Research Progress of Signal Pathways Related to Severe Community Acquired Pneumonia and Complications

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Abstract: Severe Community acquired pneumonia is one of the common critical diseases in clinic. It has the characteristics of rapid progress, difficult treatment, high mortality and many complications. Studies have shown that the pathogenesis of Severe Community acquired pneumonia may be related to the transduction of cellular signal pathways. Combined with the latest research progress at home and abroad, this paper summarizes the role of severe pneumonia related signal pathways in the pathogenesis, in order to provide potential targets for the treatment of Severe Community acquired pneumonia and provide some scientific basis for the research and development of new drugs.

Keywords: Severe community acquired pneumonia, Pathway, Research progress

1. Introduction

Early manifestations include fever, cough, sputum, chest tightness and shortness of breath, etc. As the condition worsens, it can be complicated by sepsis, multi-organ dysfunction and shock, which can lead to death in severe cases. It is now believed that severe pneumonia is not just the result of bacterial or viral infection, but a complex biological process with multifactorial and multigene interactions. With the continuous development of molecular biology, cell signaling pathways have been increasingly studied, and a large number of signaling pathways related to severe pneumonia and its complications have been discovered, mainly including TLR4/MyD88/NF-κB, JAK/STAT, PI3K/Akt/mTOR, Notch and other signaling pathways, and the related components of these cell signaling pathways may become potential targets for the treatment of potential targets for the treatment of severe pneumonia.

2. TLR4/MyD88/NF-κB signalling pathway

2.1. Composition and regulation of the TLR4/MyD88/NF-κB signalling pathway

Toll-like receptors (TLRs) are a conserved family of pattern recognition receptors in the innate immune system, consisting of three components: the extracellular leucine-rich repeat sequence structural domain, the transmembrane structural domain and the intracellular conserved Toll-IL-1 receptor (TIR) structural domain, of which the TIR structural domain is responsible for signal transduction[1]. Toll-like receptor 4 (TLR-4) is a member of the TLR family whose ligands include TLR4 recognises the corresponding ligands and then signals through MyD88, the proximal protein junction of the receptor containing the TIR domain. MyD88 recruits IL-1R-associated protein kinase via its own death structure domain to enter the downstream signaling pathway. NF-κB is a downstream effector located in the TLR4 signaling pathway, at which point the inhibitory IκB protein is phosphorylated and subjected to ubiquitination-dependent degradation by the proteasome, resulting in the NF-κB transcriptional NF-κB is an active protein with multiple transcriptional regulatory roles and is responsible for regulating the major transcription factors of the innate and adaptive immune response, mediating a variety of inflammatory processes, and its activation enhances IL-6, IL-1β, TNF-α and other pro-inflammatory cytokine expression. Notably, distinct TLRs identify distinct molecular patterns linked to pathogens, with TLR-4 mediating the response to Gram-negative bacterial lipopolysaccharides by recognising exogenous ligands considered to be the classical pathway for activating this signalling pathway. [3].Furthermore,
endogenous ligands have been proposed to activate TLR in response to tissue injury and specific disease conditions, thereby enhancing inflammation even in the absence of infection. It is now clear that at least these two distinct pathways can activate NF-κB and regulate the production and survival of pro-inflammatory factors[3].

However, it has also been shown that in the presence of epithelial cell survival and mucosal barrier integrity, the anti-apoptotic function of NF-κB can both protect against the inflammatory response and maintain it through sustained leukocyte activation[4, 5]. Conversely, NF-κB can in some cases also promote leukocyte apoptosis and contribute to the progression of inflammation[6]. To find out if the NF-κB pathway can always be a therapeutic target, future research must assess the status of these various roles of the system in inflammatory illnesses.

2.2. TLR4/MyD88/NF-κB signalling pathway and severe pneumonia

Through the aforementioned mechanism, it is known that reducing the activation of the TLR4/MyD88/NF-B signaling pathway might lessen the inflammatory response associated with severe pneumonia. Sun Zhixia’s[7] ginsenoside Rg1’s impact on myocardial tissue injury in rats with severe pneumonia was examined, and after low-dose gavage, it was found that the medication group's expression levels of TLR4, MyD88, p-NF-B, and p65 were significantly lower than those of the model group and that this difference was dose-dependent. So it was hypothesized that ginsenoside Rg1 could inhibit TLR4/NF-κB signaling The ginsenoside Rg1 was hypothesized to inhibit TLR4/NF-κB signaling pathway activation, thereby reducing the inflammatory response and myocardial apoptosis. Cai Zhang[8] et al. showed that Qingwenzhike prescription could significantly downregulate LPS-induced TLR4, p-IKKα/β, p-IκBα, p-NF-κB and NLRP3 expression, suggesting that Qingwenzhike could effectively inhibit TLR4/NF-κB signaling pathway and NLRP3 inflammatory vesicles, and was effective in protecting against lipopolysaccharide-induced acute lung injury Zhang Han[9] et al. showed that baikalin could inhibit the expression levels of TLR4, MyD88 and NF-κB and reduce the inflammatory infiltration and pathological changes in the lung tissue of mice with Mycoplasma pneumonia. Liu Jianxing[10] et al. showed that by blocking the activation of the TLR4/NF-κB signaling pathway in vivo and in vitro, Conotoxin B could attenuate lung inflammation brought on by lipopolysaccharide, diminish inflammatory cell infiltration, and down-regulate the expression of cytokines, chemokines, and inducible enzymes. Liu Tianyin[11] et al. examined the possibility that blocking TLR4/Myd88/NF-κB activation by Polygonatum kingianum polysaccharide could reduce LPS-induced acute lung damage. After adding LPS to the growth media, normal human lung epithelial cells were grown in vitro, and flow cytometry was used to identify apoptosis. It was discovered that Polygonatum kingianum polysaccharide could greatly reduce the proportion of LPS-induced apoptosis in BEAS-2B cells, but LPS was able to significantly raise the proportion of BEAS-2B cells going through apoptosis. Polygonatum kingianum was reported to be able to prevent inflammation by lowering the levels of TLR4, Myd88, and p-IκB-α expression that were triggered by LPS, as determined by protein blotting. Salidroside was demonstrated by Wang Hui[12] et al. to lower NF-κB activation levels and decrease the release of inflammatory mediators and the number of inflammatory cells in lung tissue. One study showed that curcumin[13] could effectively reduce the mRNA expression of IL-1β, IL-6 and TNF-α pro-inflammatory cytokines and inhibit NF-κB activation. The involvement of the TLR4/MyD88/NF-κB signaling pathway in the inflammatory dysregulation process of severe pneumonia is evident, and the application of TLR4/MyD88/NF-κB pathway inhibitors may represent a novel approach to treating severe pneumonia. Future research can confirm the target of this signaling pathway's inhibition of inflammation continually and identify the major target of this pathway's inhibition of inflammation, which can serve as a reference for additional research on drugs for severe pneumonia.

3. JAK/STAT signalling pathway

3.1. Composition and regulation of the JAK/STAT signaling pathway

The intracellular JAK/STAT ( Janus kinase, JAK; signal transducers and activators of transcription, STAT) signaling system is widely expressed and plays a crucial regulatory function in numerous essential biological processes, including immune control, cell proliferation, differentiation, and apoptosis. There is growing evidence[14] that sustained activation of the JAK/STAT signalling pathway is associated with the expression of key mediators of various cancers and inflammation, and therefore, inhibition of JAK/STAT pathway activation holds promise for the treatment of various related diseases. The JAK family consists of non-receptor tyrosine protein kinases that are activated and transmit regulatory signals
when cytokines bind to their receptors. The four primary members of the JAK family are JAK1, JAK2, JAK3, and TYK2. Of these, only the lymphoid system, bone marrow, and endothelium and vascular smooth muscle cells express JAK3, but the other members are expressed in nearly every tissue. The classical pathway of JAK/STAT signalling activation is the interaction of a cellular ligand with its receptor, causing the activation of JAK leads to phosphorylation of the tyrosine that binds to the receptor, forming a docking site for STAT, where JAK phosphorylates STAT, which then dissociates from the receptor and forms homodimers or heterodimers through SH2 domain-phosphotyrosine interactions, which translocate to the target gene promoter and regulate the function of STAT[15]. The JAK/STAT signalling pathway is positively and negatively regulated, with positive regulation by tyrosine kinase activation of STAT proteins, serine phosphorylation and other related proteins, and negative regulation by three main regulators: activation of STAT protein repressors, cytokine signalling repressors and protein tyrosine phosphatases.

3.2. JAK/STAT signalling pathway and severe pneumonia

STAT3 is a member of the STAT family and has two different functional splice isoforms, STAT3α and STAT3β, which are mainly involved in the negative regulation of cell growth, differentiation immune response, and apoptosis as well as tumorigenesis and metastasis, and have received a lot of attention in the existing studies on this pathway in severe pneumonia. Hu Wei et al[16] used cecal ligation and perforation (CLP) to prepare a rat model of sepsis, and detected the expression of p-JAK1 and p-STAT3 proteins in the tissues of the model rats by Western blot technique, and compared with the normal group, demonstrated that the overactivation of JAK/STAT signalling pathway plays an important role in severe pneumonia The results showed that over-activation of the JAK/STAT signalling pathway plays an important role in severe pneumonia. And in a subsequent study, it was found that intervention with type I insulin-like growth factor receptor could effectively inhibit JAK/STAT signalling pathway activation and thus reduce sepsis-induced acute lung injury. Hua Xue[17] et al. created a rat model using CLP, and in the model group’s lungs, JAK2 and STAT3 phosphorylation levels were higher than in the control group. After gavage by Pterostilbene, the expression of JAK2 and STAT3 in rats was significantly lower than that of the model group, demonstrating that Pterostilbene may exert therapeutic effects by inhibiting the phosphorylation levels of JAK2 and STAT3. Wu Ping[18] et al. studied the effect of qinpi glucoside on immune function and JAK/STAT in rats with severe pneumonia caused by Klebsiella pneumoniae. The results showed that qinpi glucoside could inhibit apoptosis and promote lung tissue damage repair by inhibiting the activation of JAK/STAT, thus alleviating the symptoms of severe pneumonia caused by Klebsiella pneumoniae. Zhang Peng[19] et al. showed that activation of JAK/STAT signaling pathway could promote exacerbation of Streptococcus pneumoniae pneumonia, and confirmed that qinpi glucoside could inhibit JAK/STAT signaling pathway to alleviate inflammatory response, lung tissue damage and exert pulmonary protective effects in young rats. Related studies have shown that curcumin, resveratrol, oleanic acid, artemisinin, catechin and other herbal medicines can inhibit the activation of the JAK/STAT signaling pathway through a variety of biological processes, but most of them are at the preclinical study stage, and later studies can continue to explore the preparation of JAK/STAT inhibitors and biomarkers for predicting efficacy and providing prognosis on this basis.

4. PI3K/Akt/mTOR signalling pathway

4.1. Composition and regulation of the PI3K/Akt/mTOR signalling pathway

The PI3K/AKT/mTOR pathway is widely distributed in cells and has a role in controlling autophagy, apoptosis, proliferation, and differentiation of cells. It consists of two components, phospatiidylinositol 3-kinase, PI3K, and its protein kinase B, PKB (AKT). PI3K proteins belong to the lipid kinase family and are classified into type III according to their different structures and substrates, of which type I is the most well studied, consisting of a p110 catalytic subunit and p85 AKT, a serine/threonine protein with three isoforms—AKT1, AKT2, and AKT3—is the primary molecule found downstream of the PI3K signaling pathway. AKT1 is widely expressed throughout tissues, AKT2 is primarily expressed in insulin-sensitive tissues and at low levels in other tissues, and AKT3 is exclusively expressed in the brain and testis. For AKT to be fully activated, Thr308 and Ser473 in the AKT-related structural domain must be phosphorylated. P13K is activated by interaction with the receptor PI3K is activated by dimerisation with the receptor tyrosine protein kinase (RTK), phosphorylation and interaction with various growth factors, or by recruitment of associated bridging proteins to facilitate binding of p110 and p85. In order to bind phosphatidylinositol-dependent kinase-1 (PDK1), which phosphorylates AKT at
the Thr308 site, which is fully phosphorylated by mTORC2 at the Ser473 site, activated PI3K converts phosphatidylinositol 3,4-bisphosphate (PIP2) to 3,4,5-trisphosphate (PIP3). This serves as a second messenger to bind PDK1. Akt Akt further activates a number of downstream factors to carry out a number of biological processes[27].

4.2. PI3K/Akt/mTOR signaling pathway and severe pneumonia

Yang Zhaohui[28] et al. established and grouped influenza virus/Streptococcus pneumoniae infection mouse models and found that p-PI3K/PI3K, p-AKT/AKT and p-mTOR/mTOR levels were significantly growing in the Flu group (H1N1 infection), SP group (Streptococcus pneumoniae inoculation) and Flu+SP group (Streptococcus pneumoniae infection after H1N1 inoculation) compared with the blank group. TNF-α, IL-6, and IFN-γ expression was also elevated, and in comparison to the Flu and SP groups, these indicators were significantly elevated in the Flu+SP group, indicating that the PI3K/AKT signaling pathway was implicated in the entire infection process and heightened cellular inflammation. In a later study, dimethyl sulfoxide (DMSO) and PI3K inhibitor were added. The expression of TNF-α, IL-6, and IFN-γ in lung tissue was also lower in the DMSO+SP group than in the PI3K inhibitor+SP and PI3K inhibitor+Flu+SP groups, as were the levels of p-AKT/AKT and p-mTOR/mTOR. These findings imply that suppressing the upregulation of the PI3K/AKT pathway can reduce pneumonia symptoms following pathogen infection. Chen Hui[29] et al. demonstrated that by blocking PI3K/AKT/mTOR activation, capsaicin could lower the production of pro-inflammatory cytokines and apoptosis, therefore lowering the inflammatory response in rats with acute lung damage generated by LPS. Wang Kai and[30] others showed that glycyrrhetinic acid could down-regulate the phosphorylation levels of PI3K and AKT to inhibit the activation of this pathway and reduce the expression of inflammatory proteins. Zhu Huahe[31] used network pharmacology to study the protective mechanism of Xuanbaichengqi Prescription against LPS-induced acute lung injury, and showed that the expression of phosphorylated mTOR and phosphorylated PI3K was significantly increased in the lung tissue of rats after LPS stimulation, while it was significantly decreased in rats treated with Xuanbaichengqi Prescription. The group postulated that a crucial mechanism in the management of ALI-induced lung damage in rats using Xuanbaichengqi Tang may involve the PI3K/mTOR signaling pathway, and that inhibition of its activation may reduce lung injury, such as excessive inflammation and pulmonary edema. There are also studies that show the PI3K/Akt/NF-κB signaling pathway is crucial in the disease process of bacterial VAP. Pathogenic bacteria can induce an increase in apoptotic proteases, which causes apoptosis of immune cells and at the same time induces a conformational change in and activation of PI3K, which binds and phosphorylates Akt with PI3K activation messenger molecules, activating the downstream NF-κB signaling pathway, leading to the release of large amounts of inflammatory factors, such as IL-4, IFN-γ, etc, and exacerbating the local tissue damage[32]. All of these studies suggest that this signaling pathway is important in either severe bacterial or viral pneumonia, and that inhibiting the activation of this pathway reduces the release of inflammatory factors and attenuates tissue injury.

5. Notch signalling pathway

5.1. Composition and regulation of the Notch signalling pathway

Notch is a transmembrane protein and the Notch signalling pathway consists of three components: Notch receptor, Notch ligand and DNA binding protein. The classical pathway of Notch signalling activation is receptor-ligand binding, with Notch receptors at site 2 (S2) being mediated by metalloproteinases and TNFα translocases to undergo a series of proteolytic cleavages, and additional proteolytic cleavages of NTDs by γ-secretase at site 3 (S2). Subsequent release of NICD into the cytoplasm and further translocation of NICD into the nucleus and recruitment of protein acetyltransferases and MAML to form an active transcriptional complex regulates the transcriptional activity of Notch target genes[33]. The differentiation, apoptosis, and proliferation of germline stem cells are all significantly influenced by the Notch pathway.

5.2. Notch signaling pathway and severe pneumonia

Wei Wei[34] et al. observed how Qingfeitouxie prescription affected the Notch signaling pathway in the lung tissue of mice with Mycoplasma pneumoniae pneumonia, and discovered that the expression levels of Notch1, Notch2, protein, and mRNA in the model group were significantly higher than those in the normal group, while the expression levels of the aforementioned indicators in the high and medium
dose groups of traditional Chinese medicine were lower than those in the model group, and the effect of Qingfeitouxie Prescription was time- and dose-dependent, and the group was interested in It was hypothesized that Qingfeitouxie Prescription could regulate the immune homeostasis by inhibiting the expression of Notch1 and Notch2, and thus anti-Mycoplasma pneumoniae infection. Xu Jingyuan et al. used CLP to prepare a mouse model of sepsis and found that Notch 2 receptors were involved in angiotensin-converting enzyme-mediated endothelial injury stimulated by intermediate factor, and the higher the expression of ACE, the more severe the lung injury release. Yao Jiami's team showed that Astragaloside A could significantly reduce the protein expression levels of Jagged-1 and Notch-3 in the lungs of model rats through the Notch signalling pathway, reversing the hypoxia-induced pulmonary vascular remodelling in rats with pulmonary hypertension. It has also been shown that curcumin effectively blocked the increase of Notch1 in lung tissue, reduced the expression levels of NLRP3, IL-1β, IL-18 and inhibited inflammatory bodies. Emendin, baikaline, paeoniflorin and compound kushen injection all modulate Notch signalling pathways to improve lung injury. Lu et al. research shows that Neonatal Streptococcus pneumoniae pneumonia may promote airway hyperresponsiveness and airway inflammation formation by activating Notch1 signaling to induce Th1/Th2 imbalance. The A549 model of Klebsiella pneumoniae-infected human alveolar type II epithelial cells A549 significantly up-regulated the expression of Notch1 and autophagy-associated protein LC3 at 24 h, 48 h, and 72 h, and also promoted the production of inflammatory factors (IL-1β, TNF-α, and INF-γ), suggesting that cellular autophagy and Notch signaling play an important role in the infection of Klebsiella pneumoniae-infected alveolar type II epithelial cells. Further elaboration of the molecular mechanism between Notch signaling and severe pneumonia will help to provide theoretical basis and new ideas to guide the clinical treatment and prevention of severe pneumonia, which will have important guiding significance in the development of new drugs and improvement of vaccines.

Table 1: Modulation of pneumonia-related signalling pathways and effects by Chinese herbal medicines.

<table>
<thead>
<tr>
<th>Single herbs or compound ingredients active ingredients</th>
<th>Signaling pathways</th>
<th>Actions</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginsenoside Rg1</td>
<td>TLR4/NF-κB↓</td>
<td>Inflammatory cells↓, apoptosis↓</td>
<td>[7]</td>
</tr>
<tr>
<td>Qingwenzhike Prescription/Conotoxin B/ Polygonatum kingianum</td>
<td>TLR4/NF-κB↓</td>
<td>inflammatory cells↓</td>
<td>[8][10][11]</td>
</tr>
<tr>
<td>Baicalin/curcumin</td>
<td>TLR4/MyD88/NF-κB↓</td>
<td>inflammatory cells↓</td>
<td>[9][13]</td>
</tr>
<tr>
<td>Salidroside</td>
<td>NF-κB↓</td>
<td>inflammatory cells↓</td>
<td>[12]</td>
</tr>
<tr>
<td>Pterostilbene</td>
<td>JAK2/STAT3↓</td>
<td>inflammatory cells↓</td>
<td>[17]</td>
</tr>
<tr>
<td>Curcumin/Fraxin/Resveratrol/Oleic acid/Artemisinin/Catechin</td>
<td>JAK/STAT1↓</td>
<td>inflammatory cells↓</td>
<td>[19-24]</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>PI3K/AKT/mTOR↓</td>
<td>Inflammatory cells↓, apoptosis↓</td>
<td>[29]</td>
</tr>
<tr>
<td>Glycyrrhetic acid</td>
<td>PI3K/AKT↓</td>
<td>inflammatory cells↓</td>
<td>[30]</td>
</tr>
<tr>
<td>Xuanbaichengqi Prescription</td>
<td>PI3K/mTOR↓</td>
<td>inflammatory cells↓</td>
<td>[31]</td>
</tr>
<tr>
<td>Qingfeitouxie Prescription</td>
<td>Notch1/Notch2/mRNA A↓</td>
<td>Immunoregulation↑</td>
<td>[34]</td>
</tr>
<tr>
<td>Astragaloside A</td>
<td>Jagged-1/Notch-3↓</td>
<td>Pulmonary hypertension↓, pulmonary vascular remodeling↑</td>
<td>[36]</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Notch1/NF-κB↓</td>
<td>inflammatory cells↓</td>
<td>[37]</td>
</tr>
<tr>
<td>Emendin / Baicalin /Paeoniflorin/ compound kushen injection</td>
<td>Notch1/2↓</td>
<td>inflammatory cells↓</td>
<td>[38-41]</td>
</tr>
</tbody>
</table>

Note: ↑ indicates promotion or up-regulation; ↓ indicates inhibition or down-regulation
6. Conclusions

Severe pneumonia is a serious, highly variable and complicated disease that can be challenging to treat clinically. The current national and international guidelines are not entirely consistent, but the emphasis can be summarised in two main areas: firstly, local symptoms of the respiratory tract, such as dyspnoea, increased respiratory rate, hypoxia and multi-lobar infiltration; and secondly, systemic symptoms, such as decreased blood pressure, impaired consciousness and septic shock\cite{44, 45}. Anti-infective therapy against the pathogen is the main treatment for the disease, and adjunctive ventilation, oxygenation, fluid replacement, correction of water-electrolyte disturbances, nutritional support and other treatments are also necessary, while the efficacy of glucocorticoids in patients with severe pneumonia is still controversial\cite{46, 47}. The above treatments can effectively improve the clinical symptoms of patients, but in recent years, with the in-depth study of Chinese medicine, it has been found that Chinese medicine interventions for severe pneumonia have certain efficacy and advantages, and the conventional treatment with Western medicine together with Chinese medicine can further reduce the morbidity and mortality rate of patients, increase the success rate of treatment and improve the prognosis of patients. At present, the mechanism of Chinese medicine in the treatment of severe pneumonia is still unclear. Modern pharmacological studies have shown that some active ingredients of Chinese medicine can reduce the inflammatory response and lung injury in severe pneumonia by inhibiting cell signalling pathways, but most of the studies are still at the pre-clinical stage. Therefore, in future research, it is inevitable to continue to explore multi-signaling pathways and multi-target combinations for the treatment of severe pneumonia.

The treatment of severe pneumonia involves a variety of signaling pathways, including but not limited to TLR4/MyD88/NF-κB, JAK/STAT, PI3K/Akt/mTOR, Notch, and other signaling pathways, these paths are listed in Table 1, and there are interactions between the pathways, the active ingredients of traditional Chinese medicine can effectively inhibit the activation of cellular signalling pathways, thereby reducing the inflammatory response, regulating the body's immunity, and promoting body The active ingredients of traditional Chinese medicine can effectively inhibit the activation of cell signalling pathways to reduce inflammation, regulate the body's immune system and promote recovery. Compound drugs for the treatment of severe pneumonia can be prepared according to the different characteristics of the active ingredients of the drugs, and better therapeutic effects can be achieved by intervening in multiple signalling pathways, multiple targets and multiple links to play a therapeutic effect. Therefore, in-depth study of the molecular mechanism of the active ingredients of the drugs for the treatment of severe pneumonia based on the signaling pathway can provide a research idea for the prevention and control of severe pneumonia as well as for the development of new drugs and vaccines.

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