



Associate editor: P.S. Foster

Mechanisms of type I food allergy

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Abstract

The gastrointestinal tract represents the biggest immune organ of the human body and has 3 distinct functions: (1) barrier and defense against potential pathogens, (2) ignorance or tolerance of innocuous agents, and (3) digestion and nutritional uptake of alimentary compounds. Recent studies have indicated that especially structural features of dietary proteins seem to be a precondition for the induction of immediate type immune responses. Crystallographic studies of allergen molecules have been fundamental for epitope studies in a 3-dimensional format using peptides or mimotopes. The identified IgE epitopes were all conformational and responsible for high-affinity interactions with specific IgE. Moreover, numerous studies have indicated that allergens, among them food allergens, preferentially form di-, tri-, or multimers, thus leading to a repetitive display of epitopes. As B-lymphocytes are pattern recognizers, this feature is essential for a memory response, but may also be critical for the very first allergen contact and initiation of the IgE response. Here we review the key candidate cells in the gut, which are capable of recognizing conformation and molecular patterns, but may also be involved in skewing the immune response towards Th2. Animal models have been basic for understanding the molecular principles of food allergy and they will be increasingly indispensable for the definition of novel vaccination strategies. Therefore, the available models are critically analyzed in this review.

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Keywords: Food allergy; Epitope; Conformation; Gastrointestinal mucosa; M-cells; Digestion; IgE

Abbreviations: AA, amino acid; APC, antigen presenting cell; IEC, intestinal epithelial cell; M-cell, Microfold cell; MALT, mucosal associated lymphoid tissue; SGF, simulated gastric fluid; CTB, cholera toxin subunit B.

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1. Introduction

Despite the knowledge of the existence of food adverse reactions in the ancient world documented in Greek and Roman literature (Cohen & Saavedra-Delgado, 1989a, 1989b), it was not until the beginning of the 19th century when clinicians started to define these reactions and to investigate their underlying mechanisms. In 1902, Portier and Richet discovered and described anaphylaxis in animal experiments (Portier & Richet, 1902). Their report prompted multiple clinical descriptions of food allergic reactions in the following years due to the analogy between reactions observed in animals and patients (Hutinel, 1908; Schloss, 1912, 1915; Blackfan, 1920; Schloss, 1920). In 1921, Carl Prausnitz and Heinz Küstner, the latter being accidentally allergic to fish, have performed the simple but nevertheless groundbreaking experiment of passive anaphylaxis: After Prausnitz had ingested fish, an immediate skin response could be evoked on his forearm at sites where Küstner's serum had been injected intracutaneously. This was the first proof for a transferable humoral factor responsible for allergy (Prausnitz & Küstner, 1921), which was 3 years later termed "reagin" by Coca and Grove (1925). This classic experiment named Prausnitz–Küstner reaction after the 2 investigators was consecutively applied by other researchers to perform first absorption studies on food allergens (Walzer, 1927; Brunner & Walzer, 1928). However, it took several decades until the reaginic agent in the serum of allergic individuals was identified as a new class of immunoglobulins (Ishizaka & Ishizaka, 1967; Johansson & Bennich, 1967), and in 1969 termed IgE (Bennich et al., 1969), which clearly represented a milestone in allergy research.

1.1. Definition of food allergic reactions

Food adverse reactions are defined as any abnormal response observed upon ingestion of food. Due to the high frequency of food hypersensitivities claimed in the general population (Sloan & Powers, 1986; Young et al., 1994; Sicherer & Sampson, 2006) and due to the diversity of terms used to describe these disorders, the European Academy of Allergy and Clinical Immunology has proposed a standardized nomenclature based on underlying mechanisms (Brujinzeel-Koomen et al., 1995).

Adverse food reactions were in a first line divided into toxic or nontoxic responses. Reactions due to toxic components occurring naturally in the foodstuff or being present

as contaminating agents are developed in anyone given the dose of the toxin is high enough. Nontoxic reactions depend on the individual susceptibility and are based on IgE- or non-IgE-mediated immune mechanisms (allergy or hypersensitivity) or non-immune mechanisms (intolerance). With regards to immune mediated reactions, the role of the so-called type I food allergies with IgE as mediator is best investigated. Food intolerances are most frequently observed among food adverse reactions and depend on metabolic characteristics of the patient (e.g. milk intolerance due to primary or secondary lactase deficiency), pharmacologic properties of the ingested food (e.g. headaches due to vasoactive mono- or diamines), nonspecific histamine-releasing properties of food (e.g. high contents of lectins, prolamins, peptones, polyamines), and undefined intolerances due to idiosyncratic responses (Sampson, 1999).

1.2. Prevalence of food allergy

About 25% of all American households change their daily alimentation practice due to perceived food adverse reactions of at least 1 family member (Sloan & Powers, 1986). Thus, hypersensitivity reactions to dietary compounds represent an important health concern in the Westernized world, even though true food allergy is less frequently diagnosed and postulated to be mainly a pediatric problem or linked to genetic predisposition (Dreskin, 2006). It is generally accepted that 6–8% of all children below 3 years of age reveal food allergic reactions (Bock, 1987; Sampson, 1996), with milk, egg and peanuts as the main triggers (Walker-Smith, 2003; Stone, 2004; Thong & Hourihane, 2004; Crittenden & Bennett, 2005). However, recent studies could show that the prevalence of these allergies seems to be rising. In a children cohort on the Isle of Wight, United Kingdom, the sensitization rate to peanuts has tripled in 5 years (Grundy et al., 2002).

In adulthood epidemiologic data on food allergy are rare and the prevalence of adverse reactions seems to be less common. Studies from the United States and Europe have led to the common opinion that 1–2% of the adult population are affected, with peanuts, tree nuts, seafood or pollen related foods as the main triggers for allergic symptoms (Jansen et al., 1994; Young et al., 1994; Sicherer et al., 1999; Vieths et al., 2002). However, on the basis of more recent epidemiological data, these numbers have to be corrected and 4% of the general population are estimated to have IgE mediated food hypersensitivities (Kanny et al., 2001; Munoz-Furlong et al., 2004).

2. The interaction of the gastrointestinal mucosa with dietary proteins

To this day the exact immunological mechanisms and the site of sensitization to food antigens remain unclear. The gastrointestinal tract with its 400 m² of surface area is the largest immune organ of the human body and represents by far the vastest site of exposure with pathogens and exogenous soluble antigens (MacDonald and Monteleone, 2005). Except the esophagus harboring squamous epithelia, a single epithelial layer represents the outer barrier towards the lumen in the whole system. Digestion and absorption of nutrients are further main functions exerted in the gastrointestinal lumen or at mucosal sites. Therefore, a delicate homeostasis between the first line defense system including immune reactions and the induction of tolerance or nonresponsiveness towards innocuous or nutritional compounds is crucial to ensure full functionality.

Several routes can be considered for food antigens to get in contact with cells of the immune system and it seems to critically depend on where and how the orally administered antigen is presented to T and B cells, to decide whether oral tolerance (Chase, 1946), or sensitization and immune reaction is the consequence.

2.1. Pre-intestinal interactions of food compounds with mucosal compartments

The first site of mucosal contact for food proteins is clearly the oral mucosa, which in some cases represents the first place of antigen uptake. The rapid and adequate drug uptake via the oral mucosa is since long well accepted for numerous indications (Carson et al., 1969; Kalsi & Kell, 2004; Lennernas et al., 2005). The effective absorption of intact peanut proteins via the oral mucosa with possible effects on responses in allergic patients has been recently reported (Dirks et al., 2005). Moreover, the sublingual route is routinely exploited for the treatment of type I food allergy (Enrique et al., 2005). Nevertheless, the oral cavity is protected by the immune system of the mouth being part of the mucosal associated lymphoid tissue (MALT), which could enable first food antigen contact with immune competent cells (Walker, 2004).

Following deglutition the food protein quickly passages the esophagus to reach the gastric lumen. Only little is known about food protein interactions with the esophageal and gastric mucosa. Nevertheless, food allergens are considered to play an important role in the pathogenesis of allergic eosinophilic esophagitis, an entity observed both in pediatric and adult patients (Potter et al., 2004; Garcia-Careaga & Kerner, 2005; Sgouros et al., 2006). Even though the mechanisms of this disease are not fully understood today, eosinophils may easily cooperate with IgE via their FcεRI. However, allergy tests are often unable to determine a causative food. Still, dietary proteins seem to be involved in the mucosal inflammatory process and feeding of hydrolysates leads to the resolving of tissue inflammation (Kelly et al., 1995; Markowitz et al., 2003; Liacouras, 2006).

Despite the role of the stomach as the first gatekeeper for protein digestion, little information is available on interactions of food antigens with the gastric mucosa. In the late 1980s the IgE-mediated gastric response upon allergen challenge was investigated revealing the stomach as a target organ for specific IgE responses only in sensitized animals (Catto-Smith et al., 1989). Moreover, only a few years later the transmural passage of immunologically intact food antigens via the gastric mucosa was reported (Curtis & Gall, 1992) and food specific IgE being found in gastric biopsies was hypothesized of representing a pathogenetic mechanism in gastric ulcer development (De Lazzari et al., 1994a, 1994b). Similarly as in eosinophilic esophagitis, eosinophils are also found here in elevated counts, indicating a direct participation of the gastric mucosa in food induced inflammation processes (Rothenberg, 2004; Hogan & Rothenberg, 2006).

2.2. Food protein interactions with the intestinal mucosa

After gastric protein digestion mainly carried out by pepsin in concert with acid, peptides and free amino acids (AAs) enter the duodenum. This represents the trigger for duodenal and jejunal epithelial cells to secrete cholecystokinin, which acts as a stimulus on pancreatic acinar cells to release trypsinogen and other pancreatic enzymes. Trypsin, chymotrypsin and procarboxypeptidases hydrolyse the peptides into AAs or oligopeptides. Furthermore, brush-border peptidases in the duodenum digest oligopeptides, which can then be absorbed via sodium-dependent AA-cotransporters located along the luminal side of the enterocytes and serve for nutrition. Approximately 50% of the protein absorption takes place in the duodenum, even though the whole small bowel is involved (Freeman et al., 1979; Sleisenger & Kim, 1979; Erickson & Kim, 1990). Oligopeptides below a length of 8 AAs are nonreactive with structures involved in antigen recognition or presentation and, thus, are immunologically ignored (York et al., 1999).

However, proteins might also escape or resist protein digestion and passage the intestinal lumen in an intact form. In newborns the digestive enzymatic activity is not fully active and the secretory IgA system is not mature until 4 years of age (Mayer, 2003), facts which might facilitate the passage of undigested proteins causing a primed immune response. This hypothesis is supported by the presence of circulating antibodies to common dietary antigens during the first 3 months of life (Falth-Magnusson et al., 1988). However, also through the mature gut of adults 2% of the ingested food proteins are absorbed in an immunologically intact form (Husby et al., 1987). These protein antigens may cross the epithelial barrier by transcytosis through enterocytes or by uptake via the Microfold cells (M-cells) (Brandtzaeg, 1997). On the other hand, there are conditions where proteins may diffuse paracellularly through the epithelial layer. Several proinflammatory cytokines do directly increase permeability when produced in large quantities in inflammation, such as celiac disease or inflammatory bowel diseases (Heyman et al., 1994; Heyman & Desjeux, 2000). In these settings, food proteins reach the MALT in large quantities, most often leading to IgG induction and immune complexes.

The resulting food-adverse reactions may thus be immunologic, but not IgE-mediated (DeMeo et al., 2002; Seibold, 2005).

3. Structural characteristics of food allergens

Despite the enormous variety of different nutrients found in the daily human diet, only relatively few proteins account for most allergic reactions observed in patients and the question which protein features absolutely account for allergenicity remains still to be answered. However, multiple research efforts have been made to characterize the similarities of molecules with proven food allergenic potential.

In a first line, food proteins triggering an allergic response were classified based on their potential of primary sensitization. Complete allergens have been ascribed both the potential to sensitize and the property to elicit allergic reactions. Incomplete allergens, which were also termed nonsensitizing elicitors, trigger allergic reactions only after sensitization with cross-reactive, complete allergens (Aalberse, 2000). Prominent examples are food proteins being homologues of the major birch pollen allergen Bet v 1, which reveal clinical symptoms mainly after primary inhalative sensitization with the pollen allergen (Vieths et al., 2002). Nevertheless, allergic reactions to the above-mentioned foods without any pollen association have been reported (Ortolani et al., 1993; Schocker et al., 2000).

The classification of dietary proteins in complete and incomplete allergens is closely linked to the postulated resistance of true food allergens to stomach degradation. Only proteins persisting the gastric transit in an intact conformation were excepted to sensitize directly via the oral route (Astwood et al., 1996). Thus, novel dietary compounds were even proposed to be tested in simulated gastric fluid (SGF) experiments for assessment of their allergenic potential (Taylor & Hefle, 2001). However, it has been repeatedly demonstrated, that allergens, such as proteins from fruits and vegetables (Yagami et al., 2000), seafood (Untersmayr et al., 2003; Untersmayr & Jensen-Jarolim, 2005), milk, egg, soy and peanuts (Fu et al., 2002), clinically known to harbor direct sensitization capacity are not resistant in these assays. Thus, these data indicate the need of revision for these safety assessment protocols (Jensen-Jarolim & Untersmayr, 2006).

The composition and the food matrix have been discussed to be of importance for allergenicity. Main food allergens seem to have a higher protein content and lipid concentrations than nonallergenic dietary compounds (Lehrer et al., 2002). Another quality of allergens seems to be the abundant presence of the involved protein in the food stuff. A good example is shrimp, which in 20% of total protein consists of Pen a 1, the major shrimp allergen (Daul et al., 1994). A high protein concentration was also shown for allergens in egg white, milk, soy, peanut, mustard and potato (Lehrer et al., 2002). An exception from this rule is the major fish allergen parvalbumin, which is recognized by over 90% of all fish allergic patients, even though it represents only 0.22–0.44% of the total muscle protein in fish (Elsayed & Bennich, 1975).

Thus, the question on features being responsible for allergenicity of proteins still needs to be answered, probably in depths analyses of IgE binding structures on the proteins could provide new answers and maybe find common motifs discriminating allergenic from nonallergenic proteins. Recently a sequence-based algorithm was presented for the prediction of allergenicity of proteins (Stadler & Stadler, 2003). As sequence is a precondition for structure, these motifs may determine 3 dimensional epitope motifs of allergens, too.

3.1. Linear versus conformational epitopes

Using different technical approaches major efforts are made to identify epitopes on allergens. In 1976 first studies on IgE binding sites on the major fish allergen parvalbumin were performed. Linear peptides of Gad c 1 generated by tryptic hydrolysis were assessed for their IgE binding potential and the presence of multiple allergenic determinants were postulated due to the high AA homology between the IgE binding regions (Elsayed et al., 1976). However, screening a constrained phage display library with parvalbumin-specific IgE purified from patients' sera and performing computational matching of deduced sequences onto the protein surface revealed the presence of conformational epitopes on this major fish allergen with overlaps to the previously determined epitopes (Untersmayr et al., 2005c).

The production of overlapping synthetic peptides for IgE binding studies represents a convenient method applied for identification of epitopes on allergens. Using this approach major IgE binding regions have been identified on a broad spectrum of food allergens, for example, the shrimp allergen tropomyosin, ovalbumin from egg white, peanut allergens or the cherry allergen Pru a 1 (Kahlert et al., 1992; Stanley et al., 1997; Scheurer et al., 1999; Ayuso et al., 2002; Shreffler et al., 2005). Peptides, which were previously used for identification of epitopes, have been spotted on carrier material and have been further applied in microarray immunoassays for diagnosis of milk and peanut allergic patients (Jarvinen et al., 2001; Shreffler et al., 2004). Especially for milk allergy these tests seem to have a special diagnostic relevance. The outcome of patients was correlated with their binding pattern to either peptides standing for linear epitopes or the intact milk protein representing conformational epitopes. Only patients with persistent cow's milk allergy showed higher levels of IgE binding to linear peptides than those who outgrew their hypersensitivities (Vila et al., 2001). This implies that for the initiation of the disease, conformation is important, whereas the immune response later broadens to smaller protein units. Turning this around, digested peptides do not have the capacity to sensitize and may even harbor tolerogenic properties, whereas structural motifs are strongly associated with sensitization and IgE induction. For example, persistence of food epitopes when pharmacologically hindering gastric digestion was shown to represent a risk factor for food allergy induction (Fig. 1; Untersmayr et al., 2003a, 2003b; Schöll et al., 2005b), and the intestinal administration of intact food proteins with conserved epitope structures was found to even

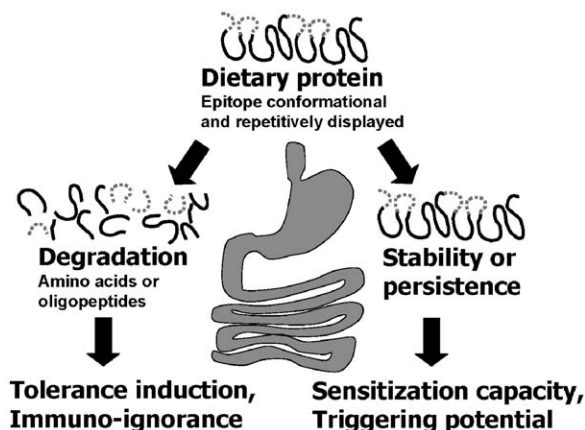


Fig. 1. Structural characteristics of food allergens in the sensitization and effector phase of food allergy. Degradation of dietary proteins during the gastrointestinal transit results in a hydrolysis of the proteins to free AAs or oligopeptides, which either induce tolerance or are immunologically ignored. However, when proteins resist gastrointestinal proteases or persist during the transit due to impairment of digestion, the epitope structure remains conserved. Thus, proteins reveal sensitization potential or trigger an allergic response by intact conformation.

abrogate previously established oral tolerance (Michael, 1989; Barone et al., 2000).

3.2. Epitope pattern and IgE binding affinity

It is well recognized that both the T cell and the B cell branch are important for inducing an immune response to food antigens. Whereas T cells interact via their receptor with small peptides in a HLA-restricted manner, the shape of a molecule is important for the recognition by B cells and consequently for the formation of antibodies (Aalberse, 1997). Based on crystallographic studies all protein epitopes have been discussed to be of conformational nature, which might also be relevant for antibody binding affinity (Aalberse, 2000). In a recent study we calculated the binding affinity of allergen-specific human IgE towards conformational epitopes to be in the outstanding range of 10^{-10} to 10^{-11} M with a 10,000-fold lower affinity for specific IgG (Hantusch et al., 2005).

In addition to these high IgE binding affinities to structurally intact epitopes, other requirements seem to be needed for antibody–allergen interaction and triggering allergic responses. It is accepted that cross-linking of cytophilic IgE represents an important feature in the effector phase of food allergy, where it triggers mediator release in mast cells and basophils. However, it is generally less well perceived that the same crosslinking procedure is already required in the sensitization phase, where cross-linking of the B-cell receptor initiates the signaling in mature B-cells (Segal et al., 1977; Pierce, 2002). This clearly indicates the importance of repetitive display of epitopes, for example, by repeats in the structure, or di-, tri- or multimerization of small allergens (Schöll et al., 2005a). Interestingly, a number of food proteins have so far been identified to assemble to multimers (Gimona et al., 1995; Shin et al., 1998; Reese et al., 1999; Maleki et al., 2000; Das Dores et al., 2002; Sen et al., 2002; Wopfner et al., 2002).

4. Cellular key players in oral tolerance or food allergy

The immune response to dietary proteins, leading either to oral tolerance or to the development of food hypersensitivity, depends on communication of numerous immunocompetent cells which are subject of intensive research.

As outlined above structurally intact food proteins might cross the intestinal mucosa in situation of enhanced permeability or via M-cells, and thereafter reach professional antigen-presenting cells (APCs). By this route, conformationally intact antigens might also pass by antigen processing and directly stimulate B cells which are found in aggregates in M-cell proximity, resulting in immunoglobulin production. Food antigens that enter intestinal epithelia through endocytosis undergo processing in these cells and presentation with MHC class II (Mayer, 1998; Blumberg et al., 1999; Hershberg & Mayer, 2000). In the first case co-stimulation by professional APC may lead to immunity, whereas the absence of co-stimulation on enterocytes may be an important factor for the maintenance of tolerance against food proteins (Sanderson et al., 1993; Hershberg et al., 1998; Mowat, 2003).

Besides, several other down-regulatory mechanisms may additionally be crucial to guarantee nonresponsiveness. Oral tolerance to basically harmless food antigens has been ascribed to T cell anergy, clonal deletion and active cytokine-mediated suppression (Brandtzaeg, 2002). By producing immunomodulating cytokines, regulatory T cells are important for keeping the Th1/Th2 profile balanced.

4.1. Microfold cells

M-cells are found in the follicle associated epithelia overlying the Peyer's patches and do, therefore, represent the gate to intestinal immunity. These cells facilitate the transport of complex antigens, mostly particles, directly to the intestinal immune induction site. Here, they are passed on to professional APCs, which process and presented them to T cells in the Peyer's patch itself or in the mesenteric lymph nodes (Mowat, 2003). The native antigens will also preferentially come in contact with membrane-immunoglobulins of B-lymphocytes, which are abundant in these lymph follicles, and result in antibody production. Therefore, M-cells could be ports for food allergens, but it is not settled whether M-cells are efficient at uptake of soluble protein antigens (Chehade & Mayer, 2005). Moreover, the immune response upon M-cell targeting is usually Th1 biased, which has been documented for several bacteria which enter the body via M-cells like Salmonella (Mastroeni et al., 2001; Clark & Jepson, 2003; Reisfeld et al., 2004). Moreover, targeting allergens to M-cells using lectin-functionalized microparticles could even shift an ongoing Th2 response towards Th1 (Roth-Walter et al., 2004, 2005). Thus, we are today critical about the participation of this site of antigen uptake in the development of food hypersensitivity.

4.2. Enterocytes

Several studies have indicated that the intestinal epithelial cell (IEC) itself might contribute to the development of oral

tolerance or food allergy. IECs were shown to express MHC class II antigens on their surface and therefore function as effective APCs (Blumberg et al., 1999; Yu & Perdue, 2001). Furthermore, IECs can take up, process and present antigen to regulatory T cells in context with MHC (Panja et al., 1994; Campbell et al., 1999). However, in food sensitized individuals an additional function of IECs may be envisaged: Luminal IgE-allergen complexes were observed to be rapidly transported through the epithelium in an IL-4 dependent manner via CD23-bearing IECs with subsequent delivery to mucosal mast cells (Berin et al., 1997; Yu et al., 2001). This pathway even seems to protect allergens from degradation during transcytosis (Bevilacqua et al., 2004) and may, on the other hand, serve as an active shuttle transport for IgE across the intestinal epithelium (Tu et al., 2005).

4.3. Antigen presenting cells

Professional APCs, such as activated dendritic cells, activated macrophages and activated B cells express costimulatory molecules and, therefore, can not only prime but also activate T cells. On the other hand, APCs without costimulatory potential (naïve B cells, resting dendritic cells and MHC II expressing tissue cells) induce tolerance rather, which is mediated by suppression of T cell effector and helper function, also referred to as anergy or peripheral tolerance (Mueller & Jenkins, 1995; Healy & Goodnow, 1998).

Besides these direct effects on T cells, another participation of APCs in the development of an immune response towards dietary proteins can be envisaged. Macrophages, dendritic cells, epithelial cells and mast cells express also pattern recognition receptors (PRPs), the so-called toll-like receptors (TLRs) on their surface (Backhed & Hornef, 2003; Bilsborough & Viney, 2004). Due to the repetitive display of allergen epitopes, TLRs might thus be involved in allergen recognition and induce signaling cascades leading to the expression of various cytokines, for example, IL-9 or IL-13, as has been shown for human mast cells (Stassen et al., 2001). Besides the clear implication of IL-13 for IgE switch, IL-9 could promote the growth of Th cells in an IL-4 dependent fashion, thereby supporting a specific IgE response (Takeda et al., 2003).

4.4. $\gamma\delta$ -T cells

Several studies performed in knockout mice indicated that $\gamma\delta$ -T cells might play an important role in oral tolerance as the transfer of tolerance was achieved in untreated mice by injection of these cells isolated from orally immunized animals (Kapp & Ke, 1997; Ke et al., 1997).

On the other hand, $\gamma\delta$ -T cells are an important source of the Th2-type cytokine IL-13 supporting IgE production and allergic inflammation (Lahn, 2000; Pawankar, 2000; Svensson et al., 2003). Physiologically, V δ 1-expressing $\gamma\delta$ -T cells constitute 50% of T-lymphocytes of the intraepithelial T cell compartment of the intestine (Porcelli et al., 1991). Children with untreated food allergy were shown to exhibit a significant increase of intraepithelial $\gamma\delta$ -T cell density in the mucosa of the small

intestine when compared to food allergic patients on diet (Kokkonen et al., 2000). Interestingly, $\gamma\delta$ -T cells recognize antigens in the form of intact proteins via their TCR1 in a non-MHC-restricted fashion (Allison et al., 2001). Thus, these cells recognize conformation, which seems to be a typical food allergen characteristic and might, therefore, contribute substantially to mucosal Th2-type responses to food allergens.

4.5. Mast cells

To date it is well recognized that mast cells have immunoregulatory and host defense effects as well as clear implications in the pathophysiology of intestinal diseases (Stenton et al., 1998). In the gastrointestinal tract these cells are found in all layers of the mucosa (2–3% of the lamina propria cells in the gut are mast cells) and in the submucosal area. The role of mast cells in the allergic tissue inflammation is well recognized. IL-4 in presence of stem cell factor (SCF) regulates the functional status of mast cells inducing enhanced proliferation and survival of mast cells, and increased IgE-dependent mediator release (Bischoff et al., 1999). Upon cross-linking of IgE bound via its high affinity receptor, a large number of preformed and newly synthesized mediators and proteases are released into adjacent tissues and exert their function in the allergic inflammation and in modulation of the gut function (Yu & Perdue, 2001). Besides an increased vascular permeability, mucosal edema and contraction of smooth muscles, a diminished barrier integrity was observed leading to an antigen-induced enhanced epithelial permeability (Crowe et al., 1993). These activated mast cells produce Th2-type cytokines, such as IL-3, IL-5 and IL-13 leading to the accumulation of eosinophils and other inflammatory cells relevant in allergic diseases (Lorentz et al., 2000). Furthermore, non-IgE-dependent mast cell activation triggers such as neurotransmitters, bacterial toxins and components of the complement system contribute to the tissue inflammation (Yu & Perdue, 2001). As outlined above (Section 4.3), mast cells dispose of TLRs, making them interesting as pattern recognizers.

4.6. Eosinophils

Eosinophil accumulation in the peripheral blood and tissues is a distinct characteristic of allergic responses. A direct correlation between disease severity of food allergy and the amount and activation status of gastrointestinal eosinophils has been observed (Gleich & Adolphson, 1989). Furthermore, eosinophils function as APCs promoting the expansion of Th2 cells in inflamed tissues and directly amplifying the Th2 immune response (Shi, 2004). In healthy conditions these cells are spread in the lamina propria of the gastric and intestinal mucosa (Mishra et al., 1999). However, in food allergic patients the distribution (i.e. intraepithelial, in lamina propria and submucosa), the number, morphology and also the functional behavior of eosinophils were distinct, because they could be easily activated by stimulation via the IgE receptor (Schwab et al., 2003). Thus, it might be speculated that eosinophils

contribute to the immediate type reaction in skin and mucosa upon allergen contact via specific, receptor-bound IgE.

Eotaxin and IL-5 have been shown to be the major chemokines responsible for eosinophil activation and recruitment (Yamaguchi et al., 1988; Griffiths-Johnson et al., 1993; Jose et al., 1994). IL-5 promotes the differentiation and proliferation of eosinophils in the bone marrow and plays a central role in the regulation of eosinophil recruitment into inflamed tissues (Coeffier et al., 1991; Rothenberg et al., 1995). As a potent chemoattractant, eotaxin is responsible for a selective accumulation of eosinophils at sites of allergic inflammation (Jose et al., 1994; Rothenberg et al., 1995). In concert, both cytokines account for eosinophilic inflammation. When mice were orally challenged with food allergen encapsulated in enteric beads, they showed an increase of antigen-specific secretory IgA and IgG1 in fecal extracts, local and peripheral eosinophilia and gastrointestinal dysfunction. In comparison, groups of eotaxin- and IL-5 deficient mice exhibited a significantly reduced allergic activity pointing towards an essential role of these cytokines in the food allergy effector phase (Hogan et al., 2000; Hogan et al., 2001). Due to the encapsulation in particles, the allergen was delivered to the small intestine in a conserved native conformation in these studies. In accordance, in our immunization protocol the antigen was kept intact by acid-suppression treatment resulting in an eosinophilic infiltration of the gastric mucosa in food allergic mice (Untersmayr et al., 2004).

5. Animal models of food allergy

Experimental animal models have become important tools providing information about the underlying pathophysiology of diseases. Especially in situations when target organs are inaccessible, such as the gastrointestinal tract in food allergy, these studies are irreplaceable and much of the above mentioned knowledge can be owed to a large degree to animal studies.

For sensitization studies several parameters, such as allergen concentration, food matrix, route and duration of allergen exposure, use of adjuvants and age of the animals, have to be taken into consideration. Moreover, the choice of the animal can dramatically affect the study, as genetic predisposition characterizes IgE responsiveness (Helm, 2002; Helm et al., 2003).

Major efforts have been made in the past years to establish suitable experimental models, not only to study disease mechanisms but also to test the allergenic potential of novel, for example, genetically modified dietary compounds (Kimber et al., 2003; Selgrade et al., 2003).

5.1. Experimental models of food allergy in dogs and pigs

Nonrodent food allergy models are of advantage as the anatomy and physiology, including the immune system is comparable to that of human patients. Moreover, samples obtained from these models are bigger and interventions, such as endoscopic analyses, are easier to perform. Dog and pig models were proven to be particularly suitable.

The prevalence of food allergies and the clinical symptoms observed such as gastrointestinal and skin reactions in dogs are comparable to that in humans and soy, chicken, milk, corn, wheat and egg proteins were confirmed as triggers of adverse reactions by provocation tests (Jeffers et al., 1991). An atopic dog model of food allergy was developed in high IgE responder inbred dog by subcutaneous injection of food allergens absorbed to aluminiumhydroxide (Ermel et al., 1997). The dogs developed high IgE titers, positive skin and mucosal tests and could be further evaluated in gastroscopic food challenges. Therefore, this model was postulated to be excellent for mimicking the human disease for the detection of hidden food allergens and for testing of bioengineered food products (Frick, 1996; Teuber et al., 2002).

The gastrointestinal physiology and mucosal immunity of pigs resembles the human situation. Compared with human infants, piglets have similar anatomy and nutritional requirements, show a transient permeability of the gut to dietary proteins, and have a comparable distribution and maturation of digestive enzymes. In a neonatal swine model newborn piglets were sensitized intraperitoneally on 3 consecutive days with peanut extract and cholera toxin subunit B (CTB) as an adjuvant. After additional boosts, pigs revealed positive oral challenges and positive passive cutaneous anaphylaxis suggested the involvement of IgE. Further, damage of the intestinal mucosa, resembled the situation in human patients (Helm et al., 2002).

Nevertheless, an oral administration of the antigen without adjuvant use would be preferable to imitate the natural sensitization route in humans. Therefore, the guinea pig model seems to be of special interest. After repeated oral feedings, sensitizations could be proven in this model, which was further used as a tool to assess allergenic potential of cow's milk proteins and hydrolysate formulas (Piacentini et al., 1994; Kitagawa et al., 1995).

5.2. Rodent models of food allergy

The advantage of rodent models in food allergy research is clearly the availability of a wide variety of strains including also knockout animals and the possibility to investigate the question of interest in groups of large animal numbers.

The Brown Norway rat seems to be especially suitable for food sensitization protocols, even though variations in immunoglobulin response levels were observed within different laboratories (Knippels et al., 1999; Pilegaard & Madsen, 2004). This strain was shown to be a high-immunoglobulin responder and thus resembles to a certain degree atopic humans in production of antigen-specific IgE. Daily intragastric feeding of the model antigen OVA during 6 weeks induced the best results regarding OVA-specific immune response both on the cellular and humoral (IgE and IgG) level (Knippels et al., 1998).

Mice do not completely mirror, but can model the human immunology in many respects, for example, T cell polarization toward Th1 or Th2 phenotypes is much more extreme in mice. Therefore, the murine system represents a valuable test model

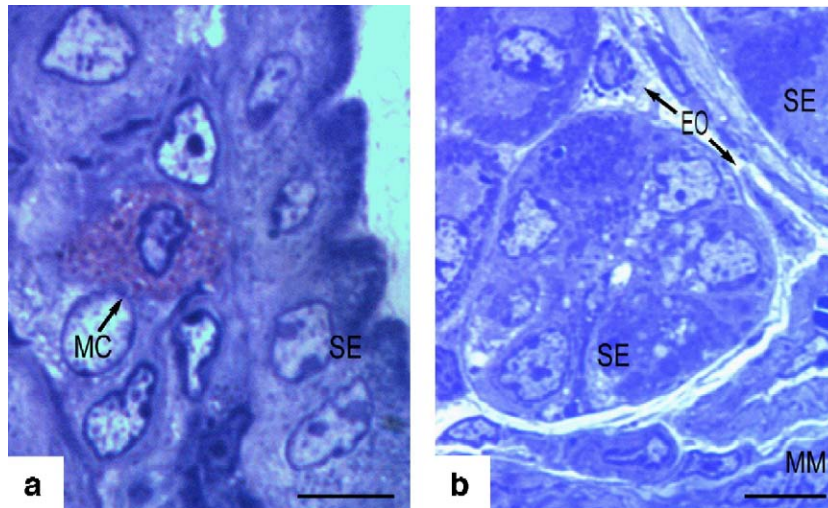


Fig. 2. Enhanced counts of mast cells (Mc) and eosinophils (Eo) are found in the gastric antrum mucosa of BALB/c mice sensitized under concomitant acid suppression. Panel A shows a mast cell residing underneath the surface epithelium (SE) between connective tissue cells. Toluidine blue staining of the semithin sections highlights the metachromatic behavior of this cell. Bar 2 μ m, original magnification, $\times 3000$. Panel B demonstrates an eosinophilic cell in close vicinity to the surface epithelium (SE) of the basal portion of gastric glands and to the muscularis mucosae (MM). Toluidine blue staining of semithin sections. Bar 2 μ m, original magnification, $\times 3000$.

for allergological questions (Mosmann et al., 1986; Finkelman et al., 2005).

Oral administration of food proteins with CTB, a potent mucosal adjuvant enhancing Th2 type responses which might also have an effect on mucosal barrier function (Marinaro et al., 1995; Lycke, 2005), is a standard protocol applied in numerous murine studies with different IgE responder mouse strains (Li et al., 1999; Li et al., 2000; Adel-Patient et al., 2005). Recently this immunization regimen was used to sensitize BALB/c mice with soybean extract to evaluate allergenicity of genetically modified soybean extract, which indeed shared B and T cell epitopes with the wild type plant (Gizzarelli et al., 2006).

Nevertheless, only an oral sensitization protocol without artificial antigen adsorption to adjuvants can reflect the situation in human food allergy. Our group has previously established an immunization protocol truly mimicking the sensitization mechanisms in food allergic patients. Dependent on concomitant pharmacological suppression or neutralization of gastric acid, feedings of digestion-labile food antigens resulted in induction of allergen-specific IgE and a food allergic phenotype including high counts of mast cells and an eosinophilia of the gastric mucosa in BALB/c mice (Fig. 2). The reliability of the animal model could be demonstrated for several food allergens (Untersmayr et al., 2003, 2004; Schöll et al., 2005b). In humans the broadly used proton pump inhibitor omeprazole elevates the gastric pH to an average of 5.0 (Prichard et al., 1985), which is certainly beneficial for gastric ulcer healing. However, pH elevation results in abrogation of protein degradation (Schöll et al., 2005b; Untersmayr et al., 2005a, 2005b), leaving intact allergens. The proof of concept was given by a recent clinical study with gastroenterological patients, who after a 3-month course of anti-ulcer treatment developed a boost or de novo IgE

formation towards random dietary proteins in 25% (Untersmayr et al., 2005a).

6. Conclusions

Animal models and clinical studies have helped a lot to understand some of the pathophysiology of food allergy. First, not only the intestinal but also the oral, esophageal and gastric mucosa might be relevant for immunological interactions with food proteins. Clearly dietary proteins are triggers for immune reactions throughout the entire gastrointestinal tract, which indicates a participation of these mucosal compartments in the allergic inflammatory process. Second, common features of food proteins still have to be defined. Very recent studies have indicated that especially the conformational nature and the repetitive display of epitopes on allergens seem to be of importance in food allergy. This underlines the role of physiological protein digestion having a control function for food allergens. Therefore, digestion resistant proteins are sensitizing elicitors. Moreover, also digestion labile proteins can be sensitizing elicitors if they persist the gastrointestinal transit in an intact conformation. Consequently, we presented a list of candidates being possible cellular key players in food allergy induction, because they are pattern recognizers of conformational epitopes.

Acknowledgment

We thank Prof. A. Ellinger from the Center of Anatomy and Cell Biology, Division of Cell Biology and Ultrastructure Research, Medical University Vienna, Austria for his help with microscopy analysis of murine specimen. This work was supported by the Austrian National Bank "Jubiläumsfond" Grant No. 11375, by a Transkoop project of the Viennese Funds

for the promotion of Economy (WWFF), and by grants F1808-B04 and DK W1205-B09 of the Austrian Science Funds.

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