REVIEW

Glycan gimmickry by parasitic helminths: A strategy for modulating the host immune response?

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Parasitic helminths (worms) co-evolved with vertebrate immune systems to enable long-term survival of worms in infected hosts. Among their survival strategies, worms use their glycans within glycoproteins and glycolipids, which are abundant on helminth surfaces and in their excretory/secretory products, to regulate and suppress host immune responses. Many helminths express unusual and antigenic (nonhost-like) glycans, including those containing polyfucose, tyvelose, terminal GalNAc, phosphorylcholine, methyl groups, and sugars in unusual linkages. In addition, some glycan antigens are expressed that share structural features with those in their intermediate and vertebrate hosts (host-like glycans), including Le^X (Galβ1-4[Fucα1-3]GlcNAc-), LDNF (GalNAcβ1-4[Fucα1-3]GlcNAc-), LDN (GalNAcβ1-4GlcNAc-), and Tn (GalNAcα1-O-Thr/Ser) antigens. The expression of host-like glycan determinants is remarkable and suggests that helminths may gain advantages by synthesizing such glycans. The expression of host-like glycans by parasites previously led to the concept of "molecular mimicry," in which molecules are either derived from the pathogen or acquired from the host to evade recognition by the host immune system. However, recent discoveries into the potential of host glycan-binding proteins (GBPs), such as C-type lectin receptors and galectins, to functionally interact with various host-like helminth glycans provide new insights. Host GBPs through their interactions with worm-derived glycans participate in shaping innate and adaptive immune responses upon infection. We thus propose an alternative concept termed "glycan gimmickry," which is defined as an active strategy of parasites to use their glycans to target GBPs within the host to promote their survival.

Keywords: C-type lectins/helminth glycans/immune modulation/parasitic helminth

Introduction

Nearly 4 billion people worldwide are infected or at risk for infections with parasitic helminths (worms), which results in tremendous health and economic problems (Hotez et al. 2007). The majority of the worm infections occur in (sub)tropical areas, where infected people generally cannot afford treatment. In the Western world, parasite infections are of increasing concern due to transmission of worm species from wild or domestic animals to humans (zoonoses), and the import of "tropical" diseases within infected immigrants or travelers coming from endemic areas. In addition, helminth infections are a major problem in ruminant production and welfare throughout the world and cause serious economic losses.

Helminths are soft-bodied, elongated invertebrate animals and include the phyla *Nemathelminthes* (roundworms) and *Platyhelminthes* (flatworms). They are multicellular organisms with an active metabolism. *Caenorhabditis elegans* is an example of a nonparasitic nematode in the phylum *Nemathelminthes*, whereas *Haemonchus contortus* is an example of a parasitic nematode in the phylum that infects sheep and goats. Parasitic helminths have a life cycle that may involve multiple hosts. In their vertebrate hosts, helminths develop from larvae to adult worms, often via different larval stages, thereby releasing large amounts of antigens in their environment, such as disposed surface layers, gut contents, and actively secreted antigens. In contrast to microbial antigens, adult worms are relatively large animals that cannot simply be removed via phagocytosis by the much smaller immune cells. During their development, helminths migrate through different tissues in the body to reach their final destination, and thus challenge the immune system to deal with a large variety of continuously changing antigens (Cummings and Turco 2009).

A hallmark of parasitic worms is their ability to survive within their hosts for long time periods through suppression of the host's immune system. Even though the infected hosts initially mount an inflammatory immune response to the invading pathogens, most helminths have the capacity to polarize the immune response toward a strong CD4$^+$ T-helper 2 (Th2) cell response and establish a chronic infection (Sher et al. 2003). More recently it has been shown that regulatory T cells (Tregs) play an important role (Van Riet et al. 2007; Hewitson et al. 2009). Tregs suppress inflammatory Th1/Th17 responses and pathology, while permitting a contained Th2 response. Interestingly, such responses are beneficial for both the host and the parasite; host pathology is reduced, and the parasites have a better chance to survive in such a "modified Th2" environment

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(Mckee and Pearce 2004; Taylor et al. 2006; Van Riet et al. 2007; Hewitson et al. 2009).

Understanding of the molecular basis of the host immunological responses, however, to parasitic helminths is still limited, which hampers the development of novel therapeutic approaches to combat helminth infections. The interaction of pathogens with dendritic cells (DCs) of mammalian hosts has received much attention, due to the insight that DCs play a key role in linking innate with adaptive immunity (Kapsenberg 2003; Steinman and Hemmi 2006). The unusual repertoire of glycans displayed by helminths has long been regarded as a potential mechanism to subvert recognition by the host immune system. Recent studies demonstrate, however, that the host-like glycan antigens expressed by many helminths are recognized by DCs via lectin receptors (Linehan et al. 2003; van Die et al. 2003; Meyer et al. 2005, 2007; Van Liempt et al. 2007). Several studies also show that recognition of pathogen-associated glycans by C-type lectins on DCs can interfere with the induction of effective immune reactions (Chieppa et al. 2003; Geijtenbeek et al. 2003; Bergman et al. 2004; Van Kooyk and Rabinovich 2008; Meyer-Wentrup et al. 2009). Therefore, helminths may have developed "glycan gimmickry" to target DCs, thereby contributing to the modulation of inflammatory T cell responses toward more anti-inflammatory responses. Glycan gimmickry can be regarded as an active strategy of helminths to use their glycans to target host GBPs to prolong their survival. In this review, we will give an overview of the host-like glycans occurring in different helminth species and discuss the possible immunological consequences of the interactions of these parasite glycans with DC receptors.

Dendritic cells orchestrate T cell responses during infection

Pathogens are recognized by many different immune cells, including macrophages and DCs, which are potent antigen-presenting cells (APCs). After antigen uptake, these APCs migrate to the lymph nodes to present antigens to naive T cells and induce their differentiation (Pozzi et al. 2005). The DC is the most important APC with respect to instructing naive T cells to polarize toward specific effector T cell subsets, which is essential for the induction of an effective adaptive immune response (Kapsenberg 2003). In a murine model of schistosomiasis, which is caused by the parasitic trematode *Schistosoma mansoni*, DCs alone were sufficient to induce schistosome-specific Th2 responses, illustrating the importance of DCs in this process (Macdonald et al. 2001). DCs are a heterogeneous group of cells including populations of nonlymphoid tissue migratory DCs, lymphoid tissue-resident DCs, and plasmacytoid DC (Ueno et al. 2007; Merad and Manz 2009). Distinct DC subsets vary with respect to their intrinsic T cell polarizing capacity and can also adapt their function in response to factors present in the local microenvironment such as cytokines (Pulendran et al. 1999). DCs not only play a key role in the orchestration of immune responses, but are also crucially involved in maintaining self-tolerance (Steinman et al. 2003). The balance between inducing pathogen-specific immunity and tolerance is controlled by a complex mechanism including many factors, but primarily guided by the antigens encountered by DCs in tissues (Kapsenberg 2003; Ueno et al. 2007; Merad and Manz 2009). For recognition of parasitic helminths, DCs that are present at environmental contact sites in the gut or skin, such as Langerhans cells and dermal and/or intestinal DCs, may play important roles.

Recognition of pathogens by cell-surface receptors on DC

To recognize a wide variety of pathogens, DCs are equipped with many different receptors such as Toll-like receptors (TLRs) and C-type lectin receptors (CLRs) (Akira et al. 2006; Diebold 2009). Recognition of a pathogen by DCs typically involves multiple receptor–ligand interactions, mediating intracellular signaling cascades leading to DC maturation, the release of cytokines, and the induction of a pathogen-specific T cell repertoire consisting of Th1, Th2, Th17, and/or regulatory T cells (Kapsenberg 2003; Medzhitov 2007). In general, recognition of "foreign" antigens is a danger signal that induces DC activation and maturation via TLRs, and the induction of pathogen-specific adaptive immune responses (Takeda and Akira 2005; O'Neill and Bowie 2007). Next to TLRs, CLRs are increasingly recognized as an important pathogen–receptor family. CLRs on DCs are transmembrane proteins that primarily recognize glycan moieties (Drickamer 1999; Figdor et al. 2002). The molecular mechanisms by which CLRs function are still poorly understood, but new studies are revealing remarkable insights into their functions. In myeloid cells, many CLRs function as endocytic receptors and play major roles in both innate and adaptive immunity. For example, endocytosis of glycoconjugate ligands by DEC-205 or DC-SIGN (CD209), which bear a triacidic internalization motif, results in efficient presentation of the antigens to major histocompatibility complex for presentation to T cells (Mahnke et al. 2000; Engering et al. 2002). Some CLRs can directly activate DCs by inducing signaling cascades and gene expression through immunoreceptor tyrosine-based activation motifs (ITAM). Activating receptors recognizing microorganisms, such as Dectin-1 which plays a role in anti-fungal immunity, can be defined as pattern recognition receptors (PRRs) (Herre et al. 2004). Several CLRs, such as DC-SIGN, can be involved in enhancing or suppressing of TLR signaling (Geijtenbeek and Gringhuis 2009). DCs express many different CLRs on their surface, which vary within distinct DC subsets. Here we have focused on the CLRs DC-SIGN, MGL and the MR, which are all expressed by DCs and shown to interact with host-like glycans of helminths.

DC-SIGN is highly expressed on DCs in lymph nodes and tonsils, as well as on dermal and intestinal DCs, but is absent on Langerhans cells. DC-SIGN typically recognizes glycans containing terminal fucose or mannose residues, such as Le^X (Galβ1-4[Fucα1-3]GlcNAc-), Le^Y (Fucα1-2Galβ1-4[Fucα1-3]GlcNAc-), LDNF (GalNAcβ1-4[Fucα1-3]GlcNAc-), and high-mannose-type *N*-glycans (Frison et al. 2003; Guo et al. 2004; Van Liempt et al. 2006). The macrophage galactose-type C-type lectin (MGL, CD301) recognizes glycans containing terminal α- and β-linked GalNAc residues, such as the LDN (GalNAcβ1-4GlcNAc-) and the Tn (GalNAcα1-*O*-Thr/Ser) antigens (Suzuki et al. 1996; Tsuiji et al. 2002; Van Vliet et al. 2005). Human MGL is exclusively expressed on myeloid APCs, on both DCs and macrophages, in the small intestine, lymph nodes, and skin (Van Vliet et al. 2008). The mannose receptor (MR, CD206) recognizes various mannose-containing glycans (Martinez-Pomares et al. 2001). It is thought that CLRs contribute to the immuno-regulatory role of DCs by acting independently or in concerted action with

TLRs and other receptors, thus participating in the induction of specific adaptive immune responses (Geijtenbeek et al. 2004).

Parasite glycans play a role in helminth-induced immune regulation

Helminths are masters in modulating the inflammatory responses of their hosts and typically cause attenuated Th1 responses and induction of Th2 and regulatory T cell populations, which favor survival of parasites in their host (Maizels et al. 2004; Thomas and Harn 2004; Van Riet et al. 2007; Hewitson et al. 2009). Whereas the network of host-parasite communication is enormously complex and involves a wide variety of immune cells and molecules, there is increasing evidence supporting a role for helminth glycans, such as Le^X, in regulation of the host immune shift toward a Th2 response, and possibly regulatory responses via induction of IL-10 (Okano et al. 1999, 2001; Faveeuw et al. 2003; Thomas and Harn 2004; Tawill et al. 2004; Hokke and Yazdanbakhsh 2005; Gomez-Garcia et al. 2006). It may be speculated that evolution has driven individual helminth species, which stand far apart phylogenetically, to acquire similar strategies to survive in their respective host species. One of the strategies employed may be the expression of parasite glycan antigens to actively target host lectins to modulate immune responses. Such use of glycans to target glycan-binding proteins, which we have termed glycan gimmickry, is an alternative approach to that of molecular mimicry, as originally postulated by Damian in 1965, where parasites exploit antigenic similarity as a mechanism to evade immune responses from their hosts (Damian 1965, 1997). The ability of helminths to bias immune responses toward Th2 responses and chronic infection may be as beneficial to the hosts as to the parasites, in that the infected hosts can use this response to survive the infection that cannot be cleared, whereas the parasite is dependent on the survival of the host.

Glycans expressed by parasitic helminths

Glycans are abundant on the surfaces of helminths and within their secreted antigens (Cummings and Nyame 1996; Khoo and Dell 2001). Like other animals, helminths have the capacity to synthesize N- and O-glycans, as well as glycolipids and polysaccharides/glycosaminoglycans. Whereas the basic glycosylation machinery among eukaryotes is quite similar, major differences are found in protein and glycolipid core structures and in the terminal modifications of the glycans. Many of the helminth glycans contain highly antigenic moieties that comprise either unusual (foreign) monosaccharides, or a foreign sequence or unusual linkage of common monosaccharides. In some cases, the immunogenic glycans appear to be restricted to one or a few species, such as the tyvelose-containing glycan antigens found within *Trichinella spiralis*, a zoonosis causing trichinellosis in humans (Reason et al. 1994), thus providing a useful serum diagnostic marker for detection of this parasite in infected hosts. Other immunogenic glycan modifications are shared by several helminths, and sometimes other organisms, such as the core α1-3-fucose moiety in N-glycans of different helminths, snails, and plants, causing cross-reactivity in serum diagnostics (van Die and Cummings 2006). Such immunogenic glycan antigens on

helminths or secreted products induce the generation of antiglycan antibody responses, which are dominant within many helminth-infected hosts (van Die and Cummings 2006). There is good evidence that humoral immunity can provide protection against infections by the parasitic trematodes in the *Schistosoma* genus, which suggests possibilities for future developments of glycan-based vaccines. For example, passive transfer of sera from *S. mansoni*-infected animals can provide partial protection (Moloney and Webbe 1990; Dunne et al., 1994; Dean et al. 1996; Fallon et al. 1996; Yole et al. 1996; Jankovic et al. 1999), and B cells are required for vaccine-induced immunity in rodents (Sher et al. 1982; Jankovic et al. 1999). Although antibodies may in principle provide protective immunity, heightened levels of antibodies are only produced several weeks after infection and coincide with egg laying, but by then the infection is established (Grzych et al. 1991). But such antibody responses upon egg laying are probably important for concomitant immunity, in which the infected animal is relatively resistant to further infections (Clegg et al. 1971) possibly due to the sensitivity of the schistosome larvae (schistosomula) to immune attack by antiglycan antibodies (Nyame et al. 2003).

In addition to immunogenic nonhost glycan antigens, many helminths express host-like glycan determinants (Cummings 2009); remarkably, these can also induce the production of antiglycan responses. The induction of antibodies that cross-react with host determinants may result from the "foreign" presentation of the host-like parasite glycan antigens, in that the antigens are often presented in highly multivalent forms, which may also be heightened by their linkage to immunogenic helminth proteins. The expression of host-like glycans by parasitic helminths is widespread, and different host-like glycans are found in a broad range of parasites. Terminal glycan structures shared by both host and parasite include Le^X, LDN, and LDNF, and the truncated O-glycans known as the T (Galβ1-3GalNAcα1-O-Thr/Ser) and Tn antigens, all glycan antigens that may interact with host lectins. In contrast to helminths where the expression of these antigens seems abundant, the expression of these glycans in mammalian hosts is restricted. In mammals, these glycan moieties are commonly capped by sialic acid, whereas helminth glycans, with perhaps some exceptions, do not contain sialic acid. Recent sequencing of the genomes of *Schistosoma mansoni* and *Schistosoma japonicum* shows that the organisms lack genes related to metabolism of sialic acid (Berriman et al. 2009; Liu et al. 2009). The occurrence and functional relevance of these host-like glycans in both host and helminths are discussed in the following sections.

Host-like glycans expressed by parasitic helminths

Le^X antigens are expressed within a few parasitic helminths

Species of the human trematode *Schistosoma*, such as *S. mansoni*, express Le^X antigens in all life stages (Nyame et al. 1998). These Le^X antigens are found on both glycoproteins and glycolipids, either on the surface of the helminth stages, or within secreted products such as the soluble egg antigens (SEA). Interestingly, the expression of Le^X moieties is poor in the molluscan stages of schistosomes (Nyame et al. 2002), and in cercariae (the infectious stage for humans which is released by the snails) Le^X expression is restricted to the oral sucker (Van Remoortere et al. 2000). After transformation of the cercariae to schistosomula
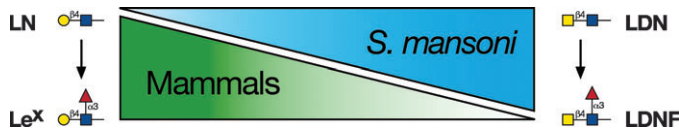
Fig. 1. Contrasting relationship between mammals and parasites such as *Schistosoma mansoni* in their expression of core glycan structures LacNAc versus LacdiNAc. Parasitic helminths, and especially *S. mansoni*, tend to highly express LDN and its fucosylated derivative LDNF, compared to mammals that more highly express LN-type glycans and the fucosylated derivative Le^X. Some helminths may be incapable of synthesizing LN and Le^X-type glycans and some mammals may be incapable of making LN and LDNF-type glycans.

shortly after invading the mammalian host, Le^X is found on the whole surface area of the larvae (Nyame et al. 2003). These data indicate that the synthesis of Le^X moieties in the helminths appears to be strongly upregulated during infection of the mammalian host, suggesting a biological relevance for the expression of this structure for the helminth. However, whether Le^X is upregulated as a result of infection or occurs independently of infection is not known.

The expression of Le^X antigens, however, is not a common property in helminths. In addition to schistosomes, Le^X moieties have been reported on bi-, tri-, and tetraantennary N-glycans of *Dictyocaulus viviparous*, a nematode that infects cattle and is the etiologic agent of bovine parasitic bronchitis (Haslam et al. 2000). However, many other parasites, including *H. contortus, Dirophilaria immitis*, or *Fasciola hepatica*, do not appear to express Le^X antigens based on probing with anti-Le^X antibodies (Nyame et al. 1998).

LDN and its fucosylated derivative, LDNF, commonly occur within parasitic helminths

Mammalian glycoproteins typically contain glycan structures based on the LacNAc (Galβ1-4GlcNAc-) core structure, which can be converted to Le^X by α1-3-fucosylation of the GlcNAc residue. By contrast, many invertebrates including helminths express instead the modified core structure LDN, which can be converted to its fucosylated derivative, LDNF (Van Den Eijnden et al. 1998) (Figure 1). In schistosomes, LDN and LDNF moieties are abundantly observed within different stages, along with the expression of Le^X antigens (Cummings and Nyame 1999; Hokke et al. 2007). In contrast to Le^X, LDN and LDNF are also found within different molluscan schistosomal stages (Nyame et al. 2002; Lehr et al. 2007; Peterson et al. 2009). In schistosomes, LDN and LDNF moieties are used as a backbone for further modifications, among others leading to several multifucosylated immunogenic structures that are found in egg and cercarial glycoproteins and glycolipids such as LDN-DF (GalNAcβ1-4[Fucα1-2Fucα1-3]GlcNAc-), or F-LDNF-DF (Fucα1-3GalNAcβ1-4[Fucα1-2Fucα1-3]GlcNAc-) (Khoo et al. 1995; Wuhrer et al. 2002; Jang-Lee et al. 2007), or repeats of LDN and LDNF as found on N-glycans of schistosomes (Wuhrer et al. 2006).

Many other trematode and nematode species express LDN and/or LDNF antigens. In *T. spiralis*, structural analysis by mass spectrometry identified N-glycans with multiantennary LDN structures modified with phosphorylcholine (PC) linked to either the GlcNAc or GalNAc residue of the LDN moiety (Morelle W, Haslam SM, Olivier V et al. 2000). In addition,

T. spiralis expresses tri- and tetraantennary N-glycans composed of LDNF antennae capped with a β3-linked tyvelose moiety (Wisnewski et al. 1993; Reason et al. 1994; Ellis et al. 1997). Also *D. viviparous* expresses LDN and LDNF moieties, although in limited amounts (Haslam et al. 2000). Probing with specific lectins and anti-glycan antibodies suggest that *D. immitis*, *F. hepatica*, and *H. contortus* also express LDN and/or LDNF antigens (Nyame et al. 1998; Vervelde et al. 2003; Geldhof et al. 2005).

Truncated O-glycans T and Tn antigen are commonly found in helminths

Several helminths have been reported to express Tn and T antigens, which are truncated mucin-type O-glycans. The larval stage of the tapeworm (cestode) *Echinococcus multilocularis* is surrounded by a tight laminated microfibrillar layer, which is in constant contact with host cells. This laminated layer is largely composed of O-glycans expressing Tn and T antigens, suggesting a role in host–pathogen interactions (Ingold et al. 2000). The Tn antigen, as well as the presence of enzymes involved in synthesis of the Tn antigen, has been reported in several other tapeworms, such as *Echinococcus granulosus* and *Mesocestoides vogae*, both zoonoses that can cause disease in humans (Alvarez Errico et al. 2001; Freire et al. 2003, 2004; Osinaga 2007; Medeiros et al. 2008). In patients with Cystic hydatid disease, caused by infection with *E. granulosus*, high levels of Tn antigen were reported to occur in serum samples (Alvarez Errico et al. 2001). In *M. vogae* the detection of both Tn and sialyl-Tn (NeuAcα2-6GalNAcα1-O-Thr/Ser) antigens has been reported. Whereas these antigens were detected in in vitro cultured parasites, which make it unlikely that they were host derived, the presence of sialyl-Tn is provocative and should still be proven biochemically since helminths are not known to express sialylated glycans. In addition to the above examples, Tn and/or T antigens have been observed in the cestodes *Taenia hydatigena* and *Mesocestoides corti*, within the trematodes *F. hepatica* (Freire et al. 2003) and *S. mansoni* (Cummings and Nyame 1999; Thors et al. 2006), as well as in some parasitic nematodes (*Nippostrongylus brasiliensis* and *Toxocara canis*) (Casaravilla et al. 2003). It is remarkable that the Tn and T antigens are so abundant in helminths. The Tn antigen is generated by the addition of a GalNAc residue to a serine or threonine of the polypeptide backbone by a UDP-N-acetyl-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase (ppGalNAc-T), as the initial step of O-glycan synthesis (Ten Hagen et al. 2003). The addition of a galactose in α1,3 linkage by the T-synthase results in formation of the T antigen (Ju et al. 2002), representing the core 1 structure, which normally forms the basis for further extension reactions by a variety of glycosyltransferases (Brockhausen 1999). In several human diseases, such as cancer, Tn syndrome (Ju and Cummings 2005) and IgA nephrophathy (Hiki et al. 2001), the appearance of the Tn antigen is well known and results from a lack of further extension of the O-glycan chains. In humans, the expression of the Tn antigen in several cases is due to loss of the mammalian T-synthase as a result of changes in expression or mutations in the gene encoding the molecular chaperone Cosmc, which is required for the expression of active T-synthase in vertebrates. The expression of the Tn antigen in invertebrates is more likely due to direct downregulation of the T-synthase(s) since invertebrates do express Cosmc and some,

such as *D. melanogaster,* have multiple types of T-synthases (Muller et al. 2005; Ju et al. 2006).

High- and oligomannose-type N-glycans (Man$_{5-9}$GlcNAc$_2$) within helminths

In mammals, the *N*-glycosylation pathway typically results in complex-type glycans, and the occurrence of high-mannose and oligomannose-type *N*-glycans on mature glycoprotein is limited and usually takes place only at specific glycosylation sites on fully folded glycoproteins that lack accessibility to processing enzymes in the ER/Golgi. However, within most pathogenic helminths, these immature *N*-glycans (Man$_{5-9}$GlcNAc$_2$) are frequently reported. They have been demonstrated in the parasitic nematodes *H. contortus, Onchocerca vulvolus, O. gibsoni, Acanthocheilonema vitae*, *Ascaris suum, T. spiralis* and *D. viviparous* (Haslam et al. 1996, 1997, 1999, 2000; Morelle W, Haslam SM, Morris HR et al. 2000; Poltl et al. 2007). High- and oligomannose-type *N*-glycans have also been reported in trematodes. Egg glycoproteins and adult worms of *S. mansoni* and *S. japonicum* carry a range of high-mannose-type and truncated oligomannosidic-type *N*-glycans (Khoo KH, Chatterjee D et al. 1997; Cummings and Nyame 1999). The latter truncated structures are also found to carry "foreign" modifications to the core, mainly α1-3-fucose or β1-2-xylose similar to those found on insects and plants (Lerouge et al. 1998; van Die et al. 1999; van Die and Cummings 2006). The *N*-glycans of cestodes are less well defined. Hydatid cysts of *E. granulosus* contain a small proportion of high-mannose-type *N*-glycan structures and truncated di- and trimannosyl core structures (Khoo et al. 1997). In addition, high-mannose-type glycans may also occur in *Taenia solium* metacestodes, as was deduced approaches of lectin-affinity and enzymatic deglycosylation (Restrepo et al. 2000). In summary, the presence of high- and oligomannose-type *N*-glycans appears to be a common feature in helminths, especially within nematodes.

Functional consequences of glycan–lectin interactions in the immune system

CLRs appear to recognize a variety of glycan antigens, ranging from host-like to non-host glycans. For example, DC-SIGN recognizes the glycan ligands Le^X, LDNF, and high-mannose-type *N*-glycans, which occur on both host and helminth-derived glycoconjugates, as well as pseudo-Le^Y (Fucα1-3Galβ1-4[Fucα1-3]GlcNAc-) and ManLam (a mycobacterial glycan), which are typical pathogen-specific glycan antigens (Geijtenbeek et al. 2003; Meyer et al. 2005; Van Liempt et al. 2006) (Figure 2). It should be noted though that these data are derived from in vitro studies, and it is not known whether all these different interactions play a role in vivo. It is interesting to consider the question of whether specific CLRs are primarily important in host–pathogen interactions and recognition of nonhost compounds such as allergens, or whether their primary role is to contribute to maintaining homeostasis of the immune system in the absence of foreign antigens. It is noteworthy that several glycan ligands that are recognized by the CLRs DC-SIGN and MGL are abundantly expressed by helminths (host-like glycans), but have a relatively restricted expression pattern in the host.

Host functions mediated by the interaction of host glycans with CLRs on DC

In the host, the restricted expression of glycan antigens such as Le^X (CD15) may enable CLRs to mediate highly specific interactions, which may be functionally relevant. For example, the Le^X antigen is a minor epitope on many types of cells, including human tumor cells, epithelial cells, and erythrocytes where it is often found as a glycolipid (Gooi et al. 1981; Hakomori et al. 1981; Knowles et al. 1982; Howie et al. 1984; Feizi 1985; Croce et al. 2007), but is more abundantly expressed in human blood leukocytes on glycoproteins and glycolipids (Urdal et al. 1983; Fukuda et al. 1985; Bogoevska et al. 2007) and in certain tissues such as kidney and brain (Gocht et al. 1996; Kudo et al. 1998; Ohtani et al. 1991). There is little information as yet for an in vivo function of Le^X in humans, although there are many examples of biological functions for its sialylated form, sialyl-Le^X (NeuAcα1-3Galβ1-4[Fucα1-3]GlcNAc-) (Rosen and Bertozzi 1994; Sperandio 2006). It should be noted that the Le^X structure is not a precursor to forming the functional sialyl-Le^X determinant recognized by selectins and other adhesion molecules in mammalian systems. In vitro studies indicate that Le^X moieties expressed on CEACAM1 of neutrophils interact with DC-SIGN on DCs (Van Gisbergen et al. 2005; Bogoevska et al. 2006). This interaction enables neutrophils to modulate T cell responses through interactions with DCs (Van Gisbergen et al. 2005). In addition, DC-SIGN binds ICAM-3 isolated from peripheral human leukocytes through Le^X residues, suggesting a role in interactions with DCs (Bogoevska et al. 2007). DC-SIGN may also be involved in migration of DCs over the endothelium via interactions with the related Le^Y determinant (Garcia-Vallejo et al. 2008). The C-type lectin hMGL recognizes LDN and LDNF (Van Vliet et al. 2005), glycan antigens that have been identified in glycoconjugates from cultured human cells (Van Den Eijnden et al. 1997); however, these antigens do not appear to be widely expressed in human tissues. LDN, for example, has been detected on pituitary hormones and tissue factor pathway inhibitor (TFPI) (Green et al. 1985; Smith et al. 1992; Manzella et al. 1995), but those LDN structures are typically capped by sulfate. In glycodelin-A, a glycoprotein in amniotic fluid carrying the LDN antigen, the LDN is at least partly capped by sialic acid (Dell et al. 1995). The Tn antigen is also a ligand for hMGL (Van Vliet et al. 2005). The Tn antigen is rarely seen in human or murine glycoconjugates, but it is commonly expressed in human and animal tumors (Springer 1984; Ju et al. 2008), and in certain human autoimmune diseases, such as Tn syndrome (Berger 1999). Recent studies indicate that MGL is involved in downregulation of effector T cell function by the interaction with glycan antigens on CD45, which may possibly be Tn antigens (Van Vliet et al. 2006). The disaccharide T (or TF) antigen, which may be recognized by certain galectins, is also not abundant in normal tissues and its biological function is unclear, but it is found in thymocytes where its expression may be important for differentiation (Gillespie et al. 1993; Balcan et al. 2008).

Host-like glycans of pathogens target CLRs on DC to suppress immune responses

The mechanisms by which parasite glycans are involved in modulating immune responses through specific recognition by cellular receptors are largely unclear. Since the primary receptors
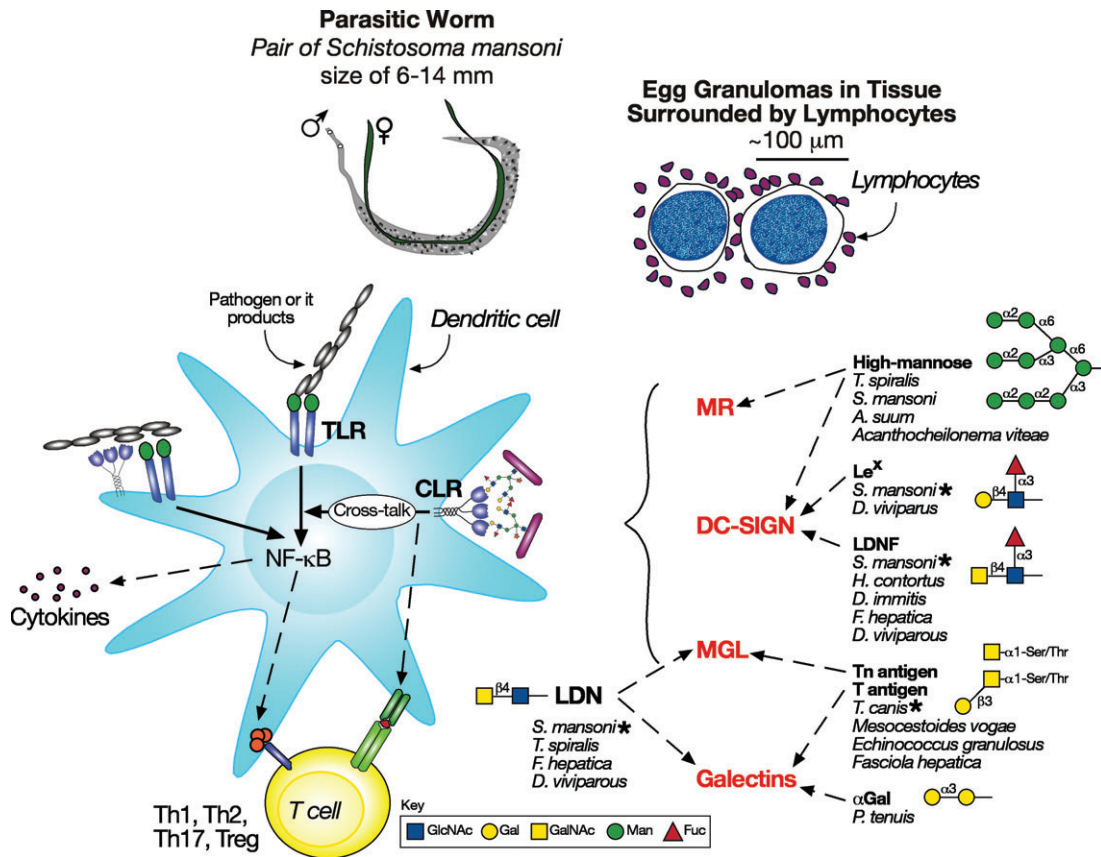
Fig. 2. Dendritic cells (DC) capture pathogens and control T cell responses. Immature DC express receptors (CLRs, TLRs) to capture pathogens. CLRs are efficient in internalization of microbial pathogens or their products, and in the presentation on MHC Class II molecules. DCs mature upon TLR signaling to activate T cells. Cross-talk between TLRs and CLRs, either on the cell surface, or intracellular, determines the final pathogen-specific T cell response (Th1, Th2, Th17, or Treg). Many helminth express glycan antigens that are putative ligands for lectins, such as DC-SIGN, MR or MGL, as indicated. Asterisks (*) indicate cases where the respective helminth–glycan–lectin interaction has been demonstrated.

for helminth glycans are glycan-binding proteins, such as the CLRs expressed by DCs, it is likely that they play a role in immune modulation (Figure 2). DC-SIGN recognizes a wide variety of pathogens, and may be a key player in the inter-action of different helminths with DCs. Within schistosomes, Le^X antigens are abundantly expressed and are reported to con-tribute to the immunomodulating properties of schistosomes (Srivatsan et al. 1992; Van Remoortere et al. 2000; Okano et al. 2001; Thomas and Harn 2004). DC-SIGN recognizes Le^X, but also LDNF and pseudo-Le^Y, a glycan antigen that has thus far been found only on schistosomal cercariae (Wuhrer et al. 2000; Meyer et al. 2005). Human DCs bind to and internalize *S. mansoni* soluble egg antigens (SEA) via interaction with the MGL, the MR, and DC-SIGN, thereby inducing a DC pheno-type capable of skewing toward Th2 responses (Van Liempt et al. 2007). The individual roles of these CLRs in schistosome Th2-skewing, however, have not been demonstrated. Mice express seven paralogs of human DC-SIGN, and one of these termed SIGNR, also binds Lewis-related antigens, such as Le^X and Le^y (Galustian et al. 2004; Koppel et al. 2005). Although SIGNR has not been reported to be expressed in DCs, it is expressed by macrophages of the spleen, lymph nodes, and peritoneum. Interestingly, SIGNR1-deficient mice have normal responses to infection with *S. mansoni*, including granuloma formation and immune responses to egg antigens (Saunders et al. 2009). Such results indicate that SIGNR receptor function may be redundant or that it is not important for immune responses to schistosome antigens.

An immunomodulatory role for DC-SIGN has been demon-strated for *Helicobacter pylori*, a bacterial human pathogen that causes chronic infection. In elegant studies using *Helicobacter* phase variants, which differ in their expression of Lewis glycan antigens, it was shown that *H. pylori* variants, which bind DC-SIGN, block skewing of naive CD4+ T cells toward Th1 cells, whereas non-DC-SIGN-binding *H. pylori* variants promote de-velopment into Th1 cells (Bergman et al. 2004). The interaction of DC-SIGN via mannose-based structures can also lead to sup-pression of DC-mediated immune responses, as is illustrated by *M. tuberculosis*, which binds DC-SIGN via mannose-capped lipoarabinomannan (LAM) (Geijtenbeek et al. 2003). Remark-ably, the immunodeficiency virus HIV1 targets DC-SIGN to be internalized in DC and transported to T cell-rich areas, to efficiently infect T cells (Geijtenbeek et al. 2003). It has been proposed that the carbohydrate domain of DC-SIGN is flexi-ble and allows binding of either mannose-containing structures, Le^X, LDNF or pseudo-Le^Y via different binding modes (Guo et al. 2004; Meyer et al. 2005). Although still hypothetical, it is conceivable that DC-SIGN induces different signaling pathways as a consequence of these different binding modes. Furthermore, data thus far suggest that signaling via DC-SIGN is dependent

on TLR activation, and the type of TLR and possibly other receptors may determine the exact function of DC-SIGN (Geijtenbeek and Gringhuis 2009). Nagaoka et al. (2005) showed that targeting the DC-SIGN mouse homolog SIGNR1 can enhance the TLR4 response induced by *Escherichia coli*. Furthermore, we recently showed that schistosome worm glycolipids induce activation of TLR4 via a mechanism that requires binding to DC-SIGN (Van Stijn et al., in preparation), indicating that DC-SIGN can also have an activating function. These data illustrate that targeting CLRs such as DC-SIGN and SIGNR1 is not sufficient for immune escape, and pathogens may have to target combinations of receptors to escape host immune responses.

MGL is another CLR that potentially can interact with many helminths expressing host-like glycan antigens. Human MGL has a strong preference for terminal α- or β-linked GalNAc, such as present on the helminth-associated glycan antigens LDN and Tn (Figure 2). We showed that MGL binds soluble egg antigens of *S. mansoni* (Van Vliet et al. 2005), *T. canis* ES (TES) (Schabussova et al. 2007), and distinct glycoproteins from several other helminths (unpublished data). The immunological role of MGL is still largely unclear, and MGL has not yet been shown to have signaling functions (Van Vliet et al. 2008). Murine MGL2, which resembles human MGL (Suzuki et al. 1996; Tsuiji et al. 2002), appears upregulated on macrophages in infection with *Taenia crassiceps* (Raes et al. 2005), suggesting a role for MGL in host–parasite interactions. Interestingly, MGL binds to MUC1, a well-known tumor antigen, which correlates with binding of the lectin *Helix pomatia* agglutinin (HPA). This lectin, like MGL, can bind the Tn antigen (Napoletano et al. 2007; Saeland et al. 2007). Since HP-reactivity of tumor tissue is associated with poor prognosis in cancer (Brooks 2000), it may be speculated that targeting MGL may promote tumor survival. Strategies to target DC-SIGN and possibly MGL may, therefore, be advantageous for pathogens, and can be regarded as an active immune escape mechanism or glycan gimmickry, which the pathogens acquired during co-evolution with their host (Van Kooyk et al. 2004). The abundance of host-like glycans on parasitic helminths that can target the CLRs DC-SIGN and MGL on DCs suggests that parasitic helminths in particular have mastered the strategy of glycan gimmickry as an active mechanism to target these CLRs of the hosts DCs, to promote their survival.

Helminth host-like glycans interact with soluble galectins to modulate immune functions

In addition to CLRs on antigen-presenting cells, helminth host-like glycans can interact with extracellular soluble lectins that play a role in immune regulation. An example is seen in the β-galactoside-recognizing family of lectins known as galectins. Many helminth glycans display terminal galactose, such as Galα1-3Galβ1-4GlcNAc-R (*Parelaphostrongylus tenuis*) (Duffy et al. 2006), Galα1-3GalNAc-R (*H. contortus*) (Van Stijn et al. 2009), or *O*-glycan core 1 (Galβ1-3GalNAcα1-Ser/Thr), T antigens), which may interact with host galectins. Helminth LDN glycans have been demonstrated to interact with galectin-3 (Van Den Berg et al. 2004). In a murine model, LDN antigens showed the capacity to induce the Th2-associated formation of liver granulomas (Van De Vijver et al. 2006), possibly via interaction with the soluble lectin galectin-3 which appeared

to be highly upregulated in granulomas. The recent observation that galectin-3 knock-out mice show a decreased granuloma formation supports these in vitro observations (Breuilh et al. 2007; Oliveira et al. 2007). While the growing evidence is compelling, clearly much more work needs to be done in animal systems to better understand the specific functions of galectins and other glycan-binding proteins in immune modulation by parasites.

Conclusions

The expression of both host-like and nonhost-like glycan antigens, as a form of molecular mimicry or glycan gimmickry, as we have defined it here, is an interesting property that allows parasites to target CLRs on host cells or interact with immunomodulating soluble lectins such as galectins. This may contribute to the parasite's ability to shift the host immune response from an inflammatory toward a more anti-inflammatory type of response. In this way, pathogens can guide the immune system to create a safer environment for them by limiting immune attack (Van Kooyk et al. 2004). Yet, many novel glycan structures remain to be identified in parasitic helminths, and their bioactivity and factors regulating their expression within the host need to be explored further. Dissecting the molecular mechanisms of host–helminth interactions and the signaling pathways induced by lectins is essential to fully understand the molecular basis for glycan gimmickry that contributes to the control of the delicate balance between immune activation and immune escape in helminth infections. In addition, targeting the biosynthesis of the unusual glycans in parasitic helminths may provide new treatments and preventatives for these infections.

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Conflict of interest statement

None declared.

Abbreviations

CLR, C-type lectin receptors; CRD, carbohydrate recognition domain; DC, dendritic cell; DC-SIGN, dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin; LDN, LacdiNAc GalNAcβ1-4GlcNAc; LDNF, GalNAcβ1-4(Fucα1-3)GlcNAc; Le^x, Galβ1-4(Fucα1-3)GlcNAc; LN, *N*-acetyllactosamine Galβ1-4GlcNAc; MGL, macrophage Galactose lectin; MR, mannose receptor; T antigen, Galβ1-3GalNAcα1-*O*-Thr/Ser; Th, T helper cell; TLR, Toll-like receptors; Tn antigen, GalNAcα1-*O*-Thr/Ser.

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