GENETICS

Chlamydia trachomatis and the HLA involvement in the development of infection and disease: a narrative review

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Abstract

Introduction. CT (*Chlamydia trachomatis*) is among the most common pathogens leading to sexually transmitted diseases. Considering the uncertain mechanism by which HLA polymorphisms influence the CT infection, reinfection, comorbidities or evolution and because there is no consensus regarding the alleles involved in the pathogenesis of the infection, we considered necessary to perform a review to summarize the current knowledge of HLA related to CT.

Methods. Pubmed was researched using key terms. Out of the 198 results found, we analyzed articles of all types which describe how the MHC, through HLA alleles, participates in the different stages of CT penetration in the body, including studies about cells or other molecules involved in the process.

Results. Almost 40% of the variation in the clinical course of CT infection depends on host genetic factors. There are haplotypes that influence the infection susceptibility/resistance, haplotypes that are involved in the recurrence of the infection, haplotypes that are related to tubal infertility, pelvic inflammatory disease development or trachoma. Antibody to Chsp60 (influenced by MHC genes) has been observed to correlate with late tissue-damaging sequelae. Toll-like receptors were found to increase the susceptibility to CT. The association of HLA-B27 creates susceptibility of reactive arthritis in the organisms infected by CT, but does not influence the carriage of CT.

Conclusion. We identified HLA haplotypes belonging both to MHC class l and ll, which influence different stages of CT infection. Genetic risk factors still need research, especially on Caucasians. Studies are moving towards designing a safe and effective vaccine.

Keywords: *Chlamydia trachomatis*, immunology, HLA, infertility, sexually transmitted disease

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Introduction

In the light of the uncertain mechanism by which HLA (human leukocyte antigen) polymorphisms influence the CT (*Chlamydia trachomatis*) infection, reinfection, the risk of medical comorbidities or evolution and because there is no consensus regarding the alleles involved in the pathogenesis of the infection with CT, there is a need for a review to summarize the current knowledge of HLA related to CT. Given the high prevalence of the CT infection worldwide and that there have been identified HLA molecules involved in the interactions between host and other sexually transmitted diseases, a deeper understanding of the immune mechanisms involved in the natural history of the disease could lead to finding a prognostic biomarker or immunotherapy strategies.

This paper aims to synthesize

published data regarding the HLA alleles that induce susceptibility or protection against the CT infection or that impact the evolution and the complications of the disease and also to describe the extent to which immunological processes are involved in the pathophysiology of this infection.

Methods

Pubmed database was searched using the key terms (chlamydia trachomatis) AND (HLA): ("chlamydia trachomatis" [MeSH Terms] OR ("chlamydia" [All Fields] AND "trachomatis" [All Fields]) OR "chlamydia trachomatis" [All Fields]) AND ("hla" [Journal] OR "hla" [All Fields]), which yielded 198 results. The last date the bibliography was consulted was July 12th, 2021.

The eligibility criteria for inclusion out of the 198 total results found in the search were: any article type, published any date, with immunology subject, which describes how the MHC (major histocompatibility complex), through HLA alleles, participates in the different stages of CT penetration in the human body (or the animal body insofar as there are biologically homologous areas), including studies about cells or other molecules involved in the process. The main focus was on identifying the exact HLA alleles and the susceptibility or protection they confer. The exclusion criteria referred to articles without immunology subject.

No language restrictions were applied. Each record was independently screened by two different reviewers (including the risk of bias), who then face to face agreed on the studies to be included in the paper. The selection of the included articles is shown in figure 1.

A meta-analysis was not possible to be conducted and the justification resides in the fact that the studied populations are heterogenous, the pathologies of the studied subjects differ and the methods of data processing and biological sampling are very different.

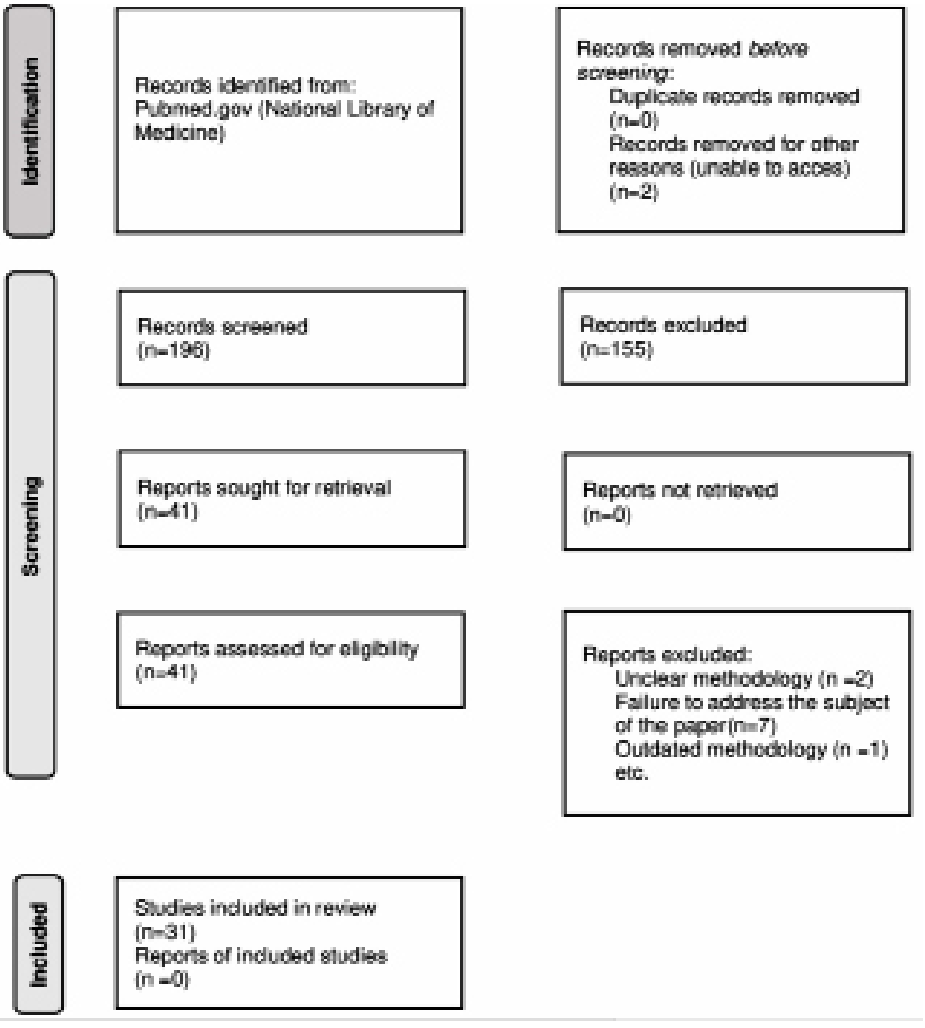

Figure 1. Studies inclusion criteria: flow diagram in concordance with PRISMA [1].

Results

HLA-studies on human population

The susceptibility to infection, reinfection and scarring as late sequelae of CT depends on the bacterial virulence factors, host susceptibility and socio-economic factors. The different evolution of the disease regarding severity or ocular/genital inflammation producing fibrosis could not be explained by a single pathophysiological mechanism, according to the medical literature up to date, suggesting the involvement of intricate factors and genes or gene interactions. Anti-infective defense could mainly depend on antigen presentation, but also on triggering immunity. It has been observed that natural disappearance of CT from the genital system occurs in almost 20% of infected cases, without producing sequelae [2].

Bailey et al. demonstrated that almost 40% of the variation in the clinical course of CT infection could depend on host genetic factors [3]. Toll-like receptors (TLR) are a group of much investigated receptors, present on antigen presenting cells (APC) and epithelial cells. TLR2 and TLR4, transmembrane pathogen receptors, recognize CT peptidoglycan and lipopolysaccharide, meanwhile TLR9, intracellular receptor, recognizes bacterial CpG islands (DNA regions, on a sequence from 5' to 3', where guanine follows cytosine). Studies did not find any association between TLR2 single nucleotide polymorphisms (SNPs) and susceptibility or severity of CT disease, but found TG (thymine-guanine) haplotype to be protective for tubal pathology [4,5]. Also, women with TLR4 +896A>G(rs4986790) SNP, who were also positive for CT IgG and antibody to the CT Hsp 60 (Chsp60) IgG, were prone to tubal pathology [6]. TLR4 SNP rs1927911 and TLR1 rs5743618 TT genotype were found to increase the susceptibility to CT infection [7]. C-C Chemokine Receptor Type 5 (CCR5), present on several immune cells, and its mutation (32-bp deletion within the CCR5 gene, CCR5 Δ32) could have a protective influence on developing tubal pathology with the condition of both alleles being mutated [8]. However, Laisk did not confirm this finding in his study [5]. Mannose-Binding Lectin (MBL) participates in the innate immune response binding to carbohydrate structures of bacteria (killing bacteria or enhancing phagocytosis) and inhibits CT infection [9,10]. Hyperproduction haplotype of MBL2, HYA/HYA, and the low-producing MBL2 genotypes are associated with tubal pathology, while the latter induces adverse outcomes of in vitro fertilization [11]. Various cytokines have been found to impact the tubal pathology in the CT infected organisms, some creating susceptibility to unfavorable outcomes (S), some offering protection against (P). The immunoregulatory functions are altered by: IL10 -1082 A allele together with HLA -DQA1 * 01:02 and HLA -DQB1*06:02 alleles (S), TNF-α -308 A allele (S) and the IL6 CC genotypes (P) [12,13,14], SNPs in NLRP3, associated with hypoproduction of IL1β [15] and the mutant allele of the IL12B rs3212227 SNP [16].

A recent study from 2021 investigated HLA-DRB1-DQB1 alleles/haplotypes that influence the CT infection in terms of greater probability (GP), earlier occurrence (EO), later occurrence (LO) and lower probability (LP). 262 Colombian women were enrolled in the retrospective study. Cervical samples were used to detect CT by PCR, whereas the HLA were typed by Illumina MiSeq sequencing. 16 HLA-DRB1 alleles significantly affected the CT outcome as follows: GP of infection (DRB1*01:02:01G), EO of infection or redetection (DRB1*01:03:01, 03:02:01, 03:02:02, 08:01:01G, 08:02:01G, 16:01:01), LO of infection (DRB1*04:10:01G, 11:01:02, 12:01:01G, 14:02:01G), LP of persistence (DRB1*10:01:01G). It was only DQB1*05:03:01G that was statistically significant among the alleles in the DQB1 locus, creating GP of clearance and also of persistence. LP of clearance and EO of persistence were observed to have a connection with DRB1 homozygous women. There were 47 out of the 142 DRB1-DQB1 haplotypes that significantly influenced infection outcome (e.g. DRB1*09:01:02G-DQB1*03:01:01G and DRB1*12:01:01G-DQB1*03:02:01G made the clearance of infection occur early). On the other hand, Pedraza et al uncovered via computer simulation several predicted peptides associated with susceptibility or resistance to CT events. There are 27 peptides that offer protection from infection, out of which 7 OMP (outer membrane protein)-derived and 17 from PMP (polymorphic OMP), and 11 show potential B-cell epitope regions (possibly serving a role in cellular or humoral immune response as mediators) [17].

Also regarding HLA haplotypes, in a study on 485 North American adolescents (mostly female and African American) with high risk of recurrent CT infection, in univariate analyses they found two positive associations with recurrent CT infection(s) (HLA-A*36 and DQB1*06), after adjusting for control variables (including other microorganisms). The association is characterized by odds ratio (OR) 2.56 (P= .040) and 1.80 (P=.018). Also a negative association was shown with Cw*16 (OR, 0.42, P= .031). There is another association, with DQB1*06 and DRB1*15-DQB1*06 haplotypes, that could possibly be explained by tight linkage disequilibrium. When defined by multivariable logistic-regression analyses, OR for these genetic markers has only changed very little, with P values less than .05. Targeting cytokine gene variants (SNPs), the same study found a negative association of recurrent CT and IL10 G-C-C haplotype at promoter positions -1082, -819, and -592 in the proximal promoter region (OR, 0.61, P= .044), in univariate analyses and multivariable logistic-regression analyses. Because IL10 is an anti-inflammatory cytokine and it was present in the genital tract infection after the CT infection, it could suggest that late sequelae of the disease might be produced by (multiple) reinfection rather than aberrant infection [2].

On the same population mentioned in the previous study (485 North American adolescents, out of which 124 males and 361 females, at high risk for HIV-1), using univariate chi-square2 or Fisher's exact tests and variable logistic regression models for the independence of genetic and nongenetic correlates of chlamydial infection, the distribution of HLA class l and ll alleles and haplotypes regarding CT infection was investigated. The case patients were the CT positive and they were compared with the CT negative group as controls. In univariate analyses, it was found that A*23 (23% versus 15%; P= .02), DRB1*15 (29% versus 19%; P= .01), and DQB1*06 (49% versus 34%; P= .0008) were more frequent among cases. Concerning high resolution DQB1*06, *06:02 and *06:03 were the most frequent. HLA-B*08 was the one more frequent in the controls (10% vs. 5%; P= .03). B*08-Cw*07 and DRB1*03:01-DQB1*02:01 were found less commonly (B*08-Cw*07, 4% versus 9%; P= .03; DRB1*03:01-DQB1*02:01, 12% versus 19%; P= .05), whilst B*44-Cw*04 and B*58-Cw*06 occurred with a higher frequency (B*44-Cw*04, 10% versus 4%; P= .01; B*58-Cw*06, 8% versus 4%; P= .05) [18].

Regarding CT infection complications, a cohort of 302 female sex workers from Nairobi, Kenya, out of whom 198 were HLA phenotyped and 54% HIV-positive at enrollment, were studied to find the risk factors for CT-associated pelvic inflammatory disease (PID). The cases number of CT associated-PID rose with declining CD4 cell count (P =.004, Mantel- Haenszel trend test). A CD4 count of <400 among HIV-infected women was a strong risk factor for CT PID (OR, 21.7; 95% CI, 1.2-383; P = .04). Only HLA-A31 statistically influenced the occurrence of CT induced PID, independent of other risk factors (OR, 5.6; 95% CI, 1.1-31.0; P = .04) [19].

Kinnunen et al. studied the relationship between CT tubal factor infertility and the host's immunoregulatory genes in 52 tubal factor infertility cases and 61 controls. The frequency of HLA DQB1*0602 was significantly higher in the tubal factor infertility cases (22/52) than in the controls (10/61), corrected P=.04. Furthermore, DQA1*01:02 and DQB1*06:02 together with IL-10 –1082 AA genotype were found statistically significant related to the tubal factor infertility cases (P=.005) [13].

The link between CT tubal infertility and HLA-DR and DQ was also assessed by Cohen et al in a study on 47 women with tubal factor infertility and 46 fertile controls from Nairobi, Kenya. They found two susceptibility alleles DQA*01:01 (P<0.02) and DQB*05:01 (P<0.01) and one resistance allele DQA*01:02 (P<0.01). Chsp60 antibody was more common among CT positive cases, even though it did not have statistical significance [20].

Three years later, Cohen et al published an article, analyzing 70 Kenyan women (50% seropositive for CT) to reassess their prior findings [21]. This study fails to confirm the statistical significance of DQA*01:01 and DQB*05:01, but finds that alleles linked to DQA*01:02 at the DRB1 and B5 loci (DRB1*15:03 and DRB5*01:01) were less common among CT-associated infertility cases. Therefore, the association between DQA*01:02 and resistance to CT tubal infertility is most likely explained by linkage disequilibrium with DRB1*15:03 [21].

Heat shock proteins (Hsps) are a group of polypeptides that are synthesized in stress conditions to preserve cellular functions, directing the folding and assembly of polypeptides in the cell [22]. Chsp60 has been observed to correlate with late tissue damage due to CT infection. The entire mechanism is unclear, but in mice the antibody responses to Chsp60 are partly influenced by genes from a MHC locus [23]. In a study on 113 sex workers from Nairobi, chosen out of 280 sex workers on whom a link between Chsp60 antibody and PID has been previously shown, it was intended to show if there was any link between HLA class ll, Chsp60 and microimmunofluorescent antibodies. By chi-squared test, it was found that HLA-DQA1*04:01 allele (OR, 3.26, 95% CI, 1.23-8.64, P = .01) and HLA-DQB1*04:02 allele (OR, 2.53, 95% CI, 0.91-7.02, P=.07) were correlated with a high number of antibodies to Chsp60. Moreover, it was checked if any DR or DQ was associated with CT induced PID, but none of them was statistically significant [24].

Early pregnancy factor (EPF) represents a homologue of Chaperonin 10, belonging to Hsp family, that has immunosuppressant and growth factor properties and serves for growing the embryo in the peri-implantation periods [25,26]. A study on 716 French women in the first trimester of pregnancy, 210 Portuguese infertile women and 1103 French males and females attending STI clinics, researched the association of selected HLA class II haplotypes with Chsp10 antibody. Therefore, a significant association was observed between the DR8 DQ4 haplotype and the concomitant presence of anti-Chsp10 antibodies (P< 0.05), but none of the subjects had EPF cross-reactive antibodies detected. It was observed Chsp10 antibody response operated through HLA class II genes, while EPF cross-reactivity did not necessarily operate through HLA class ll. Significant inhibition, indicating specific cross-reactivity, was observed in 94% serum samples with pEPF2, but not in any samples with the pEPF1 peptide. The authors suggest antibodies against Chsp10 may cross-react with human EPF peptide epitopes, with these antibodies acting as a marker of female infertility. Further research is needed to clarify if antibodies against Chsp10 neutralize EPF [27].

Ninety-two women from a randomized clinical trial collating inpatient versus outpatient antibiotherapy for PID, eligible for the PEACH study [28], aged 14 to 37, from USA, were investigated regarding the associations between HLA DQ alleles and CT cervicitis, endometritis, infertility and PID. This research has been carried out because the authors observed HLA-DQ correlated with

CT induced PID in multiple studies in African regions. For statistical analyses, in univariate analyses, chi-squared tests were utilized and for adjusting for race, logistic regression analyses were used. DQA *03:01 was found statistically significant associated with CT cervicitis and endometritis (OR, 4.4, 95% CI, 1.6–12.0), same as DQB*0201 and DQB*06:03 (1.5, 0.6–3.9) and (1.7, 0.4–6.7). The authors explain why the susceptibility alleles could be different from the ones in Kenyan studies on HLA-DQ: differences in background genes, the genetic heterogeneity among non white population and different comparison groups [29].

In a recent study, the architecture of human fallopian tube was restored from epithelial cell precursors. To investigate the innate inflammatory responses of the fallopian tube cells to CT infection, apical washes and basolateral medium were analyzed and compared to mock-infected cells. In comparison to the mock-infected cells, the apical washes showed increased levels of CXCL10, CXCL11, and RANTES (chemoattractants for multiple immune cell types). To find out the responses of CT inclusion containing cells, the fallopian tube cells were infected with CTE3024-mCherry and afterwards, the flow cytometry analysis revealed significantly increased expression of ICAM-1, VCAM-1, TLR2, interferon gamma receptor (IFN-⁄⁄R), and HLA class I and II molecules compared to mCherry negative-cells of the same culture [30].

On the other hand, Wang et al used *Chlamydia muridarum* to reproduce a murine model of female upper genital infection by CT. TC0668 in C. *muridarum* is a hypothetical chromosomal virulence protein that is involved in tubal infections and TC0668-mutant (G216∗) strain results in less pathological response in the upper genital tract. An isobaric tag for relative and absolute quantitation (iTRAQ)-based quantitative proteomics analysis was used to find differentially expressed proteins between TC0668 wild-type and TC0668 mutant strains at 6, 12, 18, and 24 h post-infection. Seven up-regulated proteins (encoded by SRPRB, JAK1, PMM1, HLA-DQB1, THBS1, ITPR1, and BCAP31) and 3 down-regulated proteins (encoded by MAPKAPK2, TRAFD1, and IFI16) from iTRAQ analysis of mutant strains were validated by (qRT)-PCR and, using Gene Ontology and Kyoto Encyclopedia of Genes and Genomes, differentially expressed proteins participating in the inflammatory responses, fibrosis, metabolic processes, and complement coagulation cascades were identified. The study concludes TC0668 may represent an important factor determining inflammatory responses and fibrosis by activating PI3K/Akt and NF-κB signaling pathways [31].

Murthy et al have used HLA-DR4 transgenic mice (which have the MHC replaced by HLA-DR4) to test the intranasal immunization with recombinant chlamydial protease-like activity factor (CPAF) to enhance CD4+ T-cell- and IFN-gamma-dependent protective immunity against murine genital chlamydial infection. The use of HLA-DR4 allele is explained by its predominant involvement in chlamydial antigen presentation to CD4+ cells in human species. Consecutive to CPAF-plus-interleukin-12 vaccination, HLA-DR4 transgenic mice showed strong CPAF-specific IFN-gamma production and high titers of anti-CPAF total antibody and immunoglobulin G2a and lower titers of IgG2b and IgG1 antibodies. The vaccinated transgenic mice resolved the infection significantly more efficiently than the mock-immunized animals, while the mice lacking MHC showed minimal antigen-specific immune responses and failed to resolve the infection. Therefore, the importance of HLA-DR4 molecules in the process of identifying and presenting CPAF epitopes should be taken into account when developing protective antichlamydial immunization [32].

Murthy AK researched forward and in 2008 there were identified 5 CD4+ T cell reactive epitopes and characterized the activation of epitope-specific CD4+ T cells following antigen immunization. The epitopes presented by the HLA-DR4 complex produced a marked cell-mediated immune response and accelerated the resolution of genital and pulmonary disease produced by Chlamydia. Recombinant CPAF-epitope fusion protein vaccination produces CPAF- specific CD4+ T cells (in the spleen of the HLA-DR4 transgenic mice). These cells can be identified by the use of HLA-DR4/CPAF-epitope tetramers. Overall, this finding counts as proof that a CPAF epitope vaccine confers protection against CT and HLA-DR4/CPAF-epitope tetramers can be utilised to identify CPAF epitope-specific CD4+ T cells in HLA-DR4 mice following C. *muridarum* or CT infection, monitor the immune response and develop human vaccines based on the murine research [33].

The cellular response of the human endocervix tissue when infected with CT is characterized by elevation of T cells and neutrophils (both CD4 and CD8 cell subsets). Independent of the infection status, the highest prevalence among cells was observed to be the effector T cells, with the numbers of CCR5 and CD103 expressing T cells a lot higher than in the blood. During the infection with CT, HLA-DR expression was significantly increased in the cytobrush sample than the blood sample(P=.0001) [34]. Sexually mature pig-tailed macaques (*Macaca nemestrina*) infected with CT serovar D were investigated also regarding complications in the genital apparatus [35].

Recently, the emphasis was moved on developing a vaccine against CT infection rather than finding risk factors. In this context, Pal et al found that HLA-DR4 transgenic mouse could be used to test vaccination antigens for humans. In mice with MHC class ll antigen being replaced by HLA-DR4, C. trachomatis serovar D (strain UW-3/Cx) was inoculated and produced infertility, the mice being equally and significantly protected by vaccination as the wild type mice C57BL/6 [36].

Table I. HLA alleles associated with CT infection.

Allele (HLA)	Discussion; OR (95% CI)	S/R	Population	Ref.
A*23	Associated with CT infection; 1.58 (0.92–2.70) P=.10	S	485 North American adolescents, mostly female and African American	18
A*28 (particularly A*6802)	Associated with trachoma;	S	Gambian	37
A*31	Associated with CT induced PID; 5.6 (1.1-31.0) P = .04	S	198 female sex workers for Nairobi, Kenya	19
A*36	Associated with recurrent CT infection; -univariate analyses 2.56 (1.04–6.30) P=.040 -full multivariable model 3.72 (1.39–9.96)) P=.009	S	485 North American adolescents, mostly female and African American	2
B*08	Associated with CT infection; 0.43 (0.17–1.07) P=.07	R	485 North American adolescents, mostly female and African American	18
B*14	Associated with inflammatory trachoma and follicular trachoma; 3.76; (1.70 – 8.33) P = .04	S	Tanzanian	42
Cw*16	Associated with recurrent CT infection; -univariate analyses 0.42 (0.19–0.92) P=.031 -full multivariable model 0.36 (0.15–0.86) P=.021	R	485 North American adolescents, mostly female and African American	2
A,B,C	3 specificities were statistically associated with susceptibility to early formation of adhesions. These specificities correspond with a B-like allele in the macaque and broadly polymorphic HLA class l region in humans. Two specificities were associated with relative resistance to adhesions formation, which are encoded by unidentified locus in the MHC class l in humans	S/R	44 sexually mature pig-tailed macaques (Macaca nemestrina) infected with the D serovar	35
DRB1*01:02:01G	Greater probability of infection 1.71-4.08 P=.000	S		17
DRB1*01:03:01	Earlier occurrence of redetection 0.00-0.05 P=.000	S		17
DRB1*03:02:01	Earlier occurrence of infection -1.29- (-0.67) P=.000	S		17
DRB1*03:02:02	Earlier occurrence of infection -0.86-(-0.25) P=.000	S		17
DRB1*04:10:01G	Later occurrence of infection 2.49-3.36 P=.000	R		17
DRB1*08:01:01G	Earlier occurrence of infection -1.20-(-0.54) P=.000	S		17
DRB1*08:02:01G	Greater probability of persistence and earlier occurrence of redetection	S		17
DRB1*09:01:02G	Greater probability of clearance 2.91-10.49 P=.000	R	262 Colombian women	17
DRB1*10:01:01G	Lower probability of persistence 0.19-0.57 P=.000	R		17
DRB1*11:01:01G	Greater probability of persistence 5.70-86.49 P=.000	S		17
DRB1*11:01:02	Later occurrence of infection 2.48-3.51 P=.000	R		17
DRB1*12:01:01G	Later occurrence of infection and greater probability of clearance	R		17
DRB1*13:05:01	Greater probability of persistence 1.74-7.75 P=.032	S		17
DRB1*4:01:01G	Later occurrence of infection and greater probability of persistence	R/S		17
DRB1*14:02:01G	Later occurrence of infection and greater probability of persistence	R/S		17
DRB1*15	Associated with CT infection	S	485 North American adolescents, mostly female and African American	2
DRB1*16:01:01	Earlier occurrence of redetection -0.27-(-0.08) P=.000	S	262 Colombian women	17
DQA*01:01	Associated with tubal infertility; 4.9 (1.3-18.6) P<.02	S	Kenyan	21
DQA*01:02	Associated with tubal infertility; 0.2; (0.005, 0.6) P<0.01	R	Kenyan	21
DQA*03:01	Associated with recurrent CT infection; 4.4 (1.6–12.0)	S	American	29
DQA*05:01	Associated with recurrent CT infection; 1.8 (0.7–4.9)	S	American	29
DQB*02:01	Associated with recurrent CT infection; 1.5 (0.6–3.9)	S	American	29
DQB*05:01	Associated with tubal infertility; 6.8 (1.6, 29.2) P<0.01	S	Kenyan	20
DQB*06:03	Associated with recurrent CT infection; 1.7 (0.4–6.7)	S	American	29
DQB1*05:03:01G	Greater probability of clearance and persistence	R<S	262 Colombian women	17
DQB1*06 and DRB1*15-DQB1*06	Associated with recurrent CT infection; -univariate analyses 1.80 (1.11–2.92) P=.018 -full multivariable model 1.95 (1.13–3.36) P=.017 (values for DQB1*06)	S	485 North American adolescents, mostly female and African American	2
DQB1*06	Associated with CT infection; 1.73 (1.12–2.66) P=.01	S	485 North American adolescents, mostly female and African American	2
DQB1*06:02	Associated with tubal factor infertility	S	Finish	13

S = susceptibility allele; R = resistance allele

HLA and trachomatous scarring

HLA-A*28 (and particularly the subtype A*6802) was more commonly found in the trachoma group of a case control study from Gambia, where the controls were matched for age, sex, ethnic group and location. Independently from the HLA class l association, it was found that G to A nucleotide substitution at position -308 of the TNF-α gene (MHC class lll region), therefore an increase in its level, was also associated with trachomatous scarring, even if the finding was not able to be demonstrated in other studies [37-39]. There is another study that sustains the hypothesis that high levels of TNF-α play a role in the trachomatous scarring process [40]. The same Gambian study reveals IL-10-1082G to be associated with scarring, fact that has also been proven in vitro [41].

Furthermore, PCR typing the Tanzanian subjects of Trichiasis Study Group and the Family Trachoma Study, HLA-B*14 was statistically significantly associated with inflammatory trachoma and follicular trachoma, whereas DR*B11 was related to the lack of trichiasis and HLA-B*07 and HLA-B*08 with the presence of trichiasis [42].

Another study did not find any HLA-DRB1 or DQB1 alleles associated to trachomatous scarring in Gambia, concluding that TH2 cells and cytokines play a part in the pathogenesis of trachoma [43].

Roberts et al found that a higher number of HLA-C2 epitope copies increases the odds of trachomatous scarring. Moreover, the odds further increase when killer-cell immunoglobulin-like receptors, KIR2DL2 and KIR2DL3, are detected [44].

In Oman, the scientists found that increased expression of HLA-DR16 and decreased expression of DR53 were correlated with trachomatous corneal opacity, but the subjects consisted of blood donors [45,46]. The expression of HLA-DR antigen by the conjunctival epithelial cells has been observed starting with 1989, using an immunoperoxidase procedure with TAL-11B3 monoclonal antibody [47].

A summary of the HLA alleles is shown in table I.

HLAB27

It is widely known that the association of HLA-B27 creates susceptibility of reactive arthritis in the organisms infected by certain pathogens like *Chlamydia, Shigella, Salmonella, Yersinia* or *Campylobacter*. The carriage of CT is not influenced by the presence of HLA-B27 [48]. In order to determine reactive arthritis or, by similar clinical patterns, other spondyloarthropathies or Reiter syndrome, the pathogen has to be a compulsory or facultative intracellular organism and to travel to the joints from the epithelium, adapt to the joint environment and escape the host defense. The CT enters monocytes and dendritic cells in the form of elementary bodies that transform into active reticulate bodies, it travels within them through the bloodstream to the joints, alters regulation of the expression of CT antigens, switches the source of ATP to that of the host, inhibits apoptosis of the host body, induces the apoptosis of the T lymphocytes and downregulates the expression of antigen presenting particles [49]. HLA-B27 inhibits CT replication and HLA-B27-restricted T cells, helping the microorganism survive [50,51].

The main role HLA-B27 plays in the human body is binding antigenic peptides and transporting them to T lymphocytes [52]. The phenomenon of molecular mimicry is involved in the process of reactive arthritis development. HLA-B27 presents CT peptides which are homologous to human derived particles. Cragnolini et al. discovered the first endogenously processed epitope involved in HLA-B27-restricted responses against CT in spondyloarthropathies and another epitope from the CT634 gene product, both showing a big proportion of homology with body sequences with HLA-B27 binding motif [53]. Alvarez-Navarro et al identified 3 chlamydial peptides which were presented by HLA-B27 endogenously, one of them structurally similar to self-derived HLA-B27 ligand [54]. Kuon et al described 9 murine peptides derived from CT proteins which stimulate CD8+ T cells and 11 peptides that stimulate patient-derived CD8+ T cells (there is an overlap of 8 of the peptides). This peptide hypothesis is thought to be the best to explain the presentation of peptides to CD8-positive T cells and the involvement of HLA-B27 [55].

On the other hand, there are studies that show HLA-B27 has no influence on infection or replication of CT serovar L2 within cell lines [56]. Bas et al. demonstrated also that lower IFN-gamma concentrations in the synovial fluid of patients suffering from CT reactive arthritis and express HLA-B27 are associated with risk of more severe or chronic arthritis [57].

Other considerations on the immunology of CT infection

It has been observed that, besides infecting human epithelial cells, Chlamydia spp. can also infect professional antigen presenting cells, such as macrophages, dendritic cells, granulocytes and lymphocytes [58]. The consequence of infecting those immune cells is that it allows the pathogen escape the immune surveillance and alter the immune response of the host. CT serovars E and L2 are able to infect and survive within peripheral blood monocyte-derived DCs, out of which MUTZ-3, a myeloid precursor obtained from a male leukemia patient can be used as surrogate for primary cells in researching the host-pathogen link in the CT infection [59]. CT L2 serovar was demonstrated to upregulate the lymph node homing receptor CCR7, meaning its ability to traffick CT to the urogenital or anorectal draining lymph node tracts (as it has already been demonstrated that the L2 is the causative agent of ulceration and blockage within lymphogranuloma venereum). When CT serovar D contaminates MUTZ-3, there is a 135-fold increase of IL8 secretion and 1.5 fold

increase in IFN-γ secretion. CT serovar D infecting the MUTZ cells was not able to upregulate CCR7, suggesting iMUTZ cell would remain within the initially infected site [60].

Ex-vivo stimulation with CT on peripheral blood mononuclear cells (PBMC) and endometrial cells determines an increase in IL-4 and a polarization towards type 2 immunity [61]. The stimulation of PBMC from infertile women with chlamydia Hsp60 determines higher production of IFN-gamma, IL-10 and IL-12 cytokines [62]. In a study comparing women with tubal infertility caused by CT and CT negative women, it resulted that level of IL-1beta was found to be significantly higher in CT positive women and these women also showed an upregulation of CXCL10, CXCL11, and HLA-A measured by qRT-PCR [63].

T cell phenotypes with implication in the CT pathology, even if not much studied so far, play a part in the adaptive immune mechanisms of the host, depending on the relationship of CD4+ and CD8+ T cells. Ogendi et al. found in the CT infected women: higher expression of T cell activation markers (CD38+HLA-DR+), Th1 and Th2-associated effector phenotypes (CXCR3+CCR5+ and CCR4+), and T cell homing marker (CCR7) for CD4+ and CD8+ T cells. After treatment, the markers decreased at their basal expression levels. The lack of reinfection was associated with higher number of CD8+ T cells co-expressing CXCR3 with CCR5 or CCR4, compared to reinfected women [64].

Discussion

Reviewing the eligible studies, it may be observed that some women are more vulnerable to reinfection and developing chronic infection and consequently sequelae than others who are able to elicit a strong Th-1 response. Therefore, our research supports that there is an underlying genetic susceptibility to inadequate immune responses. As also discussed by Debattista et al. [65], genetics could control the adequacy of Th-1 and Th-2 immune mechanisms at all the stages of infection, by influencing the pathogenesis through: the level of cytokine secretion of infected mucosal epithelial cells and by various lymphocytes and leukocytes, overstimulation or understimulation of feedback mechanisms, creating a suppression or exaggerated enhancement, or by determining the sensitivity and cross-reactivity of CD4 and CD8 T cells for a number of Chsp60 epitopes. Genetics could control also TLRs, killer-cell immunoglobulin-like receptors and T cell phenotypes.

According to literature, the allele HLA-B*08 (which confers protection) could be related to the 8.1 ancestral haplotype, which is typically a high immune responder phenotype characterized by elevated levels production of TNF-alfa production and a high risk of autoimmune diseases [66]. Therefore, the haplotype HLA-B*08, which is associated with CT infection, is part of the overall protective ancestral haplotype.

A particular situation arises in the case of HLA-B27, which does not influence the carriage of CT, but through the phenomenon of molecular mimicry, HLA-B27 presents CT peptides which are homologous to human derived particles, producing a group of spondylo-arthropathies, especially reactive arthritis.

The limitations of the review process consist of the heterogeneity of the study types and study populations, making it impossible to apply statistical methods and approximate the risk of bias. Future research is needed to investigate haplotypes of all populations, especially Caucasians - almost not included in any study. In our clinical observations, in the Dermatology Department, mostly young patients, predominantly male, presented with typical clinical symptoms of sexually transmitted diseases. Affirmatively, they had multiple sex partners, but none of them have had typed any HLA alleles. A couple of the analyzed studies date back about 20 years ago, even if they are still valuable in the present.

The latest studies concentrate more on epitopes, cells and cytokines in order to develop an efficient vaccine. As future directions, researching HLA alleles which impact the innate immune response and inflammation cascade, hopefully will lead to the development of an efficient vaccine against CT. It was found that HLA-DR4 transgenic mice could be used to test vaccination antigens for humans. Intranasal immunization with recombinant CPAF was used to enhance CD4+ T-cell IFN-gamma dependent protective immunity on HLA-DR4 transgenic mice. The transgenic mice remitted the infection much more efficiently and quickly than the mock-immunized mice [32]. A couple of human fallopian tube epithelial cell models have also been developed [67-69].

Conclusion

Similar to other infectious diseases, in the infection with CT several genes (or genes in linkage disequilibrium) are involved. Their identification and classifying as susceptibility or resistance genes for human CT pathology (any stage of the pathophysiology) is important because: it can facilitate the identification of high risk groups/ individuals who can benefit from therapy, it can guide the prevention campaigns (primary, secondary and tertiary prevention levels), it can decipher the immunological mechanisms, the protection factors against the development of chronic disease and scarring and it can be the start point in creating an effective and much needed vaccine against CT.

Almost 40% of the variations in the clinical course of CT infection could depend on host genetic factors. We have found that both MHC class l and MHC class ll alleles influence the different stages of CT infection. Not a single

haplotype has been identified by 2 or more studies to relate to the CT infection, excepting for HLA-DQB1*06.

CT is the most frequent bacterial pathological agent of sexually transmitted diseases. Epidemiological factors, clinical features, diagnosis, differential diagnosis and management have been worldwide researched. Genetic risk factors still need clarification. Future research is needed to investigate haplotypes of all populations, especially Caucasian. It has been observed that studies in the literature are moving, during the recent years, towards the design of a safe and effective vaccine, rather than towards identification of HLA haplotypes to influence the pathogenesis.

Abbreviations

Antigen presenting cells =APC
C-C Chemokine Receptor Type 5 = CCR5
Chlamydia trachomatis = CT
Chlamydia muridarum = C *muridarum*
CI = confidence interval
CPAF = chlamydial protease-like activity factor
CT heat-shock protein 60 = Chsp60
Earlier occurrence = EO
Early pregnancy factor = EPF
Greater probability = GP
Heat shock proteins = Hsps
IFN = interferon
Isobaric tags for relative and absolute quantitation= iTRAQ
Later occurrence = LO
Lower probability = LP
Mannose-Binding Lectin = MBL
MHC = Major histocompatibility complex
OMP = outer membrane protein
OR = odds ratio
Peripheral blood mononuclear cells = PBMC
PID = pelvic inflammatory disease
PMP = polymorphic outer membrane protein
R = resistance allele
Ref = reference number
S = susceptibility allele
SNP = single nucleotide polymorphism
TG = thymine-guanine
Toll-like receptors = TLR

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