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Research review paper

Molecular features of grass allergens and development of biotechnological approaches for allergy prevention

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ABSTRACT

Allergic diseases are characterized by elevated allergen-specific IgE and excessive inflammatory cell responses. Among the reported plant allergens, grass pollen and grain allergens, derived from agriculturally important members of the Poaceae family such as rice, wheat and barley, are the most dominant and difficult to prevent. Although many allergen homologs have been predicted from species such as wheat and timothy grass, fundamental aspects such as the evolution and function of plant pollen allergens remain largely unclear. With the development of genetic engineering and genomics, more primary sequences, functions and structures of plant allergens have been uncovered, and molecular component-based allergen-specific immunotherapies are being developed. In this review, we aim to provide an update on (i) the distribution and importance of pollen and grain allergens of the Poaceae family, (ii) the origin and evolution, and functional aspects of plant pollen allergens, (iii) developments of allergen-specific immunotherapy for pollen allergy using biotechnology and (iv) development of less allergenic plants using gene engineering techniques. We also discuss future trends in revealing fundamental aspects of grass pollen allergens and possible biotechnological approaches to reduce the amount of pollen allergens in grasses.

1. Introduction

Allergies are global diseases that affect a worldwide population. Among the allergic diseases, hay fever is a widespread allergic upper respiratory condition triggered by airborne pollen allergens that activate an Immunoglobulin E (IgE) response, leading to immediate release of inflammatory mediators such as histamines. Pollen allergen exposure can also exacerbate asthma in susceptible individuals (Aalberse, 2000; Bousquet et al., 2008; Davies, 2014; Greiner et al., 2011; Scala et al., 2010). Allergic diseases affect up to 20–30% of the world population, including children as young as 3, and are associated with disrupted sleep, impaired work performance and lower life quality (Andersson and Lidholm, 2003; Bousquet et al., 2008; Dykewicz and Hamilos, 2010; Suphioglu et al., 1992; Wheatley and Togias, 2015). The severity of allergic rhinitis varies between locations and seasons due to environmental effects and pollen production time (Beggs et al., 2015; Buters et al., 2015; Davies et al., 2012; Dykewicz and Hamilos, 2010; Nony et al., 2015). Genetic and environmental variations between individual plants, as well as differences between allergen proteins in various plants species, particularly grasses (Poaceae family), impact allergen exposure, sensitivity to allergens and symptoms of patients (Aiubi et al., 2015; Amardip et al., 2014; Buters et al., 2015; Y. Chen et al., 2016; Davies, 2014).

Allergic sensitization to aeroallergens frequently leads to the production of allergen-specific IgE antibodies in susceptible people (Moneret-Vautrin, 1997; Moneret-Vautrin and Kanny, 2007). IgE typically recognises motifs or conformational epitope structures on the surface of allergen proteins, which contain diverse and complex motifs, making it difficult to attribute IgE binding to any single linear peptide sequence (Adachi et al., 1993). Upon secondary exposure to allergens in sensitized individuals, IgE-mediates an immediate allergic reaction, prompting symptoms ranging from itching of the eyes, sneezing, and rashes, to severe anaphylaxis (Ramesh, 2008). Allergen abundance can be influenced by the environment and genetic predisposition of the source organism, and severity of symptoms can also be influenced by the genetic predisposition of the patient (Campbell and Mehr, 2015; Y. Chen et al., 2016; Fuhrmann et al., 2016). Allergens can be present in a variety of animal byproducts, cereal grains, and pollen

Abbreviations: AIT, allergen-specific immunotherapy; IgE, Immunoglobulin E; IgG, Immunoglobulin G; RNAi, RNA interference

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grains (Y. Chen et al., 2016; Sandrini et al., 2015). Food allergens have been extensively reviewed, especially in the context of common or severe allergies to dairy and nuts that cause gastrointestinal or systemic anaphylactic reactions and/or atopic dermatitis (Campbell and Mehr, 2015; Patel and Volcheck, 2015; Pomés, 2008; Skypala and Vlieg-Boerstra, 2014).

Grasses comprise one of the largest angiosperm families and contain many cultivated and widely distributed species that produce allergenic pollen and grains. Several reviews summarized respiratory diseases caused by grass, weed or tree pollen allergens (Andersson and Lidholm, 2003; Davies, 2014). In this review we focus on our understanding of the evolutionary events, common motifs and function of putative allergens in grass pollens, as well as efforts to alleviate allergies using biotechnological tools, and provide future research perspectives.

2. Global distribution of allergy-inducing grasses

Poaceae species are globally distributed and are the source of many pollen allergens. D'Amato et al. (2007) reported that airborne pollens from trees, weeds and grasses are associated with allergies across Europe. Smith et al. (2014) also proposed that the dominant species producing airborne pollens are grasses. Likewise, along with pollens of the ever-greens, grass pollens are dominant in the air in Calcutta, India (Mandal et al., 2008). In Lebanon, 17.75% of the allergy patients were allergic to grass pollen (Irani et al., 2013). Clinically important allergy-inducing grass species have been recorded across the USA (Fuhrmann et al., 2016; White and Bernstein, 2003). Pollen and grain allergies have been well documented among both adults and children on the Australian continent as pollen allergies are more prevalent in Australia than other countries, and airborne grass pollen is a major contributor to allergic rhinitis in Australia and New Zealand (Asher et al., 2006; Australian Institute of Health and Welfare, 2011; Davies et al., 2015; Robertson et al., 1998; Woods et al., 2002) (Fig. 1). In Australia, the levels of airborne grass pollens varies greatly between location and climate (Beggs et al., 2015) and the distribution of grass types varies with latitude (Davies et al., 2015; Medek et al., 2016). Bermuda grass and Bahia grass are among the major pollen contributors to allergic disease in subtropical Queensland, and Ryegrass is one of the major contributors in temperate Melbourne (Davies et al., 2011, 2012).

The Poaceae family, which contains approximately 780 genera and around 12,000 species, includes many important grain-producing agricultural species such as rice (*Oryza sativa*), wheat (*Triticum* spp.) barley (*Hordeum vulgare*), and maize (*Zea mays*). In Poaceae, allergen proteins are often found in pollen or grains. In higher plants, pollen grains are produced via meiosis and mitosis within the male organ stamen, which contains the anther and supporting filament (Fig. 2) (Shi et al., 2015; D.S. Zhang et al., 2010; Zhang et al., 2013). Each pollen produced within the stamen contains two sperm cells and one vegetative cell and is enclosed by specialised pollen walls. Pollen grains fertilise ovules, which later develop into seeds and grains. Cereal grains are small, hard, and dry seeds and are a major global food source that contains a substantial amount of starch, a type of carbohydrate that provides dietary energy and nutrition (H. Zhang et al., 2010; Zhang et al., 2013). Grass pollens contain many proteins, only some of which are allergenic and cause an IgE response (Abou Chakra et al., 2012; Andersson and Lidholm, 2003). Currently at least 20 grass species such as timothy grass (*Phleum pratense*) and wheat have been reported to produce pollen proteins associated with the triggering of an IgE response, and the majority of these species are prevalent in temperate climates (Andersson and Lidholm, 2003). Rice, maize and wheat are crops that are grown and consumed on every continent excluding Antarctica. Therefore investigation of pollen allergens in agricultural Poaceae species is of great importance to the prevention of pollen allergies.

3. Allergens in Poaceae species

Allergen proteins are found in both pollens and grains and the number of allergen families varies between species. Wheat for example, contains up to 27 allergen families as characterized by the IUIS/WHO guidelines (Radauer et al., 2012, 2014). A number of allergen families are reported in grass pollens and/or grains, including β-expansin proteins Phl p 1 from timothy grass and Zea m 1 from maize, the lipid-transfer protein (LTP) Zea m 14 from maize, and the gliadin proteins Tri a 19, Tri a 20 and Tri a 21 from wheat (Table 1) (Anderson et al., 1989; Golias et al., 2013; Lehto et al., 2003; Matsuo et al., 2005; Pasini et al., 2002; Pastorello et al., 2013; Russell et al., 2008; Staiger et al., 1993; Trcka et al., 2012). Expansins are cell wall-loosening proteins that at least partially mediate the pH-dependent cell wall extension and cell growth. Expansins include two families, α-expansins and β-expansins, and are reported to be involved in modulating a variety of plant developmental events besides cell expansion, including organ morphogenesis, softening of fruits, and grass pollen tube growth (Artzi et al., 2016; Cho and Cosgrove, 2002; Grobe et al., 1999; Li et al., 2003; Marowa et al., 2016; Sampedro and Cosgrove, 2005; Valdivia et al., 2003, 2009; Wu et al., 2001; Yoo et al., 2003). Plant LTPs belong to a small and abundant lipid-binding protein group that exchange lipids between membranes, and have functions in various processes such as anther development and pollen formation (D.S. Zhang et al., 2010; Zhang et al., 2008). Gluten is a mixture of hundreds of related but distinct wheat storage proteins, mainly gliadin and glutenin (Anderson et al., 1989; Gil-Humanes et al., 2008; Gil-Humanes et al., 2011; Shewry et al., 2002; Weegels et al., 1996). Gliadin proteins in wheat grains promote dough elasticity and strength, and can also trigger an IgE response in allergy patients (Matsuo et al., 2005; Shewry et al., 2002). Similar storage proteins in other species, such as secalin from rye, hordein from barley, and avenin from oats, have also been collectively called gluten (Biesiekierski, 2017). Due to the prevalence of gluten in wheat and other grains, patients need to avoid wheat-based foods. However, because it is difficult and expensive to find appropriate dietary alternatives to allergenic grains, especially in countries where grain-based diets are the primary staple, it is important to understand the fundamental aspects of grass allergens and develop tools to alleviate food allergies.

Several studies in Poaceae species have identified allergen genes based on investigations using transcriptomics and proteomics as well as sequence comparison or IgE binding assays (Campbell et al., 2015; Golias et al., 2013; Li et al., 2012; Sekhar et al., 2015). Some putative allergens have been identified in DNA or transcriptome databases based on sequence similarity, but currently little is known about the specific structural or functional properties of proteins encoded by these sequences. Moreover, in many cases the expression of such protein sequences in relevant plant tissue and the capacity of these putative allergens to bind IgE or to elicit an allergic reaction de novo have not been demonstrated. Major groups of grass allergens discussed in this review include the α-amylase/trypsin inhibitors, β-expansin-like proteins expressed in pollen, and profilins expressed in both pollen and grain (Aalberse, 2000; Radauer et al., 2008, 2012, 2014).

4. Structure and conserved features of grass allergens

Putative allergen proteins can be predicted based on sequence homology compared with previously known allergens or known IgE-binding epitopes, but must be confirmed though immunological tests such as serological IgE assays or skin prick tests (Radauer et al., 2012, 2014). IgE binding epitopes can be comprised of continuous linear or discontinuous stretches of amino acids, but these motifs can be highly varied in amino acid sequences (Matsuo et al., 2015). Understanding how these allergen encoding genes evolved may be helpful in revealing allergenic properties and for designing future allergy prevention strategies.