Insect Lectin-Mediated Immune Responses

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Lectins are carbohydrate-binding proteins that recognize and selectively bind to specific sugar structures. Interaction of lectin with sugars on cell surface can activate multiple cellular responses, including the immune response. Many insect lectins have been identified or predicted but without in-depth analysis.

insect lectin innate immunity cellular immunity humoral immunity

1. Introduction

Lectins are unique proteins that are characterized by their ability to selectively bind to specific carbohydrate residues. These sugar structures can be monosaccharides, disaccharides, or polysaccharides, and can be present as free sugars or as glycoconjugates linked to proteins and lipids. In the past, lectins were found to agglutinate red blood cells; therefore, they were often referred to as “hemagglutinins” or “agglutinins” [1]. Subsequent research indicated that agglutination is not universal for all lectins. Only some plant lectins will agglutinate certain types of cells, and this aggregation of cells can be blocked by preincubation with specific sugars. Consequently the word “lectin”, meaning “to select”, was introduced to replace the term hemagglutinin [2].

Because of their selectivity in carbohydrate binding, lectins play crucial roles in a multitude of biological processes in plants, animals, and microorganisms. For example, many plant lectins serve as defense proteins and are harmful to insects or pathogens [3]. Similarly, some animals can secrete lectins that can kill bacteria by forming pore structures on their membranes [4]. Bacteria use their surface lectins to adhere to host cells for invasion [5]. Inside cells, lectins participate in protein quality control [6]. In the extracellular matrix, some lectins alter ion transport [7]. Secreted lectins have also been reported to be involved in host immunity due to their ability in pathogen recognition [8][9].

2. Insect Innate Immunity

Animals are frequently challenged by invading pathogens such as fungi, bacteria, viruses, parasites, etc. Furthermore, they also harbor a microbiome in tissues such as the intestine and the hemolymph [10]. To maintain homeostasis and system integrity, animal hosts must regulate their own microbiota and eliminate pathogen infection through an elaborate immune system [11]. While mammalians have both an adaptive (depending on memory immune cells) and an innate immunity system, insects mainly depend on innate immunity when threatened by pathogens. Nonetheless, insects have evolved to be very successful organisms, occupying almost every habitat and ecological niche. This is due to a strong innate immune system consisting of a cellular and a

humoral component (reviewed by [12][13][14]). The cellular defense is initiated instantly when pathogens are detected and results in the phagocytosis of smaller pathogens or encapsulation of bigger invaders [13][14]. The humoral defense is a relatively slow response and involves the production of a series of antimicrobial peptides (AMPs), complement proteins, lysozymes, protease inhibitors, reactive oxygen species (ROS), and enzyme cascades leading to the formation of melanin and clotting [12][14].

The cellular or humoral immunity system depends on the presence of immune cells of different types. These immune cell types can differ between insect species. For example, the mosquito *Aedes aegypti* has more kinds of immune cells identified than *Drosophila* [15]. The immune cells, called hemocytes due to their presence in the hemolymph, have differentiated from prohemocytes and are mainly composed of three highly differentiated cell types: the plasmatocytes, crystal cells, and lamellocytes [14][16]. Plasmatocytes represent more than 90% of the hemocyte pool. These cells have been shown in vitro to possess strong adhesive features, enabling them to surround and engulf pathogens, and to produce antimicrobial peptides (AMPs) for the humoral defense [14][15]. Unlike plasmatocytes, crystal cells are not adhesive, but they can express phenoloxidase, the key enzyme in the formation of melanin involved in wound healing and melanization [17]. Lamellocytes are large adhesive cells that are only present in larva or in infected adults, and are involved in melanization and encapsulation [15].

3. Insect Lectins

Insects are the largest and most diverse group of animals, and more and more insect lectins are being discovered. Lectin classification is important to cope with the diversity of these proteins. Insect lectins can be grouped according to the animal classification system, which encompasses 16 families of lectins, each with a characteristic carbohydrate-recognition domain (CRD) [18].

In insects, most of the identified endogenous lectins belong to the C-type lectin (CTL) family. Canonical CTLs bind sugars through their CRD, and this interaction is dependent on Ca^{2+}, hence the name “C-type lectins”. The CRD motif of CTLs is versatile, resulting in broad range of carbohydrate-binding interactions. For example, the Glu-Pro-Asn (EPN) motif in the CRD binds mannose, N-acetylglucosamine, L-fucose, and glucose, while galactose and N-acetylgalactosamine are recognized by the Gln-Pro-Asp (QPD) motif [19][20]. Many other motifs have been identified in insects, such as QPS, QPN, APD, and MPP, among others [21], but their carbohydrate-binding activities need to be confirmed. According to their complexity, CTLs can further be classified into subfamilies such as collectins (collagen-containing C-type lectins), endocytic receptors, selectins, etc. [22]. Based on sequence homology, proteins with a CTL domain have been identified in at least 12 insects belonging to different orders, including model organisms such as *Drosophila melanogaster*, *Bombyx mori*, *Manduca sexta*, *Tribolium castaneum* and *Nilaparvata lugens* [9][21]. Expression of some of these putative lectins was verified by quantitative real-time PCR [21]. In each of these insect genomes, about 7–40 putative CTLs have been identified and most contain a signal peptide, indicating these proteins are probably secreted extracellularly [9]. The majority of these CTLs have a single CRD, but *M. sexta*, *Helicoverpa armigera* and *Spodoptera litura* possess lectins with a dual-CRD structure (also named the immulectin family). The CTL domain can be linked to other functional domains (CTL-X) such as an epidermal-growth-factor-like domain (EGF) or a chitin-binding domain (CBM), which greatly increases the functional diversity

among CTLs [9]. Being the largest lectin family in insects, CTLs are involved in a broad range of processes, especially the immune responses (Table 1).

Malectin and calnexin/calreticulin are protein chaperones located in the ER (endoplasmic reticulum). During translation, an N-glycan precursor (Glc3Man9GlcNAc2) is attached to the newly synthesized polypeptide. The processing of the precursor glycan by glucosidases yields bi-, mono-, and non-glucosylated N-glycans, which creates signals for glycoprotein folding and quality control mediated by the chaperone lectins. Malectin binds to Glc2-N-glycans, whereas calnexin/calreticulin binds to Glc1-N-glycans [6][23][24]. Malectins in the invertebrate scallop *Chlamys farreri* and big-belly seahorse *Hippocampus abdominalis* are regulated by pathogen infection [25][26], suggesting their participation in immunity. Orthologs of malectins have been identified in *D. melanogaster* and *A. aegypti*, but have not been studied yet [27][28]. Calnexin/calreticulin chaperones have been identified in *B. mori* [29][30] and *D. melanogaster* [31][32]. In *Drosophila*, calnexin was reported to be related to neuron functions and sodium channel regulation [31][32].

F-type lectins (FTL) preferentially bind to fucose through a carbohydrate-binding domain composed of the HX(26)RXDX(4)R/K sequence motif [33][34]. The first FTL identified in insects was the lectin encoded by the *Drosophila furrowed* gene, and the furrowed protein is associated with a CTL domain and Sushi repeats [33][35][36]. *Drosophila* furrowed participates in planar cell polarity signaling and is crucial for cell adhesion [37]. The F-type lectin domain is also predicted in *Anopheles gambiae*, but its function has not been verified yet [35][36].

Chitinase-like proteins (CLPs) gained their name due to their chitin-binding ability. In contrast to chitinases, these proteins lack the enzymatic activity to digest chitin due to the absence of essential catalytic residues in the consensus motif [38]. In *Drosophila*, the most notable CLPs are the imaginal disc growth factors (IDGFs), composed of six glycoproteins which participate in cellular functions like proliferation, mobility, and immune recognition [38][39]. Sequences encoding CLPs have been predicted in at least in 10 insects including model insects like the red flour beetle, *T. castaneum*, *N. lugens*, and mosquito, *A. gambiae*; sequences encoding CLPs were predicted, but since the homology search is based on a motif of catalytic residues, some of these CLPs identified are actually true chitinases [40][41][42][43], which are normally not considered to be lectins [44][45].

L-type lectins are soluble ER luminal compounds which contain a CRD similar to those of leguminous plant lectins such as concanavalin A (Con A), and some L-type lectins are responsible for glycoprotein sorting and trafficking [20][46]. *Drosophila* has a homolog of ER–Golgi intermediate compartment 53 (ERGIC-53), a human L-type lectin responsible for cargo transport of glycoproteins [47][48], which may be related to the adhesion protein talin [49]. *B. mori* also has an ERGIC-53 homolog which responds to insecticide treatment [50]. The L-type lectin LvLTLC1 was reported to be upregulated after pathogen stimuli in shrimp [46], but this was not reported in insects.

Galectins or S-type lectins contain a CRD that specifically binds to β-galactosides [51], although other carbohydrate ligands have also been reported. For example, the galectin Agalectin from *A. gambiae* caused agglutination that was inhibited by gangliosides, sulfated polysaccharides, and sialic acid-containing glycans [52][53]. Galectins in human can be further classified into three major groups: prototypical galectins, chimeric lectins, and tandem-repeat

galectins, according to their CRD organization [54]. Many animal lectins are glycosylated, but the galectin family seems to be an exception [55][56]. Galectins have been reported in a few insects, including *D. melanogaster*, *A. gambiae, A. aegypti*, and the sand fly *Phlebotomus papatasi* [57][58][59][60][61]. Galectins expressed in the insect gut have been shown to participate in the neutralization of bacterial toxins [57][58].

I-type lectins belong to the immunoglobulin gene superfamily (IgSF). Hemolins, the well-studied I-type lectins of *D. melanogaster*, *S. exigua*, and *M. sexta*, recognize lipopolysaccharides, and their expression was shown to be induced after bacterial infection [62]. Further studies suggest that hemolin facilitates phagocytosis of bacteria and encapsulation of synthetic beads [62][63][64].

R-type lectins have a CRD similar to ricin, the toxic plant lectin from castor bean. Most R-type CRDs are ligated to other functional domains, including the CTL domain (mannose receptor family), pore-forming domain, and GalNAc-transferase domain. In the genome of *D. melanogaster*, 14 GalNAc-transferases have been identified containing R-type CRDs at their carboxy terminals. A QxW repeat in the CRD was supposed to be an important motif for carbohydrate binding [65][66].

Other lectin families common in animals, such as P-type and X-type lectins, are seldom identified in invertebrates [18] although previous searches in insect genome sequences predicted their existence [20].

Table 1. Overview of insect lectins.

Lectin Families	Insect Species	Gene/Protein [a]	Lectin Functions	Experiment Verification		Predicted by GO/Homology	References
				RNA [b]	Protein [c]		
CTL	*Aedes aegypti*	AaeCTLs; CTL-20; mosGCTL-7	Pathogen recognition; interacts with phosphatase; reduces exogenous toxin toxicity	+	+		[9][67][68][69]
	Tribolium castaneum	TcCTL6, TcCTL3	Responds to pathogen infection; regulates AMP expression		+		[70][71]
	Spodoptera litura	*SliCTLs*	Responds to pathogen infection	+			[21]
	Mythimna separata	EPL	Promotes encapsulation	+			[72]

Lectin Families	Insect Species	Gene/Protein [a]	Lectin Functions	Experiment Verification		Predicted by GO/Homology	References
				RNA [b]	Protein [c]		
	Ostrinia furnacalis	OfCTLs, OfIMLs		+			[73]
	Spodoptera exigua	Se-LLs, Se-BLLs	Responds to virus infection	+			[74]
	Thitarodes xiaojinensis	*CTL-S*, *CTL-X*, *IMLs*	Responds to pathogen infection	+			[75]
	Helicoverpa armigera	Ha-lectin, HaCTL	Regulates ecdysone and juvenile hormone signaling; regulates AMP expression; promotes phagocytosis		+		[76]
	Drosophila melanogaster	Slf, DL2-3	Organizes the cuticle layers; enhances encapsulation		+		[77][78]
	Antheraea pernyi	Ap-CT	Binds PAMPs; activates PO		+		
	Bombyx mori	BmIML, BmMBP, CTL-S3, BmEL-1, 2, 3	Recognizes PAMPs; activates PO; promotes melanization;		+		
	Hyphantria cunea	*Hdd15*		+			
	Periplaneta americana	LPS-BP	Responds to *E. coli*		+		
	Heliothis virescens	MBL			+		Reviewed by [9]
	Manduca sexta	MsIML-1, 2, 3, 4	Responds to pathogens; binds PAMPs; activates PO;		+		

Lectin Families	Insect Species	Gene/Protein [a]	Lectin Functions	Experiment Verification		Predicted by GO/Homology	References
				RNA [b]	Protein [c]		
			enhances encapsulation				
	Anopheles gambiae	AgamCTLs	Responds to pathogens				
	Nilaparvata lugens		n.d.				
	Plutella xylostella		n.d.				
	Apis mellifera		n.d.				
	Acyrthosiphon pisum		n.d.				
Chitinase like	*Acyrthosiphon pisum*	*AcypiCht1* (IDGF homologue)	Expresses in bacteriocyte and midgut	+			[41]
	Anopheles gambiae	*AgIDGF2*, *AgIDGF4*	Expresses in different developmental stages and tissues	+			[79]
	Bombyx mori	BmIDGF	Expresses in eggs, hemocytes, fat body, and silk gland		+		[80][81]
	Drosophila melanogaster	IDGF1-6	Participates in would healing and wing development	+	+		[38][39][82]
	Nilaparvata lugens	*NlIDGF*	Expresses in female reproductive organs and fat body	+			[42]
	Tribolium castaneum	*TcIDGF2, 4*	Acts in adult eclosion	+			[83]

Lectin Families	Insect Species	Gene/Protein [a]	Lectin Functions	Experiment Verification		Predicted by GO/Homology	References
				RNA [b]	Protein [c]		
	Plutella xylostella	*PxIDGF*	n.d.			+	[84]
	Manduca sexta	*MsIDGF1*	n.d.			+	[85]
	Bemisia tabaci	*BtIDGF1-3*	Highly abundant in adults	+			[86]
Galectin	*Drosophila melanogaster*	Dmgal	Expresses in hemocytes and in different developmental stages		+		[59][87]
	Phlebotomus papatasi	PpGalec	Strong expression in adult female; binds pathogen				[61]
	Anopheles gambiae	*Agalectin*, *GALE6-8*	Expresses in salivary gland; Responds to viral infection	+	+		[52][88]
	Bombyx mori	BmGalectin-4	Responds to bacteria in fertilized eggs; binds bacteria		+		[89]
	Aedes aegypti	galectin-6, galectin-14	Reduces exogenous toxin toxicity		+		[57][58]
	Anopheles darlingi		n.d.				
	Anopheles stephensi		n.d.				
	Culex quinquefasciatus		n.d.				
	Drosophila ananassae		n.d.				

Lectin Families	Insect Species	Gene/Protein [a]	Lectin Functions	Experiment Verification		Predicted by GO/Homology	References
				RNA [b]	Protein [c]		
	Drosophila mojavensis		n.d.				
	Drosophila pseudoobscura		n.d.				
	Drosophila virilis		n.d.			+	Predicted by [87]
	Drosophila willistoni		n.d.				
	Drosophila yakuba		n.d.				
	Glossina morsitans		n.d.				
	Malus domestica		n.d.				
malectin	*Aedes aegypti*		n.d.			+	[27][28]
	Drosophila melanogaster		n.d.			+	
Calnexin/calreticulin	*Bombyx mori*	Calr/Canx; BmCNX	Responds to ER stress	+	+		[30][90]
	Drosophila melanogaster	Cnx	Regulates the function of sodium channel paralytic		+		[32]
F-type lectin	*Drosophila melanogaster*	Furrowed	Functions in planar cell polarity		+		[37]
	Anopheles gambiae		n.d.				Reviewed by [36]
I-type (immuno-globulin fold)	*Drosophila melanogaster*	hemolin	n.d.		+		Reviewed by [91]
	Manduca sexta	HEM	Recognizes PAMPs; promotes nodulation,				[63]

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Lectin Families	Insect Species	Gene/Protein [a]	Lectin Functions	Experiment Verification		Predicted by GO/Homology	References
				RNA [b]	Protein [c]		
			hemocyte aggregation, and phagocytosis				
	Spodoptera exigua	*SeHem*	Acts as opsonin; regulates phagocytic activities and encapsulation	+			[62]
	Plodia interpunctella	PiHem	Function related to gut bacteria	+			[92]
	Bombyx mori	Hemolin	n.d.			+	[93]
	Actias selene	As-HEM	Mediates immune response		+		[94]
	Antheraea pernyi	Hemolin	Regulates innate immunity		+		[95]
L-type	*Drosophila melanogaster*	ERGIC-53 homolog	n.d.				[48], reviewed by [96]
	Bombyx mori	*ERGIC-53*	Responds to ER stress	+			[50]
R-type (ricin B type)	*Drosophila melanogaster*	lectin domain of GalNAc Transferase	Binds glycopeptides		+		[97], reviewed by [65]

[a] some publications have predicted lectins but did not assign names for these lectins; therefore, there are some blanks in the table. [b] RNA verification studies included RT-qPCR, dsRNA silencing, and transcriptome analysis. [c] Protein verification included immunoblotting, recombinant protein production, etc.

4. Endogenous Insect Lectins as Immune Modulators

4.1. Pathogen Recognition

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Before hemocytes can activate their immune responses, the pathogen or immune target must be recognized. During pathogen invasion, pathogen-associated molecular patterns (PAMPs) such as bacterial peptidoglycan or fungal β-1,3-glucan are recognized by specialized proteins called pattern-recognition receptors (PRRs) [98]. The Gram-negative binding proteins (GNBPs), and peptidoglycan-recognition proteins (PGRPs) are the two major PRR families. GNBPs mainly recognize fungal and Gram-negative bacterial PAMPs, while PGRPs mainly respond to Gram-positive bacteria [98]. Since many PAMPs are carbohydrate structures, lectins constitute important parts of the membrane-bound or extracellular PRRs of hosts.

Lectins have been reported to bind and aggregate pathogens such as bacteria because of their recognition of carbohydrate structures. CTLs of *H. armigera* and *M. sexta* were shown to bind various PAMPs, such as lipopolysaccharide (LPS), fungal glucan, and peptidoglycan, to activate the humoral and cellular immune defenses [9][76][99][100]. In *Drosophila*, CTLs such as DL2 and DL3 can either be secreted or bound to the plasma membranes of hemocytes, and they were shown to bind some Gram-negative bacteria and agglutinate them [15]. While many insect PRRs belong to the C-type lectin family, lectins from other families can also function as PRRs. For example, galectins have been reported to recognize and bind pathogen surface glycans [53]. The silkworm *B. mori* possesses a dual-CRD galectin which can bind a series of PAMPs, such as LPS, LTA (lipoteichoic acid), peptidoglycan, and laminarin, and was shown to agglutinate *E. coli*, *Staphylococcus aureus*, and *Bacillus subtilis* [89][101].

4.2. Lectin-Induced Cellular Immunity

4.2.1. Phagocytosis

Many hemocytes can engulf invading pathogens as well as dead cells or other entities in a process called phagocytosis [13][102]. Upstream events of phagocytosis include the recognition of the targets by the PRRs, which activates downstream events including receptor cross-linking, membrane remodeling, phagosome formation, and maturation, and finally phagosome fusion with the endosomes and lysosomes to kill the pathogens via the acidic environment, AMPs, digestive enzymes, etc. [103]. To increase the efficiency of phagocytosis, hemocytes sometimes rely on opsonins, molecules that can coat and aggregate pathogens such as bacteria and viruses to limit their mobility and promote recognition [103]. Lectins have been proven to stimulate phagocytosis by acting as PRRs to detect pathogens or as opsonins to attract the invaders. For example, rHa, a CTL lectin obtained from *H. armigera*, has two CRDs which are both required for lectin agglutination of rabbit erythrocytes, but any single domain is sufficient for aggregation of Gram-negative bacteria, Gram-positive bacteria, and fungi. Injection of rHa lectin together with *Bacillus thuringiensis* bacteria in insects efficiently decreased the *B. thuringiensis* number in vivo, and hemocytes of *H. armigera* engulfed more *B. thuringiensis* in the presence of rHa lectin [104]. CTL-mediated phagocytosis has also been observed in mammalians and shrimps [105][106]. Besides the CTLs, the I-type lectin hemolin SeHem from *S. exigua* also helped the host cells to eliminate bacteria by enhancing phagocytosis [62]. Galectins from crustaceans have been reported to enhance host phagocytosis [107], but there are no such reports for insect galectins.

4.2.2. Encapsulation

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4.3. Lectin-Induced AMP Expression

Besides the cellular response, the insect host can secrete a series of extracellular effector molecules that can kill foreign invaders. Among these effectors, AMPs are the major participants [118]. AMPs are positively charged small

peptides consisting of 15–45 amino acids, which can bind to the naturally negatively charged surface of microbes and lead to membrane rupture and cell lysis [119]. The healthy host cells are protected from AMP damage mainly by the cholesterol-rich plasma membrane which makes healthy cells positively charged to repulse cationic AMP attachment [119]. However, when host cells are not healthy, they can be attacked by the AMPs. In a study of *Drosophila* tumor genesis, tumor cells tended to have a negatively charged cell surface due to the phosphatidylserine turning inside out, allowing the AMP defensin to locate and attack these cells to limit the tumor growth [120].

Classification of AMPs can vary based on different criteria, such as the type of the target microbe (antifungal or anti-Gram-positive/negative-bacterial AMPs) or based on the pathway by which they are activated (such as Toll-regulated or Imd-regulated AMPs) [118]. However, neither classification system can perfectly group different AMPs. While AMPs like drosomycin (Drs) are highly specific against fungal infections, other AMPs have a broader pathogen specificity. For example, metchnikowin (Mtk) can target all three groups of pathogens mentioned above. In addition, AMP regulation can also be complex; for example, while Drs is regulated by the Toll pathway, many others, such as defensin (Def), are coregulated by both pathways [118][119].

The insect fat body around the body cavity is the major tissue secreting AMPs [121]. When stimulated by a pathogen, the AMP titers in the hemolymph can drastically increase within 30 min and the concentration can reach up to 300 μM (reviewed by [15]). In addition to the fat body cells, hemocytes can also produce AMPs. For example, isolated hemocytes from the blue blowfly, *Calliphora vicina*, showed the same ability to produce AMPs such as defensin, cecropin, diptericins, and proline-rich peptides [111]. *Drosophila* hemocyte-like S2 cells have also been shown to produce all kinds of AMPs upon stimulation by *E. coli* or other protein stimuli [112][122].

Insect lectin-mediated pathogen recognition can trigger the production of AMPs. Insect lectins are commonly coregulated with AMPs [123], but a recent study gave more direct evidence that the insect lectin can regulate AMPs. After silencing of HaCTL3, a CTL from *H. armigera* participating in larval development, the fat body expressed far less AMPs than in the control group. HaCTL3 was found to regulate different AMPs, including *lebocin*, *attacin*, *cecropin 1*, *pre-gloverin*, *pre-lebocin*, and *cecropin*, of which the antimicrobial activities were confirmed by in vitro assays. Even more interestingly, the upstream PRRs, including PGRPs, β-1,3-GRPs, and even a CTL4, were also downregulated, suggesting that lectin-regulated AMP production might be initiated by affecting upstream recognition events [76].

Within host immunity, insect lectins and AMPs can have complex interactions. Insect lectins can protect the beneficial host microbiome against the toxic effects of AMPs. For example, silencing of *A. aegypti* C-type lectins (mosGCTLs), which are coregulated with AMP through the Imd pathway, leads to failure of colonization and maintenance of the gut microbial flora [124]. In addition, AMP toxicity significantly decreased when bacteria were pre-coated by mosGCTLs, which blocked AMP deposition on the bacterial surface [124]. Viruses are also reported to use host lectins. The West Nile virus (WNV), a pathogen causing West Nile fever and transmitted by mosquitos, can stimulate expression of an *A. aegypti* C-type lectin, mosGCTL-1, which can strongly interact with a mosquito

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