Current perspectives

Do lipids influence the allergic sensitization process?☆

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Allergic sensitization is a multifactorial process that is not only influenced by the allergen and its biological function *per se* but also by other small molecular compounds, such as lipids, that are directly bound as ligands by the allergen or are present in the allergen source. Several members of major allergen families bind lipid ligands through hydrophobic cavities or electrostatic or hydrophobic interactions. These allergens include certain seed storage proteins, Bet v 1–like and nonspecific lipid transfer proteins from pollens and fruits, certain inhalant allergens from house dust mites and cockroaches, and lipocalins. Lipids from the pollen coat and furry animals and the so-called pollen-associated lipid mediators are codelivered with the allergens and can modulate the immune responses of predisposed subjects by interacting with the innate immune system and invariant natural killer T cells. In addition, lipids originating from bacterial members of the pollen microbiome contribute to the outcome of the sensitization process. Dietary lipids act as adjuvants and might skew the immune response toward a T_H2-dominated phenotype. In addition, the association with lipids protects food allergens from gastrointestinal degradation and facilitates their uptake by intestinal cells. These findings will have a major influence on how allergic sensitization will be viewed and studied in the future. (J Allergy Clin Immunol 2014;■■■:■■■-■■■.)

Key words: *Allergy, food allergens, immunomodulatory lipids, lipid-binding allergens, microbial lipids, pollen allergens, pollen-associated lipid mediators, pollen lipids*

Abbreviations used
DC: Dendritic cell
iNKT: Invariant natural killer T
MD-2: Myeloid differentiation factor 2
MoDC: Monocyte-derived immature dendritic cell
nsLTP: Nonspecific lipid transfer protein
PALM: Pollen-associated lipid mediator
PPE_1: Phytoprostane E_1
TLR: Toll-like receptor

Lipids are hydrophobic or amphipathic small molecules. The International Lipid Classification and Nomenclature Committee organizes lipids into 8 well-defined categories[1] among which certain members of the fatty acids, glycerolipids, glycerophospholipids, sphingolipids, and saccharolipids have been experimentally shown to be involved in allergic sensitization. Binding or colocalization of immunostimulatory or immunomodulatory lipids could significantly contribute to the allergenicity of proteins. Although conventional activation of pathogen recognition receptors is considered to result in T_H1-dominated responses, it becomes clear that Toll-like receptor (TLR)–, NOD-like receptor–, or C-type lectin receptor–triggering stimuli are also able to induce T_H2 responses.[2] Sensitization by means of inhalation of low levels of LPS in concert with the respective allergen results in T_H2-type lung inflammation through TLR4, whereas high amounts of LPS induces a T_H1 response.[3,4] Lipid binding is a common characteristic observed for members of several protein families that include allergens, such as Bet v 1–like proteins, nonspecific lipid transfer proteins (nsLTPs), 2S albumins, secretoglobulins, lipocalins, oleosins, and mite group 2, 5, and 7 proteins (Table I).[5-28] These proteins contain hydrophobic binding sites for lipid ligands, and immunomodulation by such binding partners leads to T_H2-enhancing actions.

Allergen-bound ligands are not the only source of immunomodulatory lipids. Lipids are present in high concentrations in pollen coats and in matrices of plant and animal foods. Lipids protect pollen grains against UV light damage or attack by pathogens, and they play a key role in pollen-pistil interactions.[29] Microbial contaminations are additional sources of immunomodulatory lipids. Pollen is never sterile. Thus far, the study of pollen microbiomes has been limited to analyzing bacterial communities acquired by honey bees through a horizontal transmission from pollen and flower nectars.[30] The sensitization process is modulated by several key players, of which lipids are clearly one (Table II).[26,31-44] Hence future studies of the mechanisms of sensitization are well advised to include lipids in their experimental setups.

INTERACTION OF LIPIDS AND INHALANT ALLERGENS

Exposure to pollens as a major source of inhalant allergens can induce the production of specific IgE in predisposed subjects and thus represents a risk for development of asthma/rhinitis and eczema.

The pollen coat contains a large range of lipids that are required for pollen hydration, germination, and penetration of the stigma by the pollen tube.[45] These pollen coat lipids might possess

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TABLE I. Lipid-binding allergens

Protein family	Allergen	Source	Mode of lipid binding and ligands	Effects and mechanism of action
Bet v 1 like	Bet v 1	Birch pollen *(Betula verrucosa)*	Binds and transports diverse hydrophobic ligands in a large hydrophobic cavity[5-7]	Binding and permeabilization of membranes[5]
	Ara h 8	Peanut *(Arachis hypogaea)*	Associated with lipid fraction of raw and roasted peanuts	Ara h 8 isolated from roasted peanuts showed higher thermal and proteolytic stability[18]
	Mal d 1	Apple *(Malus domestica)*	Penetrates phospatidylcholine vesicles	Interaction with phospatidylcholine induced enhanced basophil activation[19]
MD-2–related domain	Der p 2	House dust mite *(Dermatophagoides pteronyssinus)*	Bind LPS because of structural similarity to MD-2, the LPS-binding component of the TLR4 complex[9]	Der p 2 promotes TLR4 signaling and induces a robust airway T_H2 inflammation in wild-type but not TLR4-deficient mice[8]
	Der f 2	House dust mite *(Dermatophagoides farinae)*		
Group 5/21 mite allergen	Der p 5	House dust mite	Possibly binds hydrophobic ligands in a large hydrophobic cavity[10]	Unknown
Group 7 mite allergen	Der p 7	House dust mite	Binds the bacterial lipopeptide polymyxin B[11]	Unknown
Group 1 cockroach allergen	Bla g 1	Cockroach *(Blattella germanica)*	Binds different lipids, such as palmitic, oleic, and stearic acids, through hydrophobic cavity[12]	Unknown
Fel d 1 family	Fel d 1	Cat *(Felis domesticus)*	Binds LPS	Enhances LTA/TLR2 and LPS/TLR4 signaling in both a transfected cell model and in primary macrophage-like cells[13]
Lipocalin	Can f 6	Dog *(Canis familiaris)*	Binds LPS	Enhances LPS/TLR4 signaling in both a transfected cell model and in primary macrophage-like cells[13]
	Bos d 5	β-Lactoglobulin from cow's milk	Inserts into the lipid bilayer[24]	Interaction with phospatidylcholine protects β-lactoglobulin from breakdown in an *in vitro* gastroduodenal environment[24]
Nonspecific lipid transfer protein	Par j 1	Parietaria *(Parietaria judaica)*	Binds LPS through C-terminal Par37 peptide	Inhibition of LPS-induced IL-6 and TNF-α in RAW264.7 cells, inhibition of LPS-induced INF-γ secretion in murine spleen cells and human PBMCs[27]
	Pru p 3	Peach *(Prunus persica)*	Tunnel-like lipophilic cavity capable of binding different lipid ligands[28]	Internalization by Caco 2 cells through an endocytic pathway involving lipid rafts and caveolar endocytosis accompanied by expression of T_H2 cytokines[14]
2S albumin	Ber e 1	Brazil nut *(Bertholletia excelsa)*	Potentially lipid-binding hydrophobic cavity	rBer e 1 coadministrated with lipid fractions isolated from Brazil nuts induced an IgE and IgG_1 antibody response[15]
				Ber e 1/lipid-stimulated murine and human CD1d-restricted iNKT cells produced IL-4 but not IFN-γ[16]
	Sin a 1	Mustard *(Sinapis alba)*	Interacts with acidic phospholipid vesicles	Permeabilization of lipid bilayer[17]

(Continued)