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Chlamydiacae: Polymorphic membrane proteins make the difference

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Chlamydiae are gram-negative obligate intracellular parasites preferentially targeting columnar epithelial cells of respective mucosae. Pathogenic *Chlamydia (C.) sp.* include *C. trachomatis*, a leading cause of sexually transmitted bacterial diseases and ocular infections (trachoma), potentially leading to blindness, the respiratory pathogen *C. pneumoniae*, responsible for about 10% of community-acquired pneumonia, and the zoonotic pathogen *C. psittaci*, causing a rare but severe pneumonia.[1,2] In addition to these pathogens, *Chlamydia* species and *Chlamydia*-like organisms have been found associated with vertebrates, invertebrates, and even protozoa.[2] Currently, within *Chlamydiaceae* a total of 11 species are organized in the single genus Chlamydiae: *C. psittaci*, *C. abortus*, *C. caviae*, *C. felis*, *C. avium*, *C. gallinacea*, *C. pecorum*, *C. pneumoniae*, *C. ibidis*, *C. muridarum* and *C. trachomatis.*[3] Despite major differences in host range, tissue tropism, and disease pathology they all share a characteristic biphasic developmental cycle unique among prokaryotes.[4] The infectious chlamydial form, the elementary body (EB), enters the eukaryotic cell and becomes internalized in a vacuole in the cytoplasm of the host cell. In this so called inclusion, the EB differentiate into a non-infectious, metabolically active form, the reticulate body (RB). Depending on the strain, 2 or 3 d after infection the RBs transform back into EBs, which get released by lysis of the host cell or exocytosis.[4] A lot of information concerning the life style of *Chlamydiaceae* has been obtained in the last years by the analysis of sequencing data of chlamydial genomes.[5]

Second-generation sequencing efforts have led to the completion of more than 100 chlamydial genome sequences encompassing all known spezies.[5] Comparative analysis of chlamydial genomes showed a high level of sequence and gene order conservation (shared syntheny) across members of the family and, as in other obligate intracellular bacteria, they show a considerably reduced genome, implying dependency on the host organism for many metabolic capabilities like synthesis of nucleic acids and lipids.[5] Among the species *C. psittaci*, *C. abortus*, *C. pneumoniae*, and *C. trachomatis*, 736 genes are still shared (with a total of protein coding sequences ranging from 874 to 1097), which illustrates the extremely high degree of conservation across chlamydial genomes.[6] Major deviations from sequence conservation, however, can be observed in genes encoding inclusion membrane proteins, in the hypervariable region near the predicted replication termination region known as plasticity zone, as well among the family of genes encoding polymorphic membrane proteins (Pmps).[7] The *pmp* genes make up more than 5% of the total coding capacity of the genome, and are unique to the *Chlamydiacae*, suggesting that their products are most probably virulence factors.[8] The various Pmp families show little similarity in amino acid sequence, but all members contain multiple repeats of the motifs GGA(I, L, V) and FxxN.[9] In this issue of *Virulence* Vasilevsky *et al.*[10] view Pmps under following issues: regulation, function and potential vaccine candidates. They provide in table form a complete overview of Pmp research until now including a schematic representation of all Pmp proteins described so far in *Chlamydiaceae.* For the first time, their review summarizes all the tremendous work performed so far on this important class of proteins. Furthermore, the authors focus particularly on 2 important properties of Pmps of the human pathogens *C. trachomatis* and *C. pneumoniae* – their role as adhesins and as potential vaccine candidates.

The specific receptor-adhesin interactions involved during entry of *Chlamydiacae* into host cells have proven to be somewhat elusive.[11] A large part of complexity is due to the use of different chlamydial species or strains in the analyses of attachment or entry. This, in addition to the use of different experimental parameters and cell types, has led to difficulties making comparisons among studies concerning the initial steps of entry.[11] Wehrl *et al.* investigated the ability of a polyclonal rabbit serum raised against N-Pmp21 to inhibit *C. pneumoniae* infection *in vitro.*[12] Finco and colleagues demonstrated a similar result using the mouse kidney cell line (LLC-MK2) and polyclonal mouse sera against Pmp2 and Pmp10.[13] These studies highlighted the

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importance of Pmps in the initial phase of infection. Molleken *et al.* demonstrated that the *C. pneumoniae* Pmp21 adhesion to cell surface receptors required at least 2 copies of the Pmp repeats: either FxxN +FxxN or FxxN+GGA(I, L, A).[14] Moreover, a more recent study identified EGFR (epidermal growth factor receptor) as the receptor for Pmp21.[15] However, the question of the chlamydial receptor(s) on the surface of host cells seems to be much more complex. Host cell surface proteins including the estrogen receptor complex and its subunit the protein disulfide isomerase (PDI) are involved in *C. trachomatis* infection.[16] The fibroblast growth factor receptor (FGFR) is involved in *C. muridarum* infection and is recruited to the cell surface associated EBs.[17] Finally, in a very recent work Rudel and co-workers describe EphA2 (ephidrinA2 receptor) as an invasion receptor for *C. trachomatis.*[18] Till recently there was no tractable genetic system to mutate *Chlamydiacae* and identify specific proteins that may play a role in cellular attachment. This situation has improved[19] and thus we will probably come to know in the near future which members of the family of Pmp proteins are involved in the chlamydial adhesion process and what are the functions of the other family members.

Vasilevsky *et al.*[10] state in their review that the asymptomatic nature of a chlamydial infection and its subsequent long-term consequences such as ectopic pregnancy, preterm delivery and infertility makes a chlamydial vaccine paramount. One of the major difficulties in developing an effective chlamydial vaccine is identifying the MHC-bound chlamydial protein epitopes that are recognized by T cells. Pmps generally contain only T cell epitopes and therefore have been proposed as vaccine candidates. Their review provides many examples for the use of recombinant Pmps in combination with other chlamydial surface proteins and adjuvants to protect various cell lines and mice from chlamydial infections. All these studies suggest that Pmps may be good candidates for a chlamydial vaccine because they are outer membrane proteins that are recognized by antigen presenting cells, degraded, processed and presented on their MHC class II receptors to CD4+ T cells.[10] This is in accordance with Sachse and colleagues who state in their recent review that T cell vaccines that induce cellular immune responses are holding the greatest promise for generating protective immunity against Chlamydia spp.[5]

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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