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Helminth C-type Lectins and Host–Parasite Interactions

A. Loukas and R.M. Maizels

C-type lectins (C-TLs) are a family of carbohydrate-binding proteins intimately involved in diverse processes including vertebrate immune cell signalling and trafficking, activation of innate immunity in both vertebrates and invertebrates, and venom-induced haemostasis. Helminth C-TLs sharing sequence and structural similarity with mammalian immune cell lectins have recently been identified from nematode parasites, suggesting clear roles for these proteins at the host–parasite interface, notably in immune evasion. Here, Alex Loukas and Rick Maizels review the status of helminth lectin research and suggest ways in which parasitic worms might utilize C-TLs during their life history.

C-type or Ca^{2+}-dependent lectins (C-TLs)* are a family of animal lectins that bind carbohydrates in a Ca^{2+}-dependent fashion, ranging from simple monosaccharides to complex glycoconjugates[1]. The carbohydrate-recognition domain (CRD) of C-TLs comprises ≈110–130 amino acids and contains at least four perfectly conserved Cys residues that form intrachain disulphide bonds. C-TLs are usually multidomain proteins, the CRDs (of which there can be many in one protein) being accompanied by collagen-like, Cys-rich and/or transmembrane domains. In addition, many C-TLs are homomultimeric, maximizing their binding capacities for ligands. The CRDs of different C-TLs adopt a similar fold (Fig. 1), first characterized in the crystal structure of the archetypal C-TL, rat serum mannose-binding protein A (MBP-A)[2]. MBP-A is found in serum as a bouquet of trimers organized around a collagenous stalk[3]. In this milieu, it binds directly to bacterial and fungal cell surfaces and triggers the complement protein C1q in an antibody-independent manner[4]. Subsequently, co-crystallization of MBP-A and an oligomannose ligand identified the amino acids involved in ligating Ca^{2+} and saccharides[5]. This provided lectin biochemists with the opportunity to mutagenize residues that determine sugar specificity[6,7], leading to a comprehensive understanding of lectin–ligand interactions.

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*The term C-type lectin is usually abbreviated to CTL; however, this abbreviation is also widely used for cytotoxic T lymphocytes. We have therefore used C-TL to denote C-type lectin throughout this review.

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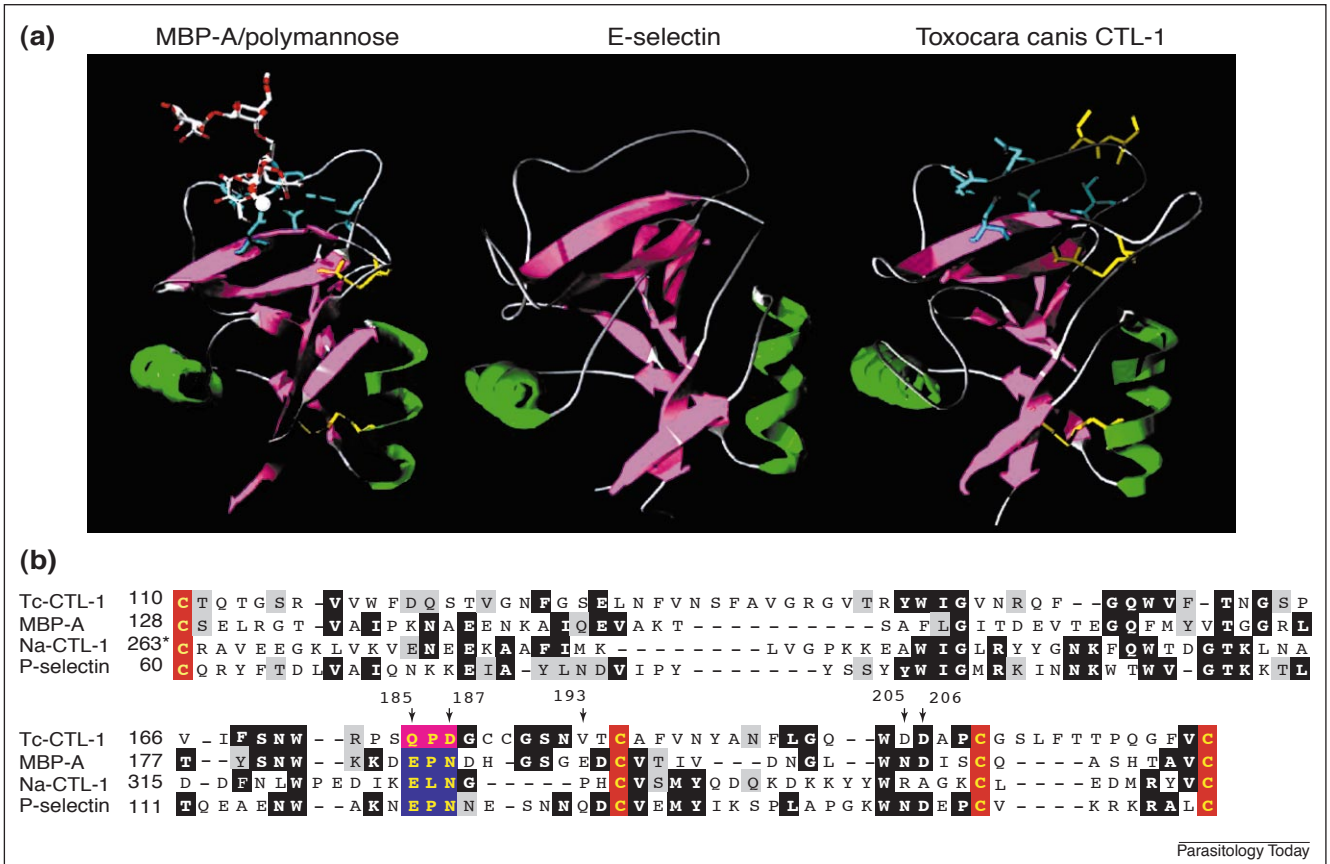

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Fig. 1. Ribbon diagrams show the remarkable conservation of structure between the carbohydrate recognition domains (CRDs) of rat mannose-binding protein A (MBP-A), human E-selectin and CTL-1 from *Toxocara canis* (a). Side chains of residues known to ligate the second Ca^{2+} ion (white sphere) and the polymannose ligand (red and white) in MBP-A are shown in blue and the four Cys residues that form disulphide bonds are in yellow; the homologous residues are highlighted in TES-32. The bonding status of the two unusual Cys residues in TES-32 is unknown and the side chains are therefore shown as free SH groups in yellow. Protein alignment of the CRDs of MBP-A, porcine P-selectin, *T. canis* CTL-1 and *Necator americanus* C-type lectin 1 (CTL-1) (b). Residues identical between any two sequences are contained in black boxes whereas conservative changes are in grey boxes. The four Cys residues that form disulphide bonds are shown in red boxes. The residues involved in determining specificity for mannose-type sugars are in blue boxes whereas those that determine galactose specificity are in pink. Arrows denote residues that ligate to Ca^{2+} and the saccharide ligand in MBP-A.

Box 1. C-type Lectins (C-TLs) Involved in Immunity

Collectins
Homo-oligomeric proteins comprising an N-terminal collagenous domain and C-terminal carbohydrate recognition domains. Members (mannose-binding protein A, pulmonary surfactant proteins) are involved in innate recognition of bacterial and viral pathogens[6,56].

Selectins
Cell adhesion molecules (E-, L-, P-selectin) involved in rolling and tethering of leukocytes to endothelial walls at sites of inflammation[7,8]. The three selectins bind related but distinct ligands, which are sialylated and/or sulphated derivatives of the Lewis^x and Lewis^a oligosaccharides, carried on glycoproteins or mucins such as cutaneous lymphocyte antigen (CLA) and mucosal addressin cell adhesion molecule (MAdCAM – for L-selectin) and P-selectin glycoprotein ligand 1 (PSGL-1).

Macrophage mannose receptor[9], DEC-205 (Ref. 57) and galactose-GalNAc receptor[58]
Surface receptors on macrophages and dendritic cells thought to bind pathogen glycans and mediate endocytosis and then direct their transport for presentation to T cells.

Natural killer (NK) cell receptors[a]
Integral membrane proteins (Ly-49, NKRP-1, CD94) on NK cells that engage major histocompatibility complex (MHC) class I molecules, inhibiting lysis of the target cell. On encountering a cell expressing aberrant class I (either altered self or foreign), a trigger is given to kill the target[10].

CD23[a]
Low-affinity receptor for IgE on haematopoietic cells; also interacts with β2 integrins on macrophages to induce production of proinflammatory mediators[11].

[a]These proteins possess a C-TL-like domain but key Ca^{2+}-binding residues are absent. The mechanisms of binding to ligands remain uncertain and might not be protein–carbohydrate mediated or Ca^{2+} dependent.

Table 1. Galectins (S-type lectins) from helminths[a,b]

Species	Gene	Accession no.	Length (aa/bp)	Most similar in *C. elegans*	Expressed by (stages)	Notes	Refs
Brugia malayi	–	AA727996	547 bp	LEC-2	L4	EST only	R. Sabarinathand, dbEST
	–	N43100	434 bp	LEC-5	L3	EST only	S. Williams, dbEST
Haemonchus contortus	*Hco-gal-1*	AF077944	278 aa	LEC-2	L3	–	18
	Hco-gal-2	AF036098	283 aa	W09H1.6b	11 day worms	–	G. Newlands, GenBank
Onchocerca volvulus	*Ov-GalBP*	U04046	280 aa	LEC-2	Adult	No Cys in sequence	16
	Ov-87	U96175	321 aa	LEC-5	L3		G. Joseph, GenBank
Strongyloides stercoralis	Galectin	N21792	360 bp	W09H1.6b	L3	EST only	59
Teladorsagia circumcincta[c]	*Tci-gal-1*	U67147, AF105337	278 aa	LEC-2	L3	–	17
	Tci-gal-2	U67148	278 aa	LEC-2		–	17
Trichostrongylus colubriformis	*Tco-gal-2*	AF077943	278 aa	LEC-2	L3	–	18
Caenorhabditis elegans	32 kDa β-galactoside-binding protein-1 (*lec-1*)	P36573, M94671	279 aa	–	Adult	No Cys in sequence, many ESTs	15
	F52H3.7 (*lec-2*)	Z66512	1262 or 278 aa[d]	–	Adult	25 ESTs	
	33 kDa β-galactoside binding protein-1 (*le33*); ZK892.1 (*lec-3*)	Z48638 Q09581	285 aa	–	Adult	6 ESTs	
	C44F1.3 (*lec-4*)	Z49067	283 aa	–	Adult	2 ESTs	
	ZK1248.16 (*lec-5*)	U29244	333 aa		Adult	No ESTs	
	W09H1.6b	Z82081	285 aa		Adult	No cys, 19 ESTs	

[a] Currently characterized galectin genes from nematodes are listed. All except *Caenorhabditis elegans* genes are derived from cDNAs representing transcribed genes; some have been designated *lec* genes (LEC proteins) in the WormPD database (http://www.proteome.com/databases/index.html). Many predicted *C. elegans* genes have corresponding cDNAs represented as expressed sequence tags (ESTs), as indicated in the table. Additional galectin-like genes are encoded in *C. elegans*; these include predicted genes R07B1.2, designated *lec-7* (accession number CAA88540), C16H3.2, designated *lec-9* (U67955 and AAB07585), F38A5.3 (U70854), W01A11.4 (U64852 and AAB04967) and ZC190.7 (AF078788).

[b] Abbreviations: dbEST, expressed sequence tag data base (http://www.ncbi.nlm.nih.gov/dbEST/index.html).

[c] *Teladorsagia circumcincta* is otherwise known as *Ostertagia circumcincta*.

[d] The GenBank entry assigns a 1262 aa protein by prediction of exon–intron boundaries from cosmid sequence. However, EST data indicate that the probable protein is 278 aa, starting at Met985 in the predicted sequence.

C-TLs in immunity

Many of the well-characterized C-TLs and C-TL-like proteins are cell surface receptors with pivotal roles in activation of the vertebrate immune system[1]. Well-known examples include collectins[6], selectins[7,8], the macrophage mannose receptor[9], natural killer (NK) cell receptors[10] and CD23 (the low-affinity IgE receptor)[11]. C-TLs are found on both effector cells and vascular endothelium, where they interact with their glycan ligands. Box 1 summarizes the major C-TLs involved in immune cell signalling and trafficking. Of the immune phenomena that are regulated by C-TL–glycoprotein interactions, selectin-mediated inflammation has received the most attention[7,8]. Selectins mediate the initial steps of adhesion, termed rolling, between leukocytes and the endothelial wall. L-selectin is prominent on the surface of lymphocytes and mediates their homing to lymph nodes. Conversely, both E- and P-selectin are found on the endothelial wall, where their expression is upregulated in response to tissue injury, and P-selectin is additionally expressed on platelets. E- and P-selectin then bind to defined glycoprotein ligands on circulating monocytes, neutrophils and T cells, initiating the leukocyte inflammatory process.

NK cell lectin-like receptors possess a domain with sequence similarity to functional CRDs of C-TLs. However, most of the residues that are crucial for binding Ca^{2+} and sugars are absent from these molecules[1], suggesting that they do not bind glycans in a C-TL-like manner. Although Ly-49A is a C-TL homologue on NK cells, it binds to a non-carbohydrate epitope on major histocompatibility complex (MHC) class I molecules[12]. Likewise, binding of CD23 to IgE might not involve protein–carbohydrate interactions, and some lecticans (proteoglycans with C-TL domains found in cartilage and neural tissues) bind to their ligands via protein–protein interactions[13]. Thus, the presence of a

Table 2. C-type lectins from helminths[a]

Species	Expression	Gene	Characteristics	Refs
Nematodes				
Ancylostoma ceylanicum	Adult	*Ac-ctl-1*	cDNA cloned; similar to CD23	[b]
Ascaris suum	Adult	*As-ctl-1*	EST with similarity to dendritic cell receptor DEC-205	[c]
Caenorhabditis elegans	Not known	Over 120 CTL-like	Predicted proteins from genome project	23
Haemonchus contortus	Adult intestinal RNA	*hcgls1C1.T3*	EST with similarity to lithostathine	[d]
Meloidogyne javanica	L2 surface	Not known	Ca^{2+}-dependent binding of neoglycoproteins	35
Necator americanus	Adult	*Na-ctl-1*	EST similar to P-selectin	34
		Na-ctl-2	EST	34
Other phytophagous spp[e]	Surface or head/tail	Not known	Ca^{2+}-dependent binding of red blood cells	36
Toxocara canis	Epicuticle, excretory/secretory products of infective larvae	*Tc-ctl-1*	Ca^{2+}-dependent binding to GalNAc and Man; 32 kDa surface and secreted protein	25
		Tc-ctl-2, *-3*	Sequence variants of Tc-CTL-1	31
		Tc-ctl-4	70 kDa surface and secreted protein, binds host cells	33
Platyhelminths				
Dugesia tigrina (free-living turbellarian)	Ubiquitous	*scarf*	Involved in body patterning	42
Schistosoma mansoni	Surface of schistosomula	Not known	Monoclonal antibody to E-selectin binds surface	47

[a] Helminths in which C-type lectin genes have been identified or C-type lectin-like activity has been identified by biochemical and immunological methods. For a list of helminth lectins and lectin-like activities, see http://www.natur.cuni.cz/~horak/lektin-rev.htm, constructed by P. Horák.
[b] L. Harrison, GenBank AF172652.
[c] J. Daub and M. Blaxter, Gen Bank AW165750.
[d] D. Jasmer, GenBank AI723481.
[e] Other phytophagous species include *Meloidogyne javanica*, *Heterodera avenae*, *H. schachtii*, *Pratylenchus mediterraneus*, *Rotylenchulus reniformis* and *Tylenchulus semipenetrans* (whole body surface); *Longidorus cohni*, *Xiphinema brevicolle* and *X. index* (head and tail only).

CRD-like domain might indicate an ancient common ancestor, but does not necessarily signify functional lectin activity as observed in true C-TLs[1].

Galectins (S-type lectins)

Galectins are a family of soluble lectins that have a specific affinity for β-galactoside sugars, with no sequence similarity to C-type lectins. Their mechanism of ligand binding is independent of divalent cations, although a free thiol group was thought to be necessary (hence the term S-type lectin). In mammals, the galectins include Mac-2, an IgE-binding protein expressed by macrophages and granulocytes[14]. Several nematode galectins have now been isolated (Table 1), including one from the free-living *Caenorhabditis elegans*, which has been verified as a functional β-galactoside-binding protein[15]. The *C. elegans* galectin, like the homologue from *Onchocerca volvulus*[16], contains no Cys residues, showing that at the very least, not all S-type lectins are thiol dependent. Homologues from gastrointestinal nematodes are particularly prominent[17,18], but the function of galectins in the host–parasite interaction has yet to be established. A range of possible roles, from cell–cell recognition to uptake of host glyconjugates, has recently been considered[19]. Curiously, the galectin family members are restricted to the β-galactoside specificity, which is likely to circumscribe the range of host glycoconjugated molecules with which these proteins can interact.

C-TLs of nematodes

Genes encoding C-TLs are widely represented among diverse invertebrate taxa, including arthropods and molluscs, in which they are produced in response to injury or infection[20–22]. The newly completed *C. elegans* genome sequence encodes more than 120 predicted proteins containing C-TL domains[23]. Until recently, C-type lectin cDNA sequences had not been reported from a pathogen of any phylum, although reports exist of Ca^{2+}-dependent lectin activity in protozoan organisms and bacteria[24].

Toxocara canis. Cloning and characterization of TES-32, the major secreted glycoprotein of the parasitic nematode *Toxocara canis*, revealed the first C-TL cDNA from a parasite[25]. Larval *T. canis* migrate through the visceral tissues of their definitive and paratenic hosts before entering a state of developmental arrest[26], in which they can survive for months or years without succumbing to immune destruction. This state of developmental arrest is akin to the dauer state of *C. elegans*, where worms temporarily suspend development during adverse conditions, such as overcrowding or the absence of food. While in this arrested state, *T. canis* larvae are metabolically active and, when cultured in serum-free medium[27], secrete a defined set of excretory-secretory (TES) antigens[28–30]. Not only is TES-32 the most prominent secreted protein, but its mRNA is among the most highly expressed of all. In an expressed sequence tag (EST) survey from a larval cDNA library, the mRNA encoding TES-32 accounted for 6% of all transcripts[31].

It is now established that TES-32 (Tc-CTL-1) contains a Cys-rich N-terminus and a C-terminal C-TL domain that shows sequence and structural similarity to host immune-related C-TLs such as macrophage mannose receptor, E-selectin and MBP-A[25] (Fig. 1). TES-32 is secreted in copious amounts into culture medium[28] and the protein has been localized to the epicuticle of larval *T. canis*[32]. Its route of secretion is thought to be transcuticular, but the mechanism involved is still

unknown. Two variants of *Tc-ctl-1* (*ctl-2* and *-3*) were also identified as ESTs, albeit at much lower frequencies[31]. A fourth cDNA, *Tc-ctl-4*, was recently determined to encode an additional secreted protein, TES-70 (Ref. 33). Tc-CTL-4 is notably different at the sequence level, with amino acid substitutions in positions that are crucial for determining ligand specificity[33]. Unlike TES-32, native TES-70 protein does not bind to simple monosaccharides[25], but it does bind to the surface of mammalian endothelial cells in a Ca^{2+}-dependent manner[33], suggesting that host glycans, possibly those involved in immunity, are ligands for these TES C-TLs.

Other nematodes. Although TES-32 was the first C-TL described from parasitic helminths, *T. canis* is by no means unique in expressing this family of proteins (Table 2). Two C-TL-encoding cDNAs have been identified recently from ESTs of the human hookworm *Necator americanus*[34], as has one from the rodent gastrointestinal parasite *Nippostrongylus brasiliensis* (Y. Harcus *et al.*, unpublished). Each of these proteins shows sequence similarities to host selectins, raising interesting questions about the role they might play in modulating inflammation in nematode infections. ESTs encoding C-TL-like proteins have more recently been identified from *Ancylostoma ceylanicum*, *Ascaris suum* and *Haemonchus contortus* (Table 2), adding to the growing number of nematode C-TL genes that share sequence similarity with mammalian immune cell lectins. Remarkably, none has been found among the >18 000 ESTs from the filarial nematode *Brugia malayi*. Thus, if ascarid and strongylid C-TLs act to downmodulate host inflammation, the filarial nematodes might have evolved an independent mechanism to achieve the same ends.

Ca^{2+}-dependent lectin-like activity is present on the surface of numerous plant nematodes, as shown by binding to both human red blood cells (RBCs) and gold-conjugated neoglycoproteins (carrier proteins such as bovine serum albumin containing artificially attached glycans)[35,36]. Phytophagous nematodes might utilize surface C-TLs to identify particular plants or plant tissues expressing defined glycans. In parallel, animal–parasitic nematodes that exhibit a tropism for certain tissues might use surface C-TLs to locate sites that uniquely express a particular glycan. Surface C-TLs might be involved in differentiating between host species, providing parasites with the necessary cues for continued development upon recognition of species-specific ligands.

With completion of the *C. elegans* genome sequence, it is now possible to enumerate the complement of C-TL-like genes in this free-living organism. Remarkably, the C-TL domain is the seventh most abundant protein signature found in the genome[23], less abundant than chemoreceptors and protein kinases, but at a level similar to zinc finger and RNA-recognizing proteins. Although this indicates a central role for C-TLs in *C. elegans* biology, it should be noted that many of these genes are quite distantly related to the C-TL profile and fewer than 20 have predicted functionality[37]. Moreover, few of the putative C-TLs are expressed at high levels; of the 120 or more C-TL-like genes, fewer than 25 have been shown to be expressed by EST analysis. In addition, phenotypic mutants have not been identified at any C-TL-like locus, and no gene product has yet been functionally confirmed as a carbohydrate-binding protein.

Although genes encoding C-TLs are abundant within the *C. elegans* genome, it is noteworthy that the *T. canis* and one of the *N. americanus* C-TLs (*Na*-CTL-1) share greater identity with mammalian C-TLs than any of the predicted *C. elegans* proteins. This divergence in sequence might be reflected in function, if parasite lectins act as receptors for host ligands. However, other C-TLs from nematodes, such as a second C-TL-encoding EST from *N. americanus*, *Na*-CTL-2, do appear to be much closer to homologues in *C. elegans*, suggesting that these proteins might fulfil other physiological functions not related to parasitism. If *Tc*-CTL-1 and *Na*-CTL-1 are involved in modulation of the host

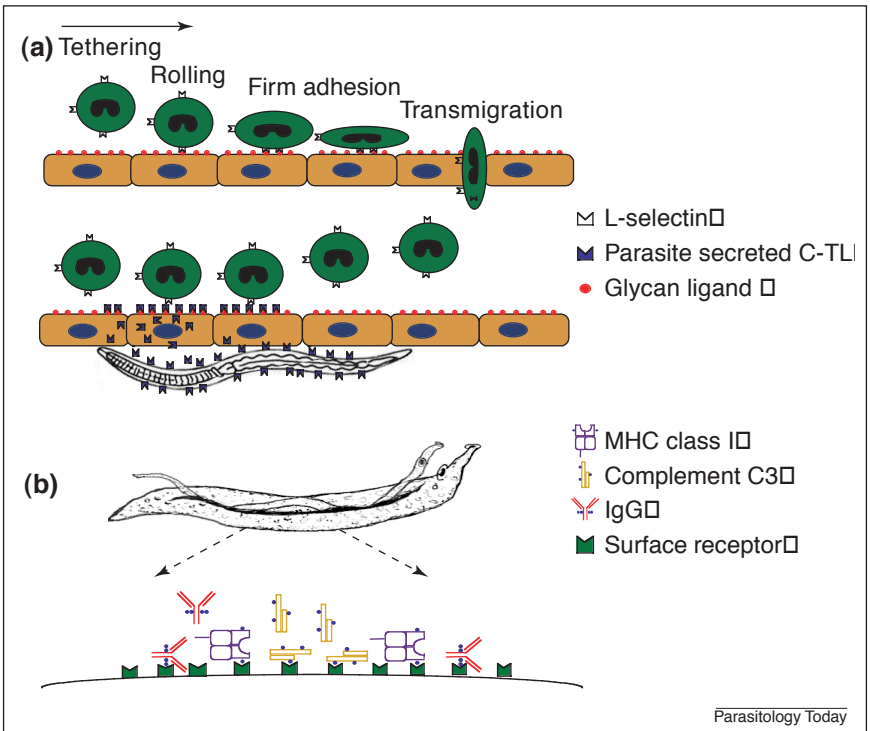

Fig. 2. Hypothetical roles for surface/secreted C-type lectins (C-TLs) of helminths. Schematic representation of how a secreted C-type lectin from a tissue-dwelling nematode might interfere with infiltration of leukocytes by competitively inhibiting selectin-mediated inflammation (a). The top diagram shows the processes involved in normal adhesion and infiltration of leukocytes into affected tissues; the lower diagram suggests a way that secreted nematode C-type lectins might bind to selectin ligands that are upregulated during tissue damage and thus inhibit binding of L-selectin on leukocytes. A hypothesis suggesting how surface C-type lectins of schistosomes might act as tegumental receptors for adsorption of host glycoproteins (b). Major histocompatibility complex (MHC) class I antigens, C3 and IgG are host glycoproteins that are adsorbed on to the tegument of larval and adult (not class I) *Schistosoma mansoni* to mask their foreign status. C-TLs might function as surface receptors for these glycoproteins *in vivo*. Blue spheres represent glycans on the host molecules.

immune response, and specifically bind mammalian glycoconjugate ligands, they might have evolved convergently in function and sequence to be closer to mammalian lectins than to those from their free-living relative.

Given that at least some parasitic nematodes secrete C-TLs that are exposed to host tissues, putative roles can be assigned to each protein when the sites of synthesis and release are determined. *Tc*-CTL-1 is secreted from the surface of arrested, tissue-dwelling *T. canis*[32], and one hypothesis for its role is interference with selectin-mediated inflammation[25]. Some *Toxocara* lectins bind to mammalian cells[33] and it is feasible that they might inhibit infiltration of leukocytes to sites of inflammation by binding to ligands expressing the sialyl-Lewis^x antigen required by immune cell C-TLs such as L-selectin (Fig. 2a). Haematophagous nematodes such as hookworms are often in intimate contact with the mucosa, and C-TLs secreted at the site of attachment might dampen the local immune response during feeding. Anticoagulation of host blood is another potential role for C-TLs secreted by blood-feeding nematodes. Snake venom contains C-TLs that inhibit clotting of blood by binding to factors IX/X of the clotting cascade in a Ca^{2+}-dependent manner[38–40], and blood-sucking arthropods as well as helminths might also use C-TLs in this manner.

Platyhelminth lectins

Among the parasitic platyhelminths, there is biochemical evidence for lectin expression in trematodes, although no genes have yet been identified, despite around 10 000 schistosome ESTs in the EST database[41]. One C-TL gene, *scarf*, associated with posterior body patterning and tissue regeneration has been cloned from the free-living turbellarian *Dugesia tigrina*[42]. The absence of prominent C-TLs from the blood-dwelling schistosomes and the filarial nematodes inhabiting lymphatic sites is striking, and indicates perhaps that helminth lectins function to protect parasites in tissue and gastrointestinal environments rather than in body fluids.

At the biochemical level, there is certainly good evidence for the presence of surface/secreted lectins at most stages of the schistosome life cycle. However, most experiments have not tested dependence on divalent cations, making it difficult to attribute lectin-like activites to a particular class of carbohydrate-binding protein. Thus, labelled neoglycoproteins bind the surface of *Schistosoma mansoni* sporocysts[19] and proteins secreted by *S. mansoni* larvae selectively bind to plasma components of the intermediate snail host *Biomphalaria glabrata*[43]. Conversely, immune recognition of schistosome larvae by molluscs is mediated by snail haemocyte surface lectins[44], and a cDNA encoding a haemocyte C-TL with similarity to selectins has recently been cloned from *B. glabrata*[45]. Lectin activity has been found on the surface and in the acetabular glands of cercariae of the avian schistosome *Trichobilharzia szidati*[46], the latter having specificity for tissue glycosaminoglycans, suggesting a role for this lectin in recognition and/or penetration of host connective tissues.

Expression of lectin-like activity in trematodes is not restricted to larvae. A monoclonal antibody to human E-selectin bound the surface of *S. mansoni* schistosomula and binding was inhibited in the presence of appropriate ligands for E-selectin[47]. This finding is particularly interesting given the ability of schistosomes to adsorb host molecules, such as antibodies and complement components[48] and MHC class I antigens, on to their surface[49] to avoid immune recognition. The mechanism by which schistosomes acquire host MHC peptides has never been determined, but it is interesting to recall that NK cells bind MHC class I by the surface C-TL-like proteins Ly-49 and CD94 (Ref. 10). Thus, the binding of MHC class I molecules by schistosomes might also be mediated by similar receptors (Fig. 2b).

C-TLs and T-helper cell responses

Host-derived C-TLs can selectively drive the immune response. At sites of tissue inflammation, P- and E-selectin bind to T-helper cell type 1 (Th1) and not to Th2 cells, imposing selective recruitment and thus skewing the type of T-helper response generated[50]. Surfactant protein A, which has a functional C-TL domain, inhibits macrophage release of proinflammatory cytokines such as tumour necrosis factor α (TNF-α) during fungal infection[51]. There is now a growing body of evidence to suggest that pathogens employ lectins selectively (and favourably) to drive the T-helper response of their hosts. For example, the surface lectin of the parasitic protozoan *Entamoeba histolytica* suppresses T-cell proliferation and promotes production of Th2 cytokines[52], two characteristic outcomes of infection with helminths[53]. Although the parasite molecules responsible for inducing these biases in helminth infections are unknown, *Toxocara* ES products contain potent Th2-stimulating antigens[54,55], for which C-TLs would now appear to be a prime candidate.

Conclusion

It is intriguing that helminth parasites secrete C-TLs with homology to host proteins that are instrumental in mounting a successful immune response against the very same pathogens. Although much is known about the role of mammalian C-TLs, little is known about parasite-derived lectins and what roles these proteins play in host–parasite interactions. From our knowledge of host lectins, it is tempting to speculate that surface/secreted parasite C-TLs are pivotal in immune evasion; however, other roles (such as identification and invasion of host tissues) must also be considered. Further research in this expanding field will increase our understanding of parasite lectins and their ligands, and provide clues for novel drug targets and vaccine development in control of these infectious agents.

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