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Visions & Reflections

Psoriasin and its allergenic bovine homolog Bos d 3

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Psoriasin, a protein with an 11-kDa molecular mass, was described more than 10 years ago as one of the proteins up-regulated in the lesions of psoriatic skin [1]. It was detected to be a member of the S100 family of proteins characteristically containing the site of the EF-hand type for calcium binding (http://www.expasy.org/cgi-bin/nicedoc.pl?PDOC00275). In addition to being able to bind Ca^{2+}, psoriasin (or S100A7) can bind Zn^{2+} [2]. Under physiological conditions, it forms homodimers [3]. Psoriasin is considered to be involved in regulating the function of keratinocytes in a variety of ways [4].

One of the cow-derived respiratory allergens, named Bos d 3, is probably the bovine equivalent of human psoriasin since they exhibit an amino acid identity of more than 60%. The highly homologous regions in both proteins also contain an identical calcium-binding motif [5]. Our preliminary experiments suggest that human psoriasin can be an autoallergen since it bound IgE from the sera of a group of cow-asthmatic patients in immunoblotting (T. Virtanen, to be published). Autoallergens, human proteins with IgE-binding capacity, are proteins conserved in evolution and are often homologs of exogenous allergens. Immunoglobulin E (IgE) to human proteins has been found in a variety of allergic conditions [6]. As the determinants of the allergenicity of proteins are basically unknown, it is interesting that a number of exogenous allergens, for example dog Can f 1 of the lipocalin family of proteins [7], the bovine oligomycin sensitivity-conferral protein of the mitochondrial adenosine triphosphate synthase complex [8], and the *Aspergillus fumigatus* manganese superoxide dismutase [9], exhibit remarkable sequential identities with human proteins. Considering the differences and similarities between an endogenous human protein and its exogenous allergenic homolog may help in understanding the enigma of allergenicity.

Allergy, a disorder of the immune system, is manifested as inappropriate reactions to allergens, inert environmental substances, from, for example, pollen, house dust mites or animals [10]. Allergens, by cross-linking IgE on mast cells and basophils, elicit within a few minutes a type I hypersensitivity reaction, which results from the action of inflammatory mediators released from the cells. The symptoms of allergy vary depending on the organs affected. They range from mild and local, such as rhinitis, to severe and systemic, such as anaphylactic shock. Sensitization to an allergen can be evaluated by measuring allergen-specific IgE in serum or by skin prick tests. Sensitization can also occur without leading to a clinical disease. It is still largely unresolved why allergens initiate the process of sensitization [6, 11], the generation of specific T helper type 2 (Th2) lymphocytes, which play a crucial role in stimulating B lymphocytes to produce allergen-specific IgE [12].

One prerequisite for a protein to be an allergen is that it is dispersed in the environment and thus able to come into contact with the immune system. The original studies by Madsen et al. [1] revealed that human psoriasin is also expressed in normal skin, although in low amounts. Since then, it has become evident that psoriasin is present in the upper part of normal epithelium [13, 14] and is abundant on the skin surface [14]. It is possibly secreted by keratinocytes [14]. Much less is known about the presence of

the bovine homolog in different tissues. Like psoriasin [15], it is found, however, in the amniotic fluid [16] and in skin [5]. DNA hybridization analysis of a cDNA library of normal bovine skin suggested that that it is expressed in the skin in significant amounts [5]. These observations suggest that an endogenous human protein and its allergenic homolog share the property of being emitted in the environment.

There is no evidence so far that any kind of biological function in general would account for the allergenic capacity of proteins. However, biological activity appears to be a factor contributing to the allergenicity of some allergens. In fact, for certain allergens from mites, fungi and pollen, their enzyme activity appears to be important [17]. Since psoriasin has not been described to be enzymatically active [18], this kind of a biological property probably cannot explain the allergenicity of Bos d 3. It is, however, noteworthy that psoriasin has been associated with various inflammatory skin diseases, including atopic dermatitis [19], since allergy is essentially an inflammatory disease. In this respect, the observations suggesting that the level of psoriasin is associated with the accumulation of $CD4^+$ T cells in the skin upon UV exposure [20] and that psoriasin is a chemotactic protein for $CD4^+$ T cells and neutrophils [21] are interesting. If the bovine homolog Bos d 3 has a similar property, it could contribute to the allergenicity of the protein by assisting the encounter of T cells with the allergen. As described above, T helper cells ($CD4^+$) play a crucial role in allergic diseases. In this context, it is surprising, however, that the level of psoriasin was recently described to be higher in the nasal fluid samples of non-allergic control subjects than in those of patients with symptomatic allergic rhinitis, an inflammatory disease [22]. The authors suggested that psoriasin can have a function not yet discovered and that the down-regulation could be related to the resolution of the disorder.

Lipocalins are a large protein family comprising proteins from animals, plants, and bacteria [23]. They are typically small extracellular proteins with capacity to bind small, mainly hydrophobic molecules. They exhibit a variety of different functions. Almost all important mammalian respiratory allergens belong to lipocalins [6]. We have proposed previously that the homology between endogenous lipocalins and exogenous lipocalin allergens could account for the allergenic capacity of the lipocalin allergens [24]. As discussed above, a number of allergens including Bos d 3 exhibit sequential similarities with human proteins. This feature could be implicated in the allergenicity. Adaptive immunity has developed to recognize foreign agents, while avoiding autoreactivity. To obtain the latter requirement, T cells with strong reactivity against self are deleted during the thymic maturation [25]. One of the consequences could be that allergens resembling self proteins may not be recognized effectively but suboptimally. Several studies have shown that a weak stimulation through T cell receptor can favor Th2 deviation [26–28]. We [29–31] and others [32] have shown that lipocalin allergens are recognized weakly. Importantly, the immunodominant T cell epitope of Bos d 2, a bovine dander allergen of the lipocalin family, was found to be suboptimal for T cells [33]. It remains to verified whether Bos d 3, the bovine homolog of psoriasin, exhibits similar immunological features as lipocalin allergens.

One possibility for bovine Bos d 3 to promote allergic sensitization could be its direct action on cell populations other than T cells. For example, the allergens with enzyme activity induce inflammation through protease-activated receptors in the airways [17]. Moreover, pathogen-associated molecular patterns found in microbial products deliver signals to dendritic cells, which selectively influence T cell differentiation [34]. As psoriasin (or Bos d 3) is not known to have such properties, they do not appear feasible alternatives for promoting sensitization to Bos d 3.

One of the intriguing recent observations on psoriasin is its inherent activity against *E. coli*, which is suggested to be mediated by the sequestration of Zn^{2+} [14]. The activity was observed to be quite specific, in that other Gram-negative bacteria tested or Gram-positive bacteria, such as *Staphylococcus aureus,* were much less sensitive. Psoriasin was found on the healthy human skin. Its expression was induced by *E. coli* and by proinflammatory cytokines interleukin-1β and tumor necrosis factor. As it is found in vernix caseosa [35], in the full-term amniotic fluid [15], and it is also expressed in the amniotic membranes [15], it may well play a role in protecting the fetus against *E. coli* infection. For the time being, it is not known whether the bovine homolog of psoriasin, Bos d 3, also shows activity against *E. coli*. Whatever the truth, it is difficult to think how such a biological property could be associated with allergenicity. It can be speculated, however, that a protein able to affect the normal bacterial flora could skew the balance of the local immunological microenviroment in such a way that it could favor sensitization. Whether the capacity of psoriasin to bind Ca^{2+} is implicated in the allergenicity of the protein also remains to be elucidated. A number of allergens, including a human autoallergen, are calcium-binding proteins [36, 37].

The allergenic capacity of proteins is still a mystery. It seems, however, that there are no simple physicochemical factors or unifying biological properties that can account for allergenicity. Since allergic diseases are a widespread health problem in the industrialized countries, clarifying the mechanism of allergy is a necessary objective for scientific research. It remains to be seen whether careful analyses of the immunological characteristics of allergenic molecules and their human homologs can resolve the problem of allergenicity.

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