UMEÅ UNIVERSITET

Umeå University Medical Dissertations, New Series No 2308

Identifying, characterizing, and targeting chlamydial virulence factors to unleash the power of host cell-autonomous immunity

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av filosofie/medicine doktorsexamen framläggs till offentligt försvar i Major Groove, Norrland's University Hospital, (NUS) 6L
Tisdagen den 28 maj, kl. 09:00.
Avhandlingen kommer att försvaras på engelska.

Fakultetsopponent: Professor Johannes Hegemann,
Heinrich Heine University Düsseldorf, Düsseldorf, Germany.

Department of Molecular Biology

Organization
Umeå University
Department of Molecular Biology

Document type
Doctoral thesis

Date of publication
07th May 2024

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Title
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Abstract
Chlamydia trachomatis is the most common infectious cause of blindness and a prevalent bacterial agent of sexually transmitted infections, with an annual incidence exceeding 130 million cases. The current therapeutic approach to *Chlamydia* infections relies on broad-spectrum antibiotics. However, while generally effective, these antibiotics carry the risk of substantial collateral damage, for instance by promoting resistance in bystander pathogens and by adversely affecting commensal microbes. Hence, the development of a more sustainable, narrow-spectrum treatment would be advantageous. In this context, the bacterium's highly specialized obligate intracellular lifestyle could offer a wealth of unique targets for intervention. This thesis specifically investigates the potential of harnessing the protective power of cell-autonomous immunity in our battle against *Chlamydia*.

It is envisaged that the therapeutic exploitation of cell-autonomous immunity will initially necessitate three pivotal steps. Firstly, it will require identifying protective host cellular defense programs and counteracting virulence factors, which could serve as potential molecular targets. Secondly, it will be crucial to determine the molecular mechanisms by which the pathogen's virulence factors suppress the host cellular defenses. Thirdly, pharmacological means to target the identified virulence factors or host cellular defense programs will need to be identified. This thesis outlines three independent projects, executed concurrently, to advance our knowledge at these three steps.

The first project involved the implementation of an innovative molecular genetic screening approach, which was devised to reveal host cellular defense mechanisms that could effectively restrict the growth of *C. trachomatis* provided they were not actively suppressed by the pathogen. This investigation culminated in the discovery of a mutant *C. trachomatis* strain that lacks the ability to effectively evade xenophagy. Overall, this finding highlighted *Chlamydia*'s ability to evade this defense mechanism as a potential novel target for therapeutic intervention.

The second project encompassed the molecular characterization of CpoS, a *C. trachomatis* virulence factor previously identified to counteract cell-autonomous immunity by inhibiting induction of type-I interferon responses and premature host cell death. The analyses revealed that CpoS manipulates host cellular membrane trafficking and suppresses host cellular type-I interferon responses through its interactions with the host factor Rab35.

The third project involved a compound screening campaign that identified several novel selective anti-chlamydial compounds. Interestingly, one molecule exhibited reduced activity in xenophagy-deficient cells, implying a potential involvement of xenophagy in its mechanism of action.

In summary, this research pinpointed xenophagy as a potential defensive mechanism against *C. trachomatis*, offered in-depth understanding of the operational mode of the virulence factor CpoS, and discovered new selective therapeutic alternatives, which in part utilize xenophagy in their mechanism of action. Consequently, this thesis provides a comprehensive overview of the transition from fundamental research to the more application-oriented domain of drug discovery and may inspire the development of more sustainable therapeutic strategies for the clinical handling of *Chlamydia* infections.

Keywords
Chlamydia trachomatis, cell-autonomous immunity, xenophagy, virulence factors, novel antimicrobials

Language
English

ISBN
print: 978-91-8070-397-0
PDF: 978-91-8070-398-7

ISSN
0346-6612

Number of pages
54 + 3 papers