Apoptosis Signaling Pathways in Lung Diseases

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Abstract: Evidence that apoptosis plays an important role in the pathophysiology of lung diseases has been accumulated. Apoptosis signaling is classically composed of two principle pathways. One is a direct pathway from death receptor ligation to caspase cascade activation and cell death. Death receptor ligation triggers recruitment of the precursor form of caspase-8 to a death-inducing complex, through the adaptor protein FADD, which leads to caspase-8 activation. The other pathway triggered by stimuli such as drugs, radiation, infectious agents and reactive oxygen species is initiated in mitochondria. After cytochrome c is released into the cytosol from the mitochondria, it binds to Apaf1 and ATP, which then activate caspase-9. Recently, endoplasmic reticulum has also been shown to be the organelle to execute apoptosis. Further understanding of molecular mechanisms of apoptosis and its regulation by novel drugs may lead to the development of effective strategies against lung diseases. We overview the signaling pathways of apoptosis and discuss the involvement of apoptosis in the pathophysiology of various lung diseases.

Key Words: Apoptosis, death receptor, mitochondria, acute lung injury, pulmonary fibrosis, bronchial asthma, pulmonary emphysema.

INTRODUCTION

Apoptosis plays a major role in homeostasis to maintain a balance between cell proliferation and cell death. There are two principle-signaling pathways of apoptosis. One is a direct pathway from death receptor ligation to caspase cascade activation and cell death. Death receptor ligation triggers recruitment of the precursor form of caspase-8 to a death-inducing complex, through the adaptor protein Fas-associating protein with death domain (FADD), which leads to caspase-8 activation. The other pathway triggered by stimuli such as drugs, radiation, infectious agents and reactive oxygen species is initiated in mitochondria. After cytochrome c is released into the cytosol from the mitochondria, it binds to Apaf1 and ATP, which then activate caspase-9 [1]. The activation of initiator caspase-8 and caspase-9 resulted in activation of effecter caspases such as caspase-3. Recently, endoplasmic reticulum has also been shown to be the organelle to execute apoptosis. Various stresses can impair protein folding and induce endoplasmic reticulum stress, and severe endoplasmic reticulum stress can transduce apoptotic signals [2]. Active effector caspases mediate the cleavage of protein substrates, resulting in morphological features of apoptosis.

Apoptosis may play important roles in lung diseases in two different ways. First, failure to clear unwanted cells by apoptosis will prolong the inflammation because of the release of their toxic contents, and also delay repair processes. Apoptotic cells should be quickly recognized and ingested by phagocytes before releasing their toxic contents, unlike accidental cell death or necrosis. Second, excessive apoptosis may cause diseases. Intratracheal instillation of agonistic anti-Fas antibody or recombinant Fas ligand (FasL) induces acute alveolar epithelial injury and lung inflammation [3, 4]. Repeated inhalations of agonistic anti-Fas antibody induce epithelial cell apoptosis and lung inflammation, which subsequently leads to pulmonary fibrosis in mice [5].

As well as death receptors/ligands, death signals such as reactive oxygen species, nitrogen species, proinflammatory cytokines, chemokines and other signaling molecules of apoptosis are involved in the pathophysiology of lung diseases. The survival and recovery of epithelial and endothelial cells and the resolution of inflammatory cells appear to be the key in the prognosis of patients. Therefore, further understanding of molecular mechanisms of apoptosis and its regulation by novel drugs may lead to the development of effective strategies against lung diseases (Fig. **1**).

1. ACUTE LUNG INJURY

Apoptosis of type I alveolar epithelial cells and endothelial cells are observed in lung tissues from patients with acute respiratory distress syndrome (ARDS) [6, 7]. The expression of Bax and Bcl-2 protein are upregulated in alveolar epithelial cells and the number of epithelial cell apoptosis is associated with the prognosis of patients with diffuse alveolar damage [8, 9].

Lipopolysaccharide (LPS) is an important factor in acute lung injury. LPS stimulates endothelial cells and induces the expression of pro-inflammatory mediators. Intravenously injected LPS induces apoptosis of endothelial cells of systemic organs in mice [10, 11]. Expression and activation of caspase-1 and –3 were detected in lung epithelial cells in LPS -induced acute lung injury in mice [12]. The tripeptide

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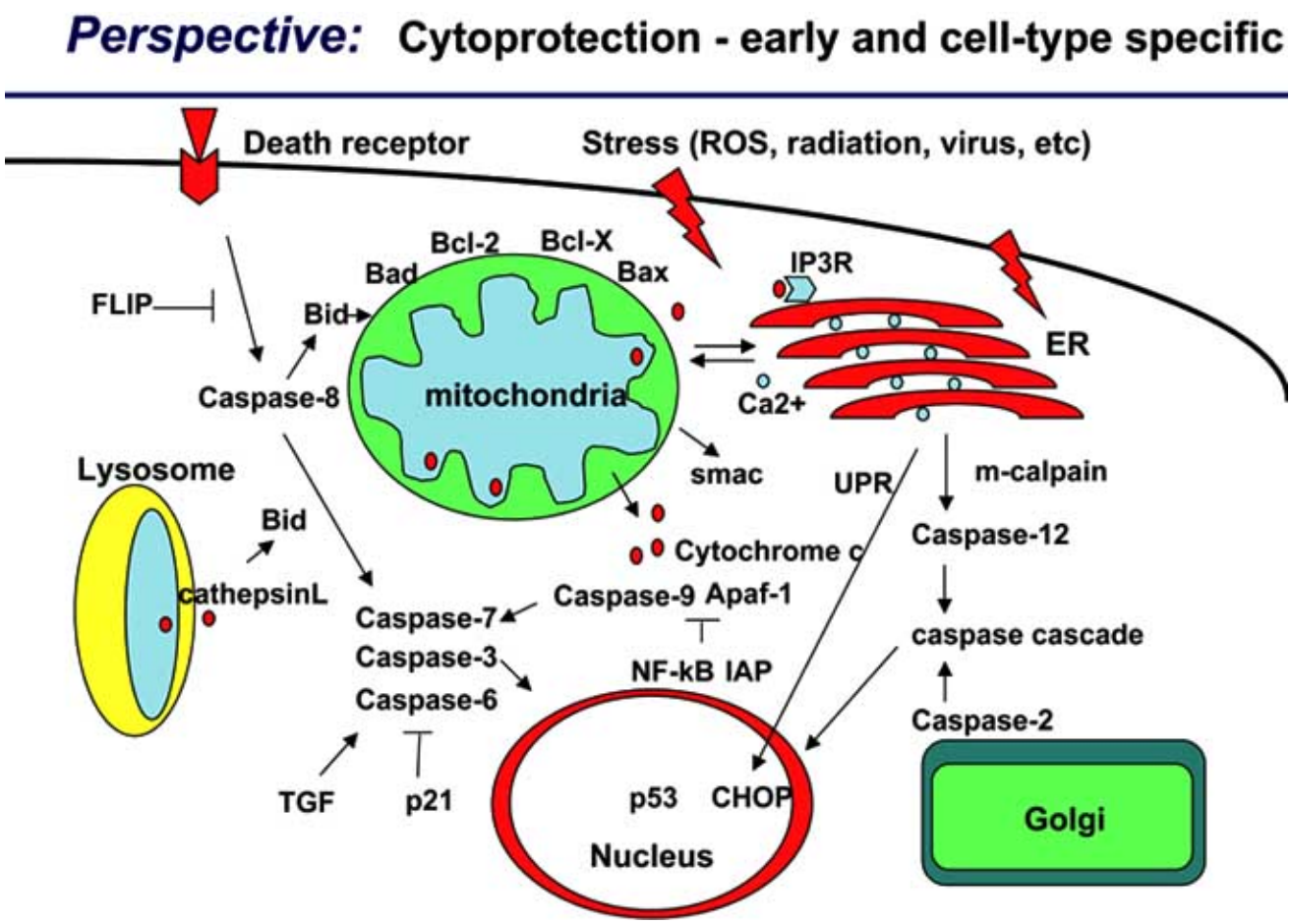

Fig. (1).

benzyloxycarbonyl-Val-Ala-Asp fluoromethylketone (Z-VAD.fmk), a broad-spectrum caspase inhibitor, inhibited the intracellular activation of caspase-like proteases *in vivo*, and protected mice against LPS-induced acute lung injury in mice [10, 12]. These results suggest that caspase cascade is involved in lung injury, and molecules, which inhibit caspase activity, may be a novel treatment in lung injury. In addition, epithelial cell apoptosis is associated with upregulation of Fas and FasL expressions after LPS instillation, and suppressed by the treatment with anti-Fas antibody [13]. These results suggest the significance of apoptosis on parenchymal cells in LPS-induced acute lung injury.

Repair after an acute lung injury requires the elimination of proliferating mesenchymal and inflammatory cells from the alveolar airspace or alveolar wall [14]. Neutrophils play an important role in endothelial and epithelial damage in lung injury. Clearance of apoptotic neutrophils by phagocytes has an important role in the resolution of inflammation and lung injury [15]. Phagocytosis of apoptotic neutrophils by macrophages suppresses the production of proinflammatory cytokines, such as interleukin (IL)-1, IL-8, Granulocyte macrophage-colony stimulating factor (GM-CSF), and tumor necrosis factor (TNF)-α by macrophages, and induces the production of transforming growth factor-β (TGF-β) and hepatocyte growth factor (HGF) to regenerate damaged tissues [16]. Accordingly, the insufficiency of this system including the appropriate rate of neutrophil apoptosis, the clearance of apoptotic neutrophils by phagocytosis, and the cytokine release by phagocytes may lead to the prolongation of inflammation and the impairment of repair.

IL-6 attenuates hyperoxic lung injury and this protection is associated with a marked diminution in hyperoxic cell death probably through the induction of bcl-2 and tissue inhibitor of metalloproteinase (TIMP)-1 [17]. Overexpression of IL-11 in the lung enhances murine tolerance of 100% oxygen and diminishes hyperoxia-induced apoptosis [18]. IL-15 overexpression can prevent TNF-α-induced apoptosis and protect against E. coli-induced shock [19]. GM-CSF enhances survival of mice through preservation of alveolar epithelial barrier function and fluid clearance because of reduction in hyperoxia-induced epithelial cell apoptosis [20].

TNF-α (TNF) has pleiotropic effects that overlap with IL-1β inflammatory and immunologic responses, and it is upregulated soon after lung injury. TNF causes inflammation by damaging tissues and by inducing the expression of adhesion molecules and cytokines in epithelial and endothelial cells as well as in inflammatory cells. The cellular effects of TNF are mediated by two distinct cell

surface receptors, termed TNF-receptor 1 (TNFR1) and TNF-receptor 2 (TNFR2) [21]. Most of cytotoxic effects of TNF are mediated by TNFR1 through interaction of its death domain with the TNFR-associated death domain (TRADD) protein [22]. TRADD interacts with Fas-associated death domain protein (FADD) [23] to activate caspase-8, thereby initiating the apoptosis pathway. TNF also activates NF-kB and induce the expression of inhibitor of apoptosis proteins (IAPs) [24]. Therefore, TNF usually does not kill most types of cells without metabolic inhibitors. There are several studies demonstrating that TNF participates in epithelial cell apoptosis in lung injury [25, 26]. The sensitivity to TNF-induced apoptosis is variable in various types of cells, and appears to be regulated by complex mechanisms including intracellular signaling molecules and microenvironment *in vivo*.

The Fas-FasL pathway is a representative system of apoptosis- signaling receptor molecules. Fas antigen is expressed in various cells and tissues including the thymus, liver, ovary, heart and lung. Mice carrying the lymphoproliferative (lpr) mutation have defects in the Fas antigen gene [27]. FasL, a cell surface molecule belonging to the tumor necrosis factor family, binds to its receptor Fas, thus inducing the apoptosis of Fas bearing cells [28]. FasL is expressed predominantly in activated T-lymphocytes and in tissues including the small intestines, kidney, testis and lung [28]. Generalized lymphoproliferative diseased (gld) mice have a point mutation in the FasL and develop lymphadenopathy and suffer from autoimmune disease [29].

The involvement of the Fas-FasL pathway in human diseases has been demonstrated. FasL can be released as a biologically active, death–inducing mediator capable of inducing apoptosis of epithelial cells during acute lung injury [30]. Alveolar epithelial damage in patients with acute lung injury or ARDS is in part associated with local upregulation of the Fas-FasL pathway and activation of the apoptotic cascade in epithelial cells [31]. Broncho-alveolar lavage fluid (BALF) from patients with ARDS could induce apoptosis on small airway epithelial cells, which are dependent on the Fas-FasL pathway [30]. Inhibiting this pathway may be one of novel targets against acute lung injury.

Reactive oxygen species (ROS) induce apoptosis in lung endothelial and epithelial cells. Apoptosis plays a central role in DNA damage during the pathogenesis of hyperoxic lung injury [32]. Hydrogen peroxide induces Fas upregulation by promoting cytoplasmic transport of Fas to the cell surface in human airway epithelial cells. The activation of the poly (ADP-ribose) polymerase-p53 pathway may be involved in this mechanism [33]. Exaggerated apoptosis through Fas-mediated signaling may accelerate hyperoxia-induced acute lung injury in Legionella pneumonia [34]. Hyperoxia, by virtue of activating NADPH oxidase, generates ROS, which mediates cell death of lung epithelium via ERK1/2 MAPK activation in lung epithelial cells [35]. Type I alveolar epithelial cells and endothelial cells are susceptible to hyperoxia. Additionally, type II alveolar epithelial cells present DNA damage induced by hyperoxia [36]. In this regard, strategies to reduce oxidants may be beneficial in decreasing alveolar epithelial cell damage.

Heme oxygenase-1 (HO-1) confers protection against a variety of oxidant-induced cell death and tissue injury mechanisms. HO-1 overexpression using adenovirus exhibited attenuation of hyperoxia-induced neutrophil inflammation and apoptosis [37]. CO, a major by-product of heme catalysis by HO-1, exhibited a marked attenuation of hyperoxia-induced neutrophil infiltration into the airways and total lung apoptotic index [38]. CO utilizes p38 MAPK and caspase-3 in exerting its anti-apoptotic effect both *in vitro* and *in vivo* during ischemia-reperfusion injury [36, 39].

Keratinocyte growth factor (KGF) prevents the induction of p53, Bax, and Bcl-x mRNAs during hyperoxia, and oxygen-induced damage of alveolar epithelium and of endothelium [40]. KGF attenuates hydrogen peroxide induced DNA strand breaks in cultured alveolar epithelial cells by mechanisms that involve tyrosine kinase, PKC, and DNA polymerases [41]. KGF is able to activate the antiapoptotic Akt signaling [42]. KGF may participate in maintaining and repairing the alveolar epithelium and has the potential to become an effective agent against lung injury. HGF inhibited hypoxia/reoxygenation-induced endothelial cell apoptosis through upregulation of anti-apoptotic protein FLICE-inhibitory protein (FLIP) and Bcl-xL, and inhibition of pro-apoptotic protein Bid and Bax [43].

2. PULMONARY FIBROSIS

Severe lung injury induces excessive cell death. Maintaining normal function and repair of parenchymal cells is key to improving the prognosis of patients. Excessive cell death of parenchymal cells means irreversible tissue damage and may lead to pulmonary fibrosis. The incidence of epithelial cell apoptosis has been demonstrated using TUNEL method and electron microscopy in idiopathic pulmonary fibrosis (IPF) [44-46]. The Fas-FasL mediated pathway and mitochondria-mediated apoptotic pathway are also activated in IPF [47].

Bleomycin-induced pulmonary fibrosis is an animal model for lung injury and fibrosis. In this model, FasL mRNA is upregulated in infiltrating lymphocytes, and Fas is upregulated in bronchiolar and alveolar epithelial cells, in which excessive apoptosis is detected [48]. The neutralization of FasL by Fas-Ig fusion protein or neutralizing anti-FasL antibody could prevent the development of this model, and Fas- or FasL-deficient mice are resistant to the induction of this model [49]. We also demonstrated that the repeated inhalation of anti-Fas antibody mimicking Fas-FasL cross-linking induced excessive apoptosis of epithelial cells and inflammation, which resulted in pulmonary fibrosis in mice [5]. Furthermore, Fas ligation not only induced apoptosis but also induced IL-8 expression via NF-κB activation in bronchiolar epithelial cells *in vitro* [50]. Expression and activation of caspase-1 and –3 were detected in lung epithelial cells in bleomycin-induced pulmonary fibrosis in mice. Pan-caspase inhibitor Z-VAD.fmk attenuates bleomycin-induced pulmonary fibrosis in mice [51, 52]. These results suggest that the Fas-mediated apoptotic pathway is essential in this model, and also suggest that inhibition of caspases may be a novel strategy against pulmonary fibrosis.

Upregulation of p53 and p21 in lung epithelial cells has been demonstrated in lung tissues from patients with IPF [44]. The wild-type p53 normally acts to suppress cell growth while the cell attempts DNA repair. It also promotes apoptosis in those cells, which have irreparably damaged DNA or continue to proliferate [53, 54]. Expression of p53 is upregulated in response to a variety of stresses. Apoptosis of type II alveolar epithelial cells is associated with upregulation of p53 and p21 expression in diffuse alveolar damage [9]. DNA damage to alveolar epithelial cells occurs in response to bleomycin, and p53 and p21 were overexpressed within these cells [55, 56]. Mice expressing dominant negative p53 in the lung epithelium have decreased induction of p21 expression, and impaired recovery from bleomycin-induced pneumopathy [57]. p53 knockout mice represent more severe inflammation and fibrosis after bleomycin instillation compared with wild-type mice [58]. In addition, alveolar macrophage apoptosis and TNF-α secretion rather than p53 expression contributes to the difference in murine strain response to bleomycin [59]. Whether p53 induces apoptosis or promotes repair in lung epithelial cells is likely to be tightly regulated by complex mechanisms within the cell.

p21 is induced in wild-type p53-containing cells following exposure to DNA-damaging agents. p21 inhibits cyclin-Cdk complex kinase activity and is a critical downstream effector in the p53-specific pathway of growth control in mammalian cells [60]. p21 directly inhibits PCNA-dependent DNA replication in the absence of a cyclin/Cdk, but does not inhibit DNA repair [61]. Forced p21 expression has been shown to have a protective effect against cell death caused by genotoxic stresses such as radiation or cytotoxic agents [63, 64]. p21 enhanced survival either by promoting DNA repair or by modifying cell death caused by exposure to hyperoxia [65]. The absence of p21 results in rapid necrotic alveolar cell death and mortality and also results in proliferating fibroblasts after oxidant injury [66]. Adenovirus-mediated transfer of p21 gene to epithelial cells attenuates bleomycin-induce pulmonary fibrosis in mice [67]. Interestingly, activation of caspase-3 is regulated by p21, and therefore procaspase-3-p21 complex formation is an essential system for cell survival [68, 69]. These findings suggest that p21 may be a key regulator of DNA replication and repair after lung injury and may be a promising molecule in the treatment of lung injury and fibrosis.

Angiotensin converting enzyme (ACE) levels in BALF and serum are increased in fibrosing lung diseases, including sarcoidosis, IPF, asbestosis, silicosis and ARDS. Angiotensin II concentrations increase during radiation-induced pulmonary fibrosis [70]. Angiotensin II and angiotensinogen induce apoptosis in alveolar epithelial cells *in vitro* [71]. Furthermore, angiotensin II induces human lung fibroblast proliferation *in vitro* via activation of the angiotensin type I (AT1) receptor and the autocrine action of TGF-β [72] ACE inhibitors inhibit Fas- and TNF-induced apoptosis of human lung epithelial cells *in vitro* [73, 74], and also inhibit the accumulation of collagens and mast cells in the irradiated rat lung [75]. The ACE inhibitor captopril ameliorates pulmonary fibrosis induced by monocrotaline in rats [76]. The angiotensin receptor AT1 antagonist ameliorates apoptosis and pulmonary fibrosis induced by bleomycin [77].

TGF-β is the most potent promoter of extra cellular matrix production, and also a strong chemotactic factor for monocytes and macrophages. In addition, TGF-β1 can induce apoptosis directly in various cells [78-81]. The mechanism of TGF-β1-mediated apoptosis varies among cell types, although caspase activation, upregulation of p21, and downregulation of Bcl-XL expression are commonly observed [82-84]. However, TGF-β1 is a potent inducer of apoptosis through the caspase-3 activation and the downregulation of p21 and is also an enhancer of Fas-mediated apoptosis of lung epithelial cells [85]. This novel function of TGF-β1 in apoptosis of lung epithelial cells should be considered in the treatment of lung injury and fibrosis.

KGF has been demonstrated to enhance the functional differentiation of rat alveolar type II cells, to increase DNA synthesis in these cells *in vitro*, and to stimulate the proliferation of these cells *in vivo*. Intratracheal instillation of KGF significantly attenuates bleomycin-induced pulmonary fibrosis in rats [86]. HGF is known to act not only as a mitogen but also as a motogen or a morphogen for many kinds of epithelial cells. The receptor for HGF is the c-Met proto-oncogene product, which is predominantly expressed in various types of epithelial cells. As well as other epithelial cells, HGF promotes DNA synthesis in alveolar type II cells *in vitro* [87]. A simultaneous or delayed administration of HGF equally represses apoptosis and pulmonary fibrosis in murine lung injury induced by bleomycin [88]. HGF administration may be a novel strategy in the effort to inhibit apoptosis and to promote repair processes in lung injury and fibrosis.

3. BRONCHIAL ASTHMA

Bronchial asthma is characterized by allergic airway inflammation, airway obstruction, hyper-responsiveness, desquamation of bronchial epithelial cells, thickening of basement membrane, and inflammatory cell infiltration to submucosal tissues. Eosinophils and lymphocytes accumulate and prolong their survival in allergic airway inflammation. Eosinophil accumulation and survival in bronchial mucosa are critical in the pathophysiology of bronchial asthma. In fact, reduced eosinophil apoptosis in induced sputum correlates with clinical severity of chronic stable asthma [89].

Eosinophil survival is affected by microenvironment in airway walls including cytokine expression and secretion of chemical mediators by neighboring cells. Eosinophil survival is prolonged by IL-3, IL-5, and GM-CSF. IL-5 inhibits the Bax translocation to mitochondria, cytochrome c release, and eosinophil apoptosis [90]. Myofibroblasts prolong the eosinophil survival through the production of GM-CSF *in vitro* [91]. STAT5 pathway activated by GM-CSF enhances survival of BAL fluid granulocytes in animal model of asthma [92]. Interleukin-15 inhibits spontaneous apoptosis of eosinophils through inducing expression of GM-CSF and NF-kB activation [93]. GM-CSF also prevents glucocorticoid-induced loss of X chromosome linked-IAP (XIAP), c-jun N-

terminal protein kinase (JNK) activation, and mitochondrial injury [94].

CD40 engagement enhances eosinophil survival through induction of cellular inhibitor of apoptosis protein 2 (cIAP2) [95]. Dominant negative phosphatidylinositol-3-kinase (PI3K) regulatory subunit suppresses Th2 cytokine secretion, airway inflammation, and hyper-responsiveness in immune-sensitized mice [96]. Extracellular signal-regulated kinase (ERK) and p38 mitogen activated protein kinase (MAPK) activation increase bcl-2 expression and suppress apoptosis in eosinophils *in vitro*. Endogenous nitric oxide (NO) inhibits ERK and p38 MAPK activation and may regulate eosinophilic inflammation in asthma [97]. NO also induces JNK activation and reverses IL-5 mediated eosinophil survival by inducing apoptosis [98]. Prostaglandin E2 (PGE2) enhances eosinophil survival *in vitro*. Cyclooxygenase-2 (COX-2) expression is increased in alveolar macrophages from patients with asthma, which contributes to the prolongation of eosinophil survival by increased PGE2 production [99].

Corticosteroids inhibit the prolonged survival of eosinophils and lymphocytes by inducing apoptosis. Theophylline also inhibits the prolonged survival of eosinophils and lymphocytes [100]. Adrenergic receptor agonists inhibit corticosteroids-induced apoptosis of eosinophils and epithelial cells [101]. Cyclosporin A induces T lymphocyte apoptosis via decreased Bcl-2 expression, which may be related to its inhibitory effect on the late asthmatic reaction [102].

Fas-mediated apoptotic response is important in resolution of inflammatory cells. Fas mRNA and Fas receptor expression on CD3+ lymphocytes are down-regulated in patients with allergic bronchial asthma, and these cells are resistant to Fas-mediated cell death [103]. Clara cell-derived FasL expression is markedly reduced in the airways of mice sensitized with ovalbumin [104]. Fas-deficient mice exhibit sustained airway hyper-reactivity and apoptotic cells in ovalbumin-sesitized mice [105]. Interferon-gamma induces the Fas and FasL expression on allergen-stimulated CD4+ T cells from asthmatic patients and caused apoptosis in these cells [106]. These results suggest that down-regulation of the Fas-FasL pathway may be involved in the pathophysiology of asthma.

The loss of columnar epithelial cells is one characteristic feature of asthma. Asthmatic bronchial epithelium is susceptible to hydrogen peroxide (H_2O_2)-induced apoptosis [107]. Cyclin-dependent kinase inhibitor p21 is over-expressed in bronchiolar epithelial cells of asthmatics, and its expression is upregulated by TGF-beta and low concentration of H_2O_2 [108]. It is possible that abnormal tissue damage and repair responses may be involved in airway remodeling. Mucous cell metaplasia is developed by differentiation of epithelial cells and maintained by Th2 milieu in asthmatics through inhibiting mucous cell apoptosis [109]. T cells and eosinophils induce apoptosis in bronchiolar epithelial cells through interferon-alpha and TNF-alpha. Eosinophil cationic protein induces necrosis in bronchial epithelial cells [110]. It is also suggested that corticosteroids may induce epithelial cell death in chronic asthma and animal models [111].

Peroxisome proliferator-activated receptor gamma (PPAR gamma) is a nuclear hormone receptor involved in cell proliferation, differentiation and apoptosis. PPAR gamma expression is upregulated in airway epithelium, bronchial submucosa, and smooth muscle cells, which is correlated with the decline of FEV_1 values. PPAR gamma expression on epithelium correlates with the subepithelial membrane thickening. Corticosteroids down-regulate PPAR gamma expression on these cells, and decrease the thickening of subepithelial membrane and collagen deposition, and also increase the number of apoptotic cells in submucosa [112]. In contrast, PPAR gamma is produced by eosinophils, and its agonists inhibit IL-5 stimulated eosinophil survival [113]. Additionally, PPAR gamma agonists regulate human cultured airway smooth muscle proliferation (Ward JE *et al*). Therefore, the therapeutic modality of PPAR gamma agonist in asthma should be examined more precisely. The increase of number of smooth muscle cells in airway walls in asthma depends on the interaction of alpha (5) beta (1) integrin as a receptor on smooth muscle cells and extracellular matrix such as fibronectin, laminin, and collagens I and IV as anti-apoptotic factors [114]. The proliferation and apoptosis of smooth muscle cells is one of promising targets for the novel treatment of asthma.

4. PULMONARY EMPHYSEMA

Pulmonary emphysema is characterized by the enlargement of distal air spaces due to the destruction and loss of alveolar structures. Recently, endothelial and epithelial cell apoptosis have been implicated as one of important mechanisms of pulmonary emphysema. Intratracheal injection of activated caspase-3 in the protein transfection reagent induces epithelial cell apoptosis, enhances elastolytic activity, and subsequently induces emphysematous changes in mice [115].

Chronic treatment of rats with the vascular endothelial growth factor (VEGF) receptor blocker induces alveolar cell apoptosis, which subsequently leads to enlargement of the alveolar spaces without inflammatory cell infiltration or fibrosis [116]. In human, apoptotic epithelial and endothelial cells in alveolar walls are significantly increased in patients with pulmonary emphysema. VEGF and VEGF receptor type 2 expressions are also decreased in lung tissues from patients with pulmonary emphysema compared with controls [117]. Rats treated with the VEGF receptor blocker show increased alveolar enlargement, alveolar septal cell apoptosis, and expression of oxidative cell markers [118]. These results suggest that the defect of alveolar wall maintenance factors may be one of pathogenesis of pulmonary fibrosis.

While neutrophils are the predominant cell in the lung parenchyma of smokers without emphysema, CD3+ and CD8+ cells are predominant cells in the alveolar wall in smokers with emphysema. Furthermore, apoptosis in smokers is correlated with the amount of smoked [119]. These results suggest that apoptosis mediated by T

lymphocytes induced by smoking may be one of factors which induce alveolar wall destruction.

The alveolar wall remodeling to emphysema occurs after intratracheal instillation of elastase. In TNF-α and IL-1β receptor deficient mice, the degree of emphysematous changes and lung cell apoptosis are decreased [120]. Inflammation following elastase treatment may account for the development of emphysema. Apoptotic cells should be removed rapidly by phagocytosis for the resolution of inflammation without damaging the tissues. Surfactant protein (SP)-D deficient mice accumulate apoptotic macrophages in the lung, and exogenous SP-D binds to apoptotic macrophages [121]. These results suggest that SP-D may have an important role in the clearance of apoptotic cells, and have preventive effects on the development of emphysema. In lung tissues from patients with emphysema, alveolar cell apoptosis and expression of PCNA in epithelium are increased [122]. Cigarette smoke extract induces oxidative stress and apoptosis in human lung fibroblast [123]. Not only the destructive phase but also remodeling process may contribute to the development of emphysema.

CONCLUSION

In animal models and human diseases, death receptors/ligands, death signals such as reactive oxygen species, nitrogen species, proinflammatory cytokines, and others are involved in the process of cell death. Promotion of inflammatory cell apoptosis and protection of parenchymal cells from cell death may be an effective therapeutic strategy against inflammatory lung diseases. Once parenchymal cells are damaged, accelerating the repair and regeneration in damaged tissues could also be an effective treatment. However, when parenchymal cells are severely damaged, rescue of these cells may leads to carcinogenesis. To avoid this problem, inhibiting apoptosis at early stage may be an effective strategy. The accumulating evidence concerning the apoptosis-signaling molecules may lead to novel treatment. The early, effective, and cell-specific treatment may enable patients to overcome devastating lung diseases.

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