Research progress on acute lung injury inflammatory network

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February 20, 2023

Abstract

Acute lung injury is a systemic inflammatory response syndrome in the lungs, with a high incidence and fatality rate of 30%–40%. Despite the abundance of research on the pathogenesis of lung injury and the great progress that has been achieved, the various number of cells, cytokines and inflammatory response pathways involved in the pathogenesis of acute lung injury (ALI) and their complex relationships, which together constitute the cell network and inflammatory factor network of ALI inflammatory response, demand more attention. This study reviews the formation of this network in the pathogenesis of acute lung injury

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Abstract : Acute lung injury is a systemic inflammatory response syndrome in the lungs, with a high incidence and fatality rate of 30%–40%. Despite the abundance of research on the pathogenesis of lung injury and the great progress that has been achieved, the various number of cells, cytokines and inflammatory response pathways involved in the pathogenesis of acute lung injury (ALI) and their complex relationships, which together constitute the cell network and inflammatory factor network of ALI inflammatory response, demand more attention. This study reviews the formation of this network in the pathogenesis of acute lung injury.

Keywords : acute lung injury; inflammatory factor network; cell network

Acute lung injury (ALI) is a primary disease caused by serious non-cardiogenic pathogenic factors such as severe infection, shock, trauma, disseminated intravascular coagulation, aspiration and so on. The clinical manifestations are mainly acute progressive aggravated dyspnoea and refractory hypoxemia. Numerous studies have investigated the relationship between a single cell type, single cytokine, or cell and molecule related to certain disease aspects; however, the study based on a single research object cannot grasp disease occurrence and development, affecting the therapeutic effects on the disease. Therefore, this review of studies on cellular inflammatory cytokine networks and cellular networks provides a more comprehensive understanding of the pathogenesis of ALI and new research ideas.

1 Cytokine network

1.1 Tumour necrosis factor-α (TNF-α) and interleukin-1β (IL-1β)

TNF-α and IL-1β are considered promoters of the development of ALI/acute respiratory distress syndrome[1][2]. TNF-α and IL-1β in the plasma are often used to distinguish the severity of systemic inflammation, increase the permeability of epithelial cells and then lead to lung tissue injury and neutrophil aggregation, resulting in pulmonary oedema. It also induces IL-8 production in alveolar macrophages, type II epithelial cells and lung fibroblasts[3][4][5]. TNF-α can also promote the expressions of IL-6 and IL-1β in fibroblasts and the differentiation of fibroblasts[6]. The transcription of TNF-α and IL-1β is mediated by the nuclear factor (NF)- ϰB, and the TNF-α promoter contains sites of NF-ϰB, which can stimulate and activate NF-ϰB, thus forming a positive regulatory loop to amplify and maintain inflammation[7].

TNF-α is secreted by activated monocytes and macrophages and can promote cytokine production and neutrophil aggregation into the lungs, stimulate fibroblast proliferation, lead to pleural septum thickening and increase collagen production.[8][9][10] It can also directly damage vascular endothelial cells and increase their permeability. Moreover, it is a major cytokine that mediates early inflammatory response and fibrosis. It is closely related to the occurrence of lung injury[11][12][13].

TNF-α can interact with endothelial cells to induce lung endothelial cell activation, increase the expression of vascular endothelial cell surface adhesion molecules and stimulate leukocyte activation and migration, both of which contribute to the aggregation of neutrophils to the injured site, thus further activating monocytes, macrophages and T lymphocytes and promoting the release of numerous pro-inflammatory factors by inflammatory cells[14]. TNF-α also regulates the expression of various pro-inflammatory factors (such as IL-1, IL-6, platelet-activating factor, IL-8 and leukotriene) and amplifies the inflammatory cascade reaction. TNF-α can also bind to receptors on the surface of alveolar epithelial cells, causing changes in cell metabolism, mediating epithelial cell apoptosis, shedding, regeneration and ultimately, pulmonary fibrosis[15][16].

IL-1β is secreted by mononuclear macrophages and is one of the major inflammatory cytokines in pulmonary oedema fluid. IL-1β stimulates the production of chemokines (e.g. IL-8), epithelial-derived neutrophil chemokines ENA-78, monocyte chemokine peptide (MCP)-1, macrophage inflammatory peptide-1 and the extracellular matrix produced by fibroblasts. IL-6 and IL-1β are precursors of inflammation and fibrosis[10][17][18][19][20][21].

1.2 IL-6

IL-6 is a water solubility mediator and is produced by dendritic cells (DCs), mononuclear macrophages, B cells, activated T cell subsets, fibroblasts, endothelial cells and keratinocytes[5][22]. It is involved in the acute-phase reaction during infection and can integrate the signals of early inflammatory response. It is also an important inflammatory factor in the early stage of inflammation and can promote the release of more inflammatory factors. Sustained levels of IL-6 can inhibit inflammation and coordinate anti-inflammatory activities required for inflammation reduction[11][23][24]. In lipopolysaccharide (LPS)-induced ALI, the formation of pulmonary oedema in rats is highly correlated with IL-6, which is one of the main inflammatory cytokines in pulmonary oedema fluid. IL-6 content can reflect the severity of local reactions in the lungs and is used to judge healing[25][26].

IL-6 regulates cell growth and differentiation[26]. It can promote the phenotype transformation of macrophages, induce macrophages to differentiate into M2 type, stimulate macrophages to secrete MCP-1, promote atherosclerosis, increase the expression of cell adhesion molecules, stimulate the proliferation and migration of vascular smooth muscle cells, regulate infection, or promote the accumulation of neutrophils at the wound site. IL-6 also delays polymorphonuclear cell (PMN) apoptosis, inhibits DC formation and NF-κB activation in these cells and the expression of chemotactic factor CCR7 and promotes keratinocyte proliferation or gliosis in dermal fibroblasts[23][24].

IL-6 signal transduction can be classified into classical activation and transactivation. Classical IL-6 receptor signalling controls both intracentric stabilisation processes and immune outcomes. IL-6 trans-signal transduction plays an important role in leukocyte recruitment and apoptosis, maintenance of T cell effector function and inflammatory activation of interstitial tissue and regulates the expression of adhesion molecules intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule 1[23]. The IL-6 trans-signal transduction mechanism ensures an effective defence mechanism, prevents excessive tissue damage and drives the transition from neutrophil recruitment to monocyte recruitment[23].

1.3 IL-8

IL-8 is mainly produced by alveolar macrophages, type II epithelial cells and lung fibroblasts[5][27]. IL-8 is the main chemokine of neutrophils and plays a chemotactic role mainly by binding to CXCL1, a homologous receptor on neutrophils[18]. In endotoxaemia models and acid inhalation models, IL-8 monoclonal antibody binds to IL-8 and prevents binding to CXC chemokine receptors on PMN, significantly reducing lung injury and PMN migration[18].

1.4 High mobility group 1 protein (HGMB-1)

HGMB-1 is a highly conserved eukaryotic protein isolated from chromosome protein and is a transcription factor[28]. It can be passively released from damaged and necrotic cells and actively secreted by immune cells stimulated by cytokines and endotoxins (DCs and macrophages)[29]. In ALI, NF-κB activation increased HMBG-1 secretion. Extracellular HGMB-1 can be used as a cytokine to mediate nonspecific inflammatory response or as an endogenous danger signal to initiate and enhance specific immune response, induce neutrophilic inflammatory pulmonary oedema, stimulate macrophages to secrete TNF-α, further promote macrophages to express HGMB-1 and maintain the inflammatory response[29][30]. Moreover, HGMB-1 is an inhibitor of the Bcl-2 family member Bak, resulting in neutrophil apoptosis inhibition and aggravation of neutrophil accumulation. Anti-HGMB-1 antibodies can reduce the migration of neutrophils to the site of lung injury[29][31].

1.5 Interferon-γ (IFN-γ)

IFN-γ is derived from the glycoprotein of activated T lymphocytes. It activates defence cells and promotes the release of IL-1β, IL-6 and TNF-α, thereby further amplifying the inflammatory response. It also mediates endothelial cell damage, increases vascular permeability, promotes neutrophils to enter the alveoli and mediates lung damage.

1.6 Haeme oxygenase-1 (HO-1)

HO-1 is a stress protein stimulated by inflammatory cytokines, heat shock, heavy metals and oxidants, which can degrade haem into Fe2+, biliverdin BV and CO[29][32]. The downstream product CO can regulate inflammation, reduce inflammatory cell production and interact through the MAPK pathway to increase the production of anti-inflammatory cytokines. Therefore, HO-1 has anti-inflammatory, antioxidant, anti-apoptotic and anti-proliferative effects. Moreover, an interaction was found between inducible nitric oxide synthase (iNOS) and HO-1. NO is a strong inducer of HO-1, and the expression of HO-1 can inhibit iNOS expression and activity[33][34]. Therefore, HO-1 and CO have protective effects on ALI, inducing HO-1 expression and inhibiting LPS-induced lung injury, iNOS expression and NO production[33]. The overexpression of HO-1 also significantly decreased the total number of cells, neutrophils, W/D ratio and EBA

exudation in the bronchoalveolar lavage fluid and significantly inhibited the increase in TNF-α concentration and HMGB1 expression[29].

1.7 IL-10

IL-10 is an important anti-inflammatory factor in inflammatory injury response. It is secreted by mononuclear macrophages and can downregulate the secretions of T-cofactors, MHCII antigens and co-stimulatory molecules on macrophages and inhibit neutrophil rolling, adhesion and transepithelial migration and the release of inflammatory factors such as TNF-α, IFN-γ, IL-1 and IL-8. IL-10 can also block cytokine-induced chemotactic and oxidative burst, reduce recruitment of neutrophils, interfere with neutrophil-mediated tissue damage, inhibit Th1-mediated immune response and enhance the body's anti-infection ability[35][36][37].

2 Cell network

2.1 Macrophages

Macrophages are a type of white blood cell that develops when monocytes migrate into the lung tissue. Macrophages are widely distributed and can be divided into alveolar macrophages (AM), interstitial macrophages (IM), bronchial macrophages, pulmonary intravascular macrophages and DCs after entering the lung tissue. These cells constitute the first line of defence for removing foreign bodies[38][39][40].

In the absence of inflammation, macrophages are in an immune resting state and can secrete large amounts of prostaglandins, which reduce the release of cytokines and inhibit cytokines from stimulating collagen synthesis[16][38]. When external substances enter the body, AM, as an important target cell, is polarised in an activated state, which has certain biological effects: it produces numerous free radicals and secretes inflammatory factors, thus activating other inflammatory reactions enzyme, and LTs can increase the expression of adhesion molecules in vascular endothelial cells at inflammatory response sites, making PMNs easy to adhere to[38][40][41]. IM promotes the removal of PMNs from the lung and secretes IL-1, IL-6, reactive oxygen species (ROS) and iNOS after stimulation[26][38][42][43]. Moreover, it can present specific antigens to T cells, induce T cell differentiation, mediate Th1 and Th17 cell immune response in Th cells and promote inflammation[47]. In a complex inflammatory environment, macrophages are simultaneously regulated by different molecular events and signalling pathways involving JAK-STAT, TLR-NF-ϰB, MAPK, hypoxia-dependent signalling pathways and differential TLR expression[40][44][45][46].

Macrophages can be classified into classically activated macrophages (M1) and selectively activated macrophages (M2) according to metabolic pathways, types of cytokines secreted and surface markers[26]. M1 are induced by bacteria, and their products, such as LPS, or cytokine IFN-γ, promote inflammation and cytotoxicity, high expression of iNOS, ROI and production of TNF-α, IL-1β, IL-6, CXCL-3, CXCL-5 and CXCL-8. Induced by IL-4, IL-10 and glucocorticoids, M2 promote damage repair and tissue regeneration while maintaining mild and continuous anti-inflammation, high expression of Arg1 (arginine) and IL-10 production[45][51]. Therefore, macrophages have both pro-inflammatory and anti-inflammatory effects and phagocytic and secretory functions[51]. They can phagocytise not only cell debris but also apoptotic polymorphonuclear leukocytes while producing numerous free radical ROS, secreting inflammatory factors and being the main source of cellular inflammatory factors TNF-α, IL-1β and IL-6 and finally initiating the inflammatory cascade[39][51].

2.2 PMNs

PMNs are mainly neutrophils, including a small number of eosinophils and basophils. PMNS are one of the main effector cells of ALI. They remove foreign bodies mainly by producing ROS and antibacterial proteins. PMNs can be activated by TNF-α, IL and chemokines produced by macrophages, and migratory recruitment occurs. Moreover, various proteases and oxygen free radicals are released, causing the inflammatory storm[47]. When PMNs are inhibited by apoptosis, excessive and prolonged activation occurs, resulting in basement membrane destruction and increased capillary barrier permeability. When neutrophil transepithelial migration occurs, it will further destroy the alveoli and damage the lungs[19].

2.3 Endothelial cells

The integrity of pulmonary microvascular endothelial cells is critical in the initiation of lung inflammation, preventing protein-rich fluid from flowing into the interstitial lung tissue and alveoli from plasma and inflammatory cells, reducing the range of inflammatory effects and reducing pulmonary oedema. Among them, cadherin (VE) and adhesive-junctional proteins play a key role in the maintenance of endothelial barrier integrity[48][49].

During inflammation, selectin on the surface of endothelial cells interacts with ligands on the surface of neutrophils to mediate immune cascade reactions such as capture, rolling and adhesion of neutrophils[48][49]. In the resting state, the expression level of ICAM-1 in vascular endothelial cells is low, which plays an important role in stabilising cell–cell interaction and promoting the migration of leukocyte endothelial cells. In the presence of inflammatory stimulators such as TNF-α and LPS, endothelial cells highly express surface p-selectin and E-selectin[48]. The expression of p-selectin on the surface of endothelial cells activates endothelial cells and interacts with leukocyte receptors, which mediates the rolling of leukocytes on activated endothelial cells, and E-selectin further mediates adhesion, makes leukocytes approach the cytokines and chemokines secreted and expressed on endothelial cells, activates leukocytes to express β2 integrin and bind to their receptors[49][50]. It can enhance the adhesion between leukocytes, inflammatory cells and endothelial cells, promote neutrophil recruitment and endothelial cell activation and destroy the integrity of endothelial cells, making it easier for them to penetrate the endothelium[48][51]. Furthermore, endothelial cells can synthesise and release vasoactive substances, prostaglandins, PGI2, NO and inflammatory mediators TNF- α, IL-1 β and IL-8 that are involved in the occurrence and development of inflammation[39].

2.4 Epithelial cells

Alveolar epithelial cells are divided into type I epithelial cells and type II epithelial cells. Type I epithelial cells express globulin-transmembrane immune advanced glycation end product receptor, and type II epithelial cells secrete surfactant D, which has anti-inflammatory effects and participates in pathogen phagocytosis and neutrophil recruitment. Type I and II alveolar epithelia are closely connected and selectively regulate the epithelial barrier[19][52].

When alveolar epithelial cells are activated by AM products such as oxygen free radicals, IL-1, TNF-α and other inflammatory mediators, diffuse damage occurs and integrity is destroyed, leading to loss of surfactant activity and decreased secretion and barrier function[19]. More monocytes will be recruited to the inflammatory site, macrophages by secreting TNF-α, IL-8, IL-6, IL-1β, cytokines and other induction of recruitment of various cells, including neutrophils, lymphocytes and eosinophils[53]. When PMNs enter the alveoli, they stimulate the epithelium to release vascular growth factors, pro-inflammatory cytokines, acute-phase proteins (C-reactive protein and protease inhibitors) and chemokines to participate in the inflammatory response[5].

2.5 Lymphocytes.

In indirect ALI, in addition to neutrophils and macrophages, lymphocytes CD4+, CD25+ and Foxp3+T are specifically recruited into the lungs. In the immune response, Th cells that play a role are differentiation antigen4+, T cells (CD4+, T cells), which are differentiated into Th1, Th2, Th17 and Treg cells[36]. Th1 mediates cellular immune response, secretes IL-2, IFN-γ, TNF-α, IFN-γ and IL-12 to initiate Th1 cell differentiation, promote T lymphocyte differentiation, maturation and proliferation, enhance macrophage phagocytosis and regulate alveolar inflammation, which are necessary to remove intracellular pathogens[22]. Th2 mediates humoral immune response and secretes IL-4, IL-5, IL-6, IL-10 and IL-13, which are the key for host cells to defend against extracellular pathogens and help B cells produce antibodies. IL-4 can induce Th2 cell differentiation[22]. Th17 secretes pro-inflammatory factors IL-17A, IL-17F and IL-22, which can cooperatively induce tissue inflammation[22]. Treg cells secrete cytokines such as IL-10 and TGF- β, which mediates immune response. In the early stage of inflammation, effector T lymphocytes (Th1 cells) are activated; with disease progression, Th2 cell transformation occurs when the effector T cells enter the stage of fibrosis[42].

In summary, the pathogenesis of ALI involves the accumulation of various key effector cells, multiple physiological and pathological changes and activation and release of various inflammatory cytokines, and all levels influence each other, forming a complex cell network and cytokine network. This will provide a new scheme for the clinical treatment of ALI for a more comprehensive and in-depth understanding of the role of inflammation and changes in the inflammatory microenvironment in the pathogenesis of ALI.

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