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Free immunoglobulin light chains: a novel target in the therapy of inflammatory diseases

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In recent years, novel therapeutic strategies have become available for the treatment of chronic inflammatory disease. Neutralizing proinflammatory mediators such as leukotrienes and TNF- α , in addition to anti-IgE therapies (Omaluzimab) that target higher in the inflammatory cascade, have shown success in the treatment of allergic or autoimmune disorders. Free immunoglobulin light chains, which are produced by B lymphocytes and secreted into serum, might play a crucial role in the pathogenesis of inflammatory disease. Concentrations of free light chains are significantly increased under diverse pathological conditions in humans, and have been linked to the progression and severity of immune diseases. Here we discuss the importance of free immunoglobulin light chains as a potential therapeutic target in the treatment of chronic inflammatory disease.

Immunoglobulin free light chains

Human immunoglobulins consist of two identical heavy chains and two identical light chains linked by disulfide bonds to form tetrameric structures. The carboxy (C)-terminal part of the heavy chain determines the class and subclass of the immunoglobulins and directs their biological activity. Plasma cells produce five different classes of immunoglobulins, termed IgG, IgM, IgA, IgD and IgE, which vary in the C-terminal part of the heavy chain. In all classes of immunoglobulin, the light chains comprise one of two subtypes, known as κ or λ . Immunoglobulin light chains are synthesized in excess during the generation and assembly of complete immunoglobulins [1–4]. These free light chains exist as monomers (molecular weight 22–27 kDa), and covalently and noncovalently bound dimers (44–55 kDa).

In healthy individuals, free polyclonal light chains are present in many biological fluids including serum, urine, cerebrospinal and synovial fluid [5,6]. It is estimated that a normal lymphoid system produces ~500 mg of free light chains per day, and these light chains are secreted and catabolized by the kidney [7]. In healthy individuals, the excretion rates of free light chains range from 1 to 10 mg per 24 h.

Abnormal levels of free monoclonal light chains (termed ‘Bence Jones proteins’) are usually linked to the malignant clonal proliferation of plasma cells;

this proliferation leads to a significant increase in the production, serum levels and secretion into urine of free monoclonal light chains (with >1 g of Bence Jones proteins secreted into urine per 24 h) [7]. Although free immunoglobulin light chains are considered to be spillover products of antibody production by plasma cells, many studies have shown that they can exert various biological activities and can interact with numerous intracellular and extracellular proteins (Figure 1). In this review, we focus on the potential role of free immunoglobulin light chains in the regulation of inflammation in various disorders.

Free immunoglobulin light chains and mast cell activation

In addition to their role as principal effector cells in allergic responses, mast cells are implicated in many other inflammatory diseases such as multiple sclerosis and rheumatoid arthritis. Activation of mast cells can occur through various antigen-specific and nonspecific stimuli [8]. The best-characterized activation pathway is stimulation by allergen binding to IgE bound to its high-affinity cell-surface receptor Fc ϵ RI. Crosslinking of the receptor activates a cascade of intracellular kinases, which ultimately results in the release of numerous prestored mediators, the synthesis of lipid mediators and the production of many cytokines.

In the past few years, we and our co-workers [9,10] have shown that free immunoglobulin light chains can induce mast cell activation, resulting in immediate hypersensitivity-like responses (Box 1). For example, intravenously administered antigen-specific light chains sensitize mast cells in mice: an immediate hypersensitivity response is induced, as judged by either cutaneous ear swelling after the sensitized mice are topically challenged with cognate antigen [9], or acute bronchoconstriction and plasma exudation after allergen provocation of the airways [10]. Crosslinking of the receptor is vital to induce mast cell activation mediated by free light chains and results in degranulation and *de novo* synthesis of inflammatory mediators [9]. Ultrastructural analysis of the light-chain-activated skin mast cells reveals swollen and emptied mast cell granules, and fusion of mast cell granules to form degranulation channels – typical signs of anaphylactic mast cell degranulation [9,11].

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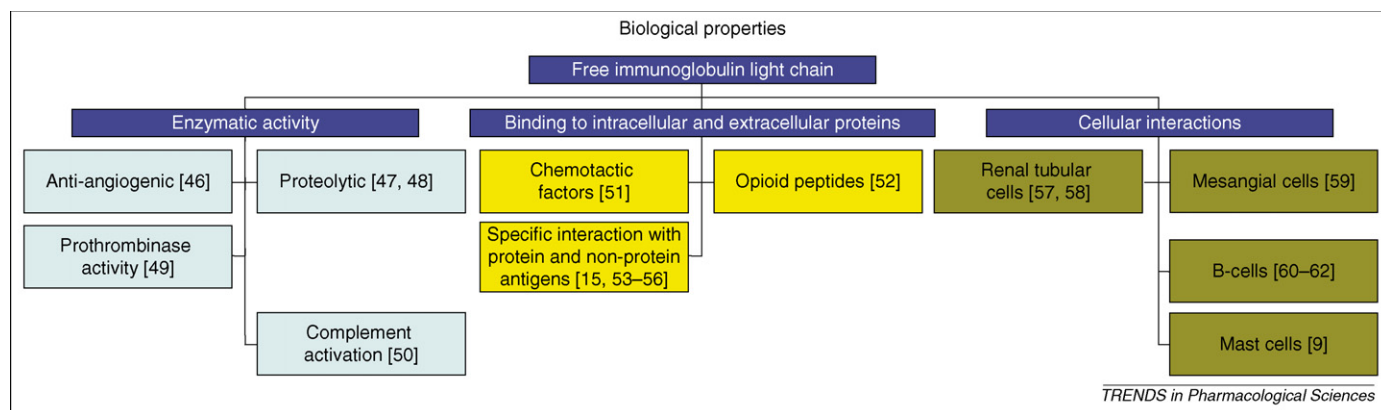


Figure 1. Biological activity of free immunoglobulin light chains. Free light chains show diverse biological activities such as enzymatic activity (proteolysis of diverse substrates) [46–50], specific binding activity for substrates and antigens [15,51–56] and binding to different cells [9,57–62]. The physiological significance of most of these biological activities is the subject of further investigation. The interaction between free light chains and mast cells might be important in the pathogenesis of inflammatory disease (Box 1).

Free light chains and mast cells in inflammatory disease

Mast cell degranulation is a common feature in many chronic inflammatory diseases, and increasing evidence indicates that mast cell activation plays a crucial role in the pathogenesis of such disorders. Activated mast cells release a broad spectrum of proinflammatory mediators with numerous biological activities [11,12]. In this section, we discuss the possible contribution of mast cell activation induced by free immunoglobulin light chains to the pathophysiology of various immune and autoimmune disorders.

Contact sensitivity and allergy

The cutaneous sensitization of mice with low molecular weight compounds, followed by a second contact with the appropriate antigen on the ear, induces contact sensitivity reactions marked by a biphasic ear swelling response,

neutrophil infiltration and local cytokine production [9,13,14]. Mast cells and B cells have been shown to be essential in the development of this typical T-cell-mediated immune response [15,16].

We and our co-workers [9] have demonstrated that contact sensitization with low molecular weight compounds results in the production of free light chains with specificity for the antigen used. Moreover, we have shown that the development of clinical signs of contact sensitivity can be completely prevented by administration of F991, a nine-residue peptide antagonist of free light chains. This compound inhibits the actions of free light chains, but not those of whole immunoglobulins [9], and it can be administered by various routes [9,10,14]. At present, there are few reports on free light chain measurements in allergic subjects, but a few studies suggest that serum concentrations are increased in this group of individuals [10,17].

Box 1. Comparison of the properties of free immunoglobulin light chains and IgE

The ability of IgE to trigger allergic responses has been well described. IgE binds to the high-affinity IgE receptor on mast cells and basophils. Crosslinking of surface-bound IgE by allergen results in mast cell activation and initiation of an allergic cascade. Free immunoglobulin light chains have been found to trigger a similar response (Table I). For example, passive transfer of antigen-specific free light chains into naive mice, followed by challenge with the appropriate antigen induces mast cell activation and vascular leakage [9]. The mechanism underlying this induction of hypersen-

sitivity-like responses might be interesting under conditions in which concentrations of free light chains are increased or when a correlation between IgE (and/or other immunoglobulins) and clinical symptoms is lacking – for example, in cases of non-atopic (idiopathic or intrinsic) syndromes. In preclinical studies, it has been shown that blocking this mechanism with F991 can prevent the development of clinical symptoms in animal models of contact sensitivity, asthma and inflammatory bowel disease [10,63] (A. Rijnierse *et al.*, unpublished).

Table I. Properties of IgE and free immunoglobulin light chains

Feature	IgE	Free immunoglobulin light chain
Serum concentration (normal)	1.5–144 kU/l	κ : 3.3–19.4 mg/l ^a λ : 5.7–26.3 mg/l ^a
Serum half-life	1–2 days	2–3 h
Receptor	FcεRI and FcεRII	Unknown (γ-chain independent)
Target cell	Mast cell, basophil, Langerhans cell	Mast cell, others unknown
Immunological response	Type I hypersensitivity	Immediate hypersensitivity-like
Increased synthesis	Antigen presentation	Type IV hypersensitivity
Therapeutic intervention	Worm infection, atopic diseases (asthma, rhinitis)	Autoimmune diseases
	Immunotherapy	Non-atopic diseases (asthma)
	Anti-IgE monoclonal antibody	F991 (peptide antagonist) ^b (tested in preclinical models)

^a95% reference intervals for serum concentrations of free immunoglobulin light chains when assayed with Freelite™ [64].

^bF991 is a peptide antagonist of free light chains that does not interfere with intact immunoglobulins, and can be administered by various routes [10,14,63]. The clinical relevance of free light chains in human disease and the therapeutic efficacy of the light chain antagonist F991 remain to be investigated.

Asthma and rhinitis

Allergic rhinitis and asthma seem to share common pathways involving T-helper type 2 cells and allergen-specific IgE. A significant percentage of individuals suffering from asthma and rhinitis, however, shows no association with increased concentrations of serum IgE [10,18]. Previously, we and our co-workers [10] reported that serum concentrations of free immunoglobulin light chains are increased in individuals with both allergic and non-allergic asthma as compared with healthy controls. More recently, we have found increased numbers of cells expressing free light chains in the nasal mucosa of individuals with persistent rhinitis, irrespective of their atopy status, as compared with healthy controls. Using laser microdissection, we found that free light chains were associated with mast cells and plasma cells in the nasal mucosa of individuals with non-allergic rhinitis (D. Powe *et al.*, unpublished). These findings also suggest that free light chains might have a role in chronic inflammation of the upper airway.

Mast cells make an important contribution to the pathophysiology of asthma and are localized in bronchial smooth muscle bundles in individuals with asthma [19]. In studies in mast-cell-deficient mice, it has been demonstrated that mast cells are necessary for the full development of both allergic and non-allergic experimental asthma [20,21]. In a model of non-atopic asthma, free immunoglobulin light chains have been shown to be essential for the development of clinical symptoms of disease such as airway hyperactivity, mucosal exudation and local inflammation [10]. In this model, free light chains trigger mast cell activation after local exposure to allergen [10], making free immunoglobulin light chains an attractive therapeutic target in non-atopic asthma.

Inflammatory bowel disease

Mast cell activation has been found to be crucial in the induction of disease in a model of experimental colitis [22,23]. Development of diarrhea, colonic lymphoid follicle hyperplasia, infiltration of inflammatory cells into the colon and mast cell activation were abrogated by administration of the light chain antagonist F991, indicating that free immunoglobulin light chains are responsible for the mast cell activation observed in this model of experimental colitis.

Interestingly, analyses of free light chains in serum and inflamed tissue from individuals with inflammatory bowel disease has revealed increased concentrations of both κ and λ light chains, as compared with healthy controls ([24] and A. Rijnierse *et al.*, unpublished).

Autoimmune diseases

Increases in serum concentrations of free immunoglobulin light chains have been reported in several autoimmune diseases. For example, a quantitative analysis of serum free light chains in rheumatoid arthritis and primary Sjögren's syndrome found that mean κ and λ levels were significantly higher in both patient groups than in controls [25]. In addition, free light chain concentrations correlated with disease activity in rheumatoid arthritis and Sjögren's syndrome, and individuals with a less favorable prognosis

showed higher concentrations of free light chains. This correlation was not found for total gammaglobulin or IgG levels.

In multiple sclerosis, increased concentrations of free light chains have been found in cerebrospinal fluid and urine [6]. A recent retrospective study over a 15-year period in 57 individuals with multiple sclerosis found that high cerebrospinal free κ light chain concentrations correlated with disability prognosis, leading to an increase in the need for ambulatory assistance and to greater disability relative to disease duration [26]. Although an increase in intrathecal IgG production is observed in individuals with multiple sclerosis, several studies have shown that increases in κ free light chains can occur without a concomitant increase in IgG production or even in the absence of oligoclonal IgG in cerebrospinal fluid [27,28]. These studies suggest that the production of free light chains might be selectively increased as the result of an ongoing intrathecal humoral immune response.

Mast cells are intimately associated with several autoimmune diseases. In animal models of multiple sclerosis, bullous pemphigoid and rheumatoid arthritis, mast-cell-deficient animals do not develop symptoms of disease. In other autoimmune diseases such as Sjögren's syndrome [29] and idiopathic urticaria [30], mast cells have been suggested to be involved in the pathogenesis of the disease, but whether this is an essential or bystander role remains to be established. Mast-cell-derived mediators have been found to be increased in cerebrospinal fluid obtained from individuals with multiple sclerosis and in synovial fluid isolated from arthritic joints of patients with rheumatoid arthritis [31,32].

Other disorders

Several other diseases such as cancer [33], AIDS [34,35], systemic lupus erythematosus [36,37] and diabetes mellitus [38] have been reported to be associated with B-cell activation and/or increased free immunoglobulin light chain concentrations in different compartments of the body. The role of mast cells in many of these disorders is less clear and awaits further experimental proof in pre-clinical models. Mast cells might have a proinflammatory or protective role in the pathogenesis of these diseases [39–41].

Concluding remarks

As we have described here, free immunoglobulin light chains express diverse biological activities. Their capability to activate mast cells (Box 1) makes free light chains an attractive therapeutic target in inflammatory disorders associated with an increase in their concentration. We have also described several allergic and autoimmune diseases that feature both an increase in free light chain production and the involvement of mast cells in the pathogenesis of human disease. In preclinical models of disease, preventing mast cell activation induced by free light chains with the antagonist F991 has been shown to potently inhibit the development of asthma, contact sensitivity and inflammatory bowel disease. These studies suggest that targeting free light chains with specific antagonists (such as F991) might be an attractive novel therapy for

inflammatory diseases. Furthermore, preclinical and clinical trials indicate that repeated administration of F991 does not cause adverse effects (http://www.fornix.nl/upload/web/files/5_March_2003_UK.doc), paving the way to test F991 for clinical efficacy.

Several challenging questions remain to be answered in future studies. For example, can global concentrations of free immunoglobulin light chains serve as a biomarker in inflammatory diseases? And can antigen-specific free light chains be detected? As discussed earlier for some autoimmune diseases, levels of free light chains, but not IgG, correlate with disease activity. Several commercial (e.g. Freelite™) and noncommercial assays might be used to validate the utility of measuring free light chains as biomarker for other chronic inflammatory diseases. At present, however, a lack of reference material for free light chains makes it difficult to evaluate the specificity and accuracy of the different analytical platforms available [42,43]. In addition, reliable assays for the detection of antigen-specific light chains should be developed. Indeed, free light chains specific for *Toxoplasma gondii* have been detected in cerebrospinal fluid from individuals affected with AIDS [44]. Although another study did not detect specific free light chains in human serum from individuals with allergy, those measurements were hampered by technical imperfections (e.g. poor recovery, absence of positive controls) [45]. Furthermore, identification of the receptor for free immunoglobulin light chains will give further insight in the mechanism of mast cell activation and might provide a novel therapeutic target for the development of specific receptor antagonists.

In summary, we conclude that current information on the role of free immunoglobulin light chains in inflammation warrants further studies to assess the importance of these molecules in other preclinical models of disease and to evaluate the value of antagonizing free light chains as a therapeutic strategy in the treatment of human inflammatory diseases.

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