

Review Article

T lymphocytes in food allergy: Overview of an intricate network of circulating and organ-resident cells

Eigenmann PA. T lymphocytes in food allergy: Overview of an intricate network of circulating and organ-resident cells.

Pediatr Allergy Immunol 2002; 13: 162–171. © 2002 Blackwell Munksgaard

Although food hypersensitivity might be divided in IgE- and non-IgE mediated food allergy, there is a large body of evidence implicating T lymphocytes overall in the pathogenesis of food allergy. Priming of naive T cells will occur mainly in Peyer's patches (PP), where surface receptors (I-selectin, CCR7 and CXCR4) will help to initiate diapedesis of the cells to the submucosa. Various antigen-presenting cells (e.g. dendritic cells, M cells) will present food antigen-derived epitopes and initiate either non-responsiveness, or a food-mediated immune response. Food-specific memory T cells express various surface receptors such as the $\alpha 4 \beta 7$ -integrin, or the cutaneous lymphocyte antigen. It is speculated, that they might also express specific chemokine receptors (CCR4, CCR7 or CCR9). Organ-specific homing will be facilitated through the corresponding receptors (i.e. MAdCAM-1 in the gut, VCAM-1 or fibronectin in other mucosal organs, or E-selectin in the skin). Locally secreted chemokines might help to attract T cells through their corresponding chemokine receptors. Finally, potential T-cell directed therapeutic interventions (peptide-derived immunotherapy, DNA vaccination, or strategies preventing T cells from trafficking to target organs) are discussed.

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Key words: chemokine; chemokine receptors; food hypersensitivity; homing receptors; lymphocyte homing; T lymphocytes

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Accepted 9 September 2001

Classified among adverse reactions to foods, food hypersensitivity results from an abnormal response of the immune system to an ingested nutrient. The classic IgE-mediated reactions with immediate symptoms are provoked by degranulation of mast cells after contact with specific food antigens (1). Symptoms most commonly observed are urticaria or atopic dermatitis, acute upper or lower respiratory manifestations, or anaphylaxis (2). Food allergy also includes several non-IgE mediated syndromes with primarily gastrointestinal manifestations (3). This category of disease is believed to result from immune mechanisms primarily involving lymphocytes and/or cytokines or other effector cells of the immune system. In any type of manifestation of food hypersensitivity, T lymphocytes are present either as pivotal cells facilitating the production of food antigen-specific IgE antibodies, or as effector cells secreting autocrine

factors such as cytokines. Unlike other allergic diseases such as allergic rhino-conjunctivitis or asthma, food allergy manifests itself in several distant effector organs after initial sensitization in the gut. This suggests that migrating cells may play a major role not only in the pathogenesis of the disease, but also in the regulation of the immune response. This review will address more specifically the role and the fate of T cells in the intricate immune network resulting in food hypersensitivity.

Food antigens in the gut: tolerance or allergy

Prior to the initial contact with lymphocytes, potentially harmful allergens must elude several protective steps located at the level of the gut mucosa. Antigens successfully crossing these protective barriers will reach the submucosa of the gut and be processed by the immune system at

preferential sites such as Peyer's patches (PP). These are disseminated along the distal part of the small intestine. A unique feature of PP is M cells, located at the luminal pole of the structure. The presence of MCH class II on M cells suggests a possible antigen-presenting function (4). While soluble antigen might be taken up and presented throughout most of the gut mucosa by intestinal epithelial cells (IEC), it is believed, that M cells mostly facilitate presentation of a particulate antigen such as bacteria or viruses. These peculiar features of M cells in the immediate proximity of PP may lead to a specific and potentially distinct immune response to common non-pathogenic microorganisms in the gut. At these sites, endocytosis by antigen presenting cells (APC) and cognate interactions with T cells will occur [reviewed in (5)]. However, the large number of professional APC [dendritic cells (DC), macrophages] in PP limits the importance of M cells or IEC as APC. Whether these possess a regulatory role is not yet defined.

Naive lymphocytes circulate to PP through high endothelial venules (HEV) (6). Endothelial cells in HEV express mucosal addressin-cell adhesion molecule-1 (MAdCAM-1). This addressin is a ligand for the $\alpha 4\beta 7$ -integrin, which specifically facilitates binding to the epithelium, and migration of lymphocytes into the mucosal tissue of the gut (7). In the PP, T-cells might be presented with antigen by different APC including M cells and DC, according to the nature of the antigen. As developed later in the review, the type of antigen presentation might greatly influence the T-cell polarization. Furthermore, the presence of microorganisms, through activation of Toll-like receptors, may promote a Th1-type immune response to other antigens processed at the same time (i.e. dietary antigens) (8). After T-cell priming by antigens in PP or other sites, memory T cells will re-circulate to other sites containing lymphoid cells, including the lamina propria of the gut. Lamina propria T cells are mainly CD4⁺/CD45RO⁺, memory phenotype (60–70%). In the lamina propria, memory T cells rest in a dormant stage, and display a much lower proliferative response to antigens than circulating cells (9). They also differ from peripheral T cells by an increased expression of IL-2, IL-4, IL-5, and IFN- γ . Taken together, these findings suggest that lamina T cells have a 'watch-dog' role, as they are capable of reacting to potentially harmful antigens, at a much higher activation threshold than other T cells. These regulatory mechanisms might be aimed to avoid detrimental reactions in an antigen-rich mucosal environment.

Other alleged sites of the gut for food-antigen sensitization have been examined, and among it the gut mucosa. A significant number of $\gamma\delta$ TCR intraepithelial lymphocytes (IEL) are thymus-independent cells and are believed, to be in part, activated by antigen presentation through CD1a (10,11). IEL proliferate poorly to a variety of signals including common gut antigens (e.g. microorganisms), mitogens and anti-TCR antibodies, although a variety of cytokines including IL-2, IL-5, IL-6, IFN- γ , TGF- β , as well as TNF- α can be detected by mRNA or in the supernatant after IEL activation (12,13). Hence, IEL provide an innate immune response believed to contribute to the immune homeostasis of the gut with a downregulating signal. In particular, the subgroup of $\gamma\delta$ TCR IEL may contribute to restrain activation of the immune response, as adaptively transferred $\gamma\delta$ TCR⁺ IEL could induce oral tolerance in mice (14). Similarly, depletion of $\gamma\delta$ TCR⁺ cells was found to abolish already established oral tolerance (15). To date, the exact role of IEL in the pathogenesis of food-induced hypersensitivity remains mostly undetermined. There is strong evidence suggesting the presence of a regulatory network including lamina propria T cells, IEL, and circulating antigen-specific T cells. Much has been speculated on mechanisms leading to oral tolerance or to immune reactions, and definite regulatory mechanisms are not yet elucidated (16).

Recent studies have shown that, although the paradigm of Th1/Th2 cells is still recognized as valuable, more complex changes in lymphocyte response may arise in allergy. The Th2 phenotype might be counterbalanced by a subset of CD4⁺ T cells suppressing antigen-specific immune responses designated as T regulatory cells 1 (Tr1) (17,18). These cells are induced by IL-10, but also produce high levels of IL-10, low levels of IL-2, and no IL-4 (19). Recent reports suggest a prominent role for Tr1 cells after successful immunotherapy (20,21), and IL-10 is believed to be included in both systemic and oral tolerance (22,23). Several evidences link Th3 cells, another subset of T helper cells, to oral tolerance. TGF- β was identified as a key cytokine produced by Th3 cells (24). Various studies have shown induction of Th3 cells after oral immunotherapy in autoimmune diseases (25,26). Whether regulatory mechanisms including Tr1 and Th3 cells play a role in food allergy remains to be determined.

Recent works have highlighted the role of APC for T helper cell polarization. In particular, two subsets of human DC have been characterized for their specific properties. Human CD11c⁺CD1a⁺IL-3R⁺ lymphoid DC secrete low amounts

of IL-12 and are believed to preferentially induce Th2-type cells. They are located in the T-cell zones of lymphoid organs and as DC precursors in the blood. Myeloid DC are CD11c⁺CD1a⁺IL-3R⁻; they can also be found in lymphoid organs as well as in organs as immature cells. IL-12 is secreted in high amounts, and a subset of myeloid DC, the Langerhans-cells-derived DC, also secrete IL-10 (27). Both types of DC found in murine PP and myeloid DC were able to prime naive T cells to secrete large amounts of IL-4 and IL-10 (28). Such findings suggest a significant role for APC in the regulation of the immune response to dietary antigens as well.

Food-antigen specific memory T cells in the peripheral blood

Besides resting and local trafficking in gut-associated tissues, food antigen-primed T cells may recirculate in the peripheral blood. Attempts were made by several authors to correlate antigen-specific T-cell activation in the pool of peripheral blood mononuclear cells (PBMC) to clinical symptoms of food allergy (Table 1). However, in most studies, the proliferation assays were not shown to be reliable for diagnosis, due to similar cell activation in food tolerant individuals.

Activation and proliferation of T cells is initiated after contact with an APC presenting a small peptide fragment (T-cell epitope) in conjunction with MHC class II molecules. T-cell epitope recognition in circulating, antigen-specific T cells provides major information for further modulation of the immune response. Usual techniques include the use of a series of overlapping peptides used to walk along the protein

sequence in order to find the antigenic sites. T-cell epitope mapping has been addressed for major food antigens. One major T-cell epitope for β -lactoglobulin (residues 145–161) was identified in newborns (29). α _{S1}casein is another major fraction of cow's milk in which different T-cell epitopes were identified by Nakajima-Adachi et al. (30). Others determined B-cell epitopes (i.e. food-specific IgE), which were found on different sequences than T-cell epitopes (31) [also reviewed in (32)]. Ovomucoid, the major hen's egg allergen (33), is composed of three domains of equal length (approximately 60 residues). The second and the third domain have been identified as immuno-dominant for T-cell stimulation (34). Ovalbumin is the second major egg allergen, and again six different epitopes were found to activate antigen-specific T cells (35–37). The third food responsible for most allergic reactions is peanuts. Major peanut allergens (Ara h1, Ara h2, and Ara h3) have been identified, cloned, and mapped for T-cell specificity (38–41).

B-cell epitopes have also been studied. Ara h1 B-cell epitope studies showed 23 allergic epitopes, and a single amino acid substitution allowed IgE-binding suppression. Hong et al. identified multiple IgE-reactive proteins in crude intact peanut extract by Western blot analysis of sera from five subjects with peanut allergy (42). IgE-dependent reactivity, but not T-cell reactivity, was eliminated after pepsin treatment of the peanut extract. Such modified proteins might be useful for immunotherapy by preventing significant IgE-mediated side-effects, while providing a tolerizing T-cell signal.

Several studies have examined food-antigen-induced cytokine production in circulating T cells.

Table 1. Studies showing activation of peripheral blood mononuclear cells with food antigens

Authors	Antigens	Diagnostic value established
May and Alberto (88)	Cow's milk	No
	Ovalbumin	No
	Soy	No
Baudon et al. (89)	Casein	No
	β -lactoglobulin	No
	α -lactalbumin	No
Albani et al. (90)	Casein	Yes
	β -lactoglobulin	Yes
	α -lactalbumin	Yes
Kondo et al. (91)	Ovalbumin	No
	Bovin serum albumin	No
Taino et al. (92)	β -lactoglobulin	(Yes)
Eigenmann et al. (93)	Cow's milk	No
	Casein	
	Whey proteins	

De Jong et al. isolated peanut-specific T cells in peripheral blood from an allergic patient and cloned them. All clones obtained were CD4+/CD8- T helper cells with a Th2 cytokine profile, secreting high amounts of IL-4 and IL-5, but little or no IFN- γ (43). In another study, T-cell clones specific to peanuts isolated from a patient allergic to peanuts and nuts exhibited a similar Th2-type phenotype, while one clone reactive to peanut and hazelnut allergens had a Th0 phenotype (44). Similarly, Katsuki et al. characterized an ovalbumin-specific T-cell line and found significant amounts of IL-4 and IL-5 but no or very little IFN- γ after antigen stimulation (37). A mixed Th2 and Th0 phenotype with predominantly IL-5 secretion was also found in ovomucoid-specific T-cell lines and clones (45).

From peripheral blood to the sites of allergic reactions

To date, the mechanisms directing 'trafficking' cells have only scarcely been explored in food allergy. However, events potentially responsible for directing T cells toward allergy sites may be extrapolated from experimental works.

Food-antigen-driven leukocyte adhesion

Similarly to other circulating cells, T lymphocytes may express through cell membrane receptors, an affinity for organ-specific endothelial cell ligands. These receptors act selectively by linking circulating peripheral blood cells to endothelial cell ligands expressed in specialized post-capillary venules. In contrast to other well-described allergic diseases such as allergic rhinitis, asthma, or atopic dermatitis, food allergy may involve several organs, with significant intraindividual clinical variability. Tentative explanations for mechanisms involved in reactions to foods need therefore to consider a network of recirculating cells in specific effector organs.

Lymphocyte homing is characterized by a multi-step lymphocyte-endothelial cell recognition mechanism involving cognate interaction (46,47). The first step occurs under high flow conditions when a constitutively functional lymphocyte receptor (mostly l-selectin) interacts with a vascular ligand. Loose rolling of the lymphocyte on the vascular endothelium (also called 'tethering') allows sufficient time for the lymphocyte to initiate a firmer contact thus allowing arrest on the endothelium surface. In a second step, lymphocytes rolling on endothelium cell surface will be further slowed and arrested by surface molecules belonging to the integrin family

(48,49). Among them, $\alpha 4\beta 7$ and $\alpha 4\beta 1$ have a specific affinity to mucosal organs. While initial rolling (first step), and integrin-mediated cell adhesion (second step) occur within seconds to a minute, activation-dependent arrest (step 3), leading to diapedesis (step 4) will usually take several minutes.

Only a few studies have addressed lymphocyte trafficking in food allergy. Abernathy-Carver et al. have activated PBMC from milk allergic patients with atopic dermatitis in the presence of cow's milk antigen or *Candida* antigen (50). Milk-specific lymphocytes were found to express significantly more cutaneous lymphocyte antigen (CLA) in milk allergic patients than in controls. Furthermore, CLA expression was specific to milk antigens, as cells expanded with *Candida* expressed only low CLA. These experiments suggested preferential homing to the skin of circulating milk antigen-specific T cells from children with atopic dermatitis and food allergy. Implication of CLA⁺ T cells was further confirmed in other allergic diseases such as drug allergy or contact dermatitis (51,52). Patients with food allergy may also present symptoms other than atopic dermatitis, or continue to suffer from food allergy after outgrowing atopic dermatitis, implying that CLA⁻ T cells may also be involved.

In initial reports, $\alpha 4\beta 7$ was described as an integrin expressed in activated T cells with homing properties to the gut (53,54). We recently found, that $\alpha 4\beta 7$ -integrin expression was highly upregulated in β -lactoglobulin (BLG)-specific T cells from patients with IgE-mediated cow's milk allergy (55). There was no significant upregulation of $\alpha 4\beta 7$ in milk-tolerant control subjects, and the integrin was not expressed in cells expanded after activation with tetanus toxoid. Similarly, other studies have also found increased $\alpha 4\beta 7$ -integrin expression on T cells in diseases related to the gut. Rott et al. found preferential rotavirus-induced proliferation of $\alpha 4\beta 7^{+}$ T cells from rotavirus-sensitized individuals, while the same cells proliferated only weakly to mumps antigen, administered i.m. (56). This work suggested, that the expression of the $\alpha 4\beta 7$ -integrin is more related to the site of sensitization than to the gut as an effector organ.

Implication of other T-cell adhesion molecules such as l-selectin or the $\alpha 4\beta 1$ -integrin remains mostly undefined so far in food allergy. Both in Abernathy-Carver's and in our studies, the expression of l-selectin could not be correlated with food-antigen T-cell activation (50,55). Beyer et al. reported a direct correlation with the severity of food allergic reaction of the donor,

and an increase of the number of CD45Ro⁺ cells together with a lower l-selectin expression on food antigen-activated T cells (57). There is direct and indirect evidence to link the expression of $\alpha 4 \beta 1$ -integrin with asthma (58,59). However, an upregulation of this integrin in patients with food hypersensitivity has not been found (55).

Chemokines, chemokine receptors, and their interaction with integrins

Chemokines are secreted in various organs and lymphoid structures (e.g. the thymus, the Peyer's patches), and constitute a large family of homogeneous proteins with four cysteins forming two disulfide bonds (60). Chemokines may be secreted in a large number of cells, and chemokine receptors have been found expressed in most circulating cells. Chemokine receptor 3, 4 and 8 (CCR3, CCR4 and CCR8) have been mostly described on Th2-type cells, while CXCR3 and CCR5 appear to be more specific for Th1-type cells (61,62). Chemokines are largely implicated in the pathogenesis of allergic diseases (63). RANTES, MCP-1, MCP-3, and MIP-1 α have been found increased in broncho-alveolar lavages, or bronchial biopsies in asthmatic patients (64,65), and increased mRNA for RANTES, MCP-3, MCP-4, and eotaxin has been found in late cutaneous reactions (66,67). Preferential CCR3 expression was recently observed in both conditions (68,69). Furthermore, chemokines can be implicated in promoting chemotaxis and adhesion of naive lymphocytes in specific organs.

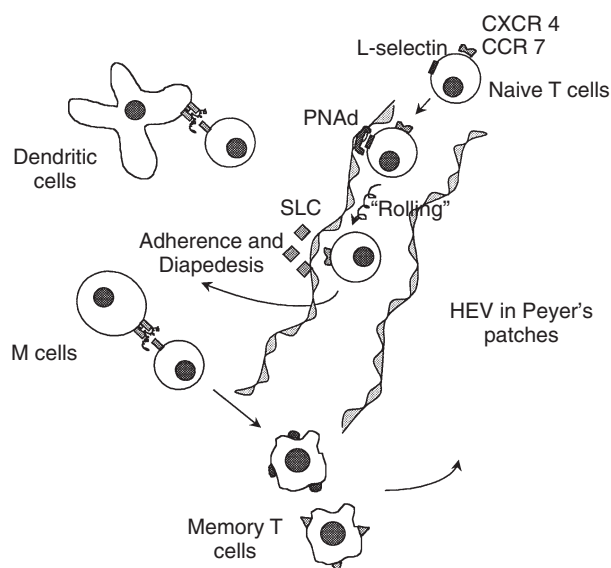


Fig. 2. Cell adhesion of naive T cells in high endothelial venules (HEV) in Peyer's patches (PP) is mediated by chemokine receptors (CXCR4 or CCR7), or by l-selectin, which will preferentially bind to their ligands (SLC or PNAd). After antigen-specific activation in the submucosa, memory T cells will recirculate to the blood flow.

Besides being chemo-attractants for inflammatory cells, chemokines may also favor leukocyte adhesion. Several chemokines (SDF-1, CK β -11, SLC, and LARC) induce adhesion to PNAd, the receptor for l-selectin (70). Secondary lymphoid-tissue chemokine (SLC), mostly expressed in lymph nodes and HEV of mucosal lymphoid tissues such as PP, may also attract both naive and activated T cells via its ligand CCR7. It was then demonstrated that SLC is displayed in a subset of PP-HEV, and that this chemokine

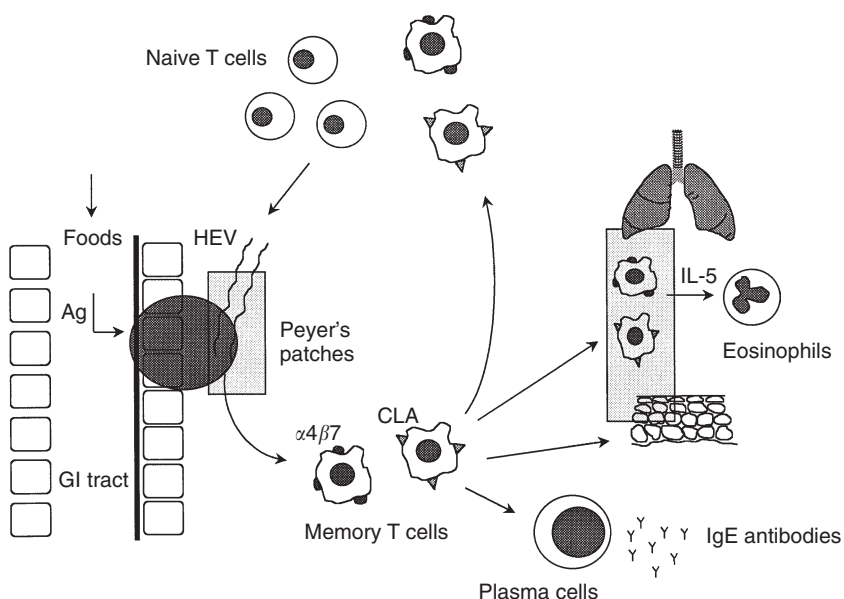
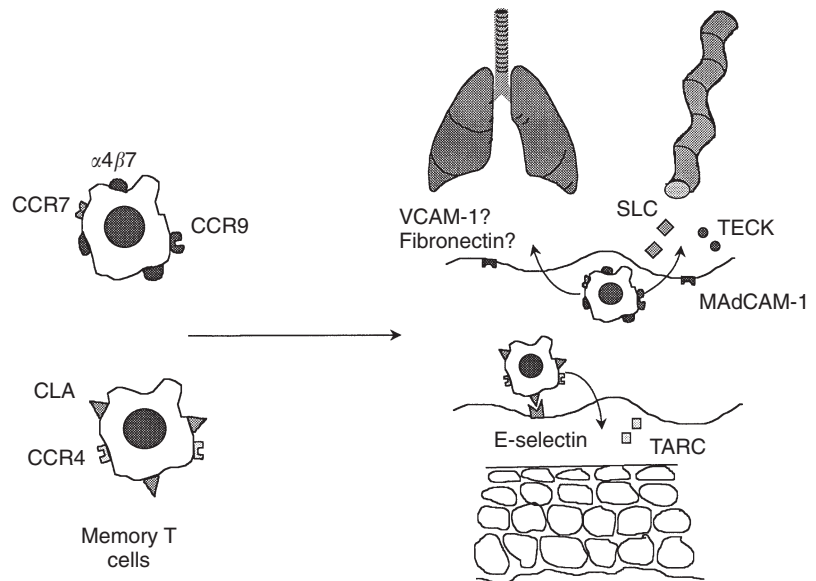


Fig. 1. Circulation of naive T cells to high endothelial venules (HEV) in Peyer's patches (PP). Antigen activation will result in homing receptors expression, such as the $\alpha 4 \beta 7$ -integrin or the cutaneous lymphocyte antigen (CLA), which will favor re-direction of food-antigen specific memory T cells to effector sites of allergic reactions. Cytokine-mediated influx of inflammatory cells and secretion of antigen-specific IgE will modulate the clinical reactions. Clinical symptoms of food allergy will result from food-specific IgE and cell-mediated inflammatory reactions in effectors organs.

Fig. 3. Food-antigen specific memory T cells expressing specific surface molecules such as homing receptors ($\alpha 4\beta 7$ -integrin or CLA) or chemokine receptors (CCR7, CCR9) will preferentially re-circulate to mucosal organs (lung and gut), and to the skin. Diapedesis to the submucosa will be mediated by the corresponding receptors (MAdCAM-1, fibronectin, VCAM-1, E-selectin) or by chemokines (SLC, TECK, TARC).



specifically recruits CCR7⁺ T cells (71,72). In preliminary results, we found high expression of CCR7 in BLG-activated T cells from patients with cow's milk allergy, suggesting a possible role for this receptor in directing cells to gut-related lymphoid organs (73).

Recent reports suggest a role for chemokines and chemokine receptors in $\alpha 4\beta 7$ -integrin mediated leukocyte adhesion. IL-8 was capable of inducing a rapid stimulation of $\alpha 4\beta 7$ -dependent adhesion, after activation of an IL-8 receptor transfected cell line (74). SLC could induce a $\alpha 4\beta 7$ -mediated adhesion to MAdCAM-1, in both static assays as well as flow chamber adhesion assays (75). SLC has also been shown to attract activated T cells to intestinal mucosal areas via CCR7 (76). Whether adhesion is regulated by both $\alpha 4\beta 7$ and CCR7 remains to be studied. Another recent report identified a novel chemokine receptor, CCR9, possibly implicated in T-cell chemotaxis to the gut. CCR9 binds to the CC chemokine TECK, which is preferentially expressed in the thymus and the small intestine. CCR9 is expressed on $\alpha 4\beta 7$ ⁺ memory T cells, but not on CLA⁺ cells (77). Whether these findings might be extrapolated to allergic diseases remains to be determined.

A hypothesis for lymphocyte trafficking in food allergy

One might therefore speculate that lymphocytes involved in food allergy may circulate following an intricate network comprising locally secreted chemokines, regulated expression of chemokine receptors, and preferential activation of naive

lymphocytes, followed by directed trafficking of memory T cells (Fig. 1).

Each individual possesses a large repertoire of naive circulating T lymphocytes. Naive blood-born T lymphocytes expressing l-selectin circulate in PP-HEV where various chemokines such as SLC interact with chemokine receptors (CCR7, CXCR4) expressed on the cell surface directing them to the submucosa (71,72) (Fig. 2). It is presumably at these sites, that antigen activation will lead to the generation of memory T cells expressing homing receptors such as CLA or $\alpha 4$ -integrins, which will in turn re-circulate to the blood flow. Most recently, Campbell et al. have linked CLA⁺ cells defined as a subset of systemic memory cells, to high expression of CCR4. Immuno-histochemistry studies have revealed a strong signal for the chemokine TARC in the skin, while it was mostly absent in the gut. TARC has a strong affinity for CCR4, a receptor found mostly on Th2-type cells, and was also shown to induce integrin-dependent adhesion of CLA⁺ cells to ICAM-1 (78). This work heralds the connection between 'classic' homing receptors such as CLA and chemokine receptors in organ selectivity for memory T cells. It might be extrapolated, that both CLA and CCR4 expression might be necessary for T-cell homing to the skin (Fig. 3).

Food-antigen activated T cells with a tropism to mucosal organs will preferentially express the $\alpha 4\beta 7$ -integrin (but not the $\alpha 4\beta 1$ -integrin). These may interact with the corresponding endothelial receptors, MAdCAM-1 in the gut, and possibly fibronectin and VCAM-1 in nonintestinal mucosal tissues. One may also speculate from recent

findings, that CCR9, the receptor for TECK, may also be involved in preferential homing. As well, CCR7 found highly expressed in milk antigen-specific cells may interact with SLC in the intestinal mucosa (Fig. 3).

Strategies for T-cell directed therapeutic intervention in food allergy

Several angles of approach for therapeutic intervention may be envisaged. Immunotherapy with whole antigen extracts was most studied. A double-blind trial with injection of peanut extracts was hampered by major side-effects, and the study had to be interrupted (79). The same group started a new study a few years later in patients with peanut allergy treated by rush immunotherapy (80). The outcome measured was the dose of peanuts eliciting a positive reaction by blinded challenges. Although some patients became partially tolerant to peanuts, a full sensitivity to peanut reappeared as soon as the immunotherapy was stopped. Again, significant side-effects were observed in most patients. These authors concluded that immunotherapy was not safe and effective with whole peanut protein extracts. Peptide immunotherapy may provide an alternative, but systemic side-effects were observed in a study involving patients with cat dander allergy treated by peptide immunotherapy as well (81).

New promising therapeutic interventions may come from Th-1 immuno-stimulatory molecules. In an initial trial of DNA immunization in an animal model of food allergy, different strains of mice were injected with DNA coding for Ara h2, a major peanut allergen (82). Sensitization resulted in antigen-specific IgG₁, IgG_{2a}, but not IgE production. Unfortunately, subsequent subcutaneous injections with Ara h2 elicited allergic reactions, suggesting that the immune response provoked by DNA injection did not protect from allergy. Further experiments with DNA vaccine may combine antigen-coding DNA to CpG motives in order to skew the immune response towards Th1. Another new approach has recently been used successfully in mice given a combination of oral DNA coding for Ara h2 (a major peanut allergen) and chitosan, a natural biocompatible polysaccharide, resulting in prevention of subsequent sensitization with peanut antigen (83). Further Th1-stimulatory strategies might involve IL-12. Preliminary data showed that oral administration of peanut antigen with IL-12, either as a prevention for sensitization or to cure food allergy, was able to suppress clinical reactions upon oral antigen challenges (84).

Whether all these results might be applicable to humans needs to be studied in therapeutic trials.

It is tempting to imagine a therapeutic intervention blocking T cells or other inflammatory cells from trafficking to target organs. Relatively few studies have addressed this question. Monoclonal antibodies against the $\alpha 4\beta 7$ -integrin have reversed experimentally induced colitis in animals (85). In an ocular model of allergic diseases, anti-ICAM-1 and anti-LFA-1 monoclonal antibodies were able to reduce the clinical signs of allergic conjunctivitis (86). Clinical studies will have to confirm these results before an application in food allergy may be envisaged.

Another promising direction for therapeutic action in food allergy might be achieved by blocking receptors for 'allergy' chemokines. Interventions on these mediators of the allergic reaction might be particularly efficient, as chemokines can influence inflammatory reactions at several distinct levels, such as cell recruitment, integrin expression, and cell maturation. A monoclonal Ab against CCR3, the receptor for eotaxin, was able to block eosinophil migration (87). Similarly, a synthetic molecule (UCB 35625) blocking CCR3 and CCR1 has been recently developed. However, future clinical trials will have to investigate if there is a place in food allergy for therapeutic agents acting at this level of the inflammation cascade.

Concluding remarks

There is much evidence implicating T cells in the pathogenesis of food allergic reactions. It appears also, that allergic reactions result from interactions involving many players (cells, mediators) of the immune system, increasing the complexity of the allergic process. Further, not only one 'dysfunction' may explain the pathogenesis of food allergy. Finally, the genetic background may predispose individuals to food hypersensitivity. While promising trials, involving therapeutic interventions for food allergy, are underway, much on mechanisms still needs to be elucidated.

Acknowledgments

The author was supported by the Swiss National Research Foundation (32-47118.96, 32-44502.95).

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