Interstitial lung disease (ILD) is characterized by alveolar and interstitial inflammation, followed by the progressive derangement of alveolar architecture and deposition of extracellular matrix components. The disease is initiated by an unknown alveolar insult, which is followed by the influx of inflammatory cells to the lung. This recruitment phase results in a several fold increase in all cell types within the airspace, including neutrophils, eosinophils, lymphocytes and macrophages. In addition, substantial interstitial inflammation is apparent, consisting predominantly of newly recruited monocytes and lymphocytes. Alveolar and interstitial inflammation is followed by the loss of type I epithelial cells and endothelial cells, proliferation of type II cells, and expansion of the pulmonary interstitium via the proliferation of fibroblasts and deposition of collagen and other extracellular matrix components [1, 2].

Alveolar and interstitial inflammation in ILD is essential to the development of lung injury and subsequent fibrosis. Neutrophils and neutrophil products have been identified in increased amounts in the airspace of patients with ILD and in animal models of lung fibrosis [3]. These cells induce parenchymal injury by producing toxic radical oxygen species, and by secreting a variety of proteolytic enzymes, including elastase, collagenase, and other neutral proteases. Recruited monocytes contribute to pulmonary inflammation by elaboration of oxygen radical species, proteolytic enzymes, and factors that attract additional inflammatory cells. T-cells and B-cells, like monocytes, are present in increased numbers in the lung interstitium in ILD [4], and the recruitment of lymphocytes to the lung has been shown to precede the development of pulmonary fibrosis in models of lung fibrosis [5]. Furthermore, the development of pulmonary fibrosis in mice can be attenuated or completely abrogated by the selective depletion of CD4+ T-cells, CD8+ T-cells, or both [6]. Activated T-cells produce a number of cytokines that can modulate lung inflammation and fibrosis, including interleukin (IL)-2, IL-4, interferon-gamma (IFN-γ), and chemotactic factors both for leucocytes and fibroblasts. B-cells also contribute to the development of cellular activation and fibrosis in ILD via the overzealous secretion of immunoglobulin, leading to immune complex formation and deposition.

The immunopathological expression of ILD involves complex and dynamic interplay between immune effector cells, including neutrophils, macrophages and lymphocytes, and cellular constituents of the alveolar-capillary membrane, most importantly lung fibroblasts. The interaction of these lung cells and the mediators that they produce culminates in parenchymal cell injury, collagen deposition, and, ultimately, end-stage fibrosis. While insults that trigger the development of various forms of ILD differ, cellular mechanisms by which inflammatory leucocytes are recruited to the lung in ILD have not been fully characterized. A number of factors that possess leucocyte chemotactic activity have been identified in the lung of patients with ILD, including platelet-derived growth factor (PDGF) [7, 8], fibronectin [9], and transforming growth factor-beta (TGF-β) [10]. The alveolar macrophage is almost certainly involved in recruitment of inflammatory cells, as this cell produces a variety of specific and nonspecific leucocyte chemoattractants. Alveolar macrophages isolated from patients with ILD have been shown to spontaneously express several leucocyte chemotactic factors, including complement factor 5α (C5α) and leukotriene B4 (LTB4). In addition, interstitial and alveolar macrophages from patients with ILD constitutively express macrophage inflammatory protein-1α (MIP-1α) and monocyte chemoattractant protein-1 (MCP-1), and cells other than lung macrophages contribute to the production of these leucocyte chemoattractants [11–13]. The latter leucocyte chemoattractants belong to the supergene families of chemotactic and activating cytokines, which include CXC, CC and C chemokines [14–28]. These chemokines may be critically involved in the migration and activation of leucocytes in ILD.

The human CXC, CC and C chemokine families of chemotactic cytokines are three closely related polypeptide families that behave, in general, as potent chemotactic factors either for neutrophils, mononuclear cells or lymphocytes, respectively [14–28]. These cytokines, in their monomeric form, range from 7 to 10 kDa and are characterized by basic heparin-binding proteins. The chemokines display highly conserved cysteine amino acid residues: the CXC chemokine family has the first two NH2-terminal cysteines separated by one nonconserved amino acid residue, the CXC cysteine motif; the CC chemokine family has the first two NH2-terminal cysteines in juxtaposition, the CC cysteine motif; and the C chemokine has one lone NH2-terminal cysteine amino acid, the C cysteine motif (table 1). CXC chemokines are clustered on human chromosome 4, and exhibit 20–50% homology at the amino acid level. CC chemokines are clustered on human chromosome 17, and exhibit 28–45% homology at the amino acid level. The one
The CC chemokine family includes many cytokines that are produced by a variety of cell types. These cytokines are important in the regulation of immune responses and inflammatory processes. The production of CC chemokines is regulated by various signals, including cytokines, chemokines, and growth factors. The expression of CC chemokines is regulated by transcription factors, such as AP-1, NF-κB, and NF-IL-6/C/EBPβ. The expression of CC chemokines is also regulated by post-transcriptional mechanisms, such as mRNA stability and translation. The expression of CC chemokines is important in the regulation of immune responses and inflammatory processes. The expression of CC chemokines is regulated by various signals, including cytokines, chemokines, and growth factors. The expression of CC chemokines is regulated by transcription factors, such as AP-1, NF-κB, and NF-IL-6/C/EBPβ. The expression of CC chemokines is also regulated by post-transcriptional mechanisms, such as mRNA stability and translation. The expression of CC chemokines is important in the regulation of immune responses and inflammatory processes.
et al. [34] have demonstrated that RANTES is not selective for CD45RO+ T-cells, and can induce chemotaxis of both CD45RO+ and CD45RA+ T-cells in vitro. Moreover, a number of studies have clearly demonstrated that RANTES is not a selective chemoattractant for T-cells, and that it has the ability in vitro to induce the chemotaxis of other leucocytes, including basophils, eosinophils, mast cells, dendritic cells, monocytes and B-cells [23].

Moreover, RANTES is not the only CC chemokine with the ability to recruit T-cells; the majority of CC chemokines have the ability to recruit these cells, including MCP-1 to MCP-4, MIP-1α, MIP-1β and I-309 [23]. While RANTES can induce migration of eosinophils, other CC chemokines have been found to be chemoattractants for eosinophils, including eotaxin, MIP-1α, MCP-3 and MCP-4 [23, 35]. This suggests a tremendous redundancy in the ability of CC chemokines to induce chemotaxis of T-cells or eosinophils. Furthermore, the discovery of at least five different CC chemokine receptors (CCR1–CCR5) [35], of which RANTES may potentially interact with four [35], suggests that the redundancy of CC chemokine-induced chemotaxis is now more complex; depending not only on the production of the ligand, but also on the pattern of expression and cellular sources of specific CCRs.

Thus, the study by Petrek et al. [31] provides additional important information on the role of chemokines in the recruitment of leucocytes in ILD, and underlines the need to further understand the biology of these cytokines and their receptors in models of pulmonary fibrosis. This strategy can then be used for translational and interventional approaches, to alter the pathogenesis of these often lethal pulmonary diseases.

References


