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Activation of MAPK/ERK and MAPK/P38 is Essential for Proinflammatory Response by *Chlamydia trachomatis**

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Abstract Chlamydial infection in human urogenital tract induces inflammation and causes tissue damage and scarring. It is thought that cytokine production by the Chlamydia-infected cells plays a key role in chlamydial disease processes. Although many cytokines have been detected during chlamydial infection, little is known about the molecular mechanisms on how Chlamydia triggers and sustains the inflammatory cytokine cascades. In the current study, chlamydial infection of the human cervical epithelial cell line HeLa cells can induce the production of IL-8, IL-1α, IL-1β and IL-6. Using inhibitors for probing intracellular kinase signaling pathways required for the Chlamydia-induced cytokines, it was found that the Chlamydia-activated MAPK / P38 pathway is required for the chlamydial induction of IL-1α and IL-6 while both the Chlamydia-activated MAPK/ERK and MAPK/P38 pathways contribute to the production of IL-8.

Key words *Chlamydia trachomatis*, MAP kinase pathway, proinflammatory

Chlamydia trachomatis, an atypical gram -negative, obligate intracellular bacterial parasite, can cause a wide variety of diseases in humans.Ocular infection by *Chlamydia trachomatis* serovar A to C leads to preventable blindness. And serovar D to K are responsible for the sexually transmitted diseases(STD), which can evolve into female pelvivc inflammatory, tubal blockage and infertility.The lymphogranuloma venereum (LGV) serova L1 to L3 yield disseminated infection of the regional lymph nodes, presenting lymphogranulomapathy.

Chlamydia trachomatis mainly infects epithelial mucosa, and shows two development forms: the infectious extracellular elementary body(EB) attaching to the host cell and entering the cell through entry vacuoles which can avoid fusion with lysosomes. In the cell EB begins to differentiate morphologically into metabolically active reticulate body (RB) within 2～6 h. After replication, RB redifferentiates into the infectious EBs for eventual release.

Infection with *Chlamydia trachomatis* has been shown to induce inflammatory cytokines both *in vitro* and *in vivo*,which may contribute to the pathogenesis of chlamydial diseases. An inflammatory response is necessary to eliminate primary *C. trachomatis* infection, but chronic inflammation leads to the long term damage observed in trachoma and chlamydial sexually transmitted diseases. *C.trachomatis* infection of nonimmune cells produces a lot of proinflammation factors such as IL-1, IL-6, IL-8, IL-18, GROa, and granulocyte-macrophage colony-stimulating factor [1]. IL-8 as a chemokine induces neutrophil infiltration to the primary site of infection, causing subepithelial accumulation of mononuclear leukocytes and tissue damage, and involves in early host response to pathogen.

Although the mechanisms that modulate host response to *C. trachomatis* are still not fully understood, the hypothesis that high level of production of proinflammatory in Chlamydial-infected

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cell may be derived from activating specific cell signaling pathway. Therefore, uncovering Chlamydia interactions with host cellular signaling pathway is essential for understanding the chlamydial pathogenic mechanisms. The MAP kinase is a very important signaling pathway in host immune response, activation of MAP kinase pathway result in a lot of cytokines releasing. The MAPK is a family of proline-directed serine/threonine protein kinases that are activated in response to many extracellular stimulis. There are three major groups of MAP kinases in mammalian cells,the extracellular signal-regulated protein kinases (ERK),the p38 MAP kinases,and the c-Jun NH_2 terminal kinases(JNK). It is known that both IL-8 and IL-6 promoter contain the binding site of AP-1,C/EBP (NF-IL6) and NF-κB transcription factor [2, 3]. The transcription factors AP-1 and C/EBP are down stream factors of these three MAP kinases pathways. In the present report, we studied the activation of MAP kinase pathways during the infection of *C.tarchomatis* shows that *C.trachomatis* infection can activate P38, ERK pathway 36 h after chlamydial infection. Inhibitors to the different MAPK pathways showed that inhibition of either P38 or ERK pathway can significantly down regulate the production of IL-8, while IL-1α and IL-6 production can only be inhibited by blocking P38 pathway during *C. trachomatis* infection.

1 Materials and methods

1.1 Cell culture and chlamydial infection

HeLa 229 comes from cervixade epithelia, is susceptive to chlamydial infection and often used in chlamydial study [4～6]. HeLa 229 (cervixade epithelia adenocarcinoma, CCL-2.1, ATCC, Manassas, VA)were maintained in Dulbecco's modified Eagle's medium (Invitrogen) with 10% FCS at 37℃ in an incubator supplied with 6% CO_2. The *Chlamydia trachomatis* serovar L2 (434/Bu) were grown, purified,and titrated as followed [7]. Aliquots of chlamydial organisms were stored at –80℃. The cells were infected by *Chlamydia trachomatis* serovar L2 (*MOI*=5) or as indicated in the individual experiment.The infected cells were cultured in 37℃ for various times in different experiments. For inhibitor experiments,the cell culture were treated with different inhibitors 2 h before L2 infection. The inhibitors U0126 and PD98059 (for MEK1/2), SB203580 and SB202190 (for P38), SP100625 (for JNK), all the inhibitors were from Calbiochem (San Diego, CA), were used at the concentrations as indicated in individual experiments.

1.2 Western blot assay

The cell samples from 60 mm culture dish were harvested with SDS sample buffer (2%SDS,50 mmol/L dithiothreitol, 62.5 mmol/LTris-HCl pH6.8). After boiled and sonicated, the sample were loaded to SDS polyacrylamide protein gel, then transferred onto nitrocellulose membranes. The first antibody used including monoclonal rabbit antibodies to P-ERk, JNK,P38(cell signaling), monoclonal mouse antibodies to P-JNK,P-P38,ERK (BD transduction), and monoclonal mouse antibody MC22 (anti-Monp) and Hsp70 (santa cruz) as control.The First antibody were probed with corresponding secondary antibody conjugated with horseradish peroxidase (Jakckson ImmunoResearch Laboratories,Inc.West Grove,PA) followed by standard ECL(Amersham Biosciences).

1.3 ELISA assay

IL-1α, IL-1β, IL-6 and IL-8 were detected by ELISA from whole cell lysate. For whole cell lysate, cells were lysed by repeated freeze-thawing to yield maximal recovery of total cytokines. IL-1α, IL-β, IL-6 were tested by ELISA kit (R&D) and the procedure was followed the kits instruction. For IL-8 detection, captured antibody was diluted to 1 ∶200 (BD Pharmingen) in 0.1 mmol/L carbonate, cultured at 4℃ overnight. After washing and blocking then added standards and samples 37℃ 1 h. After cultured with strepdvin-cojugated detect antibody for IL-8 (1 ∶ 800, BD Pharmingen) 37℃ 1 h, HRP-(Jackson West Grove, PA) were added for 37℃ 20 min ,then added ABTS (2-2'-azino-di- (3-ethylbenzthiazoline) sulfonic acid; sigma) substrate of HRP, read *A*.

2 Results

2.1 Chlamydial infection can induce IL-8, IL-1α, IL-6, IL-1β

Acute Chlamydial infection are characterized by intensive inflammation and infiltration of the mucosa predominantly with neutrophils, and also other inflammatory cytokines [8]. Our studies showed that comparing with the normal cell at different time points after L2 infection, the production of IL-8, IL-6, IL-1α and IL-1β from Chlamydia infected HeLa 229 cell began to increase at 36 h post infection, and was time-responsed by using ELISA (Figure 1a～d) and immunoblotting (data not show).

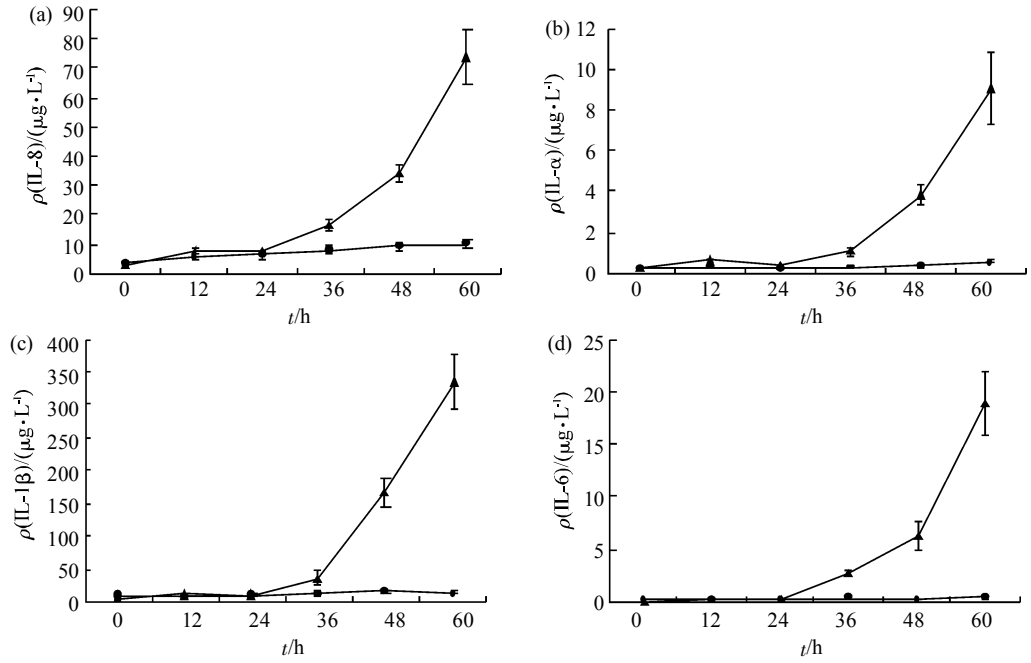

Fig. 1　Time course of different cytokines produced after chlamydia infection

HeLa 229 monolayers cells were infected with L2(*MOI*=5), whole cell lysate were collected with or without L2 infection at different time points(0 h, 12 h, 24 h, 36 h, 48 h, 60 h after L2 infection) to test the amount of IL-8, IL-6, IL-1α and IL-1β by ELISA (a,b,c,d). ELISA results shown is representative data from three experiments ($\bar{x}\pm s$). ●—●: NC, ▲—▲: L2.

2.2　Chlamydial infection activates ERK and P38 signaling pathways

Chlamydial infection can alters the profile of host transcription genes at a broad rang[9]. The MAP kinase pathway is very important to activate the proinflammatory. Chlamydial infection can activate the MAPK/ERK pathway to initial the lipid metabolism for Chlamydia growth[10].And the host lipid remodeling process which required for chlamydial growth also contributes to Chlamydia-induced IL-8 production[11].In this study,we have detected the three different MAP kinase pathways (ERK, P38 and JNK) by detecting phosphorylated-ERK, phosphorylated-P38 and phosphorylated-JNK at different time points after L2 infection compared with normal HeLa229 cells by immunoblotting. Our data showed that chlamydial infection can not only activate the MAPK/ERK pathway, but also activate the MAPK/P38 pathway (Figure 2). However, chlamydial infection can not activate JNK/MAPK pathway at all, although JNK is the upstream kinase of AP-1.The MAPK/P38 pathways is activated at later time about 36 h post infection and are in a time dependent manner. ERK pathway is the earliest activated. The phosphorylated ERK upregulated at about 24 h post infection, and is also in a time dependent manner. All of these are consistent with the time point at which the proimflammatory are induced by Chlamydia.

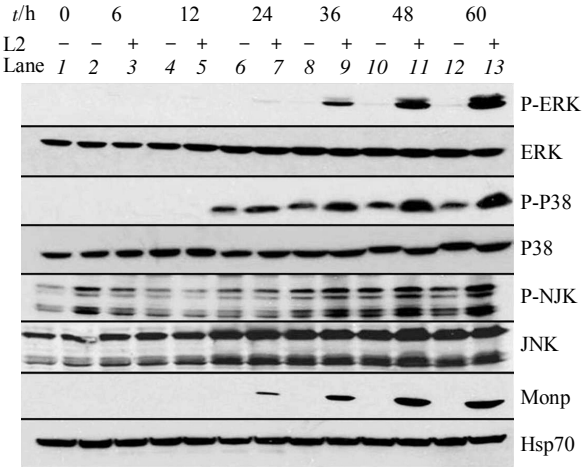

Fig. 2　Chlamydial infection can activate MAPK/ERK and MAPK/P38 pathways but not MAPK/JNK

HeLa 229 monolayer cells were infected with L2(*MOI*=5), the whole cell lysates were collected with or without L2 infection at each time point (0 h,12 h, 24 h, 36 h, 48 h, 60 h after L2 infection) to test the MAPK pathway by immunoblotting.

Chlamydial infection can activate ERK/MAPK and P38/MAPK pathways. Chlamydial infection can also induce IL-8, IL-6, IL-1α and IL-1β *et al* inflammatory factors. From the time point, there are

some association between the activation of the signaling pathway and the upregulation of the cytokines post chlamydial infection. What is the association? How does the signaling pathway contribute to production of the proinflammatory cytokines? The interaction between chlamydia and the host cell is indefinite. The next step is to identify which signaling pathway is involved in the production of proimflammatory in chlamydia-infected epithelial cells. Do all the cytokines share the same signaling pathway or there are different pathways contribute to different cytokines production ?

2.3 Inhibition of MAPK/ERK and MAPK/P38 pathway result in reduction of IL-8 response to chlamydial infection

To further establish which kinase pathway is contributed to proinflammatory cytokines production, an inhibition experiment was carried out by using different inhibitors for different pathways. Three different doses (high dose, middle dose and low dose) of each inhibitor were used to see the effects of the inhibition on different pathways and on the production of different cytokines post infection (Figure 3).

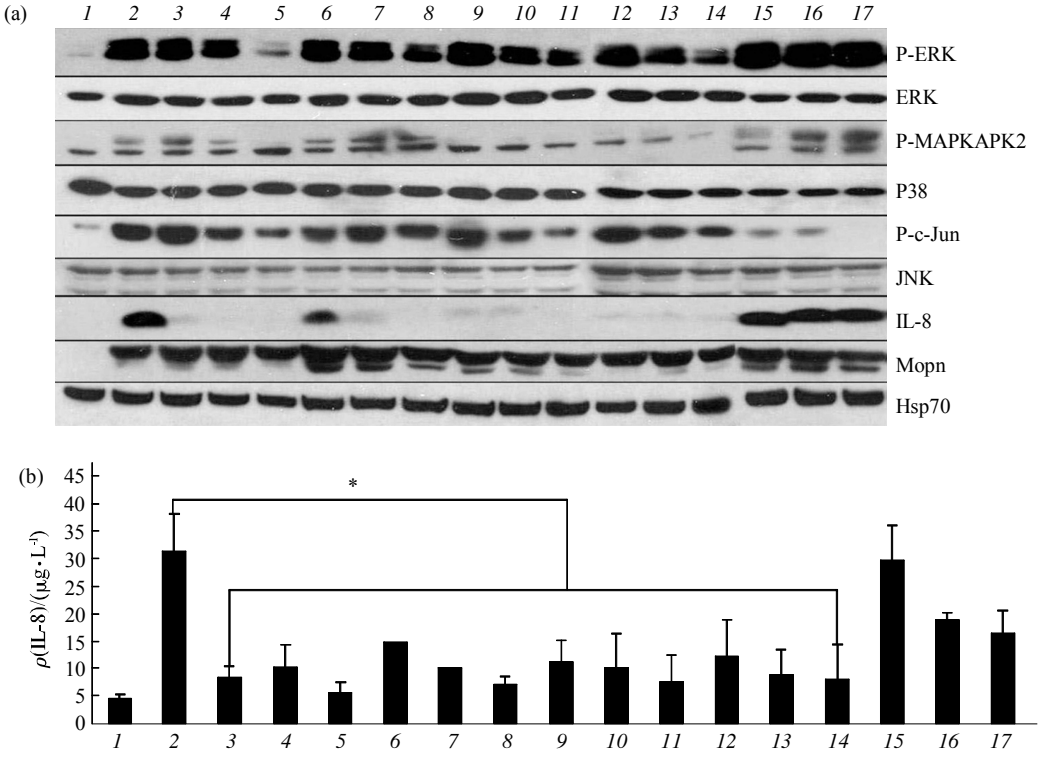

Fig. 3 Inhibition experiment for different MAPK pathway (a) and Chlamydia-induced IL-8 after treating with different inhibitors for different MAPK pathways (b)

(a)Treatment with different inhibitors to monolayer cells 2 h before L2 infection (*MOI* = 5), then collect the sample 44 h after L2 infection with SDS lysis buffer. HeLa 229 and L2 infection only as controls. The phospho-ERK, phospho-mapkapk2, phospho-c-jun,hIL-8, Mopn and Hsp70 were detected by Western-blotting to see the effect of different inhibitors on different pathways and the production of IL-8 induced by Chlamydia after inhibiting different MAPK pathway. 1: HeLa229; 2: L2 infection; 3: L2+U0126 5 μmol/L; 4: L2+U0126 10 μmol/L; 5: L2+U0126 20 μmol/L; 6: L2+PD98059 10 μmol/L; 7: L2+PD98059 20 μmol/L; 8: L2+PD98059 40 μmol/L; 9: L2+SB203580 1 μmol/L; 10: L2+SB203580 5 μmol/L; 11: L2+SB203580 10 μmol/L; 12: L2+SB202190 1 μmol/L; 13: L2+SB202190 5 μmol/L; 14: L2+SB202190 10 μmol/L; 15: L2+SP100625 1 μmol/L; 16: L2+SP100625 2 μmol/L; 17: L2+SP100625 5 μmol/L. (b)Inhibitors treatment is the same with that of inhibition experiment for different signaling pathway.Whole cell lysates were collected for the IL-8 detection by ELISA. Shown is representative data from two experiments ($\bar{x}\pm s$).*$P < 0.05$. *1*: NC; *2*: L2; *3*:U0126 5 μmol/L; *4*: U0126 10 μmol/L; *5*: U0126 20 μmol/L; *6*: PD98059 10 μmol/L; *7*: PD98059 20 μmol/L; *8*: PD98059 40 μmol/L; *9*:SB203580 1 μmol/L; *10*: SB203580 5 μmol/L; *11*: SB20358 10 μmol/L; *12*:SB202190 1 μmol/L; *13*:SB202190 5 μmol/L; *14*: SB20219 10 μmol/L; *15*: SP100625 1 μmol/L; *16*:SP100625 2 μmol/L;*17*:SP100625 5 μmol/L.

Inhibition of the epithelial MAPK/ERK by U0126 which specific inhibits the ERK/MAPK pathway can obviously block the phosphorylation of ERK and totally inhibit Chlamydia-induced IL-8 production, another MAPK/ERK inhibitor PD98059 can partially block phosphorylation of ERK, and also reduced Chlamydia-induced IL-8. It is showed that the block is in a dose-dependent manner. These suggested MAPK/ERK pathway is essential for IL-8 production in Chlamydia-infected cell.

Inhibition of epithelial MAPK/P38 by SB202190 and SB203580 have no effect on phosphorylation of P38[12], but they inhibit the function of phosphorylated P38 kinase and the activation of the downstream factors of phosho-P38. Data showed that the phosphorylation of MAPKAPK-2, one of the downstream factors of phospho-P38 kinase, was inhibited by both SB202190 and SB203580. The inhibitors SB202190 and SB203580 can efficiently block MAPK/P38 pathway and the phosphorylation of MAPKAPK-2 even in a very low dose (1μmol/L), and can totally block chlamydia-induced IL-8 production at the lowest dose in infected cells(Figure 3). It indicated that MAPK/P38 pathway was involved in production of IL-8 by chlamydial infection.

SP600125 is the inhibitor for JNK/MAPK pathway. From the western JNK inhibitor SP600125 can not inhibit the production of IL-8 induced by chlamydial infection while it can totally block the phosphorylation of c-Jun, a downstream factor of JNK, a component of AP-1 transcription complex. It is strongly suggested that JNK/MAPK pathway has nothing to do with IL-8 induced by chlamydial infection. This is consistent with our previous results that Chlamydia can not activate the JNK/MAPK pathway. From our data SB202190, SB203580 and U0126 have some effect on the inhibition of the phosphorylation of c-Jun and are in a dose-dependent manner. And there are reports that AP-1 can also be activated through ERK and P38 pathway [13,14]. The immunoblotting results also showed that SB202190 and SB203580 partially block ERK pathway at higher concentration of 5μmol/L and 10 μmol/L. Maybe there is some crosstalk between ERK and P38 pathway during chlamydial infection, which needs to be proved.

2.4 Inhibition of the MAPK/P38 pathway results in reduction of Chlamydia-induced IL-6 and IL-1α

Inhibition of MAPK/P38 by SB202190 and SB203580 also blocked the Chlamydia-induced IL-6 and IL-1α production. HeLa229 cells pre-incubation with SB202190, SB203580 can block MAPK/P38 pathway and reduce Chlamydia-induced IL-6 by 40% and almost totally block IL-1α production (Figure 4). But all the three MAPK pathways were not involved in Chlamydia-induced IL-1β (data not show).

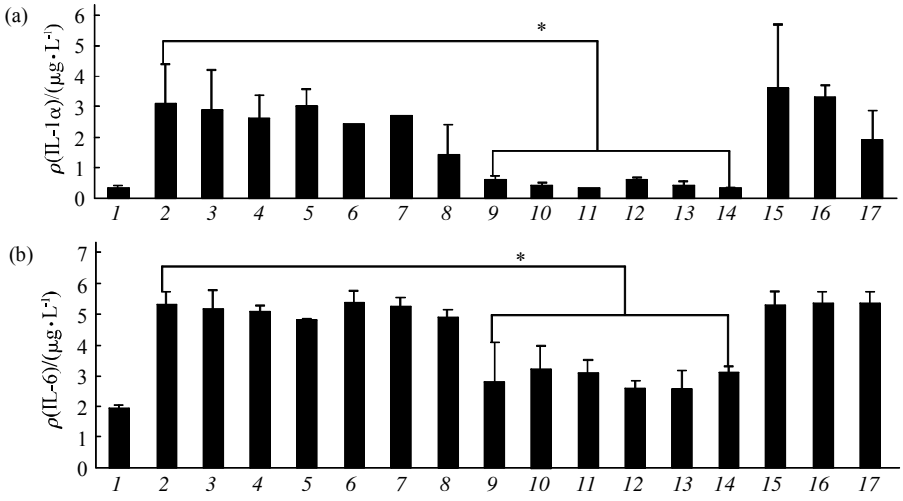

Fig. 4 Chlamydia-induced IL-6 and IL-1α after treating with different inhibitors for different MAPK pathways

Inhibitors treatment is the same with that of inhibition experiment for different signaling pathway.The whole cell lysates were collected for the IL-1α (a) and IL-6 (b) detection by ELISA. Shown is representative data from two experiments ($\bar{x}\pm s$). *P < 0.05. *1*: NC; *2*: L2; *3*:U0126 5 μmol/L; *4*: U0126 10 μmol/L; *5*: U0126 20 μmol/L; *6*: PD98059 10 μmol/L; *7*: PD98059 20 μmol/L; *8*: PD98059 40 μmol/L; *9*:SB203580 1 μmol/L; *10*: SB203580 5 μmol/L; *11*: SB203580 10μmol/L; *12*:SB202190 1 μmol/L; *13*:SB202190 5 μmol/L; *14*: SB202190 10 μmol/L; *15*:SP100625 1 μmol/L; *16*: SP100625 2 μmol/L;*17*:SP100625 5 μmol/L.

3 Disscusion

Chlamydial infection is characterized by inflammation which, exacerbated by reinfection, ultimately leads to tissue damage and scarring. Chlamydial interaction with the cytokine system is thus likely to be central to disease. Chlamydial infection can generate a cytokine response both by direct infection of host epithelia and by interaction with cells of the immune system. Chlamydia infected cervical epithelial cells, the primary target of infection, can produce a number of proinflammatory cytokines such as IL-1α,IL-6 and IL-8, which are significant mediators of the acute inflammation response, a first line of defense as well as the cause of the initial stages of disease. Unlike the transient cytokine induction following infection by other invasive bacteria, the epithelial cytokine response to Chlamydia is delayed and the production of proinflammmatory cytokines is dependent on bacterial growth[11]. Our data showed the detection of IL-6, IL-8 and IL-1α until 36 h post infection and is time dependent. However little is known about the mechanisms that initiate and sustain the inflammatory response by Chlamydia-infected epithelial cells.

In our studies, multiple signaling pathways of host cell can be activated after chlamydial infection. These pathways seem contribute to different cytokines production during chlamydial infection. For IL-8 production,both MAPK/ERK and MAPK/P38 pathway are involved. It seams that ERK pathway can be activated a little earlier than P38 pathways,we can detected very small amount of phosphorated ERK at 24 h post chlamydial infection. Previous studies showed that ERK pathway is essential for chlamydial acquisition of host glycerophospholipids in order to maintain itself growth [10] and the lipid metabolism required for chlamydial growth contributes to Chlamydia-induced IL-8 through ERK pathway [11]. When we increase the dose of MEK inhibitor(U0126) to 50 μmol/L, the growth of Chlamydia is obviously blocked (data not show). There are two mechanisms may contribute to IL-8 upregulation during chlamydial infection: one is mediated by IL-1α released into infected-cell culture supernatant at later time post infection,and the other may due to Chlamydia itself[15]. Maybe these two different pathways(MAPK/ERK and MAPK/P38 pathway) contribute to different mechanisms of IL-8 upregulation.

From our studies JNK/MAPK pathway did not involve in the proinflammatory production. MAPK / P38 is thought to be important for proinflammatory mediator expression under various conditions of infectious disease. It was reported to regulate GM-CSF releasing induced by *C. pneumoniae*[16]. From our data, MAPK/ERK pathway only contributed to IL-8 producing during chlamydial infection, while MAPK/P38 pathway seemed more important for cytokines response after chlamydial infection.When blocked MAPK/P38 pathway, IL-1α and IL-8 can be totally inhibited and IL-6 is about 40% decreased. IL-1α is a critical proinflammatory cytokine in inflammation response, it can induce other cytokines during inflammation including IL-6 and IL-8 [17]. So weather there are any associations among MAPK/P38 pathway and IL-1α, IL-8 and IL-6? Weather chlamydial infection activate MAPK/P38 pathway to induce IL-1α, IL-6and IL-8 respectively? or IL-1α upregulation is through the activation of MAPK/P38 pathway and then induce IL-8 or/and IL-6? These questions need us to do further research.

The proinflammatory cytokines play an important role in pathology as well as the immune response to chlamydial infection. The mechanisms for inducing different proinflammatory cytokines during chlamydial infection are different. Understanding the origin of the cytokines response in Chlamydia-infected epithelial cells will inform how the innate and consequent adaptive immune response are activated. Thus, discerning the mechanism of the proinflammatory induction provides insight into the host-bacteria interaction leading to activation of host signaling pathways, chemokine production, innate immune response activation, and the inflammation that leads to Chlamydia-associated disease.

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MAPK/ERK 和 MAPK/P38 信号通路的活化参与沙眼衣原体诱导前炎因子的产生 *

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摘要 沙眼衣原体感染可导致沙眼、性传播性疾病、不孕症等疾病，主要病理表现是炎症反应引起的组织损伤和瘢痕．因此，沙眼衣原体诱导产生的炎症因子是导致疾病的关键，沙眼衣原体可直接感染内皮细胞产生各种前炎因子，但其机制目前还不清楚．通过 ELISA 和免疫印迹等方法，检测到沙眼衣原体感染 HeLa229 细胞可产生 IL-8，IL-1α，IL-1β，IL-6 等前炎因子，并且沙眼衣原体感染可以主要激活宿主细胞 MAPK/ERK 和 MAPK / P38 信号通路. 抑制 MAPK/ERK 和 MAPK / P38 信号通路显示，两条通路在沙眼衣原体感染过程中参与调节不同的炎症因子产生．MAPK / P38 信号通路的活化参与调控 IL-1α，IL-6 的产生，而 IL-8 则同时受 MAPK/ERK 和 MAPK/P38 两条通路的调控.

关键词 沙眼衣原体，MAPK 通路，前炎因子

学科分类号 R374+.1，R392.3

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