—Review—

Smoking-Related Interstitial Fibrosis and Smoker's Macrophages

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Smoking-related interstitial lung diseases (SRILDs) are a group of heterogeneous diffuse pulmonary parenchymal diseases associated with tobacco exposure. Smoking-related interstitial fibrosis (SRIF) is relatively recent, a pathologically defined form of SRILDs. SRIF is characterized by the accumulation of macrophages in the alveolar spaces, which is associated with interstitial inflammation and fibrosis. The macrophages frequently contain light brown pigment and are called 'smoker's macrophages'. Patients with SRIF who have clinical evidence of interstitial lung disease are most commonly relatively young, heavy smokers with abnormalities on chest computed tomography showing ground-glass opacities, peripheral consolidation, and reticulation. Although SRIF is caused by cigarette smoking, the exact pathophysiological mechanisms by which smoking causes this type of interstitial fibrosis remain unknown. The degree of fibrosis and appearance of macrophage aggregates are important points of distinction when evaluating and diagnosing SRIF. Macrophage heterogeneity, particularly the activation and function of monocyte-derived alveolar macrophages (Mo-AMs) and interstitial macrophages (IMs), has important implications for the pathogenesis of SRIF and developing treatments. Further researches focused on smoker's macrophages are needed to understand of the pathogenesis of SRIF.
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Key words: smoking-related interstitial fibrosis, smoking-related interstitial lung disease, interstitial lung disease, smoker's macrophage, alveolar macrophage

Introduction

Interstitial lung diseases (ILDs) are a heterogeneous group of parenchymal lung disorders of unknown etiology. The relationship between smoking and a broad group of ILDs has been recognized increasingly, with a significant tendency towards overlapping and co-existing interstitial lung injury and emphysema patterns. Smoking-related interstitial lung diseases (SRILDs) develop because of smoking. Although respiratory bronchiolitis-interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP), and Langerhans cell histiocytosis (LCH) are associated with tobacco use, their role and impact on idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE), and connective tissue disease-related interstitial lung diseases remain ambiguous[1]. Thus, the relatively new umbrella term, smoking-related interstitial fibrosis (SRIF), has gained the acceptance of clinicians. The term SRIF was first introduced in 2010 by Katzenstein et al.[2] after a review of extensively sampled lobectomy specimens from current and former smokers. In its initial description, the histologic hallmark of SRIF was expansion of alveolar septa by a distinctive form of eosinophilic, paucicellular fibrosis composed of "ropey-appearing" collagen. Some reports describe identical histologic findings using alternative terminology such as "respiratory bronchiolitis-associated interstitial lung disease with fibrosis"[3], "respiratory bronchiolitis with fibrosis"[4], and "airspace enlargement with fibrosis"[5]. The 2013 American Thoracic Society and European Respiratory Society statements classified RB-ILD and DIP as smoking-related idiopathic interstitial pneumonia[6]. Recent findings have proposed SRIF as an

umbrella concept that includes a mixture of pathologies, including elements of LCH, IPF, CPFE, and air space enlargement with fibrosis[7]. The likely interconnection between the mechanisms involved in inflammation and pulmonary fibrosis often results in an overlap of clinical, radiological, and histological features in the same patient, which can lead to unclassifiable patterns of ILD. SRIF attempts to encompass diseases that have been classified as separate ILDs. Occasionally, DIP, IPF, and CPFE have overlapping features, such as a slowly progressive clinical course, radiological findings (ground-glass opacities, peripheral consolidation, and reticulation), and various degrees of fibrosis with smokers' macrophages. Additionally, cases that do not fit well within these diseases may be more appropriately diagnosed as SRIF. Therefore, in the presence of progressive exertional dyspnea and cough associated with pulmonary functional limitation, it is important to accept the mix of existing disease categories and diagnose SRIF while considering where the patient is in the pathological process.

Although SRIF is caused by cigarette smoking, the exact pathophysiological mechanisms by which smoking causes this type of interstitial fibrosis remain unknown. A clue to this is the presence of smoker's macrophages that accumulate in the alveolar space and interstitium of SRIF patients. Alveolar macrophages (AMs) are the most abundant immune cells present under homeostatic conditions, representing 90% of the alveolar immune cells. AMs play an important gatekeeping role in innate immunity within the respiratory tract[8] and perform airway surveillance, immune regulation, and surfactant homeostasis[9]. Cigarette smoke contains over 4,500 different substances with toxic, mutagenic, and carcinogenic effects, including nicotine, tar, ammonia, carbon monoxide, et al[10]. Smoking causes oxidative stress, resulting in chronic inflammation and recruitment of inflammatory cells to the airways through the activation of epithelial cells, AMs, neutrophils, and T lymphocytes[11]. This could be due to the abnormal production from alveolar cells of factors that recruit macrophages, as well as to increased survival and reduced macrophage apoptosis[12]. The different types of pulmonary macrophages and their roles in lung diseases have attracted attention in recent years. AMs, including tissue-resident alveolar macrophages (TR-AMs) and monocyte-derived alveolar macrophages (Mo-AMs), as well as interstitial macrophages (IMs) are the major macrophage populations in the lung and have unique characteristics in both steady-state conditions and disease states[13]. The different characteristics of these three

types of macrophages determine the different roles they play in the development of disease. The mechanisms by which smoking influences alveolar macrophages, including recruitment, phenotype, immune function and homeostasis, should be evaluated and explored in relation to fibrosis, which may help to identify understanding the pathogenesis of SRIF and the development of therapeutic strategies.

All procedures were performed in accordance with the Declaration of Helsinki of 1964 and later versions. Written informed consent was obtained from patients for inclusion in this manuscript.

Smoking-Related Interstitial Fibrosis (SRIF) Histopathology

SRIF is most encountered in upper lobe sections as an incidental finding in current or former smokers undergoing lung wedge biopsy or lobectomy for other reasons[2,5]. SRIF is characterized by alveolar septal thickening with a distinctive pattern of paucicellular, dense, eosinophilic collagen that has a ropy or waxy quality and is accompanied by emphysematous changes and respiratory bronchiolitis. Hypertrophic smooth muscle bundles may accompany fibrosis and, at times, predominate. Fibrosis is limited to the subpleural and peribronchiolar interstitium and does not increase to the level of diffuse chronic interstitial pneumonia. Although SRIF is associated with varying degrees of airspace enlargement, the lung architecture is relatively preserved without significant architectural distortion in the form of scarring or honeycomb change[14]. The pathological findings of a typical SRIF reported by Katzenstein[15] has been shown in **Figures 1~3**.

Separating SRIF from usual interstitial pneumonia (UIP) and non-specific interstitial pneumonia (NSIP) can be difficult in small biopsies and may require the incorporation of ancillary data. Both SRIF and UIP have a subpleural distribution; however, SRIF shows a predilection for the upper lobes, whereas UIP is commonly characterized by predominantly lower lobe involvement with traction bronchiectasis and honeycomb changes. Although fibroblastic foci can occasionally occur in SRIF, their presence should raise concerns about UIP and prompt careful review of available clinical and radiologic data to assess the presence of clinically significant diffuse interstitial lung disease[14].

Along with fibrosis, another important feature of SRIF is the filling of airspaces by numerous pigmented macrophages, so called smoker's macrophages. It makes sense to explain the importance of macrophages in the patho-
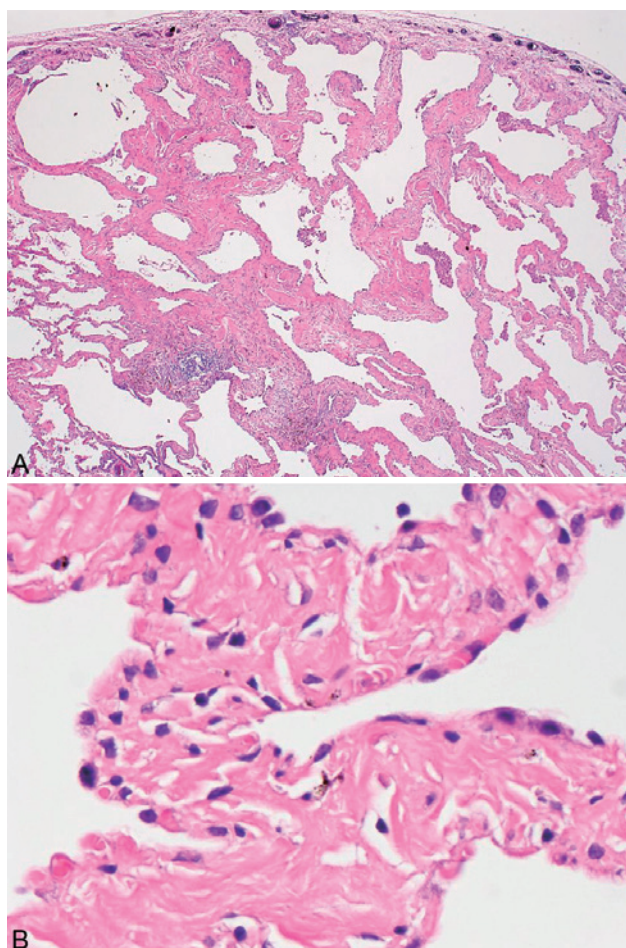
Fig. 1 (A) Low magnification view of smoking-related interstitial fibrosis (SRIF) showing the characteristic marked thickening of alveolar septa in subpleural parenchyma associated with emphysema. Clusters of pigmented macrophages indicative of respiratory bronchiolitis (RB) are present in some airspaces. The pleural surface is on the top. (B) High magnification view of same case showing the thick, ropey, hyalinised collagen deposition within alveolar septa typical of SRIF.
Figures 1 ~ 3. Pathologic features of SRIF[15].
Reproduced from Smoking related interstitial fibrosis (SRIF): pathologic findings and distinction from other chronic fibrosing lung diseases, Katzenstein AL, 66, 882-7, 2013 with permission from BMJ Publishing Group Ltd.
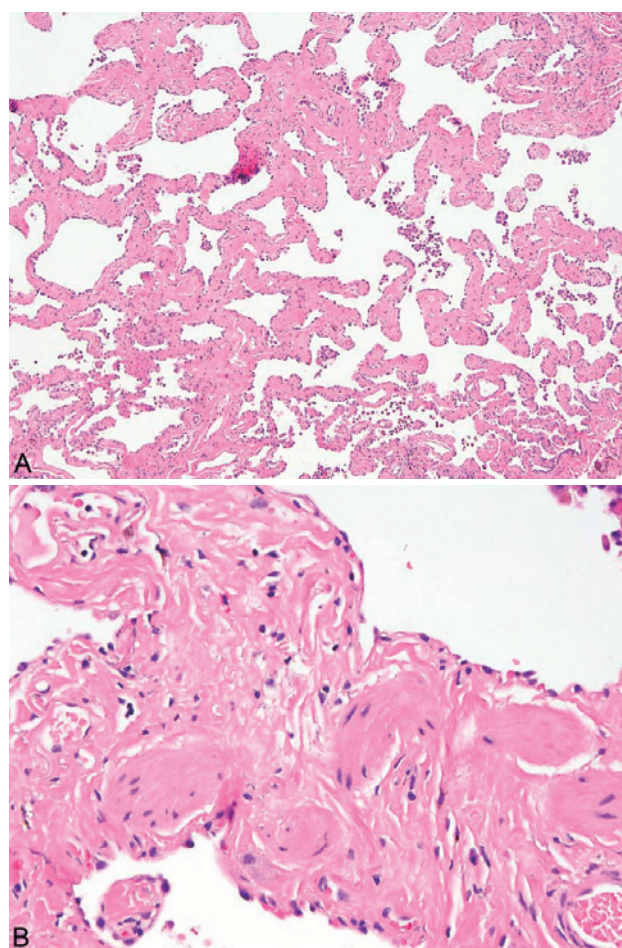

Fig. 2 (A) Low magnification view of smoking-related interstitial fibrosis within deeper lung parenchyma. (B) Higher magnification showing typical eosinophilic collagen deposition along with entrapped, hyperplastic smooth muscle bundles.

genesis of SRIF by the pathogenesis of DIP, which is also a smoking-related lung fibrosis and characterized by hyperaccumulation of macrophages. DIP was initially described by Liebow et al.[16] and was later considered the putative early stage of UIP, an idea that was abandoned in the 1990s. DIP is characterized by the widespread accumulation of intra-alveolar macrophages, with usually mild interstitial reactions, although some conditions may evolve into fibrosis and end-stage lung disease. It is well known that the histopathological patterns of RB-ILD and DIP may overlap, and the key feature to differentiate the disorders is the distribution and extent of the lesions: bronchiolocentric in RB-ILD and diffuse in DIP[17]. Accordingly, RB-ILD and DIP may be different components of the same histopathological disease spectrum, representing diverse degrees of severity in the same process caused by chronic smoking[18], and the same can be inferred for SRIF, which is characterized by the same keywords: smoking and macrophage accumulation.

Radiology

High-resolution computed tomography (HRCT) plays a prominent role in diagnosis. Vehar et al.[19] reported their review of imaging and surgical lung biopsy findings in SRIF. Bilateral ground-glass opacities (GGOs) were the dominant feature in all cases and correlated with the presence of SRIF and pigmented airspace macrophages on histopathological examination. GGOs were typically
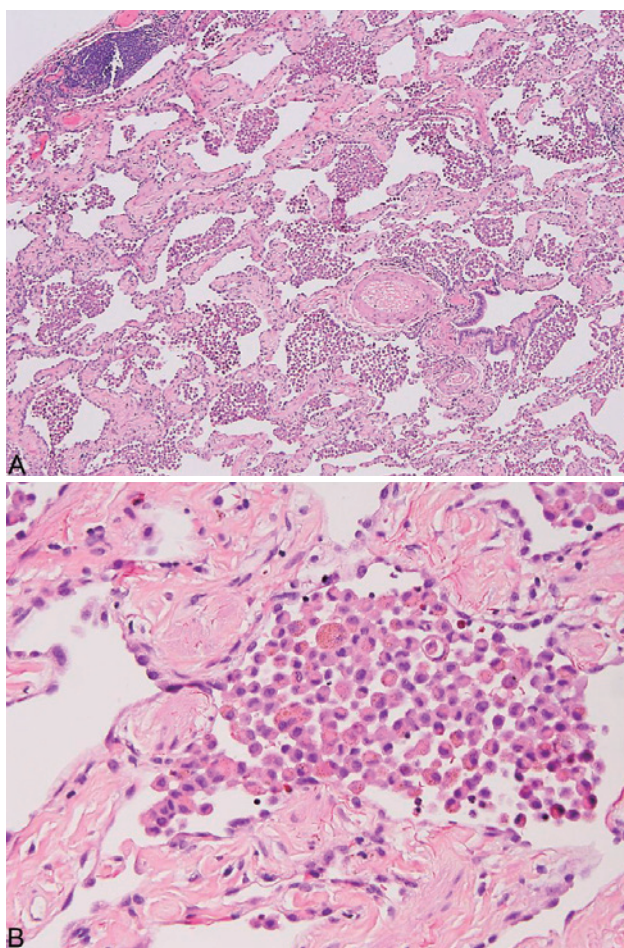
Fig. 3 In this example of smoking-related interstitial fibrosis the airspaces are filled with pigmented macrophages, a finding that is reminiscent of desquamative interstitial pneumonia (DIP). (A) Low magnification with pleural surface at upper left. (B) High magnification illustrating the hyalinised collagen and smooth muscle bundles within alveolar septa and the pigmented intra-alveolar macrophages. This marked interstitial fibrosis along with the associated emphysema excludes DIP.

diffusely distributed. When present, GGOs affect 6%-75% of the affected lobe. Mediastinal and/or hilar lymphadenopathy has been noted in some cases. Emphysema was noted radiologically in approximately 30% of cases, and its extent was less than 25% in the bilateral upper lobes. A few patients showed mild respiratory bronchiolitis in both upper lobes. Radiographic evidence of honeycombing was absent in all the cases. The authors discussed SRIF presenting as a diffuse parenchymal lung disease. Interstitial fibrosis was clearly present in multiple lobes in SRIF, but did not correlate with traditional indicators of fibrosis on chest CT, such as reticulation, traction bronchiectasis, and honeycomb change. Whether the GGOs in these cases can be explained by airspace macrophages,

interstitial fibrosis, or both remains unclear. Another observation was that emphysema was present on pathology in some cases but not on CT imaging.

For some authors, SRIF does not have defined radiological characteristics[2]; for others, the pattern is like the RB-ILD pattern, with micronodularity and GGOs[3]; and still for others, there is mild reticulation and GGOs associated with emphysema in the upper lung fields[4]. Iwasawa et al. found variable patterns on HRCT in patients with a histological diagnosis of SRIF, which included thin-walled air cysts or small cysts in the areas of reticulation, which, in some cases, were very difficult to differentiate from the UIP pattern[20]. This apparent radiological image of honeycombing can be explained by the location of fibrosis around the emphysema spaces in the subpleural parenchyma[21]. SRIF cysts have thin walls and a preference for the upper and middle areas of the lower lobes, which are slightly separated from the pleural surface, unlike the honeycombing of UIP[22].

Thus, radiological patterns reflect overlapping histological patterns, which is why they are often mixed and non-specific. **Figure 4** shows chest CT followed over a 12-year period of a clinically diagnosed SRIF patient, which is considered approximately typical images based on a synthesis of previous reports.

Pulmonary Function Tests

Only a few patients with a histopathological diagnosis of pure SRIF had pulmonary function tests (PFTs) reported. PFTs have shown preserved lung volumes with reduced forced expiratory volume in 1 s (FEV1) and disproportionate reduction in the diffusing capacity for carbon monoxide (DLCO)[14].

According to six cases of SRIF reported by Vehar et al.[19], using the Global Initiative for Chronic Obstructive Lung Disease criteria[23], two patients had obstruction on PFTs, defined by an FEV1/forced vital capacity (FVC) ratio of <0.7. All patients had a predicted FEV1% of ≥70%, with a median value of 72% and a range of 70-92%. Three patients had FVC values below the normal lower limit. For all patients, the median predicted FVC% was 75%, with a range of 63%-95%. Testing for DLCO was performed in all six patients, revealing a median predicted DLCO% of 53%, with a range of 33-68%. An important feature of the pulmonary function pattern of SRIF is markedly reduced gas exchange capacity, as indicated by DLCO, despite mild ventilatory impairment.

Biomarkers

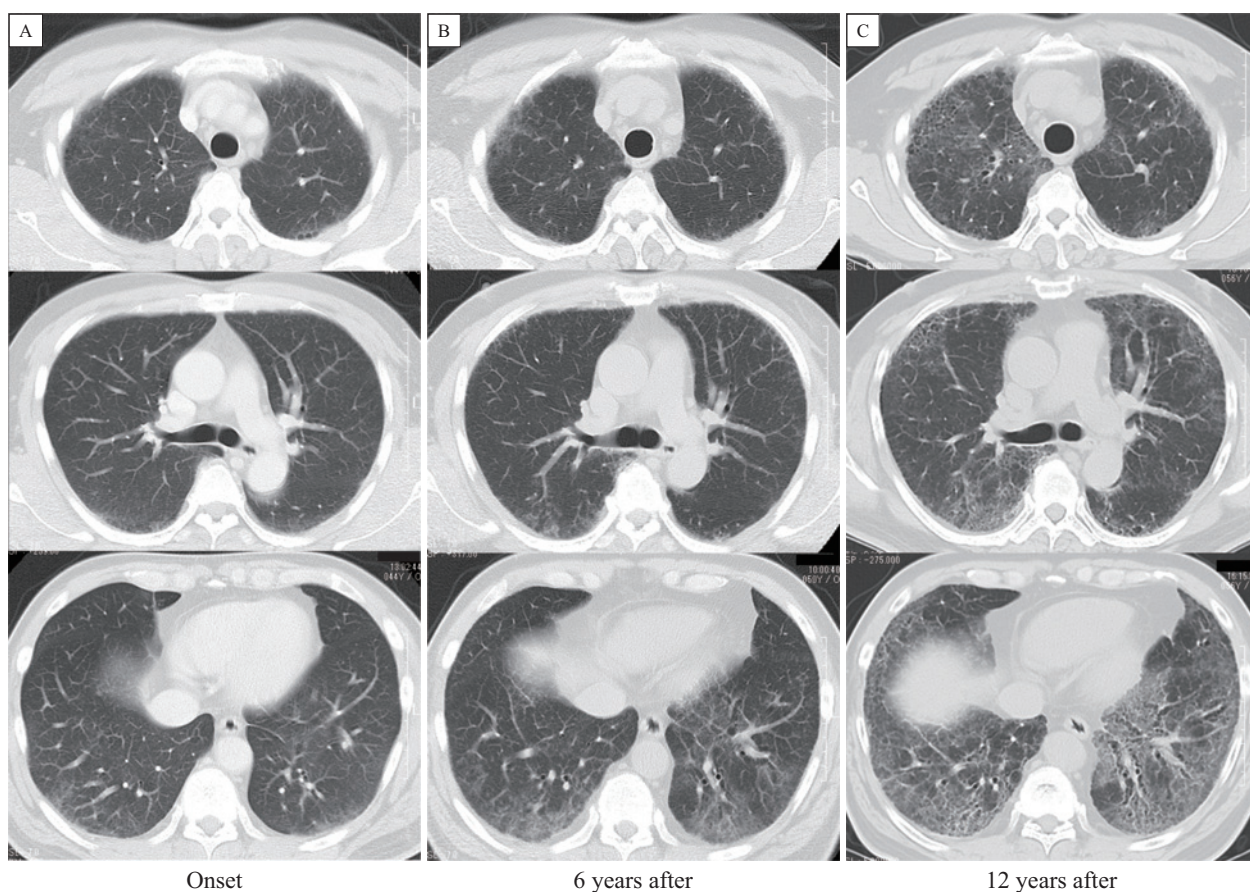There is no unified view on whether serum markers such as Krebs von den Lungen-6 (KL-6), serum surfactant

Fig. 4 Comparison of chest computed tomography (CT) of a case with clinically diagnosed SRIF at the time of onset (A), 6 years after (B), and 12 years after (C).

Chest CT revealed patchy, bilateral ground-glass opacities and reticular abnormalities in the upper and lower lobes; these anomalies predominated in the posterior territories. Over the course of 12 years, peripheral cystic spaces appeared and traction bronchiectasis in the bilateral lower lobes became evident.

protein-D (SP-D) and -A (SP-A), which are commonly measured in interstitial pneumonia, are also higher in patients with SRIF. The reasons behind this are that SRIF is found incidentally in some cases in lung specimens resected for other diseases, and the lack of large case data on SRIF. The selection of appropriate biomarkers and criteria for judging them is an issue to be addressed in the future.

Treatment and Prognosis

Reports on the prognosis and longitudinal follow-up of patients with SRIF are sparse. Several reports suggest that although symptoms such as dyspnea and cough may persist, SRIF does not progress significantly over nearly 10 years of clinical follow-up and may show slight improvements in pulmonary function and long-term stability of radiologic findings with smoking cessation or reduction[12,15,19,24]. Accordingly, in cases of clinical or imaging features of progressive pulmonary fibrosis, the so-called progressive fibrosing interstitial lung disease (PF-ILD), the diagnosis itself should be re-evaluated, and indica-

tions for anti-fibrotic therapy should be considered.

In contrast, SRIF may be found incidentally and asymptomatically. Large screening studies on lung cancer using HRCT have reported interstitial abnormalities in a significant proportion (2.2-22%) of otherwise asymptomatic smokers[25,26].

SRIF discussed based on pathological diagnosis and SRIF considered from a clinical perspective do not align. Therefore, determining the true treatment and prognosis of SRIF is a subject for future studies.

Smoker's Macrophages

AMs are the most abundant immune cells and are the first line of defence against inhaled particulates and pathogens in the interface between the airway lumen and the alveolar spaces. Recently, there has been a better understanding about the ontogeny, phenotype and function of AMs and their role, not only in phagocytosis, but also in initiating and resolving immune response. Many of the functions of the AMs have been shown to be dys-
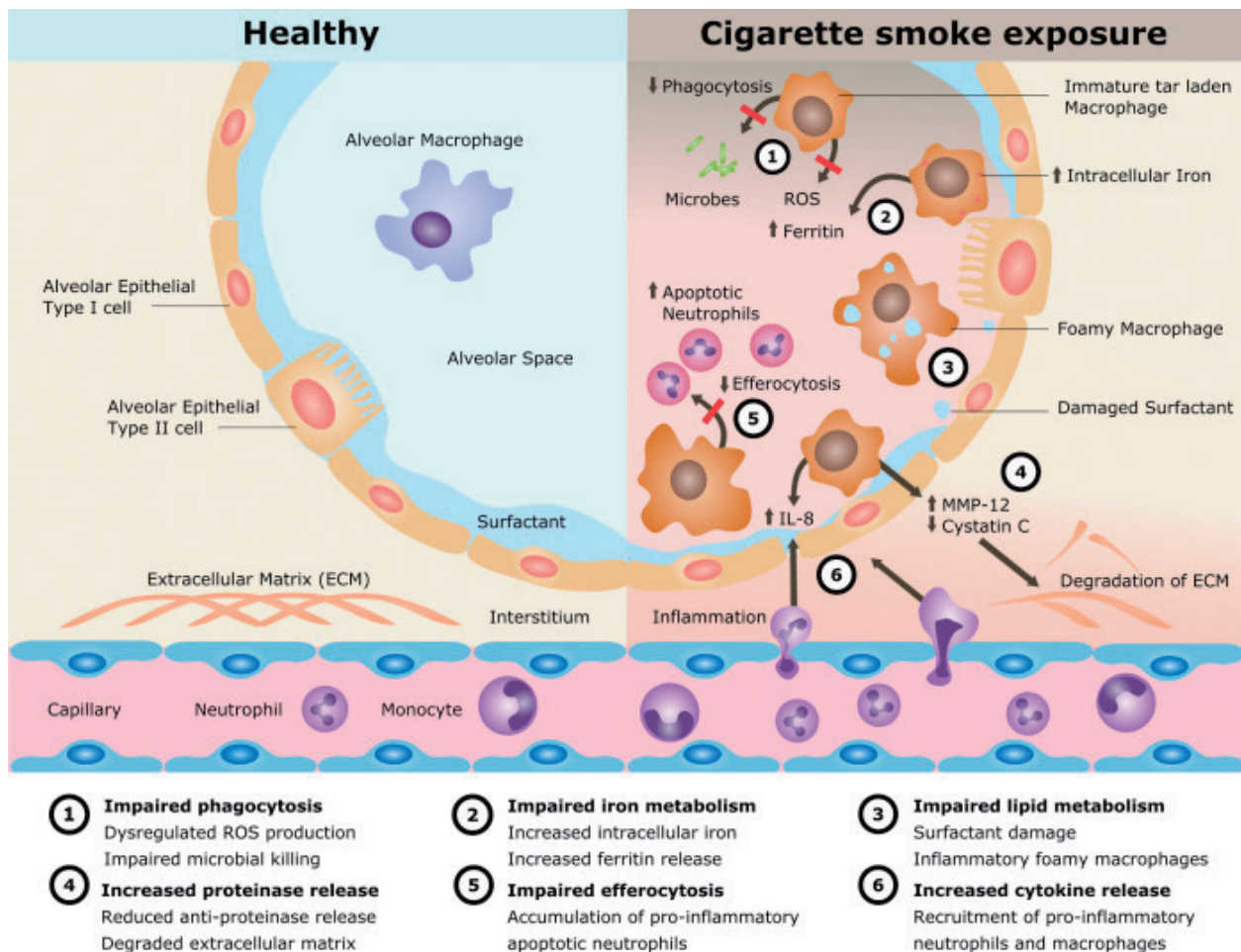
Fig. 5 Mechanisms for disease in cigarette smoke exposure of alveolar macrophages[8].
IL, interleukin; MMP, matrix metalloproteinase; ROS, reactive oxygen species.
The processes in cigarette smoke-related disease are multifaceted involving oxidative stress, inflammation, proteinase/anti-proteinase imbalance, tissue destruction and inadequate repair. Alveolar macrophages play an important role in these processes. ① Impaired phagocytosis: Dysregulated reactive oxygen species (ROS) production, Impaired microbial killing, ② Impaired iron metabolism: Increased intracellular iron, Increased ferritin release, ③ Impaired lipid metabolism: Surfactant damage, Inflammatory foamy macrophages, ④ Increased proteinase release: Reduced anti-proteinase release, Degraded extracellular matrix, ⑤ Impaired efferocytosis: Accumulation of pro-inflammatory apoptotic neutrophils, ⑥ Increased cytokine release: Recruitment of pro-inflammatory neutrophils and macrophages.
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regulated following exposure to cigarette smoke[8]. While the mechanisms for these changes remain poorly understood, they are important in the understanding of cigarette smoking-induced lung disease. Microscopic pigmented macrophages, so-called 'smoker's macrophages' containing a light brown, finely granular pigment, appear in the alveoli and interstitium of SRIF and phagocytose various dust particles contained in cigarettes. Smoker's macrophages are not disease-specific and are known to occur in smoking-related lung diseases. In 2022, Lugg et al.[8] have summarized and reported the current understanding: **Figure 5**, Mechanisms for disease in cigarette smoke exposure of alveolar macrophages.

Phenotype and Function of Alveolar Macrophages

AMs exert regulatory effects via non-specific immune-defense mechanisms, such as phagocytosis; the production of inflammatory mediators, such as reactive oxygen species; and the expression of inflammatory cytokines, such as interleukin (IL)-1, IL-2, IL-4, IL-6, IL-8, tumor necrosis factor-α (TNFα), and interferon gamma (IFNγ). AMs also resolve inflammation via the release of anti-inflammatory mediators and clearance of apoptotic bodies[8].

Recent studies have focused on AM heterogeneity. To examine AM heterogeneity, Tabary et al. used single-cell RNA sequencing (scRNA-seq) and reported four AM

clusters (Clusters 1 to 4)[9]. They assessed the identity and heterogeneity of AMs among healthy non-smokers, non-COPD smokers, and COPD smokers using a combination of approaches, including flow cytometry and bulk and scRNA-seq of BAL cells. They found that Cluster 2 was more prominent in smokers than in non-smokers. Cluster 2 was highly enriched in genes involved in oxidative stress, detoxification, and pro-inflammatory responses. Thus, they suggested that Cluster 2 represents a classical AM subset that responds to the toxic effects of cigarette smoke. Hou et al. reported the different characteristics of three types of lung macrophages[13]: AMs, including TR-AMs, Mo-AMs, and IMs, are the major macrophage populations in the lung and have unique characteristics in both steady-state conditions and disease states. Monocyte-derived cells acquire profibrotic phenotypes more easily and thereby promote fibrosis. Generally, Mo-AMs are more easily controlled by the environment than TR-AMs and are associated with cytokine storms and immune imbalance in severe infections. IMs may play a profibrotic role similar to that of Mo-AMs, as both interstitial and alveolar macrophages are detected in radiation-induced lung fibrosis. TR-AMs are long-lived cells shaped by a microenvironment that has immuno-suppressive functions in the steady state and less plasticity in the defense state. TR-AMs play an indispensable role in fighting pathogens, as they activate the inflammatory response in early stages and promote the recovery of inflammation in late stages. Misharin et al.[27] used a genetic lineage-tracing system to demonstrate that Mo-AMs and TR-AMs play distinct roles in the development of lung fibrosis. Using bleomycin-induced pulmonary fibrosis in a mouse model, Mo-AMs expressed consistently higher levels of proinflammatory and profibrotic genes than TR-AMs, and selective depletion of Mo-AMs, but not TR-AMs, ameliorated the severity of lung fibrosis. Depletion of TR-AMs using intratracheal liposomal clodronate before bleomycin administration was found to have no effect on fibrosis, suggesting that they were dispensable for the development of fibrosis.

SRIF and Macrophages

Katzenstein[15], who proposed SRIF as a new disease, has described: Intra-alveolar pigmented macrophages (smokers' macrophages) that are indicative of respiratory bronchiolitis are invariably present and usually numerous in SRIF. They may be so numerous in some cases as to fill the alveolar spaces adjacent to the thickened alveolar septa (**Fig. 3**). Though SRIF is a distinct form of interstitial fibrosis with a pathologic appearance characterized by hyalinized fibrosis and thickens alveolar septal walls that occurs in smokers, the role of macrophages in SRIF and the relationship between fibrosis and macrophages has never been studied or discussed and is unknown. The degree of fibrosis and appearance of macrophage aggregates are important points of distinction when evaluating and diagnosing SRIF. Macrophage heterogeneity, particularly the activation and function of Mo-AMs and IMs, has important implications for the pathogenesis of SRIF and developing treatments. Within the broad category of SRILDs, there are several diseases that share the common characteristics of cigarette smoke, smoker's macrophages, and fibrosis, and we hope that the dissimilarities in disease will inspire a macrophage-focused understanding of the pathogenesis of SRIF.

Conclusion

SRIF is a relatively newly proposed disease characterized by its etiology (smoking) and disease-defining pathology (interstitial fibrosis and macrophage accumulation). The diagnosis of SRIF requires a combined interpretation of histological and radiological findings, while considering the clinical context. Further research focusing on the role of macrophages is required to characterize the long-term clinical implications and optimal management of SRIF.

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