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Molecular modelling of the major peanut allergen Ara h 1 and other homotrimeric allergens of the cupin superfamily: a structural basis for their IgE-binding cross-reactivity

Annick Barre, Jean-Philippe Borges, Pierre Rougé *

Surfaces Cellulaires et Signalisation chez les Végétaux, UMR-CNRS 5546, Pôle de Biotechnologie végétale, 24, chemin de Borde Rouge, 31326 Castanet-Tolosan, France

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Abstract

Three-dimensional models of the major vicilin allergens from peanut (Ara h 1), lentil (Len c 1) and pea (Pis s 1), were built by homology-based modelling from the X-ray coordinates of the structurally closely related soybean β-conglycinin. All the allergen monomers exhibit the typical cupin motif made of two modules related by a pseudo-dyad axis. Each module consists of a β-barrel core domain associated to a loop domain which mainly contains α-helices. The three cupin motifs are assumed to be arranged in a homotrimeric structure similar to that observed in β-conglycinin, phaseolin or canavalin. Most of the sequential B-cell epitopes characterized on the C-terminus of the Ara h 1 allergen are well conserved in both Len c 1 and Pis s 1 allergens. They occupy very comparable areas on the molecular surface of the allergens and exhibit a similar three-dimensional conformation. This antigenic community readily accounts for the IgE-binding cross-reactivity commonly observed between the vicilin allergens from edible legume seeds. The clinical implication of this cross-reactivity is addressed for a definite diagnosis of legume seed allergy.

Keywords: Peanut allergen; three-dimensional model; B-cell epitopes; T-cell epitopes; allergy

1. Introduction

Soybean and, to a lesser extent, peanut, kidney bean, pea and lentil are among the most commonly used dietary seeds for their good nutritional value and balanced amino acid content. However, IgE-mediated food allergy to legume seed proteins and, especially, to peanut proteins, appears to be on the increase [1] and has currently become a worrying health problem in many countries [2,3]. Peanut allergy is the third most prevalent food allergy [4] that mostly contributes to the fatal issued anaphylactic reactions in both children and adults [5]. Seed storage proteins [6] have been recognized as being the major peanut allergens Ara h 1 (vicilin) [7], Ara h 2 (2S albumin conglutin) [8], and Ara h 3 (glycinin with a Bowman–Birk trypsin inhibitor activity) [9] responsible for the allergenic response of susceptible individuals. Ara h 1 is a homotrimeric protein belonging to the cupin superfamily [10,11] which contains structurally related proteins built from the β-barrel cupin motif but display very different functions [12]. Ara h 1 is particularly important since it is recognized by over 90% of individuals sensitised to peanut [7]. At least 23 IgE-binding sequential B-cell epitopes have been characterized along the polypeptide chain of the Ara h 1 monomer [13,14]. In addition, an IgE-binding cross-reactivity was identified with other legume vicilins from lentil (Len c 1) [15] and pea (Pis s 1) [16]. Other IgE-binding cross-reacting vicilin allergens include β-conglycinin from soybean [17] and Jug r 2 from walnut [18]. This hypersensitivity reactions to multiple dietary seeds has relevant clinical implications, e.g.,

Abbreviations: Ara h1, *Arachis hypogea* (peanut) allergen 1; HCA, hydrophobic cluster analysis; IgE, immunoglobulin E; Len c 1, *Lens culinaris* (lentil) allergen 1; Pis s 1, *Pisum sativum* (pea) allergen 1; SCR, structurally conserved regions; Vic f 1, *Vicia faba* (faba bean) allergen 1.

* Corresponding author. Tel.: +33 05 62 19 35 58; fax: +33 05 62 19 35 02.
E-mail address: rouge@scsv.ups-tlse.fr (P. Rougé).

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to accurately characterize the allergen(s) responsible for the sensitisation or to determine the risk of reaction to related foods in previously sensitised individuals [19]. In this context, the epitopic community of ubiquitous allergens has to be characterized at the molecular level to improve both the accuracy and interpretation of the diagnostic tests (skin prik tests, RASTs, in vivo IgE-binding tests, oral food challenges) by using carefully selected purified allergens or chemically synthesized specific epitopes. Here, we present a homology-based molecular modelling approach used to characterize the structural features responsible for the epitopic community among the major vicilin allergens from peanut (Ara h 1), lentil (Len c 1) and pea (Pis s 1).

2. Material and methods

Multiple amino acid sequence alignments were carried out with CLUSTAL-X [20] and displayed with ESPript [21].

The HCA (Hydrophobic Cluster Analysis) [22] was performed to delineate the conserved secondary structural features (strands of β-sheet and stretches of α-helix) along the amino acid sequence of Ara h 1, Len c 1 and Pis s 1 by comparison with the soybean (*Glycine max*) β-conglycin [23] used as a model. HCA plots were generated using the program drawhca of L. Canard (http://www.lmcp.jussieu.fr/~soyer/www-hca/hca-form.html).

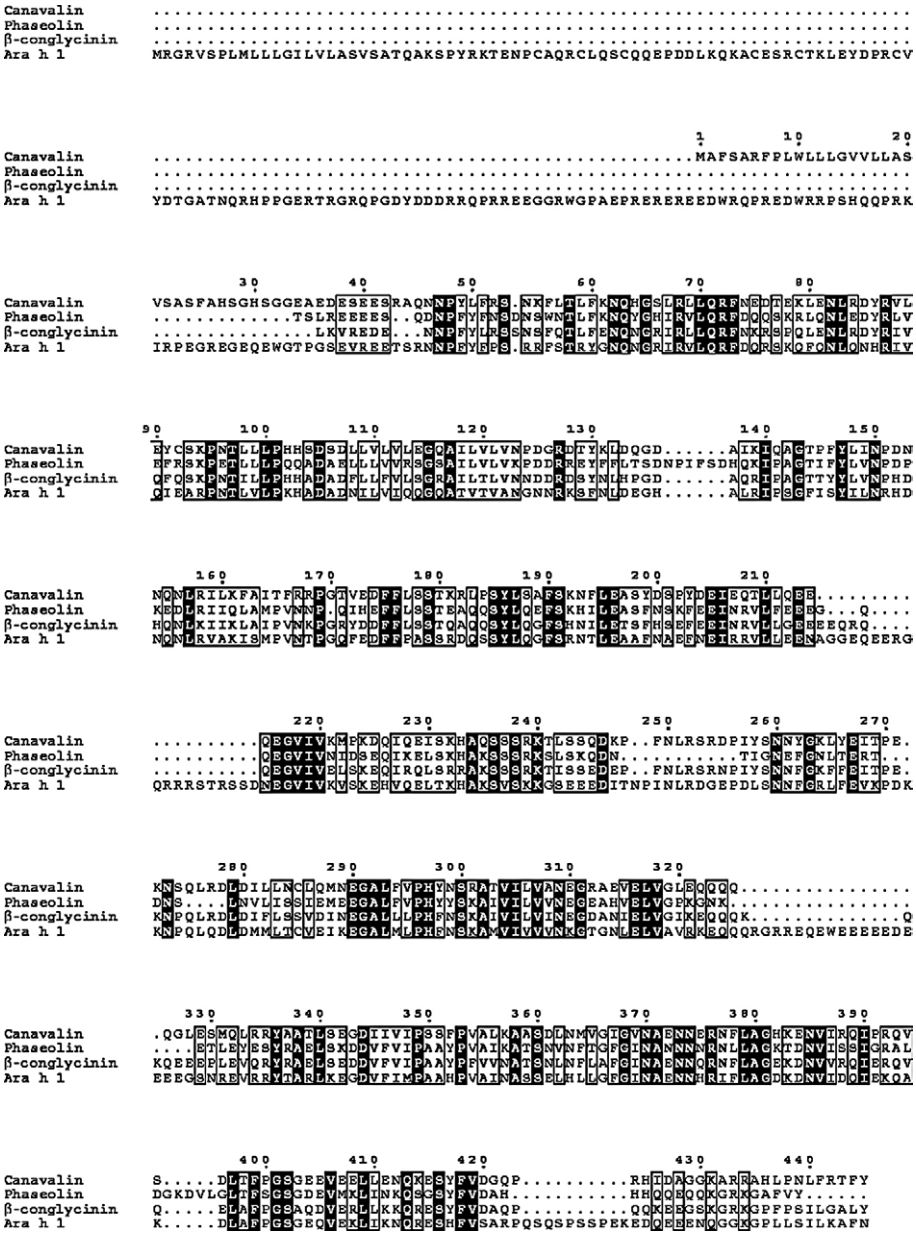

Fig. 1. Amino acid sequence alignment of Ara h 1 and other cupin proteins of known three-dimensional structures: canavalin, β-conglycinin and phaseolin. Identical residues are in black boxes and homologous residues are in open boxes. The alignment was performed with CLUSTAL-X [20] and represented with ESPript [21].