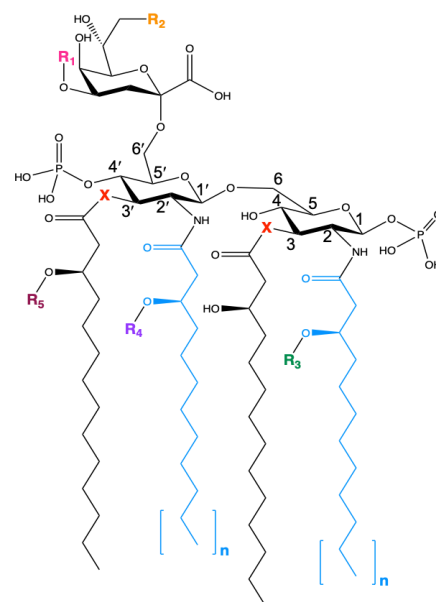


Supplementary Information to  
**Pushing the envelope: LPS modifications and their consequences**  
 Brent W. Simpson and M. Stephen Trent

**Supplementary Information S1. Variations to Kdo-lipid A introduced during the Raetz pathway.** Tabular summary (left) and structural depiction (right) of sites that have variations between organisms or under different growth conditions within an organism.

Site of variation	Group in <i>E. coli</i> under standard lab conditions (enzyme)	Alternate group (enzyme, organism)
X	-O- (GlcNAc synthesis)	-NH- (GnnA/B, <i>Campylobacter/Leigoneilla</i> /etc.)
R1	Kdo	PO <sub>4</sub> (KdkA, <i>Vibrio/Haemophilus</i> /etc.)
R2	-OH (Kdo synthesis)	NH <sub>2</sub> (KdnA/B, <i>Shewanella</i> )
2 and 2' primary acyl	3-OH, C14:0 (LpxD)	3-OH, C18:0 (LpxD1, <i>Francisella</i> )
	3-OH, C14:0 (LpxD)	3-OH, C16:0 (LpxD2, <i>Francisella</i> )
R3	-H (unmodified)	3-OH, C12:0 (LpxD1, <i>Leptospira</i> )
		3-OH, C12:0 (LpxD2, <i>Leptospira</i> )
R4	C12:0 (LpxL, 37°C)	2-OH, C12:0 (LpxL1, <i>Pseudomonas</i> )
		C12:1 (LpxP, <i>Salmonella/E.coli</i> /etc low temp)
		C14:0 (LpxL2, <i>Klebsiella</i> )
R5	C14:0 (LpxM)	-H (unmodified, <i>Francisella</i> /etc.)
		C12:0 or C14:0 (LpxJ, <i>Helicobacter</i> /etc.)
		3-OH, C12:0 (LpxN, <i>Vibrio</i> )



## Supplementary Information S2. Enzymes that modify the Kdo-lipid A domain of LPS

Enzyme <sup>a</sup>	Protein localization	Active site topology	Pathogenic organisms <sup>b</sup>	Activity	Published structures (PDB ID)	Contributors to regulation	Effect of modification	References
AlmG	Inner membrane	Cytoplasmic	<i>Vibrio</i>	Glycine transfer to hydroxyl group of 3' acyloxyacyl chain		VprAB (CarRS)	AMP resistance	1-3
ArnT (PmrK)	Inner membrane	Periplasmic	<i>Bordetella bronchiseptica</i> , <i>Burkholderia</i> , <i>Klebsiella</i> , <i>E. coli</i> , <i>P. mirabilis</i> , <i>Pseudomonas</i> , <i>Salmonella</i> , <i>Shigella</i> , <i>Yersinia</i>	Aminoarabinose addition, Glucosamine addition (Bordetella)	5EZM, 5F15	PmrAB, ParRS, CprRS	AMP resistance	4-9
EptA (PmrC, Mcr)	Inner membrane	Periplasmic	<i>Acinetobacter</i> , <i>Capnocytophaga</i> , <i>Cronobacter</i> , <i>E. coli</i> , <i>Haemophilus</i> , <i>Helicobacter</i> , <i>Klebsiella</i> , <i>Neisseria</i> , <i>Pseudomonas</i> , <i>Salmonella</i> , <i>Shigella</i> , <i>Vibrio</i>	Phosphoethanolamine addition	4KAV, 4KAY, 5FGN,	PmrAB, ColRS	AMP resistance	7,10-16
EptB	Inner membrane	Periplasmic	<i>E. coli</i> , <i>Salmonella</i> , <i>Yersinia</i>	Phosphoethanolamine transfer to Kdo		PhoPQ, sRNA MgrR	Modest AMP resistance	7,17
EptC	Inner membrane	Periplasmic	<i>Campylobacter</i>	Phosphoethanolamine transfer to lipid A, flagellar rod, and other substituents	4TN0	Present under normal laboratory conditions	TLR4 evasion, AMP resistance, motility	18,19
FImF1	Inner membrane	Periplasmic	<i>Francisella</i>	Glucose, mannose addition to lipid A		Present under normal laboratory conditions	Possible role in AMP resistance	20
FImF2	Inner membrane	Periplasmic	<i>Francisella</i>	Galactosamine addition to lipid A		Present under normal laboratory conditions	Possible role in AMP resistance	20,21
FImK	Inner membrane	Periplasmic	<i>Francisella</i>	Glucose, mannose or galactosamine addition to lipid A		Present under normal laboratory conditions	Possible role in AMP resistance, TLR4 evasion	21
KdkA	Inner membrane	Cytoplasmic	<i>Actinobacillus</i> , <i>Bordetella</i> , <i>Haemophilus</i> , <i>Pasteurella</i> , <i>Shewanella</i> , <i>Vibrio</i>	Phosphorylation of Kdo		Present under normal laboratory conditions	Possible effect on toxin delivery	7,22
KdhA, KdhB (KdoH1, KdoH2)	Inner membrane	Cytoplasmic	<i>Francisella</i> , <i>Helicobacter</i> , <i>Legionella</i>	Removal of outer Kdo		Present under normal laboratory conditions	AMP Resistance	23-25
KdoO	Inner membrane	Cytoplasmic	<i>Burkholderia</i> , <i>Yersinia</i>	Hydroxylation of Kdo	5YKA, 5YVZ, 6A2E, FYWO	Present under normal laboratory conditions	Unknown	26

LmtA	Inner membrane	Cytoplasmic	<i>Leptospira interrogans</i>	Methylation of lipid A		Present under normal laboratory conditions	Unknown	27
LpxE	Inner membrane	Periplasmic	<i>Capnocytophaga, Francisella, Helicobacter, Porphyromonas</i>	1-phosphatase		Present under normal laboratory conditions	AMP resistance, TLR4 evasion	7,14
LpxF	Inner membrane	Periplasmic	<i>Capnocytophaga, Francisella, Helicobacter, Porphyromonas</i>	4'-phosphatase		Present under normal laboratory conditions	AMP resistance, TLR4 evasion	7,14
LpxO	Inner membrane	Cytoplasmic	<i>Bordetella, Klebsiella, Legionella, Pseudomonas, Salmonella</i>	Hydroxylation of lipid A acyl chains		Fnr and ArcA (oxygen sensing)	Stress response coordination	7,28
LpxR	Outer membrane	Extracellular	<i>E. coli O157:H7, Helicobacter, Salmonella, Vibrio, Yersinia</i>	3'-O-deacylase	3FID	sRNA MicF, Lrp in <i>E. coli O157:H7</i> , aminoarabinose lipid A modification	TLR4 evasion	7,29,30
LpxT	Inner membrane	Periplasmic	<i>E. coli, Pseudomonas, Salmonella, Yersinia</i>	Phosphorylation of lipid A, recycling of undecaprenyl pyrophosphate		PmrAB, small peptide PmrR	Unknown	7,13,31
PagL	Outer membrane	Extracellular	<i>Bordetella, Burkholderia, Pseudomonas, Salmonella</i>	3-O-deacylase	2ERV	PhoPQ, aminoarabinose lipid A modification	Lowered TLR4 activation	5,7
PagP	Outer membrane	Extracellular	<i>Bordetella, Erwinia, E.coli, Klebsiella, Legionella, Pseudomonas, Salmonella, Shigella, Yersinia</i>	Palmitate addition	1MM4, 1MM5, 1THQ, 3GP6	PhoPQ, membrane perturbation, RcsB (osmotic stress)	Selective AMP resistance, membrane integrity	7,32-35

<sup>a</sup> Alternative enzyme names in certain species are given in parentheses.

<sup>b</sup> Organisms containing homologs of these enzymes were excluded from the table if the respective modification has not been observed. This table is likely to expand as the lipid A-core is further characterized from a variety of species.

## Supplementary Information S3. Regulatory mechanisms that affect LPS modifications

Two component systems				
Response regulator/ Sensor kinase	Stimuli	Modification enzymes regulated	Organisms	References
PhoP/Q	low Mg <sup>2+</sup> /Ca <sup>2+</sup> , AMPs, acidic pH, osmotic shock	Direct: PagL, PagP Indirect: increased MgrR (see below) Indirect: increased PmrD which binds PO <sub>4</sub> -PmrA	widespread	36-43
PmrA/B (BasR/S)	Fe <sup>3+</sup> , Al <sup>3+</sup> , acidic pH, vanadate	ArnT, EptA, LpxT	widespread	44-47
ArcA/B	Ubiquinone/Menaquinone redox states	LpxO	<i>Salmonella</i>	28
ParR/S	AMPs	ArnT	<i>Pseudomonas</i>	48
CprR/S	AMPs	ArnT	<i>Pseudomonas</i>	49
ColR/S	Zn <sup>2+</sup>	EptA	<i>Pseudomonas</i>	13
CrrA/B	Unknown	Indirect: increased CrrC that regulates PmrAB	<i>Klebsiella</i>	50,51
VprA/B (CarR/S)	AMPs, bile, acidic pH	AlmG	<i>Vibrio</i>	1,3
Other transcriptional regulators				
Regulator	Stimuli	Modification enzymes regulated	Organisms	References
Fnr	O <sub>2</sub>	LpxO	<i>Salmonella</i>	28
Lrp	Butyrate	LpxR	EHEC	29
RcsB	Osmotic stress, independent of RcsC	PagP	<i>E. coli</i>	35
Small RNA regulators				
Small RNA	Regulation of small RNA	Modification genes / mechanism of regulation	Organisms	References
MicA	Up regulated by $\sigma^E$	<i>phoP</i> / inhibit translation	widespread	52
MicF	Down regulated by Lrp stability by StpA and HU	<i>lpxR</i> / inhibit translation and decrease mRNA stability	widespread	53
MgrR	Up regulated by PhoP	<i>eptB</i> / inhibit transcription	widespread	39
Post-translational regulation				
Post-translational effector	Mechanism of regulation	Modification enzyme regulated	Organisms	References
MgrB	Feed back, deactivation of PhoQ	Indirect: PagL, PagP, EptA, ArnT	widespread	54
PmrR (small peptide)	Inhibition of enzyme	LpxT	widespread	45
Disruption of OM asymmetry	Activation of enzyme	PagP	widespread	55
Aminoarabinose-lipid A	Prevents substrate recognition	PagL, LpxR	<i>Salmonella</i> , <i>Yersinia</i>	56,57

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