Mechanisms of allergic diseases

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T_H2 adjuvants: Implications for food allergy

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Activity Objectives

1. To review how cytokines and dendritic cells lead to $CD4^+$ T-cell differentiation.
2. To discuss adjuvants that promote T_H2 differentiation.
3. To understand the role of T_H2 immune responses and adjuvants in food allergy.

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A persistent question for immunologists studying allergic disease has been to define the characteristics of a molecule that make it allergenic. There has been substantial progress elucidating mechanisms of innate priming of T_H2 immunity in the past several years. These accumulating data demonstrate that T_H2 immunity is actively induced by an array of molecules, many of which were first discovered in the context of antihelminthic immune responses. Similar intrinsic or associated activities are now known to account for the T_H2 immunogenicity of some allergens, and may prove to play a role for many more. In this review, we discuss what has been discovered regarding molecules that induce innate immune activation and the pathways that promote T_H2-polarized immune responses generally, and specifically what role these mechanisms may play in food allergy from models of food allergy and the study of T_H2 gastrointestinal adjuvants.
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Key words: *Adjuvant, T_H2, food allergy, allergen, cholera toxin, helminth, glycan, DC-SIGN, protease, protease activated receptor, superallergen, OX40L, TSLP, T-cell immunoglobulin mucin protein, Notch, Jagged, Delta*

Purified foreign proteins vary widely in their capacity to induce an immune response. This fact has led to an effort to define the features of an antigen that make it immunogenic. In the field of allergy, this question is often posed more specifically as follows: what features of an antigen not only promote its recognition by the mammalian immune system but also specifically promote an allergic response—at least in a subset of susceptible individuals? In other words, what makes an allergen an allergen? Recognizing that features such as lack of self-homology, structural stability, and route of administration play significant roles, an important answer to that question remains: an adjuvant.

Immune adjuvants are "substances and formulations that have the capacity to increase the immune response to an antigen."[1] It has been recognized for many years that adjuvants promote the uptake of antigen by antigen-presenting cells (APCs)—especially ***dendritic cells (DCs)***—and in many cases promote the activation of those APCs. These adjuvant factors include rendering antigen particulate rather than soluble, promoting slow antigen release, and, perhaps most importantly, associating

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Terms in boldface and italics are defined in the glossary on page 1312.

Abbreviations used
APC: Antigen-presenting cell
CSL: CBF1-suppressor of hairless-Lag-1
CT: Cholera toxin
DC: Dendritic cell
DC-SIGN: Dendritic cell specific intercellular adhesion molecule–grabbing nonintegrin
DLL: Delta-like ligand
LP: Lamina propria
MLN: Mesenteric lymph node
PAMP: Pathogen-associated molecular pattern
PAR: Protease-activated receptor
PG: Prostaglandin
PRR: Pathogen recognition receptor
SEB: *Staphylococcus* enterotoxin B
TIM: T-cell immunoglobulin mucin
TLR: Toll-like receptor
TSLP: Thymic stromal lymphopoietin

with molecules that target and, either directly or indirectly, activate APCs.

Since the discovery and elucidation of the role of mammalian Toll-like receptors (TLRs) beginning in the late 1990s,[2] many of the mechanistic details have been filled in to explain how a number of adjuvant molecules (eg, LPS, unmethylated cytosine-guanine rich nucleotide sequences [CpG], single-stranded RNA) activate innate immune cells, including DCs, to enhance adaptive immunity. TLRs, along with a growing list of other molecules (C-type lectin receptors, nucleotide binding oligomerization domain protein 1), have been termed ***pattern recognition receptors*** (PRRs) for their ability to sense pathogen-associated molecular patterns (PAMPs).

Pattern recognition receptor–mediated adjuvants have been largely associated with the enhancement of T_H1 (or T_H17) and not T_H2 immunity. More recently, several examples of T_H2-promoting pathways have been described, and these are the focus of this review. Although relatively little has been shown that is directly implicated in the development of food allergy, we discuss molecules and pathways that have been shown to favor T_H2 immunity in either *in vitro* or *in vivo* systems with an emphasis on non-TLR pathways, and where possible, we discuss what has been shown from murine models of food allergy and potential implications with an emphasis on the early sensitization events that are necessary for the subsequent manifestations of food allergy.

Food allergy is a broad term for immune-mediated adverse reactions to food, which includes conditions that are not strongly associated with T_H2 immunity (eg, gluten-sensitive enteropathy, food protein–induced enterocolitis syndrome, and so forth). However, most manifestations of food allergy, including IgE-mediated food allergy, as well as inflammatory skin or gut diseases that can be driven by food antigens, are T_H2-mediated—as evidenced clinically by the production of high-affinity specific IgE, the presence of inflammation characteristic of a T_H2 cytokine milieu (eg, eosinophilia, mastocytosis), and the efficacy of therapeutics that

GLOSSARY

CD MARKERS ON DENDRITIC CELLS: Dendritic cell (DC) subsets can be distinguished by the expression of surface markers. In mouse, all DCs are positive for the surface marker CD11c (an adhesion molecule). Other markers used to distinguish DC subsets in mice include CD11b, CD8α, B220, Gr-1, and others. In human beings, other surface markers are commonly used to distinguish DCs and DC subsets. The surface markers have various functions, but they are primarily used as tools in flow cytometry or by immunohistochemistry to identify DC subsets that have specialized functions.

CENTRAL MEMORY T LYMPHOCYTES: After activation of naive T cells (CD4 and CD8 T cells), differentiation can lead to the generation of memory T cells with either a central or effector memory phenotype. Effector memory cells rapidly secrete large amounts of cytokines after restimulation and express homing markers that make them specialized for entry into inflamed peripheral tissues. Central memory cells stay in the lymph nodes (and express the lymph node homing chemokine receptor CCR7 and the lymph node homing adhesion molecule CD62L). They are slower to become activated and secrete lower levels of cytokines, but can differentiate into effector memory T cells after reactivation.

DENDRITIC CELLS (DCs): Antigen presenting cells (APCs) that capture antigen in the periphery, traffic to draining lymph nodes, and process and present antigen to T lymphocytes through major histocompatibility complex (MHC) II–T-cell receptor (TCR) interactions. DCs can respond to exogenous stimuli to upregulate costimulatory molecules and cytokine secretion that can influence the response of the responder T cell.

PATTERN RECOGNITION RECEPTORS (TLRs, NODs, DECTIN, DC-SIGN): Innate recognition of microorganisms occurs through pattern recognition receptors (PRRs), of which many different types have been described. These include Toll-like receptors (TLRs), NOD1 and NOD2 (containing a nucleotide-binding oligomerization domain, which gives them their name), and a number of C-type lectin receptors such as Dectin-1 and DC-SIGN. PRRs recognize pathogen-associated molecular patterns (PAMPs), which are repeating structures common to categories of microorganisms (gram negative bacteria, gram positive bacteria, fungi, viruses). PRRs can be on the cell surface (such as TLR4 that recognizes lipopolysaccharide) or within the cell (such as NOD1 or NOD2 that recognize fragments of bacterial cell-wall proteoglycans or TLR9 that recognizes unmethylated CpG DNA). PRRs are found on a wide range of cell types, including DCs, and can promote phagocytosis of microorganisms, promote chemotaxis to sites of infections, and induce the release of effector molecules such as chemokines and cytokines. Several of the PRRs use common signaling pathways, such as the adaptor molecule MyD88 which is involved in signaling through the TLRs (except TLR3). The use of genetically modified mice with a deleted MyD88 gene (MyD88-/-) allows investigators to test the broad role of TLRs in different immune responses.

PEYER PATCH (PP): Together with the mesenteric lymph node (MLN), PPs are the major immune inductive site of the gastrointestinal tract. PPs are lymphoid aggregates within the gastrointestinal mucosa, and are found throughout the small intestine and in the rectum. The epithelium overlying PPs consist of specialized cells called microfold (M) cells, that have sparse cytoplasm and microvilli and transport particulate antigens (including viruses, bacteria) to the lymphoid cells of the PP.

T_H1, T_H2, T_H17, AND REGULATORY T CELLS: After activation by DCs, naive $CD4^+$ T cells differentiate into cytokine-secreting cells that can be divided into categories based on their cytokine secretion. T_H1 cells secrete IFN-γ, T_H2 secrete IL-4 and IL-13 (and others including IL-5, IL-9, IL-10), T_H17 secrete IL-17, and regulatory T cells produce IL-10 and/or TGF-β. This specialized cytokine secretion is associated with a specialization of function, such that T_H1 cells promote clearance of intracellular pathogens, T_H2 cells provide B cell help and promote humoral immunity, T_H17 cells enhance neutrophil responses and promote clearance of extracellular bacteria, and regulatory T cells suppress the other T cell subsets to prevent excess or damaging immune responses.

target T_H2 pathways.[3] Additional supporting evidence comes from *in vitro* T-cell studies and animal models of disease.

ANTIGEN DELIVERY

The main site of exposure to food allergens is the gastrointestinal tract, although that does not necessarily preclude a role for other sites such as skin or the respiratory tract in the sensitization to food proteins.[4,5] The main function of the gastrointestinal tract is digestion and absorption of nutrients. To facilitate that process, the intestine is composed of a very large surface area with a single layer of columnar epithelial cells forming the barrier between the external (lumen) and internal environments. Although M cells overlying ***Peyer patches*** have traditionally been thought of as the main sites of antigen entry, soluble antigens can traffic across enterocytes intact and gain access to immune cells in the lamina propria (LP),[6-9] where they may then be transported via DCs to the draining mesenteric lymph node (MLN).[10-12] Particulate antigens, in contrast, are preferentially taken up by M cells and can be presented by subepithelial dendritic cells to T cells within the Peyer patch.[13,14]

Antigens delivered via the oral route normally evoke an immune response characterized as regulatory or tolerogenic, and this active regulatory response is one mechanism responsible for the phenomenon of oral tolerance (see review of oral tolerance[3]). Although oral tolerance was initially defined experimentally in rodents by demonstrating a systemic nonresponsiveness to antigens after oral exposure, this process has also been demonstrated to occur in human beings.[15,16] Food allergy is generally thought to be a result of a defect in the generation of these normal regulatory responses, whereas outgrowing food allergy is a result of the acquisition of immune tolerance.[17] Thus, it is not the presence of an immune response to food antigens that is the basis for food allergy; it is the type of immune response. Therefore, molecules with intrinsic or associated T_H2-skewing adjuvant activity may play a significant role in the development of allergic sensitization to food proteins.

For food allergens to initiate allergic sensitization, they must first breach the normal gut barriers, including acidity, digestion, motility, mucin layers, IgA, and the tight junctions of the enterocytes that prevent passage of macromolecules. Resistance to heat, acidity, and digestion are important characteristics common to many food allergens.[18] Factors that interfere with these normal barriers to antigen penetration have been shown in some experimental systems to promote allergic sensitization. Inhibition of gastric acid (by sucralfate or by H2 receptor blockade) facilitates allergic sensitization to fish roe antigen in mice,[19] although the aluminum in sucralfate has adjuvant activity when given parenterally,[20] and therefore may contribute to the effect seen in the gastrointestinal tract. Psychological stress, which perturbs tight junctions of the small and large intestine and allows macromolecular passage across the epithelial barrier,[21,22] has also been shown to facilitate alum-induced sensitization to luminal antigens.[23] Yamaguchi et al[24] used gastrointestinal colonization with the microorganism *Candida albicans* to induce allergic sensitization to a coadministered protein antigen. They observed that colonization with *C albicans* was associated with a decrease in epithelial barrier function (tested by appearance of a fed antigen in the serum) and hypothesized that this barrier defect was playing a significant role in sensitization, although they did not address the likely contribution of PAMPs associated with *C albicans*. Taken together, facilitating antigen entry may promote allergic sensitization, although it is unlikely to do so in the absence of another T_H2-promoting signal.

T_H DIFFERENTIATION

Naive CD4 T cells are a pluripotent population capable of differentiating into a number of distinct phenotypes after activation by an APC. DCs are the most efficient cells for inducing naive T-cell activation and differentiation. Some differentiating T cells will become ***central memory T lymphocyte cells*** that will be maintained for long periods and home predominantly to lymph nodes, where they will be poised to expand and differentiate on future exposure to the same antigen. Effector T_H memory cells, in contrast, secrete cytokines on activation and play a role in orchestrating the immune response to a particular antigen. Distinct effector populations can be defined by generally exclusive patterns of cytokine expression. ***T_H2*** cells have been defined by expression of IL-4, IL-5, and IL-13, whereas ***T_H1*** cells express high levels of IFN-γ, and ***T_H17*** cells express IL-17.[25,26]

The dominant signal for differentiation toward the T_H1 phenotype is IL-12 derived from DCs. IL-12 is sufficient for *in vitro* polarization of naive T cells to T_H1, and *in vivo* knockout of either the p40 or p35 subunits of IL-12 results in a deficiency of T_H1 cells.[27] DC-derived cytokines including IL-23 (which shares the p40 subunit with IL-12), IL-1, IL-6, and TGF-β (in the mouse) promote T_H17 differentiation.[28]

In contrast, a necessary and sufficient, soluble, DC-derived signal for T_H2 differentiation is not known. Naive T cells express the IL-4 receptor, and exogenous IL-4 promotes the development of T_H2 cells *in vitro*. Furthermore, activated naive T cells can secrete low levels of IL-4, and this may contribute to T_H2 differentiation in an autocrine and paracrine manner, especially in the absence of strong T_H1-inducing signals.[29] IL-4 is also a potent inhibitor of T_H1 differentiation (as is IFN-γ an inhibitor of T_H2), and this combination of cross-inhibition with positive feedback may help naive T cells commit to a T_H2 differentiation pathway.[25] In addition, innate cells such as mast cells and basophils have been shown to be potent sources of early IL-4, which can support T_H2 differentiation.[30,31]

However, DCs, which are thought to be the essential antigen-presenting population for the instruction of naive T cells, do not express IL-4 (or IL-13). Furthermore, both IL-4Rα and ***signal transducer and activator of transcription 6*** knockout mice, which are incapable of responding to IL-4, still produce ample numbers of T_H2 cells in response to experimental parasite infection.[32,33] To whatever extent IL-4 and IL-13 from any source normally participate in early priming or amplification of T_H2 differentiation, the cumulative data from knockouts of IL-4Rα, signal transducer and activator of transcription 6, and hematopoietic innate lineage–specific IL-4/IL-13 suggest that there are additional, IL-4/IL-13–independent pathways of T_H2 differentiation.[32-34]

This uncertainty regarding early T_H2-inducing signals has contributed to the advancement of the default T_H2 hypothesis, which posits that in the absence of T_H1 or other polarizing signals, naive T cells preferentially differentiate into T_H2 cells. Eisenbarth et al[35] were able to show that activation of DCs with low-dose exposure of LPS—sufficient for DCs to upregulate MHC class II and costimulatory molecules, but not for production of IL-12—induced T_H2 immune responses in an *in vivo* allergic airway model. This supports the default hypothesis, because weakly activated DCs drove T_H2 immunity in the absence of the T_H1-polarizing signal from IL-12. In contrast with these data, Spörri et al[36] showed that DCs activated without direct ligation of TLR induced naive T-cell proliferation without commitment to T_H1 or T_H2. They used TLR-4 or MyD88 deficient/wild-type chimeric animals together with transgenic T cells to restrict the T-cell response

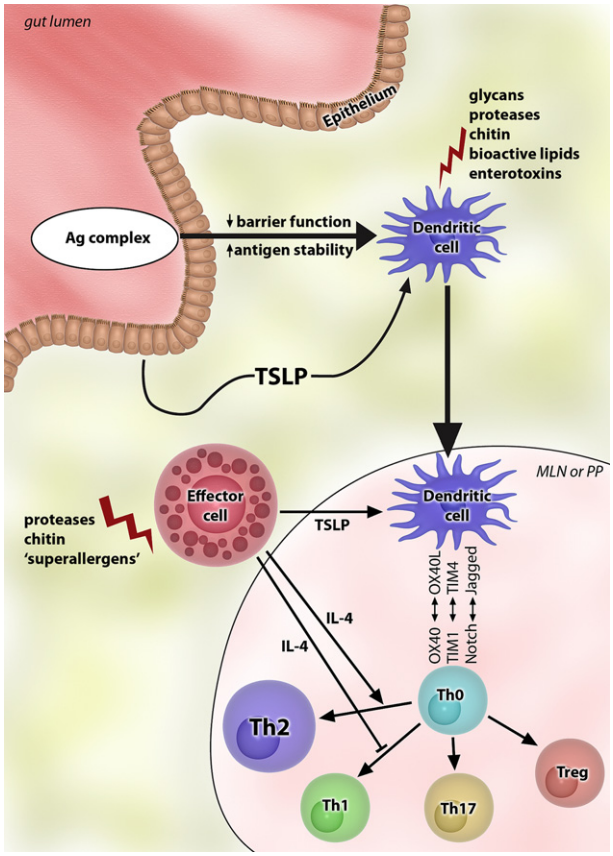

FIG 1. Possible mechanisms of allergic sensitization to gatrointestinal antigen. Antigen *(Ag)* complex is sampled by the gut-associated immune system via M cells or across enterocytes. Antigen delivery to APCs, such as DCs, is enhanced by physical factors such as antigen stability or compromised epithelial barrier. Instrinsic or associated features of allergens (listed next to *lightning bolts*) may then activate DCs and other innate immune cells to enhance signals that instruct naive T cells to differentiate preferentially to a T_H2 phenotype. These innate signals may include membrane-bound ligands expressed on DCs, such as OX40L, TIM-4, and Jagged, that interact with their respective receptors on T cells, as well as soluble mediators from other cells, such as IL-4 and TSLP. *Treg*, Regulatory T cell.

to either the wild-type or TLR-signaling deficient DCs—both of which were activated by autocrine/paracrine effect of IL-15—to show that there was no default differentiation of T cells in response to intravenously administered antigen.

MECHANISMS OF T_H POLARIZATION

To induce allergic sensitization rather than tolerance, adjuvants could have 1 of 2 effects: the selective migration and activation of an allergenic subset of DCs from the LP or within the Peyer patch, or the qualitative modulation of DC phenotype from tolerogenic to T_H2-polarizing.

In the lung, there are functionally distinct subsets of DCs, with myeloid DCs capable of promoting allergic sensitization and plasmacytoid DCs promoting inhalational tolerance.[37,38] Within the gastrointestinal tract, it has also been shown that DC subsets differ in their cytokine secretion patterns and their ability to prime naive T cells to T_H1, T_H2, or ***regulatory T cells***.[39-41] By using the experimental T_H2-polarizing adjuvant, cholera toxin (CT), Anjuère et al[42] reported selective migration and activation of a unique subset of DCs to the MLN (expressing ***CD11c*** but not ***CD11b*** or ***CD8***α) previsously described by Kelsall and Strober[41] and Iwasaki and Kelsall.[43] We also found that CT induced a selective migration of this DC population from the LP; however, we also observed a maturation of all DC subsets in the MLN that bore the LP marker, CD103, including $CD11b^+$ and $CD8\alpha^+$ DCs. In addition, the $CD103^+$ fraction of all of these DC subsets was T_H2-skewing.[44] Therefore, we concluded that CT could transform all DC subsets migrating from the LP into a proallergenic phenotype, rather than inducing the selective migration of a proallergenic DC subset.

Although a soluble DC-derived signal analgous to IL-12 has not been described for T_H2 polarization, there are a number of proposed mechanisms by which allergenic DCs may specifically signal naive T cells to induce T_H2 differentiation (Fig 1).

OX40 ligand

OX40 is a TNF receptor superfamily member that is transiently expressed on activated T cells. OX40 binds to its ligand, which is expressed on APCs including DCs and activated B cells, as well as on endothelial cells and T cells, and functional roles for OX40L on DCs, B cells, and T cells have been established.[45-48] One major effect of OX40-OX40L interactions is enhanced survival and expansion of T cells with little effect on the early proliferative response to T-cell receptor stimulation.[49-51] There is considerable evidence that OX40-OX40 ligand interactions are critical for T_H2 immune responses, and they have been shown to play a role in T_H2-skewed immune responses *in vivo* including experimental airway hyperresponsiveness[49,52-54] and nematode infection.[55,56] There is also evidence that OX40-OX40L signaling inhibits the development of regulatory cells,[56] although the T_H2 skewing induced by OX40L is not dependent on the suppression of regulatory responses.[45] There is controversy regarding the specificity of OX40L in promoting T_H2 responses. OX40-OX40L interactions have been shown to be important in promoting both T_H1 and T_H2 antigen-specific immune responses[57,58]; however, Ishii et al[59] showed that transgenic OX40L expression *in vivo* results in selective T_H2 immune responses and argued that the role of OX40L in T_H1 responses may be dependent on exogenous adjuvant. Despite this controversy, there is clear evidence for an important role of OX40L in T_H2 cytokine responses and associated pathologies *in vivo*.

Notch signaling

Notch signaling pathways are highly conserved accross species and involved in cell differentiation in metazoans. Notch recognizes cell membrane–bound ligands, which exist in 2 families: Jagged and Delta. In human beings, there are 4 Notch genes, and 5 cannonical ligands: Jagged1, Jagged2, Delta-like ligand (DLL)–1, DLL3, and DLL4.[60] Notch has been known to play a crucial role in early hematopoiesis[61] and more recently has been implicated in T_H differentiation.[62-67] Maekawa et al[63] first showed that coculture of purified CD4 T cells with DLL1 promoted T_H1 differentiation. This was confirmed by Amsen et al[64] by using DLL1-expressing APCs. However, they also went on to show that Jagged1-expressing APCs drove T_H2 differentiation instead of T_H1, and that this was dependent on the downstream transcription factor CBF1-suppressor of hairless-Lag-1 (CSL, also called RBP-J). The same group has gone on to show that CSL/RBP-J directly induces the master T_H2 transctiption factor, GATA-3, which is necessary for the ability of Notch ligands to promote T_H2 fate.[65] Tu et al[66] independently showed that mice that are defficient for the CSL cofactor Mastermind-like 1 are unable to mount a T_H2

TABLE I. Exogenous T_H2 adjuvants

Category	Example	Comments	Reference
Glycans	Ara h 1; *Schistosoma* glycoproteins	Facilitated uptake and activation of DCs via recognition by C-type lectin receptors	88, 89, 92
Nonmammalian biopolymer	Chitin	Innate immune activation leading to eosinophilia and T_H2 polarization	84
Proteases	Papain; Der p 1	Activation of innate immune cells via protease-activated receptors and other pathways; perturbation of epithelial barrier function	83, 102
Superallergens	Plant lectins; gp120; low-molecular-weight peanut antigen	Binding to nonvariant regions of IgE or other mechanisms for direct activation of mast cells and macrophages	106, 108, 109, 110, 112
Bioactive lipids	Phytoprostanes	Mimic PGE to suppress IL-12, activate DCs to promote T_H2 polarization	114, 115

immune response sufficient for clearing nematode infection, although they have normal T_H1-mediated clearance of the obligate intracellular parasite, *Leishmania major*. Notch signaling has also been implicated in the generation of regulatory T cells.[68]

T-cell immunoglobulin mucin proteins

The T-cell immunoglobulin mucin (TIM) gene family was discovered during a screen for genes differentially expressed during T_H1/T_H2 differentiation, which revealed TIM-3 as a protein that was preferentially expressed on T_H1 cells.[69] There are 3 known TIM genes in human beings: TIM-1, TIM-3, and TIM-4. From a number of lines of evidence, these genes seem to be important in T_H2 immunity. They are located on chromosome 5q33—a region repeatedly linked to asthma susceptibility—and some are differentially expressed on T_H subsets (TIM-3 to T_H1, TIM-1 $T_H2 > T_H1$). TIM-1 is the receptor for hepatitis A, an infection that has been repeatedly linked by epidemiologic data as protective against atopy.[70] TIM-3 appears to be a negative regulator of T_H1 cells because blocking and knockout experiments enhance T_H1 proliferation and function.[71] TIM-1 function is somewhat less clear. Recently, the TIM-1 ligand was shown to be TIM-4 expressed on APCs. Interactions between TIM-1 and TIM-4 appear most likely to enhance T_H2 responses. Soluble TIM-1–Ig fusion protein induces expansion and activation of T_H2 cells *in vivo*, which could suggest that TIM-1 is a negative T_H2 regulator analogous to the role of TIM-3 for T_H1 cells. However, the converse experiment using soluble TIM-4–Ig fusion protein does not suppress T_H2 proliferation but appears to enhance T-cell proliferation generally, leading Meyers et al[72] to conclude that cross-linking TIM-1 stimulates T_H2 responses.

Recently TIM-3 and TIM-1 have been shown to be constitutively expressed on mouse peritoneal mast cells, and their stimulation (by anti–TIM-3 or by soluble TIM-4, respectively) enhanced IL-4, IL-6, and IL-13 by mast cells activated via IgE cross-linking.[73] Human mast cells treated with TGF-β also express TIM-3.[74] Recently, Yang et al have shown that APC expression of TIM-4 can be induced by *Staphylococcus* enterotoxin B (SEB) and that SEB can enhance the allergenicity of oral antigen in a model of food allergy.[75,76]

T_H2 ADJUVANTS

Exogenous T_H2 adjuvants

If there is some default bias toward T_H2 polarization, recently there has been a growing appreciation that a variety of molecules can actively induce T_H2 responses (Table I). The earliest and best characterized examples come from studies of helminth parasites.[77-80] Parasitic worms express a remarkable array of immunomodulatory molecules, many of which are either suppressive or T_H2-inducing (see review[17]). In fact, all of the classes of exogenous T_H2-inducing molecules described to date in any context are represented by helminths. These include glycans,[81,82] proteases,[83] chitin,[84] mast cell/basophil–activating molecules,[85] arachidonic acid metabolites,[86] and other immunomodulatory lipids.[87] A number of these molecules have also been clearly implicated as playing a role in allergic responses (Fig 1).

Glycans

Helminths are rich in glycosylated proteins and lipids that have T_H2-skewing activity, some of which are uniquely nonmammalian. The C-type lectin receptor, DC—specific intercellular adhesion molecule–grabbing nonintegrin (SIGN), has been identified as an important glycan receptor that functions as a PRR to activate DCs.[81] One of the carbohydrate motifs implicated from helminth studies as T_H2-skewing is the α3-fucosylated and/or β4-xylosylated chitobiose core N-glycans that have been shown to drive strong T_H2 responses *in vivo*.[88] These structures are ubiquitous in helminths, arthropods, and plants; are not expressed in mammals; and are known to contribute to the allergenicity of plant and insect glycoproteins.[89,90] We have recently found that incubation of human monocyte–derived DCs with soluble peanut extract activates them to induce T_H2 differentiation of naive T cells. The purified major allergen, Ara h 1, which has been shown to contain a β4-xylosylated core,[91] was sufficient for this effect.[92] Ara h 1–activated DCs promoted T_H2 polarization even when those DCs were coactivated with proinflammatory cytokines, IL-1 and TNF-α. Ara h 1 was also found to be the unique DC-SIGN ligand of peanut extract, and is capable, like DC-SIGN cross-linking by antibody,[93] of inducing extracellular signal–related kinase (Erk) phosphorylation in monocyte-derived DCs, consistent with the possible role of this receptor in mediating Ara h 1–induced T_H2 skewing.[92] There are a number of additional C-type lectin recptor family members that function as PRRs, including Dectin-1, which is a coreceptor for zymosan that cooperates with and modulates TLR-2–mediated signaling.[94]

Proteases

Parasites express a number of proteases that are likely to play a role in immune subversion. Recognition of protease activity by

the host, however, is thought to be a mechanism of innate immune defense. A number of respiratory allergens are themselves proteases or are associated with proteolytic activity, such as those from house dust mite, cockroach, and fungi. Protease activity has been shown to contribute to allergenicity in the case of dust mite.[95] Serine proteases are recognized by the innate immune system by a family of proteinase-activated receptors (PARs 1 to 4).[96] Ebeling et al[97] recently showed that activation of PAR-2 with coadministration of inhaled antigen promoted allergic sensitization. There have been no reports to our knowledge supporting a role for PARs in food allergy; however, PAR-1 has been implicated in colitis,[98] and several PARs are expressed in a variety of gastrointestinal cells, including enterocytes, where they may play a role as signaling molecules induced by luminal digestive enzymes.[99] In addition, PAR-2 on intestinal epithelial cells is activated by mast cell tryptase and increases tight junction permeability,[100] suggesting that activation of this pathway by allergens could at least promote their intact absorption.

Phillips et al[83] reported IL-4, IL-5, and IL-13 expression from basophils induced by incubation with dust mite (and hookworm) extracts that could be inhibited by preincubation with protease inhibitors. The mechanism of protease-induced activation was not defined but would appear to be unrelated to the PAR signaling pathway discussed, because Falcone et al[101] have reported that, unlike mast cells and eosinophils, PARs are not expressed on basophils. However, there are apparently additional mechanisms of basophil activation by protesases, because the cyteine protease papain (but not inactivated papain) induced T_H2 immune responses *in vivo* by a basophil-dependent, TLR pathway–independent mechanism.[102]

Direct effector cell activation (superallergens)

Proteins from both helminths and allergen extracts have been reported to activate basophils or mast cells directly. For example, Rao et al[103] have identified and cloned a protein from *Schistosoma mansoni* that activates mast cells as indicated by histamine release, although the mechanism is unclear. *Schistosoma* and *Echinococcus* extracts also induce IL-4 secretion by a distinct IgE-dependent (but not antigen-specific) pathway.[85,104,105] In the case of schistosomes, this activity is accounted for by the IL-4–inducing factor from schistosome eggs (IPSE), which is secreted from the parasite eggs and functions as a superallergen by binding to the variable heavy chain 3 region of IgE, independent of antibody specificity.[106] This capacity to bind directly to polyclonal IgE may also facilitate association with APCs, especially in human beings, where expression of the high-affinity IgE receptor is broader than in the mouse and includes DCs.[107] Of note, pathogen interaction with IgE is not unique to parasites or allergens because both viral (including HIV gp120) and bacterial proteins may exploit this pathway to escape T_H1 immune responses.[108] Of potential relevance to food allergy, several authors have reported that plant lectins may act as superallergens by binding IgE glycans and inducing cross-linking.[109,110] In addition, Lavelle et al[111] have reported that a number of plant lectins have mucosal adjuvant activity when administered orally. Finkelman[112] has reported that an undefined low-molecular-weight constituent of peanut extract can directly induce an anaphylactoid response in a complement-dependent manner, although whether this biological activity may also be important for innate immune activation and contribute to T_H2 polarization has not been reported.

Chitin

Chitin is the major structural polymer of invertebrates. It is known to be recognized by plant immune systems, and its role as a PAMP recognized by the mammalian immune system was recently supported by the findings of Reese et al.[84] They showed that chitin administered to the lungs or intraperitoneally induced the accumulation of eosinophils and other T_H2-associated cells because of the induction of leukotriene B_4 synthesis from macrophages. The mechanism of chitin recognition is still not known. Previously, it had been reported that expression of acidic mammalian chitinase, which is induced by exposure to chitin, was elevated in allergic inflammation and that the enzyme itself induces T_H2 inflammation.[113] However, transgenic overexpression of acidic mammalian chitinase by Reese et al[84] did not induce inflammation. There is no direct evidence for chitin playing a role in food allergy, although it is perhaps noteworthy that allergy to crustaceans is both common and persistent.

Lipids

Prostaglandins are known endogenous immune modulators that have also been shown to influence T_H skewing when derived exogenously. Helminths specifically synthesize prostaglandin (PG) E_2 and PGD_2, both of which suppress IL-12 production and migration by DCs.[86,114] Recently, Traidl-Hoffman et al have shown that aqueous extracts of birch pollen grains are rich in bioactive lipids that promote activation and migration of DCs to elicit T_H2 immune responses.[115,116] The activity of these extacts appears to be a result of phytoprostanes that have structures that mimic PGE_2. Phytoprostanes are abundant in all plant tissues and have been shown in plasma and urine after ingestion of vegetable oils,[117] but there is no evidence published to date addressing their potential role in food allergies.

ENDOGENOUS T_H2 ADJUVANTS

Thymic stromal lymphopoietin (TSLP) is a cytokine expressed by epithelial cells at mucosal surfaces and upregulated in allergic diseases of the skin and lung.[118,119] Soumelis et al[118] showed that TSLP could mature human DCs (without promoting proinflammatory cytokine production), and TSLP-exposed DCs could support the differentiation of proinflammatory T_H2 cells producing IL-4, IL-5, IL-13, and TNF-α. Overexpression of TSLP in murine lung or skin results in allergic inflammation at those respective sites.[120-122] In addition, mice lacking the TSLP receptor are protected from the development of experimental airway hyperresponsiveness.[120,123] TSLP induces T_H2 skewing via upregulation of OX40L expression on DCs.[124] TSLP derived from intestinal epithelial cells has been shown to promote T_H2 responses, but these have been characterized as regulatory T_H2 responses that suppress inflammatory T_H1 or T_H17 responses in the gastrointestinal tract.[125,126] There are no data published yet on the role of TSLP in food-allergic diseases.

A number of other epithelial-derived molecules such as chitinases[126-128] and RELM family members[129] have been shown to play a role in allergic inflammation; however, the data suggest that they are downstream of T_H2 cytokines and therefore would be categorized more as effector molecules rather than having T_H2-skewing adjuvant activity.

EXPERIMENTAL T_H2 ADJUVANTS

Experimental T_H2 adjuvants have been used primarily to achieve T_H2 sensitization to study mechanisms of established

allergic inflammation.[112] Although it may be more artificial to use these molecules to explore mechanisms of sensitization and T_H2 adjuvanticity, we believe that they are likely to provide insight that is relevant to natural sensitization—for example, with respect to the mechanisms of DC–T-cell interactions that lead to T_H2 polarization.

CT

The most widely used model of oral sensitization to food proteins uses the mucosal adjuvant CT. Co-administration of CT has been used to sensitize mice to antigens including ovalbumin,[130] hen egg lysozyme,[130] buckwheat,[131] lupin proteins,[132] milk or individual milk proteins,[133-136] and peanut or peanut allergens.[137-141] The finding that feeding antigens alone can induce oral tolerance, yet feeding antigen in the presence of CT can lead to allergic sensitization, suggests that determining the mechanisms by which this experimental tool can induce allergic sensitization may provide insights into potential mechanisms responsible for food-allergic sensitization in human beings.

Although CT clearly has an immunomodulatory effect on a variety of immune cells *in vitro*, it is not known whether these effects are also seen *in vivo* at doses normally used for adjuvant effect. CT has adjuvant effects when given parenterally,[130] suggesting that its adjuvant activity is not limited to facilitating antigen access across the intestinal epithelium. The importance of DCs in the response to CT was demonstrated by enhanced responses after expansion of DC populations with FMS-like tyrosine kinase 3 ligand.[142] One important effect of CT *in vivo* is on migration of DCs to sites of interaction with T cells. Feeding of CT induces the migration of DCs from the subepithelial dome region of Peyer patches to the interfollicular T-cell areas.[143] Recently it was shown that CT (as well as the closely related heat-labile enterotoxin from *Escherichia coli* [LT]) could also drive DCs into the follicle-associated epithelium to capture antigens from the lumen.[144] CT and LT also induce the expansion of DC subsets in the MLN together with the egress of DCs from the LP.[42,44,145] Taken together, these studies show that CT and related adjuvants enhance capture of antigens from the gut lumen and migration of DCs to areas of interaction with naive T cells. However, enhanced antigen capture and migration by DCs is unlikely to be sufficient to induce allergic sensitization to food proteins, because it has been demonstrated that gastrointestinal DCs (and migration of these DCs to the MLN) are also necessary for the induction of oral tolerance.[146,147]

Further analysis of the phenotype of DCs in the MLN after CT feeding demonstrated that although cytokine production (including IL-12, IL-10, and IL-23) was not significantly altered, there was a significant upregulation of the costimulatory molecules OX40L and Jagged2. As discussed, both of these molecules have been shown to have T_H2-skewing effects on naive T cells *in vitro*. Neutralization of OX40L abolished the T_H2-promoting effect of CT but did not influence the IFN-γ or IL-17 response,[44] indicating that OX40L upregulation by CT on DCs *in vivo* was a critical mediator of T_H2 skewing of responder T cells. The functional role of Jagged2 *in vivo* has not yet been determined.

Not addressed by these studies was the role of the epithelium in the phenotypic changes in subepithelial DCs. It is not clear whether CT acts directly on DCs or facilitates these changes by inducing changes in gene expression in intestinal epithelial cells. Anjuère et al[42] reported that CT induced an upregulation in ***CCL20*** expression in mouse intestine, which could theoretically facilitate the migration of DCs to the subepithelial space. However, CCR6 has been shown to be limited to the DCs of the mouse Peyer patch, and $CCR6^+$ DCs are not observed in the small intestinal LP.[148] The expression of T_H2-promoting factors from the epithelium, such as TSLP, has not been examined in the context of mucosal adjuvant stimulation.

TABLE II. Key points

Factors acting on DCs can determine the nature of antigen-specific T-cell differentiation
Factors promoting T_H2 skewing by DCs include intrinsic properties of allergens, endogenous adjuvants produced by microbial stimulation, or experimental adjuvants such as microbial-derived toxins
Understanding how natural and experimental mucosal adjuvants work to promote T_H2 cytokine production and IgE will identify immune pathways that may be modified (by genetics or environment) in patients at risk for development of food allergy

SEB

As described, the TIM gene family is thought to contribute to allergic disease through the modulation of T-cell function.[70,72,149] Recently, Yang et al[76] described a model of gastrointestinal allergy induced by a combination of systemic and oral administration of ovalbumin together with the enterotoxin, SEB, from *Staphylococcus aureus.* SEB could induce the upregulation of TIM-4 on DCs isolated from the small intestine either when cocultured with the DCs or administered to mice before isolation of the DCs. In addition to TIM-4, expression of the costimulatory molecules CD80 and CD86 was upregulated. Of relevance to food allergy, these DCs could skew naive T cells to a T_H2 phenotype by a TIM-4 and TIM-1–dependent mechanism. Finally, neutralizing anti–TIM-4 or anti–TIM-1 antibodies could prevent sensitization to ovalbumin using SEB as an adjuvant, and prevent local hypersensitivity reactions in the small intestine. The role of SEB in human food-allergic disease is not clear. Unlike *Vibrio cholera*, *S aureus* is commonly found at mucosal sites, and its superantigen has the potential to play a role in human allergic disease, as has been suggested by studies in atopic dermatitis.[150,151]

Conclusion

Although our knowledge of the mechanisms of allergic sensitization to food allergens is still very limited, there has been a flurry of research in just the past few years uncovering more and more mechanisms leading to the induction of T_H2 immune responses. Increasingly it appears that, far from being the result of passive differentiation in the absence of T_H1 polarization signals, T_H2 induction is often regulated by DCs that are responding to evolutionarily conserved signals associated with parasitic pathogens. To what extent allergens function as, or are intimately associated with, T_H2 adjuvants remains to be seen, but the better we understand the mechanisms of innate instruction of T_H2 adaptive immunity, the more likely we will be to apply this knowledge to intervene at the earliest stages of allergic disease pathogenesis (see Table II for a summary of key points from this study).

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