

The proteolytic activity of Der p 1 selectively enhances IgE synthesis: a link between allergenicity and cysteine protease activity

Introduction

The immune system is exposed to a countless number of potentially antigenic proteins, yet only some of those proteins elicit IgE antibody responses, hence referred to as allergens. Although allergens, such as those from house dust mite and pollen, are normally innocuous foreign proteins, they could have devastating effects in those individuals who are predisposed to producing large amounts of allergen-specific IgE. Therefore there must be a common structural feature (e.g. topology) or intrinsic property (e.g. hydrolytic activity) which enable allergens to elicit powerful Th2 responses and a consequent bias towards IgE-mediated allergic disease. We have recently suggested that nonimmunological properties of some allergens, such as proteolytic activity, might contribute to their allergenicity [1]. This is best exemplified by the house dust mite *Dermatophagoides pteronyssinus* allergen Der p 1 which, in addition to acting as immunogen, has the intrinsic ability to subvert the regulatory process controlling IgE synthesis, thereby favouring an allergic outcome [2].

Der p 1 biases the immune response in favour of Th2

Der p 1 has long been recognized as the most immunodominant allergen involved in the expression of dust mite-specific IgE-mediated hypersensitivity [3]. The reason for this potent IgE-eliciting property of Der p 1 is likely to be due to its cysteine protease activity, which has been shown to cleave CD25, the 55 kDa α subunit of the T cell IL-2 receptor, and as a result these T cells show markedly diminished proliferation and interferon- γ (IFN γ) secretion [4]. Given that IL-2, along with IFN γ , and IL-4 are considered to be autocrine growth factors for Th1 and Th2 subsets, respectively [5], Der p 1-induced cleavage of CD25 is likely to lead to impaired growth of cells of the Th1 subset and consequent augmentation of those of the Th2 subset. This notion is further underlined by the demonstration that the administration of Der p 1 to mice promotes a Th2 response by modulating the balance between IL-4 and IFN γ [6]. The proteolytic activity of Der p 1 has also been shown to stimulate IL-4 synthesis and secretion from mast cells and basophils [7], thereby helping further in creating a microenvironment conducive for Th2 subset development.

A link between the allergenicity of Der p 1 and its cysteine protease activity

Recent work from our laboratory has shown for the first time that immunization of mice with proteolytically active Der p 1 results in a selective enhancement in total IgE and Der p 1-specific IgE synthesis compared to animals immunized with Der p 1 that has been irreversibly blocked with the cysteine protease inhibitor E-64 [8]. This is direct evidence that the cysteine protease activity of Der p 1 induces a significant increase in IgE responses. The Th2 bias induced by the proteolytic activity of Der p 1 could potentially be reversed by administering Der p 1 in a proteolytically inactive (mutant) form. There is already a precedent for such a strategy, namely the recent demonstration in mice that *Leishmania mexicana* cysteine proteinase-deficient mutants potentiate a Th1 response, compared to the Th2 response normally seen in response to infection with wild-type parasite [9]. Alternatively, one may contemplate the use of selective Der p 1-specific cysteine protease inhibitors which, if they become available, can be evaluated for potential therapeutic use.

Novel inhibitors of the proteolytic activity of Der p 1

Given that the proteolytic activity of Der p 1 is a major factor contributing to its allergenicity, there is now considerable interest in generating selective inhibitors of its cysteine protease activity. This issue of the journal contains an article describing the biological characterization of PTL11028, a newly identified specific peptide-based irreversible inhibitor of the cysteine protease activity of Der p 1 [10]. PTL11028 appears to be selective for Der p 1, since it has only limited inhibitory activity against cathepsins B and H. However, it remains to be seen if PTL11028 shows such selectivity for Der p 1 in an appropriate animal model. It would be particularly important to investigate its effect on IgE antibody responses in such a model.

Concluding remarks

The demonstration that the cysteine protease activity of Der p 1 enhances total IgE production, apart from increasing Der p 1-specific IgE [8], suggests that this allergen may play a central role in destabilizing the micro-environment within target tissues to one that is pro-allergic, and thus aid in the

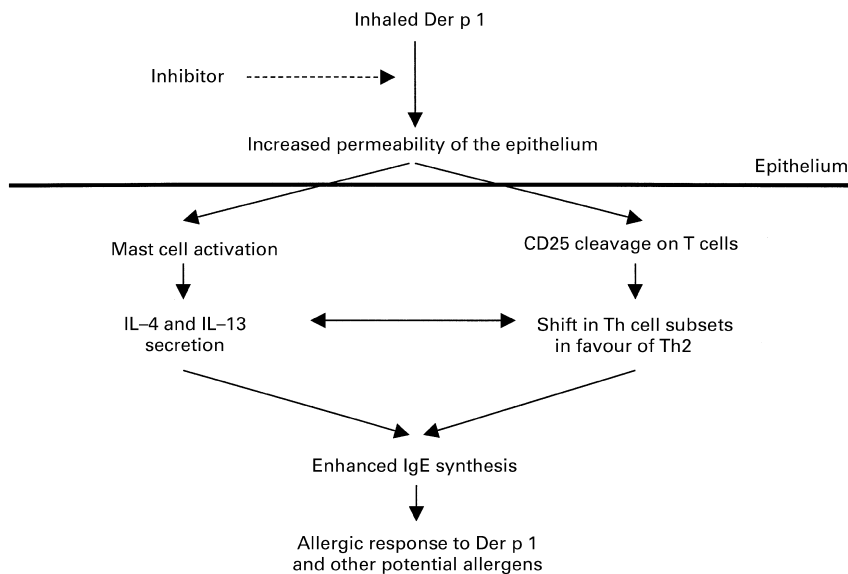


Fig. 1. Suggested mechanisms by which the proteolytic activity of Der p 1 enhances allergenicity, and the possible blockade of this process by a selective inhibitor. Adapted from our previous article [2].

initiation and propagation of the allergic cascade. In other words, the proteolytic activity of Der p 1 may exert an IgE-specific adjuvant effect. In addition to its newly demonstrated direct effect on the immune system [8], the proteolytic activity of Der p 1 is known to increase the permeability of the human respiratory epithelium to macromolecules [11,12]. Such observations firmly indicate that the proteolytic activity of Der p 1 is a major contributor to its allergenicity, and as such the generation of selective inhibitors is justified (Fig. 1).

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