Cell Regeneration in Lung Injury

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The acute respiratory distress syndrome (ARDS) is a lethal inflammatory disorder of the lung. Its incidence is estimated at 75 cases per 100,000 population and appears to be increasing [1]. Even with optimal treatment, mortality is about 30% [1–3]. As such, ARDS represents a major public health problem. The effects of two recent crises created by unusual viral infections of the respiratory tract – the severe acute respiratory syndrome (SARS) epidemic caused by the novel SARS coronavirus [4, 5] and the bird flu [6] highlight the importance of research into ARDS. Both viruses cause an ARDS-like picture. Because lung repair and regeneration contribute substantially to the pathophysiology of ARDS, understanding these processes is essential [7]. This chapter focuses on specific cell populations and markers involved in cell division and regeneration. In addition, a brief review of two pathways intimately associated with cell division is provided because of their potential for pharmacologic manipulation.

The Alveolar Epithelium in Acute Lung Injury

ARDS is primarily a disease of disordered inflammation. Early ARDS is characterized by increased inflammation where alveolar epithelial cells are damaged and ultimately may be destroyed [1–3]. While some mechanisms contributing to the pathophysiology of ARDS have been identified, most are poorly understood. As a result, treatment is largely supportive. A better understanding of the fundamental biological changes leading to ARDS would be of scientific and therapeutic value. The magnitude of injury to the alveolar epithelial barrier is one of the most important determinants of the severity of lung injury [8]. Similarly, early repair of epithelial injury may be a major determinant of recovery. Most recent therapeutic approaches were developed to attenuate pulmonary inflammation and thus minimize the initial injury [8]. Unfortunately, specific interventions to accelerate alveolar epithelial repair do not exist. This reflects our limited understanding of the cellular mechanisms that modulate alveolar epithelial repair in ARDS.

Histological sections from patients dying of ARDS and from animal models of the disease demonstrate that the first abnormality is interstitial edema. This is followed by severe damage that is characterized primarily by extensive necrosis of alveolar type I (ATI) cells [9]. Pathological examination of lung tissue from patients with SARS was similar to changes seen in established ARDS. This included diffuse alveolar damage, desquamated epithelial cells, ATII hyperplasia, fibrin and collagen deposition in the alveolar spaces, and a loss of the normal barrier crucial for gas exchange [5, 10–13]

Cell regeneration is a fundamental biological response to cell damage. Through adult life, multicellular organisms must generate new cells to maintain the structure and function of their tissues [14]. This is especially important in the lung. The adult lung is a vital and complex organ that normally turns over slowly. Nevertheless, it is able to respond to specific injuries that mimic damage caused by environmental or infectious agents [15]. In most cases, pulmonary injury predominantly affects ATI cells. These highly differentiated and flat cells facilitate gas exchange. In contrast, the cuboidal, metabolically-active ATII cells that produce surfactant and other products essential to pulmonary function may be relatively spared. Following injury, regeneration of alveolar epithelial cells proceeds via an organized paradigm where ATII cells and other specific stem cells appear to function as progenitor cells for ATI cells [16–17] (Fig. 1). Most research in ARDS has focused on the finding that ATII cells

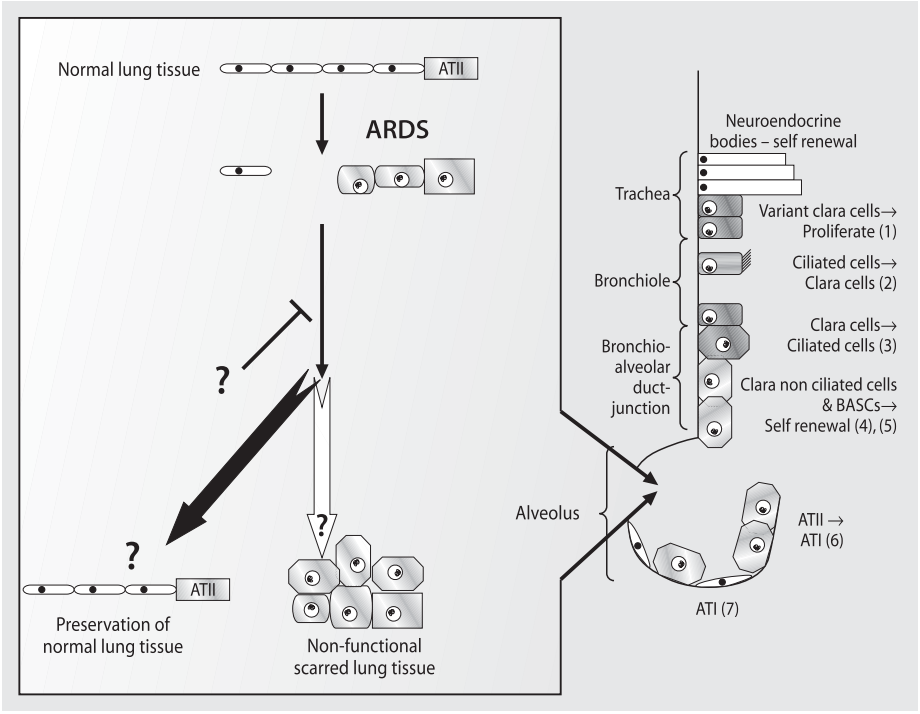

Fig. 1. Right panel: Cell populations participating in lung regeneration. In the trachea, variant Clara cells (1) can be found adjacent to neuroendocrine bodies. Within proximal bronchioles, two types of cells can transdifferentiate. Ciliated cells may proliferate and transdifferentiate into Clara cells after injury (2) while Clara cells may proliferate after injury and give rise to ciliated cells (3). At the bronchioalveolar duct junction (BADJ) between the conducting and respiratory epithelium, columnar Clara cells (4) can serve as progenitors. A sub-population of Clara cells termed bronchioalveolar stem cells (BASCs) (5), retains features of stem cells and may also participate in lung repair. In the alveolus, ATII cells (6) give rise to ATI cells (7) after injury. Left Panel: Following lung injury ATII cells may reenter the cell cycle, differentiate into ATI cells and spread along alveolar septa. This results in coverage of denuded basement membrane and re-establishment of epithelial continuity. In severe inflammation or pulmonary fibrosis, however, proliferation of ATII cells may become excessive. This can prevent appropriate replacement of ATI cells and lead to fibrosis and scarring. The precise control mechanisms and pathways involved in these processes are unknown. Modified from [14] with permission

reenter the cell cycle, differentiate into ATI cells and spread along alveolar septa. This results in coverage of denuded basement membrane and re-establishment of epithelial continuity [16, 18, 19]. In severe inflammation or pulmonary fibrosis, however, proliferation of ATII cells may become excessive (Fig 1). This can prevent appropriate replacement of ATI cells and lead to fibrosis and scarring [19, 20]. In such a situation, the fibrinous alveolar exudate characteristic of acute lung injury (ALI) will be covered by the migrating ATII cells. This transforms the intra-alveolar debris into interstitial tissue and stimulates fibrosis [21 – 23]. The significant morbidity and mortality associated with these pathological changes accentuates the importance of deciphering the mechanisms involved in cell division, repair and differentiation.

The Cell Cycle

For all living eukaryotic organisms it is essential that the different phases of the cell cycle be precisely coordinated and that one phase be completed before the next phase is entered (Fig 2). In the first phase, G1, the cell enlarges. When it has reached

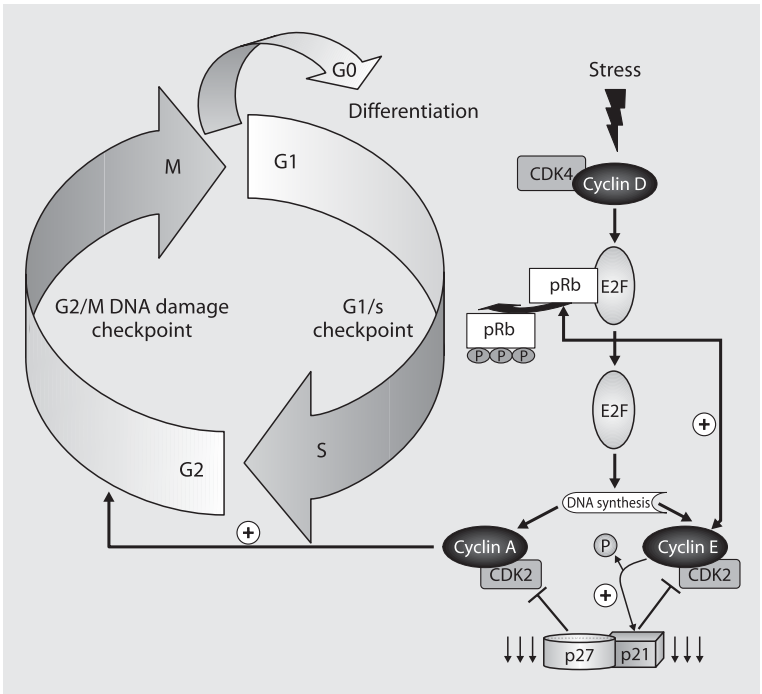

Fig. 2. The E2F-retinoblastoma (Rb) cell signaling pathway controlling the G1/S restriction point of proliferating cells. Passage through the restriction point and transition to S phase is triggered by the activation of the cyclin D1/cdk4 complex. This phosphorylates Rb. Phosphorylated Rb dissociates from E2F and is degraded further by the proteasome. E2F binds to the chromosome and initiates DNA replication. Cyclin E/cdk2 accumulates during late G phase and triggers passage into S phase. The entire genome is replicated during the S phase. Cyclin A/cdk2 accumulates during S phase and activates transition to the G2 phase. This results in inhibition of DNA replication, cell growth and new protein synthesis

a certain size, it enters S phase, in which DNA is replicated. This is followed by the G2 phase, where there is an internal check to assure that DNA-replication is completed and that the cell is prepared to divide. Finally, in the mitosis or M phase, chromosomes separate and cell division occurs. After M phase, most cells exit the cell cycle and enter a resting stage [G0]. However, some re-enter the cycle and remain in the G1 phase for a prolonged period, awaiting a signal to proceed on to the S phase. This resting point in the G1 phase is often referred to as the 'G1 restriction point'. Cell division is initiated when the integration of diverse metabolic, stress and environmental signals stimulate a transition past the G1 restriction point and facilitate entry into S phase [24].

Several pathways control pulmonary cell replication at the G1 restriction point. We will briefly describe two major pathways: E2F-retinoblastoma (Rb) and Wnt/β-catenin. These pathways may prove to be important sites for future pharmacological interventions.

The E2F-Rb pathway

The E2F-Rb pathway is critical in controlling progression beyond the G1 restriction point (Fig. 2) [25, 26]. Passage through the restriction point and transition to S phase is triggered by the activation of the cyclin D1/cdk4 complex that phosphorylates Rb. Phosphorylated Rb dissociates from E2F. E2F binds to the chromosome and initiates DNA replication. Cyclin E/cdk2 accumulates during late G phase and triggers the passage into S phase. The entire genome is replicated during S phase. Cyclin A/cdk2 accumulates during S phase and its activation triggers the transition to G2, a phase characterized by the accumulation of cyclin B/cdc2, which results in the inhibition of DNA replication, cell growth and new protein synthesis [26, 27]

The Wnt/βcatenin Cell Signaling Pathway

The Wnt/β catenin cell signaling pathway has been shown to be fundamental for cell division, regeneration, and differentiation processes [28]. Within this pathway, β-catenin is a key effector of the Wnt signaling pathway (Fig. 3), and persists as an important regulator of homeostasis in adult self-renewing tissues. β-catenin has been shown to participate in signal transduction in epithelial cells. Specifically, activation of β-catenin results in a loss of differentiation and trans-differentiation of mammary epithelial cells into epidermis-like structure [29]. Others have shown that the Wnt/β-catenin cell signaling pathway is activated in idiopathic pulmonary fibrosis [30]. Further, β-catenin has been shown to regulate differentiation of respiratory epithelial cells *in vivo*. An activated form of β-catenin was expressed in respiratory epithelial cells of the developing lung. Activation of β-catenin caused ectopic differentiation of ATII-like cells in conducting airways, goblet cell hyperplasia, and airspace enlargement, demonstrating a critical role for the Wnt/β-catenin signal transduction pathway in the differentiation of the respiratory epithelium in the postnatal lung [31].

Cell Populations Participating in Lung Regeneration

Stem cells are cells capable of limited self-renewal. They can develop into more differentiated cell types [32]. Stem cell turnover is relatively slow, allowing them to act

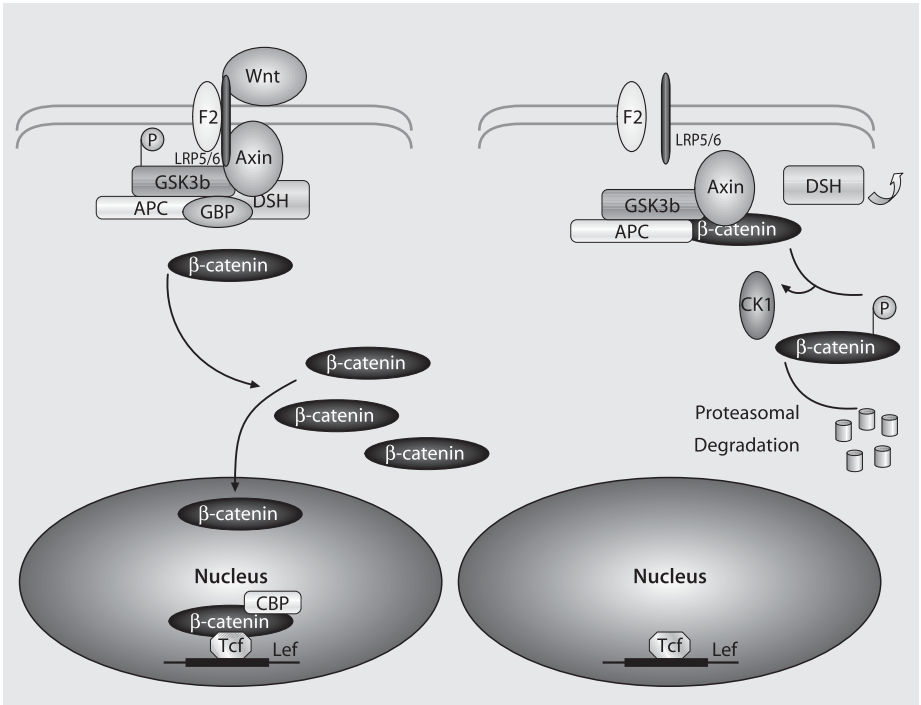

Fig. 3. Cell replication at the G1 restriction point-Wnt/β-Catenin cell signaling pathway. Left panel: Wnt-stimulation leads to reduction of GSK-3β kinase activity via phosphorylation. As a result, β-catenin is retained in the cytoplasm. Once β-catenin accumulates it can further translocate to the nucleus. In the nucleus, β-catenin binds to Tcf/Lef and acts as a co-activator to stimulate transcription of target genes such as *c-myc* and Cyclin D1. This facilitates cell proliferation. Right panel: in the absence of Wnt activation, *Dsh*, through its receptor *frizzled*, causes GSK-3β dissociation from Axin**.** Axin and adenomatous polyposis coli (APC) gene products serve as a scaffolding for phosphorylation of β-catenin by the enzyme GSK-3β. The phosphorylated form of β-catenin is targeted for ubiquitination and proteasomal degradation. This prevents transcription of β-catenin target genes**.**

as a source for differentiated cells throughout the lifespan of the organism [33]. Embryonic stem cells are divided from the inner cell mass of the blastocyte and are considered 'totipotent' in that they can regenerate all three germ layers of an organism. In contrast, adult stem cells are considered multi-or 'unipotent', able to give rise to one or several mature cell types [33, 34]. Two major categories of tightly regulated adult stem cells have been described: The 'dedicated' stem cells capable of long term self renewal and the transient amplifying (TA) daughter cells characterized by a high rate of proliferation. TA cells can self-renew over a short period [14, 35]. In addition, adult stem cells, called 'progenitor cells', are found in a number of adult tissues, including the lungs [33, 34, 36, 37], where constant exposure to potential toxic agents and pathogens in the environment may require that cells regenerate rapidly and effectively. These progenitor cells are patterned very early in embryogenesis [33, 34]. There is evidence that some differentiated epithelial cell types can act as progenitor cells and proliferate and 'transdifferentiate' in response to specific conditions [14].

The pulmonary tree contains cells with potential stem cell properties in distinct anatomical regions of the respiratory tree and lung [38, 39]. These include the submucosal gland ducts and intercartilagenous region of the tracheobronchial tree, neuroepithelial bodies in the bronchioloes, and the bronchoalveolar duct junctions [38, 39]. In the trachea and bronchioles, secretory progenitor cells can be found. Immunostaining for the nuclear proliferative marker, Ki67, expressed in proliferating cells, has been shown in human proximal airways to correlate with the most highly proliferative cells [40]. Within the proximal area, ciliated Clara cells are present in small numbers adjacent to neuroendocrine bodies. Non-ciliated, columnar Clara cells located at the junction between the conducting and respiratory epithelium (bronchioalveolar duct junction [BADJ]) label with bromodeoxyuridine (BrdU, a thymidine analog incorporated into DNA during the S phase). Such label retaining cells could repair the tracheal airway epithelium after polidocanol detergent or inhaled SO_2 injury [36]. Another mouse model of lung injury using naphthalene inhalation resulted in loss of most of Clara cells of the BADJ area. However, these cells can be divided into two distinct populations, based on their susceptibility to naphthalene injury [39]. One sub-population of Clara cells retains features of stem cells. This regional pulmonary stem cell population was termed bronchioalveolar stem cells (BASCs) [39]. These cells, identified by a dual expression of the Clara cell secretory protein (CCSP) and surfactant protein-C (SP-C) [39], are resistant to bronchiolar and alveolar damage and proliferate during epithelial cell renewal.

Circulating progenitor cells also may have a role in lung repair. Recently, one distinct population of blood-borne, mesanchymal stem cells was found to be associated with engraftment of donor derived ATII cells [41]. Thus use of exogenous cells to supplement the regenerative process in the lung may be feasible.

Type II pneumocytes also may function as stem cells. ATII cells have been shown to self renew and to give rise to ATI cells after lung injury [32, 42]. This ATII progenitor function may depend on the nature of the airway injury and the microenvironment [32, 42]. Specifically, there appear to be two subpopulations of ATII cells. These are distinguished by expression of a specific marker. Hyperoxic injury in rats induces expression of E-cadherin in some ATII cells [43]. This E-cadherin positive subpopulation has minimal levels of telomerase activity, indicating a low proliferative index. In contrast, the E-cadherin negative subpopulation expresses high levels of telomerase activity and proliferates well in culture. Several well differentiated cell lines in the lung can undergo 'transdifferentiation'; these include the Clara cells that differentiate into ciliated cells and the ATII cells that differentiate into ATI cells.

Cellular Markers and Factors Regulating Lung Epithelial Repair

Accumulated evidence suggests that epidermal growth factor (EGF), transforming growth factor-β (TGF-β) and the related receptor, epidermal growth factor receptor (EGFR), may regulate epithelial repair *in vivo* and *in vitro*. TGF-β is elevated in pulmonary edema fluid from patients with ARDS and has been shown to induce alveolar epithelial repair *in vitro* [8]. Other studies have reported an increased concentration of cytokines (tumor necrosis factor [TNF]-α, interleukin [IL]-6, IL-8, and IL-10) in the broncholaveolar lavage (BAL) fluid of patients with acute phase ARDS [44]. Among the cytokines implicated in lung fibrosis, TNF-β, a multifactorial peptide capable of enhancing mesenchymal cell proliferation and extracellular matrix synthesis [45], plays a fundamental role. The presence of receptors for this protein

after lung injury may contribute to the upregulation of TGF-β expression [46]. Additionally, TGF-β has been associated with the pathogenesis of pulmonary fibrosis [45].

A variety of pro-inflammatory cytokines have been shown to upregulate keratinocyte growth factor (KGF) and hepatocyte growth factor (HGF). The roles of these proteins have been investigated widely and it appears that they play an important role in both normal lung development and in injured lung repair. Indeed, KGF and HGF may have therapeutic potential in lung disease. Endogenous KGF plays an important role in epithelial repair. Studies in animal models of hyperoxia, demonstrated a 12-fold increase in KGF mRNA [47]. This increase was followed by increased ATII cell proliferation, suggesting that KGF stimulates ATII hyperplasia [47]. Endogenous HGF from both bronchial epithelial cells and alveolar macrophage participates in the reparative response to lung injury [48]. It is of interest that the lung may be a source of HGF after injury to other organs. Six hours after partial hepatectomy, HGF levels within the lung were increased [49]. Similar elevations in lung, liver, and kidney were noted in acute pancreatitis [49]. These findings suggest that the lungs serve as an endocrine organ, contributing to organ repair and regeneration by excreting HGF [50]. A feedback mechanism may be operative as ATII cells express the c-met receptor for HGF [50].

IL-6 plays a key role in liver regeneration [51]. For example, this cytokine appears to initiate HGF synthesis [52]. Absence of IL-6 has been associated with failed regeneration in septic liver injury [53]. IL-6 is elevated in lung injury and also may impact on repair mechanisms in chronic pulmonary inflammatory disorders. Previously published studies have examined the role of IL-6 on proliferation and cell-cycle kinetics in primary human lung fibroblasts obtained from patients with idiopathic pulmonary fibrosis. IL-6 was mitogenic for idiopathic pulmonary fibrosis fibroblasts. This effect appears to involve a sustained activation of mitogen-activated protein kinase (MAPK) that, in turn, inhibited the production of $p27^{Kip1}$. This allowed activation of cyclin D_1 and hyperphosphorylation of Rb protein [54] (Fig 2). In an ozone/cigarette smoke model of lung injury, BrdU labeling within terminal bronchiolar epithelium and proximal alveolar regions was significantly reduced in IL-6 knowck-out mice compared to IL-6 sufficient mice. Further, CCSP abundance was markedly reduced in the terminal bronchiolar epithelium of these IL-6 knock-out mice [55].

Pulmonary surfactant forms the surface-active film that is crucial for normal lung function. This substance consist of complexes of phospholipids and four protein components known as surfactant-associated proteins [1, 56]. Among them, SP-A has important autocrine effects on cells of the lung epithelium. ATII cells produce and secrete pulmonary surfactant proteins. SP-A signals through an ATII cell surface receptor and regulates anti-apoptotic gene expression. Hence, surfactant proteins may represent a local regulatory system for cell regeneration.

Conclusion

In ARDS, cell proliferation may be either beneficial or detrimental (Fig. 1). Early in the disease process, when loss of pulmonary epithelial cells may contribute to pathology, enhancing cell division may be of value. However, cell division also may increase vulnerability to oxidative stress-induced DNA damage. In contrast, in the fibroproliferative phase of the disease, cell overgrowth contributes to pathological

scarring and fibrosis. Hence, increased knowledge on the mechanisms and pathways of cell division and regeneration may stimulate the development of novel pharmacological interventions. Due to the complex nature of the mechanisms and time course involved in the pathophysiology of ARDS, understanding of the role of ARDS-associated cellular proliferation is essential.

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