The Role of *Chlamydia Trachomatis* in the Pathogenesis of Female Reproductive Organs Cancers

REVIEW

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Abstract

Chlamydia trachomatis (*C. trachomatis*) is an intracellular obligate bacterium. It is the most common cause of pelvic inflammatory disease (PID) amongst a spectrum of diseases. Chlamydia infection is of a major public health concern especially in developing countries. It is estimated that about 600 million people are infected worldwide annually yet its roles in the pathogenesis of gynecological cancers are poorly understood and has not been fully elucidated. An understanding of the mechanisms underlying cancer development following PID due to *C. trachomatis* will be essential in prevention and providing more rational treatments. This review discusses the mechanisms and sequence of events linking Chlamydial infections to carcinogenesis in the female reproductive organs. Possible links between *C. trachomatis* infection and cancer development in the female reproductive organs are proposed. *C. trachomatis* infection as a co factor is also re-examined in light of these possible mechanisms.

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Introduction

Chlamydia trachomatis (*C. trachomatis*) is an intracellular obligate gram-negative bacterium. It exists in two forms, alternating between elementary body (EB) that is metabolically inactive but highly infectious and reticulate body that is metabolically active and involved in its replication. *C. trachomatis* depends on its host for energy, metabolism and reproduction (as reviewed by Ajonuma et al.) [1]. Chlamydia infection is of a major public health concern and it is estimated that about 600 million people are infected worldwide annually [2]. *C. trachomatis* infect epithelia of many organs leading to a spectrum of pathological

Keywords

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conditions such as cervicitis, endometritis, salpingitis epididymitis, prostatitis, lymphangitis, pneumonitis, conjunctivitis, keratitis and trachoma the main cause of preventable blindness [1]. Different serovars do have tropisms for different epithelia and tissues. Serovars A to C infects the eye, while serovars D to K the genitourinary tract [3]. Majority of the cases are sub-acute leading to persistence and /or chronic infection, which elicits immune response, tissue scarring, damage and other cascade of events such as epithelial transformation.

However, there is little information in the literature regarding the mechanisms of *C. trachomatis* infection in the pathogenesis of gynecological cancers. This review proposes the possible links between *C. trachomatis* in pelvic inflammatory disease and the subsequent gynecological cancers. The roles of *C. trachomatis* as a cofactor in the pathogenesis of gynecological cancers are examined in light of these mechanisms. New research on elucidating the involvement of *C. trachomatis* in gynecological cancers is suggested.

Results

Chlamydial infection of the Pelvic organs

C. trachomatis infection is the most common sexually transmitted bacterial infection worldwide [4] and the leading cause of pelvic inflammatory disease (PID) [5, 6]. There is evidence that about 20% of women with chlamydial lower genital tract infection develop PID [7] while Jones et al. reported that 41% of women with *C. trachomatis* infection had endometrial infections [8]. Endometritis due to *C. trachomatis* has also been reported [9-12]. *C. trachomatis* was recovered from uteri and Fallopian tubes of women with acute salpingitis [11] and its DNA detected in women with post-infectious infertility [13, 14]. Serological studies on women who had salpingitis demonstrated strong association of tubal factor related infertility with previous *C. trachomatis*

infection [8]. There is increased prevalence of spontaneous abortion in women who had chlamydial salpingitis [15] or had been previously exposed to *C. trachomatis* [16]. Interestingly, most *C. trachomatis* infections are sub-acute, leading to persistent and /or chronic infections, eliciting immune response.

Heat shock proteins (HSP) are increased in women with previous chlamydial infections [17]. Persistent infection through constant exposure to *C. trachomatis* leads to production of HSP that elicits intense immune and inflammatory reactions, leading to tissue scarring and endometrial and Fallopian tube damage. HSP 10 is associated with tubal factor infertility in a *C. trachomatis* exposed population [18] and HSP 57 with elementary and reticulate bodies showed delayed hypersensitivity response [17]. HSP 60 is capable of eliciting intense mononuclear inflammation and elaboration of inflammatory cytokines [14, 19]. Chlamydial HSP may function in at least two different ways to promote chronic disease. Firstly, through direct antigenic stimulation and secondly as signal transducers that result in macrophage activation [19].

Despite *C. trachomatis* being recognized for long as the most important cause of chronic PID worldwide, the sequence of events linking Chlamydial infections to carcinogenesis in the female reproductive organs has not been elucidated to a satisfactory extent.

Pathogenesis of Chlamydial infections in carcinogenesis

Chronic and or persistent bacterial infections have been implicated in the occurrence of cancer [20]. Several studies have associated chlamydial infection with the development of cervical [21, 22] and ovarian [23] carcinoma.

Chlamydia can establish asymptomatic, persistent infections by several mechanisms, including antibiotic resistance, immune evasion, and apoptosis suppression [24]. *C. trachomatis* triggers activation of oncogenic Ras-Raf-MEK-ERK pathway components

[25, 26] and production of reactive oxygen species (ROS) to support its growth [27].

It has been reported in various human and other mammalian cell lines that Chlamydia infection can lead to significant increases in host cell multinucleation [28], a condition well linked to tumorigenesis [29, 30].

Bacterial pathogens are known to modify the chromatin architecture of host cells, thus manipulating host transcriptomes, such as to suppress immune responses [31]. *C. pneumoniae* induces modifications of histones H3 and H4, which plays an important role in cytokine production [32]. Recently, it has been reported that chlamydial nuclear effector protein (Nue) has histone methyltransferase activity that targets histones H2B, H3, and H4 [33]. Chromatin alterations, such as histone modifications, may induce somatically heritable changes of gene activity and thus have oncogenic potential [34]. Collectively, these data establish that bacterial pathogens induce multiple types of histone PTMs, although the mechanisms and extent of this phenomenon requires elucidation.

Chlamydia trachomatis infection causes mitotic spindle pole defects [35] and resists apoptosis induction in actively dividing cells [36, 37] leading to cell transformation and carcinogenesis.

Chlamydia infection has been reported to increase supernumerary centrosomes, abnormal spindle poles, and chromosomal segregation defects [38], centrosome amplification and multipolar spindle formation that may lead to chromosomal instability. Inappropriate activation of ERK and elevated global heterochromatin is a hallmark of many cancers [39, 40].

It has been reported that Chlamydial infection alters the transcription of host cell genes including those for cell differentiation, transcription factors and inhibition of apoptosis [41]. It has also been demonstrated that *C. trachomatis* infection results in increased tyrosine phosphorylation of several host proteins including those involved in signal transduc-

tion pathways [41, 42, 43, 44]. During Chlamydial infection, bacteria binding may stimulate receptor signaling leading to protein tyrosine phosphorylation.

Recently, the role of chromatin and histone modifications in promoting DNA damage responses (DDRs) and genome stability have gained prominence [45]. Upon detection of DNA double-strand breaks (DSBs), cells activate DDR pathways that detect DNA lesions and signal their presence by mediating responses such as cell-cycle arrest, DNA repair, and, under some circumstances, apoptosis. Phosphorylation of H2AX Ser139 (γ H2AX) is a prominent chromatin modification in response to DSBs that acts as a signal for recruitment of repair proteins including pATM and 53BP1 to DNA break sites. Deficiencies in DNA damage signaling and repair pathways lead to genetic instability, which in turn might enhance oncogenesis [46].

Deficiencies in DNA damage signaling and repair pathways lead to genetic instability, which in turn might enhance oncogenesis [46]. Chromatin alterations, such as histone modifications, may induce somatically heritable changes of gene activity and thus have oncogenic potential [34]. Histone posttranslational modifications (PTMs) are typically induced by signal transduction pathways activated in response to cellular stimuli. One prominent pathway implicated in histone PTMs is the mitogen-activated protein kinase (MAPK) cascade, which leads to histone H3 serine 10 (H3S10) phosphorylation in a promoter-specific manner, targeting only a subset of genes [47]. Bacterial pathogens such as *Mycobacteria*, *Shigella*, *Listeria*, and *Helicobacter* are known to modify the chromatin architecture of host cells, thus manipulating host transcriptomes, e.g., to suppress immune responses [31]. Furthermore, *C. pneumoniae* induces modifications of histones H3 and H4, which play an important role in cytokine production [32]. More recently, the chlamydial nuclear effector protein (Nue) was shown to have histone methyltransferase

se activity that targets histones H2B, H3, and H4 [33]. Collectively, these data establish that bacterial pathogens induce multiple types of histone PTMs, although the mechanisms and extent of this phenomenon requires elucidation.

Furthermore, Chlamydia infection has been shown to increase supernumerary centrosomes, abnormal spindle poles, and chromosomal segregation defects [38]. Inappropriate activation of ERK and elevated global heterochromatin is a hallmark of many cancers [39, 40].

Chlamydiae produce a unique family of T3SS effectors termed inclusion membrane proteins (Incs) [48, 49]. These effectors are translocated across, and inserted into, the inclusion membrane, in which they are ideally positioned to mediate host-pathogen interactions [50]. They have hydrophobic domains composed of two closely spaced membrane-spanning regions that are separated by a short hairpin loop, with their amino terminus and/or carboxyl terminus predicted to extend into the cytoplasm of the host cell [51]. Incs are primarily expressed early during infection, when they may be important in the establishment of the inclusion, and at mid-cycle, when they may be involved in the maintenance of the inclusion and the acquisition of nutrients [50]. Genome-wide comparisons reveal a core set of Incs that are shared across Chlamydia spp. as well as diverse species-specific Incs that may be key determinants of host tropism and site-specific disease [48, 49]. Incs share little homology to each other or to other known proteins, with the exception of coiled-coil or soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE)-like domains, which provides limited insight into their functions [51]. Incs are hypothesized to recruit host proteins to the inclusion membrane to promote fusion with nutrient-rich compartments, inhibit fusion with degradative compartments, hijack host machinery or organelles, disrupt normal host pathways, or as-

semble novel complexes with new functions [50]. The Inc-host interactions identified thus far indicate that Incs participate in numerous processes, including the rearrangement of the host cell cytoskeleton, membrane dynamics, centrosome tethering, lipid acquisition and resistance to apoptosis [50]. In addition, Incs form homotypic or heterotypic complexes on the surface of the inclusion [52, 53]. Finally, Incs may provide structural stability to the growing inclusion membrane [54]. A large-scale proteomic screen of Incs in *C. trachomatis* has revealed putative host binding partners for approximately two-thirds of Incs [55]. All these complex formations and cytoskeleton rearrangements may lead to host cell tissue transformation. *C. trachomatis* infection also shown to upregulate the expression of cystic fibrosis transmembrane regulator (CFTR) gene in reproductive organs [56] and in hydrosalpinx [57] induced epithelial transformation to pseudostratification and focally attenuated epithelium. These epithelial transformations may irreversibly progress to cancer. **Figure 1** shows the proposed sequence of events linking *C. trachomatis* infection to increased chromosomal instability and then gynecological cancers.

***C. trachomatis* as a co-factor in carcinogenesis**

Although human papilloma virus (HPV) is known to cause cervical cancer, there is some evidence that *C. trachomatis* may also act as a co-factor [58]. Chlamydial infections have been epidemiologically linked to cervical cancer in women co-infected with the HPV [59] and when several studies from different countries were pooled [60]. Studies have also shown that *C. trachomatis* infection confers an increased risk of squamous cell carcinoma, after adjusting for HPV infection, smoking, and depending on the serotype involved [61-65]. Some *C. trachomatis* serotypes B, D, E, G, I, and J have been found to increase the risk of squamous cell cancer [66, 67], while serotypes C, F, H, and K

Figure 1.

A schematic illustration of proposed mechanisms and sequence of events linking *C. trachomatis* infection and cancer development in the female reproductive organs. *C. trachomatis* infection results in the production of Heat Shock Proteins (HSP), histone chromatin alterations and chronic and or persistent infection. This leads to increased expression of oncogenes and suppression of apoptosis induction. As well as tyrosine phosphorylation of genes, centrosome amplification, spindle formation and delayed DNA damage response. All these lead to increased chromosomal instability, cell differentiation and cancer formation.

have not. How *C. trachomatis* exactly enhance oncogenesis as a co factor to HPV infection is not fully understood but it has been suggested to be due to chronic inflammation and metaplasia [68]. Other mechanisms have also been proposed. *C. trachomatis* may promote the persistence of HPV infection [69, 70]. HPV can remain latent for years after infection. In the presence of *C. trachomatis*, HPV high risk oncogenes E6 and E7 may undergo activation leading to chromosomal abnormalities and immortalization.

In vitro infection of fibroblasts and cervical tissue that were free of HPV showed decreased expression of the tumor suppressor gene caveolin-1 and increased expression of the proto-oncogene

c-myc, indicating there may be other possible ways that *C. trachomatis* may promote oncogenesis [71]. Since *C. trachomatis* infection can induce centrosome abnormalities, spindle effects, and chromosome segregation errors leading to cell transformation, the presence of these defects within infected actively dividing cells is a possible mechanism for *C. trachomatis* as a co factor in cancer formation. **Figure 2** shows the proposed possible sequence of events linking *C. trachomatis* infection to increased chromosomal instability, epithelial cell differentiation and immortalization in the presence of HPV.

Figure 2.

A schematic illustration of proposed mechanisms and sequence of events linking *C. trachomatis* infection and cancer development in the female reproductive organs. *C. trachomatis* infection results in the production of Heat Shock Proteins (HSP), histone chromatin alterations and chronic and or persistent infection. This leads to increased expression of oncogenes and suppression of apoptosis induction. As well as tyrosine phosphorylation of genes, centrosome amplification, spindle formation and delayed DNA damage response. All these lead to increased chromosomal instability, cell differentiation and cancer formation.

Conclusions

In summary, chronic and persistent inflammation of the female reproductive organs epithelia following chlamydial infections leads to subsequent tissue transformation, causes mitotic spindle pole defects, alters the transcription of host cell genes, decreased expression of the tumor suppressor genes, increased tyrosine phosphorylation of several host proteins including those involved in signal transduction pathways, increased expression of the proto-oncogenes like c-myc, leading to delayed DNA damage response and chromosomal instability then promoting oncogenesis. New research focusing on

the above mentioned pathways may provide crucial information for a better understanding on the role of *C. trachomatis* infection in pathogenesis of gynecological cancers.

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