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The role of the *Chlamydia trachomatis* inclusion in the evasion of host cell-autonomous immunity

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Academic dissertation

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Abstract

Chlamydia trachomatis is the most prevalent bacterial cause of sexually transmitted infections, with ~128 million new cases reported annually. In addition, it is the agent of trachoma, making it also the leading infectious cause of blindness worldwide. Current treatment relies on broad-spectrum antibiotics, which are usually effective but can disrupt the microbiota and contribute to resistance development. These limitations underscore the urgent need for narrow-spectrum therapeutic strategies that exploit the pathogen's unique obligate intracellular lifestyle and vulnerabilities.

This thesis investigated how *C. trachomatis* maintains its parasitophorous vacuole, the inclusion, and how host cells respond when inclusion integrity fails, focusing on the pathogen's dependence on host-derived sphingolipids and the interplay with autophagy to identify mechanisms that could be harnessed for therapeutic targeting.

The first chapter details the identification of the inclusion membrane protein CpoS – a secreted *C. trachomatis* effector that inserts into the vacuole membrane – as a multifunctional virulence factor. Specifically, CpoS was found to organize inclusion membrane microdomains, modulate the host cytoskeleton, and interact with Rab GTPases, thereby manipulating membrane trafficking while also suppressing STING-dependent interferon responses and a defensive form of premature host cell death.

The second chapter presents findings from a genome-wide CRISPR screen and validations using novel microscopic inclusion damage reporters, collectively revealing that CpoS stabilizes inclusions by mediating acquisition of sphingolipids. Pharmacologic inhibition of sphingolipid synthesis further destabilized CpoS-deficient inclusions, resulting in infection clearance and host cell survival rather than death.

The third and final chapter describes how the application of inclusion damage reporters in electron microscopy and live cell imaging revealed that destabilization of CpoS-deficient inclusions initially involved small inclusion membrane breaks, followed by inclusion rupture and host cell death. Bacteria released from damaged inclusions were targeted by the xenophagic machinery. However, xenophagic degradation was incomplete due to the rapid progression toward cell death.

Collectively, this thesis established novel spatiotemporal imaging tools, elucidated the role of the inclusion in the evasion of host cell-autonomous immunity, and laid the groundwork for potential future therapeutic strategies focused on destabilizing the inclusion to combat *C. trachomatis* infection.

Keywords: *Chlamydia trachomatis*, CpoS, inclusion microdomains, inclusion integrity, cell-autonomous immunity, sphingolipids, xenophagy, split-GFP reporters

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