

Significant Roles Played by IL-10 in *Chlamydia* Infections

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Abstract—*Chlamydia* species are obligate intracellular parasites which cause usually asymptomatic genital tract infections and also are associated with several complications. Previous studies demonstrated that immune responses to *Chlamydia* species are different and the diseases will be limited to some cases. Additionally, *Chlamydia* species are able to modulate immune responses *via* regulating expression of some immune system molecules including cytokines. IL-10, as the main anti-inflammatory cytokine, plays important roles in the induction of immune-tolerance against self-antigen and also immune-homeostasis after microbe elimination. Furthermore, it has been documented that ectopic expression of IL-10 is associated with several chronic infectious diseases. Therefore, it can be hypothesized that changes in the regulation of this cytokine can be associated with infection with several species of *Chlamydia* and their associated complications. This review collected the recent information regarding the association and relationship of IL-10 with *Chlamydia* infections. Another aim of this review article is to address recent data regarding the association of genetic variations (polymorphisms) of IL-10 and *Chlamydia* infections.

KEY WORDS: IL-10; *Chlamydia*; polymorphism.

INTRODUCTION

Chlamydia species are obligate intracellular parasites which cause several complications [1]. It has been evidenced that immune responses to *Chlamydia* species participate in *Chlamydia* complications [2]. Moreover, previous studies demonstrated that *Chlamydia* species are able to regulate immune responses *via* modulated expression of some immune system molecules including cytokines [3, 4]. These studies also demonstrated that cytokines play important roles in the regulation of immune responses against infectious agents which have been revealed to be important in either eradication or pathogenesis of microbial infections [5]. IL-10 is the main anti-inflammatory cytokine which is produced by several immune cells (see next section). This cytokine plays pivotal roles in the induction of either immune-tolerance against self antigen or immune-homeostasis after microbe elimination [6–8]. Additionally, there are studies indicating that up-regulation of IL-10 is

associated with several chronic infectious diseases and their complications [9, 10]. Therefore, it can be hypothesized that alteration in the expression of this cytokine can be associated with infection of pathologic *Chlamydia* species and their associated complications. Thus, the main aim of this review was to collect the recent information regarding the association and relationship of IL-10 with *Chlamydia* infections. Additionally, studies reported that single nucleotide polymorphisms (SNPs) within IL-10 gene are associated with the regulation of IL-10 expression [11]; hence, another aim of this review article was to address recent data regarding the association of genetic variations (polymorphisms) of IL-10 and *Chlamydia* infections.

IL-10

IL-10 is an anti-inflammatory cytokine which is produced by several types of immune cells including B and T regulatory and Th2 lymphocytes, activated macrophages and other cells [12]. Two transcription factors, Sp1 and Sp3, are responsible for the regulation of IL-10 expression by immune cells. The IL-10 gene is located on 1q31–1q32 and is approximately 5.2 kB. There are five exons within

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IL-10 gene [13] which encodes a 178 amino acid protein that is called pro-IL-10 [14]. Pro-IL-10 is activated after cleavage of 18 amino acids, the signal peptide, from the N-terminal of the cytokine [14]. IL-10 affects target cells *via* interaction with its corresponded receptor, IL-10 receptor (IL-10R) [15]. IL-10R belongs to type II cytokine receptor and consists of two chains, α and β [15]. IL-10/IL-10R interaction leads to activation of several intracellular signaling pathways which are discussed in the next section. IL-10 is the most important regulatory factor to suppress the inflammatory functions of Th1, Th2, and B lymphocytes, NK cells, macrophages, and dendritic cells [14, 16]. Therefore, it appears that this cytokine plays key roles in the suppression of immune responses during prolonged course of infections.

IL-10 RECEPTOR INTRACELLULAR SIGNALING

As mentioned in the previous section, IL-10 has immunoregulatory functions which regulate the activities of many of the immune cells [7]. IL-10 binding to the extracellular domain of α chain of IL-10R results in phosphorylation of two protein kinases, JAK1 (Janus kinase-1) and TYK2 (tyrosine kinase-2), which are associated with IL-10R α and β chains, respectively [17]. Interestingly, the phosphorylated (activated) kinases then phosphorylate tyrosine residues at Y446 and Y496 positions of IL-10R α chain intracellular domain [18]. Signal transducer and activator of transcription 3 (STAT3) binds to phosphorylated Y446 and Y496 *via* its SH2 (Src homology-2) domain, and the receptor-associated JAKs phosphorylate STAT3 tyrosine residues [19]. Following tyrosine phosphorylations, STAT3 homodimerizes and translocates into the nucleus and interacts with STAT-binding element (SBE) regions within the promoters of IL-10 target genes which leads to the up-regulation of target genes including suppressor of cytokine signaling 3 (SOCS3), anti-apoptotic, cell-cycle-progression genes, and so on [20]. It has also been documented that IL-10/IL-10R interaction also activates another pathway (PI3K (phosphoinositide-3 kinase) as well as its downstream substrates p70S6K (p70 S6-kinase) and Akt/PKB (protein kinase-B)) which leads to the survival of target cells [21]. IL-10 also regulates the p38/MAPK (mitogen-activated protein kinase) pathway (Fig. 1) [22].

IL-10 GENE POLYMORPHISMS

According to the fact that IL-10 expression is genetically regulated by promoter region [23, 24], so, it appears

that the polymorphisms within this region can be considered as potential candidates for studying in the immune system related diseases. It has been reported that there are three biallelic polymorphisms including -1082G/A (rs1800896), -829C/T (rs1800871), and -592C/A (rs1800872) within promoter region of IL-10 [25]. Since, these single nucleotide polymorphisms (SNPs) are associated with changes in IL-10 expression [26], alteration in the expression of IL-10, which is reported in chronic infectious diseases, can be associated with the polymorphisms within this region of IL-10 gene. Next sections present recent data regarding the association between *Chlamydia* infections and the polymorphisms within the promoter region of IL-10 gene.

CHLAMYDIA

The order *Chlamydiales* currently comprises four families including *Chlamydiaceae*, *Parachlamydiaceae*, *Simkaniaceae*, and *Waddliaceae* [27]. *Chlamydiaceae* family is divided into two genera including *Chlamydophila* and *Chlamydia* [28]. The genus *Chlamydia* has four species as follows: (1) *Chlamydia trachomatis*, (2) *Chlamydia suis*, (3) *Chlamydia muridarum*, and (4) *Chlamydia pecorum* [28]. *Chlamydia* species as obligate intracellular bacterial pathogens with a unique and host-cell dependent biphasic developmental cycle has caused a great health problem throughout the world [29]. Latest studies from the World Health Organization (WHO) indicated that there were an estimated 101.5 million new cases per year of *Chlamydia* infection among adults aged 15 to 49 years [30]. In Europe, the prevalence of *Chlamydia* infection among unscreened asymptomatic women ranges between 1.7 and 17 % [31], with sexually active women and men under the age of 20 and 25 years respectively being most affected. *Chlamydia* infections are asymptomatic in up to 90 % of women and more than 50 % of men [32]. In Italy, the prevalence of chlamydial infection among infertile couples was reported about 8 % [33]. Recent studies from North America and Europe revealed that the role of *C. trachomatis* in pelvic inflammatory disease (PID) is greater than *Neisseria gonorrhoea* [34]. In the Middle East countries, few data regarding the epidemiologic aspects of this infection is available. Two studies performed in the United Arab Emirates and Jordan reported that the frequency of *C. trachomatis* infection was 3 and 5 % respectively [35]. Also, limited studies in Iran demonstrated a wide range of frequency among female patients from 3 to 15.5 % [36].

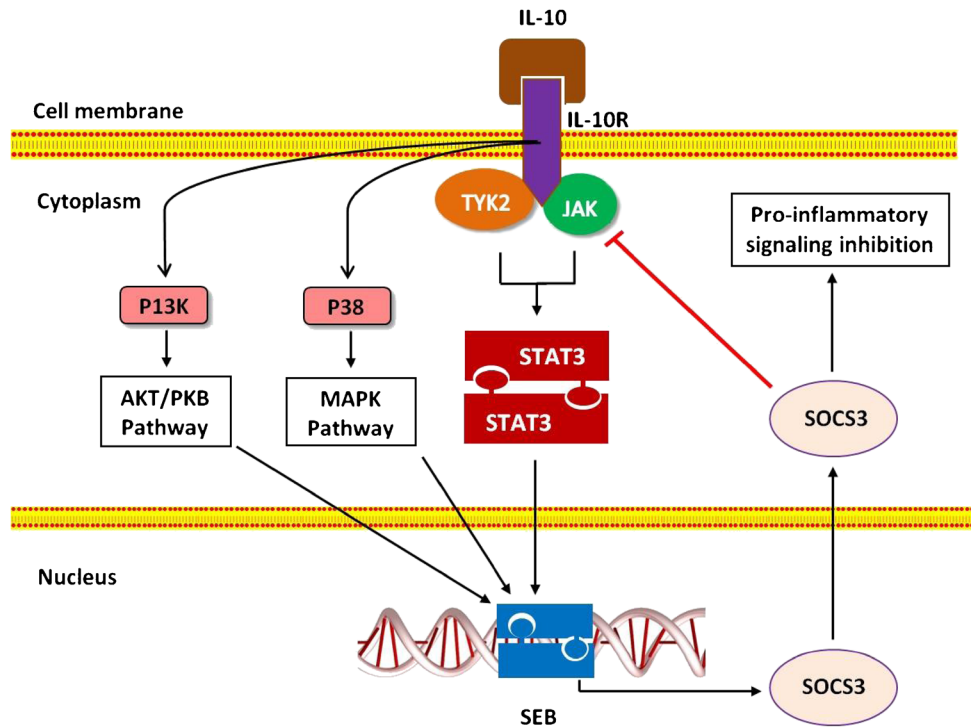


Fig. 1. Intracellular signaling of IL-10 receptor (IL-10R). The figure shows that IL-10/IL-10R interaction leads to the phosphorylation of STAT3 as well as activation of MAPK and AKT/PKB pathways. Activated STAT3 is translocated to the nucleus and bind to SEB region that result in transcription from SOCS3. SOCS3 inhibits intracellular signaling of pro-inflammatory cytokines and Jak molecules.

Despite this wide range of contamination, only a minority of infected individuals develop severe long-term complications such as trachoma or tubal factor infertility (TFI). A number of factors *may be involved in the occurrence* of these consequences including the presence of different strains among infected patients, pathogen genetic variability, the pathogen burden of each infected individual, and polymorphisms in host genetic risk factors [37]. This pathogen comprises different serovar groups causing diverse diseases in terms of severity and tissue tropism. To date, three well-known serovar groups are; lymphogranuloma venereum (L1–L3), ocular (A–C), and genital (D–K), serovars. *C. trachomatis* genital infections are global and cause considerable morbidities including PID and infertility, especially in women [38]. Since different *C. trachomatis* serovars can infect and survive in diverse host cells, they are responsible for a wide range of diseases in humans. For example, genital serovars contaminate genital tract epithelial cells causing a number of male and female genital tract infections while ocular serovars infect conjunctival epithelial cells affecting people with poor healthcare and resulting in trachoma, and the lymphogranuloma venereum (LGV) serovars infect macrophages and

spread systemically through lymph nodes [38]. Several studies have investigated the correlation between host genetic factors and *Chlamydia* disease severity.

IL-10 AND *CHLAMYDIA* INFECTION

According to the aforementioned information, *Chlamydia* species may result in distributed infection in some patients, while, some of the infected patients are able to limit the infection. Researchers believe that the differences in genetic and immunological factors determine the outcome of infections in the *Chlamydia* infected patients. Due to the fact that IL-10 plays important roles in the regulation of immune responses (see previous sections), hence, it appears that this cytokine may be involved in the pathogenesis of *Chlamydia* infection. Interestingly, previous studies demonstrated that IL-10 suppresses expression of several pro-inflammatory molecules which are involved in immune responses against *Chlamydia* infections [39]. Additionally, Gao *et al.* reported that IL-10 suppresses expression of inducible co-stimulator-ligand (ICOS-L), an activator of T lymphocytes, on DC in an animal model

with *C. muridarum* lung infection [40]. Yilma and colleagues also revealed that exogenous IL-10 is able to inhibit the secretion of TNF, IL-6, and IL-8 by *C. trachomatis* infected human epithelial cells and mouse macrophages [41]. Therefore, it appears that IL-10 up-regulation can be used by *Chlamydia* species to modulate immune responses. Interestingly, investigations demonstrated that IL-10 expression was increased during *Chlamydia* infections. For example, our previous study revealed that expression levels of IL-10 in the semen of patients suffering from *C. trachomatis* were significantly increased when compared to healthy controls [3]. Fedina *et al.* revealed that *C. trachomatis* induces expression of IL-10 by human monocytes [42]. Another study demonstrated that *C. trachomatis*-infected macrophages, Jurkat cells, and THP-1 cells present more IL-10 receptors than non-infected cells [43]. Campbell and co-workers also reported that single intra-nasal inoculation of *Chlamydia pneumoniae* results in increased serum levels of IL-10 in C57BL/6J mice [40]. A study by Azenabor and York demonstrated that *C. trachomatis* induces IL-10 production by infected macrophages *via* increasing of intracellular Ca^{2+} levels [42]. Moniz and colleagues indicated that *C. muridarum* induces expression of IL-10 by plasmacytoid dendritic cells [44]. Interestingly, another study reported that infection of human gingival fibroblasts with *Chlamydia pneumoniae* leads to up-regulation of IL-10 [45]. Moreover, several studies also confirmed that there is a positive correlation between *Chlamydia* infections and production of IL-10 by immune cells [46]. Vats and co-authors revealed that stimulation of peripheral blood mononuclear cells (PBMCs), which were obtained from *C. trachomatis* infected women, with the *Chlamydial* antigen resulted in a higher production of IL-10 compared to the PBMCs from healthy controls [47]. Several studies also reported that the immune cells derived from *Chlamydia* species infected patients produce higher IL-10 than non-infected individuals [48–52].

Gupta *et al.* also showed that IL-10 serum levels were increased in *C. trachomatis* infected infertile, but not fertile, women [41]. Therefore, it appears that increased expression of IL-10 not only is associated with persistent *Chlamydia* infection but also may be associated with *Chlamydia* infection complications such as infertility. Interestingly, Agrawal and colleagues reported that cervical lymphocyte infection with *C. trachomatis* leads to up-regulation of IL-10 by the infected cells which support the findings from the previous studies [53]. It has been also documented that *C. trachomatis* 60 kDa heat shock protein (CHSP60) induces IL-10 production in infertile women

[54, 55]. Therefore, it may be concluded that *Chlamydia* modulate immune responses *via* up-regulation of IL-10 through its damage associated molecular patterns (DAMPs), such as CHSP60, and pathogen associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS). It has been also reported that toll-like receptors play important roles in the *Chlamydia* infections which recognize *Chlamydia*-derived DAMPs and PAMPs. Moreover, as mentioned before, variations in IL-10 gene may be associated with different expression of IL-10; hence, the polymorphisms within IL-10 gene may also be considered as another risk factor for persistence of *Chlamydia* infections. Although, there are three functional polymorphisms within promoter region of IL-10 gene, but previous studies reported the polymorphisms at position -1082 only in *Chlamydia* infected patients. For example, Ohman and colleagues demonstrated that *C. trachomatis* infected patients carried out IL-10-1,082 GG genotype produced higher levels of IL-10 in comparison to the patients with AA genotypes [56]. Another study revealed that the IL-10 -1082 AA genotype is associated with an increased risk of severe tubal damage in unfertilized *C. trachomatis* infected women [43]. Based on the fact that tubal damages are associated with lower expression of IL-10, hence, it appears that IL-10 -1082 AA genotype is associated with the lower expression of IL-10. Natividad *et al.* and Wang *et al.* also revealed that IL-10 -1082 G allele is associated with higher expression of IL-10 productions [57, 58]. Interestingly, Kinnunen and colleagues showed that IL-10 -1082 AA genotype were significantly associated with *C. trachomatis* tubal factor infertility, which is an inflammatory condition [59]. Therefore, it confirmed that this genotype is associated with lower expression of IL-10. In parallel with the results, a study by Mozzato-Chamay *et al.* revealed that IL-10 -1082 G allele is associated with higher levels of IL-10 in *C. trachomatis* endemic population [60]. Thus, based on these considerations, it may be concluded that IL-10 -1082 G allele and GG genotype can be considered as a risk factor for the up-regulation of IL-10 which is associated with persistent *Chlamydia* infection. Additionally, since there are other polymorphisms within IL-10 gene which have not yet been evaluated in infected patients, it appears that future investigations are essential to complete our knowledge.

CONCLUSION

Due to the aforementioned studies, it seems that IL-10 plays critical roles in the pathogenesis of *Chlamydia* infections and accordingly, *Chlamydia* species up-regulate this

anti-inflammatory cytokine to suppress immune responses against their antigens. In addition to bacterial factors which up-regulate IL-10, genetic variations within IL-10 gene also determine the outcome of *Chlamydia* infection. Additionally, it has also been documented that *Chlamydia* infections are responsible for the severe damage of Fallopian tube tissue resulting in tubal infertility and ectopic pregnancy [61]. It appears that inflammation processes induced by *Chlamydia* infections are responsible for several complications including fallopian tube tissue damages. Hence, it may be hypothesized that IL-10 is also involved in the incidence of the complications of *Chlamydia* infections. On the other hand, IL-10 can reduce the pathologic effects of *C. trachomatis* infection on the Fallopian tube tissue [61]. Another study demonstrated that, although, the lack of anti-inflammatory action of IL-10 is associated with enhanced *Chlamydia* eradication, but leads to severe inflammation in IL-10 knock out (IL-10 KO) mice [62]. Thus, it seems that modulation of IL-10 expression in the *Chlamydia* infected patients is cautiously performed.

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