

Review article

Chemokines as allergic mediators –
relationship to histamine-releasing factors

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Interest in histamine-releasing factors (HRF) stems from the initial studies of Thuesen et al. (57, 58), which indicated that mononuclear cells secrete one or more substances capable of degranulating human basophils to release histamine. HRF was distinguished from IgE antibody and from the anaphylatoxin fragments such as C3a and C5a. We now know that HRF is not a single substance, but a mixture of closely related molecules, most of which are members of the chemokine group of cytokine-like molecules (Table 1).

The term “chemokines” denotes a series of structurally related cytokines which are chemotactic factors, and therefore recruit inflammatory cells into an area of tissue injury, and also activate them. There

are two subgroups of chemokines, as shown in Table 1, termed α and β . All chemokines have a mol. mass of approximately 8 kDa, and have four critical cysteine residues positioned similarly. The first two cysteines may have a single amino acid between them (C–X–C) characteristic of the α subgroup, or these two cysteines may be adjacent (C–C), as seen in the β subgroup. All of these cytokine-like molecules bind to heparin, although their relative affinity varies, and the α and β subgroups are encoded on different chromosomes, i.e., chromosomes 4 and 17, respectively. Once purified, the α chemokines can be sequenced readily since the N-terminus is free, whereas the β chemokines are more difficult by virtue of having a blocked N-terminus. The potent HRFs thus far identified are members of the β chemokine family although both α and β chemokines may have a role in the recruitment and activation of basophils, eosinophils, monocytes, and lymphocytes.

HRF-dependent basophil activation

Various reports have confirmed the original observation that mononuclear cells (24, 25, 29, 38, 39, 51) or platelets (44) can produce cytokines that cause basophil degranulation and histamine release; however, there was little progress in isolating and char-

Table 1. The chemokine family

Subfamily α	Subfamily β
Platelet factor 4	MCAF/MCP-1
β Thromboglobulin	MCP-2
CTAP III/NAP-2	MCP-3
Interleukin-8 (NAP-2)	RANTES
Melanoma growth factor (GRO/MGSA)	MIP 1 α
Macrophage inflammatory protein (MIP-2)	MIP 1 β
IP-10	I-309
	HC 11, 14

acterizing such factors on a molecular basis until the chromatographic separation reported by Baeza et al. (8). A combination of ion-exchange chromatography and gel filtration separated HRF into at least three fractions, each of which released histamine upon incubation with human basophils. Thus, HRF appeared to be either a single factor with multiple molecular forms or multiple gene products with overlapping functions. The latter proved to be correct. Application of high-performance liquid chromatography (HPLC) and preparative elution from sodium dodecyl sulfate (SDS) gels led to purification of an 8–10-kDa protein (9), and amino acid sequence analysis revealed it to be CTAP III/NAP-2, an α chemokine. In this instance, there was microheterogeneity because the gel band was broad and the amino acid sequence of the upper half of the broad band corresponded to connective-tissue-activating protein (CTAP) III, while the amino acid sequence of the lower half was identical except that the *N*-terminus began with amino acid no. 16. Enzymatic cleavage of purified CTAP III (produced from platelets) with purified elastase or supernatants from activated monocytes (61) removes the *N*-terminal 15 residues and converts them to neutrophil-activating protein (NAP)-2. These proved to be plentiful chemokines, each of which acted on basophils in the 0.5–10.0 $\mu\text{g/ml}$ range; therefore, they were relatively weak on a molar basis. CTAP III was originally described as an activator of fibroblasts to stimulate synthesis of DNA, sulfated glycosaminoglycans, hyaluronic acid, and prostaglandin E_2 (18). Removal of the *N*-terminal 15 residues generates NAP-2, which retains the activities of CTAP III but acquires the capacity to attract neutrophils and to activate them. CTAP III and NAP-2 are equipotent in capacity for basophil histamine release (46). NAP-1, described earlier, is identical to interleukin (IL)-8 (Table 1), a potent chemotactic factor and activator of neutrophils (66).

Subsequent studies proceeded either by further purification and characterization of HRF by HPLC, or by assaying all of the described α or β chemokines for activity on human basophils or mast cells. Kuna et al. (33) and Alam et al. (4) showed that MCAF or MCP-1, a β chemokine, is a potent HRF (Fig. 1). MCAF/MCP-1 accounts for 50–60% of the total histamine-releasing capability of mononuclear cell supernatants, and about 90% of the activity of the initial chromatographic peak, which also contains CTAP III/NAP-2 and IL-8. For example, immunoprecipitation of peak I with monoclonal antibodies against CTAP III leaves a faint band in the same position upon SDS gel electrophoresis which retains approximately 90% of the original activity and corresponds to MCAF/MCP-1 by immunoblotting (32). This protein was discovered by two research groups

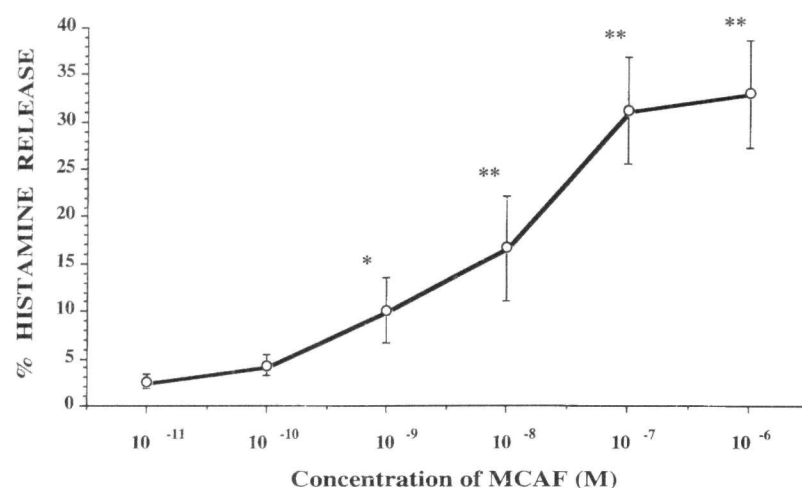


Fig. 1. Dose-dependent histamine release by MCAF. Basophils of six subjects were challenged with MCAF from 10^{-11} to 10^{-6} M, and the percent histamine release was determined. Results are expressed as mean percentage of histamine release $\pm$ SEM. * $P \leq 0.022$; ** $P \leq 0.014$, as compared with histamine release induced by 10^{-11} M MCAF (Wilcoxon's rank sum test).

— hence the two designations — who named it, respectively, monocyte chemotactic and activating factor or monocyte chemotactic protein-1 (41, 66). It is produced by monocytes (and other cells) and attracts monocytes and activates them. It is also chemotactic for basophils (37) and, as HRF, activates them to release histamine. Histamine release is G-protein dependent (15) and is exceedingly rapid with a $t_{1/2}$ of approximately 30 s (33) (Fig. 2), and its potency is equal to that of IgE plus antigen (35) (Table 2). Since the late-phase allergic reaction is characterized by basophil infiltration (10, 23, 55) and protracted histamine release (26, 45, 47, 52), MCAF/MCP-1 production must be considered to be one of the contributing factors. Soon thereafter Bischoff et al. (14) confirmed the activity of MCAF/MCP-1

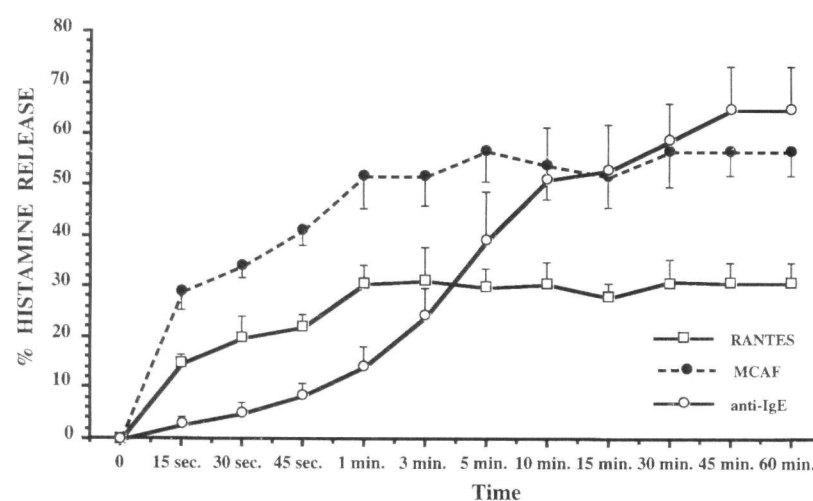


Fig. 2. Kinetics of histamine release by RANTES, MCAF/MCP-1, and anti-IgE. Leukocytes from six subjects were incubated with RANTES (10^{-7} M), MCAF/MCP-1 (10^{-7} M), or anti-IgE (1 $\mu\text{g/ml}$) for given time. Ice-cold HEPES-buffered saline containing 10 mM EDTA at pH 7.4 was then added, and supernatant was separated immediately by centrifugation at 10 000 g for 15 s, and assayed for histamine content. Results are expressed as mean $\pm$ SEM.

Table 2. Histamine release from human basophils induced by most active secretagogues, expressed in U of histamine-releasing activity^a

Factor	Protein concentration used to induce histamine release	Units of histamine-releasing activity
Anti-IgE	1 µg/ml	1094
C5a	800 ng/ml	1188
MCAF	860 ng/ml	1041.9
RANTES	800 ng/ml	522.5
IL-3	500 ng/ml	356
FMLP	4.37 µg/ml	219.6
MIP-1α	800 ng/ml	190
MIP-1β	800 ng/ml	137.5
CTAP III	10 µg/ml	51.8
NAP-2	10 µg/ml	19.2

^a One U of histamine-releasing activity is equal to 50% of total histamine release from basophils caused by 1.0 mg of given protein, and was calculated according to the formula:

$$U = \frac{1.0 \text{ (mg)}}{\text{protein amount used to induce histamine release}} \times \frac{\% \text{ histamine release}}{50}$$

upon basophils. MCP-2 and MCP-3 are closely homologous to MCP-1, but can be separated from it by ion-exchange chromatography (60). MCP-2 is a trace protein possessing about half the HRF activity of MCP-1 (unpublished observations), but its contribution to the total activity of mononuclear cells or platelet supernatants is not known. MCP-3 has not been tested.

Another β chemokine with basophil chemotactic activity and HRF activity is RANTES (36). This chemokine was first described as a product of T cells (50) which is chemotactic for monocytes and a subpopulation of "memory" lymphocytes (49). Because RANTES is a β chemokine like MCAF/MCP-1, we tested recombinant material for HRF activity and found it to be half as potent as MCAF/MCP-1. It had the same dose-response (10^{-9} – 10^{-7} M) range with equally rapid histamine release (Fig. 2), but, on average, the percent histamine release was half of that seen with MCAF/MCP-1. Whereas virtually all subjects tested were responsive to MCAF/MCP-1, whether atopic or not, 80% of subjects responded to RANTES, and atopic subjects' cells were more responsive (35). RANTES is more difficult to work with than MCAF/MCP-1; it is more readily denatured, an incubation temperature of 37°C is critical, and binding to any red blood cell present may affect its activity, as has been shown for IL-8 (21).

Macrophage inflammatory protein (MIP) Iα and MIP Iβ are closely related molecules originally described in rodents as macrophage inflammatory factors (22). Both are β-type chemokines that are chemotactic for activated human lymphocytes. MIP Iβ recruits primarily CD4(+) T cells, while MIP Iα recruits CD8(+) T cells (56). MIP Iα has been re-

ported to have HRF activity on basophils of atopic subjects (14/20 responded at 10^{-9} – 10^{-7} M) (56) which is similar to the activity of RANTES. Our own studies of both MIP Iα and MIP Iβ found only 6/20 responders, and the potency was 30–40% of that of RANTES (35). MIP Iα is chemotactic for basophils, and this activity is comparable to that of MCAF/MCP-1 (2).

IL-8 (NAP-1) is an α chemokine reported to have histamine-releasing activity upon basophils; however, its contribution to the activity seen in mononuclear cell/platelet supernatants is uncertain. No significant histamine is seen unless basophils are first primed (pretreated) with IL-3, IL-5, or granulocyte/macrophage-colony stimulating factor (GM-CSF). Then significant release of both histamine and leukotriene C₄ has been reported (11, 13, 20); however, the priming effect is more pronounced on leukotriene secretion. We have found that only an occasional subject has significant histamine release to IL-3 plus IL-8, and our data are, in general, negative (35). Furthermore, IL-8 is contained in the peak I of fractionated supernatants and accounts for less than 5% of the activity present. Thus, we do not feel that IL-8 is a major contributor to HRF activity on basophils. The most potent factors thus far reported are MCAF/MCP-1 and RANTES, with lesser contributions by MIP Iα and β and CTAP III/NAP-2 (35) (Table 2).

Priming of basophils for HRF-induced secretion

The responsiveness of basophils to HRF can be modulated by preincubation with low concentrations of cytokines which are unable themselves to induce secretion. Thus, preincubation of basophils with (10^{-9} – 10^{-8} M) IL-3 or IL-5, or GM-CSF can augment the release of histamine by a subsequent exposure to 10^{-7} M MCAF/MCP-1 or 10^{-7} M RANTES. The overlapping activities (in this instance, priming) by this group of cytokines may be related to the fact that the receptors for these cytokines share a subunit; that is, they consist of an α-chain that is specific for each, and a common β-chain (40). Higher concentrations of IL-3, and, to a lesser degree, GM-CSF, can directly induce histamine release from basophils (27, 35). In general, the responsive subjects are atopic patients whose cells are probably primed *in vivo*. Immunoabsorption of IL-3 from cell supernatants depletes HRF activity by about 15–20%. This is probably due to the priming effect of IL-3 rather than its ability directly to induce secretion based on the relative concentrations required. Therefore, IL-3 is unusual because it is the only cytokine that is not a chemokine which can cause basophil secretion and contribute sig-

nificantly to HRF activity (Table 1). Immunoabsorption of MCAF/MCP-1, RANTES, and IL-3 accounts for 75–80% reduction in the total HRF activity of mononuclear cells/platelet-derived supernatants.

Cytokine-dependent activation of mast cells

In general, mast cells are less responsive to cytokines/chemokines than are basophils. Mast cells derived from different species or different sites/organs of the same species may also respond differently. Bischoff & Dahinden (12) surveyed a large variety of cytokines, including many of the chemokines, using human lung mast cells, and reported that stem-cell factor (also known as c-kit ligand) was the only one with significant histamine-releasing activity. MCAF/MCP-1, in particular, was negative. Columbo et al. (19) then showed that stem-cell factor also causes histamine release from cutaneous mast cells, and that it can prime both mast cells and basophils for histamine release caused by other agonists. It does not, however, cause histamine release from basophils. Thus, the activity on mast cells may be of particular importance. MIP I α is active on rodent mast cells; human mast cells have not been tested (2).

Chemokine-dependent inhibition of basophil histamine release

Soon after the concept of HRF evolved, mononuclear cell supernatants were found to contain an inhibitor of HRF-dependent histamine release, and this inhibitor was designated histamine release inhibitory factor (HRIF) (3). IL-8 has been thought to fulfill the function attributed to HRIF because preincubation of basophils with concentrations ranging from 10^{-11} to 10^{-8} M inhibits HRF-induced histamine release (31), as well as histamine release by recombinant MCAF (Fig. 3). Subsequently, preincubation with low concentrations of RANTES has been shown to inhibit HRF- or MCAF-induced histamine release (1), suggesting that inhibition may be a more general phenomenon. However, the mechanism is unclear because there are few data available on chemokine receptors.

It is of interest that preincubation of basophils with concentrations of MCAF that are insufficient to cause histamine secretion prevents secretion in response to a subsequent challenge with 10^{-7} M MCAF. Washing the cells after the initial incubation does not reverse the process, suggesting either receptor blockade by a high-affinity ligand that cannot be removed by simple washing, or induction of some active process that inhibits secretion. This phenom-

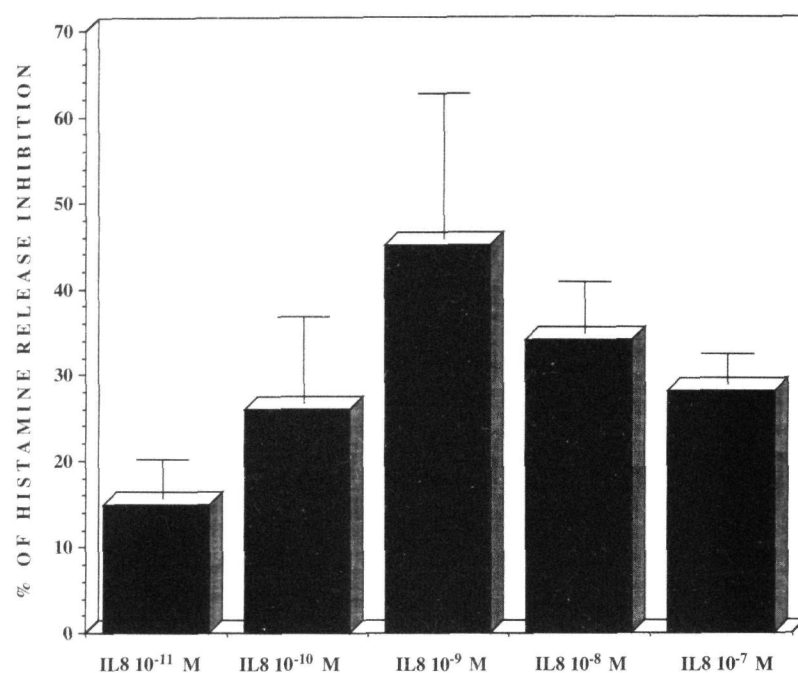


Fig. 3. Dose-dependent inhibition of histamine release by IL-8. Basophils were preincubated with or without 10^{-11} – 10^{-7} M IL-8. Cells were then exposed to HRF_{crude} for 40 min. Results are mean $\pm$ SEM of two experiments in four subjects.

enon is referred to as homologous “desensitization” as in ligand-receptor interactions that are coupled to the G proteins described previously for chemotactic factors. Preincubation with RANTES (10^{-9} M) similarly desensitizes to a subsequent challenge with 10^{-7} M RANTES.

However, we have found that preincubation of basophils with a wide variety of α or β chemokines tested at 5×10^{-9} M inhibits subsequent secretion by optimal MCAF/MCP-1 (10^{-7} M). Washing the cells after the initial incubation reverses the inhibition. Inhibition by RANTES was 69%; by MIP I α , 49%; by MIP I β , 43%; by PF4, 57%; by IL-8, 41%; by CTAP III, 27%; and by IP10, 15% (34). This may reflect “receptor class desensitization” in which the agonists act on different receptors which couple to the same or very similar G proteins. The kinase that phosphorylates the occupied receptor to uncouple it from the G protein acts also on other unoccupied receptors to uncouple them also and diminish the response.

Chemokine receptors

The data accumulated thus far suggest that the α and β chemokines interact with separate receptors although there may be multiple receptor types within each group. Neote et al. described a receptor on HL60 cells which binds MIP I α , MIP I β , RANTES, and MCAF (43). It has seven transmembrane domains, is linked to a pertussis-sensitive G protein, and has 32% homology with the IL-8 receptor, but is not stimulated by IL-8. Wang et al. characterized a high-affinity receptor for RANTES on the human monocyte leukemia cell THP-1 which also reacts with MCAF and MIP I α (62). Yet preincubation

with MCAF desensitizes the cells to RANTES, while preincubation with RANTES does not desensitize to the other factors. Such data suggest a shared receptor as well as a specific RANTES receptor. On the other hand, a human NK cell line (YT) reacts with MIP 1α and β but *not* with MCAF (MCP-1) (63).

Human monocytes appear to have a separate, specific high-affinity MCAF/MCP-1 receptor (59, 63, 65), as well as a receptor reactive with β chemokines in general, but not with α chemokines. On the other hand, the IL-8 receptor has been cloned, and other α chemokines compete with IL-8 for binding (42). Of particular interest is the fact that MIP 1α , MIP 2α , MCAF, IL-8, and PF4, a mixture of α and β chemokines, inhibit proliferation of human myeloid progenitor cells. Synergistic effects are obtained when low concentrations of any two of these are combined in concentrations in which neither alone was active (16). This resembles the common effects of α and β chemokines we found in studies of inhibition of basophil histamine secretion. The molecular nature of basophil chemokine receptors is unknown.

Activation of eosinophils

Since eosinophils are major effector cells of allergic inflammation and may be derived from the same precursor cell as the basophil, it is of interest to test the various chemokines for eosinophil activity, eosinophil activation and degranulation, or both. Recently, Kameyoshi et al. (28) have shown that RANTES is chemotactic for eosinophils, while Rot et al. (48) showed that RANTES also degranulates them. However, the concentration necessary and the time course of activation were not specified, and cytochalasin-B-treated cells were utilized in studies of secretion. A later report by Alam et al. (5) confirmed that RANTES is chemotactic for purified eosinophils between 10^{-8} and 10^{-9} M and showed that it upregulated the expression of CD11b/CD18, caused release of eosinophil cationic protein (ECP), and rendered the cells "hypodense", suggesting an activated phenotype. Fig. 4 shows a dose response of the release of ECP upon incubation of purified human eosinophils with recombinant RANTES.

Conclusion: chemokines, HRF, and allergic diseases

One of the areas of particular relevance to these findings is the potential contribution of chemokines to the late-phase allergic response. There are some data to suggest that HRF is functionally present in cutaneous late-phase reactions (64) and that injection of chemokines in rodents (7) can elicit a re-

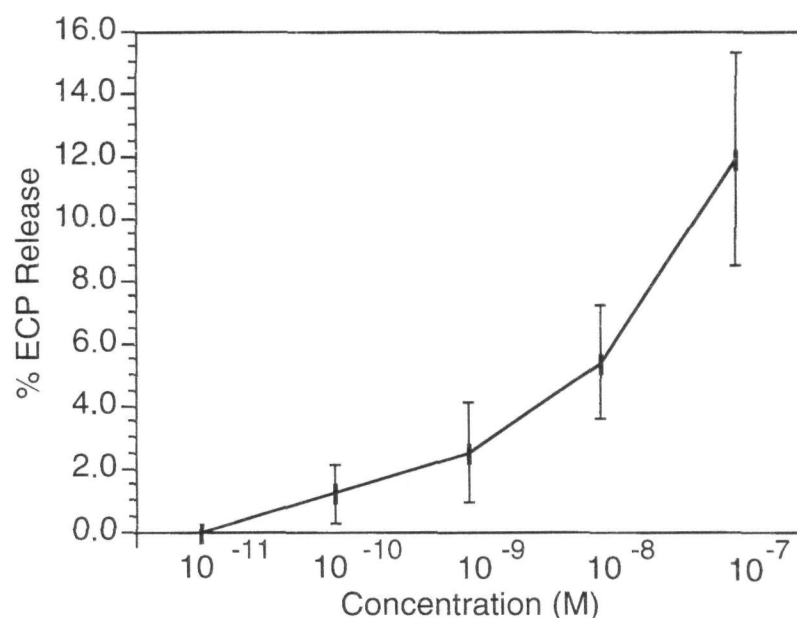


Fig. 4. Dose-dependent ECP release by RANTES. Eosinophils of six atopic donors were challenged with RANTES from 10^{-11} to 10^{-7} M, and the percent ECP release was determined.

sponse that resembles the late phase. Findings in human diseases are only preliminary; however, identification of the specific proteins involved and development of specific reagents for their quantitation and detection in body fluids and within tissues will allow such studies to be completed. In nasal washings of allergic subjects, HRF activity has been found which decreases with topical steroid therapy (53, 54) or immunotherapy (17). It is also found in bronchoalveolar lavage fluids (6). Preseasonal immunotherapy also modulates HRF production in seasonal asthmatic patients (30).

There are numerous data indicating that basophils infiltrate tissues during the late phase and that there is protracted histamine release in the absence of tryptase secretion; this suggests basophil degranulation. It is unclear whether persisting antigen is a prerequisite for a late-phase reaction, but there is certainly a ready mechanism by which such histamine release can occur in the absence of antigen or IgE antibody. Quantitatively, the most striking change during the late phase is the infiltration and activation of eosinophils. RANTES and MIP 1α and β may be key factors in the recruitment and activation of such cells. The increment in $T_4(+)$ helper cells and monocytes is small, but such cells are activated and may provide a ready source of chemokines. The possibility that mast cells, basophils, eosinophils, or all three produce chemokines as well must also be examined because they secrete various cytokines that were heretofore unsuspected.

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