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Novel insights into the immunomodulatory role of the dendritic cell and macrophage-expressed C-type lectin MGL

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ABSTRACT

Based on their ability to balance tolerance and inflammation, antigen presenting cells, such as dendritic cells and macrophages contribute to the maintenance of immune homeostasis as well as the instigation of immune activation. Acting as key sensors of tissue integrity and pathogen invasion, they are well equipped with a wide variety of pattern recognition receptors, to which the C-type lectin family also belongs. C-type lectins are glycan-binding receptors that mediate cell–cell communication and pathogen recognition, besides participating in the endocytosis of antigens for presentation to T cells and the fine-tuning of immune responses. Here we review the current state-of-the-art on the dendritic cell and macrophage-expressed C-type lectin macrophage galactose-type lectin (MGL), highlighting the binding specificities, signaling properties and modulation of innate and adaptive immunity by its human and murine orthologues.

Macrophage galactose-type lectin: carbohydrate specificity and ligands

The C-type lectin receptor (CLR) family consists of a variety of transmembrane and soluble receptors that recognize glycan structures in a Ca^{2+}-dependent manner through a common carbohydrate recognition domain. CLRs have been implicated in the clearance of circulating glycoproteins; however within the immune system the membrane-associated CLRs mediate cell-cell interactions as well as pathogen recognition. On dendritic cells (DCs) and macrophages, CLRs facilitate uptake of antigens for antigen presentation, whereby certain family members actively modulate subsequent immune responses (Sancho et al. 2012). One of the CLRs exclusively expressed by DCs and macrophages is the macrophage galactose-type lectin (MGL, also known as CLEC10A, DC-ASGPR or CD301).

Within the CLR family, MGL is unique as it is the only CLR within the human immune system that exclusively recognizes terminal N-acetylgalactosamine (GalNAc) residues, including the sialylated and non-sialylated Tn antigen (αGalNAc-Ser/Thr) and the LacdiNAc epitope (GalNAcβ1-4GlcNAc) (van Vliet et al. 2005; Iida et al. 1999; Mortezai et al. 2013). This glycan specificity of human MGL is shared by the mouse MGL2 protein, which additionally binds terminal galactose moieties (Tsuiji et al. 2002; Singh et al. 2009). In contrast, the mouse MGL1 orthologue has an exclusive specificity for the Lewis X (Galβ1–4(Fucα1–3)GlcNAc) and to a lesser extent the Lewis A (Galβ1–3(Fucα1–4)GlcNAc) structure. This differential ligand binding can be explained by secondary binding sites present in the carbohydrate recognition domains of MGL1 and MGL2 (Oo-Puthinan et al. 2008; Sakakura et al. 2008) and is also reflected by a divergence in function between MGL1 and MGL2 (see below).

The Tn antigen is a relatively rare sugar within the healthy body and is normally elongated to longer *O*-glycan structures. Therefore, human MGL only interacts with a limited amount of self-ligands, namely CD45 on effector T cells (van Vliet et al. 2006a) and some unidentified ligand on sinusoidal and lymphatic endothelial cells of lymph node and thymus (van Vliet et al. 2008). Even though the carbohydrate specificity of mouse MGL1 is different compared to human MGL, it also recognizes an unidentified ligand on high endothelial venules in the lymph node (Singh et al. 2009). In addition, MGL1 has been shown to interact with apoptotic cells (Yuita et al. 2005) and the sialic acid-specific Siglec-1 receptor (Kumamoto et al. 2004). The MGL1 ligands on apoptotic cells and in the lymph node are not shared by MGL2, which does specifically recognize glycans present in murine skin (Singh et al. 2009).

Abbreviations: CLR, C-type lectin receptor; DC, dendritic cell; dDC, dermal dendritic cell; GalNAc, N-acetylgalactosamine; KO, knockout; MAG, multiple antigenic peptides; MGL, macrophage galactose-type lectin; OVA, ovalbumin; PSA, prostate-specific antigen.

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Table 1
Summary of human and murine MGL homologues and their ligands.

Species	Orthologue (alternative names)	Carbohydrate specificity	Expression pattern	Ligands
Human	MGL (CD301, CLEC10A, DC-ASGPR)	Terminal α- and β-GalNAc (Tn antigen, LacdiNAc), sialyl-Tn	Immature and tolerogenic DCs, macrophages, dermal CD1a$^+$ DCs, blood CD1c$^+$ myeloid DCs[a]	*Self*: CD45 (effector T cells), lymphatic endothelial cells (unidentified ligand) *Altered self*: tumor-derived MUC1 and MUC2 *Pathogens*: *Neisseria gonorrhoeae*, *Campylobacter jejuni*, Ebola virus, *Schistosoma mansoni, Trichuris suis*
Mice	MGL1	Lewis X, Lewis A	F4/80$^+$ macrophages, inflammatory monocytes and (CD8α$^-$) conventional and plasmacytoid DCs	*Self*: Sialoadhsion/Siglec-1, high endothelial venules in lymph node, apoptotic cells *Pathogens*: commensal *Streptoccocus* and *Lactobacillus* species, Influenza virus, *Taenia crassiceps*
Mice	MGL2	Terminal galactose and GalNAc (Tn antigen, TF antigen, Gb4)	Dermal DCs and CD8α$^-$CD4$^+$ DCs in lymph node, spleen and lung	*Self*: unidentified ligand(s) in skin *Altered self*: tumor-derived Tn-containing glycoproteins

[a] Human MGL is not expressed by plasmacytoid DCs (van Vliet et al. 2006b).

During oncogenic transformation and progression to cancer, Tn antigens are unveiled and therefore highly abundant on cancers especially of epithelial origin. Based on their preference of Tn antigens, both human MGL and MGL2, but not MGL1, selectively recognize tumor-derived mucin proteins, such as tumor-derived MUC1 and MUC2 (Saeland et al. 2007; Singh et al. 2009; Saeland et al. 2012; Nollau et al. 2013). Our latest data indicates that patients with advanced stage colon cancer that carry high levels of MGL binding glycans have a significantly worse disease-free survival, indicating that anti-tumor immunity could be influenced by the MGL-Tn antigen interaction (S. van Vliet personal, unpublished data).

In addition to its ability to recognize tumor cells, MGL acts as a pattern recognition receptor. Yet, compared to other well-known CLRs and based on the rarity of the GalNAc sugar on pathogenic structures, the human MGL homologue only interacts with a limited array of pathogens. Bacteria that bind human MGL through their GalNAc-terminated lipopolysaccharide (LPS) and/or glycoproteins, include *Neisseria gonorrhoeae* (van Vliet et al. 2009) and *Campylobacter jejuni* (van Sorge et al. 2009). Recently, expression of MGL on mouse mast cells was reported to mediate binding to the gram-negative coccobacillus *Bordetella pertussis*, however due to the use of a dual-specific antibody this interaction could not be attributed to either MGL1 or MGL2 (Vukman et al. 2013). Furthermore, human MGL enhances the infectivity of Ebola virus through the interaction with the viral envelope protein GP2 (Takada et al. 2004). MGL1 acts as attachment and entry receptor for influenza virus, independent of sialic acid expression which mediates influenza infectivity *via* the interaction with the viral hemagglutinin (Upham et al. 2010; Ng et al. 2014). Lastly, the parasites *Schistosoma mansoni* (Meevissen et al. 2012; van Liempt et al. 2007) and *Trichuris suis* (Klaver et al. 2013) interact with human MGL through the presence of (fucosylated) LacdiNAc and terminal α-GalNAc residues respectively. The helminth *Taenia crassiceps* is recognized by mouse MGL1 (Terrazas et al. 2013). MGL-specific binding to fungi has not been described so far. An overview of the carbohydrate specificity and ligands recognized by the different MGL orthologues is given in Table 1.

Modulation of innate and adaptive immunity by MGL

Over the past years some intriguing aspects of the MGL-mediated immunomodulation have become apparent. MGL is expressed *in vivo* on both human DCs and macrophages in the so-called barrier tissues and tissue draining lymph nodes, blood CD1c$^+$ mDCs and *in vitro* on monocyte-derived DCs (moDCs) (van Vliet et al. 2006a; Schutz and Hackstein 2014). When moDCs are generated under tolerizing conditions, for instance through incubation with dexamethasone, MGL expression is further enhanced (van Vliet et al. 2006b). These tolerogenic DCs are able to dampen effector T cell responses in a MGL-dependent manner (van Vliet et al. 2006a). Human T cell activation is accompanied by a dramatic change in cell surface glycosylation and the appearance of Tn antigens exclusively on CD45 of effector T cells (van Vliet et al. 2013b). These Tn-glycoforms of CD45 are specifically recognized by MGL (van Vliet et al. 2006a). The interaction between CD45-Tn antigens on effector T cells and MGL on the tolerogenic DC decreases the phosphatase activity of CD45, thereby reducing T cell proliferation and inflammatory cytokine production that ultimately lead to T cell apoptosis. A similar MGL-mediated suppression of T cell immunity has not yet been reported to exist in mice. Nevertheless, MGL1 knockout (KO) mice possess slightly higher levels of antigen-experienced T cells in the blood (data available on the website of the Society for Functional Glycomics, www.functionalglycomics.org), suggesting that this function may be conserved between human MGL and MGL1. In addition, MGL may be involved in the retention of immature DCs, as DC migration and trafficking was improved when MGL binding was blocked using a blocking antibody (van Vliet et al. 2008).

Strikingly, the murine homologues MGL1 and MGL2 possess non-redundant functions, as MGL1 KO mice display some unique features, even when MGL2 is still expressed. This functional divergence could be related to their respective expression profiles, whereby MGL1 is widely expressed on F4/80$^+$ macrophages, plasmacytoid DCs, several conventional DC subsets and inflammatory monocytes (Westcott et al. 2009; Denda-Nagai et al. 2010). In contrast, under homeostatic conditions MGL2 expression is specific for DCs present in the subepithelial layers of mucosal organs and the skin (Denda-Nagai et al. 2010; Kumamoto et al. 2009, 2013). CD8$^-$ conventional DCs in the lung and to a lesser extent in the spleen carry both the MGL1 and MGL2 receptors (Denda-Nagai et al. 2010). However, during parasitic infections or under allergic airway inflammation MGL1 and MGL2 expression can be induced on alternatively activated (M2) macrophages (Raes et al. 2005).

MGL1 KO mice are more susceptible to dextran sulfate sodium salt-induced colitis, showing significantly more inflammation compared to wild type littermates, which could be attributed to diminished IL-10 secretion by macrophages in the colonic lamina propria (Saba et al. 2009). IL-10 production was elicited by commensal *Streptococcus* species through their interaction with MGL1$^+$ colonic macrophages and absent in the MGL1 KO mice. These findings are consistent with the seminal paper of Kuhn et al. that demonstrated that IL-10 deficient mice develop colitis