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Chlamydia, Hepatocytes and Liver

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1. Introduction

The genus *Chlamydia* includes a unique group of aerobic Gram-negative obligate intracellular parasitic bacteria of eubacterial origin which cause numerous infectious diseases in humans and animals. Despite some inherited genomic and phenotypic variations there is one distinctive feature of all chlamydial pathogens, most cases of chlamydial infection are initiated, developed and resolved within the epithelium of the bronchoalveolar system, urogenital system or conjunctivae. Generally, mucosal epithelial tissue and its residing/migrating cellular constituents serve as the primary focus of microbial insult as well as a preferential cell population supporting chlamydial growth. Despite strict tissue tropism and the unique capability of chlamydial pathogens to infect, propagate and finalize their life cycle in mucosal epithelial cells, there is a growing body of evidence that chlamydial species can grow in other cell types thereby invading multiple tissues and organs far beyond the primary locus of infection. The purpose of this chapter is to analyze some novel observations revealing the ability of chlamydial species to grow in hepatic cells along with reports on liver involvement in the pathogenesis of chlamydial infection. This has been done within the modern framework of understanding the molecular biology of chlamydial species and their growth requirements in host cells .

All chlamydial strains have a similar genetic background and share major cutoff points in their developmental cycle, phenotypic characteristics and mechanisms of infectivity . The separation of genus *Chlamydia* into two genera – *Chlamydia* and *Chlamydophila* introduced in 1999 (Everett et al 1999) reflects some variations in the clustering of the 16S rRNA gene and was disputed soon after proposal/introduction (Schachter et al., 2001) . It has been opposed recently by new data on complete chlamydial genome sequencing (Stephens et al., 2001; Myers et al., 2009). Although there are several exceptions, all chlamydial species are >97% similar by 16S rRNA gene sequence comparison which undermines taxonomic separation of the genus (Stephens et al., 2001) . With this proviso a reunited genus *Chlamydia* includes 3 clinically relevant obligate pathogens: *C. trachomatis*, *C. pneumoniae* and *C. psittaci*.

2. Chlamydia as a pathogen

The first member of genus *Chlamydia* was identified and reported by Ludwig Halberstaedter and Stanislaus von Prowazec (Halberstaedter & von Prowazec, 1907) during an expedition to the island of Java when they reproduced conjunctival lesions in orangutans by inoculation of eye scrapings from patients with trachoma . Although they did not propose a

name for the new pathogen, they pointed out that the etiologic agent identified microscopically in the conjunctiva of the trachoma patients had nothing to do with the kingdom of bacteria and had to be distinguished equally from the protozoan organisms . Instead, vonProwazec introduced a new taxon "*Chlamydozoa*" to include the newly discovered pathogen under investigation (von Prowazec, 1907).

Another pathogen belonging to the genus *Chlamydia* – *Chlamydia psittaci* had been initially shown to infect birds and can be transmitted to humans via direct contact causing psittacosis or parrot fever (Verminnen et al., 2008). The first cases of the human disease were reported in 1893 in Paris, France (Morange, 1895). However, detailed insight into the microbiology of *Chlamydia psittaci* was gained only after the introduction of cell culture technique and a large epidemic of psittacosis in the USA and Europe in 1930 (Vanrompay et al., 1995).

Extensive trachoma research paved the way for the discovery of another member of genus *Chlamydia*. An atypical strain designated as TW-183 was isolated in 1965 from the eye of a child participating in a vaccine study led by Prof J. T. Grayston in Taiwan . However, it was not until 1985 that Grayston and collaborators accumulated multiple pieces of evidence to show that the Taiwanese isolate is linked to respiratory infections in adults and represents a new member of genus *Chlamydia* named *Chlamydia pneumoniae* (Saikku et al., 1985).

From 1935 all chlamydial species were categorized as viruses since they could not synthesize ATP, did not grow in media and required a eukaryotic cell for propagation (Fields & Barnes, 1992). However, in 1963 the presence of the cell wall and its major chemical component - muramic acid was confirmed in several chlamydial strains (Perkinsh & Allsona, 1963; Garrett et al., 1974). This fact along with identification of ribosomes, DNA and RNA structures revealed that all chlamydial species belong to the kingdom of bacteria (Moulder, 1982) .

Although the infections caused by chlamydial pathogens are mostly asymptomatic, exposure to chlamydial pathogens worldwide is remarkably high. About 50-80% of the human population has detectable antibodies to *C. pneumoniae*, while 10-20% of adults show seropositivity to *C. trachomatis* (den Hartog et al., 2005; Asquith et al., 2011). Antibody specific to *C. psittaci* is found in a much smaller human population (0.1-3.0 %). However, the real infection rate might be seriously underestimated (Fenga et al., 2007).

The incubation period for Chlamydia-induced infections is generally believed to vary, depending on the strain, from several days (*C. trachomatis*) to month and years (*C. pneumoniae).* Despite of extreme fluctuations in the time span of chlamydial disease, chronic course of infection and persistency in chlamydial biovar colonization is an ultimate feature of chlamydiosis (den Hartog et al., 2005; Asquith et al., 2011; Fenga et al., 2007).

There is a remarkable variety of human disease attributable to the chlamydial pathogens. The spectrum of human disease is closely related to the subdivision of chlamydial pathogens into biological variants (biovars) and serological subtypes (serovars).

C. trachomatis is represented by two biovars relevant to human pathology: the trachoma and lymphogranuloma venereum (LGV). Serovariants belonging to both *C. trachomatis* biovars differ in major outer membrane protein (MOMP) antigenicity and are known to cause various diseases: trachoma, sexually transmitted urogenital disease, some forms of arthritis,

and neonatal inclusion conjunctivitis and pneumonia (Carlson et al., 2004). The existence of different chlamydial "pathotypes" is attributed to small genomic differences (Miyairi et al., 2006). Although the original classification includes 15 MOMP serovars of *C. trachomatis,* there are currently > 20 genovars and serovariants of the pathogen (Byrne, 2010). Their propagation is limited primarily to epithelial cells of mucous membranes . In contrast, it is believed that LGV serovars are more invasive due to their ability to invade the lymphatic system (Martin-Iquacel et al., 2010) .

There are three distinct *C. pneumoniae* biovars: human biovar TWAR, equine biovar and koala biovar. All human isolates representing the TWAR group are almost indistinguishable from each other with 0.1% variation in 16S rRNA and 0.4% difference in the *ompA* gene (Kutlin et al., 2007). *C. pneumoniae* is a proven causative agent of acute and chronic respiratory infections (bronchitis, sinusitis, pneumonia *etc*) and possibly some other diseases. However, unequivocal proof of direct causal relationship between persistent *C. pneumoniae* infection and these internal diseases (atherosclerosis, multiple sclerosis, bronchial asthma and stroke) has not yet been presented (Burillo et al., 2010; Cochrane et al., 2005).

Despite the obvious possibility of zoonotic transmission and identification of animal strains in humans (Dickx et al., 2010), the clinical manifestations of *C. psittaci* infection do not seem to reflect serovar specificity. All eight serovars of *C. psittaci* have similar virulence, tissue tropism and highly conserved 16S rRNA (Grinblat-Huse et al., 2011; Fraeyman et al., 2010). Infection in birds and animals is often manifested by conjunctivitis and respiratory disease followed by septicemia and multi-organ failure in the most severe cases (Harkinezhad et al., 2009). In humans, zoonotic psittacosis is most commonly represented by flu-like symptoms, fever and pneumonia (Beeckman & Vanrompay, 2009).

3. Life cycle

Chlamydiae are aerobic non-motile pear-shaped bacteria with a circularly arranged genome typically containing one plasmid. *Chlamydia* has a unique and dual faceted life cycle involving a switch between two naturally occurring biological forms: a large (~1.0 μM) intracellular, metabolically active and self-reproducing reticulate body (RB) and an extracellular, metabolically dormant, infectious elementary body (EB) of smaller (~0.3 μM) size (Kariagina et al., 2009) .

Internalization of the chlamydial EB into eukaryotic cells is the first step of the chlamydial infectious cycle. Several mechanisms are implemented for chlamydial attachment/entry into phagocytic and non-phagocytic cells . Generally, receptor-mediated endocytosis in clathrin-coated pits, pinocytosis in non-clathrin-coated pits and phagocytosis are among them (Puolakkainen et al., 2005). However, RNA interference experiments (Hybiske & Stephens, 2007) have emphasized the predominant role of the clathrin-mediated pathway whereas caveolae, phagocytosis and macropinocytosis are less relevant, at least for *C. trachomatis* entry into non-phagocytic cells. Ligand-receptor interactions seem to be essential for chlamydial internalization, since attachment dynamics often display a saturation pattern (Hackstadt et al., 1985) . There are a number of chemical ligands on the chlamydial surface promoting attachment to eukaryotic cell membranes. Among them are heparan sulfate, major outer membrane protein, glycosaminoglycans, heat shock protein 70, and OmcB (Puolakkainen et al., 2005; Abromatis & Stephens, 2009).

Although identification of a single eukaryotic receptor responsible for chlamydial attachment and subsequent entry into host cells remains elusive, a number of membrane receptors are implemented in the internalization of chlamydial species. These include insulin-like growth factor 2, epithelial membrane protein 2, polymorphic membrane proteins (PMP), mannose 6-phosphate receptor, estrogen receptor complex, platelet-derived growth factor receptor and possibly LDL-receptor (Dautry-Varsat et al., 2004; Puolakkainen et al.,2005; Abromatis & Stephens, 2009; Bashmakov et al., 2010) . It is obvious that the variety of receptors and other polyvalent interactions between chlamydial pathogens and host cell membrane implemented for chlamydial entry reflect some differences in the mode of exposure to the pathogen, presence or absence of centrifugation force during inoculation, as well as electrolyte composition of the incubation medium. However, there is a genus-specific mechanism promoting initial interaction of *Chlamydia* with eukaryotic cell membrane. Protein disulfide isomerase (PDI) is believed to play an essential role in the internalization mechanism utilized by multiple chlamydial species and serovars (Conant & Stephens , 2007). Nevertheless, the initial attachment of chlamydial particles to the host cell membrane leads to the recruitment of actin cytoskeleton to the attachment locus, formation of actin-rich tubular structures at the base of the attachment site, membrane invagination and final internalization of the bacteria (Clifton et al., 2004). Once internalized and incorporated into a non-acidified lysosome-free vacuole, termed an inclusion body, EB within begin to transform into metabolically active RB which are capable of dividing by binary fission (Hammerschlag, 2002) . The metabolic phenotype of RB characterized by active RNA and protein synthesis becomes established within 6-8 hours of the postinfection period and continues for the next 24-48 hours until reverse transformation to EB driven by unknown developmental stimuli takes place (Scidmore et al., 2003). The classic developmental cycle of chlamydial species terminates with membrane rupture and the release of newly synthesized EB initiating a new round of infection in the host cells.

4. Dissemination

Mucosal epithelial cells are a primary target for all major chlamydial biovars. Once inoculated to susceptible mucosa, chlamydial species accomplish their infectious cycle in the epitheliocytes, rupture their apical surface and spread canalicularly to the adjacent cells (Perry & Hughes, 1999). Canalicular spread of *Chlamydia* was traditionally attributed to the cases of *C. trachomatis* infection complicated by endometritis and salpingitis (Guaschino & De Seta, 2000). However similar horizontal spread of *C. pneumoniae* and *C. psittaci* within the epithelium leading to appearance of chlamydial EB and inflammatory cells in the alveolar lumen takes place in the lungs (Gieffers et al., 2004; Theegarten et al., 2008). This initial stage of chlamydial infection provides a short window of opportunity when the mechanism of local innate immunity may terminate developing infection due to continuous exposure of the pathogen to numerous antibacterial constituents of the epithelial secretion fluid (Perry & Hughes, 1999; Jayarapu et al., 2009) . Infected epithelial cells have been shown to secrete pro-inflammatory cytokines (INF-γ, TNF-α, interleukin 1 and 6, granulocyte-macrophage colony-stimulating factor) promoting cell migration to the infection site (Roan & Starnbach, 2008). It is important that epitheliocyte-derived cytokines, rather than T-lymphocyte mediators, are believed to trigger tissue fibrosis and scarring in urogenital chlamydiosis (Derbigny et al., 2005). Regardless of the type of epithelium, granulocytes and macrophages are the first cells to migrate to the site of primary microbial insult. Both cell types can harbor

viable chlamydial pathogens (Rupp et al., 2009; Chong-Cerrillo et al., 2003; Buendia et al., 1999). Although granulocytes do not re-enter the systemic circulation (Yamagata et al., 2007) they can pass on viable *Chlamydia* to the macrophages whose ability to migrate through mucosal epithelium is a well established fact (Gieffers et al., 2004; Yamagata et al., 2007). Moreover, granulocytes are responsible for initiation of long-term immune response to chlamydial pathogens. Their systemic depletion ameliorates migration of $CD4^+$ and $CD8^+$ T cells to conjunctivae infected with *C. trachomatis* (Lacy et al., 2011).

Chlamydial pathogens do not remain confined to the primary locus of infection. Identification of chlamydial pathogens in different organs and tissues reveals the obvious involvement of haemotogenic and lymphatic pathways in the generalization of chlamydial infection. The cell-mediated hypothesis for *C. pneumoniae* dissemination proposed by Gieffers and others in 2004, has remained unchallenged so far and acquired further confirmation. It has been proposed that alveolar macrophages infected by granulocytes can penetrate mucosal barriers and gain access to the systemic circulation via lymphatic efferent flow as peripheral blood mononuclear cells with further spread to the endothelium, internal organs and tissues (Gieffers et al., 2004; Blasi et al., 2004) . A crucial piece of supporting evidence comes from reports describing the detection of chlamydial biovars in the regional lymph nodes and peripheral blood (Buxton et al., 1996; Sessa et al., 2007; Castro et al., 2010).

There is ongoing discussion related to bacteremia and its role in dissemination of chlamydial infection. It is believed (Gieffers et al., 2004) that there is a low probability of free and sustained circulation of chlamydial EB in the bloodstream since chlamydial particles are likely to be the subject of rapid clearance by elements of the reticuloendothelial system. Furthermore, multiple surface-located adhesins, represented by the family of polymorphic membrane proteins (Molleken et al., 2010), are known to promote the adherence of chlamydial biovars to the endothelial cell and lymphocytes . However, according to our recently published results, EB of *C. pneumoniae* are identifiable by both electron microscopy and RT-PCR in serum specimens obtained from the patients with acute coronary syndrome (Petyaev et al., 2010). By a conservative estimate, our finding may be attributed to the partial lysis of blood cells during serum isolation. On the other hand, there is a certain possibility that free circulation of chlamydial pathogens in blood may take place *in vivo* under some pathophysiological conditions and/or stages of chlamydial disease.

Although bacteremia becomes an indisputable pathophysiological feature of chlamydial infection, determination of chlamydial pathogens in the blood of patients by nucleic acid amplification protocol and/or bacterial culture has not yet become part of the algorithm in the laboratory diagnostics of chlamydiosis. This can be explained by some clinical cases where negative blood culture and PCR readings are observed in seropositive patients with obvious clinical signs of generalized chlamydial infection (Lamas & Eykyn 2009). The unknown prognostic value of the blood tests for chlamydial pathogens creates another issue. Further investigation is required to clarify the significance of bacteremia in the clinical manifestations and outcomes of chlamydiosis.

Alternatively, the lymphatic pathway of generalization may represent a self-sufficient mechanism for sustaining dissemination of chlamydial pathogens in the human body. As an example, the nasal lymphatic system alone may provide a direct route for dissemination of bacterial pathogens colonizing the nasopharyngeal mucosa to the subarachnoid space (Filippidis & Fountas, 2009) . Similarly, liver involvement in the clinical manifestation of *C.*

trachomatis infection can be explained by direct connections between the pelvic lymphatic network and hepatic tissue (Park et al., 2008).

There is an unresolved controversy about the role of chlamydial pathogens in neurological disorders. Although ultimate proof of the association between chlamydial infection and neurological disease has not presented yet, there are multiple reports on the identification of chlamydial species in brain specimens (Piercy et al., 1999; Beagley et al., 2009; Hammond et al., 2010). Along with direct lymphogenic dissemination mentioned above, monocyte-mediated translocation through the blood/brain barrier is claimed to be a key mechanism for brain entry of chlamydial pathogens (Contini et al., 2010). On the other hand, cerebrospinal fluid may promote spread of chlamydial pathogens within brain structures (Contini et al., 2008). Whether chlamydial pathogens circulate in cerebrospinal fluid in free form or require macro-microphages as the vehicle for transport inside the central nervous system remains under investigation . Although axonal transport plays a definite role in the spread of some infectious agents (Kalinke et al., 2011), there is no evidence that axonal delivery is any way involved in the dissemination of chlamydial infection in the nervous system. Reports on rare cases of sepsis induced by *C. pneumoniae* (Bustamante et al., 2002), *C. psittaci* (Janssen et al., 2006) and *C. trachomatis* (Kaan et al., 2002) require thorough evaluation and further conformation.

5. Liver involvement: Clinical evidence

Fitz-Hugh-Curtis syndrome is a complication of inflammatory pelvic disease involving inflammation of the hepatic capsule (perihepatitis) in patients infected with *C. trachomatis* and/or *N. gonorrhoeae.* From a clinical point of view, Fitz-Hugh-Curtis syndrome mimics the basic clinical features of acute cholecystitis and affects almost exclusively young women. This medical condition was initially observed by Carlos Stajano in 1920 who noticed formation of adhesion between Glisson's liver capsule and the anterior abdominal wall in patients with venereal infection complaining of abdominal pain in the right upper quadrant (Stajano, 1920). Thomas Fitz-Hugh and Arthur Curtis gave a detailed description of the syndrome in the 1930s, establishing causative relation between "violin-string" adhesions on the liver capsule, inflammatory pelvic disease and gonococcal infection (Curtis, 1930; Fitz-Hugh, 1934). It was not until the late 1970s, however, that *C. trachomatis* was linked to the etiology of Fitz-Hugh-Curtis syndrome (Wang et al., 1980). Presence of *C. trachomatis* in urogenital specimens, confirmed by PCR assay, is seen in up to 87% of patients with Fitz-Hugh-Curtis syndrome (Yang et al., 2008). According to modern understanding, clinical manifestations of the syndrome arise from the direct colonization of the liver capsule by *C. trachomatis* . Canalicular spread of the pathogen in peritoneal fluid via the right paracolic gutter as well as lymphogenic and hematogenous dissemination are believed to be implicated in the pathogenesis of perihepatitis (Peter et al., 2004). Despite the long-lasting belief that Fitz-Hugh-Curtis syndrome is exclusively attributed to inflammation within the hepatic capsule, perihepatic space and diaphragm, there is some evidence that the liver parenchyma, especially subcapsular regions of the liver, are involved in the course of disease (Lee et al., 2008). Subcapsular enhancement of the liver parenchyma and mildly elevated liver function tests in Fitz-Hugh-Curtis patients have been reported by many researchers (Kim et al., 2007; Lee et al., 2008) . These abnormalities are correctable with antibiotic treatment suggesting their direct association with infection. Moreover, *C. trachomatis* is reportedly isolated not only from the liver

capsule of patients (Wolner-Hansen et al., 1982), but also from hepatic parenchyma obtained by biopsy (Dan et al., 1987).

To date there is neither an independent nosologic entity nor liver disease attributable specifically to *C. pneumoniae.* However, there are some reports on *C. pneumoniae* identification in human liver. The pathogen was identified in hepatocytes and sinusoidal cells of the periportal zone in a significant number of patients with acute liver allograft rejection (Lotz et al., 2004). A high occurrence rate of *C. pneumoniae* is also reported in both the explanted livers and hepatic biopsies of patients with primary biliary cirrhosis (Abdulkarim et al., 2004) . Although causative association between *C. pneumoniae* infection and primary biliary cirrhosis has been disputed by other researchers (Taylor-Robinson et al., 2005) there have been new attempts to link some other hepatobiliary diseases (acute intrahepatic cholestasis, nonalcoholic steatohepatitis) to persistent *C. pneumoniae* infection (Bolukbas et al., 2005; Bogdanos & Vergani, 2009).

In contrast, there is a relatively extensive body of scientific literature suggesting that identification of *C. psittaci* in the internal organs is quite a common phenomenon in cases of avian chlamydiosis. Recent advances in the molecular diagnostics of infection in birds have allowed routine detection of *C. psittaci* markers in different tissues, including liver (Nordentoft et al., 2011). The pathogen was identified by using PCR and immunohistochemistry protocols in the livers of budgerigars (Perpinan et al., 2010), canaries (Ferreri et al., 2007) and Amazon parrots (Raso et al., 2004). It has also been isolated from the livers of laying hens (Jizhang et al., 2010). A crucial piece of evidence comes from the analysis of human cases of *C. psittaci* infection. It is widely reported that the clinical manifestation of psittacosis is often associated with abnormal liver function in the patients (Ciftci et al., 2008; Maegawa et al., 2001., Goupil et al., 1998).

6. Hepatotropism

The tissue distribution of chlamydial pathogens has been extensively studied by many researchers using different routes of administration, dosage, strain virulence and type of experimental animals. Irrespective of these variables, the liver was a major site for clearance of *C . trachomatis* (Tuffrey et al., 1984), *C. pneumoniae* (Saikku et al.,1998) and *C. psittaci* (Iversen et al., 1976). Cell-mediated retention of the pathogens has also been seen in the spleen, bone morrow and lungs with the appearance of infected immune cells in their structure.

The liver is one of the largest organs of the human body receiving about a quarter of cardiac output and releasing half of the lymph flow into the thoracic lymphatic duct (Bertolino et al., 2002) . This unique positioning results in the constant exposure of liver cells to different foreign agents such as bacteria, viruses and parasites as well as immune cells infected with them. Very little is known about how and why chlamydial pathogens enter the liver tissue.

In order to enter hepatocytes, chlamydial particles have first to depart from the site of primary colonization and navigate through the systemic circulation in cell-associated (neutrophils, monocytes and lymphocytes) or free form. It is believed that "sense of direction" in the migrating cells is driven by coordinated expression of cytokines and cell adhesion molecules on the surface of endothelium in the tissues and organs. Indeed, it has been recently shown (Jupelli et al., 2010) that the involvement of internal organs in

chlamydial infection is somehow controlled by Th1-type immune mediators, interleukin 12 (IL-12) and interferon–γ (IFN-γ). In particular, mice genetically deficient in IL-12, IFN-γ or IFN-γ receptor-1 showed 100% mortality and markedly enhanced liver dissemination of *C. muridarum* after intranasal challenge with the pathogen. This observation is well supported by previously published results. A similar finding has been reported with anti-IFN-γ monoclonal antibody treatment in mice infected with *C. psittaci* (McCafferty et al., 1994) . Moreover, liver has been recently shown to express in a constitutive manner Intercellular Adhesion Molecule-1 (ICAM-1), a protein facilitating leukocyte endothelial transmigration, whose participation in dissemination of chlamydial pathogens has been recently discussed (Ochietti et al., 2002).

Once chemotactic stimuli are recognized, bacterial pathogens in cell-associated form, enter the liver via highly fenestrated sinusoid capillaries, which are composed of sinusoidal lining cells - endothelial cells, macrophages and Kupffer cells (Celton-Morizur & Desdouets, 2010). In their concert action these cells implement clearance of bacteria, endotoxins and microbial debris from the bloodstream and regulate intra-sinusoidal cell migration (Gregory et al., 2002). Kupffer cells are known to ingest and destroy adherent granulocytes containing infectious pathogens (Holub et al., 2009). In this regard, it becomes extremely important that Kupffer cells are shown to support chlamydial growth resulting in productive *C. pneumoniae* infection under "*in vitro*" and "*in vivo*" conditions (Marangoni et al., 2006). Kupffer cells can migrate to Disse's space and establish direct contact with hepatocytes through their cytoplasmic extensions delivering some internal constituents (pro-inflammatory cytokines, mediators *etc*) to the liver trabeculae (Perrault & Pecheur, 2009). In this setting, initial attachment of Chlamydia-infected granulocytes to Kupffer cells with further propagation of chlamydial pathogens in Kupffer cells and their final transmission to the hepatic microenvironment becomes a conceivable chain of events explaining the appearance of chlamydial pathogens in the liver.

It is worth noting that some other infectious pathogens use a similar strategy to invade hepatocytes. As an example, hepatitis B virus is revealed to invade liver tissue by scavenging liver sinusoidal endothelial cells, rather than hepatocytes themselves (Breiner et al., 2001). Therefore, initial invasion of non-hepatic cells might be a general mechanism in the development of hepatocyte infection.

Hepatocytes are polarized epithelial cells with basolateral and apical poles facing blood or bile respectively. The integrity of hepatic trabeculae and separation of blood and bile flows are maintained by tight junctions among adjacent hepatocytes. The basolateral surface of hepatocytes is considered to be a major gate for infectious pathogens delivered to the liver with the blood flow (Perrault & Pecheur, 2009). General mechanisms underlying chlamydial entry in hepatocytes are very likely to resemble those seen in other epithelial cells. Hepatocytes express most of the receptors required for chlamydial attachment and entry into the eukaryotic host cell. Liver has a remarkably high expression level for insulin-like growth factor 2, estrogen receptor complex and platelet-derived growth factor receptor required for chlamydial entry (Leung et al., 2004) . Moreover, liver is known to express abundantly LDL-receptor (Dietschy & Turley, 2002), which can be implemented in our view in the pathogenesis of chlamydiosis. Using an immunoprecipitation approach we have found (Petyaev et al., 2010) that two chlamydial biovars – *C. trachomatis* and *C. pneumoniae* can bind ApoB-containing lipoproteins under "*in vitro*" conditions. This was strikingly

distinct from no interaction with the HDL fraction. Furthermore, preincubation of the chlamydial pathogens with LDL particles enhanced in our experiments their ability to infect an immortalized hepatic HepG2 cell line, known to express abundantly LDL receptor. Association of bacterial particles with plasma lipoproteins and subsequent receptor-facilitated uptake does not seem to be an absolute requirement for chlamydial entry since it is possible to establish productive chlamydial infection under serum-free conditions . However, LDL- receptor appears to play an as yet poorly understood role in the initial stages of chlamydial infection. The likelihood of the *Chlamydia*-lipoprotein interactions under *in vivo* conditions becomes even more clear due to our recent identification of cross-reactive antibodies against chlamydial lipopolysaccharide and human ApoB (Petyaev et al., 2011). Besides adding a new variant to the physico-chemical aspect of interaction between *Chlamydia* and lipoproteins, the cross-protective immunological response and subsequent emergence of lipoprotein–specific antibodies may have a detrimental impact on the vascular endothelium. LDL-containing immune complexes are known to be taken up by lipid-laden macrophages and extensively deposited in atherosclerotic plaque (Miller et al., 2010). Therefore association of immune complexes with *Chlamydia* encouraged with cross-reactive antibody will endorse the pathogen delivery into atherosclerotic plaque.

It is worth mentioning that other infectious pathogens utilize lipoproteins and lipoprotein receptors in mechanisms of infectivity. It is well known that hepatitis C virus particles in human plasma are bound to very low density lipoproteins (VLDL) and low density lipoproteins (LDL) forming "viral lipoparticles" (Andre et al., 2005) . Their attachment and entry into hepatocytes requires LDL-receptor and surface receptor CD81 providing a dual receptor mechanism for viral attachment and entry into the target cells (Bartosch et al., 2003). Therefore, the ability of some infectious agents to invade hepatocytes seems to exploit the mechanism of molecular mimicry when an infectious particle "hijacks" a eukaryotic ligand and utilizes the corresponding eukaryotic membrane receptor as well as cross-reactive immunity for invasion of the host cell.

7. Hepatocytes

Extensive *in vitro* studies using cultured hepatocytes are required to understand the molecular mechanisms of liver involvement in chlamydial disease and its outcomes. A major methodological problem emerges from the fact that hepatocytes lose their tissue-specific phenotype and expression of liver-specific genes within 24-48 hours of isolation. For this reason immortalized hepatic cell lines have only a remote resemblance to the metabolic phenotype of whole liver (Guillouzo & Guguen-Guillouzo, 2008). This difficulty can be partially overcome by the use of freshly isolated hepatocytes plated onto collagen-coated dishes in the presence of certain hormones (Shimomura et al., 1999). It has been shown during the last few years that major chlamydial species can efficiently propagate in cultured hepatoma cells (Wang et al., 2007; Bashmakov et al., 2010) and accomplish their entire developmental cycle with the final release of infective progeny from ruptured hepatocytes. A similar observation has been made in experiments with freshly isolated hepatocytes from rat liver (I.M. Petyaev *et al*, 2011, unpublished results). Nevertheless, the nature of the multifaceted relationship emerging between *Chlamydia* and hepatocytes during infection can be understood only in the context of the unique properties of chlamydial pathogens as obligate intracellular parasites.

The chlamydial genome is relatively conserved. Among 1009 genes of *C. caviae* (formerly *C. psittaci*), 798 have orthologs present in *C. pneumoniae* and *C. trachomatis* (Read et al., 2003). These genes supposedly embody a nominal set of genetic material required for the survival of chlamydial species in host cells. The chlamydial genome contains genes encoding complete glycogen turnover, aerobic respiration and various transporter systems. However, genes responsible for biosynthesis of purine/pyrimidine bases, lipids and amino acids are absent or poorly represented (Vandahl et al., 2004). Moreover, the *C. trachomatis* genome encodes some genes for *de novo* synthesis of fatty acids, phosphatidylethanolamine and phosphatidylglycerol, although genes involved in polyunsaturated fatty acid pathways, biosynthesis of cholesterol, sphingolipids and glycerophospholipids have not been identified (Stephens et al., 1998) . Therefore chlamydial inclusions have to acquire major lipids such as cholesterol, sphingomyelin, and neutral lipids from the host cells by intercepting Golgi-derived lipid-containing vesicles (Moore et al., 2008) . Chlamydial pathogens are obligate parasites completely relying on the host cell metabolism. Nutrient deficiency in the host cells is not a matter of "discomfort" for replicating chlamydial pathogens it is rather a matter of ultimate survival and their ability to propagate. As an example, *C. trachomatis* is unable to replicate in the Chinese hamster ovary-derived cell line SPB-1, a mutant cell line deficient in sphingolipid biosynthesis (van Ooij et al., 2000). Similarly, severe tryptophan deficiency in the host cells leads to early developmental arrest of *C. trachomatis* and other chlamydial pathogens (Leonhardt et al., 2007). The metabolic profile of host cells predetermines the efficiency of chlamydial growth. It is believed, that endothelial cells provide a better metabolic environment for *C. pneumoniae* than monocytes due to distinct differences in iron homeostasis (Bellmann-Weiler et al., 2010).

If availability of substrates were the single requirement for sustaining chlamydial infection in eukaryotic cells, hepatocytes would certainly be a most advantageous type of host cell for chlamydial pathogens. Hepatocytes contain an enormous variety of compounds essential for *Chlamydia* . Liver is the organ with the highest rate of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase expression, a rate limiting enzyme of cholesterol biosynthesis (Dietschy & Turley, 2002). Hepatic cells also synthesize and store various fatty acids, triglycerides and phospholipids. They also operate a highly sophisticated system for endoplasmic vesicular transport of lipids (Jump, 2011). In addition, liver is the central organ of tryptophan turnover (Brandacher et al., 2007) with a remarkable ability to synthesize and catabolize different amino acids .

Recent studies demonstrate that chlamydial pathogens affect hepatocyte-specific functions. *C. trachomatis* infection in hepatocytes has been shown to be accompanied by enhanced transcription of fatty acid binding protein (FABP) leading to increased fatty acid uptake, while overexpression of FABP promotes chlamydial growth in transfected hepatocytes (Wang et al., 2007) . *C. trachomatis* infection also impairs endogenous transcription of another crucial gene of lipid homeostasis – LDL-receptor (LDL-R). We found that the decline in LDL-R mRNA in HepG2 hepatoma cells reflects multiplicity of infection and can be reversed by treatment with mevastatin, an inhibitor of HMG-CoA reductase. A similar tendency has been observed in HepG2 cells infected with *C. pneumoniae* (Y.Bashmakov *et al,* 2010 unpublished results). In both cases mevastatin treatment also reduced infection rate in cultured cells . First of all these results are in good agreement with the anti-chlamydial effects of statins reported in animal studies (Erkkaila et al., 2005; Tiirola et al., 2007). Secondly, the anti-chlamydial effects of statins observed under *in vivo* and *in vitro* conditions

open a new perspective in treatment of chlamydiosis whose "signature feature" is drug-resistance of the intracellular bacterial pathogen. Unlike other anti-microbial agents, statins have recently been shown to mediate their effects on infection by inhibiting post-translational protein prenylation in both host cell and infectious agent in a manner independent of cholesterol depletion (Khan et al., 2009; Amet et al., 2008). At the same time, protein prenylation is vital for *Chlamydia* and the functioning of the chlamydial Rab protein family represented by almost 70 members . Silencing of Rab 6 and Rab 11 by siRNA inhibits replication of *C. trachomatis* and impairs lipid acquisition from the host cells (Capmany et al., 2010). Extensive studies are required to show if targeting the geranylgeranylation system does indeed hold promise in the treatment of persistent chlamydial infection.

8. Conclusions

To the best of our knowledge, this chapter represents the very first attempt to discuss the small but growing body of evidence suggesting liver involvement in chlamydiosis. The variety of extragenital and extraocular manifestations of *C. trachomatis* infection as well as the frequent appearance of *C. pneumoniae* and *C. psittaci* in extra-respiratory tissues suggest the systemic character of chlamydial disease and validate a systemic therapeutic approach to the treatment of chlamydiosis. However, conventional diagnostic interventions in modern hepatology impose a substantial limit on direct assessment of chlamydial pathogens in the liver. Nevertheless, presence of chlamydial pathogens in the liver tissue can be verified in a considerable number of patients in particular those with inflammatory hepatobiliary disease. According to our recent results, genomic and immunohistochemical markers of *C. pneumoniae* are identifiable in the liver biopsies of 10.2% of patients with calculous cholecystitis, whereas *C. trachomatis* markers were found in 20.5% of patients from the same category (I.M. Petyaev *et al*, 2011, unpublished results). It has yet to be addressed whether the identification of chlamydial markers in the liver has any pathophysiological significance and possible relation to the course of disease or viability of the bacteria. Thorough bacteriological analysis of liver isolates, their susceptibility to antibiotics and their ability to cause aberrant and persistent variants of infection need to be studied .

To date, liver involvement in chlamydiosis constitutes a subject of rare and often casuistic communications overshadowed by reports on association of chlamydial infection with atherosclerosis and other inflammatory diseases . However, the apparent hepatotropism of chlamydial pathogens creates in our opinion a missing link between chlamydial infection and vascular disease since the liver plays an indispensable role in both lipid homeostasis and systemic inflammatory response. LDL receptor-mediated hepatic clearance of pro-atherogenic lipoproteins is a main route for cholesterol disposal in the human body. Therefore, the negative effect of chlamydial pathogens on LDL receptor expression in cultured hepatocytes may constitute an extremely important mechanism in explaining abnormalities of plasma lipid profile in the patient with chlamydiosis . It remains to be answered in future if the presence of chlamydial pathogens in liver or hepatocytes has any impact respectively on hepatic clearance or uptake of plasma lipoproteins via the LDL receptor-mediated mechanism.

Special consideration should be given to the evaluation of the possible clinical significance of interaction between chlamydial biovars with ApoB-containing lipoproteins. It is conceivable that persistent increase in plasma LDL and VLDL can promote dissemination of

chlamydial pathogens, in particular *C. pneumoniae,* to host cell with high or moderate expression of LDL-receptor. Finally, a question as to what extent chlamydial pathogen propagation in liver may affect systemic inflammatory response and hepatic insulin sensitivity has to be explored in the future.

9. References

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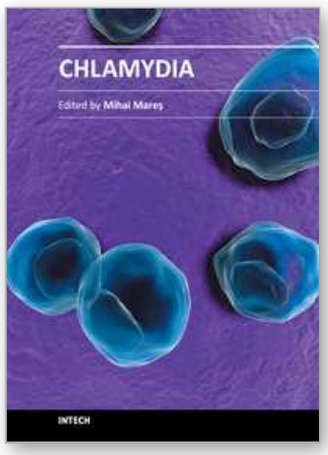

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Nowadays, Chlamydia still represents a redoubtable pathogen. Among its consequences, the blindness in children and severe impairment of reproductive health in adults are the most mutilating. Worldwide, it is estimated that six million of people suffer from post-trachoma blindness and almost 90 million become sexually infected each year. Due to its silent evolution and sexually transmission, the chlamydial infection can occur in anyone. The book “Chlamydia - A Multifaceted Pathogen” contains an updated review of all-important issues concerning the chlamydial infection. It comprises 18 chapters grouped in four major parts dealing with etiology and pathogenicity, clinical aspects, diagnosis and prevention. The new molecular data about the pathogenicity and the exhaustive presentation of clinical findings bring novelty to the book and improve our knowledge about Chlamydia induced diseases.

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