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Chlamydia trachomatis infection of the male genital tract: An update

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ABSTRACT

Chlamydia trachomatis (CT) is the most prevalent cause of sexually transmitted diseases. Although the prevalence of chlamydial infection is similar in men and women, current research and screening are still focused on women, who develop the most severe complications, leaving the study of male genital tract (MGT) infection underrated. Herein, we reviewed the literature on genital CT infection with special focus on the MGT. Data indicate that CT certainly infects different parts of the MGT such as the urethra, seminal vesicles, prostate, epididymis and testis. However, whether or not CT infection has detrimental effects on male fertility is still controversial. The most important features of CT infection are its chronic nature and the presence of a mild inflammation that remains subclinical in most individuals. *Chlamydia* antigens and pathogen recognition receptors (PRR), expressed on epithelial cells and immune cells from the MGT, have been studied in the last years. Toll-like receptor (TLR) expression has been observed in the testis, epididymis, prostate and vas deferens. It has been demonstrated that recognition of chlamydial antigens is associated with TLR2, TLR4, and possibly, other PRRs. CT recognition by PRRs induces a local production of cytokines/chemokines, which, in turn, provoke chronic inflammation that might evolve in the onset of an autoimmune process in genetically susceptible individuals. Understanding local immune response along the MGT, as well as the crosstalk between resident leukocytes, epithelial, and stromal cells, would be crucial in inducing a protective immunity, thus adding to the design of new therapeutic approaches to a *Chlamydia* vaccine.

1. Chlamydial infection: an introduction

Chlamydia trachomatis (CT) is the most prevalent bacterial cause of sexually transmitted infections in humans (Brunham and Rey-Ladino, 2005). Approximately 100 million new cases of genital CT infection are diagnosed worldwide every year, although it is believed that this number is underestimated (Mylonas, 2012; Senior, 2012). Most cases occur in the developing world, where diagnostic tools and antimicrobial treatment are almost rudimentary. However, chlamydial control programs in developed countries, most of which were devised more than 20 years ago, have had little impact on the incidence of CT infections. The quantity of diagnoses has increased over the past ten years,

Abbreviations: CM, *Chlamydia muridarum*; CT, *Chlamydia trachomatis*; EB, elementary body; FGT, female genital tract; MGT, male genital tract; NOD, nucleotide oligomerization domain; PEC, primary cultures of epithelial cells; TLR, toll-like receptor; PRR, pathogen recognition receptors; RB, reticular body.

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probably because of the use of more sensitive tests and increased awareness of this pathogen. CT is transmitted almost exclusively by sexual intercourse, and like all other sexually transmitted diseases, young and sexually active people are primarily affected. Additionally, it can be transmitted vertically from mothers to newborns during labor, resulting in children with chlamydial conjunctivitis and pneumonia. Although the prevalence of chlamydial infection is similar in men and woman, current research and screening strategies are still focused mainly on women (Chen and Basil, 2003). In consequence, the importance of this pathogen in infections of the male genital tract (MGT) has been underestimated.

In this study, we aimed to review the literature on genital CT infection with a special focus on the biology of CT infection in the MGT. Reassessing the importance of studying the MGT as a reservoir of CT, we focused on chlamydial prostatitis and on the innate as well as adaptive immune response triggered after infection. These data provided an overview of the current knowledge about the pathophysiology of male genital CT infection, in order to understand the effects of chronic infections, which are of therapeutic relevance in reproduction topics. As a consequence, the data synthesized here highlight the gap in *Chlamydia* vaccine development.

2. Epidemiology

The first isolation of CT from the genital tract was performed in the 1950s. Although this finding was reported several decades ago, until the 1990s most CT genital infections in both genders were underestimated because of their asymptomatic clinical course (Paavonen, 2011). The current high incidence of CT genital infection is the result of its chronic nature and the absent or mild symptoms, which lead to an undiagnosed disease. Although the true prevalence of genital CT infection is unknown, after reviewing the epidemiological data, it can be accepted that it varies between 1 and 40%, depending on the population (Mylonas, 2012). The prevalence in our local population is 8.7% (Cuffini et al., unpublished data), comparable to the reported prevalence of a Brazilian population attending health care centers, which presented an average prevalence rate of 11.7%, ranging from 4 to 25.7% (Rodrigues et al., 2011; Ramos et al., 2011). It has been become clear that the prevalence of chlamydial infection is very similar in both men and women (Lewis et al., 2012). CT infections occur mainly in women younger than 25 years and men younger than 35 years. The mean prevalence estimated by setting is similar for men and women (Cunningham and Beagley, 2008). A typical feature and major problem of genital CT infection is to assess the extent of the infection. This occurs because the onset of the infection is generally unknown, re-exposure is quite common, and pathogen clearance is rarely followed up. Therefore, screening for chlamydial infections is not common, but remains very important in preventing bacterial spread. Since 1 January 2008, in Germany, all women younger than 25 years with statutory health insurance are eligible for yearly screening for urogenital CT infections, as well as women undergoing a planned induced abortion. The primary goal of this new preventive measure is the reduction of severe sequelae, such as tubal infertility and ectopic pregnancies (Mund et al., 2008). Primary prevention by educational programs to promote behavioral changes has not proved to be very effective. Although routine screening for CT in men and women is insufficient based on feasibility, efficacy, and cost-effectiveness, well-established screening programs administered to the sexually active young population should be considered in clinical settings with a high prevalence of *Chlamydia*, in order to reduce bacterial spread in the general population (Peipert, 2003). An accurate diagnostic screening and rescreening by physicians differentiating between acute or persistent infection might help to resolve the infection and thus avoid possible fertility-related complications. Furthermore, CT infection facilitates the transmission of HIV and might be a co-factor in human papilloma virus (HPV)-induced cervical neoplasia (Anttila et al., 2001). Understanding the natural history of infection, the host immune response, and the impact they have on subsequent pathologies is crucial for a rational vaccine design.

A vaccine against CT would be of benefit to human health and is likely to have a significant impact on health care costs. Vaccine development would be essential for controlling CT infection, especially in developing countries where a major increase in prevalence has been reported during the last decade (Götz et al., 2002; Lewis et al., 2012). Sanitary programs for diagnosis and control of CT infection carried out in developed countries cannot be used in these places, mainly because of their expensive costs, thus highlighting vaccine development as a major issue in CT infection control (Iwasaki, 2010). However, primary prevention by vaccination is problematic since the development of a CT vaccine is still a major challenge (Brunham and Rey-Ladino, 2005; Pal et al., 2010; Paavonen, 2011). CT vaccine development is difficult because of the complex antigenic structure and limited knowledge of protective antigens. Also, the nature of protective immune response and correlates of protection are not well known. Performing a protective vaccine without harmful effects is a complex task that needs further research on immune correlates of protection against CT and disease pathogenesis (Rockey et al., 2009).

3. Microbiology and infection

Chlamydia trachomatis is a small obligate intracellular Gram-negative bacterium surrounded by a rigid cell wall that needs living cells to multiply because of its inability to synthesize essential nutrients, thus strictly depending on host biosynthesis pathways (Wyrick, 2000). The chlamydial chromosome consists of approximately one million base pairs and has a capacity to encode for up to 600 proteins. Nineteen different serotypes of CT can be distinguished based on their major outer membrane protein (MOMP) characteristics. Serotypes A, B and C cause trachoma; serotypes D through K are responsible for urogenital infections, and serotype L is responsible for lymphogranuloma venereum (Brunham and Rey-Ladino, 2005; Wagenlehner et al., 2006). The cell cycle of *Chlamydia* is different to those of other bacteria. *Chlamydia*