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Inflammation Research

1. Histamine in allergy, inflammation, tissue growth and repair

Functional role for Ig free light chains in immediate and delayed hypersensitivity responses

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Antibodies play an important role in the humoral response of the adaptive immune system. B cells produce different isotypes of immunoglobulins (Ig) and, depending on the incorporated Ig heavy chain, they can have different effector functions. For instance, IgE is well known because of its central role in allergic responses by activating mast cells and basophils via their high affinity IgE receptor (FcεRI). Besides complete Ig, B cells also produce considerable amounts of Ig free light chains [1]. Under physiological conditions, polyclonal free kappa and lambda light chains can be found in different body fluids. Reported normal serum levels range from 1.2–20.6 mg/ml and 3–41.4 mg/ml for kappa or lambda free light chains [2], respectively. Interestingly, under chronic inflammatory conditions and during autoimmune diseases, the levels of free light chains in serum or other body fluids can increase sharply [3]. However, it was not clear what role these free light chains as part of the humoral system could play in immune responses.

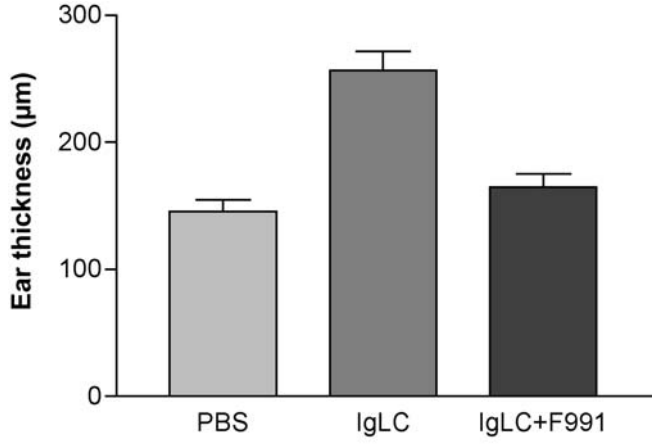

Fig. 1. Ear swelling induced after topical hapten challenge of Ig light chain sensitised mice: inhibition by the light chain antagonist F991. Mice were passively sensitised by an intravenous injection of trinitrophenol-specific Ig free light chains or vehicle (PBS). Thirty min after injection, mice received a topical ear challenge with trinitrophenyl chloride and ear thickness was measured two h afterwards. The specific light chain antagonist F991 was administered intraperitoneally at 4 h before sensitisation with Ig light chains.

Ig free light chains elicit immediate hypersensitivity-like responses in mice

Recent work from our group indicated that Ig free light chains can play a crucial role in hypersensitivity-like responses. We have shown that Ig free light chains can dose-dependently transfer hapten sensitivity upon intravenous injection into naive mice [4]. A second encounter with the cognate antigen induced mast cell activation and oedema formation (e. g. ear swelling) in sensitised animals (Fig. 1). Mast cells in ear tissue showed morphological signs of degranulation. Moreover, mast cells were shown to be crucial in the hypersensitivity response elicited by Ig light chains: no response could be initiated in genetically mast cell-deficient animals. Furthermore, we developed a peptide antagonist, F991, for Ig free light chains preventing binding of light chains to their putative receptor on effector cells. F991 is a peptide compound homologous to the Ig light chain binding moiety of Tamm-Horsfall protein [5]. We were able to inhibit development of ear swelling by treating the sensitised animals with F991 (Fig. 1). Another set of experiments provided direct evidence that crosslinking of surface proteins of cultured mouse primary mast cells with Ig free light chains stimulated release of granule mediators and production of lipid mediators [4]. This mast cell activation is independent of gamma chain-associated receptors such as FcεRI and FcγRIII and the nature of the surface protein interacting with Ig light chains is presently under investigation. Taken together, these results indicate that Ig light chains can mediate a novel route for immediate hypersensitivity(-like) responses independent of IgE and IgG_1.

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Ig free light chains are crucial in contact sensitivity responses in mice

Cutaneous sensitisation 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. Earlier work indicated a crucial role of mast cells in the early and late swelling response, although it was unclear what mechanism of mast cell activation would be involved [6]. In addition, B cells were shown to be essential in the development of contact sensitivity, indicating that also the humoral immune system played an important role in this T-cell-mediated immune response [7]. We have demonstrated that contact sensitisation with low molecular weight compounds such as dinitrofluorobenzene, picryl chloride and oxazolone results in rapid production of Ig free light chains specific for the hapten used. In subsequent experiments, it was shown that the light chain antagonist F991 completely blocked development of hapten-induced contact sensitivity, which demonstrates a crucial role for Ig free light chains in the development of this immune response [4]. Currently, our working model features the production of Ig free light chains upon active sensitisation, which bind to mast cells and a subsequent encounter with the appropriate antigen results in mast cell activation setting off a cell-mediated local immune reaction (Fig. 2).

Ig free light chains and allergy?

The manifestation of allergy symptoms is believed to correlate with presence of elevated levels of specific IgE. However, about 10–30% of atopic dermatitis patients do not show raised levels of specific or total IgE and conversely a considerable percentage of subjects with high serum IgE does not suffer from clinical symptoms of allergy [8, 9]. In light of our findings that Ig free light chains can induce immediate hypersensitivity(-like) responses, it is tempting to speculate that allergen-specific Ig free light chains might be involved in the induction of allergic syndromes independent of IgE. However to date, no data are available on the presence of allergen-specific Ig free light chains in allergic patients to support this hypothesis (work in progress).

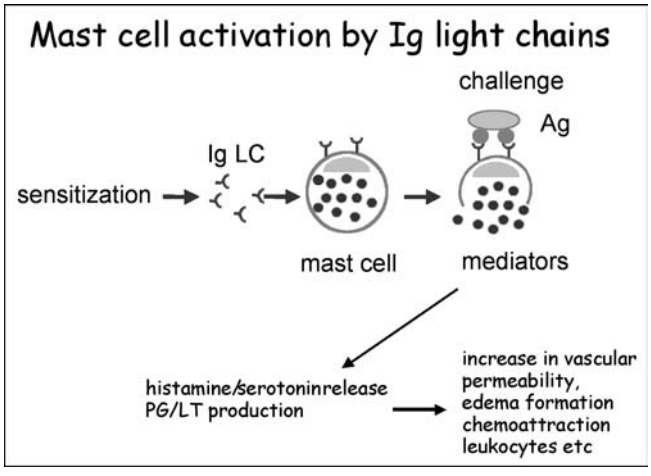

Fig. 2. Sequence of events leading to immediate hypersensitivity-like responses after mast cell sensitisation and activation via antigen-specific Ig free light chains. Sensitisation results in production Ig free light chains (IgLC) by B cells. IgLC bind to cell surface receptors on mast cells and a subsequent encounter with the appropriate antigen (Ag) results in mast cell activation and the release of vasoactive and chemoattractive mediators.

Ig free light chains in T-cell directed immune responses

We have shown that Ig free light chains were essential in the development of contact sensitivity responses in mice. Vasoactive mediators and chemoattractant and proinflammatory products (e.g. tumor necrosis factor-alpha and macrophage inflammatory protein-2) released from activated mast cells can facilitate extravasation and attraction of specific and non-specific immune cells such as T lymphocytes and neutrophils eventually leading to a full-blown local inflammatory response.

In immune disorders such as chronic active sarcoidosis, Sjögren's disease, systemic lupus erythematosus, multiple sclerosis (MS), and rheumatoid arthritis (RA) it has been reported that Ig free light chain levels increase sharply [reviewed in 10] and it has been suggested that these increases correlate with the progression of disease [11]. In animal models for MS and RA, the mast cell seems to play an indispensable role [12, 13]. Also from clinical studies it becomes clear that mast cell numbers increase and mast cell mediators accumulate in affected tissues [reviewed in 14, 15]. Presently, we are investigating if this mast cell-free light chain interaction may also be important in the pathogenesis of these immune diseases (work in progress).

In conclusion, we have demonstrated that Ig free light chains can stimulate IgE/IgG1-independent immediate hypersensitivity-like reactions. Besides the induction of features of an immediate 'allergic' response, this mast cell activation may also be of crucial importance in subsequent steps leading to cell-mediated immune responses [10]. We propose that this pathway may be of great interest for the development of novel treatment strategies for (auto)immune disorders.

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