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Chlamydia trachomatis overrides the Spindle Assembly Checkpoint causing host cells to fail in cytokinesis

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Chlamydiae are obligate intracellular bacteria, which live in a membrane-bound vacuole termed an inclusion. Cytopathically, infection with *C. trachomatis* can lead to host cell multinucleation. The two mechanisms that can initiate multinucleation are cell fusion and failure in cytokinesis. By differential labeling of two cell populations we were able to demonstrate infected cells fail in cytokinesis while eliminating the possibility of cell fusion. Our goal was to determine the mechanism by which a chlamydial infection leads to cytokinesis failure. To investigate the role of steric inhibition on contractile ring formation and actin dynamics by *Chlamydia* we compared cytokinesis failure induced by infection, to cytokinesis failure caused by actin depolymerization. Infected cells that fail in cytokinesis due to cytochalasin D have a different nuclei:centrosome ratio than multinucleated chlamydial infected cells alone, suggesting that the failure in cytokinesis is not related to actin dynamics.

Cytokinesis failure can occur through failure in abscission. The cell aborts abscission if DNA is detected in the midbody. Our studies of the host cell cycle show that 12 hours after infection, we see a higher ratio of cells in prometaphase than metaphase compared to uninfected cells. Infected cells also have a reduced mitotic index suggesting infected cells spend less time in mitosis. This result is consistent with the hypothesis that chlamydial infected cells are preceding prematurely into anaphase. The spindle assembly checkpoint (SAC) prevents progression from metaphase to anaphase of cells with unaligned chromosomes by inhibiting the anaphase promoting complex (APC), but we found that *Chlamydia* mimics two core functions of the APC, degrading both cyclin B1 and securin, leading to premature exit from metaphase. Finally, we showed there is DNA in the midbody of infected cells due to early onset of anaphase, leading to failure in abscission and ultimately failure in cytokinesis.

Keywords: Chlamydia, Cell Cycle, Spindle Assembly Checkpoint, Cytokinesis