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The Protease CPAF Is a Major Factor of Chlamydial Pathogenicity and Impairs Host Cell Defense

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Chlamydia trachomatis causes eye infections on a large scale and is the most frequent bacterial agent of sexually transmitted disease. *Chlamydia trachomatis* replicates only inside human cells, and chlamydial infections cause substantial changes in host cell systems such as in lipid trafficking, gene expression and apoptosis susceptibility. The chlamydial protease Chlamydial Protease-like Activity Factor (CPAF) translocates from the inclusion to the cytosol in the course of chlamydial intracellular development, where it cleaves various host cell substrate proteins, including cytoskeletal components and transcription factors. We tested the hypothesis that CPAF-activity is important for a number of the known cell-biological changes during infection. By the bacteria, CPAF is synthesized as an inactive precursor, which is cleaved to produce the active enzyme; expression of CPAF in human cells produces no activity. We were however able to generate active CPAF in human cells by forced clustering of the full-length precursor, leading to its auto-catalytic activation. This caused the cleavage of cellular CPAF substrates and produced a number of changes usually seen during chlamydial infection. One new aspect of CPAF activity is its interference with inflammation associated NF-κB- signaling. Cleavage of the NF-κB-family member p65/RelA, has been found during chlamydial infection. We show that this cleavage occurs also upon isolated expression of active CPAF in human and murine cells. CPAF from both *C. trachomatis* and *C. pneumoniae* had this activity. As a consequence of CPAF dependent substrate cleavage, NF-κB-activation upon extrinsic stimulation with IL-1β was impaired in reporter gene assays. In conclusion, the human pathogens *C. trachomatis* and *C. pneumoniae* employ CPAF to target a number of host cell systems, including the interference with the NF-κB signaling pathway. This mechanism is likely of substantial importance to counteract host cell defense and to permit growth of the bacteria inside human cells and inside the human body.

Keywords: Chlamydia, CPAF, NF-κB signaling, p65/Rel A