

Emerging roles of the protease allergen Der p 1 in house dust mite-induced airway inflammation



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The first fully documented report on isolation of the house dust mite (HDM) allergen Der p 1 was published by Chapman and Platts-Mills in 1980,¹ but, actually, our understanding pertaining to the molecular nature of Der p 1 received a substantial boost in 1988 with the cloning of its cDNA.² This first-ever cloned allergen marked the emergence of a new discipline termed molecular allergology. The year 2018, and therefore the 30th anniversary of this cloning, offers a great opportunity to review the different paradigms associated with Der p 1 over the past 3 decades together with the gray areas that remain to be explored further.

Pioneering studies showed that Der p 1 is not only the most abundant allergen from mite fecal pellets but also a major inducer of IgE response in patients with HDM allergy. However, the initial simplistic representation of Der p 1 as a mere HDM-digestive cysteine protease with IgE-binding properties shifted progressively over the last 3 decades to a much more complex picture. Although Der p 1 is present mainly in the mite digestive tract, its actual biological functions remain to be fully elucidated. Recent evidence on the pivotal role of Der p 1 in the maturation of HDM serine protease allergens suggests that the processing of protein substrates by Der p 1 could also shape the allergenic potential of HDM proteins.³

Answering the question “What makes an allergen an allergen?” has always posed a considerable challenge to molecular allergologists. As the first allergen characterized, Der p 1 was naturally chosen to develop a general paradigm for predicting protein allergenicity based on protease activity. However, the biochemical and structural characterization of allergens from other sources demonstrated later that only a minority display

proteolytic activities. Tremendous progress concomitantly highlighted the key role of environmental and microbial adjuvant factors in activation of innate immune pathways, which are essential for development of allergic responses. Taken together, the Der p 1 paradigm inevitably shifted to a more broadly applicable model of protein allergenicity: the intrinsic biological activity of an allergen was now intimately associated with its ability to stimulate innate immune pathways leading to allergy.

Although it is well known that the cysteine protease activity of Der p 1 promotes the T_H2 allergic response, elucidation of the different cellular pathways triggered by active Der p 1 was always rendered arduous by the difficulties of isolating natural Der p 1 from HDM allergen extracts in appropriate amounts that were free of serine protease contaminations or to prepare reproducible batches of biologically active rDer p 1. Because of these limitations, the contribution of the protease activity of Der p 1 to the development of the HDM-induced allergic response was investigated mainly by means of papain, a structurally similar cysteine protease considered a surrogate for Der p 1 or HDM allergen extracts in the presence or absence of cysteine protease inhibitors.

After inhalation of mite fecal pellets into the human airways, Der p 1 accumulates at the apical surface of the airway mucosa and exerts different key activities, including (1) degradation of soluble antiprotease-based lung defenses (α_1 -antitrypsin, elafin, and secretory leukocyte protease inhibitor) and surfactant proteins (SPs; SP-A and SP-D); (2) cleavage of tight junction proteins (occludin, zonula occludens-1, and cadherins) to facilitate the access of HDM allergens to immune cells (ie, type 2 innate lymphoid cells [ILC2s] and dendritic cells [DCs]) in subepithelial tissue; and (3) stimulation of production of innate proinflammatory cytokines/chemokines/alarmins (ie, IL-6, IL-8, GM-CSF, CCL2, and CCL20).⁴ Although the contribution of Der p 1 to production of the pro-T_H2 epithelium-derived cytokines thymic stromal lymphopoietin, IL-25, and IL-33 needs experimental confirmation, preparation of a suitable environment through protease activity of Der p 1 is more than likely to promote T_H2-type airway inflammation. Proteolytically active papain was shown recently to stimulate an innate cell network formed by the IL-33/ILC2–IL-5/IL-13 axis, which is able to trigger eosinophilia in patients with early airway inflammation in the absence of specific IgE production.⁵ Therefore it is tempting to speculate that a similar mechanism could be activated by Der p 1. Remarkably, Der p 1 was shown recently to regulate the cytokine activity of the alarmin IL-33 through cleavage of its sensor domain.⁶

Several surface molecules from B cells, T cells, or DCs, including CD23, CD25, CD40, dendritic cell–specific intercellular adhesion molecule 3–grabbing nonintegrin (DC-SIGN), and DC-SIGN receptor, were also shown to be cleaved or shed by Der p 1 to further create a pro-T_H2 environment and/or to downregulate T_H1/regulatory T-cell differentiation.⁴ By contrast, to this day, the innate immune receptor or receptors of the airway epithelium targeted by Der p 1 remain largely unknown.

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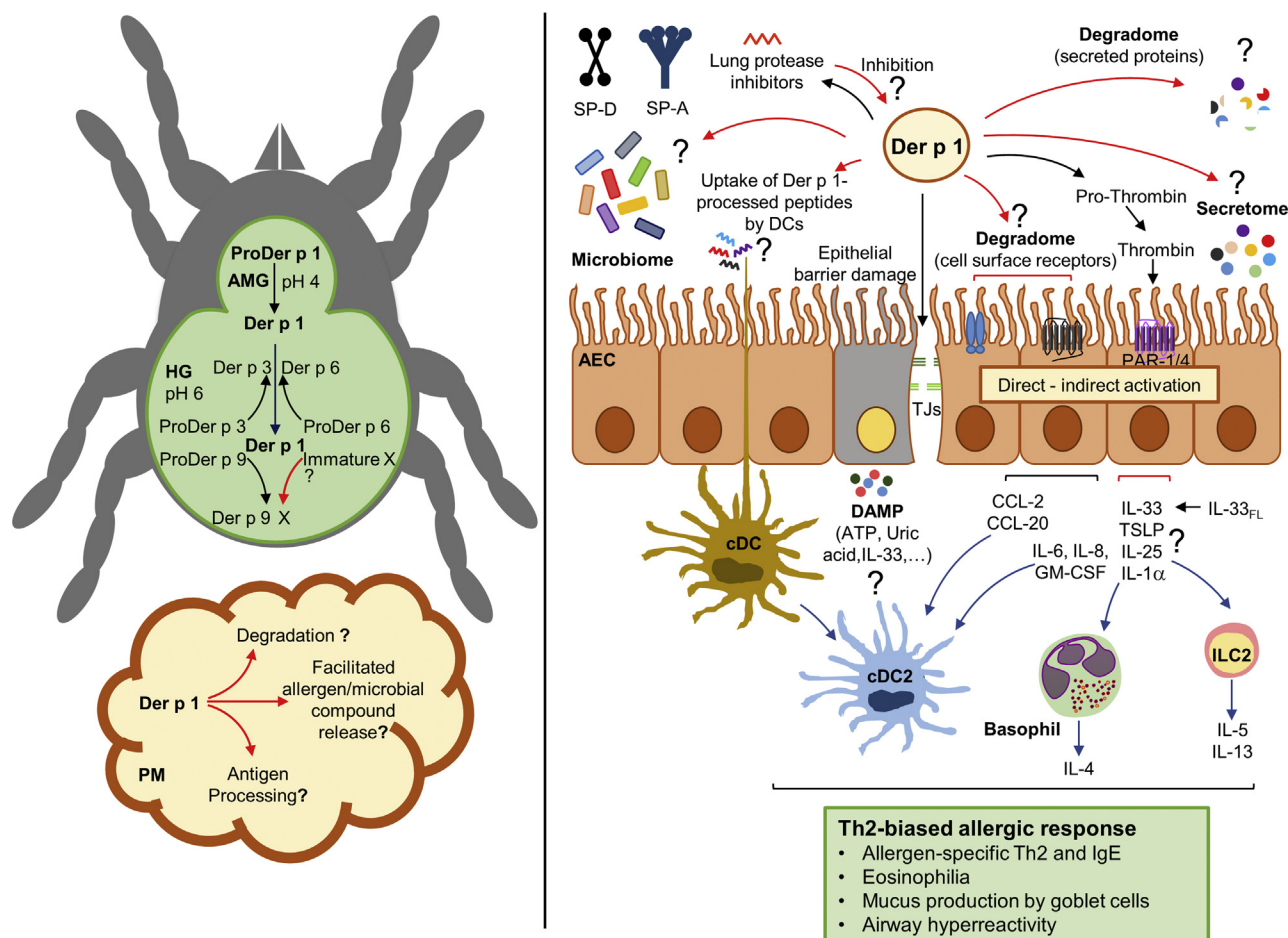


FIG 1. Schematic representation of the reported and potential hidden functions of Der p 1 in the HDM-induced inflammatory response. Der p 1 triggers a proteolytic activation cascade in the digestive tract of the mite *Dermaphagoides pteronyssinus*, leading to maturation of the serine protease allergens Der p 3, Der p 6, and Der p 9 and possibly other unknown mite protein targets. Within mite fecal pellets, Der p 1 could selectively cleave and/or extensively degrade several proteins, including HDM allergens and endosymbiotic bacteria. These activities could modulate the respective stability of HDM allergens and facilitate their release from the peritrophic matrix, as well as affecting generation of peptides for antigen processing. When fecal pellets reach the airway mucosa, elution of the microbial compounds and intact and fragmented allergens leads to initiation of the HDM-induced allergic response. Active Der p 1 could exert direct and indirect pleiotropic effects at the level of the airway epithelium, lung microbiome, and secretome, leading to release of proinflammatory cytokines (IL-6, IL-8, GM-CSF, thymic stromal lymphopoietin, and IL-25), alarmins (IL-1α and IL-33), and chemoattractants (CCL2 and CCL20), which activate DCs, basophils, and ILC2s to initiate the T_H2 -biased HDM-induced allergic response. Red and black arrows or parentheses represent the different hypothetical and experimentally evidenced effects of active Der p 1, respectively. AEC, Airway epithelial cell; AMG, anterior midgut; cDC, conventional DC; cDC2c, type 2 conventional DC; HG, hindgut; IL-33_{FL}, full-length IL-33; PM, peritrophic matrix; TJ, tight junction protein.

The hypothesis of the direct epithelial stimulation of protease-activated receptors (PARs) by Der p 1 remains controversial. Indeed, the capacity of Der p 1 to activate PAR-2, thus leading to proinflammatory cytokine release, was contradicted by further studies showing PAR-2 inactivation by Der p 1.⁷ Such discrepancies could be attributed to the contamination of Der p 1 by residual HDM serine proteases because PAR-2 is not activated commonly by cysteine proteases. The global picture seems even more complex because Der p 1 was shown recently to indirectly stimulate PAR-1/PAR-4 signaling pathways through their canonical activator thrombin.⁸ Alongside the recent observation that HDM cysteine proteases can drive direct cleavage of the membrane-bound chemokine CX₃CL1,⁹ all these results confirm the pleiotropic effect of Der p 1 on the airway mucosa.

Elucidation of Der p 1 degradomics (ie, the complete repertoire of its cellular substrates) is now greatly needed because it could represent a key step in unraveling the different pathways triggered by this protease allergen. Using a combination of bioinformatics tools and peptide substrate libraries, recently, we have predicted new potential targets for Der p 1 within the human cell-surface proteome that could play a role in allergic airway inflammation.¹⁰ Although the potential cleavage of IL-10 receptor or IL-12 receptor by Der p 1 could constitute a new pathway for promotion of T_H2 polarization, the predicted cleavage of cell-surface inflammatory receptors, such as IL-1 receptor type II, IL-17 receptor, IL-18 receptor, or IL-23 receptor, by Der p 1 suggests a more complex balance between the proinflammatory and anti-inflammatory effects of Der p 1.

Despite successive paradigm shifts in the representation of Der p 1 from a digestive enzyme to a potent activator of other mite allergens and innate immune pathways (Fig 1), numerous questions remain unanswered. Together with degradomics approaches, a comparative analysis of the secretome of the airway epithelium exposed or not to Der p 1 seems key to understanding the crucial role of this allergen in initiation of the HDM allergen response. The spatiotemporal control of Der p 1 biological activity in the lung by endogenous cysteine protease inhibitors remains to be explored as well. Moreover, the potential contribution of the lung and mite microbiome in airway inflammation triggered by HDM opens the way to careful characterization of the effect of Der p 1 on host-microbe communication. It also appears reasonable to think that the protease activity of Der p 1 could have a drastic effect on intact allergen content and release from mite fecal pellets. Investigations to support these novel assumptions will definitively confirm the role of Der p 1 as a key coordinator of the HDM-induced allergic response.

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REFERENCES

1. Chapman MD, Platts-Mills TA. Purification and characterization of the major allergen from *Dermatophagoides pteronyssinus*-antigen P1. *J Immunol* 1980; 125:587-92.
2. Chua KY, Stewart GA, Thomas WR, Simpson RJ, Dilworth RJ, Plozza TM, et al. Sequence analysis of cDNA coding for a major house dust mite allergen, Der p 1. Homology with cysteine proteases. *J Exp Med* 1988;167: 175-82.
3. Dumez ME, Herman J, Campisi V, Galleni M, Jacquet A, Chevigne A. Orchestration of an uncommon maturation cascade of the house dust mite protease allergen quartet. *Front Immunol* 2014;5:138.
4. Jacquet A. The role of innate immunity activation in house dust mite allergy. *Trends Mol Med* 2011;17:604-11.
5. Kubo M. Innate and adaptive type 2 immunity in lung allergic inflammation. *Immunol Rev* 2017;278:162-72.
6. Cayrol C, Duval A, Schmitt P, Roga S, Camus M, Stella A, et al. Environmental allergens induce allergic inflammation through proteolytic maturation of IL-33. *Nat Immunol* 2018;19:375-85.
7. Adam E, Hansen KK, Astudillo Fernandez O, Coulon L, Bex F, Duhant X, et al. The house dust mite allergen Der p 1, unlike Der p 3, stimulates the expression of interleukin-8 in human airway epithelial cells via a proteinase-activated receptor-2-independent mechanism. *J Biol Chem* 2006; 281:6910-23.
8. Zhang J, Chen J, Allen-Philbey K, Perera Baruhupolage C, Tachie-Menson T, Mangat SC, et al. Innate generation of thrombin and intracellular oxidants in airway epithelium by allergen Der p 1. *J Allergy Clin Immunol* 2016;138: 1224-7.
9. Loxham M, Smart DE, Bedke NJ, Smithers NP, Filippi I, Blume C, et al. Allergic proteases cleave the chemokine CX3CL1 directly from the surface of airway epithelium and augment the effect of rhinovirus. *Mucosal Immunol* 2018;11: 404-18.
10. Jacquet A, Campisi V, Szpakowska M, Dumez ME, Galleni M, Chevigne A. Profiling the extended cleavage specificity of the house dust mite protease allergens Der p 1, Der p 3 and Der p 6 for the prediction of new cell surface protein substrates. *Int J Mol Sci* 2017;18.