WOGONIN ON THE MECHANISM OF INFLUENZA VIRUS INFECTION OF ALVEOLAR MACROPHAGE INFLAMMATORY SUBSTANCES

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Abstract: Backgroud: Influenza caused by influenza virus infection is a highly contagious re spiratory disease. It spreads rapidly and leads to a high mortality rate. R ecently it often happened severe global influenza pandemic, and threatened the public health seriously. Pulmonary pathological change caused by influe nza virus is characterized by pulmonary edema and extensively inflammatory exudates.

Keywords: Alveolar macrophage, Wogonin, Influenza virus, NF-κB, TLR7, Inflammation, Inflammatory substances.

It has been reported that the pathological changes in lungs of in fluenza virus infection are always accompanied with a large number of infla mmatory cells, including neutrophils, monocytes, macrophages and high level s of pro-inflammatory cytokines, chemokines, which indicates that the exces sive host immune response is one of the main factors responsible for the pa thological lesions caused by influenza virus. Therefore, anti-inflammatory treatment has become more and more important in the treatment of influenza. Traditional-Chinese-Medicine(TCM) consists of many components which has lo ts of effects. TCM not only has direct antiviral effects, but also can regu late the complicated process of the pathological change caused by excessive immune response against influenza virus. Therefore, it has a specific adva ntage in the treatment of influenza.Wogonin is one of the major components of Scutellaria which is a TCM us ed in the treatment of influenza. A large number of clinical experience and experimental studies have shown that Scutellaria has good effects to treat influenza. Studies have reported that wogonin has antioxidant, anti-inflam matory and immunomodulatory properties. Based on that, we investigated the effects and mechanism of wogonin in alleviating the excessive inflammatory response caused by influenza virus to reveal the function of wogonin in the treatment of influenza, to provide the scientific evidence for wogonin app lication in treatment of viral pneumonia caused by influenza, and to provid e the experimental basis for the pharmacological effects of Scutellaria.Objectives:To observe the effects of wogonin on the inflammation related factors a nd the key molecules of the TLR7 mediated MyD88-dependent pathway in alveol ar macrophage of rats (NR8383) infected by influenza virus, and to specify the function of worgonin in the treatment of viral pneumonia.Methods:After infection of NR8383 by influenza virus A(FMl) for 1 h, virus was r emoved, and NR8383 cells were treated with wogonin for different hours: 1 To study the effects of wogonin on oxygen free radical from alveolar macrophages (NR8383) infected by influenza virus:At 8 h,24 h,36 h,48 h after wogonin(0.016 g/L,0.008 g/L,0.004 g/L) application, griess reagent was used to measure the concentration of NO. At 8 h,24 h,36 h,48 h after wogonin(0.016 g/L) application, biochemical detection was used to measure the

concentration of intracellular iNOS; At 4 h,8 h,18 h,24 h after wogo nin application, biochemical detection was used to measure SOD activity and the concentration of MDA.2 To study the effects of wogonin on inflammatory mediators from NR8383 infected by FM1:At 6 h,12 h,24 h after wogonin(0.016 g/L) application, radioimmunoassay (RIA) was used to detect the concentration of inflammatory mediators, Prostaglandin E2 (PGE2), Phospholipase A2 (PLA2), and leukotriene (LTB4).3 To study the effects of wogonin on cytokines from NR8383 infected by FM1:At 6 h,12 h,24 h after wogonin(0.016 g/L) application, ELISA method was used to detect the concentration of tumor necrosis factor-alpha (TNF-α) and monocyte chemotactic protein-1 (MCP)-1 in the supernants; At 24 h afte r drug application, realtime PCR was used to detect the mRNA level of TNF-a and MCP-1.4 To study the effects of wogonin on TLR7 mediated MyD88-dependent path way in NR8383 infected by FM1:At 24 h after wogonin(0.016 g/L) application, RT-PCR was used to detect the mRNA level of MyD88, NF-κB and TLR7.5 To study the effects of wogonin on nuclear translocation and expressi on of NF-κB in NR8383 infected by FM1:After incubation with virus, immuno cytochemistry was used to detect nuclear translocation of NF-κB in the cel ls at 2 h,4 h,6 h,8 h,24 h. At 4 h,6 h,24 h after wogonin(0.016 g/L) application, immunocytochemistry was used to detect nuclear translocation o f NF-κB in the cells and to do semi-quantity analysis; At 24 h after wogon in application, western-blot was used to detect the expression of NF-κB pr otein.Results:1 After infection of influenza virus, NO, iNOS and MDA levels from NR83 83 increased significantly, and the total SOD activity decreased. At 24 h, 36 h,48 h after wogonin application, NO level was decreased($P<0.01$); at 24 h,36 h,48 h, iNOS activity was significantly reduced ($P<0.05$). At 4 h,8 h after wogonin application, total SOD activity was increased ($P<0.05$) and MDA level was decreased ($P<0.05$).2 After infection of influenza virus, PLA2, PGE2, LTB4 levels from NR8383 were significantly increased. At 6 h after adding wogonin, PLA2 activity wa s decreased ($P<0.01$). After wogonin application, PGE2 level was lower than t he level of the virus group, however there was no significant difference be tween the results ($P>0.05$). At 12 h,24 h, LTB, level was decreased ($P<0.01$, $P<0.05$).3 After infection of influenza virus, TNF-α,MCP-1 transcription and ex pression in NR8383 were significantly increased. At 24 h after adding wogon in, MCP-1 mRNA level was greatly decreased ($P<0.01$). At 6 h,12 h,24 h, th e concentration of MCP-1 was reduced ($P<0.01$). At 24 h after wogonin applic ation, TNF-αmRNA level was decreased ($P<0.01$). At 12 h,24 h, the concent ration of TNF-αwas reduced ($P<0.01$).4 After infection of influenza virus, MyD88,NF-κB and TLR7 mRNA level s in NR8383 were significantly increased. At 24 h after adding wogonin, MyD 88,NF-κB and TLR7 mRNA levels were decreased ($P<0.05$, $P<0.01$, $P<0.05$).5 After infection of influenza virus, NF-κB nuclear translocation was not obvious in NR8383. in contrast to cells in normal group, NF-κB express ion was increased in the cytoplasm at 2 h; At 4 h,6 h, NF-κB nuclear tran slocation was obvious. NF-κB expression in the nuclei was increased, and N F-κB expression in the cytoplasm was increased in contrast to that of cell s in normal group; At 8 h, NF-κB expression in the nuclei was decreased; A t 24 h, NF-κB expression in the nuclei reduced, NF-κB expression in the c ytoplasm was significantly increased in contrast to that of cells in normal group. At 24 h, the result of western-blot was the same with that of immun ocytochemistry, NF-κB expression in the cytoplasm was significantly increa sed in contrast to that of cells in normal group, NF-κB in the nuclei did not exist. At 4 h,6 h after wogonin application, NF-κB in the nuclei and cytoplasm were reduced. At 24 h after wogonin application, NF-κB protein e xpression in the cytoplasm was reduced.Conclusions:Wogonin significantly decreased NO

concentration by controlling iNOS ac tivity. Wogonin also increased total SOD activity, and decreased MDA during early periods (4 h,6 h) after the infection of virus. It indicates that wo gonin can alleviate damages by free radical such as NO. Wogonin decreased L TB4, PGE2 by repressing PLA2, and relieve inflammation induced by them. Wogon in also controlled the transcription and expression of TNF-α, MCP-1, and de creased the activation of other cytokines and inflammatory cells. As a resu It, it can alleviate the inflammatory damages by the viral pneumonia. Wogon in decreased the transcription of the key signal molecules of the pathway w hich influenza virus stimulates macrophages through, TLR7 mediated MyD88-de pendent pathway. Wogonin also controlled NF-κB nuclear translocation and e xpression. Therefore, wogonin can reduce the transcription and generation of inflammatory protein. As a result, Wogonin can relieve excessive immune r esponse in the treatment of viral pneumonia.

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