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[Simone Filardo](#)^{*}, [Giulia Chicarella](#), [Rosa Sessa](#)[†], [Marisa Di Pietro](#)^{*,†}

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Review

Anti-*Chlamydia trachomatis* Host Defence Arsenal Within the Cervicovaginal Environment

Simone Filardo ^{1,2,*}, Giulia Chicarella ², Rosa Sessa ^{2,†} and Marisa Di Pietro ^{2,*,†}

¹ Regional Department of Clinical Microbiology, University Hospital Waterford, X91 ER8E Waterford, Ireland

² Department of Public Health and Infectious Diseases, "Sapienza" University, 00185 Rome, Italy

* Correspondence: S.F. simone.filardo@live.com; M.D.P. marisa.dipietro@uniroma1.it

† M.D.P. and R.S. contributed equally to this work.

Abstract

Chlamydia trachomatis has a significant impact on public health, especially among adolescents and young women; it primarily affects urogenital epithelial cells leading to cervicitis and urethritis with > 90 % of cases showing no symptoms. Consequently, chlamydial infections are commonly misdiagnosed and, if untreated, they may result in severe reproductive sequelae including infertility. A better understanding of *C. trachomatis* cell biology as well as bacterial-host cell interactions may be helpful to identify strategies able to counter its transmission among populations as well as its dissemination in reproductive tissues, reducing the risk of developing severe reproductive sequelae. Therefore, the present review aims to summarize the evidence on the interplay amongst host defence factors within the cervicovaginal environment to resist *C. trachomatis* infection and on sophisticated strategies employed by this clinically significant pathogen to counter these mechanisms.

Keywords: *Chlamydia trachomatis*; cervicovaginal environment; host defence factors

1. Introduction

Chlamydia trachomatis, the leading cause worldwide of sexually transmitted bacterial diseases in humans, has significant public health implications, particularly for women of reproductive age. According to the 2020 World Health Organization's report, approximately 129 million new cases of *C. trachomatis* occur each year, with young people and adolescents particularly vulnerable to chlamydial infections; in 2023, the highest rate of *C. trachomatis* cases was reported among young women aged 15-24 years in the United States (15-19 years: 3,435.1 per 100,000; 20-24 years: 2,566.1 per 100,000) and in Europe (15-19 years: 400 per 100,000; 20-24 years: 700 per 100,000) [1,2].

In women, *C. trachomatis* primarily affects urogenital epithelial cells leading to cervicitis and urethritis, with > 90 % of cases showing no symptoms. Consequently, chlamydial infections are commonly misdiagnosed and, if untreated, may result in severe reproductive sequelae including pelvic inflammatory disease, ectopic pregnancy, and obstructive infertility. Furthermore, *C. trachomatis* genital infections also play a role in the acquisition of other sexually transmitted infections, such as HIV, and seem to be involved in the pathogenesis of HPV-mediated cervical cancer [3,4]. In addition to genital infections, *C. trachomatis* has harmful effects on pregnancy outcomes and neonatal health, including pre-term birth, stillbirth, and low-birthweight babies [5,6].

In recent years, the phenomenon of antibiotic resistance has also been described in *C. trachomatis*, as shown by several treatment failures with first- and second-line antibiotics (azithromycin and doxycycline) towards urogenital infections, and by *in vitro* studies reporting diverse mutations in *C. trachomatis* genome associated with the resistance to antibiotics [7].

In this scenario, a greater understanding of *C. trachomatis* cell biology as well as bacterial-host cell interactions is of particular importance to identify strategies able to counter its transmission among populations as well as its dissemination in reproductive tissues, reducing the risk of

developing severe reproductive sequelae. Therefore, the present review aims to summarize the evidence on the interplay between *C. trachomatis* and host defence factors within the cervicovaginal environment.

2. *C. trachomatis* Interaction and Host Defence Factors

2.1. *C. trachomatis* Developmental Cycle

C. trachomatis, a gram-negative obligate intracellular bacterium, has a unique biphasic developmental cycle characterized by two morphologically and functionally distinct forms: the elementary body (EB) and the reticulate body (RB). EB is the extracellular infectious form, classically considered metabolically inactive, whereas the RB is the intracellular, metabolically active, replicative form.

The developmental cycle begins when EBs attach and enter the host cell by endocytosis. It is thought that the interaction of EBs with the host cell occurs in a two-step process involving a reversible interaction with heparan-sulphate glycosaminoglycan (GAG) receptors, followed by an irreversible binding to the cell surface via membrane proteins. Several *C. trachomatis* adhesins, including outer membrane complex protein B (OmcB) and the major outer membrane protein (MOMP), are able to bind directly, or via heparan sulphate, to GAG receptors. Other chlamydial adhesins and host receptors involved in the adhesion of *C. trachomatis* to host cells are polymorphic membrane proteins (Pmps) and human epidermal growth factor receptor. Also, *C. trachomatis* lipopolysaccharides (LPS) has been described to interact with the host cell cystic fibrosis transmembrane conductance regulator (CFTR), resulting in the uptake of the pathogen within the host cell.

Soon after the attachment to the host cell membrane, EBs are internalized and confined to a vacuole termed inclusion, through a process requiring the secretion of Type III secretion system (T3SS) effector proteins, including the translocated actin -recruiting phosphoprotein and the translocated membrane-associated effector A, able to modulate the host cell actin. Then, the chlamydial inclusion is decorated with T3SS proteins, known as inclusion membrane (Inc) proteins, that subvert host cellular processes to establish the infection and promote the survival of *C. trachomatis*. Indeed, Incs play a key role in nutrient acquisition through the recruitment of Golgi and endoplasmic reticulum vesicles, and in the escape of EB-containing endosomes from the endocytic-lysosomal pathway. In addition to Incs, other chlamydial proteins, like the chlamydia protease-like activity factor (CPAF) and the high temperature requirement A protein (HtrA), have an important role in maintaining the integrity of the inclusion and in promoting the intracellular survival of *C. trachomatis* [8,9]. Within the inclusion, EBs shift to RBs, which replicate by binary fission and, after several rounds of replication, differentiate back into EBs. Interestingly, recent studies have proposed a further mechanism for *C. trachomatis* cell division, namely budding, as evidenced by fluorescent imaging and live cell microscopy used to visualize the localization of divisome proteins and dividing RBs, respectively [8–11]. After approximately 48–72 h, the EBs, released by inclusion extrusion or cell lysis, spread and infect neighbouring epithelial cells, perpetuating the infectious process [8].

Over the years it has been evidenced that *C. trachomatis* can enter into a persistence state when exposed to stress conditions such as treatment with penicillin, interferon-gamma (IFN- γ) or iron depletion; RBs become enlarged, leading to atypical forms, namely persistent forms, with no production of infectious progeny. Following the removal of the inducer, the persistent forms can transition back into RBs, resuming the developmental cycle. Persistent forms are considered critical for inducing a chronic inflammatory state and the consequent tissue damage underlying the severe reproductive sequelae related to *C. trachomatis* urogenital infections, for they are more suited to evade the host immune response and harder to eradicate with antibiotics [12].

2.2. Cervicovaginal Defence Factors Towards *C. trachomatis*

In the female genital tract, the anti-chlamydial host arsenal involves the cervicovaginal microbiota, various proteins, and the immune system (Figure 1).

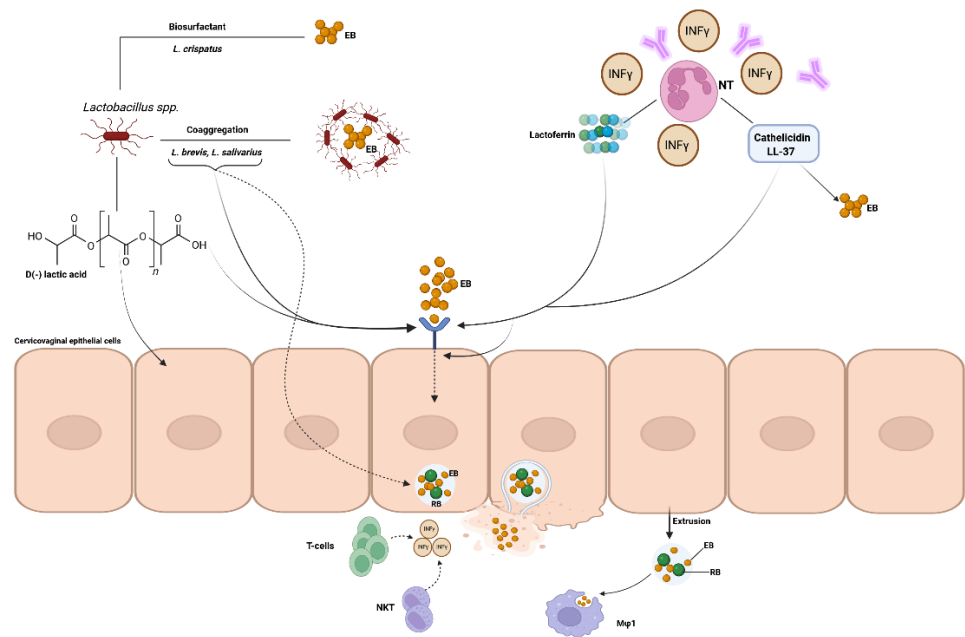


Figure 1. Schematic representation illustrating how cervicovaginal host defense arsenal can counter *C. trachomatis* infection. *L. crispatus*, *L. salivarius* and *L. brevis* have adverse effects on elementary chlamydial bodies (coaggregation, bio-surfactant production), on chlamydial adsorption to epithelial cells (competitive exclusion or reduced exposure and expression of the host receptor) as well as on the intracellular phases of chlamydial replication; *L. crispatus* also shows anti-chlamydial activity by inhibiting epithelial proliferation and cell-cycle regulation by D (-) lactic acid production. Lactoferrin inhibits the early phases (adhesion and invasion) of *C. trachomatis* infection whereas cathelicidin LL37 inactivates EBs or prevents their entry into the host cell as well as their intracellular growth. Neutrophils, in the presence of IFN-γ and anti-Chlamydia antibodies, and IFN-γ/LPS induced macrophages (M1-type macrophages) can kill *C. trachomatis*. IFN-γ-produced by T and natural killer cells can kill *C. trachomatis* via depletion of tryptophan and the ubiquitylation and destruction of chlamydial inclusions.

2.2.1. Cervicovaginal Microbiota

The cervicovaginal microbiota of healthy women is dominated by facultative anaerobes, mostly represented by *Lactobacillus* species. On average, the concentration of lactobacilli is between 10⁷ and 10⁹ colony-forming units (CFUs) per gram of vaginal secretion, while other bacteria, such as *Prevotella* spp., *Peptostreptococcus* spp, *Atopobium vaginae*, *Gardnerella vaginalis*, etc., are present in low abundance [13].

Over the years, a growing body of evidence has shown that the cervicovaginal microbiota composition is highly dynamic and affected by age, ethnicity, lifestyle, poor hygiene practices, antibiotic and hormonal therapies, use of probiotics as well as hormonal fluctuations across the female lifespan, and the activity of the immune system. Recent evidence has also suggested that increased psychological stress, the consumption of processed food rich in fat and carbohydrates, and higher levels of urbanization may be emerging factors impacting cervicovaginal microbiota composition [14].

Thanks to the development of metagenomic approaches based on the sequencing of the bacterial 16s rRNA gene via Next Generation Sequencing, it is currently possible to have a more accurate profiling of the human cervicovaginal microbiota composition leading to a deeper understanding of

the importance of microbiota in maintaining cervicovaginal health. Nowadays, five Community State Types (CST) based on the dominant lactobacillus species have been described [15]. CST I and CST II are dominated by *Lactobacillus crispatus* and *Lactobacillus gasseri*, respectively; both *Lactobacillus* species are known for their strong protective properties and the maintenance of a low vaginal pH. CST V is characterized by the high abundance of *Lactobacillus jensenii*, also considered as a stable and beneficial commensal. On the contrary, CST III, dominated by *Lactobacillus iners*, has been described to play an ambiguous role in the maintenance of cervicovaginal health, since *L. iners* has been found in both healthy cervicovaginal environments and pathological conditions [16]. Lastly, CST IV is characterized by a scarcity of *Lactobacillus* spp. and the presence of a diverse array of strict and facultative anaerobes such as *Gardnerella vaginalis*, *Atopobium vaginae*, *Prevotella* spp., etc. [15,17,18]. Clinically, CST IV is referred to as bacterial vaginosis (BV), considered the most common pathological condition globally among reproductive-age women with an estimated prevalence of 23 -29 %, and associated with an increased risk for the acquisition of sexually transmitted infections [19].

To date, clinical metagenomic studies on cervicovaginal microbiota show that the dominant bacterium in healthy women is *L. crispatus* (CST I), followed by *L. gasseri* (CST II) and *L. jensenii* (CST V). By contrast, a cervicovaginal microbiota dominated by *L. iners* (CST III) or by a diverse mix of anaerobes (CST IV) is associated to *C. trachomatis* infection [20,21]. The high rate of *C. trachomatis* infection in women with CST IV microbiota can be correlated to the presence of anaerobes like *Prevotella* spp., able to produce indole, an intermediate of tryptophan, a well-known key nutrient for the intracellular growth of Chlamydia. *C. trachomatis* cannot synthesize tryptophan de novo and urogenital *C. trachomatis* strains have evolved a strategy to bypass tryptophan starvation related to IFN- γ exposure; specifically, these chlamydial strains express a functional tryptophan synthase, encoded by the *trpBA* genes, which allows them to convert indole into tryptophan [22]. In addition to the presence of indole-producing anaerobes, the cervicovaginal environment harbouring a CSTIV microbiota is likely poor in iron, another critical nutrient required by *C. trachomatis* [23]; specifically, the anaerobic bacteria associated with bacterial vaginosis (CST IV) metabolize all the available iron, inducing *C. trachomatis*, in response to iron depletion, to switch to the tryptophan salvage pathway by increasing the production of tryptophan synthase [24,25] (Figure 2).

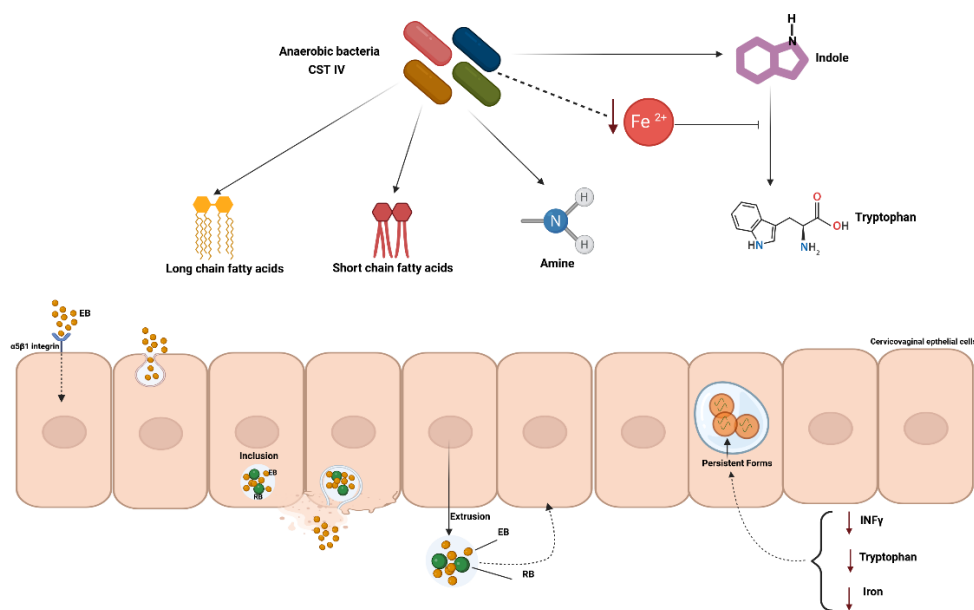


Figure 2. Schematic representation illustrating cervicovaginal risk factors for *C. trachomatis* infection. A microbiota dominated by a diverse mix of anaerobes (CST IV), clinically referred as bacterial vaginosis, can produce several key metabolites, such as indole and long chain fatty acids, for *C. trachomatis* intracellular growth

and maintaining the inclusion. Anaerobic bacteria also metabolize iron inducing *C. trachomatis*, in response to iron depletion, to switch to the tryptophan salvage pathway by increasing the production of tryptophan synthase. In presence of low levels of iron, tryptophan, or IFN- γ (during chronic infection), *C. trachomatis* can generate persistent forms, responsible for the inflammatory state underlying tissue damage.

Other interesting data on the association between CST IV and *C. trachomatis* came from metabolome studies identifying distinct metabolic features (cadaverine, putrescine, long chain fatty acids like decanoic, pentadecanoic, heptadecanoic, arachidic, behenic, cerotic, and myristic acid) and some metabolites, such as oleic acid, as important for chlamydial genital infection [26]. Indeed, in the literature, there is evidence that *C. trachomatis* is dependent on long chain fatty acids, mainly oleic acid, for maintaining the inclusion and sustaining the infection [27]. Metabolome and microbiome analyses alongside *in vitro* studies have evidenced that a cervicovaginal fluid containing a CST IV microbiota, biogenic amine (e.g. putrescine and cadaverine) and short chain acids had poor anti-chlamydial activity [28,29].

The high rate of *C. trachomatis* genital infection related to CST IV microbiota is also supported from *in vitro* studies highlighting that the biofilm produced by *Gardnerella vaginalis* may be a reservoir of *C. trachomatis*. Specifically, by using *in vitro* co-culture transwell-based biofilm model, it has been demonstrated to ability of *C. trachomatis* to survive, for up to 72 hours, inside the biofilm produced by *G. vaginalis*, retaining its infectious properties [30].

Concerning the protective effect of specific cervicovaginal *Lactobacillus* species against *C. trachomatis*, Gong et al., [31] was the first to demonstrate the anti-chlamydial activity of several standard strains of *L. crispatus*, *L. gasseri* and *L. jensenii* towards *C. trachomatis* EBs through a lactic acid-dependent mechanism. Then, Edwards et al. [32], in 2019, by using a three-dimensional cervical epithelium model, demonstrated the D (-) lactic acid mediated-inhibition of epithelial cell proliferation as a further protective mechanism by which *L. crispatus* and *L. jensenii* were able to reduce *C. trachomatis* infectivity. By contrast, *L. iners*, which produces the L (-) isoform of lactic acid, did not reduce cell proliferation, resulting in a lower anti-chlamydial activity [32,33]. A further interesting finding observed by Edwards et al. [32] was the ability of D (-) lactic acid producing *Lactobacillus* spp. to modulate host functions by regulating epigenetic mechanisms involving histone deacetylase-controlled pathways, leading to a reduction in cell cycling and, hence, reduced *C. trachomatis* vulnerability (Figure 1).

Other protective mechanisms include the ability of several cervicovaginal *Lactobacillus* species to negatively impact on the different phases of *C. trachomatis* developmental cycle. Specifically, *Lactobacillus* spp. had adverse effects on elementary chlamydial bodies, on chlamydial adsorption to epithelial cells and on the intracellular phases of chlamydial replication [34–37]. For example, *L. crispatus*, *Lactobacillus salivarius* and *Lactobacillus brevis* showed co-aggregation abilities with chlamydial elementary bodies as well as inhibitory activity toward their adhesion to host cell surface reducing, hence, *C. trachomatis* infectivity [34–37]. In addition, *L. crispatus* clinical isolates reduced *C. trachomatis* infectivity via the production of a bio-surfactant that may act on the fatty acids in the lipopeptide structure of elementary bodies [38]. Lastly, *L. crispatus* reduced *C. trachomatis* infectivity in cervical epithelial cells by altering the lipid composition of the host cell membrane as well as reducing both the exposure and expression of the $\alpha 5$ subunit of $\alpha 5 \beta 1$ integrin, a crucial receptor for Chlamydia entry into the host cell [39]. Recently, the down-regulation of *ITGA5* gene encoding the $\alpha 5 \beta 1$ integrin and genes involved in cell-cycle regulation (*CCND1*, *CDKN1A* and *HER-1*) related to D (-) lactic acid produced by *L. crispatus*, suggests changes in the state of histone lactylation as a further anti-Chlamydia epigenetic pathway [34] (Figure 1).

In addition to a direct anti-chlamydial effect of cervicovaginal *Lactobacillus* spp., there is also evidence that they may indirectly counter chlamydial genital infection by, for example, limiting the availability of metabolites essential for chlamydial growth, such as glucose. In support of this mechanism, low levels of glucose were found in the cervicovaginal fluid collected from women with a microbiota enriched in *L. crispatus*, and possessing anti-chlamydia activity [28,36].

2.2.1. Cervicovaginal Proteins with Anti-Chlamydial Activity

Among the several immune factors present within the cervicovaginal environment, there is lactoferrin, an 80-kDa multifunctional cationic glycoprotein belonging to the transferrin family. It possesses iron-binding capacity, and it is predominantly found in milk and, to a lesser extent, in the cervical mucus, where it is released by mucosal epithelial cells and neutrophils following an infection [40]. In *C. trachomatis* infected women, lactoferrin levels were higher when compared to uninfected women [41–43]. The protective role of lactoferrin against *C. trachomatis* was mostly evidenced by *in vitro* studies demonstrating its ability to inhibit its entry into host cells when incubated with cervical cell monolayers before or at the moment of the infection [35,44]. As potential mechanism of anti-chlamydial activity it was hypothesized that lactoferrin can bind to cell surface glycosaminoglycans as well as to heparan sulphate proteoglycans [45,46] recognized as potential receptors for *C. trachomatis* adhesion [47]. Particularly interesting is also the intriguing interplay of lactoferrin/*L. brevis* in inhibiting the early phases (adhesion and invasion) of *C. trachomatis* infection of cervical epithelial cells, as evidenced by a stronger anti-chlamydial activity exerted by their combination. Specifically, different effects of *L. brevis* and lactoferrin on *C. trachomatis* were demonstrated, being *L. brevis* able to inhibit the adhesion and lactoferrin the internalization of chlamydial EBs into host cell [35]. In addition to lactoferrin, other host defence peptides, mainly cathelicidin LL-37, released in the cervicovaginal fluid from genital epithelial cells and/or recruited neutrophils, have been demonstrated to inhibit *C. trachomatis* infection by inactivating EBs or by preventing their entry into the host cell as well as their intracellular growth [48].

2.2.2. Immune Response

The female reproductive genital tract is lined by epithelial cells overlaid by a mucus layer representing an important protection barrier against sexually transmitted infections, such as *C. trachomatis*. Upon breach of this barrier, infected epithelial cells release cytokines and chemokines, mainly IL-8, that recruit innate immune cells including neutrophils, and monocytes at the infection site. Neutrophils and monocytes/macrophages engage free chlamydial EBs or extrusion, an inclusion-like structure liberated from non-lytic epithelial cells; only neutrophils, in the presence of IFN- γ and anti-Chlamydia antibodies, and IFN- γ /LPS induced macrophages (M1-type macrophages) are able to kill *C. trachomatis* [49,50]. In addition, neutrophil degranulation products such as lactoferrin and cathelicidin as well as neutrophil extracellular traps, extracellular DNA associated with antimicrobial proteins, have been described to be effective against *C. trachomatis* [49].

Genital tissue is also composed of dendritic cells and T lymphocytes; recent studies using mouse and *in vitro* models of infections have demonstrated that an efficient CD8⁺ T cell response was not generated upon chlamydial infection of dendritic cells due the ability of this pathogen to induce cell death via apoptosis [51]. On a different note, IFN- γ -producing CD4⁺ T cells were strongly associated with a protective response against *C. trachomatis*. Indeed, IFN- γ -mediated depletion of tryptophan in human epithelial cells has been demonstrated to inhibit chlamydial growth, potentially eradicating the infection under continuous IFN- γ exposure. However, CD4⁺ T cells cannot produce IFN- γ during the early stages of infection, and, hence, natural killer cells, present throughout the female genital tract as part of the mucosal immune system, have been described to play a critical role in limiting Chlamydia infection by producing IFN- γ early and contributing to the Th1 immune response [52].

To date, IFN- γ is well known to activate the catabolic depletion of L-tryptophan via indoleamine-2,3-dioxygenase, restricting *C. trachomatis* growth within host cells. More recent research has also shown IFN- γ -mediated restriction of chlamydial growth within human epithelial cells through the depletion of other essential nutrients (glucose; amino acids: glutamate, aspartate, glycine, and alanine; Krebs cycle intermediates: citrate, aconitate, α -ketoglutarate; pyrimidine/purine nucleosides: nucleotide triphosphates adenosine triphosphate, cytidine triphosphate, uridine triphosphate), dependent on metabolic transcription factors such as c-Myc and HIF- α . Interestingly, the depletion of c-Myc has been demonstrated to restrict intracellular chlamydial growth even in the absence of IFN- γ , while the over expression of c-Myc protect *C. trachomatis* from IFN- γ -mediated

persistence within human epithelial cells [53,54]. Additionally, IFN- γ has been described to counter *C. trachomatis* infection by inducing pyroptosis in macrophages, a pro-inflammatory type of cell death via Nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3 (NLRP3) inflammasome [53].

Of pathological and clinical importance is the different immune response observed in mouse models during acute, and chronic *C. trachomatis* infections. During acute infection, macrophages were driven to the M1 phenotype with increased production of IFN- γ from both CD4+ T helper type 1 (Th1) cells and CD8+ T cells and consequent control of chlamydial replication and its clearing. Otherwise, during a chronic infection, a macrophage-T cells mediated immune suppression characterized by the presence of macrophages with an M2 phenotype, a reduced number of CD4+ and CD8+ T cells secreting mostly immunosuppressive cytokines (Transforming growth factor β and Interleukin-10), instead of IFN γ , was observed. As a result, *C. trachomatis* generated persistent forms and M2 macrophages with low CD40 expressions promoted the differentiation of CD4+T helper type 2 (Th2) cells and regulatory T cells leading to sustained *C. trachomatis* genital infection in mouse models [55].

3. Discussion

Important advances in the understanding of *C. trachomatis* interaction with host **defence** factors have been achieved in the field of genital infections. It has been acknowledged for over a decade that a cervicovaginal microbiota dominated by *Lactobacillus* spp. plays a key role in maintaining the homeostasis and protecting the women reproductive health towards sexually transmitted pathogens, including *C. trachomatis*. However, the recent development of metagenomic approaches based on the sequencing of the bacterial 16s rRNA gene has evidenced that not all *Lactobacillus* species have protective activity against *C. trachomatis*. Indeed, a growing number of sequencing studies and in vitro experiments based on 2D models have shown that cervicovaginal microbiota populated by *L. crispatus* plays a protective role against *C. trachomatis*. By contrast, a cervicovaginal microbiota dominated by *L. iners* (CST III) or by a diverse mix of anaerobes (CST IV) is associated with *C. trachomatis* infection [20,21]. Then, thanks to metabolomic analyses, several interesting metabolites have been associated with protective or harmful bacterial signatures in regard to *C. trachomatis* infection. For example, D (-) lactic acid was associated with *L. crispatus* but not to *L. iners*; biogenic amines, short-chain and long chain fatty acids were related to CST IV microbiota [26,28,29].

In the literature, there are proofs of several anti-chlamydial mechanisms attributed to *L. crispatus* or lactoferrin, released by neutrophils, including EB coaggregation and competitive exclusion [31,34–39]. The strong anti-chlamydial activity of *L. brevis* in combination with lactoferrin, and the anti-chlamydial epigenetic pathways such as the inhibition of epithelial proliferation and cell-cycle regulation mediated by D (-) lactic acid producing lactobacilli, evidence the crosstalk between cervicovaginal microbiota and host defense factors in the fight against *C. trachomatis* infection [32,34,35]. Also, the anti-inflammatory activity related to cervicovaginal specific *Lactobacillus* spp. and lactoferrin underscores the critical role of cervicovaginal host defense factors in the pathogenesis of *C. trachomatis* genital infection [56]. However, the major player in clearing infections remains the IFN- γ , produced by natural killer cells and T cells, via the depletion of critical nutrients for *C. trachomatis* such as tryptophan, or via the ubiquitylation and destruction of chlamydial inclusions [53].

In spite of the different host-defence mechanisms, *C. trachomatis* has evolved successful counter strategies to ensure its long-term relationship with the host. Firstly, *C. trachomatis* urogenital strains can synthesize tryptophan from indole or from its precursor, chorismate, produced by anaerobes harbouring in the CST IV microbiota [57,58]. Interestingly, the production of tryptophan is further increased following iron depletion which generally may occur when *C. trachomatis* and anaerobic bacteria harbouring CST IV microbiota coexist within cervicovaginal environment [24]. Secondly, *C. trachomatis* can generate persistent forms responsible for chronic inflammatory state underlying tissue damage associated with *C. trachomatis* genital infection. Recently, it has been evidence that IFN- γ not only deplete tryptophan but also other nutrients (intermediates of host cell tricarboxylic acid

cycle, alanine, glucose) with consequent development of chlamydial persistent forms [53,54]. Thirdly, *C. trachomatis* can escape cervicovaginal immune surveillance via several chlamydial effector molecules like CPAF, HtrA and membrane protein gamma resistance determinant (GarD); CPAF and HtrA degrade cathelicidin LL-37, anti-chlamydial peptide released by epithelial cells and neutrophils in response to Chlamydia infections, whereas GarD protects inclusions by ubiquitination and proteasomal degradation [49,59]. Lastly, extrusion formation utilized by *C. trachomatis* to exit epithelial and dendritic cells as well as macrophages represents an evasion strategy and a dissemination mechanism to more distant sites, thus, promoting ascension of genital infection to reproductive system [60–62].

All these evasion mechanisms triggered by *C. trachomatis* result in a chronic infection responsible for the inflammatory state underlying tissue damage associated with chlamydial genital infection. Such a condition may be further worsened by exacerbated immune response and the presence of a CST IV microbiota. This latter has been described to induce multiple proinflammatory molecules including interleukin (IL)-6, IL-8, TNF- α , IL-1 α , matrix metalloproteinase (MMP)-9, MMP-10, MMP-1 involved in epithelial barrier disruption by inducing oxidative stress, miRNA alteration, and promoting cell cycle arrest, apoptosis, and necrosis [56].

4. Conclusions

In conclusion, the intricate interactions between the host microbiota and immune responses have emerged to affect the risk of *C. trachomatis* acquisition and dissemination of genital infection in women. In the future, methodological advances *in vitro* investigations, like, for example, the introduction of 3D organoid models, that better mimic the cervicovaginal microenvironment, alongside multi-omics approaches, will be of great help to better characterize the complex interaction network between *C. trachomatis* and host defences and, hence, to discover novel therapeutic targets for this clinically significant pathogen.

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