Lung Healing After Injury

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Introduction

The lung possesses a remarkable capacity for structural and functional recovery after injury. In daily clinical practice, clinicians routinely encounter diverse forms of pulmonary damage, including infection, aspiration, toxic inhalation, autoimmune inflammation, mechanical ventilation–associated injury, and ischemia–reperfusion injuries. In many patients, gas exchange normalizes and radiographic abnormalities resolve within days to weeks. In others, however, similar initial insults evolve into persistent architectural distortion, impaired diffusion capacity, and ultimately pulmonary fibrosis. Understanding why repair succeeds in some cases and fails in others remains a central question in pulmonary medicine.

Acute lung injury (ALI) and its most severe manifestation, acute respiratory distress syndrome (ARDS), illustrate this dichotomy. ARDS is characterized by diffuse alveolar damage, increased alveolar–capillary permeability, and hypoxemia. The traditional view conceptualized ARDS as an inflammatory disorder driven primarily by neutrophil-mediated tissue injury. Current evidence indicates that epithelial and endothelial injury, dysregulated immune responses, impaired regeneration, and maladaptive tissue remodeling collectively determine outcome rather than inflammation alone.

From a biological standpoint, lung healing follows a broadly conserved sequence: injury, inflammation, regeneration, and remodeling. These phases overlap temporally and interact dynamically. Alveolar epithelial type 2 (AT2) cells serve as facultative stem cells of the distal lung, proliferating and differentiating into alveolar epithelial type 1 (AT1) cells to restore the gas-exchanging surface. When debris clearance and resolution processes by immune cells proceed in a coordinated manner, normal architecture is largely restored. However, when regulation fails due to persistent inflammation, cellular senescence, or sustained profibrotic signaling, repair transitions into fibrosis.

For clinicians, the distinction between regenerative repair and fibrotic remodeling is not merely academic. It influences ventilatory strategy, fluid management, anti-inflammatory therapy, and the timing of antifibrotic interventions. Moreover, emerging data suggests that early biological signals may predict progression toward chronic fibrotic disease.

This chapter reviews lung healing after injury using a clinically oriented framework. We first examine mechanisms of initial tissue injury. We then discuss the inflammatory response and its role in both protection and pathology. Next, we explore epithelial regeneration and the cellular programs that restore alveolar structure. Finally, we address remodeling and the transition to fibrosis, highlighting factors that

shift repair from resolution toward irreversible scarring. Throughout, emphasis is placed on pathobiological concepts that inform bedside decision making and future therapeutic strategies.

Lung Injury: Initiation of Tissue Damage

Lung healing begins with disruption of the alveolar–capillary unit. Regardless of etiology, clinically significant pulmonary injury converges on a limited set of structural and cellular events: epithelial damage, endothelial dysfunction, and breakdown of the alveolar barrier. This shared pathway explains why diverse insults can produce a similar clinical phenotype.

1. Structural Target: The Alveolar–Capillary Barrier

The distal lung is optimized for gas exchange. The alveolar surface consists primarily of:

- Alveolar type 1 (AT1) cells, which cover approximately 95% of the alveolar surface area and facilitate diffusion.
- Alveolar type 2 (AT2) cells, which produce surfactant and function as progenitor cells.
- A thin interstitial compartment containing fibroblasts and extracellular matrix.
- Capillary endothelial cells forming the vascular interface.

Acute injury disrupts tight junctions, increases permeability, and allows protein-rich fluid to enter the alveolar space. Clinically, this manifests as non-cardiogenic pulmonary edema and hypoxemia.
Histologically, diffuse alveolar damage (DAD) represents the prototypical pattern, characterized by epithelial necrosis, hyaline membrane formation, and interstitial edema.
Importantly, the extent of epithelial loss, particularly AT2 cell depletion, strongly influences the lung's capacity to regenerate.

2. Epithelial Injury: Loss of Barrier and Progenitor Function

AT1 cells are highly susceptible to mechanical and inflammatory injury. Their loss compromises gas exchange but is typically followed by replacement if sufficient AT2 cells remain viable. AT2 cells serve two essential functions:

1. Surfactant production, maintaining alveolar stability
2. Stem/progenitor capacity for epithelial regeneration

When AT2 injury is limited, regeneration can occur efficiently. However, extensive AT2 loss or functional impairment reduces reparative capacity and predisposes to aberrant remodeling.
Several mechanisms contribute to epithelial injury:

- Direct cytopathic viral effects (e.g., influenza, SARS-CoV-2)
- Neutrophil-derived proteases and reactive oxygen species
- Cytokine-induced apoptosis

- Mechanical stretch from high tidal volumes or elevated transpulmonary pressures

From a clinical standpoint, ventilator-induced lung injury (VILI) exemplifies how iatrogenic mechanical stress can amplify epithelial damage. Excessive cyclic stretch activates inflammatory pathways and alters mechanotransduction signaling, predisposing to both acute permeability injury and later fibrotic remodeling.

3. Endothelial Injury and Microvascular Dysfunction

Endothelial injury is equally central. Capillary barrier breakdown increases vascular permeability and promotes microthrombi formation. Dysregulated coagulation, impaired fibrinolysis, and endothelial activation contribute to:

- Intravascular thrombosis
- Impaired perfusion
- Local hypoxia
- Further epithelial stress

Clinically, this endothelial component explains the association between ARDS and thrombotic complications. It also highlights why lung injury should not be conceptualized solely as an epithelial disease.

4. Damage Signals and Early Molecular Activation

Injured epithelial and endothelial cells release danger associated molecular patterns (DAMPs). These signals activate pattern recognition receptors on resident macrophages and recruited immune cells, initiating the inflammatory cascade.

Early molecular responses include:

- Activation of NF-κB signaling
- Release of IL-1β, TNF-α, and IL-6
- Induction of TGF-β signaling

While these responses aim to contain injury and promote clearance, excessive or prolonged activation shifts the microenvironment toward maladaptive repair.

5. Determinants of Injury Severity

Not all injuries progress similarly. Several variables influence downstream repair:

- Extent of AT2 preservation

- Duration of inflammatory exposure
- Mechanical stress burden
- Age and cellular senescence
- Genetic susceptibility (e.g., telomere dysfunction)
- Preexisting interstitial lung disease

Older patients and those with shortened telomeres exhibit impaired regenerative capacity, increasing the likelihood that acute injury transitions into fibroproliferation rather than resolution.

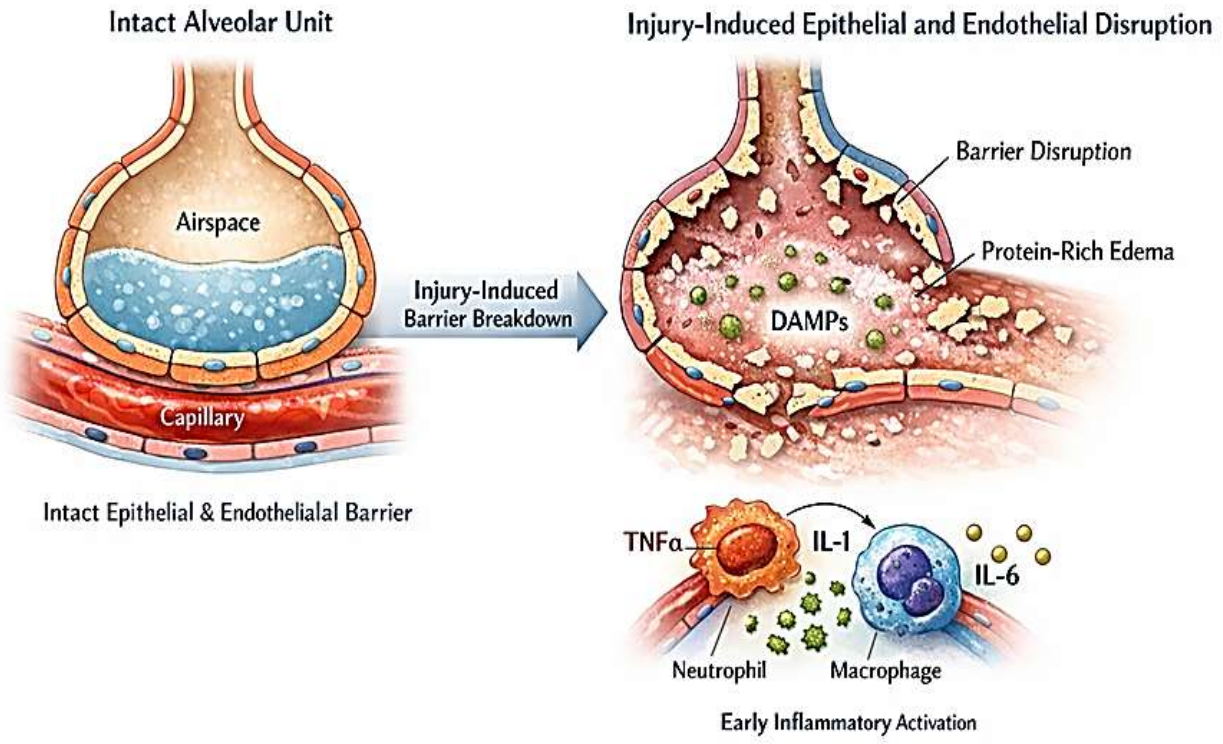

Figure 1: An intact alveolar unit has a distinct barrier between the airspace and capillary space normally. In the setting of inflammation and lung injury, the epithelial and endothelial barrier is disrupted, triggering formation of protein-rich edema and ongoing inflammatory response through the release of DAMPs. This leads to ongoing early inflammatory activation, through the stimulation and release of primary inflammatory cytokines such as TNFα, IL-1, and IL-6.

In summary, lung healing begins with structural disruption of the alveolar–capillary barrier. The severity and distribution of epithelial and endothelial injury, particularly the preservation of AT2 progenitor cells, set the trajectory for either effective regeneration or progression toward fibrosis.

Next, we examine how the inflammatory response determines whether injury resolves or amplifies into chronic disease.

Inflammation: Protective Response or Maladaptive Amplification

Following structural injury to the alveolar–capillary barrier, the lung mounts a rapid inflammatory response. This response is essential for pathogen clearance, removal of necrotic debris, and initiation of tissue repair. However, the same inflammatory processes that protect the host can also propagate tissue injury and impair regeneration when excessive or prolonged. The inflammatory phase therefore represents a critical inflection point that determines whether lung healing progresses toward resolution or toward chronic remodeling.

1. Early Innate Immune Activation

Resident alveolar macrophages are among the first cells to respond to tissue injury. Recognition of damage associated molecular patterns (DAMPs) and pathogen associated molecular patterns (PAMPs) activates pattern recognition receptors, including Toll-like receptors and inflammasome pathways. This activation triggers the rapid release of proinflammatory cytokines and chemokines such as IL-1β, TNF-α, IL-6, CXCL8, and CCL2.

These mediators recruit circulating leukocytes to the injured lung. Within hours, the pulmonary microvasculature becomes populated with activated neutrophils and monocytes. Increased vascular permeability facilitates leukocyte extravasation into the interstitium and alveolar space.

Although this response is protective in the context of infection, uncontrolled activation contributes to epithelial injury and microvascular damage.

2. Neutrophils and Amplification of Tissue Injury

Neutrophils play a dominant role in the early inflammatory phase of lung injury. Once recruited to the alveolar space, they release a range of effector molecules including:

- Reactive oxygen species
- Proteases

These molecules contribute to microbial clearance but can also degrade epithelial junctions, injure endothelial cells, and impair surfactant function. Excessive neutrophil activation therefore amplifies alveolar permeability and tissue damage.

Clinically, elevated neutrophil counts in bronchoalveolar lavage fluid correlate with disease severity in ARDS and other inflammatory lung diseases.

3. Monocyte Recruitment and Macrophage Heterogeneity

Circulating monocytes are recruited to injured lung tissue through chemokine signaling, particularly via the CCL2–CCR2 axis. These monocytes differentiate into monocyte derived alveolar macrophages, which coexist with the resident macrophage population.

Recent single cell studies demonstrate that macrophage phenotypes in lung injury are highly heterogeneous. Rather than fitting a simple M1/M2 polarization model, macrophages display a spectrum of transcriptional programs reflecting inflammatory activation, phagocytic clearance, and tissue repair. Some macrophage subsets promote resolution by clearing apoptotic cells and secreting pro-repair mediators. Others produce profibrotic cytokines, including TGF-β and platelet derived growth factor (PDGF), which stimulate fibroblast activation.

Experimental models have shown that persistent monocyte derived macrophages can drive progressive lung fibrosis by maintaining a profibrotic signaling environment.

4. Resolution of Inflammation

Successful healing requires termination of the inflammatory response. Resolution is an active biological process rather than a passive decline in cytokine production. Several mechanisms contribute to this transition:

- Apoptosis and clearance of neutrophils
- Reprogramming of macrophages toward pro-resolution phenotypes
- Restoration of epithelial barrier integrity

Macrophage mediated efferocytosis is particularly important in terminating inflammation. Failure of this process leads to persistent inflammatory signaling and ongoing tissue injury.

5. Inflammation as a Driver of Fibrotic Remodeling

When inflammatory signaling persists, the lung microenvironment shifts toward fibroproliferation. Several pathways link inflammation to fibrotic remodeling:

- Sustained TGF-β signaling, which stimulates myofibroblast differentiation
- Continued monocyte recruitment, maintaining profibrotic macrophage populations
- Oxidative stress, which damages epithelial progenitor cells
- Mechanical stress, which activates fibroblast mechanotransduction pathways

These mechanisms highlight that inflammation is not merely an early phase of injury but can actively shape long-term structural remodeling.

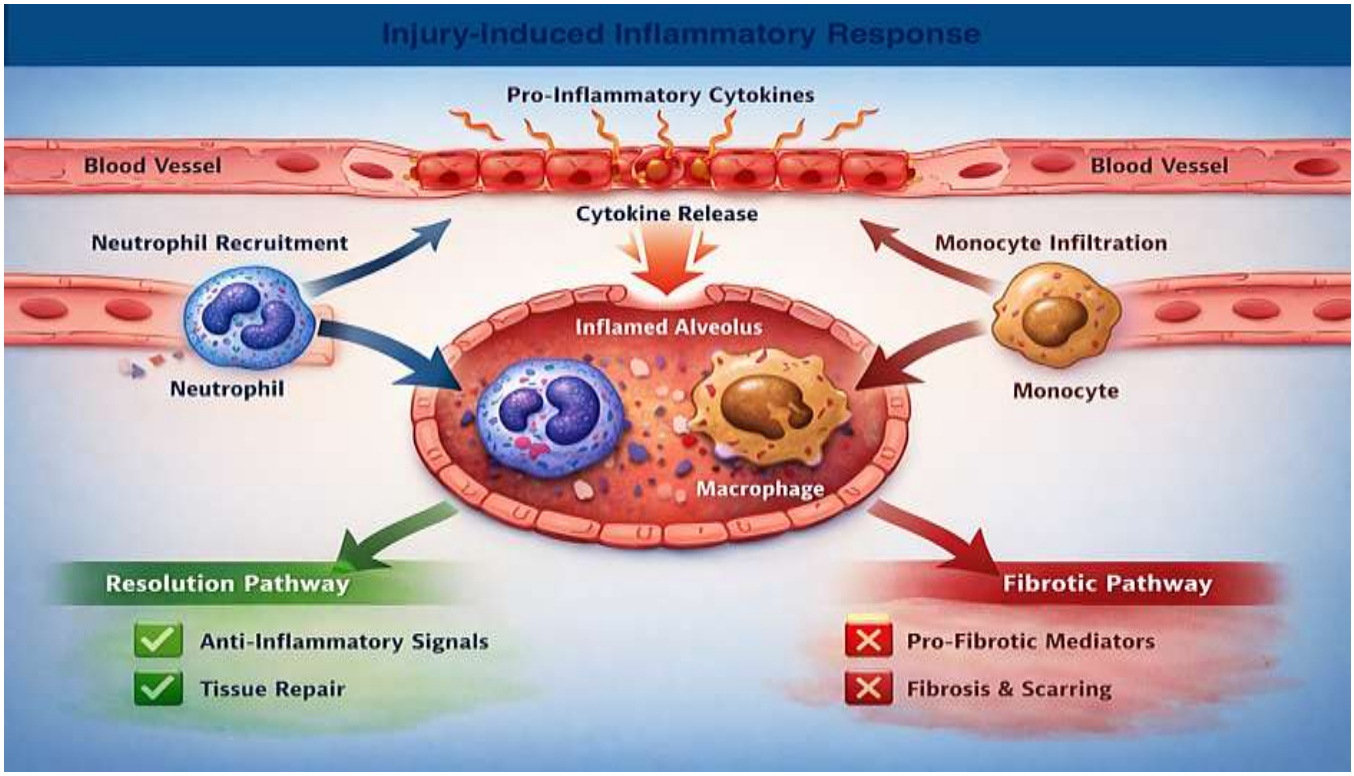

Figure 2: Injury-induced inflammation involves the release of pro-inflammatory cytokines which introduce various inflammatory cells, through mechanisms such as neutrophil recruitment and monocyte differentiation into macrophages. These cells can take two major pathways, either leading towards resolution versus maladaptive fibrotic pathways.

In summary, inflammation serves as both a protective response and a potential amplifier of lung injury. While early immune activation is essential for pathogen clearance and debris removal, prolonged or dysregulated inflammation disrupts epithelial regeneration and promotes fibrotic remodeling. Understanding this balance is critical for identifying therapeutic strategies that support resolution without impairing host defense.

Regeneration: Restoration of the Alveolar Epithelium

Following the initial inflammatory phase, successful lung healing requires restoration of the epithelial barrier and reestablishment of normal alveolar architecture. This regenerative process is centered on the proliferative and differentiation capacity of alveolar epithelial progenitor cells. Among these, alveolar type 2 (AT2) cells play a central role. When epithelial injury is limited and the microenvironment supports repair, AT2 cells proliferate and differentiate to restore the gas-exchanging surface. However, when regeneration is incomplete or dysregulated, abnormal epithelial states emerge that may predispose the lung to fibrotic remodeling.

1. Alveolar Type 2 Cells as Facultative Stem Cells

AT2 cells function as the principal progenitor population of the distal lung. Under homeostatic conditions, these cells maintain surfactant production and contribute minimally to epithelial turnover. After injury, however, AT2 cells rapidly enter the cell cycle and expand within damaged regions of the alveolus.

Lineage-tracing experiments in animal models have demonstrated that AT2 cells differentiate into alveolar type 1 (AT1) cells, which form the thin epithelial surface required for efficient gas exchange. This transition restores the structural integrity of the alveolar barrier and re-establishes normal diffusion capacity.

The regenerative capacity of AT2 cells depends on several regulatory signals. These pathways are tightly regulated within the alveolar niche and are influenced by neighboring fibroblasts, endothelial cells, and immune cells.

2. Transitional Epithelial Cell States

Recent advances in single cell transcriptomics have revealed that AT2-to-AT1 differentiation occurs through intermediate epithelial states. Among the most studied are KRT8-positive transitional epithelial cells, which appear transiently during lung repair.

These transitional cells exhibit gene expression signatures associated with cellular stress, cytoskeletal remodeling, and epithelial differentiation. Under normal regenerative conditions, this state is temporary, ultimately giving rise to mature AT1 cells. However, in conditions such as severe lung injury or chronic inflammation, transitional epithelial cells may persist.

Persistent transitional states have been observed in fibrotic lung disease and are thought to reflect incomplete epithelial differentiation. These cells produce profibrotic mediators and may contribute to fibroblast activation, linking defective regeneration with fibrotic progression.

3. Mechanotransduction and the Hippo Pathway

Mechanical forces within the lung strongly influence epithelial regeneration. Stretch generated by breathing and by regional changes in tissue stiffness regulates epithelial proliferation and differentiation.

A central mediator of this mechanosensitive signaling is the Hippo pathway, particularly the transcriptional regulators YAP and TAZ. Activation of YAP/TAZ promotes epithelial proliferation and supports regenerative responses after injury. Experimental studies demonstrate that loss of YAP/TAZ signaling impairs alveolar regeneration and leads to defective epithelial repair.

However, persistent or dysregulated activation of these pathways may also contribute to abnormal epithelial states and fibroblast activation, suggesting that mechanotransduction must be carefully balanced during the repair process.

4. Cellular Senescence and Impaired Regeneration

Age and genetic susceptibility influence regenerative capacity. Cellular senescence of epithelial progenitor cells reduces proliferative potential and impairs differentiation into functional AT1 cells.

Telomere shortening represents one of the most important biological mechanisms underlying this phenomenon. Mutations affecting telomerase components have been linked to familial pulmonary fibrosis and increased susceptibility to fibrotic remodeling following lung injury.

In this context, epithelial regeneration fails not because injury is excessive, but because progenitor cells cannot mount an adequate repair response.

5. Crosstalk with the Mesenchymal and Immune Microenvironment

Epithelial regeneration does not occur in isolation. Fibroblasts, endothelial cells, and immune cells collectively form the regenerative microenvironment that supports epithelial repair.

Fibroblast subsets adjacent to the alveolar epithelium produce growth factors that support epithelial proliferation. Endothelial cells contribute angiocrine signals that coordinate vascular and epithelial recovery. Macrophages also participate by releasing mediators that stimulate epithelial proliferation and remove apoptotic debris.

When this cellular crosstalk becomes dysregulated, regenerative signals can shift toward profibrotic pathways.

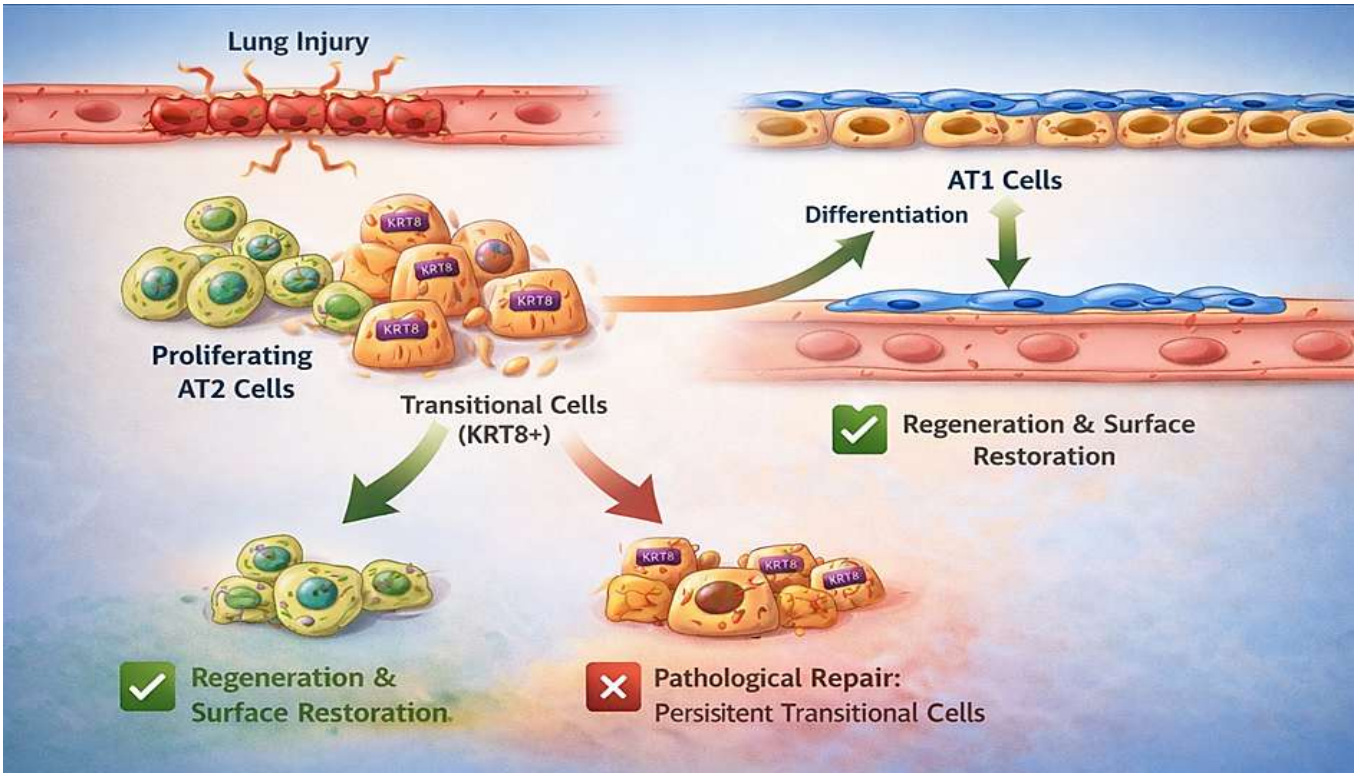

Figure 3: Following lung tissue injury, AT2 will proliferate in response and can differentiate into AT1 cells that restore the alveolar surface and allow for appropriate repair. In addition, there are transitional epithelial cells (KRT8+) that are usually temporary and eventually give rise to these AT1 cells. However, when they persist, they can release profibrotic mediators that prolong a pathologic state that lead to progressive and maladaptive fibrosis.

In summary, regeneration of the alveolar epithelium represents the central restorative process in lung healing. AT2 cells act as progenitors that replenish the epithelial surface through controlled proliferation and differentiation. When this regenerative program proceeds efficiently, normal lung structure can be largely restored. When it fails, the repair process becomes arrested, setting the stage for fibrotic remodeling.

Remodeling and Progression to Fibrosis

When epithelial regeneration fails to fully restore alveolar architecture, the lung enters a remodeling phase characterized by fibroblast activation, extracellular matrix deposition, and structural reorganization of the alveolar compartment. Remodeling is not inherently pathological; limited matrix deposition and structural reorganization are necessary components of tissue repair. However, when these processes become excessive or self-sustaining, remodeling progresses toward pulmonary fibrosis, leading to irreversible distortion of lung architecture and progressive impairment of gas exchange.

1. Fibroblast Activation and Myofibroblast Differentiation
Fibroblasts are the primary effector cells responsible for extracellular matrix production during lung repair. In the injured lung, fibroblasts are activated by cytokines and growth factors released from epithelial cells, macrophages, and platelets. Among these signals, transforming growth factor–β (TGF-β) plays a central role.

Under the influence of TGF-β and related signaling pathways, fibroblasts differentiate into myofibroblasts, a contractile cell type characterized by expression of α–smooth muscle actin and increased production of structural matrix proteins.

Myofibroblasts accumulate within injured regions and generate contractile forces that contribute to wound closure and matrix remodeling. In normal repair, these cells undergo apoptosis once tissue integrity is restored. In fibrotic lung disease, however, myofibroblasts can evade apoptosis through pro-survival pathways such as the anti-apoptotic BCL-2 family of proteins. These persistent cells continue to maladaptively deposit and modify extracellular matrix (ECM), leading to progressive architectural distortion.

2. Extracellular Matrix Deposition and Tissue Stiffness
Extracellular matrix proteins form the structural scaffold of the lung interstitium. During remodeling, activated fibroblasts increase production of collagen, fibronectin, and proteoglycans. While modest matrix deposition is necessary for structural stability, excessive accumulation leads to thickening of the alveolar septa and loss of alveolar compliance.

Importantly, the extracellular matrix is not simply a passive structural component. Changes in matrix composition and stiffness influence cellular behavior through mechanotransduction pathways. As

collagen accumulates and tissue stiffness increases, fibroblasts receive mechanical signals that further enhance profibrotic signaling, including activation of the TGF-β pathway.

This creates a positive feedback loop, in which matrix deposition promotes further fibroblast activation and fibrosis progression.

3. Epithelial–Mesenchymal Crosstalk

Interactions between epithelial cells and mesenchymal cells strongly influence the trajectory of lung remodeling. Injured epithelial cells release signals that regulate fibroblast behavior, while fibroblasts in turn influence epithelial differentiation.

Persistent epithelial stress responses can sustain fibroblast activation through production of TGF-β, connective tissue growth factor, and other profibrotic mediators. Conversely, activated fibroblasts can alter epithelial differentiation by modifying the extracellular matrix environment and by producing paracrine signaling molecules.

This bidirectional communication contributes to the self-perpetuating nature of fibrotic remodeling.

4. Cellular Senescence and Aging

Aging is a major risk factor for pulmonary fibrosis. Senescent epithelial cells and fibroblasts accumulate with age and display altered secretory profiles characterized by increased production of inflammatory and profibrotic mediators. This phenomenon, often referred to as the senescence associated secretory phenotype (SASP), can amplify fibrotic signaling within the injured lung.

Telomere shortening is one of the best characterized mechanisms linking aging to pulmonary fibrosis. Individuals with telomerase mutations exhibit impaired epithelial regeneration and increased susceptibility to fibrotic lung disease following injury.

In this context, fibrosis may reflect a failure of regenerative capacity rather than an excessive wound-healing response alone.

5. Mechanical Forces and Progressive Fibrosis

Mechanical stress within the lung further contributes to fibrotic progression. As extracellular matrix accumulates and lung compliance decreases, regional mechanical forces become increasingly heterogeneous. Areas of relatively preserved lung tissue experience greater mechanical stretch during ventilation, which can activate mechanosensitive pathways in epithelial cells and fibroblasts.

These mechanical signals reinforce profibrotic pathways, including activation of TGF-β and YAP/TAZ signaling, thereby linking structural remodeling to continued cellular activation.

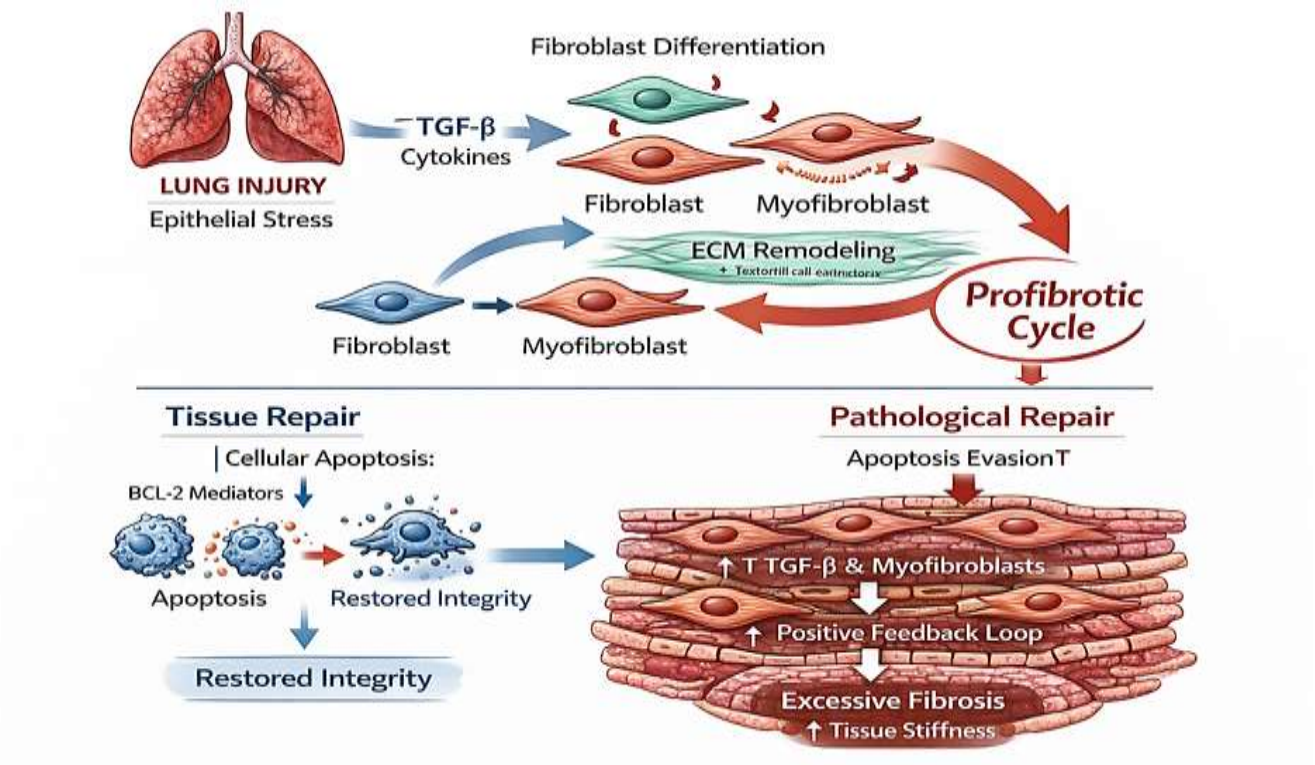

Figure 4: In response to lung injury and thereby epithelial stress, fibroblasts will differentiate into myofibroblasts that assist with extracellular matrix remodeling (ECM) via cytokines like TGF-β. Normally once tissue integrity is restored, then these cells will undergo apoptosis through BCL-2 mediators. However, pathological repair leads to these cells evading apoptosis and creating a positive feedback loop that continues to reinforce a profibrotic state and increase tissue stiffness.

In summary, remodeling represents the final stage of lung healing, in which structural repair either resolves or progresses toward fibrosis. Fibroblast activation, extracellular matrix accumulation, and mechanical feedback loops collectively determine whether lung architecture is restored or irreversibly altered. Persistent epithelial injury, aging-related regenerative impairment, and dysregulated immune signaling all increase the likelihood that repair transitions into progressive fibrotic disease.

Conclusion

Lung healing after injury is a dynamic and tightly regulated process that requires coordinated interactions among epithelial cells, immune cells, and mesenchymal populations. In the initial phase, disruption of the alveolar–capillary barrier triggers an inflammatory response aimed at clearing pathogens and removing cellular debris. When appropriately controlled, this inflammatory phase creates the conditions necessary for epithelial regeneration. Alveolar type 2 cells then proliferate and differentiate to restore the epithelial barrier, while the surrounding microenvironment gradually returns to homeostasis.

However, successful repair depends on the precise balance of these processes. Persistent inflammation, impaired epithelial regeneration, or dysregulated signaling between epithelial and mesenchymal cells can shift the repair trajectory toward maladaptive remodeling. In this setting, continued fibroblast activation and extracellular matrix deposition progressively alter lung architecture, leading to irreversible fibrosis and impaired gas exchange. Increasing evidence indicates that this transition reflects not only excessive wound healing but also failure of epithelial regenerative programs, particularly in the context of aging, cellular senescence, and genetic susceptibility.

For clinicians, understanding the biological continuum from injury to fibrosis has important therapeutic implications. Strategies that minimize epithelial injury, limit excessive inflammation, and preserve regenerative capacity may influence long-term outcomes after acute lung injury. At the same time, advances in molecular and single-cell technologies are beginning to clarify the cellular states and signaling pathways that determine whether lung repair resolves or progresses to fibrosis. Continued integration of these mechanistic insights with clinical practice will be essential for developing interventions that promote effective regeneration while preventing chronic structural remodeling of the lung.

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