

## LPS from pathogenic *Coxiella burnetii* prevents trafficking to microbicidal phagolysosomes

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Variations in lipopolysaccharide (LPS), a bacterial outer membrane component, determine virulence of the obligate intracellular bacterium *Coxiella burnetii*, but the underlying mechanisms are unknown. We find that while avirulent *C. burnetii* LPS (avLPS) stimulates host p38 $\alpha$ -MAPK signaling required for proper trafficking of bacteria containing compartments to lysosomes for destruction, pathogenic *C. burnetii* LPS (vLPS) does not. The defect in vLPS and pathogenic *C. burnetii* targeting to degradative compartments involves an antagonistic engagement of TLR4 by vLPS, lack of p38 $\alpha$ -MAPK-driven phosphorylation, and block in recruitment of the homotypic fusion and protein-sorting complex component Vps41 to vLPS-containing vesicles. An upstream activator of p38 $\alpha$ -MAPK or phosphomimetic mutant Vps41-S796E expression overrides the inhibition, allowing vLPS and pathogenic *C. burnetii* targeting to phagolysosomes. Thus, p38 $\alpha$ -MAPK and its crosstalk with Vps41 play a central role in trafficking bacteria to phagolysosomes. Pathogenic *C. burnetii* has evolved LPS variations to evade this host response and thrive intracellularly.

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