

REVIEW

Histamine-releasing factors, a heterogeneous group of different activities

I. Kleine Budde and R. C. Aalberse

Department of Immunopathology, Sanquin Research at CLB, Amsterdam, and Landsteiner Laboratory, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

Summary

Histamine-releasing factor or HRF is a collective term used for a heterogeneous group of factors with different modes of action. The current review is focussed on IgE-dependent HRF that require the presence of certain types of IgE (designated IgE⁺) to induce histamine release. IgE⁺ might be a structurally different IgE molecule, or, alternatively, autoreactive IgE. A subgroup of IgE-dependent HRF does not bind to IgE, such as cloned HRF p23. This factor turned out to be a basophil-priming cytokine. Alternatively IgE-dependent HRF might be an autoallergen. Several groups demonstrated IgE antibodies to human proteins. However, not all IgE autoallergen-containing extracts induce histamine release of appropriately sensitized basophils. In culture supernatants of human mononuclear cells an autoallergenic activity (Ag_{mn}) is found, but no binding to IgE⁺ was found yet. Ag_{mn} might be an autoallergen, since it is cross-reactive with a grass pollen allergen in the stripped basophil assay.

IgE-dependent HRF and IgE⁺ may play a role in the late allergic reaction (LAR). However, IgE⁺ responsiveness to Ag_{mn} (IgE^{mn+}) was not required for a bronchial LAR. IgE^{mn+} is associated with chronic allergic disease, since the prevalence of IgE^{mn+} is high in the serum of severe asthmatics and atopic dermatitis patients. Our hypothesis is that exogenous allergens induce IgE antibodies cross-reactive with an endogenous protein. During a LAR, these endogenous proteins are released and the subsequent IgE-mediated reaction prolongs and aggravates the allergic and/or asthmatic symptoms. In conclusion, HRF is a confusing term since it is used for different activities. It might be better to avoid this terminology on and just describe the activity of the factors. Autoallergenic activity is likely to explain most, if not all, IgE-dependent activity.

Introduction

First reports of an activity derived from human cells capable of inducing release of histamine from human basophils, called 'histamine-releasing factor (HRF)', originated from the late 1970s [1]. Histamine-releasing activity (HRA) was found in culture supernatants of different human cell types, such as thoracic duct lymphocytes [2], T lymphocytes [3], B lymphocytes [3], alveolar macrophages [4], monocytes [3], platelets [5], and neutrophils [6]. This activity turned out to be a mixture of IgE-independent [7] and IgE-dependent factors [8]. At least one of the components induced histamine release similar to IgE-mediated stimuli in dose dependence, calcium and temperature requirements, and kinetics [8]. There are factors, such as soluble (s)CD23 and autoanti-IgE, which do not discriminate between different IgE subpopulations. Other stimuli release histamine from basophils only in the presence of a special type of IgE, called IgE⁺ [9]. Since the introduction of the term 'HRF', several speculations have been made about the nature and mode of reactivity of this IgE molecule. IgE⁺ or HRF-responsive IgE might be an autoantibody, or alternatively a structurally different IgE molecule. Prelimin-

ary results indicated that they play a role in the late allergic reaction [10–12]. Initially, the search for IgE-dependent factors and IgE⁺ was hindered by the presence of fast-acting IgE-independent histamine-releasing factors, such as MCP-1. Since IgE-independent histamine release was already near to maximum after 1 min, these factors interfered with the measurement of IgE-dependent activity [13]. The influence of the IgE-independent factors was minimized by treatment with heparin-agarose, which binds chemokines [13]. A breakthrough in the HRF field was the cloning of an IgE-dependent HRF (p23) in 1995 [14]. However, this factor turned out not to be responsible for the IgE-dependent histamine releasing activity found in culture supernatants of cells [15]. Very important was also the demonstration of IgE binding to human proteins in 1996 by two groups [16, 17].

Overall, it can be concluded that HRF is a heterogeneous group of proteins with different modes of action. 'Histamine-releasing factor' is a confusing term, and thus from now on it might be better to avoid this nomenclature, and just mention individual activities. The new terminology is depicted in Fig. 1. In summary, some HRFs are independent of IgE for their activity, such as chemokines. The IgE-dependent HRFs can be subdivided into non-IgE binding and IgE-binding factors. Priming factors, such as IL-3 and cloned HRF p23, belong to the first group. These factors do not induce release itself, but up-regulate IgE-dependent histamine release. At first

Correspondence: Ilona Kleine Budde, PhD, Sanquin Research at CLB, Plesmanlaan 125, 1066 CX Amsterdam, The Netherlands.

E-mails: i.kleinebudde@sanquin.nl; f.muntar@sanquin.nl

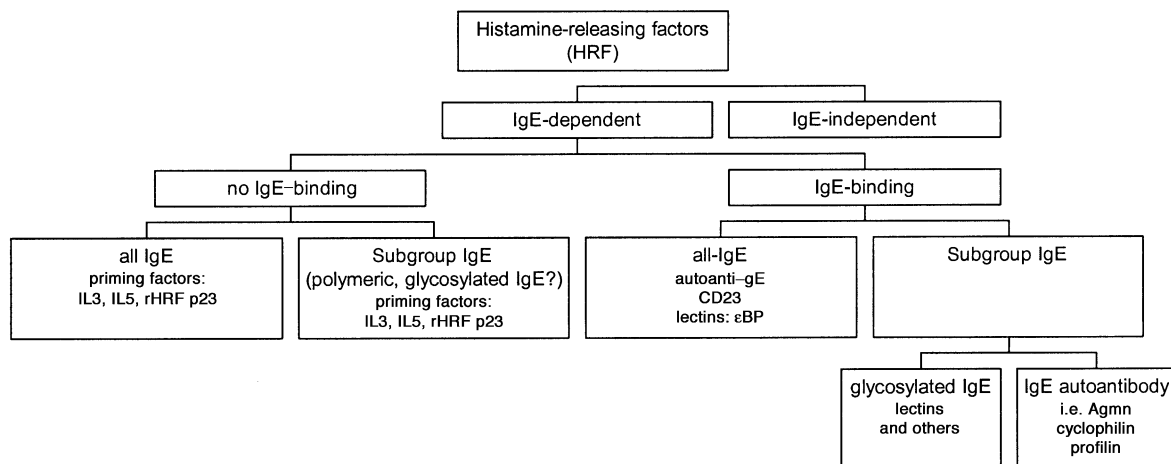


Fig. 1. Overview of histamine-releasing factors.

recombinant (r)HRF was thought to be a 'classical IgE-dependent HRF', but it turned out not to bind IgE and at least for its cytokine-like activity it seems not to be dependent on IgE⁺. The nature of the IgE antibody is not clear yet; glycosylated or polymeric IgE might be candidates. However, other priming factors might not discriminate between different subgroups of IgE. The same is true for IgE-dependent HRF binding to IgE: some only react with a subgroup of IgE (auto-allergens, lectins), whereas others do with all IgE (autoanti-IgE, sCD23 [18], εBP [19]). The current report is focussed on IgE-dependent factors that need a subgroup of IgE to exert their activity. Autoallergen Ag_{mn}, the HRF produced by human mononuclear cells is discussed in more detail.

IgE-independent histamine-releasing factors

The group of IgE-independent HRFs consists mainly of chemokines [20]. Members of the monocyte chemotactic protein (MCP) family are the most potent IgE-independent factors [21–24]. Other chemokines such as RANTES (regulated upon activation, normal T cell expressed and secreted) [25], MIP-1α (macrophage inflammatory protein-1α) [26], and eotaxin [27] also act as IgE-independent HRF, but are weaker than the MCP family. In HRF preparations, it is sometimes difficult to measure IgE-dependent activity in the presence of IgE-independent HRA, because IgE-independent histamine release is induced extremely fast: approximating maximum release already within 1 min [13]. Pasmans et al. [13] demonstrated that IgE-independent activity was removed from culture supernatants by treatment with heparin-agarose. Some cytokines also induce histamine release from human basophils, such as interleukin (IL)-1 [28, 29] and IL-3 [30, 31]. However, these data are controversial. The activity of IL-3 was only demonstrable at relatively high concentrations of Ca²⁺ (5 mM) [30] or in the presence of D₂O [31]. Moreover, the HRA of IL-1 [32] and IL-3 [33] could not be reproduced by other groups.

IgE-dependent histamine-releasing factors

The activity of IgE-dependent HRFs discussed in this review depends on some special features of the cell surface IgE [12]. This IgE was called IgE⁺, whereas IgE that does not induce responsiveness to HRF is IgE[−] [9]. IgE-dependent HRFs are produced by different cell types, for instance by macrophages [8], mononuclear cells [34], and platelets [9], and are present in nasal washings [12], blister fluids during the late allergic reaction in the skin [11], and broncho-alveolar lavages [12]. Histamine release by IgE-dependent factors is a relatively slow process, 50% of maximal release after 5–10 min, which is similar to that by anti-IgE or allergen [8, 12]. The IgE dependency of HRF was supported by the observation that the removal of IgE from basophils with lactic acid abolished the response to HRF [8, 12]. The responsiveness to HRF of the stripped basophils was restored by *in vitro* re-sensitization with IgE⁺ serum, but not with IgE[−] serum [12]. In contrast, both IgE[−] and IgE⁺ sera restored the reactivity to anti-IgE. IgE⁺ serum also conferred responsiveness to basophils with IgE[−] on their surface. Moreover, pre-incubation of basophils containing IgE⁺ with anti-IgE in a calcium-free medium resulted in a complete desensitization to HRF-induced histamine release [8, 12]. Desensitization with HRF reduced the response to anti-IgE, but not to an IgE-independent stimulus such as fMLP. Furthermore, IgE dependency was demonstrated by heating IgE⁺ serum at 56 °C that destroys IgE antibodies, and by removal of IgE by absorption with Sepharose-coupled anti-IgE [12, 34]. Finally, wortmannin, an inhibitor of IgE-mediated activation of basophils by inhibiting PI3 kinase, abolished the response to HRF [34].

There are at least three possibilities to explain the responsiveness of IgE⁺: (i) IgE⁺ reactivity is mediated by IgG anti-IgE antibodies, (ii) IgE⁺ is structurally different from IgE[−], or (iii) IgE⁺ is autoreactive IgE. In the following paragraphs these hypotheses are described in more detail.

Hypotheses concerning the nature of IgE⁺

Anti-IgE antibodies IgE⁺ reactivity might not be mediated by IgE alone, but in combination with IgG anti-IgE

antibodies [35, 36]. Anti-IgE antibodies have been described to modulate basophil histamine release in a stimulating as well as in a blocking manner [36, 37]. Purification of IgE⁺ indicated that IgG anti-IgE antibodies are not likely to be responsible for the IgE⁺ reactivity [38].

Heterogeneity of IgE⁺

The feature discriminating IgE⁺ from IgE⁻ might be present in the constant region of IgE. According to this hypothesis, both HRF and a structurally different form of IgE are necessary to achieve full basophil activation. HRF might then exert a priming effect on basophils. The histamine-releasing activity of the IgE-dependent HRF p23 cloned by MacDonald et al. [14] might be due to such a priming process.

It has been suggested that variations in glycosylation of IgE molecules account for the functional heterogeneity of IgE⁺ and IgE⁻ [12]. This hypothesis was tested by stimulating basophils with lectins [39], some of which are known to release histamine from basophils by interaction with carbohydrate groups on IgE antibodies [40]. However, none of the eight tested lectins differentiated between basophils with IgE⁺ or with IgE⁻ on their surface [39]. These findings, of course, do not exclude the possibility that there are differences in glycosylation.

Another possibility is that IgE⁺ is an alternative splice variant of the IgE molecule. Besides the 'classic' secreted form, isoforms with an altered carboxyl terminus of the heavy chain have been characterized and expressed using recombinant techniques [41–43]. In the 'tailpiece' isoform, two carboxy-terminal amino acids present in 'classic' secreted IgE (190 kDa) are replaced by eight novel amino acids. It contains a C-terminal cysteine that could be involved in the formation of dimers/multimers [41, 42]. The 'IgE tailpiece' was shown to be primarily present in human plasma as complexes of approximately 300 and 338 kDa [44]. However, by size exclusion chromatography of IgE⁺ serum, it was shown that IgE⁺ to Ag_{mn} is not likely to be polymeric IgE. Ag_{mn} reacted with monomeric IgE, whereas high molecular weight fractions did not sensitize basophils to release histamine to HRF [45]. Another isoform is 'IgE grandé', which contains 134 additional C-terminal amino acids [41], and 'IgE chimeric', in which the last 37 amino acids are replaced by 27 amino acids from the CH5 site (a cryptic exon, revealed by the use of a novel splice site within CH4), making it 10 acids shorter than 'IgE classic' [41]. It is possible that IgE⁺ is one of these isoforms, and is preferentially expressed in severe or chronic allergy.

Another possibility is that the structural difference of IgE⁺ is present in the variable region of the heavy chain (VH) of IgE. A variable binding of polyclonal human IgE antibodies to staphylococcal protein A has been described [46]. This binding is dependent on the VH subgroup. Correlation between VH subgroups and IgE⁺ has not yet been demonstrated.

Autoreactive IgE A third possibility is that IgE⁺ plays a role in autoallergy. According to this theory, IgE⁺ is an HRF-specific IgE antibody, and HRF is an IgE autoantigen. Autoallergy might be a driving force behind chronic airway inflammation, and explain how an intermittent disease

becomes a chronic disease. Some exogenous allergen might induce IgE antibodies that are cross-reactive with an endogenous protein. A triggering event (such as allergen-induced inflammation) causes the release of endogenous protein (HRF or autoallergen). This potentially results in a self-sustained allergic inflammatory reaction.

IgE-dependent HRF not binding to IgE

Priming factors are known to influence the histamine release of basophils. Chemokine-depleted HRF preparations produced by human mononuclear cells (Ag_{mn}) contain, besides IgE-dependent histamine-releasing activity, a priming factor that up-regulates allergen-induced histamine release even from basophils not releasing histamine to Ag_{mn}. Several cytokines have been described that enhance activation of basophils, such as rHRF p23 [47], IL-3 [48], IL-5 [49], and granulocyte macrophage-colony stimulating factor (GM-CSF) [48]. The identity of the factors responsible for the priming capacity of the Ag_{mn} preparation is not known.

HRF p23, also known as translationally controlled tumour protein (TCTP) [50], has been purified from a culture supernatant of the human U937 monocyte macrophage cell line by MacDonald et al. [14]. Despite the fact that this HRF induces histamine release from basophils of IgE⁺ donors, this factor does not seem to be an IgE-dependent HRF as defined in previous publications. HRF p23 primes basophils of IgE⁺ as well as IgE⁻ donors for anti-IgE mediated histamine release and secretion of IL-4 and IL-13 [47]. With affinity chromatography or enzyme-linked immunosorbent assays it was shown that rHRF p23 did not interact with IgE⁺ [51]. The signalling pathway triggered by rHRF p23 differs from that of IgE-dependent stimuli. Recombinant HRF p23 did not release histamine from a rat basophilic leukaemia cell line transfected with the functional human high-affinity IgE receptor and sensitized by IgE⁺, whereas anti-IgE did [52]. Moreover, it was shown that agents such as rottlerin enhanced histamine release induced by rHRF p23 in basophils from IgE⁺ donors, whereas histamine release induced by anti-IgE or allergen was not altered [53]. Recently, it has been shown that the reactivity of rHRF p23 did not appear to involve the IgE⁺ molecule, but that basophils of IgE⁺ donors were hyper-releasing, which was associated with low intracellular levels of the 5'-inositol phosphatase SHIP [15]. Thus, rHRF p23 discriminates between basophils, not between different IgE molecules (IgE⁺ or IgE⁻). In some cases rHRF p23 also act as a 'classical' HRF; however, this activity is quite rare. Only four of 106 sera of atopic patients with and without asthma exhibited IgE⁺ reactivity to rHRF p23 in the stripped basophil assay, and histamine release required high concentrations of rHRF (64 µg/mL) [54] (manuscript in preparation).

Recombinant HRF p23 also activates other cells besides basophils. It induced IL-8 secretion from GM-CSF primed eosinophils and enhanced TNF-α-stimulated IL-8 secretion [55]. Moreover, rHRF p23 was shown to be chemotactic for human eosinophils, and to induce calcium flux in eosinophils from 25% of donors [55]. This was also found in the eosinophil-like cell line, AML-3D10, which does not express the FcεR1α [55]. Preliminary findings also indicate that rHRF affects T cells [15].

All these results suggested that rHRF signals through its own receptor on basophils and other cells [47]. The nature of this HRF p23-specific receptor is still unknown.

IgE-dependent histamine-releasing factors binding to IgE: autoallergens

Histamine-releasing activity found in culture supernatants of human cells resembles that of conventional allergens, which might suggest that IgE autoallergens are involved. Structural and immunological similarities between exogenous allergens and human proteins have been described. IgE cross-reactivity was demonstrated between profilin from birch pollen and from human platelets using immunoblotting techniques [56]. Human profilin induced basophil histamine release from two individuals allergic to birch pollen profilin, whereas it did not from control subjects. Moreover, the allergens manganese-dependent superoxide dismutase, acidic ribosomal phosphoprotein type 2 and cyclophilin A, B and (to a minor extent) C from *Aspergillus fumigatus* were shown to be IgE cross-reactive with their human homologues [17, 57, 58]. Both human and fungal proteins elicited a strong immediate-type allergic skin reaction in individuals allergic to *A. fumigatus*, and induced comparable proliferative responses of mononuclear cells.

In immunoblotting experiments, Valenta et al. [16] showed that patients suffering from severe forms of atopy have IgE autoantibodies. IgE autoantibodies have been detected in sera from atopic dermatitis (AD) patients, recognizing different proteins in human cellular extracts. A strong IgE binding was associated with severe forms of atopic eczema [59]. However, we recently showed that IgE autoantigen-containing extracts did not induce histamine release of appropriately sensitized basophils [60].

HRF produced by mononuclear cells, HRF_{mn}, has intensively been studied in the stripped basophil assay by our group [54, 61]. Since this culture supernatant contains autoallergenic activity it was called autoallergen(s) Ag_{mn}. The exact nature of the factor(s) is still not clear. Results indicated that Ag_{mn} is distinct from HRF p23 and that the IgE responsiveness to Ag_{mn} is much more common than rHRF p23 [54]. Out of 82 atopic non-asthmatics and asthmatics with mild/moderate asthma, 46% had IgE^{mn+} in their serum, whereas only one serum of a rhinitis patient responded to rHRF p23. The difference of the factors was also obvious from another study: in sera from 2/13 patients with AD and 0/11 with severe asthma IgE responsiveness to rHRF p23 was found, whereas sera from 10 of the AD patients and 8 of the severe asthmatics contained IgE^{mn+}. Other results indicated IgE binding to immunoblotted human protein as found by Valenta et al. [16] and IgE responsiveness to Ag_{mn} are also not the same activities. No significant association was found between the presence of IgE autoantibodies to blotted human proteins and IgE^{mn+} in serum. These antibodies might be distinct entities that may co-occur in atopic patients [60].

There are data to suggest that at least one of the factors present in culture supernatants of human mononuclear cells is cross-reactive with a grass pollen allergen. By sensitization of stripped basophils with serum of atopic patients, we found that 33 out of 38 IgE^{mn+} serum were RAST positive to grass pollen (>0.4 IU IgE/mL), whereas only 11/44 from the

IgE^{mn-} were RAST positive to grass pollen [54]. Also, in our previous study an association with IgE to grass pollen was found [61]. To study this putative cross-reactivity, IgE antibodies to grass pollen were removed from IgE^{mn+} sera. Basophils sensitized by four out of five depleted sera had a decreased IgE responsiveness to Ag_{mn}. In one serum the IgE responsiveness to Ag_{mn} was not changed at all, which suggests that more than one activity is present in the preparation. Variation in cross-reactivity is a known phenomenon. For instance, IgE to grass pollen profilin is not always cross-reactive with birch profilin [62]. In addition, it is possible that the Ag_{mn} culture supernatant, which is only partially purified, contains more than one autoallergen. In Fig. 2, the results obtained by absorption of one patient serum is shown. By removing specifically IgE against high or low molecular weight fractions it was found that most IgE responsiveness to Ag_{mn} was removed after absorption to a >20 kDa grass pollen fraction. These results do not support the fact that Ag_{mn} is profilin, from which cross-reactivity between birch and human has been described [63], as a possible autoallergen.

If the factor present in culture supernatants of mononuclear cells is an autoallergen, it should be possible to show IgE binding to this factor. So far, IgE binding to Ag_{mn} has not been detected by RAST and radioimmunoprecipitation assays. Possibly the concentration of autoallergens is too low for detection in IgE-binding assays. The 'putative' autoallergen represents only a minor fraction of the total protein in the allergen preparation, and the sensitivity of IgE-binding assays is expected to be compromised by the irrelevant proteins before the bioassay is affected.

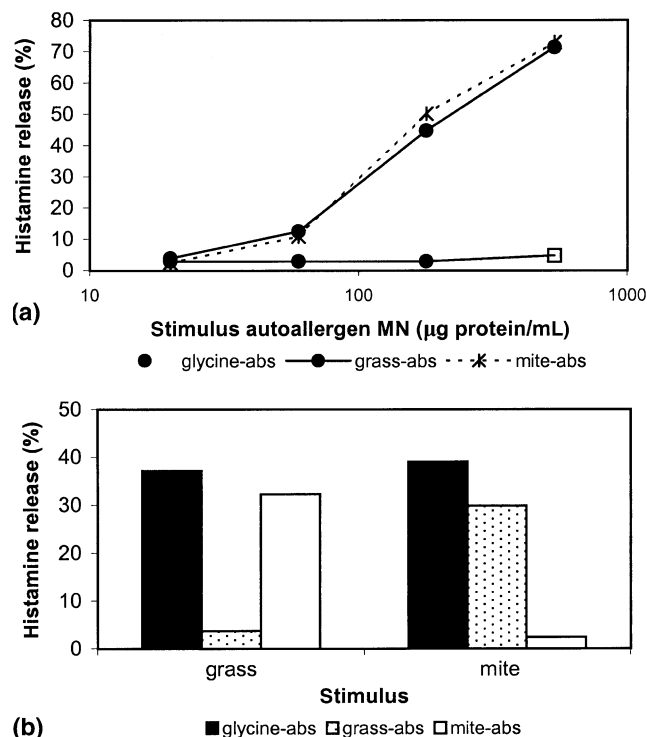


Fig. 2. Cross-reactivity between Ag_{mn} and a grass pollen allergen. IgE against grass pollen was removed from the IgE^{mn+} serum obtained from a mild asthmatic patient. As control, the serum was absorbed to glycine and house dust mite. Subsequently, basophils were sensitized by the absorbed serum, and stimulated by Ag_{mn} (a), grass pollen, or house dust mite extract (b).

Putative *in vivo* role of IgE⁺ and Ag_{mn}

The clinical relevance (if any) of IgE⁺ and IgE-dependent factors *in vivo* is also still not clear.

The relation between IgE⁺ and the clinical status of patients was investigated by studying the sensitizing capacity of serum to release histamine in response to Ag_{mn} in the stripped basophil assay. In serum from non-atopic non-asthmatic subjects a low prevalence of IgE responsiveness to partially purified Ag_{mn} was found (<5%) [54, 61]. Of atopic non-asthmatics and mild asthmatics, 42% and 49% had IgE^{mn+}, respectively [54]. These results confirmed those of another study, in which IgE^{mn+} was found in serum of 44% of patients with allergic asthma, 11% with non-allergic asthma, and 29% with rhinitis [61]. The presence of IgE⁺ in asthmatic patients was associated with a high bronchial sensitivity to histamine, which might indicate that IgE⁺ contributes to allergic disease.

For decades it has been assumed that IgE-dependent HRF and IgE⁺ play a role in the induction of the late allergic reaction (LAR). In many individuals, the acute allergic reaction is followed by an LAR 4–11 h later [64, 65]. During the acute allergic reaction, IgE antibodies on the surface of mast cells are cross-linked by environmental allergens, which cause the release of mediators. This, in turn, attracts inflammatory cells, such as basophils, neutrophils, eosinophils, monocytes, and lymphocytes to the allergic site [66–69]. Since the LAR occurs without a renewed exposure to allergen, the hypothesis was that the activation of basophils during the late reaction [70–72] was induced by the reaction of IgE⁺ with IgE-dependent HRF [73]. HRF might also exert an effect in the LAR by binding to IgE molecules present, for instance, on eosinophils [74, 75] and monocytes [76, 77], or by binding to an 'HRF'-specific receptor on cells [78]. The role of HRF/IgE⁺ in the LAR was supported by the observation that IgE-dependent HRF was present in late-phase skin blister fluids [11] and late-phase nasal lavages [12].

However, recent results did not support the hypothesis that IgE^{mn+} is an essential component in the induction of a late allergic reaction [54]. Atopic patients without and with mild/moderate asthma were bronchially provoked with house dust mite, and the mean change in forced expiratory volume in 1 s (FEV₁) during the LAR (4–10 h after provocation) was measured. The presence of IgE^{mn+} was shown not to be essential for an LAR: 63% of the patients with an LAR had no IgE^{mn+} in their serum. Moreover, 71% of patients with IgE^{mn+} did not have an LAR. No positive correlation was found between the prevalence of IgE^{mn+} and the LAR. In conclusion, IgE responsiveness to Ag_{mn} did not play a significant role in the drop of FEV₁ during the LAR, and is not the cause of a bronchial late allergic reaction. However, the presence of IgE^{mn+} might be an aggravating factor in asthma (manuscript in preparation): IgE responsiveness to Ag_{mn} was higher in the serum of severe asthmatics (81% of patients) than that in the serum from mild/moderate asthmatics (49% of patients) (Fig. 3) [54]. Also in atopic dermatitis, IgE^{mn+} was shown to be very common; it was found in 77% of tested sera. The hypothesis is that Ag_{mn} is released during the late or chronic reaction and if Ag_{mn}-responsive IgE is present, it may lead to an aggravation of atopic symptoms.

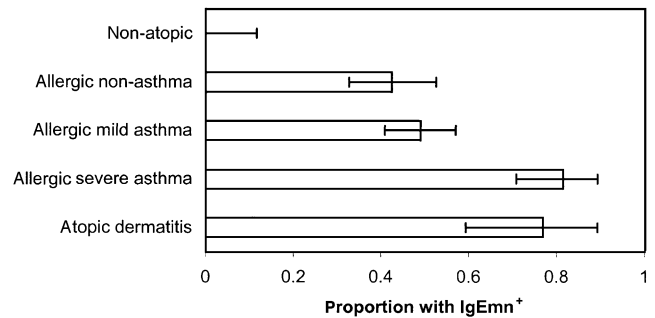


Fig. 3. Prevalence of IgE^{mn+} in different patient groups. Stripped basophils were sensitized by incubation with the serum of non-atopic controls ($n = 15$), or of patients with atopic non-asthma ($n = 33$), allergic mild asthma ($n = 49$), allergic severe asthma ($n = 27$), and atopic dermatitis ($n = 13$), and stimulated by Ag_{mn}.

Hypothesis about HRF_{mn} and IgE^{mn+}

Combining the results obtained during our studies to Ag_{mn}, we can hypothesize about the role of IgE^{mn+} and Ag_{mn} *in vivo*. IgE^{mn+} is proposed to contribute to chronicity of allergic disease. More specifically, IgE^{mn+} is a risk factor for severe asthma, since prevalence in this group is very high (manuscript in preparation). Additionally, it might also play a role in other chronic allergic disease, like atopic dermatitis. It is still not entirely clear if IgE^{mn+} is produced during an allergic reaction to exogenous allergens and subsequently induces a chronic allergic reaction, or, alternatively, that IgE⁺ is induced by endogenous allergens released during the chronic allergic reaction. Since some IgE^{mn+} is cross-reactive with a grass pollen allergen, it is most likely that IgE⁺ production is induced by an exogenous allergen.

In summary, Ag_{mn} might be released during the late or chronic allergic reaction. If IgE antibodies with cross-reactivity to Ag_{mn} (induced by exogenous allergens, such as grass pollen) are also present, the subsequent IgE-mediated reaction to the Ag_{mn} might prolong and aggravate the allergic and/or asthmatic symptoms even in the absence of exogenous allergen exposure. This hypothesis is summarized in Fig. 4.

Our results might indicate that patients with IgE^{mn+} in their serum are at risk of getting a more severe and chronic allergy. This theory might have therapeutical consequences, for instance a more aggressive pharmacological treatment. Moreover, if the grass pollen allergen cross-reactive with Ag_{mn} is identified, the effects of immunotherapy might be investigated.

Concluding remarks

Even after more than 20 years of research in relation to histamine-releasing factors the identity is still not clear. However, it is obvious that we are not dealing with a single factor. HRF is a heterogeneous group of proteins with different modes of action. Some factors influence histamine release of basophils independent of IgE, whereas others need IgE to exert their activity. However, the group of IgE-dependent HRF is also very diverse: some factors do and

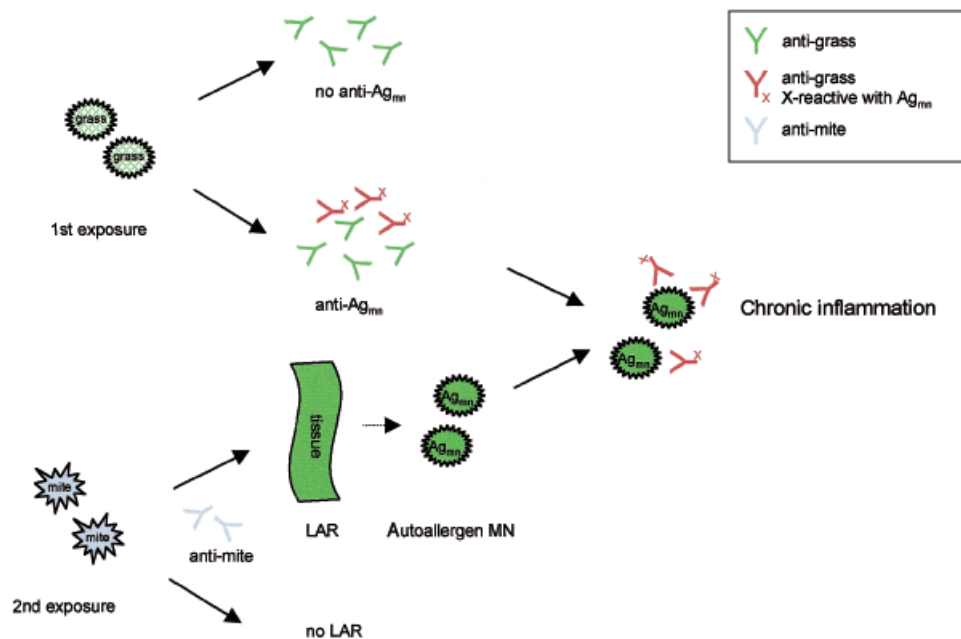


Fig. 4. Hypothetical role of Ag_{mn} and IgE^{mn+} . Anti-grass antibodies are produced during an acute allergic reaction to grass pollen. Some of these IgE antibodies might be cross-reactive to Ag_{mn} (IgE^{mn+} or anti- Ag_{mn}). If a second allergic reaction, for instance to house dust mite is followed by a late allergic reaction (LAR), endogenous proteins (autoallergens) might be released into the allergic site by tissue damage. If anti-MN and Ag_{mn} are present, the IgE antibodies will react with Ag_{mn} and aggravate the allergic reaction and the severity of asthma.

other factors do not bind to IgE. Moreover, both groups consist of factors discriminating between subpopulations of IgE, and of factors that do not.

IgE-dependent HRFs found in culture supernatants of human cells, the 'classical HRF', is likely to belong to the category of autoallergens.

References

- Thuesen DO, Speck LS, Lett-Brown MA, Grant JA. Histamine-releasing activity (HRA). 1. Production by mitogen-or antigen-stimulated human mononuclear cells. *J Immunol* 1979; 123:626–32.
- Lett-Brown MA, Thuesen DO, Plank DE, Duffy L, Grant JA. Histamine-releasing activity. V. Characterization and purification using high-performance liquid chromatography. *Cell Immunol* 1984; 87:445–51.
- Alam R, Forsythe PA, Lett-Brown MA, Grant JA. Cellular origin of histamine-releasing factor produced by peripheral blood mononuclear cells. *J Immunol* 1989; 142:3951–6.
- Schulman ES, Liu MC, Proud D, MacGlashan DWJ, Lichtenstein LM, Plaut M. Human lung macrophages induce histamine release from basophils and mast cells. *Am Rev Respir Dis* 1985; 131:230–5.
- Orchard MA, Kagey-Sobotka A, Proud D, Lichtenstein LM. Basophil histamine release induced by a substance from stimulated human platelets. *J Immunol* 1986; 136:2240–4.
- White JM, Kaliner MA. Neutrophils and mast cells. I. Human neutrophil-derived histamine-releasing activity. *J Immunol* 1987; 139:1624–30.
- Baeza ML, Haak-Frendscho M, Satnick S, Kaplan AP. Responsiveness to human mononuclear cell-derived histamine-releasing factor. Studies of allergic status and the role of IgE. *J Immunol* 1988; 141:2688–92.
- Liu MC, Proud D, Lichtenstein LM et al. Human lung macrophage-derived histamine-releasing activity is due to IgE-dependent factors. *J Immunol* 1986; 136:2588–95.
- Lichtenstein LM. Histamine-releasing factors and IgE heterogeneity. *J Allergy Clin Immunol* 1988; 81:814–9.
- Ezeamuzie IC, Assem ES. Antigen-induced formation of a lymphokine with a possible role as a mediator of the late component of dual allergic reaction. *Int Arch Allergy Appl Immunol* 1987; 82:221–4.
- Warner JA, Pienkowski MM, Norman Plaut M, Lichtenstein LM. Identification of histamine releasing factor(s) in the late phase of cutaneous IgE-mediated reactions. *J Immunol* 1986; 136:2583–7.
- MacDonald SM, Lichtenstein LM, Proud D et al. Studies of IgE-dependent histamine releasing factors: heterogeneity of IgE. *J Immunol* 1987; 139:506–12.
- Pasmans SGMA, Aalbers M, Daha MR, Knol EF, Jansen HM, Aalberse RC. Histamine-releasing activity in supernatants of mononuclear cells: contribution of monocyte chemotactic protein-1 activity compared with IgE-dependent activity. *J Allergy Clin Immunol* 1996; 98:962–8.
- MacDonald SM, Rafnar T, Langdon J, Lichtenstein LM. Molecular identification of an IgE-dependent histamine-releasing factor. *Science* 1995; 269:688–90.
- Vonakis BM, Gibbons S Jr, Sora R., Langdon JM, MacDonald SM. Src homology 2 domain-containing inositol 5' phosphatase is negatively associated with histamine release to human recombinant histamine-releasing factor in human basophils. *J Allergy Clin Immunol* 2001; 108:822–31.
- Valenta R, Maurer D, Steiner R et al. Immunoglobulin E response to human proteins in atopic patients. *J Invest Dermatol* 1996; 107:203–8.
- Cramer R, Faith A, Hemmann S et al. Humoral and cell-mediated autoimmunity in allergy to *Aspergillus fumigatus*. *J Exp Med* 1996; 184:265–70.
- Haak-Frendscho M, Sarafi M, Delespesse G, Kaplan AP. Comparison of mononuclear cells and B-lymphoblastoid histamine-releasing factor and their distinction from an IgE-binding factor. *Clin Immunol Immunopath* 1988; 49:72–82.
- Robertson MW, Albrandt K, Keller D, Liu FT. Human IgE-binding protein: a soluble lectin exhibiting a highly conserved

- interspecies sequence and differential recognition of IgE glycoforms. *Biochemistry* 1990; 29:8093–100.
- 20 Kuna P, Reddigari SR, Rucinski D, Oppenheim JJ, Kaplan AP. Monocyte chemotactic and activating factor is a potent histamine-releasing factor for human basophils. *J Exp Med* 1992; 175:489–93.
 - 21 Alam R, Lett-Brown MA, Forsythe PA et al. Monocyte chemotactic and activating factor is a potent histamine-releasing factor for basophils. *J Clin Invest* 1992; 89:723–8.
 - 22 Bischoff SC, Krieger M, Brunner T, Dahinden CA. Monocyte chemotactic protein 1 is a potent activator of human basophils. *J Exp Med* 1992; 175:1271–5.
 - 23 Dahinden CA, Geiser T, Brunner T et al. Monocyte chemotactic protein 3 is a most effective basophil- and eosinophil-activating chemokine. *J Exp Med* 1994; 179:751–6.
 - 24 Stellato C, Collins P, Ponath PD et al. Production of the novel C–C chemokine MCP-4 by airway cells and comparison of its biological activity to other C–C chemokines. *J Clin Invest* 1997; 99:926–36.
 - 25 Kuna P, Reddigari SR, Schall TJ, Rucinski D, Viksman MY, Kaplan AP. RANTES, a monocyte and T lymphocyte chemotactic cytokine releases histamine from human basophils. *J Immunol* 1992; 149:636–42.
 - 26 Alam R, Forsythe PA, Stafford S, Lett-Brown MA, Grant JA. Macrophage inflammatory protein-1 α activates basophils and mast cells. *J Exp Med* 1992; 176:781–6.
 - 27 Forssmann U, Ugucioni M, Loetscher P et al. Eotaxin-2, a novel CC chemokine that is selective for the chemokine receptor CCR3, and acts like eotaxin on human eosinophil and basophil leukocytes. *J Exp Med* 1997; 185:2171–6.
 - 28 Subramanian N, Bray MA. Interleukin 1 releases histamine from human basophils and mast cells *in vitro*. *J Immunol* 1987; 138:271–5.
 - 29 Haak-Frendscho M, Dinarello C, Kaplan AP. Recombinant human interleukin-1 beta causes histamine release from human basophils. *J Allergy Clin Immunol* 1988; 82:218–23.
 - 30 MacDonald SM, Schleimer RP, Kagey-Sobotka A, Gillis S, Lichtenstein LM. Recombinant IL-3 induces histamine release from human basophils. *J Immunol* 1989; 142:3527–32.
 - 31 Haak-Frendscho M, Arai N, Arai K, Baeza ML, Finn A, Kaplan AP. Human recombinant granulocyte-macrophage colony-stimulating factor and interleukin 3 cause basophil histamine release. *J Clin Invest* 1988; 82:17–20.
 - 32 Massey WA, Randall TC, Kagey-Sobotka A et al. Recombinant human IL-1 α and -1 β potentiate IgE-mediated histamine release from human basophils. *J Immunol* 1989; 143:1875–80.
 - 33 Hirai K, Morita Y, Misaki Y et al. Modulation of human basophil histamine release by hemopoietic growth factors. *J Immunol* 1988; 141:3958–64.
 - 34 Pasmans SGMA, Witteman AM, Aalbers M et al. Variability of IgE-dependent activity in supernatants of human mononuclear cells. *Int Arch Allergy Immunol* 1994; 103:44–52.
 - 35 Marone G, Casolaro V, Paganelli R, Quinti I. IgG anti-IgE from atopic dermatitis induces mediator release from basophils and mast cells. *J Invest Dermatol* 1989; 93:246–52.
 - 36 Marone G, Spadaro G, Palumbo C, Condorelli G. The anti-IgE/anti-Fc ϵ R1 α autoantibody network in allergic and autoimmune diseases. *Clin Exp Allergy* 1999; 29:17–27.
 - 37 Shakib F, Smith SJ. *In vitro* basophil histamine-releasing activity of circulating IgG1 and IgG4 autoanti-IgE antibodies from asthma patients and the demonstration that anti-IgE modulates allergen-induced basophil activation. *Clin Exp Allergy* 1994; 24:270–5.
 - 38 MacDonald SM, Lichtenstein LM. Histamine-releasing factors and heterogeneity of IgE. *Springer Semin Immunopathol* 1990; 12:415–28.
 - 39 Kleine-Tebbe J, Kagey-Sobotka A, MacGlashan DW, Lichtenstein LM, MacDonald SM. Lectins do not distinguish between heterogeneous IgE molecules as defined by differential activity of an IgE-dependent histamine releasing factor. *J Allergy Clin Immunol* 1996; 98:181–8.
 - 40 Shibasaki M, Sumazaki R, Isoyama S, Takita H. Interaction of lectins with human IgE: IgE-binding property and histamine-releasing activity of twelve plant lectins. *Int Arch Allergy Immunol* 1992; 98:18–25.
 - 41 Lyczak JB, Zhang K, Saxon A, Morrison SL. Expression of novel secreted isoforms of human immunoglobulin E proteins. *J Biol Chem* 1996; 271:3428–36.
 - 42 Batista FD, Efremov DG, Burrone OR. Characterization of a second secreted IgE isoform and identification of an asymmetric pathway of IgE assembly. *Proc Natl Acad Sci USA* 1996; 93:3399–404.
 - 43 Hellman L. Characterization of four novel ϵ chain mRNA and a comparative analysis of genes for immunoglobulin E in rodents and man. *Eur J Immunol* 1993; 23:159–67.
 - 44 Chan LA, Lyczak JB, Zhang K, Morrison SL, Saxon A. The novel human IgE ϵ heavy chain, ϵ tailpiece, is present in plasma as part of a covalent complex. *Mol Immunol* 2000; 37:241–52.
 - 45 Kleine Budde I, Knol EF, Aalbers M, van der Zee JS, Aalberse RC. Reactivity to IgE-dependent histamine-releasing factor is due to monomeric IgE. *Allergy* 2000; 55:653–7.
 - 46 Johansson SG, Inganas M. Interaction of polyclonal human IgE with protein-A from *Staphylococcus aureus*. *Immunol Rev* 1978; 41:248–60.
 - 47 Schroeder JT, Lichtenstein LM, MacDonald SM. Recombinant histamine-releasing factor enhances IgE-dependent IL-4 and IL-13 secretion by human basophils. *J Immunol* 1997; 159:447–52.
 - 48 Bischoff SC, de Weck AL, Dahinden CA. Interleukin 3 and granulocyte/macrophage-colony-stimulating factor render human basophils responsive to low concentrations of complement component C3a. *Proc Natl Acad Sci U S A* 1990; 87:6813–7.
 - 49 Bischoff SC, Brunner T, de Weck AL, Dahinden CA. Interleukin 5 modifies histamine release and leukotriene generation by human basophils in response to diverse agonists. *J Exp Med* 1990; 172:1577–82.
 - 50 Gross B, Gaestel M, Bohm H, Bielka H. cDNA sequence coding for a translationally controlled human tumor protein. *Nucleic Acids Res* 1989; 17:8367.
 - 51 MacDonald SM. Histamine-releasing factors. *Curr Opin Immunol* 1996; 8:778–83.
 - 52 Wantke F, MacGlashan DW, Langdon JM, MacDonald SM. The human recombinant histamine releasing factor: functional evidence that it does not bind to the IgE molecule. *J Allergy Clin Immunol* 1999; 103:642–8.
 - 53 Bheekha-Escura R, Chance SR, Langdon JM, MacGlashan DWJ, MacDonald SM. Pharmacologic regulation of histamine release by the human recombinant histamine-releasing factor. *J Allergy Clin Immunol* 1999; 103:937–43.
 - 54 Kleine Budde I, Lopuhaa CE, de Heer PG et al. Lack of correlation between bronchial late allergic reaction to *Dermatophagoides pteronyssinus* and *in vitro* Immunoglobulin E reactivity to histamine-releasing factor derived from mononuclear cells. *Ann Allergy Asthma Immunol* 2002; 89:606–12.
 - 55 Bheekha-Escura R, MacGlashan DW, Langdon JM, MacDonald SM. The human recombinant histamine releasing factor (HrHRF) activates human eosinophils and the eosinophilic-like cell line, AML 14-3D10. *Blood* 2000; 96:2191–8.
 - 56 Valenta R, Duchene M, Pettenburger K. et al.. Identification of profilin as a novel pollen allergen; IgE autoreactivity in sensitized individuals. *Science* 1991; 253:557–60.
 - 57 Fluckiger S, Fijten H, Whitley P, Blaser K, Cramer R. Cyclophilins, a new family of cross-reactive allergens. *Eur J Immunol* 2002; 32:10–7.
 - 58 Mayer C, Hemmann S, Faith A, Blaser K, Cramer R. Cloning, production, characterization and IgE cross-reactivity of different manganese superoxide dismutases in individuals sensitized to *Aspergillus fumigatus*. *Int Arch Allergy Immunol* 1997; 113:213–5.

- 59 Natter S, Seiberler S, Hufnagl P et al. Isolation of cDNA clones coding for IgE autoantigens with serum IgE from atopic dermatitis patients. *FASEB J* 1998; 12:1559–69.
- 60 Kleine Budde I, de Heer PG, Natter S. Studies on the association between IgE autoreactivity and IgE-dependent histamine-releasing factors. *Immunology* 2002; 107:243–51.
- 61 Pasmans SGMA, Aalbers M, van der Veen MJ et al. Reactivity to IgE-dependent histamine-releasing activity in asthma or rhinitis. *Am J Respir Crit Care Med* 1996; 154:318–23.
- 62 van Ree R, Voitenko V, van Leeuwen WA, Aalberse RC. Profilin is a cross-reactive allergen in pollen and vegetable foods. *Int Arch Allergy Immunol* 1992; 98:97–104.
- 63 Miadonna A, Roncarolo MG, Lorini M, Tedeschi A. Inducing and enhancing effects of IL-3, -5, and -6 and GM-CSF on histamine release from human basophils. *Clin Immunol Immunopath* 1993; 67:210–5.
- 64 MacGlashan DWJ, Schleimer RP, Peters SP et al. Comparative studies of human basophils and mast cells. *Fed Proc* 1983; 42:2504–9.
- 65 Busse WW, Calhoun WF, Sedgwick JD. Mechanism of airway inflammation in asthma. *Am Rev Respir Dis* 1993; 147:S20–S24.
- 66 Bascom R, Pipkorn U, Lichtenstein LM, Naclerio RM. The influx of inflammatory cells into nasal washings during the late response to antigen challenge. Effect of systemic steroid pretreatment. *Am Rev Respir Dis* 1988; 138:406–12.
- 67 De Monchy JG, Kauffman HF, Venge P et al. Bronchoalveolar eosinophilia during allergen-induced late asthmatic reactions. *Am Rev Respir Dis* 1985; 131:373–6.
- 68 Liu MC, Hubbard WC, Proud D et al. Immediate and late inflammatory responses to ragweed antigen challenge of the peripheral airways in allergic asthmatics. Cellular, mediator, and permeability changes. *Am Rev Respir Dis* 1991; 144:51–8.
- 69 Charlesworth EN, Hood AF, Soter NA, Kagey-Sobotka A, Norman PS, Lichtenstein LM. Cutaneous late-phase response to allergen. Mediator release and inflammatory cell infiltration. *J Clin Invest* 1989; 83:1519–26.
- 70 Schleimer RP, Fox CC, Naclerio RM et al. Role of human basophils and mast cells in the pathogenesis of allergic diseases. *J Allergy Clin Immunol* 1985; 76:369–74.
- 71 Guo CB, Liu MC, Galli SJ, Bochner BS, Kagey-Sobotka A, Lichtenstein LM. Identification of IgE-bearing cells in the late-phase response to antigen in the lung as basophils. *Am J Respir Cell Mol Biol* 1994; 10:384–90.
- 72 Naclerio RM, Hubbard W, Lichtenstein LM, Kagey-Sobotka A, Proud D. Origin of late phase histamine release. *J Allergy Clin Immunol* 1996; 98:721–3.
- 73 Charlesworth EN, Iliopoulos O, MacDonald SM, Kagey-Sobotka A, Lichtenstein LM. Cells and secretagogues involved in human late-phase response. *Int Arch Allergy Appl Immunol* 1989; 88: 50–3.
- 74 Gounni AS, Lamkhioed B, Ochiai K et al. High-affinity IgE receptor on eosinophils is involved in defence against parasites. *Nature* 1994; 367:183–6.
- 75 Dombrowicz D, Woerly G, Capron M. IgE receptors on human eosinophils. *Chem Immunol* 2000; 76:63–76.
- 76 Maurer D, Fiebiger E, Reininger B et al. Expression of functional high affinity immunoglobulin E receptors (Fc ϵ RI) on monocytes of atopic individuals. *J Exp Med* 1994; 179:745–50.
- 77 Maurer D, Ebner C, Reininger B et al. The high affinity IgE receptor (Fc ϵ RI) mediates IgE-dependent allergen presentation. *J Immunol* 1995; 154:6285–90.
- 78 MacDonald SM. Human recombinant histamine-releasing factor. *Int Arch Allergy Immunol* 1997; 113:187–9.