

Figure S1. Related to Fig. 1 and 3: Lactate utilization by *S. Tm* *in vitro*. (A-C) Mucin broth supplemented with 20 mM lactate and 40 mM of the indicated electron acceptors was inoculated with an equal mixture of the *S. Tm* wild-type strain (WT) and the indicated mutants. The culture was incubated anaerobically (mock, tetrathionate, nitrate) or aerobically (O_2) with shaking for 18 h. After incubation, diluted samples were plated on selective media to determine the competitive index. (A) Effect of various terminal electron acceptors on LldD and Dld-mediated lactate utilization. (B) Stereospecificity of LldD in *S. Tm*. (C) Effect of sodium oxamate on *S. Tm* lactate oxidation *in vitro*. Sodium oxamate was added at a final concentration of 5 % (w/v) as indicated.

$S_4O_6^{2-}$, tetrathionate; NO_3^- , nitrate. DL-lactate is an equal mixture of the two enantiomers. Composite data for at least 4 biological replicates is shown. Bars represent geometric means \pm standard error. **, $P < 0.01$; ***, $P < 0.001$. ns, not statistically significant.

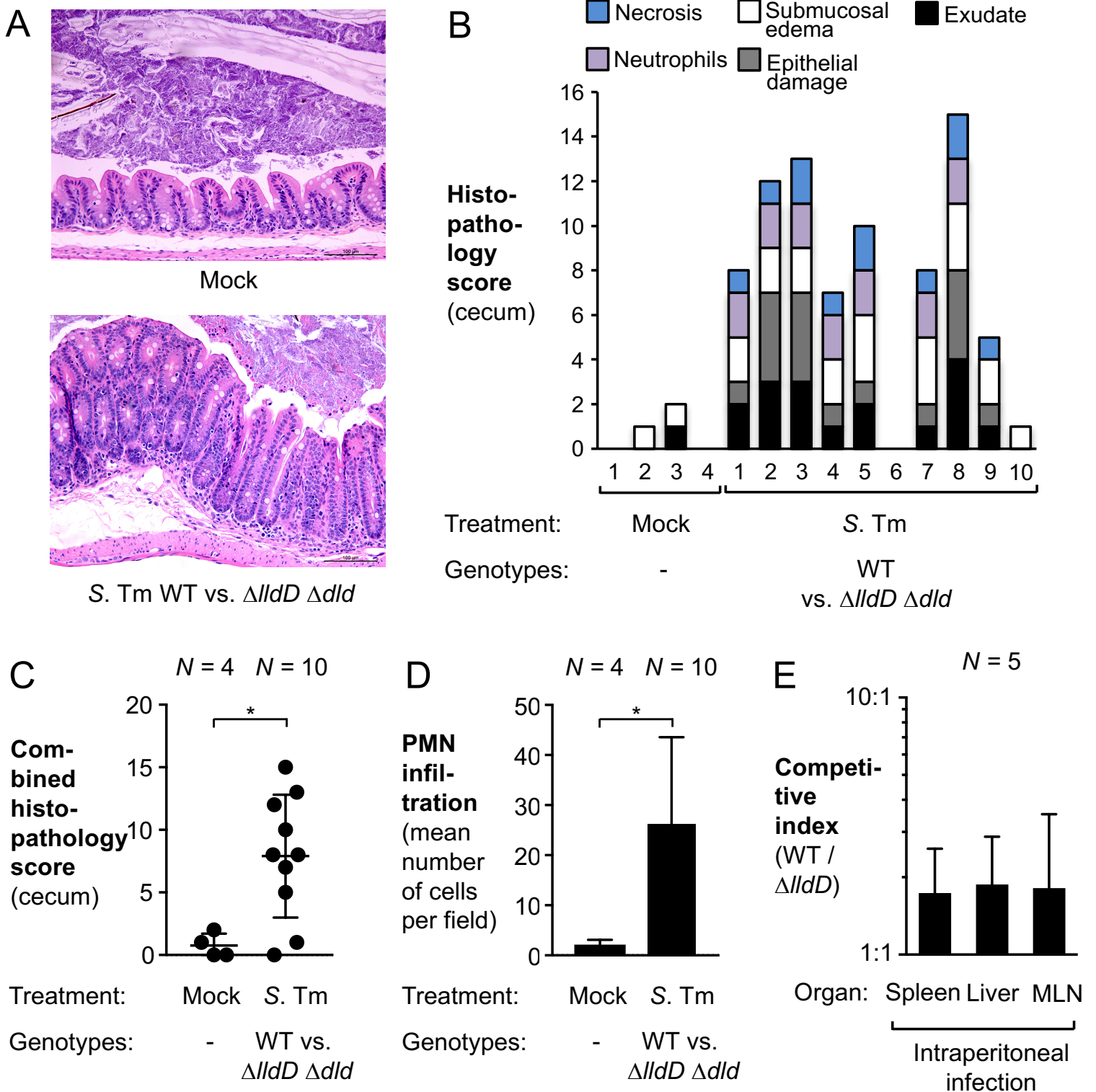


Figure S2. Related to Fig. 1: S. Tm-induced pathological changes in the cecal mucosa of Swiss Webster mice. (A-D) Groups of Swiss Webster mice were intragastrically inoculated with a 1:1 ratio of the S. Tm wild-type strain (WT) and the $\Delta IldD \Delta dld$ mutant or were mock-treated with LB broth as described in Fig. 1B. Samples were collected 8 days after infection. One mouse was not analyzed due to the lack of samples. (A) Representative images of H+E stained cecal tissue. Scale bar, 100 μ m (B) Individual histopathology scores for pathological changes in the cecum. Each bar represents one animal. (C) Combined Histopathology Score from data shown in panel B. Each symbol represents one animal; centerlines represent the average \pm standard deviation. (D) Infiltration of PMNs into the cecal tissue. 10 fields per animal were examined. Bars are means \pm standard deviation. (E) C57BL/6 mice were infected with S. Tm wild-type and the $\Delta IldD$ mutant in equal numbers via intraperitoneal injection. 3 days after infection samples of liver, spleen, and mesenteric lymph nodes (MLN) were collected, homogenized and plated on selective agar to determine the competitive index. Bars are geometric means \pm SEM. The number of animals per group (N) is indicated above each bar. *, $P < 0.05$.

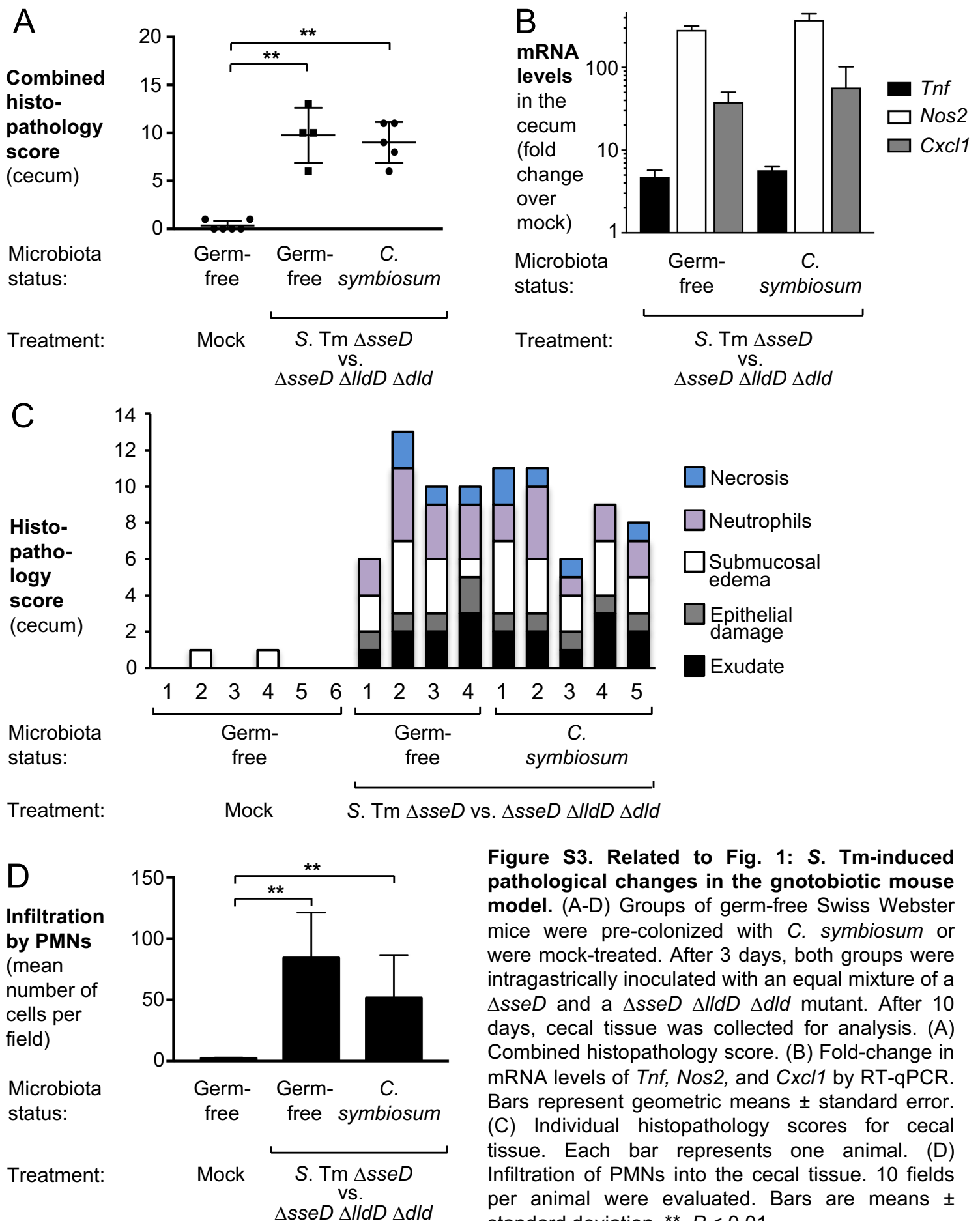


Figure S3. Related to Fig. 1: *S. Tm*-induced pathological changes in the gnotobiotic mouse model. (A-D) Groups of germ-free Swiss Webster mice were pre-colonized with *C. symbiosum* or were mock-treated. After 3 days, both groups were intragastrically inoculated with an equal mixture of a Δ *sseD* and a Δ *sseD* Δ *lldD* Δ *dld* mutant. After 10 days, cecal tissue was collected for analysis. (A) Combined histopathology score. (B) Fold-change in mRNA levels of *Tnf*, *Nos2*, and *Cxcl1* by RT-qPCR. Bars represent geometric means \pm standard error. (C) Individual histopathology scores for cecal tissue. Each bar represents one animal. (D) Infiltration of PMNs into the cecal tissue. 10 fields per animal were evaluated. Bars are means \pm standard deviation. **, $P < 0.01$. The number of animals per group (N) is indicated in panel C. See also Fig. S4.

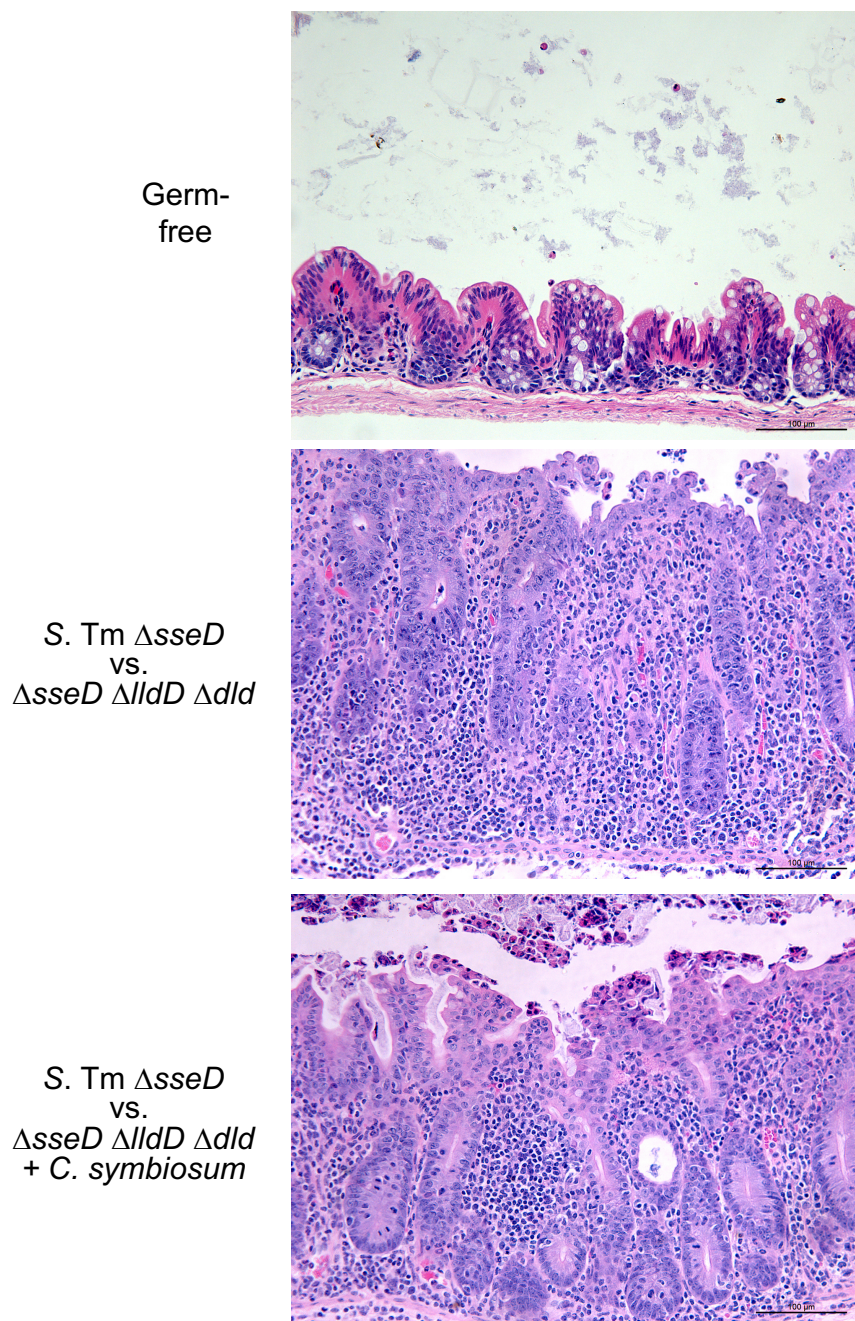


Figure S4. Related to Fig. 1: *S. Tm*-induced pathological changes in the gnotobiotic mouse model. Groups of germ-free Swiss Webster mice were pre-colonized with *C. symbiosum* or were mock-treated. After 3 days, both groups were intragastrically inoculated with an equal mixture of a Δ *sseD* and a Δ *sseD* Δ *lldD* Δ *dld* mutant. After 10 days, cecal tissue was collected for analysis. Representative images of H+E stained sections of the cecum. Scale bar, 100 μ m. See also Fig. S3.

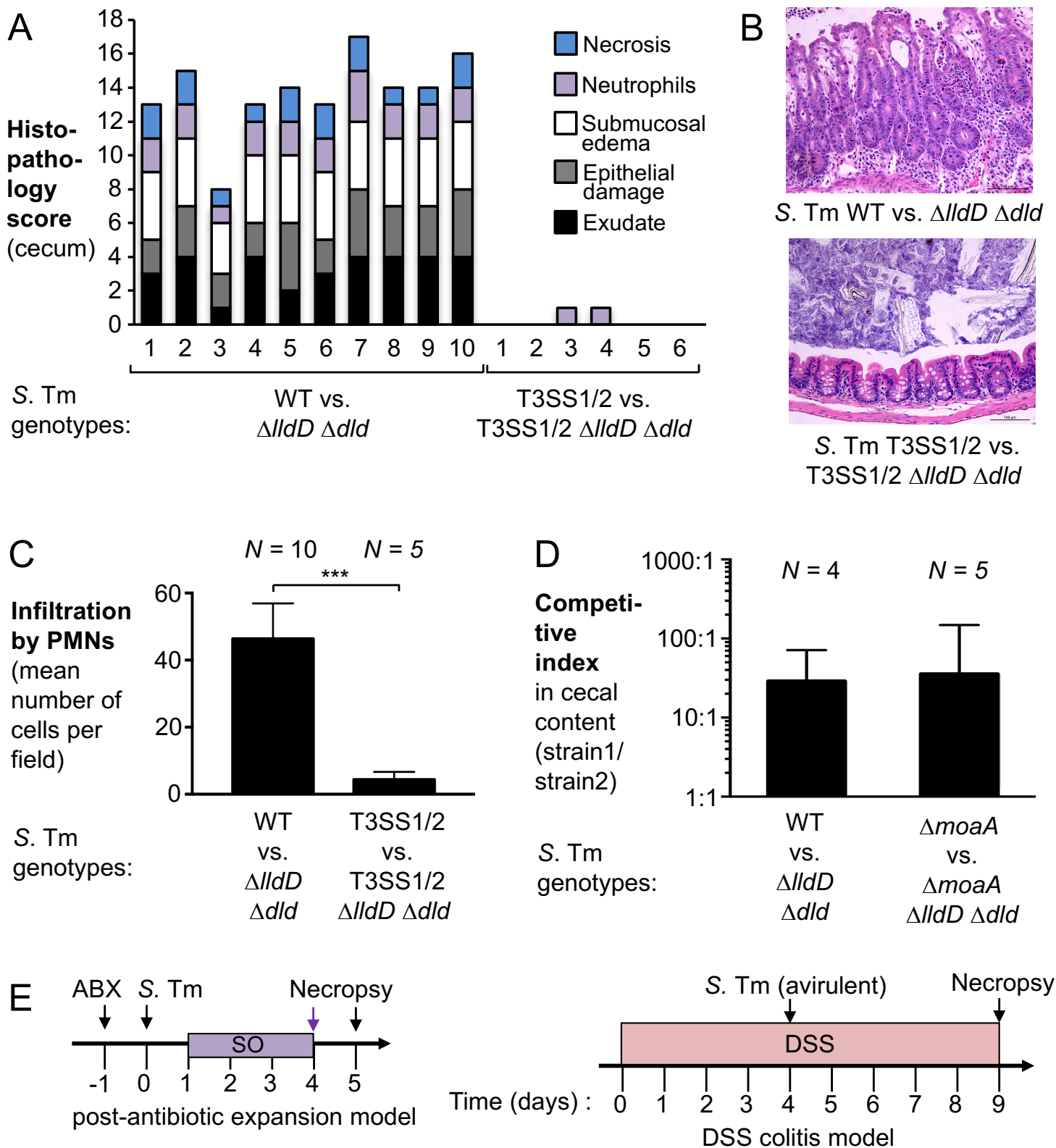


Figure S5. Related to Fig. 3 and 6: Lactate utilization in the streptomycin-treated mouse model of Salmonellosis. (A-D) Streptomycin-pretreated C57BL/6 mice were intragastrically infected with an equal mixture of the indicated *S. Tm* strains. Five days after infection, samples were collected for analysis. T3SS1/2, $\Delta invA \Delta spiB$ mutant. (A) Individual histopathology scores of cecal tissue. Each bar represents one animal. (B) Representative images of H&E stained cecal sections. Scale bar, 100 μm . (C) Infiltration of PMNs into cecal tissue. 10 fields were evaluated per animal. (D) Cecal content was collected and the competitive index of the indicated strains was determined. (E) Schematic representation of the post-antibiotic expansion model and the dextran sulfate sodium (DSS)-induced colitis model. ABX, oral antibiotic treatment. In one experiment, animals were treated with sodium oxamate (SO). Bars represent means \pm standard deviation. ***, $P < 0.001$. The number of animals per group (N) is indicated above each bar.

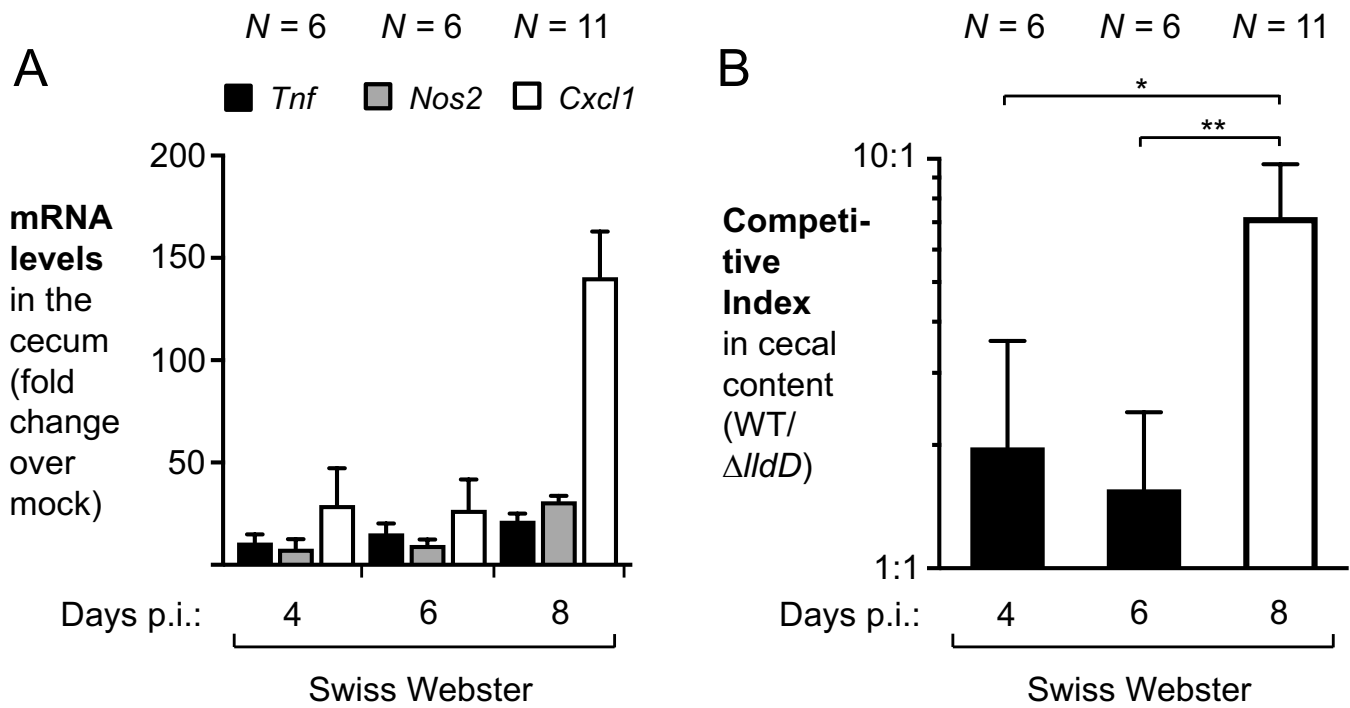


Figure S6. Related to Fig. 1 : Time course of *S. Tm* infection in Swiss Webster mice. Swiss Webster mice were intragastrically infected with with an equal mixture of the *S. Tm* wild-type strain (WT) and the Δ *lldD* mutant. Samples were collected 4, 6, and 8 days post infection (p.i.). (A) mRNA levels of *Tnf* (black bars), *Nos2* (gray bars), and *Cxcl1* (white bars) in cecal tissue were determined by RT-qPCR. (B) The competitive index in the cecal content at each time point was determined. The data for the day 8 time point (white bar) is also shown in Fig. 1B and is given here for reference. Bars represent the geometric mean \pm standard error. *, $P < 0.05$; **, $P < 0.01$. The number of animals per group (N) is indicated above each bar.

Supplemental Table 1: Metabolic profiling of cecal content. Related to Fig. 1.

Putative Compound	Relative abundance (average peak area as % of total)	
	Un- infected	S. Tm infected
Lactic acid	0.005	0.38
3-Hydroxy-azetidine-1-carboxylic acid	0.005	0.14
Propargyl alcohol	0.005	0.075
Cholesterol	0.005	0.04
<i>N</i> -Acetylaspartic acid	0.005	0.04
cis-1,4-Cyclohexanedicarboxylic acid	0.005	0.03
Pentanedioic acid	0.005	0.03
Uric acid	0.005	0.03
5-Bromoisatin-3-oxime	0.005	0.02
3,3-Dimethyl-2-butanol	0.005	0.02
Tryptophan	0.005	0.02
3-Methoxy-5-prop-2-en-1-yl-2-[(trimethylsilyl)oxy]- <i>N</i> -{2-[(trimethylsilyl)oxy]ethyl}benzamide	0.005	0.01
4-Coumaric acid	0.005	0.01
Butanal	0.005	0.01
Dodecane	0.005	0.01
Hexanoic acid	0.005	0.01
Nonanoic acid	0.005	0.01
Tetrapentacontane	0.005	0.01
Urea	0.005	0.005
Sinapinic acid	0.005	0.005
Thymidine	0.005	0.005
Isosorbide	0.005	0.005
Hexadecanedioic acid	0.005	0.005
4'-(Salicylideneamino)acetanilide	0.005	0.005
9-methylheptadecane	0.005	0.005
Aconitic acid	0.005	0.005
Cyclooctasiloxane	0.005	0.005
Phenol	0.005	0.005
Dodecanoic acid	0.01	0.02
Glycerol	0.01	0.01
Ferulic acid	0.01	0.005
Alpha-ketoglutaric acid	0.01	0.005
Phenylalanine	0.015	0.04
5-Aminovaleric acid	0.015	0.01
Methionine	0.02	0.02
Aspartic acid	0.02	0.015
2-Phenylquinoline-4-carboxylic acid <i>N</i> -oxide	0.02	0.01

Threonine	0.02	0.01
4,4-Dimethoxy-2-methyl-2-butanol	0.02	0.005
4-Hydroxybenzoic acid	0.02	0.005
Docosanoic acid	0.02	0.005
Glucuronic acid	0.02	0.005
Hexasiloxane	0.02	0.005
Isocitric acid lactone	0.02	0.005
Methyldiethanolamine	0.02	0.005
Valine	0.025	0.04
Glycolic acid	0.025	0.005
Leucine	0.03	0.05
Tyrosine	0.03	0.03
Meglutol	0.03	0.005
Bisphenol A	0.03	0.005
2,8,10,12,18-Pentamethyl-3,7,13,17-tetraethyl-21H,23H-porphine	0.03	0.005
Pyroglutamic acid	0.03	0.005
Serine	0.035	0.02
Hypoxanthine	0.035	0.01
Citric acid	0.035	0.005
3-amino-1,2,4-triazole	0.04	0.045
Piperidine	0.04	0.04
2-Hydroxy-4-(methylsulfonyl)isophthalic acid	0.04	0.01
Lysine	0.045	0.055
2-Hexanol	0.05	0.005
5-nitrobarbiturate	0.05	0.005
Alanine	0.06	0.055
Pentanoic acid	0.08	0.005
Dimethyl 2-methoxyhexane-1,6-dioate	0.085	0.005
Glyceric acid	0.095	0.005
Tartaric acid	0.11	0.005
Guanidine	0.18	0.005
Glutamic acid	0.33	0.055
Butyric Acid	0.65	0.09

Supplemental Table 2: Histopathology scoring criteria. Related to Fig. 3, S2, S3, and S5.

Score	Exudate	Epithelial damage	Infiltration by PMNs*	Necrosis	Submucosal edema
0	No changes	No changes	No changes (0-5)	No changes	No changes
1	Slight accumulation	Desquamation	6-20	Slight	Detectable (<10%)
2	Mild accumulation	Mild erosion	21-60	Mild	Mild (10-20%)
3	Moderate accumulation	Marked erosion	61-100	Moderate	Moderate (20-40%)
4	Marked accumulation	Ulceration	>100	Marked	Marked (>40%)
* Number of cells per high power field (400x)					

Supplemental Table 3: Oligonucleotides used in this study. Related to Materials and Methods.

5'-ACTCCTACGGGAGGCAGC-3' 5'-GCTTCTTTAGTCAGGTACCGTCAT-3'	16S (Clostridia)
5'-GGTTCTGAGAGGAGGTCCC-3' 5'-GCTGCCTCCCGTAGGAGT-3'	16S (Bacteroidetes)
5'-GTGCCAGCMGCCGCGGTAA-3' 5'-GCCTCAAGGGCACAACTCCAAG-3'	16S (Enterobacteriaceae)
5'-TGTAGACCATGTAGTTGAGGTCA-3' 5'-AGGTCCGGTGTGAACGGATTTG-3'	<i>Gapdh</i> (<i>mus musculus</i>)
5'-TGCACCCAAACCGAAGTCAT-3' 5'-TTGTGAGAAGCCAGCGTTCAC-3'	<i>Cxcl1</i> (<i>mus musculus</i>)
5'-TTGGGTCTTGTTCACTCCACGG-3' 5'-CCTCTTTCAGGTCACCTTTGGTAGG-3'	<i>Nos2</i> (<i>mus musculus</i>)
5'-AGCCAGGAGGGAGAACAGAAAC-3' 5'-CCAGTGAGTGAAAGGGACAGAACC-3'	<i>Tnf</i> (<i>mus musculus</i>)
5'-GCCATCTCCTTGCATGCGTGATTGTGATGCCAAAAC-3' 5'-ACTGATTTCTCATGATTTATTCTCCCTGG-3' 5'-TAAATCATGAGAAATCAGTGGCGATTCAC-3' 5'-CAAGGAATGGTGCATGCTTACGACCGCAATACCGC-3'	Deletion of <i>lldD</i>
5'-GCCATCTCCTTGCATGCCAGGTCAATTCAGGCC-3' 5'-GCACGGTGTGTGGTGGGACAAAATATC-3' 5'-CCACCACACACCGTGCGGTTTACCGT-3' 5'-CAAGGAATGGTGCATGCCAGACGCCGGAATGAAAG-3'	Deletion of <i>dld</i>
5'-GCCATCTCCTTGCATGATAACGTATCTGCTGAATGAC-3' 5'-GCGACAGGTGACCTTCTCCAGTGATG-3' 5'-GAAGGTCACCTGTCGCTCCCCTGCGC-3' 5'-CAAGGAATGGTGCATGGCACATGTTTCGCCAGGGATGAAAG-3'	Deletion of <i>ldhA</i>
5'-CTAGAGGTACCGCATGCAGCTGCAAAAGTGCTTG-3' 5'-ACCTCGTTTCAGATTAAGCGCGATAG-3' 5'-CTTAATCTGAAACGAGGTAAACATGGTGCAAG-3' 5'-AGCTCGATATCGCATGCGCCAACCTCCATGGCTGG-3'	Deletion of <i>sseD</i>
5'-CTAGAGGTACCGCATGTGAAGTAACAACACTCCC-3' 5'-TTCTCCCTGAGAACCACACGCATAATG-3'	Amplification of <i>lldD</i> promoter region
5'-TGGTTCTCAGGGAGAATAAATCATGATTATTTTCAGCAGC-3' 5'-AGCTCGATATCGCATGTCAGGCGGCATCGCCTTT-3'	Amplification of <i>lldD</i> coding sequence
5'-GCCATCTCCTTGCATGAATGTGGAATGTTTTTACTGG-3' 5'-CTCCTGTCCATGACTCCTTGCTCATC-3' 5'-GAGTCATGGACAGGAGTCGTCAAATG-3' 5'-CAAGGAATGGTGCATGACTGGAAGAAGTTACCGG-3'	Deletion of <i>cydA</i>