Review

Research Progress on *Chlamydia trachomatis* Infection and Related Cytokines

Li Han

Department of Ophthalmology, Yidu Central Hospital Affiliated to Weifang Medical College, Qingzhou, China

Keywords

Chlamydia trachomatis; Infection; Cytokines

Correspondence

Li Han,
E-mail: hanliqz@163.com

DOI: 10.1515/ii-2017-0109

Abstract

Chlamydia trachomatis (Ct) infection can induce host cells to produce numerous cytokines. Cytokines play important roles in inflammatory response. Although inflammation can protect the body, persistent inflammation can lead to pathological changes and tissue damages. Further research should determine whether cytokine production directly affects development and outcomes of inflammation. This study summarizes Ct infection and related cytokines.

Chlamydia trachomatis (Ct) is a prokaryotic microorganism, an endotrophic obligatory parasite, and is characterized by a unique biphasic developmental cycle. Ct displays broad spectrum of pathogenicity. Ct infection on conjunctival epithelial cells can cause trachoma. Ct infection in the urinary tract can lead to pelvic inflammatory diseases, ectopic pregnancy, infertility, and other diseases. Persistent inflammation serves as basis of chronic Ct infection and pathogenesis. In vivo and *in vitro* experiments of Ct infection showed that it can induce cells to produce interleukin (IL), interferon (IFN), tumor necrosis factor (TNF), chemokines, growth factors, and other cytokines. Cytokines play important roles in inflammatory responses to Ct infection.

Interleukin (IL)

According to different effects of IL during inflammatory response, IL can be divided into proinflammatory IL and antiinflammatory IL.

Proinflammatory IL

Ct infection can induce host cells to produce IL-1, IL-6, IL-8, IL-18, IL-33, IL-17A, and many kinds of proinflammatory IL.

IL-1 family IL-1 family includes IL-1 α , IL-1 β , IL-18,

IL-33, and other cytokines. After host infection, Ct activates caspase 1 through NALP3 pathway to induce IL-1 β , IL-18, IL-33, and other proinflammatory factors and mediate inflammatory response [1]. IL-1 β mainly plays a regulatory role in cellular immune activation through an important cytokine and a polypeptide regulatory factor produced by monocyte-macrophages. During Ct infection, IL-1 β induces secretion of adhesion molecules and chemotactic factor to initiate inflammatory reaction of fallopian tubes. This phenomenon primarily causes genital tract lesions [2]. IL-18 is generated by a variety of macrophages, dendritic cells, and monocytes. After transcription, Ct-infected host cells regulate and induce cells to secrete mature IL-18, which can participate in tissue repair [3]. Meanwhile, increased IL-18 secretion causes Th1/Th2 ratio imbalance and affects clearance of Ct and development of pathological injury in fallopian tubes. IL-33, a new member of IL-1 family, induces IL-6, TNF- α , and other cytokines to directly participate in Ct inflammatory reaction. Ct infection can induce epithelial cells and various immune cells to produce IL-1 α . After production of IL-1 α , the molecule can induce itself and generation of IL-6 and IL-8 and other cytokines, causing fallopian tube injury [4].

IL-6 IL-6 is a proinflammatory cytokine with multiple biological effects and is mainly produced by dendritic cells and monocytes. IL-6 produces different biological effects on

different organs through different secretory ways. This factor can control leukocyte recruitment, promote neutrophil apoptosis, and mediate inflammation and immune responses. High-level IL-6 is closely related to persistent Ct infection of fallopian tubes. IL-6 opposes the trend of TNF- α in the course of diseases. IL-6 dose-dependently inhibits production of TNF- α . TNF- α is associated with fallopian tube injury, maintaining persistent status of the disease. During early stage of Ct infection in fallopian tubes, high levels of IL-6 is observed, TNF- α level is low, and fallopian tube features low-degree injury. With extension of the course of disease, fallopian tube injury aggravates and causes obstruction. Thus, production of IL-6 decreases. High levels of TNF- α are produced, resulting in aggravation of fallopian tube injury [5].

IL-8 IL-8 is an important inflammatory chemotactic factor, which is associated with tissue injury mediated by immune responses. During Ct infection, IL-8 is induced by extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase pathway [6]. IL-8 activates host cell lipid metabolism pathway. IL-8 metabolites provide nutrients for growth and development of Ct, benefitting Ct persistent infection. Some studies reported that IL-8 may promote Ct infection complicated with reactive arthritis [7].

IL-17A IL-17A comes mainly from secretion of Th17 cells and can also costimulate production of T lymphocytes, natural killer (NK) cells, macrophage, neutrophils, and epithelial cells through tumor growth factor- β (TGF- β), IL-1 β , IL-6, and IL-23 [8]. Ct infection stimulates host cells to produce IL-17A and recruits neutrophils to sites of infection to promote inflammation. IL-17A and INF- γ jointly upregulate nitric oxide (NO) synthase to produce NO for inhibition of Ct growth. These molecules play important roles in proinflammatory responses of trachoma caused by Ct-infected conjunctival epithelial cells [9].

Antiinflammatory ILs

ILs associated with antiinflammation mainly include IL-10, IL-11, and IL-4. These ILs interact with inflammatory factors to maintain balanced inflammatory response.

IL-10 IL-10 belongs to Th2 cytokines, which are mainly secreted by Th cells. This IL can inhibit inflammatory mediators of human epithelial cells, reduce level of cytokine

production, and especially reduce excessive inflammatory reaction. IL-10 is an important regulatory factor in initial inflammatory reaction of Ct infection and significantly participates in clearance of Ct infection and regulation of induced inflammation in hosts [10]. Level of IL-10 is associated with recurrent genital Ct infection [11].

IL-11 IL-11 is a pleiotropic cytokine that inhibits activation of nuclear factor (NF)- κ B, regulates macrophage phenotype, promotes cell survival and differentiation and tissue repair, and decreases inflammatory reactions. Skwor *et al.* studied and discovered that IL-11 exists in ocular secretion of trachoma patients [12]. This cytokine can upregulate collagen and other connective tissue proteins, leading to fibrosis. IL-11 is also involved in pathogenesis of inflammation associated with Ct diseases [13].

IL-4 IL-4 is a pleiotropic antiinflammatory cytokine mainly produced by activated T cells. IL-4 promotes expression of major histocompatibility complex (MHC) class II molecules in B cells and enhances antigen-presenting ability of B cells. IL-4 acts on monocytes and downregulates TNF- α , IL-1 α , IL-1 β , IL-6, IL-8, and other inflammatory cytokines to regulated inflammation. IL-4 is the most important and persistent cytokine produced by peripheral T cells. This cytokine acts as the major effector for peripheral T cells in response to Ct antigen stimulation in vivo and in vitro. Some studies showed that during Ct infection, high-level IL-4 is closely related to Th2-delayed hypersensitivity. High-level IL-4 also plays an important role in protective immunity and immune pathology of Ct [14,15].

Interferon (IFN)

IFN is a cytokine with various functions and is produced mainly by monocytes and lymphocytes. This cytokine is divided into type I IFN (IFN- α/β) and type II IFN (IFN- γ). Type I IFN starts downstream STAT signal transduction through IFN- α/β receptor to activate macrophages, enhance cytolytic activity of NK cells, and promote secretion of IFN- γ and differentiation of Th1 cells. Importantly, type I IFN can activate dendritic cells and their functions by enhancing MHC expression and secretion of cytokines. Thus, innate and adaptive immune responses are regulated. Type I IFN features very low physiological levels. After Ct infection, cyclic di-adenosine monophosphate is synthesized

to drive IFN reaction. IFN- β depends on synthesis of Toll-like receptor 3 and IFN transcription factor 3. Effect of type I IFN in Ct infection remains unidentified. Some studies showed that type I IFN exhibits toxic effects on Ct infection of the genital tract in mice. However, some studies indicated that type I IFN can induce host defense mechanism and inhibit Ct infection of the genital tract in female mice [16–18].

Type II IFN (IFN- γ) is an important cytokine for host bacterial infection, and it mainly comes from CD4⁺ and CD8⁺ T lymphocytes. IFN- γ can induce and activate indole amine-2,3-dioxygenase (IDO). IDO limits proliferation of Ct by decomposing key metabolic enzymes of hosts. TNF can further strengthen tryptophan restriction by combining IFN effects. IFN- γ can activate inducible NO synthase and induce iron deficiency pathway to inhibit Ct growth, activate adaptive and innate immunity of epithelial cells, and enhance infiltration and activation of lymphocytes. Clinical research revealed that IFN- γ can enhance local inflammation and tissue remodeling. High-level concentration of IFN- γ is closely associated with histopathology, inflammation, and follicular inflammation induced by Ct [18,19]. Therefore, different effects of IFN- γ on immune responses are associated with concentration of IFN- γ , microenvironment, and time phase and stage of immune responses [20].

Tumor necrosis factor (TNF)

TNFs include TNF- α and TNF- β . TNF- α is mainly secreted by mononuclear macrophages. TNF- β is mainly secreted from activated T lymphocytes. TNF- α and TNF- β share 28% of the same amino acid sequence and similar biological activity. Two similar receptors (TNFR1 and TNFR2) can be competitively combined to produce different biological effects. TNF signal transduction pathways mainly include apoptosis, activation of transcription factor NF- κ B, and c-Jun N-terminal protein kinase. These three pathways interact with each other to coordinate pleiotropic functions of TNF [21]. Ct infection can induce host cells to produce TNF- α . On the one hand, TNF- α can interact with IFN- α and IFN- γ to inhibit Ct infection and growth through downregulation of tryptophan content [20]. TNF- α can also stimulate proliferation of fibroblasts, promote release of collagenase, and participate in tissue injury. Injury of fallopian tube tissue in patients with Ct infection is closely related to increase in TNF- α . Dose-dependency and blocking of TNF- α production can decrease degree of damage in mucosal cells

of fallopian tubes. TNF- α level is related to extent of damage in fallopian tubes [5].

Growth factor

Fibroblast growth factor 2 (FGF2) is a newly discovered heparan sulfate glycoprotein (HSPG). HSPGs are dependent growth factors. Ct can produce and secrete FGF2 by activating ERK1/2 signaling pathway. After combination of FGF2 with Ct prototype (EB), it can bridge molecules to promote interaction between EB and cell surface FGF receptor (FGFR). Combination of EB with FGF2 promotes activation of FGFR. Therefore, this phenomenon benefits nonphagocytic phagocytosis. During this course, FGF2 enhances combination of Ct with host cells in HSPG-dependent manner and strengthens Ct infection and dissemination. FGF2 signaling pathway plays an important role by enhancing inflammatory response, inhibiting apoptosis, or regulating gene expression in pathogenesis of Ct infection [22].

Connective tissue growth factor (CTGF) is a strong and effective fibrosis factor. This molecule can regulate occurrence and development of many fibrosis diseases. During Ct infection, CTGF expression is significantly enhanced and regulated by TGF- β . CTGF also regulates effects of TGF- β . Both factors coordinate with each other during fibrosis development. CTGF stimulates migration and proliferation of fibroblast and produces extracellular matrix. CTGF can also stimulate transformation of epithelial cells into mesenchymal cells and plays an important role in occurrence of Ct infection of conjunctival scarring trachoma [23].

Chemokines

Chemokines are important mediators of leukocyte trafficking. These molecules can attract specific white cells to infected sites and amplify inflammatory process during host defense against infection and inflammation. Level of chemokine production is influenced by type of cytokines in inflammatory environment. High-level IL-6, TNF- α , and IL-1 α favor adhesion of chemokines to endothelial cells. Infected macrophages, which produce different types of chemokines, are related to high-level IL-6, TNF- α , and IL-1 α . Chemokine (C-C motif) ligand 18 (CCL18) is a kind of Th2 inflammatory chemotactic factor that is produced

by selectively activated macrophages. Expression of CC chemokine was detected by gene chip analysis in patients with active Ct infection. Results showed significantly increased level of CCL18. Thus, CCL18 can amplify the inflammatory process and plays an important role in pathogenesis of Ct infection. Macrophage inflammatory protein (MIP) is a cytokine superfamily composed of small-molecule-secreted proteins. This protein can induce leukocytes to perform directional movement and plays an important role in clearance of pathogens, inflammation, angiogenesis, tumor metastasis, and viral infection. Ct respiratory infection can induce upregulated expressions of MIP-2 and MIP-1 β and participate in occurrence and development of lung diseases [24,25].

Status quo and prospect

Ct infection can induce a variety of cells to produce different cytokines. Cytokines play important roles in inflammatory responses of organisms. During early stage of infection, Ct induces host cells to produce IL-1 β , IL-6, IL-8, and other cytokines [4]. As a potent neutrophil chemotactic factor, IL-8 can induce neutrophil to migrate to sites of infection and cause acute infection. IL-8 can also promote clearance of pathogens. On the other hand, neutrophils can produce monocyte chemotactic factors to activate T cells, generating IFN- γ and TNF- α and further inducing synthesis of IL-6 and IL-8. This phenomenon leads to chronic Ct infection and pathological damage of multiple tissues, such as the fallopian tube. Thus, during Ct infection, cytokines participate in mutual promotion, mutual antagonism, and other dynamic processes. Imbalance of Th1 and Th2 cytokines causes diseases. To date, source and function of cytokines are clearly defined. However, with a wide variety of cytokines and complex cascade network systems from their mutual interaction, further studies should explore mutual regulatory mechanism of cytokines in Ct infection and occurrence and development of related diseases. With the progress of research on cytokines and development of molecular immunology, effects of cytokines in Ct infection and molecular mechanism will be further explained and applied to prevention and treatment of Ct-induced diseases.

Declarations

Acknowledgements

No.

Competing interests

The author declares that he has no competing interest.

Authors' contributions

L Han made the literature analysis and wrote, discussed and revised the manuscript of this review.

References

- 1 Cheng W, Shivshankar P, Li Z, *et al.* Caspase-1 contributes to Chlamydia trachomatis-induced upper urogenital tract inflammatory pathologies without affecting the course of infection. *Infect Immun*, 2008,76:515-522.
- 2 Hvid M, Baczynska A, Deleuran B, *et al.* Interleukin-1 is the initiator of Fallopian tube destruction during Chlamydia trachomatis infection. *Cell Microbiol*, 2007, 9:2795-2803.
- 3 Lu H, Shen C, Brunham RC. Chlamydia trachomatis infection of epithelial cells induces the activation of caspase-1 and release of mature IL-18. *J Immunol*, 2000, 165:1463-1469.
- 4 Cheng W, Shivshankar P, Zhong Y, *et al.* Intracellular interleukin-1 α mediates interleukin-8 production induced by Chlamydia trachomatis infection via a mechanism independent of type I interleukin-1 receptor. *Infect Immun*, 2008, 76: 942-951.
- 5 Li H, Liang Z. Determination of tumor necrosis factor α and interleukin 6 in tubal fluid of patients with tubal infertility caused by the infection of Chlamydia trachomatis. *Chin J Obstet Gynecol*, 2000,35:26-27.
- 6 Buchholz KR, Stephens RS. The extracellular signal-regulated kinase/mitogen-activated protein kinase pathway induces the inflammatory factor interleukin-8 following Chlamydia trachomatis infection. *Infect Immun*, 2007, 75:5924-5929.
- 7 Schrader S, Klos A, Hess S, *et al.* Expression of inflammatory host genes in Chlamydia trachomatis-infected human monocytes. *Arthritis Res Ther*, 2007, 9:R54.
- 8 Gao X, Gigoux M, Yang J, *et al.* Anti-chlamydial Th17 responses are controlled by the inducible costimulator partially through phosphoinositide 3-kinase signaling. *PLoS One*, 2012, 7:e39214.
- 9 Zhang Y, Wang H, Ren J, *et al.* IL-17 synergizes with IFN- γ to upregulate iNOS and NO production and inhibit chlamydial growth. *PLoS One*, 2012, 7:e39214.
- 10 Yilma AN, Singh SR, Fairley SJ, *et al.* The anti-inflammatory cytokine, interleukin-10, inhibits inflammatory mediators in human epithelial cells and mouse macrophages exposed to live and UV-inactivated Chlamydia trachomatis. *Mediators Inflamm*, 2012, 2012:520174.
- 11 Wang C, Tang J, Geisler WM, *et al.* Human leukocyte antigen and

- cytokine gene variants as predictors of recurrent Chlamydia trachomatis infection in high-risk adolescents. *J Infect Dis*, 2005, 191:1084-1092.
- 12 Skwor TA, Atik B, Kandel RP, *et al.* Role of secreted conjunctival mucosal cytokine and chemokine proteins in different stages of trachomatous disease. *PLoS Negl*, 2008, 2:e264.
 - 13 Buckner LR, Lewis ME, Greene SJ, *et al.* Chlamydia trachomatis infection results in a modest pro-inflammatory cytokine response and a decrease in T cell chemokine secretion in human polarized endocervical epithelial cells. *Cytokine*, 2013, 63:151-165.
 - 14 Vicetti Miguel RD, Harvey SA, LaFramboise WA, *et al.* Human female genital tract infection by the obligate intracellular bacterium Chlamydia trachomatis elicits robust type 2 Immunity. *PLoS One*, 2013, 8:e58565.
 - 15 Clancy R, Ren Z, Pang G, *et al.* Chronic Chlamydia pneumoniae infection may promote coronary artery disease in humans through enhancing secretion of interleukin-4. *Clin Exp Immunol*, 2006, 146:197-202.
 - 16 Prantner D, Sikes JD, Hennings L, *et al.* Interferon regulatory transcription factor 3 protects mice from uterine horn pathology during Chlamydia muridarum genital infection. *Infect Immun*, 2011, 79:3922-3933.
 - 17 Barker JR, Koestler BJ, Carpenter VK, *et al.* Sting-dependent recognition of cyclic diAMP mediates type I interferon responses during Chlamydia trachomatis infection. *MBio*, 2013, 4:e00018-00013.
 - 18 Burian K, Endresz V, Deak J, *et al.* Transcriptome analysis indicates an enhanced activation of adaptive and innate immunity by chlamydia-infected murine epithelial cells treated with interferon gamma. *J Infect Dis*, 2010, 202:1405-1414.
 - 19 Ishihara T, Aga M, Hino K, *et al.* Inhibition of Chlamydia trachomatis growth by human interferon- α : mechanisms and synergistic effect with interferon- γ and tumor necrosis factor- α . *Biomed Res*, 2005, 26:179-185.
 - 20 Zhang C, Tian Z. Negative immunomodulatory effect of interferon- γ . *Current Immunology*, 2007, 2:89-92.
 - 21 Zha J, Shu H. Molecular mechanism of signal transduction of tumor necrosis factor. *SCIENTIA SINICA (C series: Life Sciences)*, 2002, 01:1-12.
 - 22 Kim JH, Jiang S, Elwell CA, *et al.* Chlamydia trachomatis co-opts the FGF2 signaling pathway to enhance infection. *PLoS Pathog*, 2011, 7:e1002285.
 - 23 Burton MJ, Ramadhani A, Weiss HA, *et al.* Active trachoma is associated with increased conjunctival expression of IL17A and profibrotic cytokines. *Infect Immun*, 2011, 79:4977-4983.
 - 24 Belay T, Eko FO, Ananaba GA, *et al.* Chemokine and chemokine receptor dynamics during genital chlamydial infection. *Infect Immun*, 2002, 70:844-850.
 - 25 Mathai SK, Gulati M, Peng X, *et al.* Circulating monocytes from systemic sclerosis patients with interstitial lung disease show an enhanced profibrotic phenotype. *Lab Invest*, 2010, 90:812-823.