Molecular Immunology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Molecular Immunology

journal homepage: www.elsevier.com/locate/molimm

Tree nut allergens

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ARTICLE INFO

Keywords:
Allergy
Component resolved diagnosis
Prevalence
Recombinant allergens
Tree nuts

ABSTRACT

Tree nuts are considered as part of a healthy diet due to their high nutritional quality. However, they are also a potent source of allergenic proteins inducing IgE mediated hypersensitivity often causing serious, life-threatening reactions. The reported prevalence of tree nut allergy is up to 4.9% worldwide. The general term "tree nuts" comprises a number of nuts, seeds, and drupes, derived from trees from different botanical families. For hazelnut and walnut several allergens have been identified which are already partly applied in component resolved diagnosis, while for other tree nuts such as macadamia, coconut, and Brazil nut only individual allergens were identified and data on additional allergenic proteins are missing. This review summarizes the current knowledge on tree nut allergens and describes their physicochemical and immunological characterization and clinical relevance.

1. Introduction

Tree nuts are a potent and frequent allergen source inducing IgE mediated food allergic reactions which can cause serious and sometimes even fatal reactions. Tree nut allergy has been reported from all over the world with a prevalence of up to 4.9% of the general population (McWilliam et al., 2015).

Botanically, a tree nut is composed of a dry hard shell protecting the seed or dormant embryo such as the nuts from trees from the botanical order Fagales. The strict botanical definition is not always in line with what is generally accepted as a tree nut – an edible seed originating from a tree. Tree nuts are found in both, dicots and monocots, some of them are phylogenetically closely related, while others are not. This relationship is also reflected by sequence similarity which in turn provides the molecular background for potential IgE cross reactivity.

Usually, these seeds contain a high number of essential nutrients to provide the germinating seeds with energy for survival and proliferation. For example, seed storage proteins are highly abundant in tree nuts packed in protein bodies. Due to their high nutritional quality tree nuts are also regarded as part of a healthy diet and their consumption is recommended. This is also reflected by the annual worldwide production of tree nuts, which ranges from 4.9 M tons of cashew nuts to 1.1 M tons of pistachios (FAOSTAT, 2018).

Tree nuts can be consumed as a snack alone, as a nut mix, or as an ingredient in a range of dishes. Furthermore, they are also present in different food products such as chocolate, nougat, marzipan, nut milk and oil, pesto, cereals, baked goods, flavored coffee, and salads. Exposure to tree nuts can also occur via using cosmetics, handling pet food, and bean bags. Food processing such as roasting, heating or enzymatic treatment may affect the allergenicity of food allergens. It has been shown that heating and dry roasting of hazelnuts and walnut can destroy some allergenic fractions, while other proteins remain stable and maintain their IgE binding activity, thus still posing a risk for the tree nut allergic patient (Downs et al., 2016; Hansen et al., 2003; Muller et al., 2000).

2. Protein families involved in tree nut allergy

The majority of proteins involved in tree nut allergy belong to protein families of 2S albumins, vicilins, legumins, and nsLTPs. Bet v 1-homologues and profilins are involved in pollen associated tree nut allergy (Fig. 1). Also, oleosins and thaumatin-like proteins were shown to be important allergens. An overview of the already identified allergens is given in Tables 1–3.

2.1. 2S albumins

2S albumins together with nsLTPs belong to the prolamin superfamily. These proteins provide an overall alpha helical dominating structure and share 6–8 conserved cysteine residues forming disulfide bridges facilitating a compact structure. Besides these conserved structural determinants sequence similarities are rather low among members of these protein families. 2S albumins are encoded by a multigene family and contain a high number of sulfur rich amino acids.

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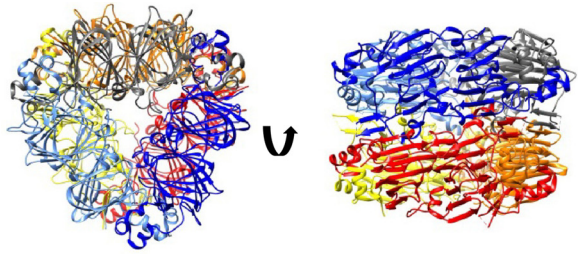
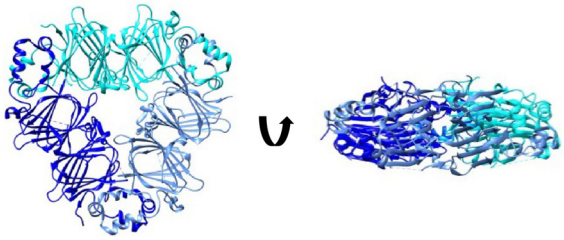
https://doi.org/10.1016/j.molimm.2018.03.011
Received 15 March 2018; Accepted 19 March 2018

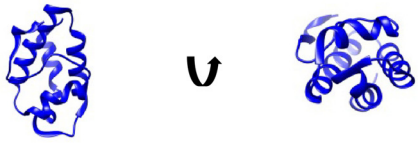


Legumin: Coconut (PDB: 1XGF)

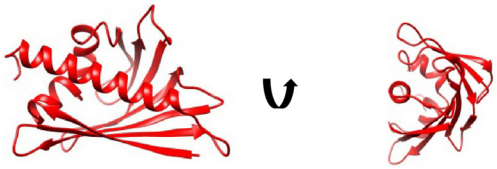


Vicilin: Pecan (PDB: 5E1R)

2S albumin: Brazil nut (PDB: 2LVF)



nsLTP: Hazelnut (PDB: 4XUW)



Bet v 1: Birch pollen (PDB: 1BV1)

Fig. 1. Representative 3D structures of tree nut allergens as well as Bet v 1 from birch pollen as a representative for Bet v 1-like proteins identified in hazelnut and walnut.

Most of them are cleaved into a large subunit of approx. 9 kDa and a small subunit of approx. 4 kDa (Moreno and Clemente, 2008). Post-translational modifications such as C-terminal truncations of the small subunit contribute to the heterogeneity of 2S albumin fractions. Their compact structure accounts for a high resistance when subjected to thermal and enzymatic treatment.

2.2. Non-specific lipid transfer proteins (nsLTPs)

NsLTPs are thought to transport phospholipids across membranes and are upregulated during plant defence upon fungal and bacterial infections (De Lucca et al., 2005). NsLTPs are characterized by a shared structure based on 4 disulfide bridges forming an internal cavity that allows carrying ligands. It has been shown that this cavity can host different types of ligands such as fatty acids, fatty acyl CoA, phospholipids, glycolipids, hydroxylated fatty acids, and prostaglandin B2 (Carvalho and Gomes, 2007; Zachowski et al., 1998). 3D-structures of several nsLTPs have been resolved, e.g. from hazelnut, peach, and barley by either X-ray crystallography or NMR (Lerche and Poulsen, 1998; Offermann et al., 2015; Pasquato et al., 2006). Recent studies provided evidence for nsLTPs from apple, peach, and walnut that they preferentially bind unsaturated fatty acids and via this binding the C-terminal part of the tunnel undergoes a conformational change thus exposing amino acid residues to the surface (Dubiela et al., 2017). NsLTPs have been identified as allergens from a vast range of dicot plants, present in pollen, fruits, tree nuts, and seeds. Primarily, these allergens are regarded as true food allergens, indicating that sensitization occurs via the gastrointestinal tract. These allergens are accumulated in the outer layers of fruits and seeds. They display a remarkable stability against heat treatment and enzymatic degradation, however, their stability is pH dependent.

2.3. Vicilins

Vicilins (7S globulins), together with legumins (11S globulins), belong to the cupin superfamily characterized by a β-barrel structure. Typically, these glycoproteins are proteolytically processed thus providing a range of isoforms. In their native form vicilins appear as trimers with an overall molecular mass of approx. 150–190 kDa. They display an intermediate stability when subjected to heat and enzymatic treatment.

2.4. Legumins

Legumins are high molecular weight proteins (approx. 350 kDa) consisting of six subunits. The precursor protein is processed to form trimers in the endoplasmatic reticulum and then transferred to the protein storage vacuoles. There each subunit is cleaved into an acidic (40 kDa) and basic polypeptide (20 kDa). These subunits remain linked by a disulfide bridge and finally form a hexameric structure (Fig. 1) (Shewry et al., 1995).

2.5. Oleosins

Oleosins, abundantly expressed in seeds and nuts, are structural proteins of oil bodies. These bodies consist of neutral lipids (92–98%), predominantly triacylglycerols, an outer monolayer of phospholipids (1–4%) and proteins (1–4%), mostly oleosins (Alexander et al., 2002). The proteins (~15–26 kDa) share similar structures, with a hydrophobic central well conserved domain of about 68–74 amino acid residues which is inserted into the triacylglycerol matrix, flanked by hydrophilic N- and C-terminal domains of variable length (50–70 and 55–98 residues). In addition to their role as structural proteins in the oil bodies there is growing evidence that they may also assist in the biosynthesis and mobilization of oils (Parthibane et al., 2012). Although oleosins have been identified as allergens from hazelnut, peanut, and seeds, further information is missing due to their low solubility in aqueous solutions (Akkerdaas et al., 2006; Leduc et al., 2006; Schwager et al., 2017).

2.6. Bet v 1-like proteins

Bet v 1-related proteins have been identified from species all over the plant kingdom. Proteins from the Bet v 1 family (154–160 amino acid residues) are non-glycosylated, share high sequence similarity and are usually encoded by a multigene family. The overall structure is also highly conserved, formed by seven stranded antiparallel β-sheets