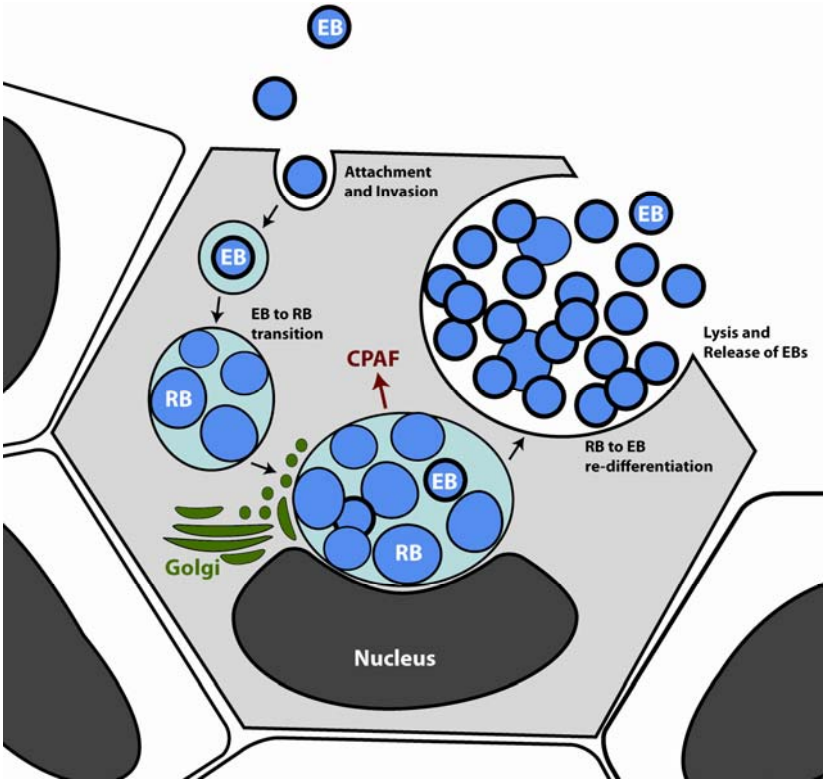
***Chlamydia*: an example of adaptation**

Chlamydia trachomatis as a pathogen

With the chlamydiae, we are mostly working with the species most relevant to human health, *C. trachomatis*. *C. trachomatis* is an obligate intracellular bacterium and the most common bacterial agent of sexually transmitted disease (chlamydial genital infections are surprisingly common, especially in young women). A severe disease caused by *C. trachomatis* is a condition referred to as pelvic inflammatory disease (PID), which can lead to infertility of the woman (one estimate is that 100,000 women in Germany cannot naturally conceive children because of a chlamydial infection in their history). In some other countries in the world (especially in Africa) *C. trachomatis* causes trachoma, an eye infection leading to blindness. Other chlamydial species cause upper airway infection (*Chlamydia pneumoniae*) or a complex infection named ornithosis (typically a severe form of pneumonia).



Developmental cycle of *Chlamydia trachomatis* in epithelial cells

Life style of Chlamydia

Chlamydiae are obligate intracellular bacteria: they can grow only inside (for instance human) host cells; they cannot be cultured on an agar-plate like most bacteria. Chlamydiae have a unique developmental cycle with two morphologically and functionally distinct forms, the infectious but metabolically little active, extracellular elementary body (EB) and the metabolically active, intracellular reticulate body (RB). Upon invasion of a cell in the epithelium of the genital tract or the conjunctivae, *Chlamydia* resides in an unusual cytosolic vacuole, the chlamydial inclusion, where EBs differentiate to RBs. Over the next 2-3 days (*in vitro*) RBs differentiate and the inclusion grows massively in size, in the end filling almost the entire cell. Expansion of the inclusion is facilitated by acquisition of lipids (mainly sphingolipids and cholesterol) from the Golgi network, which in turn requires the Chlamydia-induced fragmentation of the Golgi apparatus. During their replication, RBs divide by binary fission, acquiring nutrients such as lipids from the host cell, which are essential for

intracellular bacterial growth. Following an ill-understood signal, RBs re-differentiate into EBs and a great number of these infectious particles are released.

What are we doing?

We would like to understand a number of issues: how can *Chlamydia* establish itself and exploit the host for its purpose of replication? What is the host cell doing against it? What are the crucial components of the chlamydial endeavour to establish its niche in the cell? Another point we find intriguing is how this sophisticated interaction of bacteria and host cell evolved.

In our previous work we have in particular investigated the role of cell death during the infection with *C. trachomatis*. Since the bacteria depend on the host cell for their replication, and since all human cells have a signalling system they can use to kill themselves (most often by apoptosis), the question of whether cell death is disturbed during chlamydial infection is relevant (during viral infection apoptosis is often inhibited). Indeed, infected cells are protected against extrinsic apoptotic stimuli whereas non-apoptotic cell death is sometimes induced; this to a degree depends on the cell type infected. In trying to understand the mechanism of protection against apoptosis by *Chlamydia* we came across the chlamydial protease CPAF. CPAF appears to mediate chlamydial anti-apoptotic activity by triggering the proteasomal degradation of host pro-apoptotic BH3-only proteins (we still don't know exactly how this works). CPAF is secreted into the host cell cytosol approximately 16 h post infection and proved to be of major importance for the bacteria-host-interaction: CPAF cleaves a number of host cell proteins, for instance the subunit p65/RelA of the transcription factor NFκB (other targets include cytokeratin 8, vimentin, cyclin B1 and the poly (ADP-ribose) polymerase PARP). We don't actually know whether such cleavage is important for the infection but it seems to occur.

Inducible expression and experimentally induced oligomerization of CPAF in epithelial cells reproduced the cytopathic effects caused by chlamydial infection. One effect of CPAF in human cells is the induction of Golgi apparatus (GA) fragmentation, which is linked to the cleavage of the integral GA-protein golgin-84, and which is probably required for at least lipid acquisition of the bacteria. Inhibition of CPAF greatly reduces chlamydial development. CPAF therefore but has likely greater importance for the chlamydial infection. CPAF is a promising target in anti-chlamydial treatment and some of our current work looks at its role and its molecular activity.

More recent *Chlamydia*-publications:

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Paschen, S., Christian, J. G., Vier, J., Schmidt, F., Walch, A., Ojcius, D. M. and Häcker. G. (2008) Cytopathicity of *Chlamydia* infection can be largely reproduced by expressing a single chlamydial gene, Chlamydial Protease-like Activity Factor. J Cell Biol, 182(1):117-27

Ying, S., Pettengill, M., Latham, E.R., Walch, A., Ojcius, D.M. and Häcker, G. (2008) Premature apoptosis of *Chlamydia*-infected cells disrupts chlamydial development. J. Infect. Dis., 198(10):1536-44.

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Ying, S., Seiffert, B.M., Häcker, G. and Fischer, S.F. (2005) Broad Degradation of Pro-Apoptotic BH3-only Proteins During Infection with *Chlamydia trachomatis*. Infect. Immun.,73:1399-1403.

Fischer, S.F., Vier, J., Kirschnek, S., Klos, A., Hess, S., Ying, S. and Häcker, G. (2004) Chlamydia inhibit host cell apoptosis by degradation of pro-apoptotic BH3-only proteins. J Exp Med., 200:905-16.