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REVIEW

Acute Lung Injury: IL-17A-Mediated Inflammatory Pathway and Its Regulation by Curcumin

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Abstract— Acute lung injury (ALI) is characterized by acute inflammation and tissue injury results in dysfunction of the alveolar epithelial membrane. If the epithelial injury is severe, a fibroproliferative phase of ALI can develop. During this phase, the activated fibroblast and myofibroblasts synthesize excessive collagenous extracellular matrix that leads to a condition called pulmonary fibrosis. Lung injury can be caused by several ways; however, the present review focus on bleomycin (BLM)-mediated changes in the pathology of lungs. BLM is a chemotherapeutic agent and has toxic effects on lungs, which leads to oxidative damage and elaboration of inflammatory cytokines. In response to the injury, the inflammatory cytokines will be activated to defend the system from injury. These cytokines along with growth factors stimulate the proliferation of myofibroblasts and secretion of pathologic extracellular matrix. During BLM injury, the pro-inflammatory cytokine such as IL-17A will be up-regulated and mediates the inflammation in the alveolar epithelial cell and also brings about recruitment of certain inflammatory cells in the alveolar surface. These cytokines probably help in up-regulating the expression of p53 and fibrinolytic system molecules during the alveolar epithelial cells apoptosis. Here, our key concern is to provide the adequate knowledge about IL-17A-mediated p53 fibrinolytic system and their pathogenic progression to pulmonary fibrosis. The present review focuses mainly on IL-17A-mediated p53-fibrinolytic aspects and how curcumin is involved in the regulation of pathogenic progression of ALI and pulmonary fibrosis.

KEY WORDS: Acute lung injury (ALI); Pulmonary fibrosis (PF); Bleomycin (BLM); Interleukin-17A (IL-17A); urokinase plasminogen activator (uPA); urokinase plasminogen activator receptor (uPAR); plasminogen activator inhibitor-I (PAI-I); p53; curcumin.

INTRODUCTION

Lung is a major site of continuous immune reactions as it encounters various antigens and foreign particles entering the respiratory system [1]. Ventilation and respiration generate an environment where both inflammatory and anti-inflammatory response takes place continuously. Despite distinct etiological and clinical features, most lung disorders exhibit common occurrence of irritants, which sustain the production of macrophages, neutrophils, cytokines, growth factors, etc., [2]. These factors may promote lung inflammation, fibrosis, cancer, or any lung disease [2, 3]. Alveolar macrophages play an important role in the defensive system of the lung. These macrophages initiate the phagocytosis and release the cytokines along with the

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other products, which adapt host cellular defense [1, 4]. Acute lung injury (ALI) disrupts the alveolar epithelium, which results in the inflammation [3]. The small glycoprotein messengers called cytokines, which is actively involved in the immune response of an organism. This promotes the acute inflammation to make up the innate immune response [4]. The role of acute and chronic inflammation is driven by cytokines, the cytokine called tumor necrosis factor-alpha (TNF-α), which promotes the initiation of inflammatory cytokines such as IL-17A, IL-17F, IL-22, and IL-13 [3–5]. Such cytokines play a protective role in epithelial repair of the lung. The progression of lung injury leads to the condition called idiopathic pulmonary fibrosis (IPF), which is characterized by chronic, irreversible, progressive, and usually lethal lung disease of unknown cause [6, 7].

IPF occurs in middle-aged and elderly adults, the annual incidence of IPF in the USA is about 6.8 to 16.3 cases per 0.1 million population and 0.22 to 7.4 cases per 0.1 million population in Europe [8]. In the USA, the estimated incidence of ALI is 22 person per 0.1 million populations, and the mortality rate is about 40–50% [9, 10]. In India, the incidence of ALI is clearly not known, but the mortality rate among those patients is about 30–40% [9]. In idiopathic pulmonary fibrosis (IPF), progression of the disease is characterized by the inappropriate accumulation of fibroblasts and collagen-producing myofibroblasts in lung tissue [2, 7]. The resulting fibrotic changes in lungs lead to decreased gas exchange and pulmonary distress [7]. Median survival for IPF patients is below 5 years, and there are no any approved treatments for this clinical condition [2]. Some standard treatment regimens are available in the form of anti-inflammatory agents such as prednisone and various immunomodulatory agents [11]. These medications offer only the modest effectiveness, and many drugs cause significant adverse effects on lungs. Lung transplantation is only the possible way for the long-term survival of IPF patients [2, 7].

Bleomycin as a Model for Lung Injury Studies

Lung injury can be caused by several factors like drugs, fumes, dust, infection, autoimmune diseases, etc. [3]. The cancer chemotherapeutic drug called BLM partially intercalates DNA helix as well as pyrimidine and imidazole structures [12]. This forms an activated complex capable of releasing oxidants, which damage the polynucleotide chains of DNA in the close proximity [12, 13]. This modification leads to the release of free bases or their propanol derivatives [12]. BLM is able to cause cell damage independent from its effect on DNA by induction of lipid peroxidation, and this may cause alveolar cell damage and subsequent pulmonary inflammation (Fig. 1) [12]. BLM has toxic effects on lungs, and it also involves in oxidative damage and the elaboration of inflammatory cytokines, ultimately bleomycin-induced

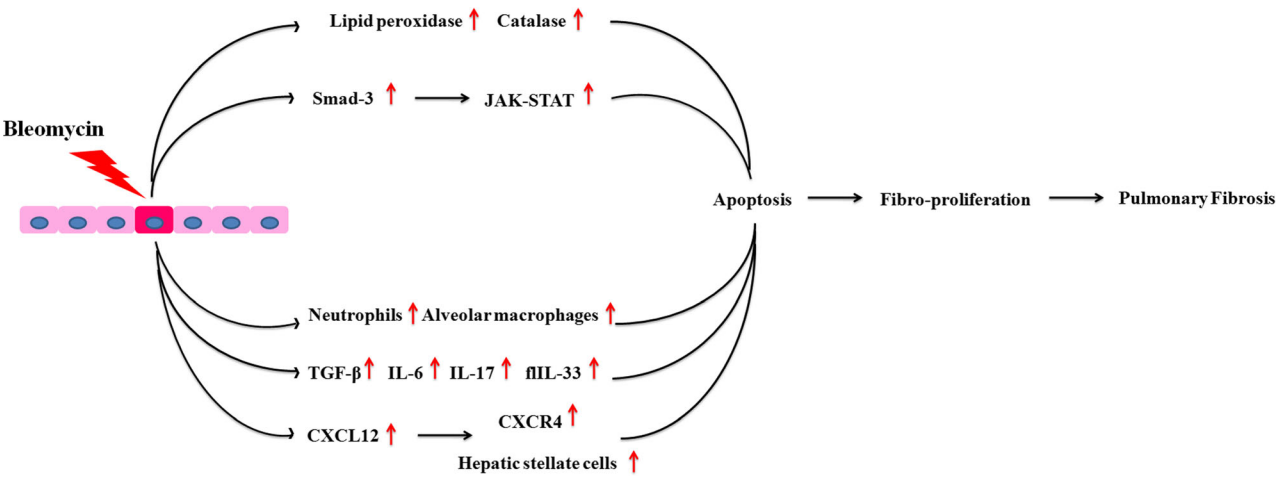

Fig. 1. BLM-induced biochemical changes during ALI and fibrosis. BLM causes the toxic effects on lung and results in the oxidative damage to the AECs. The elevated expression of inflammatory cytokines can be seen in response to the BLM-induced lung injury. The overall biochemical changes in the AECs and its viability are responsible for the fibro-proliferative phase during the progression of ALI. In turn, the excess deposition of ECM alters the alveolar architecture and leads to the pulmonary fibrosis.

pneumonitis can progress to lung fibrosis [4, 13]. IPF usually alters the balance between proliferation and apoptosis of fibroblasts leads to the accumulation of extracellular matrix (ECM) [14, 15]. More recent studies have focused on the epithelial-mesenchymal interplay, and it plays a key theme in pulmonary fibrosis [14–17]. In which altered lung mesenchymal cells coupled with alveolar epithelial cell injury results in the accumulation of ECM and remodeling of lung architecture [18, 19].

The BLM also promotes the expression of chemokines such as CXCL12 and its receptors CXCR4. The CXCL12 is known to promote hepatic stellate cells (HSC), and they are the key biomolecules that plays a major role in the progressive fibrosis [20]. The chemokine receptor CXCR4 is activated by the CXCL12 in response to induce the progression of injury (Fig. 1) [20]. The CXCL12 induces the production of fibrocytes in the circulation, which in turn promotes the collagen deposition during lung injury and progression. The basic study on alveolar macrophages suggests that the role of BLM in the induction of alveolar macrophages in turn activates the secretion of fibroblast growth factor (MDGF) [21, 22]. The BLM is known to induce the expression of TGF-β1 and smad-3 in the alveoli in response to the injury [22]. The activated smad-3 plays a major role in the activation of JAK-STAT pathway by binding with the promoter region of IL-31 (Fig. 1) [22].

The BLM-induced inflammation can be possible through the proteolytically uncleaved full length (fl) IL-33 expression. The IL-33 proteolytic maturation and cell surface receptor binding is composed of biological effects of IL-1 receptor accessory protein and T1/ST2 glycoprotein [23]. The flIL-33 remains chiefly intracellular and besides intranuclear, which in turn influence the inflammation in a T1/ST2-independent fashion [23]. Especially in IPF patients, the elevated expression of flIL-33 can be seen in the lungs and it will persuade the inflammation of pulmonary lymphocytes without engaging the T1/ST2 receptor, this can be independent of Th2 cytokine pattern activation [23]. The recent studies reported that BLM involved in the over-expression of lung lavage fluid biomarkers such as angiotensin converting enzyme (ACE), *N*-acetyl-β-D-glucosaminidase (NAG), total protein, lipid peroxidation (LPO) products, and catalase (Fig. 1) [24].

Role of IL-17 in ALI and Fibrosis

The cytokine called IL-17 involved in the regulation of lung immunity and mediates pro-inflammatory responses [25]. IL-17 is classified into six types namely, IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F, out of those the biological function of IL-17A and IL-17F are best understood [25–27]. IL-17A and IL-17F hetero-dimer mediate their function through a hetero-dimeric receptor complex of IL-17RA and IL-17RC. Th17 cells produce IL-17A and IL-17F in many types of adaptive immunity [25, 28]. Some recent studies reported that TGF-β, IL-6, IL-1β, and TNF-α also regulate the IL-17A release from Th17 cells (Fig. 2). TGF-β and IL-6 can induce Th17 activation and proliferation and IL-17 production [26, 27]. In the case of lung injury, the IL-17R subunits and the post-translational modification of Act1 and IL-17A mediate tissue inflammation and host defense in many facets of signaling regulation [25–27, 29]. IL-17A also mediates the changes in p53 expression and increased expression of IL-17A results in the increased level of p53 leads to the progression of pulmonary fibrosis (Fig. 2) [26, 27, 30]. IL-17A-induced production of pro-inflammatory cytokines, chemokines, and antimicrobial peptides by multiple cell type in the airway is critical for mounting successful host defense against pathogens [25, 28].

Literatures suggest that IL-17A is also involved in the accumulation of macrophage in cigarette smoke-exposed lungs and targeting non-conventional T cell sources of IL-17A [26]. It may afford an alternative strategy to control pathogenic macrophages [31–34]. Concurrent activation of TLR2 and IL-17R in bronchial epithelium results in the sequestration of MyD88 by Act1/CIKS, thereby turning off TLR2 signaling to restore homeostasis [27]. Morphine shows the inhibitory action against the early IL-17 release and interaction between Act1 and MyD88, leading to decreased pathogenic clearance and sustained inflammation [35–38]. Thymosin-β4 (Tβ4) is a highly conserved peptide with immunomodulatory properties, the effects of Tβ4, or bleomycin-induced lung damage changes in the number of IL-17-producing cells as well as the IL-17 expression in the lung [28, 38]. The decreased amount of IL-17-producing cells inhibits that IL-17 expression in the lung with Tβ4 treatment correlates with its anti-inflammatory and anti-fibrotic effects [38]. IL-17A mainly mediates its immune regulatory function by promoting the generation of proinflammatory cytokines and chemokines, which leads to the attraction of neutrophils and macrophages to the inflammation site [39, 40]. The receptor for IL-17A is widely expressed in non-hematopoietic cells, such as fibroblasts and epithelial cells [29].

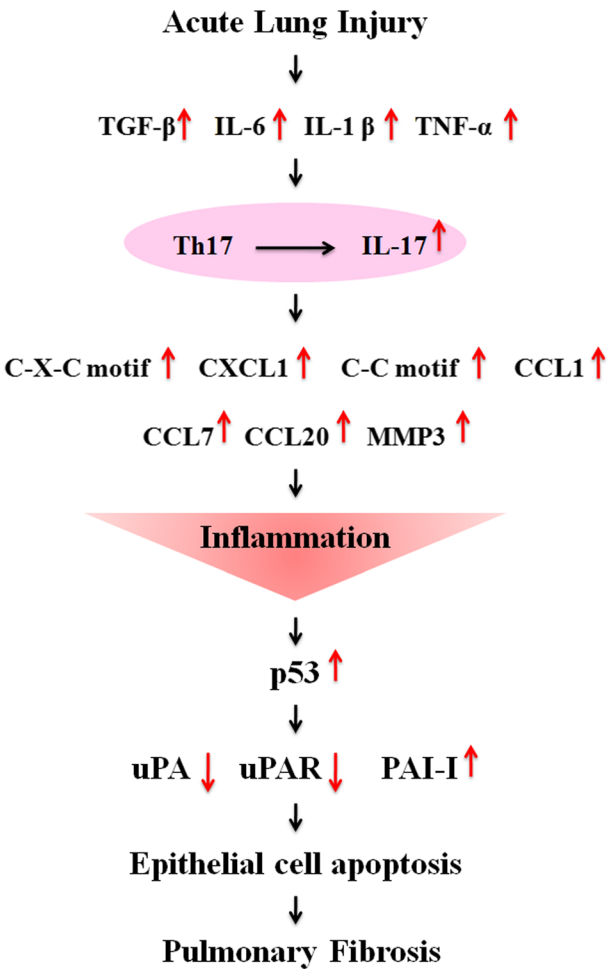

Fig. 2. IL-17-mediated changes during ALI and fibrosis. During ALI, the pro-initiation of pulmonary inflammation is mediated by inflammatory cytokines such as IL-17. The expression inflammatory cytokines are also associated with the certain chemokines which induce the inflammatory response during ALI. The underlying mechanism between IL-17 and p53 mediates the impairment of fibrinolytic system to initiate the progression of fibrosis.

The treatment of IL-17A on lung epithelial cell line results in the up-regulation of several cytokines, including chemokines (C-X-C motif), ligand (CXCL1), chemokine (C-C motif), ligand 2 (CCL2), CCL7, CCL20, and matrix metalloproteinase 3 and 13 [31, 32, 35, 37]. The elevated expression of IL-17A also cross-linked with p53 expression and its regulation. The increased expression of p53 has been found during IL-17A-mediated changes during lung injury, which results in the increased expression of p53 [30–33]. If there is a lung injury, the p53 expression will increase in type-II alveolar epithelial cells, and p53 acts at transcriptional and post-transcriptional levels to control gene expression. Increased interaction of p53 with UTRs of uPA, uPAR, and PAI-1 mRNAs helps to prevent the development of pulmonary fibrosis [31, 32].

The IL-17-producing γδT cell induces the pathogenesis in repeated lung injury and subsequent inflammation persuades the pulmonary fibrosis [38, 39]. The studies have been found that neutralization of IL-17A leads to the significant down-regulation of neutrophil recruitment in the BALF and involved in the reduction of IL-1β, IL-6, and tissue inhibitor matrix mettaloprotenase-1 (TIMP-1) [38, 39]. The neutralization of IL-17A plays a pivotal role which blocks the triggering of late inflammation IL-17RA signaling pathway, which describes the importance of IL-17A in pulmonary fibrosis (Fig. 2) [38, 40]. According to literatures, the innate existence of IL-1β-IL-23-IL-17A axis exhibits their direct consequences in early pulmonary inflammation and progressive evolution to fibrosis after injury [39, 40]. IL-17A is also a downstream regulatory molecule of TGF-β1, which is the central mediator of pulmonary fibrosis [38, 39].

p53-Fibrinolytic Changes in ALI and Fibrosis

ALI and their progression affect the systems like fibrinolysis and extravascular fibrin deposition in alveolar epithelial cells. The elaborated action of uPA and uPAR is shown by type II alveolar epithelial cells (AECs), which mediate changes in ALI and their regulation [18, 41, 42]. The uPA-fibrinolytic system and the tumor suppressor protein, p53, are mainly involved in the regulation of AEC viability (Fig. 3) [43]. According to the literatures, bleomycin (BLM) model of lung injury results in the induction of IL-17A in alveolar epithelial cells [12, 13]. IL-17A mediates the expression of p53 and important components of uPA-fibrinolytic system in alveolar epithelial cells [18, 42, 43].

Production of extracellular matrix by myofibroblasts changes the alveolar architecture with thickening of the air-blood barrier and consecutive impairment of blood gas exchange and lung compliance [44]. Some factors like active TGF-β mediate profibrotic effects such as epithelial cell apoptosis, epithelial to mesenchymal transition, extracellular matrix production, and differentiation of fibroblast into myofibroblasts [44–49]. The uPA is a multifunctional serine protease involved in the activation of plasminogen as well as the uPAR, which mediates signal transduction in the pathogenesis of ALI [31, 32, 50, 51].

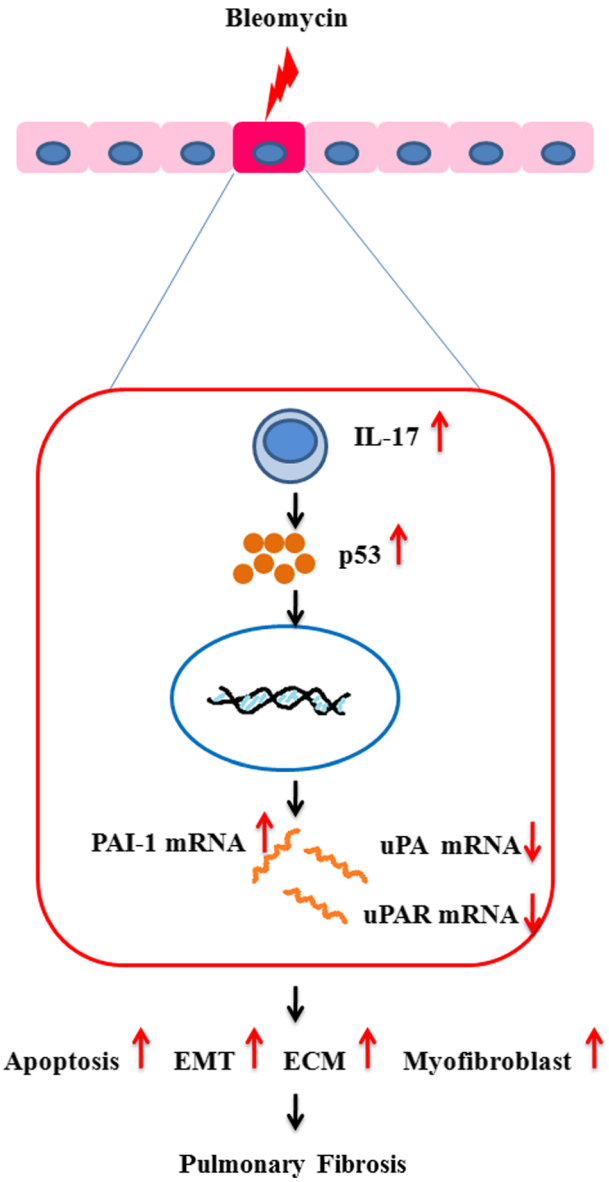

Fig. 3. p53 mediated fibrinolytic changes during BLM-induced ALI and fibrosis. The BLM-induced pro-inflammatory response results in the elaboration of IL-17A in the lung. The IL-17A shares its cross-linked pathway with the tumor suppressor protein p53. The induced p53 will bind to the transcripts of uPA, uPAR, and PAI-1, which induces the stabilization of PAI-1 transcript and destabilization of uPA and uPAR transcripts in ATII cells. The impaired fibrinolytic system mediates the access accumulation of ECM and subsequent development of pulmonary fibrosis.

The associated function of uPA with uPAR involves proteolysis, cell adhesion, migration, proliferation, and differentiation, which are dependent on its association with uPAR [31, 43]. During the progression of lung injury, the expression of p53 increases in type II alveolar epithelial cells, which is associated with the induction of plasminogen activator inhibitor-1 (PAI-1) and suppression of uPA and uPAR expression (Fig. 3) [32, 43, 49–51]. The uPA and uPAR prevent the expression of pro-inflammatory cytokines in the lungs [14, 42].

The recent scientific investigations have revealed that the p53 and PAI-1 have the crucial role in the development of pulmonary fibrosis [52, 53]. In a study, the PAI-1-deficient mice were induced with p53 to evaluate the p53-PAI-1 mechanism, which has shown that the PAI-1-deficient mice were failed to develop the pulmonary fibrosis because of the absence of PAI-1 [52, 53]. The miR-34a has the determining role in the AEC regulation in response of injury, which has the ability to promote the expression of p53-uPA-fibrinolytic system and AEC apoptosis during the progression of pulmonary fibrosis (Fig. 3) [53]. The miR-34a that promoted acetylation of p53 can be reversible in the process of pulmonary fibrosis, which in turn the pathway can be easily targeted as a therapy to bring down the progression of pulmonary fibrosis [53]. It is also found that the expression of pulmonary surfactant protein-C (SP-C) in the AECs is significantly reduced in several forms of lung injury and its progression associated with the fibrosis [54]. The Sp-C gene silencing model study has shown the over-expression of p53 and activation of caspase-3 in response to the AEC apoptosis during the subsequent development of pulmonary fibrosis [54].

Curcumin as an Effective Intervention for Pathway Studies in ALI and Fibrosis

Curcumin is a naturally occurring polyphenolic phytochemical isolated from the rhizome of the turmeric plant. It is a potent immunomodulatory agent that has several pharmacologic effects including anti-inflammatory, anti-proliferative, antioxidant, antitumoral, and wound-healing activities [55–57]. Recent studies revealed curcumin as a potential compound to control acute lung injury. Curcumin can selectively activate or inactivate gene expression for the improvement of the cell [56, 58]. Antitumoral activity of curcumin occurs through suppression of cell proliferation and cell apoptosis activation by down-regulation of various proinflammatory cytokines [55, 56]. Curcumin down-regulates the expression of proinflammatory cytokines including TNF-α, IL-1, and IL-6 (Fig. 4) [56, 57, 59].

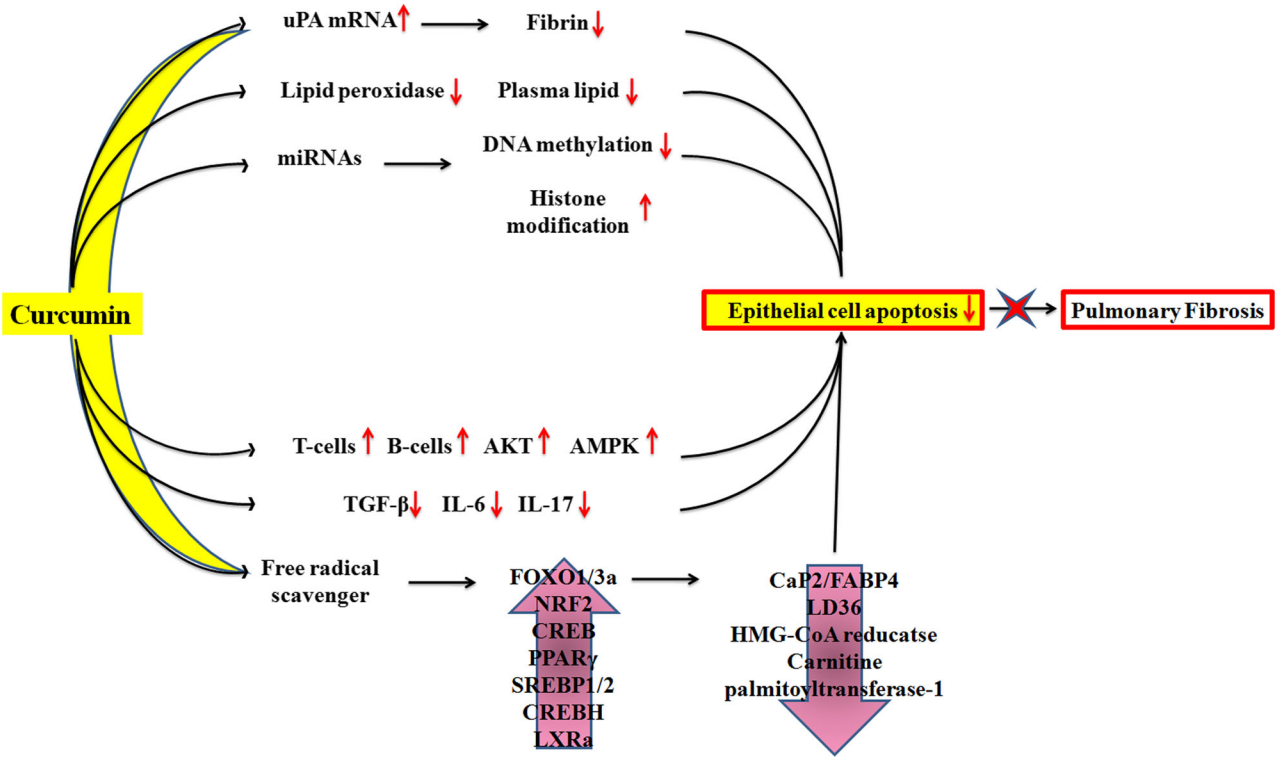

Fig. 4. Curcumin alleviated changes during ALI and fibrosis. The bioactive phyto-chemical curcumin has its pivotal role in lung injury repair mechanism. Curcumin induces the changes in the transcripts of uPA, which in turn helps to break down the fibrin in the lungs. The curcumin regulates the pro-inflammatory changes by reducing the expression of TGF-β, IL-6, and IL-17. The curcumin inhibits the lipid peroxidation process to attenuate the oxidative damage to the AECs. Curcumin also acts as free radical scavengers, which involved in the up-regulation of transcription factors such as FOXO1/3a, NRF2, CREB, PPARγ, SREBP1/2, CREBH, and LXRa. The up-regulation of these factor results in the regulation of cell injury and AEC apoptosis. The curcumin has their own ability to regulate the multiple signaling pathways during ALI and fibrosis.

The curcumin plays a major role in the regulation of inflammatory cytokines IL-17A andalveolar epithelial cell repair during lung injury (Fig. 4) [60, 61].

Some of the recent studies have assured the effective role of curcumin in lung injury. It is a natural product that exhibits broad anti-inflammatory activities both in vivo and in vitro [56, 62, 63]. The monocarbonyl analog of curcumin (MACs) demonstrates excellent chemical stability and pharmacokinetic profiles [57]. Curcumin is an immunomodulatory agent that can attenuate the activation of T cells, B cells, macrophages, neutrophils, natural killer cells, and dendritic cells (Fig. 4) [55]. Dietary administration of curcumin effectively suppresses NTHi-induced COPD-like airway inflammation and lung cancer progression in mice [55]. Anti-tumoral activity of curcumin occurs through suppressing cell proliferation and activating cell apoptosis by down-regulation of various pro-inflammatory cytokines [55, 56, 58–60]. It can selectively activate or inactivate gene expression. Curcumin can epigenetically regulate the expression of important genes by reversing DNA methylation and altering histone modifications and by targeting several miRNA that play a key role in diseases like COPD, ALI, ARDS, IPF, etc. [55–59]. The uPA plays a vital role in the early phases of wound healing by aiding fibrin dissolution and promoting the migration, proliferation, and adhesion of various cells to the wound bed [31, 32, 43]. Curcumin can up-regulate the uPA mRNA and protein in human fibroblast [59, 63].

The curcumin is also a potential scavenger for reactive oxygen or nitrogen species; it may be scavenge either directly or by modulating the activity of signal transduction enzymes, which are responsible for the expression of anti-oxidant genes (Fig. 4) [64]. The

curcumin may show their alternative effect to reduce the plasma lipid levels by lipid metabolic gene modulation in the tissues [64]. This further may involve in the reduction of stress of lipid-mediated oxidation and endoplasmic reticulum through their hypolipidemic effect [64]. This polyphenolic phytochemical also acts as free radical scavenger and persuade the signal transduction of Akt and AMPK. The curcumin involved in the attenuated activity of some specific transcription factors like FOXO1/3a, NRF2, CREB, PPARγ, SREBP1/2, CREBH, and LXRa; these factors are responsible for the regulation of gene expression of free radical scavengers CaP2/FABP4, CD36, HMG-CoA reductase, and carnitine palmitoyltransferase-1 (CPT-1) (Fig. 4) [64].

The recent advancement about curcumin-related works has evaluated their role in regulation of tissue malondialdehyde levels [65]. The literatures suggest that the administration of curcumin reduces the elevated expression of tissue malondialdehyde and induces the activity of superoxide dismutase and glutathione peroxidase enzymes in lung tissues. The curcumin therapy may also regulate the intestinal ischemia/reperfusion (I/R)-induced lung injury by reducing the nitric oxide synthase activity and modulating the expression of surfactant protein-D in lung tissues [65]. Another in vivo experimental study has said that curcumin is a potential phytochemical result in the reduction of harmful biomarkers of lavage fluid and exhibits the restoration of antioxidant status during BLM-induced lung injury [48]. The promising results have been found with using curcumin intervention on different models of lung injury, which shows their protective action against LPS-induced expression of cytokine-mediated changes in neutrophil chemoattractant-1 in lung tissues [66]. It is possible to regulate the recruitment and activity of neutrophils in the alveolar epithelial cells. The membrane stabilizing properties of curcumin mediates the significant reduction in the BALF cell count, which in turn curcumin inhibits the inflammatory cell migration through the epithelial and endothelial basement membrane at the site of inflammation [67]. The curcumin can inhibit the pulmonary fibrosis by regulating the inflammatory cells and by neutralizing the excess accumulation of collagen in the lung [67].

LIMITATIONS

IL-17A-mediated inflammatory pathway exhibits a complicated mechanism which has been involved in the several other pathways of lung injury [68, 69]. We reported the major and important role of IL-17A in the regulation of p53-mediated fibrinolytic system and AECs apoptosis [68, 69]. Still, the existing knowledge seems to be very narrow to understand the mechanism of injury and fibrosis in depth. Apart from this, we tried to provide the adequate knowledge about the medical efficacy of promising polyphenolic bioactive compound curcumin [68, 69]. Phase I and II clinical trials have been shown that the high dose of curcumin (12 g/day) is safe for human, but it is not enough when we consider the bioavailability [70, 71]. The poor absorption, rapid systemic elimination, and rapid metabolism of curcumin limit its levels in plasma and tissues. There are few novel approaches that have been undertaken to improve the curcumin levels in the biological system [70, 72]. The structural modifications such as the addition of piperine that will interfere with glucuronidation, use of liposomal curcumin, formulation of nano-curcumin, complex formation of curcumin phospolipid, and make use of curcumin structural analogs could be very useful in terms of medical efficacy [70, 73]. It could be a great advancement in the medicinal chemistry if one could enhance the bioavailability of curcumin and to prove it as a novel therapy to treat several diseases including acute lung injury and fibrosis.

CONCLUSIONS

Alveolar epithelial cells with increased inflammatory cytokines expression are more susceptible for the progression of lung injury. The mechanism discussed here shows a valuable evidence for IL-17A-mediated changes in fibrinolytic system. It is very important to understand the patho-physiology of lung injury and their progression at the molecular level. The regulation of lung injury through p53 is a specific hallmark for the evidence-based experimental studies and to find out a proper intervention. Here, we have given an easy and compatible model to study the complex molecular mechanism such as interaction between IL-17A and p53. According to the existing knowledge, curcumin is a very potential bioactive compound to delineate the IL-17A-mediated changes during lung injury and fibrosis. Curcumin plays a role at the molecular level to alter the changes happened with the lung injury and to carry out a normal functioning of the cell.

AUTHORS' CONTRIBUTIONS

The manuscript has been originally prepared and reviewed by Mr. Mahesh Manjunath Gouda in correspondence with Dr. YashodharPrabhakarBhandary.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest. The authors declare that they have no conflict of interest.

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