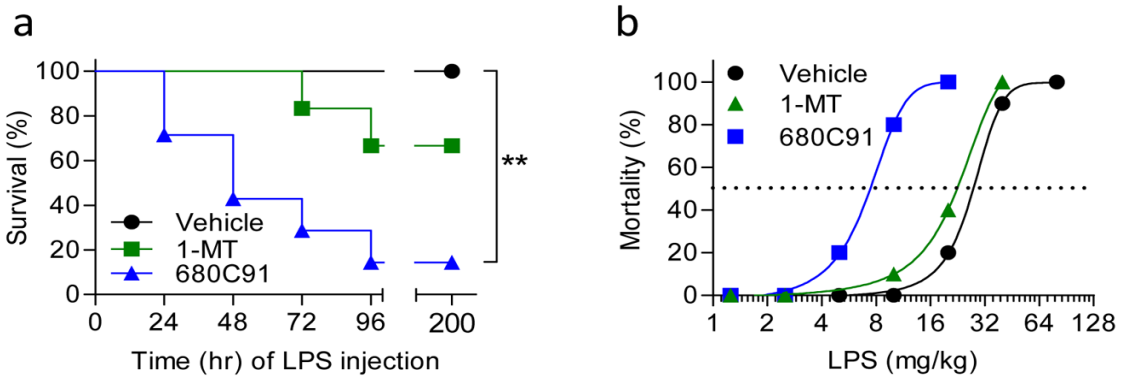
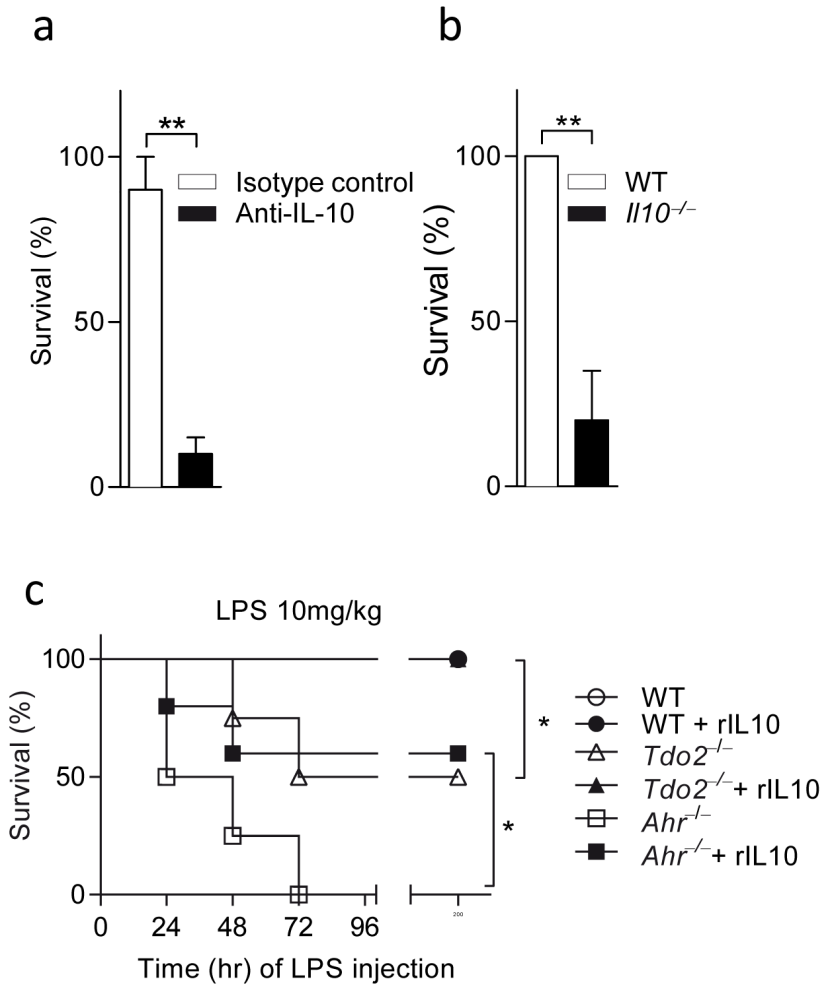
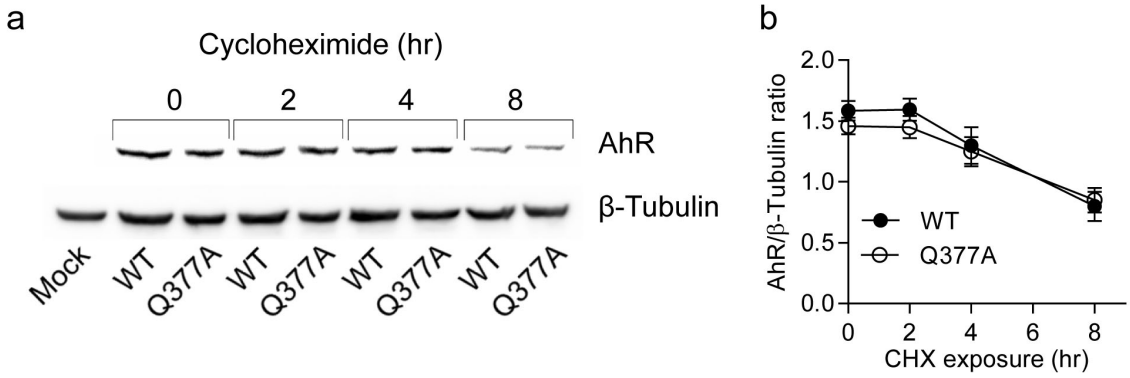


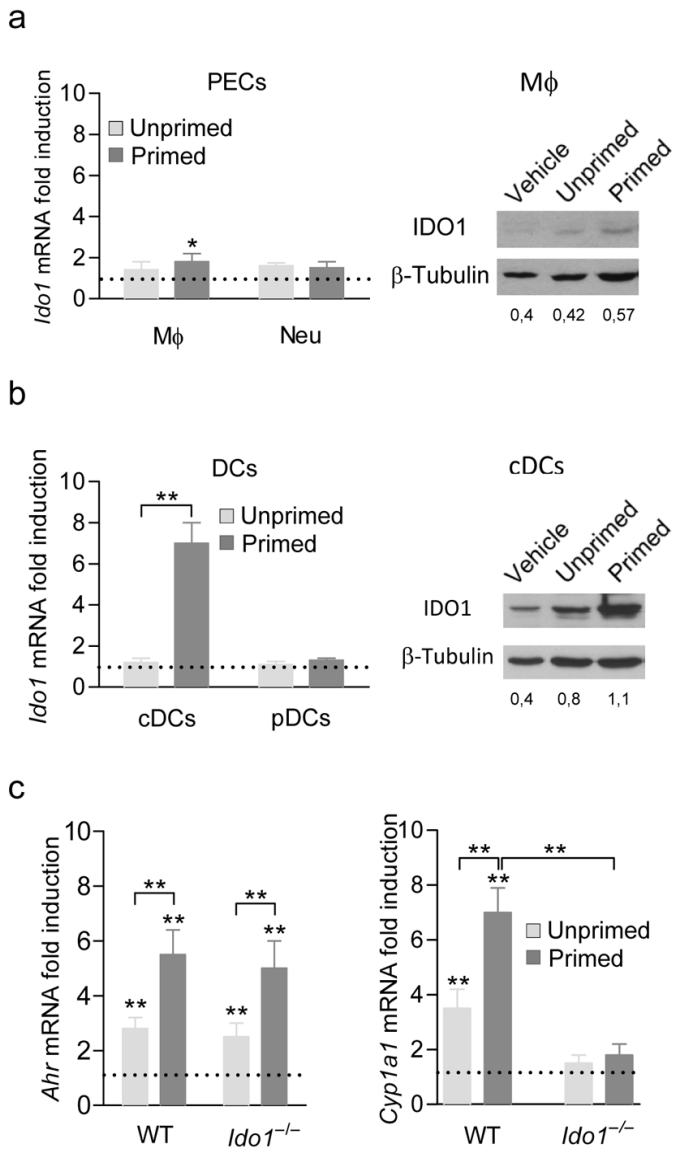

**Extended Data Fig. 1. Increased susceptibility to primary LPS challenge in mice treated with a TDO2 inhibitor.** (**a**) Twelve hours before LPS challenge (10 mg/kg), WT mice were treated with vehicle, the IDO1 and IDO2 inhibitor 1-MT (200 mg/kg), or the TDO2 inhibitor 680C91 (10 mg/kg), control groups receiving 1-MT or 680C91 but no LPS. Survival was monitored every 24 h through day 8 of LPS challenge ($n$ = 10 mice per group per experiment, in one out of three). $^{**}P < 0.001$ (log-rank test). (**b**) Estimation of $LD_{50}$ (mg/kg) in mice treated with 1.25, 2.5, 5, 10, 20, 40, or 80 mg/kg LPS. $n$ = 10 per group per dose. $LD_{50}$ values were calculated by curve-fitting ($r^2 \geq 0.95$) in one experiment representative of two.



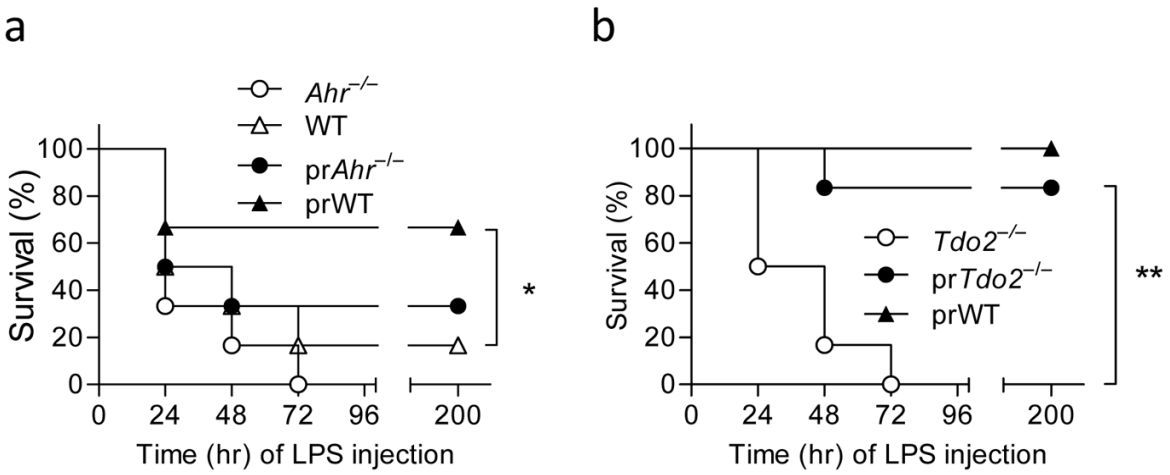

**Extended Data Fig. 2. Lack of endogenous IL-10 increases susceptibility to endotoxemia.** (**a**) Survival of WT mice exposed to 10 mg/kg LPS in the presence of anti–IL-10 (0.2 mg/mouse daily, for 4 d, commencing 6 h before challenge) or an isotype control. Data are from three independent experiments (mean ± s.d.). (**b**) Survival of WT and *Il10*$^{-/-}$ mice treated with 10 mg/kg LPS. $^{**}P < 0.001$ (log-rank test). (**c**) Survival curves of mice of different genotypes challenged with 10 mg/kg LPS, with or without therapeutic subcutaneous IL-10 at 250 ng/mouse, daily, from challenge (day 0) through day 5. $^{*}P < 0.05$ (IL-10 *vs.* vehicle). The data show that exogenous IL-10 compensates for both the TDO2 and AhR defects at the lower LPS dosage. IL-10 is protective only in TDO2 knockouts when 20 mg/kg LPS is used.



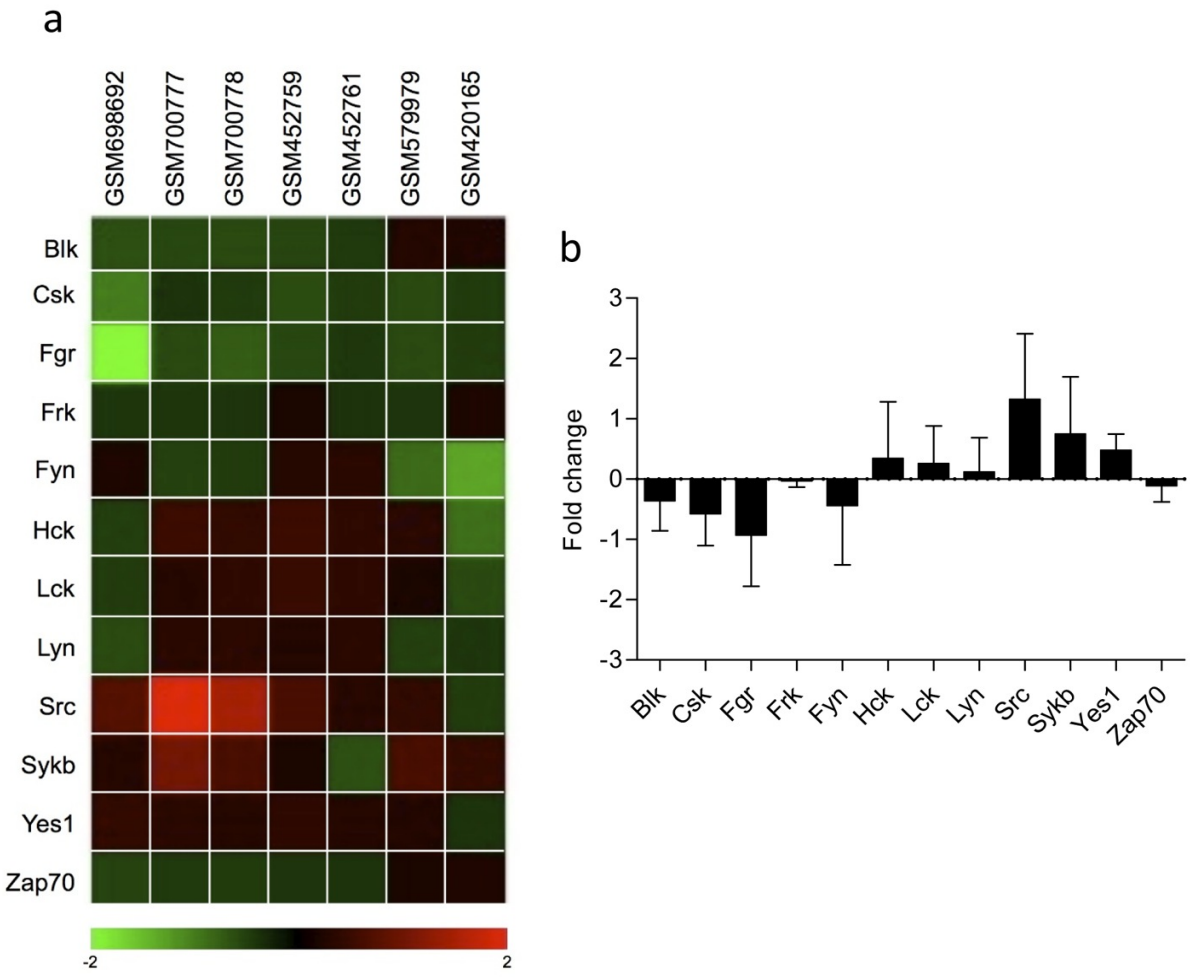

**Extended Data Fig. 3. Mutation of Gln377 to Ala in AhR PAS-B domain does not alter receptor half-life, and apparently results in increased TCDD ligand potency.** (**a**) AhR-deficient cDCs were transfected with WT or Q377A AhR. After 24 h, cells were incubated with cycloheximide (CXM) (10 μg/ml) and harvested at different times, lysed, and analyzed for AhR expression by immunoblotting, using a specific antibody. β-tubulin was used as a loading control. Data are from one experiment of three. (**b**) Ratios (means ± s.d. of three experiments) of WT or Q377A AhR to β-tubulin in transfected cDCs at different times of CHX treatment . (No differences by Student's *t*-test.)



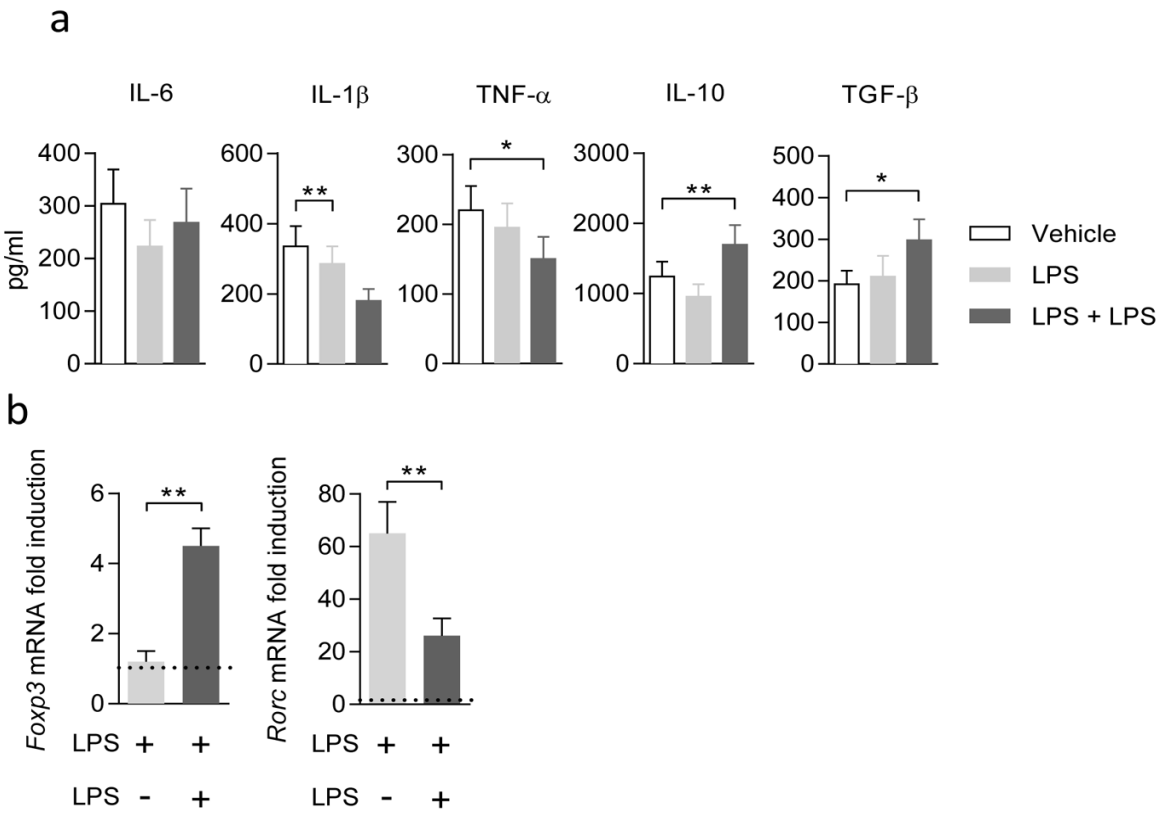

**Extended Data Fig. 4. LPS tolerance potentiates IDO1 expression and AhR activation in splenic cDCs.** (**a**) Real-time PCR analysis of *Ido1* mRNA expression and immunoblot analysis of IDO1 protein in peritoneal exudate macrophages (MΦ) and neutrophils (Neu) (**a**), as well as in splenic conventional DCs (cDCs) or plasmacytoid DCs (pDCs) (**b**). Cells were harvested and purified at 24 (**a**) or 72 (**b**) h of LPS rechallenge. For comparison, samples were included from mice on first exposure to 40 mg/kg LPS (unprimed), as opposed to tolerized mice (primed). Data of *Ido1* mRNA fold induction are presented as in **Fig. 2a** (mean ± s.d. of three experiments; **P* < 0.05 and ***P* < 0.001, Shapiro test). Immunoblotting data are from one experiment of three. (**c**) Real-time PCR analysis of *Ahr* and *Cyp1a1* transcript expressions in cDCs from the same mice as in **b.** ***P* < 0.001, Shapiro test.



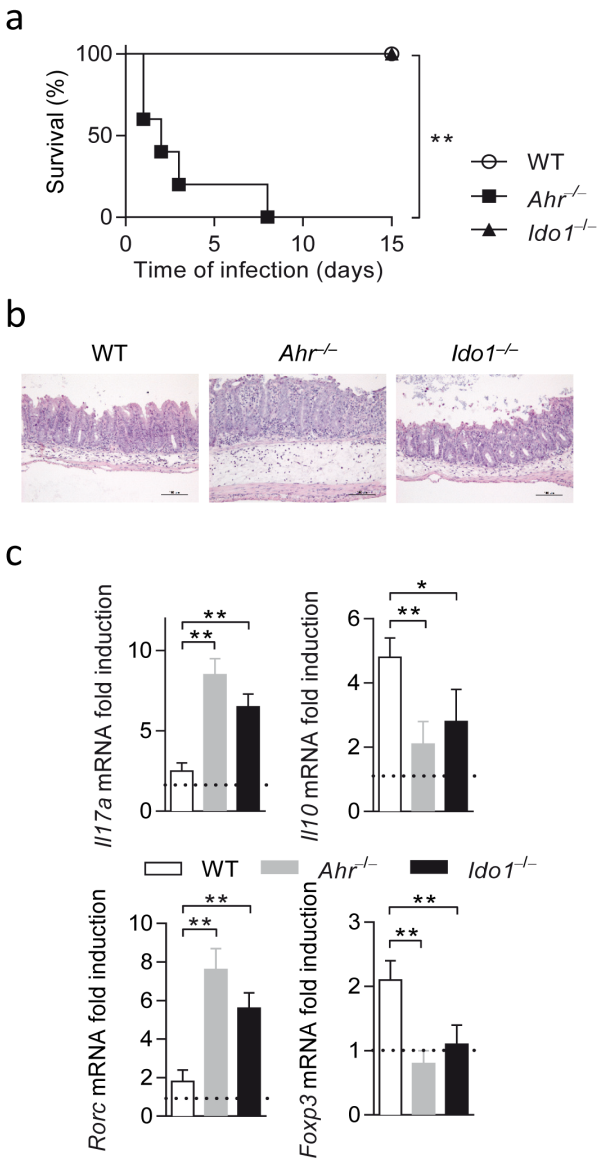

**Extended Data Fig. 5. Absolute requirement for functional AhR, but not TDO2, in LPS tolerance manifestations.** (**a**) Survival curves of WT and LPS-primed (0.5 mg/kg, day 0) WT (prWT) and AhR-deficient (pr*Ahr*$^{-/-}$) mice after a second challenge (on day +7) with 40 mg/kg LPS. Survival was monitored every 24 h through day 8 of LPS challenge. $n$ = 8–10 mice per group per experiment. One experiment of three. *$P$ < 0.05, log-rank test. (**b**) Survival curves of WT and LPS-primed (10 mg/kg, day 0) WT (prWT) and TDO2-deficient (pr*Tdo2*$^{-/-}$) mice after a second challenge (on day +7) with 40 mg/kg LPS. Survival was monitored every 24 h through day 8 of LPS challenge. $n$ = 8–10 mice per group per experiment. One experiment of three. **$P$ < 0.001, log-rank test.



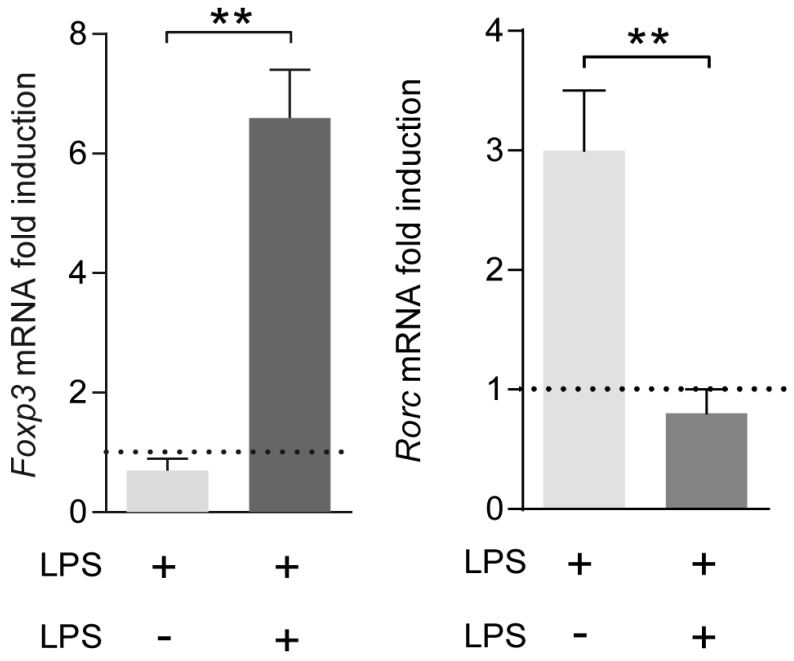

**Extended Data Fig. 6. Bioinformatic data from myeloid cDCs data sets, as follows**, (**a**) expression changes of tyrosine kinases in LPS-primed myeloid DCs as compared to untreated counterparts, and (**b**) $\log_2$ fold changes, depicted as mean values and standard errors.



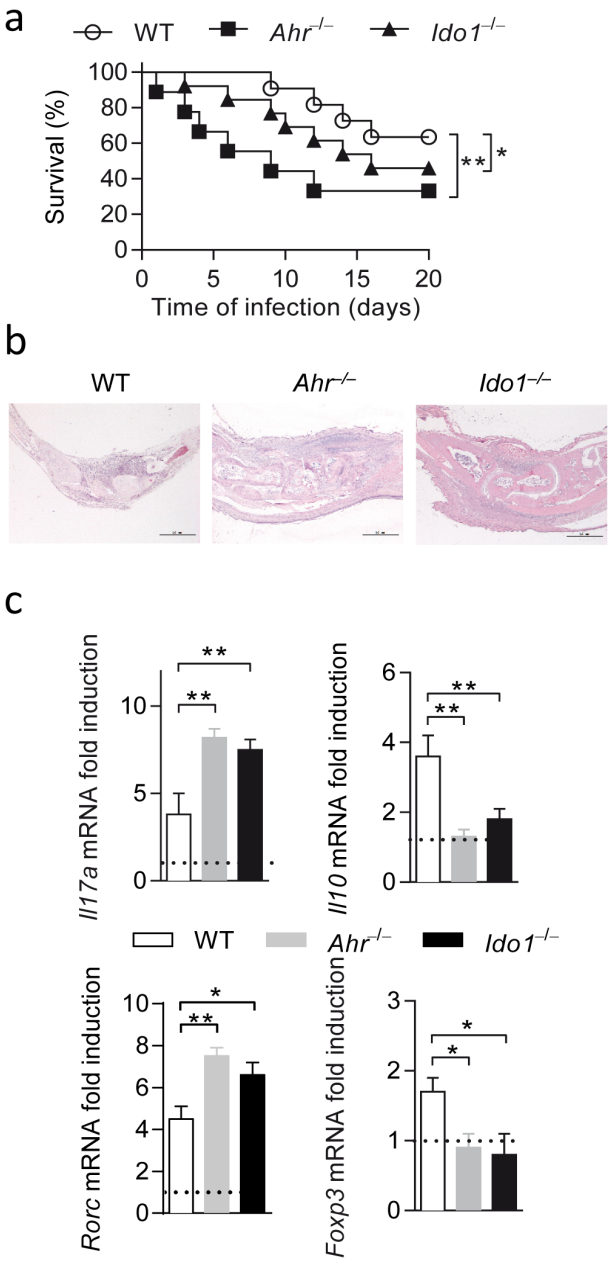

**Extended Data Fig. 7. LPS tolerance modulates cytokine production and *Foxp3* and *Rorc* transcription in *S.* Typhimurium infection.** (**a**) IL-6, IL-1β, TNF-α, IL-10, and TGF-β were measured in cecum cell supernatants from LPS-tolerant mice infected with *S. enterica* Typhimurium. Data are from three independent experiments (means ± s.d.). **P* < 0.05 and ***P* < 0.001 (Student's *t*-test). (**b**) RT-PCR expression of *Foxp3* and *Rorc* transcripts in mesenteric lymph node cells from LPS-tolerant, *Salmonella*-infected mice. Data (mean ± s.d. of three experiments) are presented as normalized transcript expression in the samples relative to normalized transcript expression in control cultures (that is, cells from vehicle-treated mice, in which fold change = 1; dotted line). **P* < 0.05; ***P* < 0.001 (Shapiro test).




**Extended Data Fig. 8. *Ahr*$^{-/-}$ and *Ido*$^{-/-}$ mice are more susceptible than WT mice to *S.* Typhimurium infection.** (**a**) Naïve mice of different genotypes were challenged intragastrically with *S.* Typhimurium. Mortality data were recorded (**$P$ < 0.001, WT *vs.* all other genotypes; log-rank test) and (**b**) H&E staining of mouse ceca was performed at 7 days of infection. Scale bars, 50 μm. One of three experiments. (**c**) Transcript expressions of *Il17a*, *Rorc*, *Il10*, and *Foxp3* were quantified in mesenteric lymph node cells. Data (mean ± s.d. of three experiments) are presented as normalized transcript expression in the samples relative to normalized transcript expression in cells from uninfected donors, in which fold change = 1. **$P$ < 0.001 (Shapiro test).




**Extended Data Fig. 9. LPS tolerance modulates Foxp3 and *Rorc* transcription in GBS infection**. RT-PCR expression of *Foxp3* and *Rorc* transcripts in joint-draining lymph node cells from LPS-tolerant, GBS-infected mice. Data (mean ± s.d. of three experiments) are presented as normalized transcript expression in the samples relative to normalized transcript expression in control cells (that is, cells from vehicle-treated mice, in which fold change = 1; dotted line). $^{**}P < 0.001$ (Shapiro test).




**Extended Data Fig. 10. *Ahr*$^{-/-}$ and *Ido*$^{-/-}$ mice are more susceptible than WT mice to GBS immunopathology.** (**a**) Naïve mice of different genotypes were infected with GBS ($1 \times 10^7$ CFU). Mortality data were recorded (*$P < 0.05$ and **$P < 0.001$, WT *vs.* all other genotypes; log-rank test). (**b**) H&E staining of joints was performed at 10 days of infection. Scale bars, 100 μm. One of three experiments. (**c**) Transcript expressions of *Il17a*, *Rorc*, *Il10*, and *Foxp3* were quantified in joint-draining lymph nodes. Data (mean ± s.d. of three experiments) are presented as normalized transcript expression in the samples relative to normalized transcript expression in cells from uninfected donors, in which fold change = 1. **$P < 0.001$ (Shapiro test).