



Review

Dimerization of TCTP and its clinical implications for allergy


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ABSTRACT

Following the detection of histamine-releasing activity (HRA) in the supernatants of peripheral blood mononuclear cell cultures, research efforts were directed at characterizing the source of this activity, mostly focusing, on IgE-dependent histamine-releasing factors (HRFs). HRF is now variously called translationally controlled tumor protein (TCTP), p21, p23, and fortilin. TCTP exhibits cytokine-like functions including release of histamine, induction of TH₂ cytokines and chemoattractants, augmentation of B cell proliferation, and immunoglobulin production during late phase allergic inflammation. Because of its association with the allergic status of patients, TCTP emerged as a potential key agent in the modulation of allergic diseases. Several lines of evidence suggest that TCTP exhibits its cytokine-like functions only after it is modified by the proteases, altered oxidant–antioxidant balance and immunoglobulin E, present in the inflamed sites. This review will try to show that dimerization is the critical modification of TCTP if not the only modification, responsible for its cytokine-like activity causing allergic diseases.

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1. Introduction

Generation of histamine-releasing activity (HRA) in cultured peripheral blood mononuclear cells (PBMC) was first demonstrated in 1979 [1]. Supernatants of human mononuclear cell cultures induced the release of histamine from basophils, and the production of HRA was stimulated by agents such as concanavalin A, streptokinase/streptodornase (SK/SD), and *Candida albicans*. Efforts were soon launched to chemically characterize the new cytokine, the ‘histamine-releasing factor (HRF)’ that induces the release of histamine from human basophils. MacDonald et al. [2] found extensive homology between HRF, and the human protein, p23 and its mouse homolog, p21, both of which have been associated with tumor growth.

HRF, now variously called translationally controlled tumor protein (TCTP), p21, p23, and fortilin, is found to be ubiquitously expressed in eukaryotes, and is a highly conserved molecule from humans to alfalfa plants [3]. TCTP, hereafter referred to as TCTP/HRF, and its homologs are present in various tissues and cells, and even several parasites [4–9] such as *Plasmodium falciparum* [10], *Wuchereria bancrofti* [5], *Brugia malayi* [5], and *Schistosoma mansoni* [8]. The primary structure of TCTP/HRF [11] consists of

approximately 170 residues and its tertiary structure contains three domains, β -stranded ‘core’ domain, α -helix, and flexible loop structure [3]. Though TCTP/HRF is devoid of secretion signaling residues in its primary sequence [11], it can be exported out of the cells. In our study, the cell-penetrating peptide sequence [12] and Ca²⁺ binding region [13] were mapped to the NH₂-terminal region and helical domain, respectively. Invariant residues are largely clustered on one side of β -stranded ‘core’ domain, implying its importance in molecular interactions [3].

HRF was originally found to be a heterogeneous mixture of IgE-independent [14] and IgE-dependent [15] factors. However, the levels HRA generated by IgE-independent HRF did not correlate with the allergic status of the donor [14], while IgE-dependent HRF seemed to correlate with the clinical status in patients with chronic allergic reactions such as asthma and rhinitis [16]. It was shown that TCTP/HRF did not bind to IgE [17], and that HRF-responsive IgE (IgE⁺) donors had less Src homology 2 domain-containing inositol 5′ phosphatase (SHIP) protein than IgE[−] donors. Also, IgE⁺ donors do not have a specific isoform of IgE such as polymeric IgE [18,19]. Because SHIP is known to be a negative regulator of antigen receptor signaling in B cells and high affinity IgE receptor (Fc ϵ RI) signaling in mast cells [20,21], histamine-releasing property of basophils from IgE⁺ donors appears to be linked with low expression of SHIP rather than IgE, in basophils.

The potential clinical significance of secreted TCTP/HRF in human allergic inflammation has been noted in many studies. Elevated amounts of TCTP/HRF were found in skin blister fluids

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from patients with late phase allergic inflammation [22] and in bronchoalveolar lavage (BAL) fluids from patients with idiopathic eosinophilic pneumonia and asthma [23]. TCTP/HRF was also shown to be responsible for spontaneous release of histamine in patients with atopic dermatitis and food hypersensitivity [24]. Basophils from these patients exhibit higher rates of spontaneous release of histamine than those from control groups and the mononuclear cells from persons with food allergies spontaneously produce TCTP/HRF *in vitro*. It was also suggested that secreted TCTP/HRF induces the release of mediators indispensable for late phase reaction (LPR) [22,25–29].

Several lines of evidence pointed to the possibility that TCTP/HRF becomes active only when transformed to a structure distinct from its intracellular form. How TCTP/HRF manifests histamine-releasing activity and why it is important in allergy were not clearly understood until our group demonstrated that dimerization of TCTP/HRF is a critical prerequisite for its acquiring cytokine-like activity [30]. In the present review, we focus on the modification of TCTP/HRF leading to its dimerization, and discuss how the extracellular environment of allergic status *in vivo* is functionally linked to this modification. The clinical relevance of dimerized TCTP/HRF to the allergic status and its potential as a target in the therapy of various inflammatory allergic diseases are also explored.

2. Extracellularly released TCTP/HRF acquires cytokine-like function after physico-chemical modification in extracellular environments

In the physiologic environment, the normal function of intracellular form of TCTP/HRF involves regulation of downstream target signaling in the cytoplasm. However, following export out of the cell it does not necessarily mediate inflammatory response in allergic, pathologic status because TCTP/HRF can be found in unstimulated condition in extracellular milieu without any histamine-releasing ability. MacDonald et al. noted that TCTP/HRF is present in nasal lavage fluids from unstimulated individuals [26] as well as in supernatants of U937 cell cultures [2]. A recent report shows that the secretion of TCTP/HRFs with the same apparent molecular weight as that in cell lysates are also secreted from unstimulated embryonic kidney cells (293T), hepatocytes (HepG2), and erythroleukemia cells (K562) [31]. Thus TCTP/HRF can reside in the cell interior or exported out into the human serum in its intact form, without any HRF activity in unstimulated, normal individuals.

It has been hypothesized that for the secreted TCTP/HRF to become a histamine-releasing factor, it has to be activated by some chemical modification following exposure to inflammatory environment in the serum in allergic patients. In other words, to act as a histamine-releasing factor following secretion into inflamed tissue sites via endoplasmic reticulum (ER)/Golgi-independent pathway [31], TCTP/HRF has to undergo some chemical modification. This hypothesis is supported by studies of MacDonald et al. who compared the basophil histamine-releasing abilities of mouse recombinant TCTP (MrTCTP), human recombinant TCTP (HrTCTP), TCTP/HRF from nasal lavages, and TCTP/HRF from supernatants of peripheral blood mononuclear cell (PBMC) cultures [2]. They found that recombinant TCTP/HRFs were less active than the native TCTP/HRFs purified from biological fluids. Budde et al. [32] who compared the basophil histamine-releasing activity of HRF produced by mononuclear cells (HRFmn) with that of recombinant HRF p23 (HrHRF), also reported that HrHRF was much less active than HRFmn. Thirty eight out of 82 sera from atopic patients could sensitize basophils to respond to HRFmn, while only one serum out of 82 sensitized basophils to respond to HrTCTP [32]. HRFmn could not be detected in the sera by an HrHRF-specific enzyme-linked immunosorbent assay (ELISA) and it was speculated that the

recombinant proteins were probably post-translationally, aberrantly modified [32]. Thus, it was inferred that differences in the activity of HRFmn and HrTCTP is due to some modifications occurring in TCTP/HRF in the altered microenvironment *in vivo*.

One speculation on the kinds of molecular modifications that may be involved was offered by Teshima et al. [33]. TCTP/HRF is recognized as a 23 kDa protein in humans and its mouse homolog is a 21 kDa protein [34,35]. This group noted that the 30 kDa TCTP/HRF detected in the supernatants of ovalbumin (OVA)-elicited macrophages was probably N-glycosylated mouse TCTP/HRF [33]. Following treatment with N-glycosidase F, this 30 kDa protein migrated to the same position as intracellular form of the TCTP/HRF in the sodium dodecyl sulfate (SDS) polyacrylamide gel [33], as is also supported by that TCTP/HRF has an N-glycosylation site [11]. Another study by Yoneda et al. also found 30 kDa TCTP/HRF in the culture media of BEAS-2B cells, and bronchial epithelial cells treated with hydrogen peroxide (H₂O₂) [23]. However, N-glycosylation of TCTP/HRF may not be associated with the generation of the cytokine-like activity *in vivo*, because non-glycosylated recombinant TCTP/HRF also induces eosinophil migration in OVA-immunized mice, but not in normal mice [33]. Taken together, these findings suggest that some molecular modification other than N-glycosylation of TCTP/HRF may responsible for its acquiring cytokine-like activity.

3. What is the modification of TCTP/HRF that causes it to acquire its cytokine-like activity?

We showed that one key modification that enables TCTP/HRF to acquire cytokine-like activity associated with allergic response, is dimerization of TCTP/HRF via an intermolecular disulfide bond [30]. We also demonstrated the presence of dimerized TCTP/HRF in sera from atopic or atopic/asthmatic patients, and in BAL fluids from airway inflamed mice. Also, employing non-reducing sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and immunoblotting by rabbit polyclonal anti-TCTP antibody we showed that TCTP/HRF released from U937 cells is a monomer [30]. Our studies further showing that dimerization is the critical modification essential for its cytokine-like activity are described below.

MacDonald et al. showed that extracellular TCTP/HRF purified from culture supernatants of U937 cells contains the NH₂-terminal sequence [2]. In contrast to TCTP/HRF *in vitro*, TCTP/HRF, *in vivo* loses its NH₂-terminal sequence because it undergoes partial proteolysis by endogenous proteases such as elastase [36] or tryptase [37] resulting from recruitment and activation of neutrophils or mast cells in the inflame sites. Our group demonstrated that NH₂-terminal truncated TCTP/HRF shows cytokine-releasing activity unlike the full-length TCTP/HRF. Thus partial proteolysis and truncation have to be included among the modifications endowing TCTP/HRF with cytokine-like activity. NH₂-terminal truncated TCTP/HRF forms dimers through intermolecular disulfide bonds [30]. NH₂-terminal truncated rat recombinant TCTPs (RrTCTP)s including Del-N11TCTP (residues 11–172), Del-N35TCTP (residues 35–172) potentially stimulate inflammatory responses even at low concentration (1 µg/ml) by stimulating interleukin-8 (IL-8) release from BEAS-2B bronchial epithelial cells while RrTCTP at the same concentration did not. Also, *in vivo*, truncated RrTCTP promotes allergic airway inflammation in mice, increasing goblet cell hyperplasia in both lung and rhinal cavity [30]. Therefore, NH₂-terminal truncation is believed to activate TCTP/HRF *in vivo*.

The binding between truncated TCTP/HRF and its putative receptor has been investigated using fluorescence-activated cell sorting (FACS) analysis. The TCTP/HRF receptor has yet been

identified [38,39]. When the affinity of TCTP/HRFs to its receptor was evaluated by confocal microscopy, stronger fluorescence was detected in the cellular membrane of BEAS-2B cells when it was incubated with Del-N11TCTP than when incubated with RrTCTP [30]. Thus, the conformational difference between RrTCTP and NH₂-terminal truncated RrTCTP may lead to differential affinities to its receptor in the plasma membrane.

3.1. Dimerization of TCTP/HRF

Generation of new conformations different from the full-length monomer TCTP/HRF is responsible for acquisition of cytokine-like activity and this modification includes truncation and dimerization of TCTP/HRF. There are several reports regarding dimerization of TCTP/HRF homologs [5,40] and its self-interaction [41]. Gnana-sekar et al. proposed self-interaction by Lupas coiled coil structure of residues 92–124 in *B. malayi* TCTP (Bm-TCTP) and formation of dimers under non-reducing conditions [5].

Using size exclusion column chromatography of truncated form, the oligomer of TCTP/HRF was found to be a dimer. And the presence of TCTP/HRF dimers was confirmed in sera of allergic patients and BAL fluids of allergic mouse [30]. Furthermore, the intermolecular crosslink leading to dimer formation was demonstrated to be a disulfide bond between cysteine residues of the two molecules [30]. Intact NH₂-terminus bearing TCTP/HRFs were detected with molecular sizes corresponding to a monomer, regardless of the presence or absence of β -mercaptoethanol (β -ME), the NH₂-terminal truncated forms shifting to the size of dimers under non-reducing conditions. Thus, truncated TCTP/HRFs form dimers through intermolecular disulfide bridge. Among the two cysteine residues, Cys28 and Cys172, present in TCTP/HRF, Cys172 is the major player in the cross-linking of TCTP/HRF, although both these residues appear to be involved in its linkage [30].

Studies of the structure of TCTP/HRF from *Schizosaccharomyces pombe* [42] revealed that parts of NH₂- and the COOH-termini of TCTP/HRF are stacked as antiparallel β -sheets. Thus it can be concluded that a portion of the NH₂-terminus of this protein may interfere with disulfide-linkage formation. For, when the NH₂-terminus is truncated, thereby exposing COOH-terminal Cys172, which is the major site for dimerization, TCTP/HRF is able to form intermolecular disulfide bond. Furthermore, we found that truncation of at least four amino acids (residues 1–4) is required for RrTCTP to dimerize. In the inflammatory circumstances, intermolecular disulfide bond between truncated TCTP/HRFs is possibly formed from oxidative conditions provided by recruited inflammatory cells. This possibility is supported by the observation that the NH₂-terminal truncated RrTCTP can be dimerized by oxygen species such as H₂O₂ [30].

3.2. Dimerization, may be the underlying process that promotes the activation of TCTP/HRF by NH₂-terminal truncated TCTP

As two seemingly unrelated modifications, NH₂-terminal truncation and dimerization, of TCTP/HRF generate cytokine-like activity, the question arises as to the nature of the underlying mechanisms in the two cases. To answer this question, we evaluated the activity of dimerized but non-truncated, full-length TCTP/HRF by fusing it to rabbit Fc region (Fc-HrTCTP). The CH3 of Fc region can form a non-covalent homodimer which is not formed by chemical crosslinkers [43,44]. Therefore Fc can work as a link between two TCTP/HRF molecules at their COOH-terminus. The dimerized form of untruncated full-length protein (Fc-HrTCTP) was more active than full-length TCTP (HrTCTP) in BEAS-2B cells. This result implies that dimerization of TCTP/HRF, rather than truncation, is required for TCTP/HRF activation [30]. Thus we believe that

the dimer is the biologically active form of TCTP/HRF, consistent with recent work [45], and that the cytokine-like activity shown by NH₂-terminal truncated RrTCTP may be due to the dimerization.

4. Hypothetical extracellular contributing factors for modification of TCTP/HRF in vivo

Monomeric TCTP/HRF probably becomes dimerized and acquires cytokine-like activity only when it becomes a component and substrate/target of the altered cellular milieu of mediators, cells and enzymes, among others, that appear during the development of LPR and the associated allergic phenomena. Allergic status may affect the normal biochemical composition and physiology of the cellular milieu, leading to posttranslational modification of some proteins including TCTP/HRF, and the activation of inflammatory cells that promote the LPR, including the production of a great variety of cytokines, proteolytic enzymes, reactive oxygen species (ROS), and TCTP/HRF-reactive immunoglobulin E. Among these components, three possible contributors may cause the dimerization of TCTP/HRF in vivo: (i) Proteolytic enzymes released from endogenous inflammatory and immune cells, as well as from exogenous sources such as house dust mites *Dermatophagoides pteronyssinus* [46] and *Dermatophagoides farinae* [47] which are the catalysts of the NH₂-terminal truncation of TCTP/HRF, (ii) Oxidants that favor the formation of intermolecular disulfide bonds in TCTP/HRF, and (iii) TCTP/HRF-reactive immunoglobulin E possibly conferring autoantigen activity on the TCTP/HRF. These three components of the inflammatory environment are discussed in some detail below.

4.1. Proteolytic enzymes

We have previously demonstrated proteolytic modification of rat recombinant TCTP/HRF. NH₂-terminal truncated, but not COOH-terminal truncated, TCTP/HRF exists as dimers and shows elevated cytokine-releasing activity. Thus the cytokine-like activity of full-length TCTP/HRF, reported in other studies might actually be from contamination from partially cleaved TCTP/HRF by proteolysis, followed by its dimerization during the preparation of TCTP/HRF. Extracellularly secreted TCTP/HRF is possibly truncated by endogenous proteases from neutrophils [36], mast cells [37], and cytotoxic T cells [48] in inflamed site during LPR. Other molecules having protease activities such as granzyme K (GrK) [49,50], elastase or cathepsin G from immune cells [51–53], or tryptase Clara [54], human airway trypsin-like protease [55] from bronchial and tracheal cells into the inflammatory milieu may also be recruited to the inflammatory site to activate the extracellular TCTP/HRF. Other possible sources of proteolytic enzymes include: allergens like grass pollen [56,57], fungi [58,59], or house dust mite [46,60]. All of these allergens can provoke allergic disease by causing the cleavage of TCTP/HRF by their constituent proteolytic enzymes, such as serine protease and cysteine protease. However, role of proteolytic modification of TCTP/HRF as a cause of allergic phenomena will not be discussed in this review. We will address only the role of dimerization of TCTP which we consider to be the major modification responsible for the generation of cytokine-like activity of TCTP/HRF.

4.2. Cellular oxidants

Various studies show the development of an oxidative environment in the sites of inflammation during the allergic response from the shift of oxidant–antioxidant balance in favor of oxidants. Cellular oxidants in the inflamed site provide another pathway for dimerization of truncated TCTP/HRF via linkage of two monomers

RAST-negative patients, have HRFmn-reactive IgE. Budde et al. [77] found 87% of HRFmn-responders, in contrast to 25% of HRFmn-nonresponders, were RAST positive to grass pollen. The correlation coefficient, *R*, between HRFmn-reactive IgE in serum and the RAST to grass pollen was 0.75. Attempts to detect the binding of IgE to HRFmn with Western blotting and immunoprecipitation [77] failed because of low purity of the HRFmn preparation.

Another TCTP/HRF analog, ClaTCTP, which was characterized in the mold *Cladosporium herbarum*, an allergenic fungal species [78], is another example of presence of autoreactive IgE. It has 42% sequence homology with human TCTP/HRFs, and a notable point was that IgE from five out of nine individuals who were ClaTCTP-reactive patients could bind both the human and the fungal protein in immunoblot analyses. Also, the fungal protein could function as a histamine-releasing factor from human basophils. Likewise, the proposed mode of activation of ClaTCTP suggests a possible role of TCTP/HRF as an autoreactive IgE-binding allergen. A subsequent study from this group noted *Alternaria alternata* TCTP as a minor cross-reactive allergen [79]. Western blot analysis and in vitro inhibition assay revealed that *A. alternata* TCTP shares cross-reactive IgE epitopes with its *C. herbarum* and human homologs. Five of nine patients sensitive to the mold allergens showed strong IgE reactivity to *A. alternata* and *C. herbarum* TCTP suggesting a significant cross-reactivity between the mold and human TCTPs.

A recent work by Kashiwakura et al. suggested that TCTP/HRF together with TCTP/HRF-reactive IgE induced mast cell activation in vitro [45]. This group identified a subset of TCTP/HRF-interacting IgE and IgG antibodies contradicting the previous claim of Wantke et al. that HrTCTP does not bind to the IgE molecules [17]. Kashiwakura et al. found that TCTP/HRF binds to Igs via interactions of its NH₂-terminal 19-residue peptide (N19) and H3 region (residues 107–135) with the Fab region of Igs. In addition, they speculated that bioactive TCTP/HRF (i.e., dimers and oligomers) could interact with IgE and crosslinked IgE-bound FcεRI, subsequently induces the aggregation of FcεRI complexes with IgE thereby activating the mast cell. They proposed IgE and IgG as long-sought receptors for TCTP/HRF in the lung [45]. However, this concept does not exclude the possibility that a specific IgE acting as a TCTP/HRF receptor, might link two TCTP/HRF monomers and thereby producing dimerized TCTP/HRF that binds to the TCTP/HRF dimer-specific receptor.

In this regard, mounting evidence suggests that TCTP/HRF can stimulate target cells via IgE-independent pathways and that its signaling is distinct from classical FcεRI pathway [17,27,29,38,39,80–82]. To summarize this evidence: 1) TCTP/HRF modified the cytokine release not only from FcεRI-stimulated basophils [29], but also from cells that do not constitutively express the FcεRI, such as eosinophils [27], T cells [82], and B cells [38]. 2) TCTP/HRF did not phosphorylate FcεRIγ in basophils [39]. 3) Rotterlin, a nonstaurosporine-derived kinase inhibitor, mediated HrHRF-mediated histamine release without affecting basophil activation by either anti-IgE or antigen [80]. Therefore, dimerized TCTP/HRF binds to as yet unknown cell surface receptor, which is distinct from Igs, although some subsets of Igs may also act as TCTP/HRF receptor [45]. TCTP/HRF binding either to IgE or to TCTP/HRF-specific receptor might depend on the expression of FcεRI in target cells or on the presence of IgE. It is possible that cross-linking of FcεRI by dimeric TCTP/HRF reduces the signal threshold or acts as a co-stimulatory signal to activate target cells via TCTP/HRF dimer-specific receptor.

5. Clinical implications of dimerized TCTP/HRF to allergy

As the modulators and mediators of the allergic/immune process became better understood, many new therapies were

developed directed at the regulation of the modulators. Thus, TH₂ cytokine inhibitors [83,84], TH₂ cytokine receptor blockers [85], TH₁ cytokines [86], inhibitors of intracellular adhesion molecules, and phosphodiesterase 4 (PDE4) inhibitors [87] among others, became therapeutic targets of chronic allergic diseases. These approaches and anti-IgE therapy have been the subjects of clinical trials in patients with moderate-to-severe persistent asthma [88]. Despite these efforts, there remains a need for new anti-allergy drugs. Targeting TCTP/HRF therefore is a promising approach to the development of novel drugs, as it focuses on intervening upstream of the LPR, a step proved effective in allergy model.

Secretion of TCTP/HRF is known to be facilitated by macrophage colony-stimulating factor (M-CSF) [33], H₂O₂ [23], or dioxin [89] and its export is reported to be mediated by H,K-ATPase [90] or TSAP6 via non-classical routes [31]. TCTP/HRF itself cannot evoke allergic inflammation unless activated by appropriate conformational changes. Once released TCTP/HRF is exposed to proteases, which fragment TCTP/HRF into a TCTP/HRF residue containing 11–172 residues and an NH₂-terminal fragment (residues 1–10). Our group identified the latter as a protein transduction domain (PTD) [12]. The 11–172 residue of TCTP/HRF is subsequently oxidized and dimerized by disulfide linkages in oxidant-filled cellular fluids. Any intact TCTP/HRF remaining can also form dimers by binding to a variable region of TCTP/HRF-reactive IgE. In addition, a subset of IgE also can serve as a receptor for dimerized TCTP/HRF in cells expressing FcεRI [45]. We believe that in addition to oxidants or TCTP/HRF-reactive IgE, other agents which can dimerize both full-length or truncated TCTP/HRF may also be possibly involved in the activation of extracellular TCTP/HRF. The hypothetical modification of TCTP/HRF based on our results is depicted in Fig. 2. This figure suggests that dimerized TCTP/HRF binds to its specific receptor on the cell membrane leading to the release of histamine or cytokines causing allergic responses via receptor-mediated signal transduction. In normal individuals, extracellular TCTP/HRF is not cleaved or oxidized because of the normally low levels of proteases and oxidants in sera or BAL fluids. In patients with allergic disease, in whom inflamed sites and the levels of proteases and oxidants are high, extracellular TCTP/HRF is activated promoting the late phase or chronic allergic inflammation. TCTP/HRF modification(s) involved in its acquiring cytokine-like activity. In on-going studies, we are attempting to generate a better picture of TCTP/HRF modification(s) involved in its acquiring cytokine-like activity.

Based on the above postulated role of dimerization of TCTP/HRF in the pathogenesis of allergic inflammation blocking the activation or generation of the dimerized TCTP/HRF offers a rational therapeutic approach to allergic diseases. Several specific approaches to inhibiting the activation of TCTP/HRF are available. 1) Using protease inhibitors to prevent the truncation of TCTP/HRF. 2) Use of antioxidant agents to interfere with the generation of disulfide bond-based dimerization. 3) Targeted inhibition of interaction between TCTP/HRF and TCTP/HRF-reactive immunoglobulin without affecting TCTP/HRF's intracellular functions [45] and 4) Use of peptides mimicking those in the Ig-binding sites of TCTP/HRF to inhibit the interaction between TCTP/HRF and Ig, and the resulting IgE/antigen-induced skin hypersensitivity and allergen-induced mast cell-dependent airway inflammation [45].

Recently we isolated a peptide that binds to dimerized TCTP/HRF and examined its potential usefulness in anti-allergy therapy [91]. Not surprisingly, this peptide showed stronger affinity to dimerized TCTP/HRF than to the monomer. Studies are in progress to define the critical conformational differences that exist between dimeric and monomeric TCTP/HRFs. Understanding these conformational differences that define the clinical properties of dimerized TCTP/HRF is another area of current interest in our laboratory.

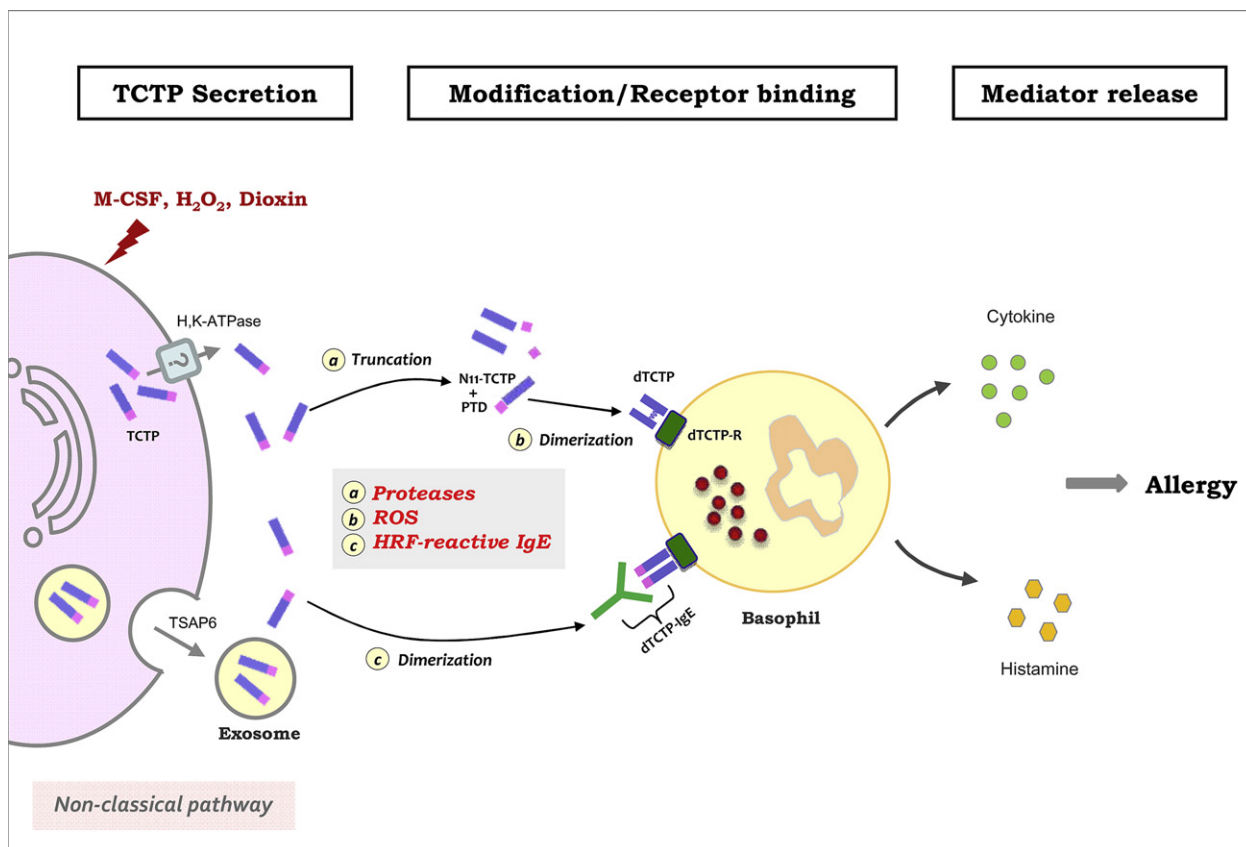


Fig. 2. Hypothetical modification of TCTP/HRF. Secretion of TCTP/HRF is enhanced by hydrogen peroxide, M-CSF, dioxin, and so forth during late phase allergic inflammation. Once TCTP/HRF is secreted outside of cells through H,K-ATPase- or TSAP6-mediated non-classical pathway, TCTP/HRF may get the cytokine-like effects by alteration of tertiary structure. In microenvironment of allergic inflammation, elevated proteases and ROS might process exposed region of TCTP/HRF, and also IgE that might be cross-reactive with TCTP/HRF homologs might connect a TCTP/HRF monomer with another TCTP/HRF monomer. (a) Processing of secreted full-length TCTP/HRF by proteolytic enzyme releases truncated TCTP/HRF (N11TCTP) and short-length N-terminal fragments (PTD). (b) Oxidants can form an intermolecular disulfide linkage between two of TCTP/HRF that produces the dimerized TCTP/HRF (dTCTP). (c) Alternatively, TCTP/HRF also can be activated by TCTP/HRF-reactive IgE, which dimerize the intact TCTP/HRF (dTCTP-IgE). Hypothetical interaction between IgE and TCTP/HRF is presented though it needs to be clarified. Active structure of TCTP/HRF now can bind to its specific receptor (dTCTP-R) to stimulate the mediator release from basophils. In addition to dTCTP-R, subset of IgE can serve as a receptor for TCTP/HRF dimer [45] in FcεRI-expressing cells. Since these modifications might be possible at inflamed site, extracellular TCTP/HRF will affect around cells only during the late phase or chronic allergic inflammation.

In addition to the extracellular homo-dimerization of TCTP/HRF for cytokine-like properties, TCTP/HRF can form complexes with a variety of intracellular proteins. Binding of TCTP/HRF with a plethora of cytosolic partners enables it to exert its intracellular pleiotropic activities, reviewed by Kawakami et al. [92]. For example, intracellular binding of TCTP/HRF with Plk or with tubulins plays a role in cell cycle regulation [93,94]; binding of TCTP/HRF with p53, Bcl-xL and Mcl-1 [95–98] is involved in the anti-apoptotic function of TCTP/HRF; binding of TCTP/HRF with translational elongation factors helps it regulate protein synthesis [99]; and interactions of TCTP/HRF with TSAP6 [31], as well as with Na,K-ATPase [100], promote its secretion through exosome, and the suppression of Na,K-ATPase, respectively.

Exactly how the ‘switch signal’ operates to differentiate between the homo- and hetero-interactions of TCTP/HRF in extra- and intracellular spaces, is not fully understood. Toggling the switch signals seems to be performed by the micro-environmental stimuli that regulate the export of TCTP/HRF, including M-CSF [33], H₂O₂ [23], and dioxin [89] as well as those that cause the dimerization of TCTP/HRF, discussed earlier. The regulatory factors that influence TCTP/HRF’s intracellular and extracellular roles clearly have far reaching clinical implications and need to be better understood since their strategic modulation offers a rational therapeutic approach to allergy and other diseases, such as hypertension [101] and cancer [102] in which TCTP/HRF may play roles.

6. Concluding remarks

This review shows that dimerization is the critical modification of TCTP if not the only modification, responsible for its cytokine-like activity causing allergic diseases. Several studies have demonstrated binding between TCTP/HRF and its as yet unidentified receptor [30,38,39]. Identifying this TCTP/HRF receptor may help in developing TCTP/HRF-specific anti-allergic strategies and strategies for modulating the activation of downstream signaling targets. Identification of the TCTP/HRF receptor has thus far remained elusive, probably because the monomeric form of TCTP/HRF and not its dimer was used in previous experiments. Once the putative receptor for dimerized TCTP/HRF is identified, the next step will be to develop TCTP/HRF-receptor blocking molecules which should pave the way for designing new classes of anti-allergic drugs.

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