The role of lectins in allergic sensitization and allergic disease

Fabián Salazar, MSc, Herb F. Sewell, MBChB, PhD, FRCP, FRCPath, Farouk Shakib, PhD, FRCPath, and Amir M. Ghaemmaghami, MD, PhD *Nottingham, United Kingdom*

Allergic diseases are a global public health issue affecting millions of persons around the world. However, full understanding of the molecular basis of this group of chronic inflammatory disorders remains rather elusive. Recently, the role of carbohydrates on allergens and their counterstructures on antigen-presenting cells (lectins) have been highlighted as crucial factors in allergen sensitization, which culminates in T_H2 cell differentiation and the production of deleterious specific IgE antibodies. Here we review recent progress on the role of different lectins in patients with type I hypersensitivity or allergy, their interplay with other determinants of allergenicity, and ways of developing therapeutic modalities against newly identified targets. (J Allergy Clin Immunol 2013;132:27-36.)

Key words: *C-type lectin receptor, lectin, glycosylation, allergen, type-I hypersensitivity, asthma, house dust mite, mannose receptor, DC-SIGN, Toll-like receptor, dendritic cells, galactins*

Abbreviations used

AHR:	Airway hyperresponsiveness
CCD:	Cross-reactive carbohydrate determinant
CD:	Cytoplasmic domain
CLR:	C-type lectin receptor
CRD:	Carbohydrate recognition domain
CTLD:	C-type lectin–like domain
DC:	Dendritic cell
DC-SIGN:	Dendritic cell–specific intracellular adhesion molecule 3–grabbing nonintegrin
Gal:	Galectin
HDM:	House dust mite
Man-LAM:	Mannose-capped lipoarabinomannan
MBL:	Mannose-binding lectin
MC:	Mast cell
MR:	Mannose receptor
OVA:	Ovalbumin
PRR:	Pattern recognition receptor
SP:	Surfactant protein
TLR:	Toll-like receptor

Type I hypersensitivity or allergy is an exacerbated immune response against specific antigens called allergens. The re-exposure to those molecules by means of inhalation, ingestion, injection, or direct contact triggers the allergic reaction characterized by the synthesis of IgE. In general terms the sequence of events starts with the recognition of an allergen by dendritic cells (DCs), followed by T_H2 cell differentiation, IgE production, and mast cell (MC) sensitization and triggering. During re-exposure, the cross-linking of Fc receptor–bound IgE on MCs by allergens promotes the release of soluble mediators and onset of the allergic reaction.[1] DCs have been shown to have a crucial role in the induction and re-elicitation of T_H2-mediated allergic diseases; however, the molecular processes underpinning these events are still unclear.[2]

Recognition and internalization of antigens by DCs is an important first step in the sequence of events that leads to the induction of the adaptive immune response. Immature DCs take up antigens in the periphery, process them into peptides, and then migrate to the lymph nodes, where, through expression of costimulatory molecules and cytokines, they can stimulate naive T cells or induce tolerance, depending on the nature of the antigen and other microenvironmental factors.[3] DCs efficiently sample their milieu for foreign antigens by using pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), C-type lectin receptors (CLRs), or scavenger receptors, which increase their internalization efficiency and deliver information regarding the presence of danger signals.[4]

This review will focus on the role of different membrane-associated CLRs, soluble lectins, and galectins in allergen recognition and downstream events leading to T_H2 cell polarization. We will also discuss the interplay between lectins, PRRs, and other determinants of allergenicity, such as molecular mimicry and enzymatic activity, and how such interactions could collectively determine the outcome of the immune response to allergens.

MEMBRANE-ASSOCIATED CLRs

CLRs play a key role in antigen uptake by DCs and are particularly involved in the uptake of glycoantigens. A number of CLRs, including mannose receptor (MR), dendritic cell–specific intracellular adhesion molecule 3–grabbing nonintegrin (DC-SIGN), and Dectin-2 have been recently shown to act as receptors for allergens.

From the Faculty of Medicine and Health Sciences, University of Nottingham.

Supported by Asthma UK (06/001) and the Wellcome Trust V.I.P. fund. F. Salazar is a recipient of a PhD scholarship from the National Commission for Scientific and Technological Research (CONICYT), Chile.

Disclosure of potential conflict of interest: A. Ghaemmaghami has received grants from Asthma UK. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication October 19, 2012; revised January 3, 2013; accepted for publication February 1, 2013.

Available online March 25, 2013.

Corresponding author: Amir M. Ghaemmaghami, MD, PhD, Allergy Research Group, Division of Immunology, West Block, A Floor, Queen's Medical Centre, University of Nottingham, Nottingham NG7 2UH, United Kingdom. E-mail: amg@nottingham.ac.uk.

0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2013.02.001

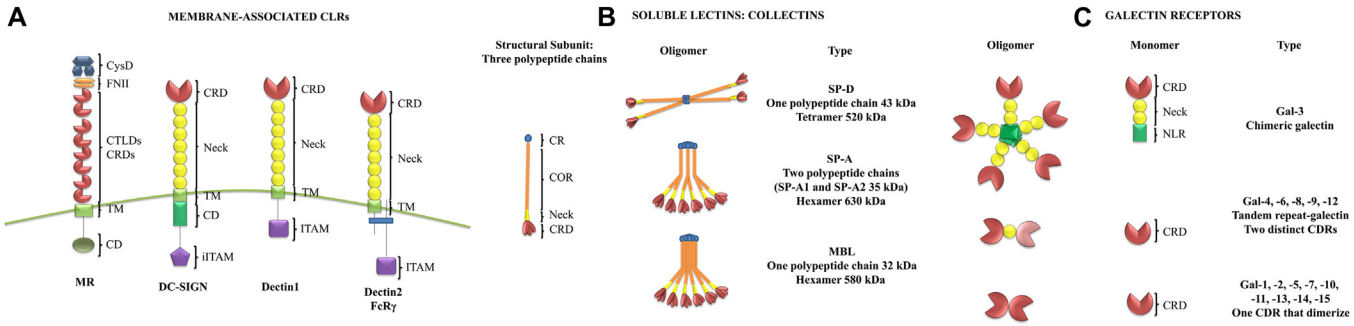

FIG 1. The domain structure of lectins: schematic representation of the polypeptide and domain structures of membrane-associated CLRs **(A)**,[5-8] soluble lectins **(B)**,[9] and galectins **(C)**.[10] *CRD*, Carbohydrate recognition domain; *COR*, collagen region; *CysD*, cysteine-rich domain; *FNII*, fibronectin type II–like domain; *iITAM*, incomplete immunoreceptor tyrosine-based activation motif; *NLR*, nonlectin region; *TM*, transmembrane region.

MR

Structure. The MR is a 175-kDa type I integral transmembrane glycoprotein with established roles in homeostasis and immunity. It recognizes a wide range of carbohydrates on microbial cell surfaces and mediates endocytic clearance of host-derived glycoproteins. The domain structure of the MR contains 3 regions: a cysteine-rich domain, a fibronectin type II–like domain, and 8 C-type lectin-like domains (CTLDs). These are followed by a transmembrane region and a short COOH terminal hydrophilic cytoplasmic domain (CD), which participates in receptor internalization and recycling (Fig 1, *A*).[5-10] The MR is a multifunctional receptor with 2 lectin activities involving Ca^{2+}-dependant recognition of carbohydrates terminated in L-fucose, D-mannose, or N-acetyl glucosamine through CTLDs, as well as Ca^{2+}-independent binding of acidic glycans sulfated at positions 3 or 4 through the cysteine-rich domain, whereas the fibronectin type II–like domain mediates collagen binding.[5]

Role in allergen recognition. Some data suggest an association between the MR and airway diseases. In a clinical study it was found that DCs from allergic patients expressed more MR and were also more efficient in the uptake of the house dust mite (HDM) allergen Der p 1.[11] Interestingly, gene-mapping linkage analyses in both human subjects[12] and mice[13] have identified *Mrc1* (MR C-type 1) as a positional candidate gene for allergen-induced airway hyperresponsiveness (AHR), which indicates a clear association between the MR and asthma. In line with these observations, recent data have shown that the MR on human DCs is a common receptor for several clinically relevant allergens, including those from HDMs (Der p 1 and Der p 2), cockroach (Bla g 2), dog (Can f 1), and peanut (Ara h 1), and that recognition of these allergens is mediated by the CTLD4-7 region of the MR (Table I).[14-23] Also, it was shown that the MR plays a crucial role in T_H2 cell polarization, as demonstrated by a biased T_H1 response when MR-deficient DCs were stimulated with Der p 1 and cocultured with naive T cells. Interestingly, the reversal of a biased T_H1/T_H2 balance in the absence of the MR was shown to be mediated, at least in part, through upregulation of indoleamine 2,3-dioxygenase activity in DCs,[14] an immune-modulatory enzyme that participates in tryptophan metabolism.[24] Later, it was shown that the MR was also an endocytic receptor for the uptake of the major cat allergen Fel d 1 and it mediated production of Fel d 1–specific IgE and IgG_1 in a mouse model of allergy.[15]

TABLE I. Interactions of lectins with various allergens

Lectin	Allergen	Source	Reference
MR	Der p 1	HDM	14
	Der p 2	HDM	14
	Bla g 2	Cockroach	14
	Can f 1	Dog	14
	Ara h 1	Peanut	14
	Fel d 1	Cat	15
DC-SIGN	Der p 1	HDM	18
	Der p 2	HDM	17
	Can f 1	Dog	18
	Ara h 1	Peanut	16
	BG-60	Pollen	17
Dectin-2	*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* extracts	HDM	19
	Aspergillus fumigatus extract	Mold	19
SP-A	Der p 1	HDM	22
	Der f 1	HDM	22
	Populus nigra var. italica, *Poa pratensis*, *Secale cereale*, and *Ambrosia artemisiifolia* var. elatior extracts	Pollen grains	20
	Glycoproteins 55 and 45 from *Aspergillus fumigatus*	Mold	23
SP-D	Der p 1	HDM	22
	Der f 1	HDM	22
	Dactylis glomerata and *Phleum pratense*	Pollen starch granules	21
	Glycoproteins 55 and 45 from *Aspergillus fumigatus*	Mold	23

DC-SIGN

Structure. DC-SIGN is a 44-kDa type II transmembrane protein receptor that is able to bind mannose- and fucose-containing ligands and is exclusively expressed by antigen-presenting cells.[25] Moreover, it functions as a cell adhesion receptor mediating migration and antigen internalization by DCs.[26] DC-SIGN consists of 3 regions: an extracellular domain