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Immunoglobulin Free Light Chains in the Pathogenesis of Lung Disorders

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ABSTRACT

Inflammation is an important component of numerous cancers and chronic diseases and many inflammatory mediators have been shown to have potential prognostic roles. Tumor-infiltrating mast cells can promote tumor growth and angiogenesis, but the mechanism of mast cell activation is unclear. Early studies have shown that immunoglobulin free light chains (FLC) can trigger mast cell activation in an antigen-specific manner. Increased expression of FLC is observed within the stroma of many human cancers including those of breast, colon, lung, pancreas, kidney, and skin. These overexpressed FLCs are co-localized to areas of mast cell infiltration. Importantly, FLC expression is associated with basal-like cancers with an aggressive phenotype. Moreover, FLC is expressed in areas of inflammatory cell infiltration and its expression is significantly associated with poor clinical outcome. In addition, serum and bronchoalveolar fluid FLC concentrations are increased in patients with idiopathic pulmonary fibrosis (IPF) and hypersensitivity pneumonitis (HP) compared to control subjects. In this review, we provide an update on the role of FLC in the pathogenesis of several lung disorders and indicate how this may contribute to new therapeutic opportunities.

Keywords: Asthma; Chronic obstructive lungs disease (COPD); Free light chain; Hypersensitivity pneumonitis (HP); Idiopathic pulmonary fibrosis (IPF); Lung cancer

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INTRODUCTION

Many of the pathological mechanisms that mediate inflammatory- and immune-related disorders in the lung ranging from allergy to cancer are still poorly understood and are the subject of extensive research. Mast cells and neutrophils are recognized as critical players in the sensitization and effector phase of chronic inflammatory immune responses of the lungs.[1] Immunoglobulins form the backbone of the adaptive humoral immune response and recognition of a specific antigen can initiate various immune responses directed at the removal or neutralization of potential threats.[2] It has been long recognized that B cells not only produce and secrete tetrameric immunoglobulins, but also secrete a substantial quantity of free immunoglobulin light chains (FLC). In the mammalian immune system, two isotypes of FLC are produced: κ and λ.[3] The ratio in which both types are produced varies significantly among species. For instance, in humans, 50-60% of the FLC produced are κ isotype, whereas this increases to 95% in mice.[4,5]

FLCs are found in virtually all body fluids and tissues and can initiate inflammation by antigen-specific activation of mast cells.[6-9] FLC can also exert other biological activities including binding to intracellular and extracellular proteins and modulation of cellular interactions.[6] The presence of Ig-FLC in both atopic and non-atopic diseases may provide an alternative approach to the treatment of such diseases. The highly selective FLC antagonist (F-991) has demonstrated remarkable biological activity in a number of animal models of allergic diseases, and holds promise for the potential treatment of allergic diseases in humans.[10]

Currently, serum FLCs are mainly used to monitor plasma-cell dyscrasia.[11] However, a growing body of studies suggests that serum FLCs could be useful biomarkers in immunopathological conditions as they reflect polyclonal B-cell activation. For example, serum FLC levels are elevated in lupus, [12] rheumatoid arthritis and Sjögren syndrome,[13-15] and changes in their levels are associated with disease activity. Serum FLC has also recently been reported as biomarkers of systemic sclerosis activity and severity.[16] In addition, B-cell activation markers including serum FLC, beta 2-microglobulin and B lymphocyte activating factor of the tumor necrosis factor family (BAFF) correlate with disease severity and activity (Figure 1). It is likely, therefore, that serum FLC levels may alter in various pulmonary disorders and that this will provide insights into disease mechanisms. In this review, we will discuss the possible role of FLC in allergic and non-allergic inflammatory lung diseases and highlight the potential FLC antagonist as a therapeutic option for several lung disorders.

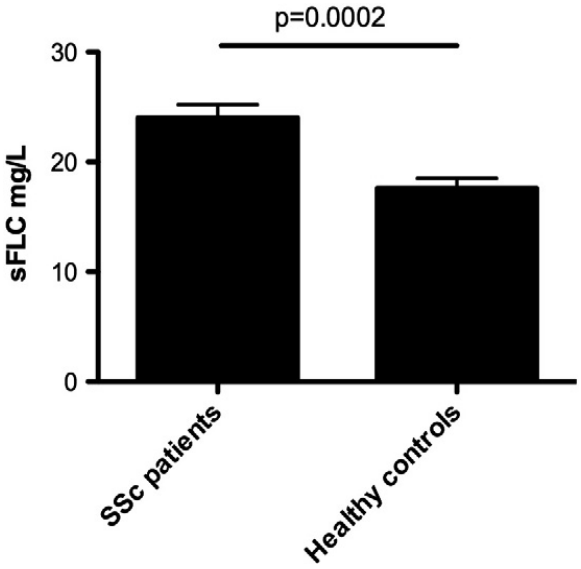

Figure 1. Comparison of serum FLC (sFLC) levels between systemic sclerosis (SSc) patients and healthy controls.[13]
FLC; Free Light chain

Chronic Obstructive Lungs Disease (COPD)

Chronic obstructive pulmonary disease (COPD) is characterized by an irreversible, progressive airflow limitation which is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, most commonly cigarette smoke and other indoor pollutants such as biomass fuels.[17,18] Neutrophils, monocytes/macrophages, T cells, and mast cells are the inflammatory cells implicated playing role in COPD pathophysiology.[19-25] Interestingly, FLCs are able to prolong the life of neutrophils[26] suggesting that they could contribute to the chronic neutrophilia associated with COPD. In support of this concept, Braber et al. described elevated serum and lung FLC levels in COPD patients compared with healthy volunteers. The increase in FLCs was associated with increased neutrophils both in humans and an animal model of COPD.[27] FLC

binding to neutrophils increased the release of CXCL8, which is a major chemokine for neutrophil recruitment into the airways, suggesting that FLCs may act in a feed-forward manner to enhance neutrophilia in COPD.[27] The enhanced expression of FLCs in COPD lung tissue and serum correlates with airflow limitation[28] and suggests that FLC may play a pro-inflammatory role in COPD pathogenesis. It will be important to test this hypothesis in animal models of COPD.

Allergic Lung Diseases Including Asthma

Allergic diseases are a serious health problem in the developed world. IgE interacting with its high-affinity receptor, FcεRI, is a major driver of most types of allergies. However, a subgroup of allergic patients display similar symptoms but without elevated levels of total serum IgE and/or antigen-specific IgE. Asthma is a relatively common disorder manifested by airway inflammation that leads to bronchoconstriction and respiratory symptoms. Approximately 50% of adults with this disorder are atopic with IgE-mediated tissue sensitization and Th2 cell responses leading to eosinophilia.[29,30] However, an equal percentage of asthmatic patients are non-atopic as evidenced by negative skin-prick test as well as by normal serum IgE levels and eosinophil counts.[29,30] This suggests that other causative factors may be involved in the etiology of this type of asthma. Analysis of FLC levels in non-atopic subjects should be initiated in future studies.

Increased FLC levels can be detected in patients suffering from a number of immunological disorders. For example, it has been shown that antigen-specific FLCs mediate hypersensitivity-like responses. Importantly, these hypersensitivity-like responses in the lung could be initiated by adoptive transfer of allergen-specific FLC. This suggests that these FLCs may be important in the pathophysiology of asthma as well as other non-IgE-mediated inflammatory diseases. Furthermore, the FLC antagonist, F991, completely inhibited both the early- and late-phase of dinitrofluorobenzene (DNFB)-induced pulmonary hypersensitivity in a mouse model of non-atopic asthma.[10,31] The role of IgE and FLCs in allergic and non-allergic disease has been extensively reviewed[3,32,60] and it underlines a possible role for targeting FLC biology in the development of novel therapeutic approaches in these diseases. Since F991 has demonstrated remarkable biological activity in several animal models of disease this needs to be translated into human clinical trials.[32]

Lung Sarcoidosis

Sarcoidosis is a chronic disorder that affects virtually all organ systems in the body. Histologically, it is characterized by the presence of T lymphocytes, mononuclear phagocytes and non-caseating granulomas with 90% of the reported cases involving the lungs. Sarcoidosis is defined as an inflammatory, granulomatous, multisystem disorder of unclear etiology[33,34] which highlights the fact that although the lungs are predominantly involved, other organs such as the skin, lymphatics, heart, musculoskeletal, neurological, and gastrointestinal systems are also targeted.[35] Granulomatous inflammation in sarcoidosis is believed to be caused by the host response to a persistent poorly degradable antigen. This antigenic stimulus can arise from non-infectious or infectious sources. Various non-infective agents have been suspected primarily because of their epidemiologic association; however, these have not stood the test of time.[37]

Increased concentrations of serum FLC in sarcoidosis was initially reported 30 years ago[38] and have subsequently been associated with active sarcoidosis and to reflect disease activity.[39] This link to disease activity is also seen in sero-positive rheumatoid arthritis (RA) patients.[39] Recently, we demonstrated the increased levels of FLC in serum of pulmonary sarcoidosis patients [40]. Further studies are required to determine the role of FLCs in the etiology of sarcoidosis and the use of F991 in disease models may help address this question.

Lung Cancer

A modest increase in serum FLCs was also observed in patients with lung cancer.[38] The expression of FLCs is also associated with the progression of other human cancers indicating its possible use as a prognostic biomarker of cancer generally.[41] Lung cancer is the leading cause of the cancer-related deaths worldwide. Non-small cell lung cancer (NSCLC) is the most frequent type of lung cancer and is usually only diagnosed at more advanced stages accounting for much of the poor prognosis. A biomarker is urgently needed, which is capable of aiding the diagnosis of lung neoplasms at an early stage or even help to clarify the pathogenesis of lung cancer.

Hypersensitivity Pneumonitis and Idiopathic Pulmonary Fibrosis

Interstitial lung diseases (ILD) comprise a diverse group of disorders affecting the lung parenchyma that are classified together because they share similar clinical, radiographic, and physiologic features.[42] Idiopathic pulmonary fibrosis (IPF) and hypersensitivity pneumonitis (HP) are two important complex diseases within the ILD group. IPF is a chronic fibrosing interstitial pneumonia of unknown etiology, restricted to the lungs and associated with the histopathologic pattern of usual interstitial pneumonia (UIP).[43] It is characterized by alveolar epithelial cell injury and activation, expansion of the fibroblast/myofibroblast population forming the so-called fibroblastic foci and the exaggerated accumulation of extracellular matrix.[44,45] The disease is usually progressive and there are no effective therapies that reverse the disease.[46-48] One of the major issues surrounding IPF is that its diagnosis is by elimination of other diseases and it may represent several distinct phenotypes due to divergent pathological causes.[49] This makes the development of an effective therapy difficult without the means of defining these sub-phenotypes of patients at an early stage. HP consists of a group of lung disorders resulting from exposure to a wide variety of organic particles causing an immunopathological reaction of the lungs in susceptible individuals.[50] One of the most frequent etiologies of HP is the inhalation of bird-derived proteins that provoke the so-called pigeon breeders' disease (PBD). The clinical behavior is heterogeneous and may present as acute, sub-acute or chronic forms, often with overlap between these interrelated categories.[51] Importantly, chronic HP may evolve into interstitial fibrosis, and in advanced stages may be very difficult to distinguish from IPF/UIP.[52,53] Strong evidence indicates that sub-acute and chronic HP are primarily a T-cell-mediated hypersensitivity.[54] However, less is known about the involvement of B lymphocytes although their potential role is indicated in sub-acute cases by the presence of high titers of circulating specific antibodies and the presence of plasma cells in the bronchoalveolar lavage.[55,56]

FLC concentrations are increased in the serum and bronchoalveolar fluid of IPF and HP patients and they are present within affected lung tissue.[57] Further studies are needed to investigate whether FLCs may make effective diagnostic markers of disease or may even be involved in mediating the pathology of both diseases.

Future Perspective

The biology of FLCs provides evidence for their role in several inflammatory and immune diseases as well as a number of cancers. The measurement of total and antigen-specific FLC might be of primary interest and indicate a causal role in several lung diseases (Figure 2). Their measurement may be useful as a diagnostic marker of lung disorders such as allergic reactivity, ILDs, sarcoidosis and hypersensitivity pneumonitis. However, co-morbidities may affect the specificity of these measurements since FLC are also reported as potential prognostic markers in autoimmune diseases such as RA and multiple sclerosis.[14,58,59] Future studies are warranted to further understand their role in the pathogenesis of lung disorders in which mast cells and B cells are implicated in the disease pathophysiology.

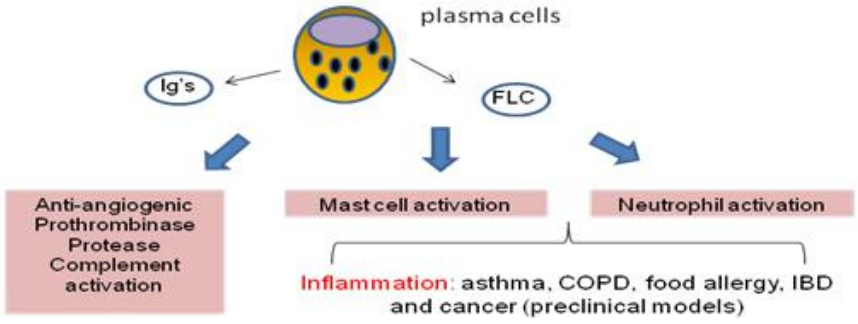

Figure 2. The putative role of free light chains (FLC) in inflammatory diseases
COPD: Chronic obstructive lungs disease, IBD: Inflammatory bowel disease

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