Chapter 11
MGL/CD301 as a Unique C-Type Lectin Expressed on Dendritic Cells and Macrophages

Kaori Denda-Nagai and Tatsuro Irimura

Abstract Macrophage (MØ) galactose-type calcium-type lectin, MGL, also termed CD301 or Clec10A, is a type 2 transmembrane glycoprotein having a calcium-dependent carbohydrate recognition domain. Orthologous genes seem to be present throughout the vertebrates, and the lectin binds galactose and *N*-acetylgalactosamine among monosaccharides. Although mammalian MGL resembles the hepatic asialoglycoprotein receptor in its structure and its carbohydrate specificity, the cellular distribution of MGL is limited to specific subsets of dendritic cells (DCs) and MØs. Mouse MGL2, apparently the direct counterpart of human MGL, strongly binds clusters of carbohydrate chains with terminal *N*-acetylgalactosamine residues, a molecular feature characteristic to mucins. MGL was also shown to recognize carbohydrate chains from exogenous organisms. Comparisons of various oligosaccharides for their binding and identification of ligands/counter receptors by biochemical means strongly suggest that the important structural features recognized by MGL depend on the biological context. It is also likely that MGL functions on DCs to recognize and distinguish the self, altered self, pathogens, and commensal organisms, and that the regulatory outcomes depend on the unique nature of the DC/MØ subsets. Mice lacking the *Mgl1* or *Mgl2* gene do not show any abnormality as long as they are maintained under a controlled environment. However, upon encountering a pathogenic insult, they show a variety of outcomes depending on the organ sites and the type of the insult. Further investigations are necessary to explore how endogenous ligand/counter receptors are involved in the regulation of immunological and inflammatory responses by MGL.

Keywords MGL (CD301) • Calcium-type lectin • Dendritic cells • Macrophages • Tissue inflammation • Carbohydrate ligands

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11.1 Introduction: History and Facts on MGL/CD301

First reports on the presence of a C-type lectin on macrophages (MØs) that has specificity toward galactose and related monosaccharides appeared in the early 1980s (Imamura et al. 1984). Purification of the protein and subsequent molecular cloning from rats (Ii et al. 1988, 1990), mice (Sato et al. 1992; Oda et al. 1988), and humans (Suzuki et al. 1996) in the 1980s and 1990s revealed a lectin having a very similar structure to that of the hepatic C-type lectin, asialoglycoprotein receptor. Despite the subsequent discovery of a variety of C-type lectins in the immune system, its galactose-type specificity and the presence of a corresponding recognition motif at its carbohydrate recognition domain make this lectin distinct from others. The name MGL represents MØ galactose-type lectin.

MGL2, which shows strong homology to MGL1, was later found in mice (Tsuiji et al. 2002). Humans have a single MGL which apparently is more similar in its sequence, carbohydrate specificity, and expression profile to MGL2 than to MGL1, posing an unsolved question as to what kind of molecules cover the role of MGL1 in humans. MGL orthologues appear to be present in all vertebrates, suggesting that the molecule is evolutionally linked to the acquired immune system. MGL genes are located near the hepatic asialoglycoprotein receptor gene on chromosome 17 in humans and 6 in mice.

MGL in humans, MGL 1 and 2 in mice, and MGL in rats are type 2 transmembrane proteins with a ~M_r of 42 kDa. They have a *C*-terminal extracellular carbohydrate recognition domain, a stem domain responsible for multimer formation, a transmembrane domain, and a cytoplasmic *N*-terminal domain. They appear to form multimers, most likely trimers, and were shown to be present on the surfaces of activated or inflammatory MØs and on bone marrow-derived immature dendritic cells (DCs). A human MGL-specific antibody was used to define this molecule as CD301 and to show that it serves as a marker for myeloid DCs (Zola et al. 2005; Sano et al. 2007). CD301 expression is almost exclusive to MØs and DCs, with the only apparent exception being an expression on chondrocytes in embryonic mice as shown by the binding of a monoclonal antibody cross-reactive to MGL1 and MGL2 (Mizuochi et al. 1997, 1998). Antibodies specific for human MGL, mouse MGL1, or mouse MGL2 were generated and characterized for their specificity and other properties (Kimura et al. 1995; Denda-Nagai et al. 2010). In addition, knockout mice were prepared and backcrossed to C57BL/6 and BALB/c. Although they did not show any abnormality in their embryonic development, growth, behavior, or aging under controlled environmental conditions, they responded differently from wild-type mice upon the placement of a pathological insult. These observations are briefly described in the following chapters. For a summary of the milestones in the studies of MGL/CD301, refer to Table 11.1.

Table 11.1 Milestones in the studies on MGL/CD301

Year	Milestone	Reference
1984	Osawa's laboratory found Ca^{2+}-dependent carbohydrate-binding activity on activated MØs	Imamura et al. (1984)
1988	Galactose-binding lectin was purified from MØs of mice and rats	Oda 1988, Ii et al. (1988)
1990	cDNA cloning of the lectin later called MGL was done	Ii et al. (1990), Sato et al. (1992)
1995	Specific mAbs for mouse and human MGL were prepared	Kimura et al. (1995), Sano et al. (2007)
1996	Human MGL was identified and cloned	Suzuki et al. (1996)
1997	Tissue distribution of MGL^+ cells was determined in mice	Mizuochi et al. (1997, 1998)
2002	The second MGL, MGL2, was found in mice	Tsuiji et al. (2002)
2002	*Mgl1*−/− mice were generated	Onami et al. (2002)
2002	MGL was found highly expressed on DCs	Denda-Nagai et al. (2002), Higashi et al. (2002)
2005	Human MGL was assigned as CD301 and became a marker for myeloid DCs	Zola et al. (2005)
2010	MGL2-specific mAb and *Mgl2*−/− mice were prepared	Denda-Nagai et al. (2010)
2013	$MGL2^+$ DC subset was found to promote Th2 response	Murakami et al. (2013); Kumamoto et al. (2013); Gao et al. (2013)

11.2 Carbohydrate Specificity and Ligands/Counter Receptors for MGL/CD301

It is important to keep in mind that the structural characteristics of ligands and counter receptors for MGL depend on the biological context. Considering that MGL orthologues are membrane-associated lectins exclusively expressed on MØs and DCs, i.e., cells specialized in surveying altered self and exogenous substances and organisms, MGL seemed to have evolved to recognize endogenous glycans and glycans from the outer milieu. This type of cellular distribution presents a strong contrast to the distribution of galectins (S-type lectins), which are expressed intracellularly and extracellularly by a variety of cells. Even though the monosaccharide and oligosaccharide specificity of some galectins and MGL may be similar, MGL is likely to perform functions associated with the initiation of immune and inflammatory processes. MGL is a family member of C-type lectins, which recognize saccharides in a Ca^{2+}-dependent manner. Most other C-type lectins are categorized as being either "mannose-specific" or "a protein having a C-type lectin fold but no carbohydrate ligands identified." Therefore, MGL and hepatic asialoglycoprotein receptors, which recognize galactose and *N*-acetylgalactosamine as a monosaccharide, were categorized into a unique and distinct category (Drickamer 1993).

Oligosaccharide specificity of recombinant mouse MGL1 and MGL2 as well as human MGL have been investigated by several methods employing defined

collections of purified oligosaccharides. The most comprehensive comparison of K_D values was performed by frontal affinity chromatography, and the results corresponded well with fragmentary data from previous work (Suzuki et al. 1996; Tsuiji et al. 2002; Oo-Puthinan et al. 2008; Yamamoto et al. 1994). MGL1 has high affinity with oligosaccharides containing a terminal Gal-(Fuc-)GlcNAc, i.e., Lewis^X (Le^X) structure. MGL2 preferentially binds oligosaccharides with a terminal GalNAc residue (Fig. 11.1a). Our previous reports also indicated that MGL2 and human MGL preferentially bind clusters of *O*-linked GalNAc, i.e., Tn antigen and the cluster effect, is more prominent with the oligomeric form of intact MGL than with monomeric carbohydrate recognition domain of MGL (Fig. 11.1b) (Iida et al. 1999). Human MGL seems to have an affinity for sialylated Tn antigen, but MGL2 does not, making a slight distinction.

Important amino acid residues responsible for the differential specificity between MGL1 and MGL2 were investigated using pair-wise site-directed mutagenesis in the recombinant carbohydrate recognition domain (CRD) of MGL1 and MGL2 followed by the use of soluble polyacrylamide conjugated with either Le^X oligosaccharides or GalNAc (Oo-Puthinan et al. 2008). Mutation of Ala-89 to Arg and Thr -111 to Ser of MGL1 CRD caused significant reductions in Le^X binding. Significant increase in GalNAc binding was observed by single mutation of Ala-89 to Arg of MGL1. Likewise, mutation of Arg-89 to Ala and Ser-111 to Thr of MGL2 CRD resulted in the loss of β-GalNAc binding. MGL2 assumed Le^X binding by mutation of Arg-89 to Ala (Fig. 11.1c). Molecular modeling illustrated the potential for direct molecular interactions of Leu-61, Arg-89, and His-109 in MGL2 CRD with β-GalNAc (Fig. 11.1d).

To identify the Le^X-binding site on MGL1, a saturation transfer experiment for the MGL1-Le^X complex was carried out (Sakakura et al. 2008). To obtain sugar moiety-specific information on the interface between MGL1 and the Le^X trisaccharide, saturation transfer experiments where each of galactose-H5-, fucose-CH3-, and *N*-acetylglucosamine-CH3-selective saturations was applied to the MGL1-Le^X complex were performed. Based on the results, we proposed a Le^X-binding mode on MGL1 where the galactose moiety was bound to the primary sugar-binding site, including Asp-94, Trp-96, and Asp-118, and the fucose moiety interacted with the secondary sugar binding site, including Ala-89 and Thr-111. Ala-89 and Thr-111 in MGL1 are replaced with arginine and serine in MGL2, respectively. The hydrophobic environment formed by the small side chain of Ala-89 and the methyl group of Thr-111 seemed to be a requisite for the accommodation of the fucose moiety of the Le^X trisaccharide within the sugar-binding site of MGL1.

Cell surface lectins could potentially function as an uptake receptor (known for asialoglycoprotein receptor), as a regulator of cellular trafficking (known for selectins), or as a signaling molecule (according to recent reports). MGL could serve these functions for MØs and DCs. As described in the following sections, we have identified the cells expressing MGL1 and MGL2 in the skin and found that they migrate to regional lymph nodes (LNs) upon antigenic and other stimuli (Chun et al. 2000). The route of migration of these cells within the LNs, i.e., from subcapsular sinus to T cell areas, appeared to be unique. Thus, we assumed that

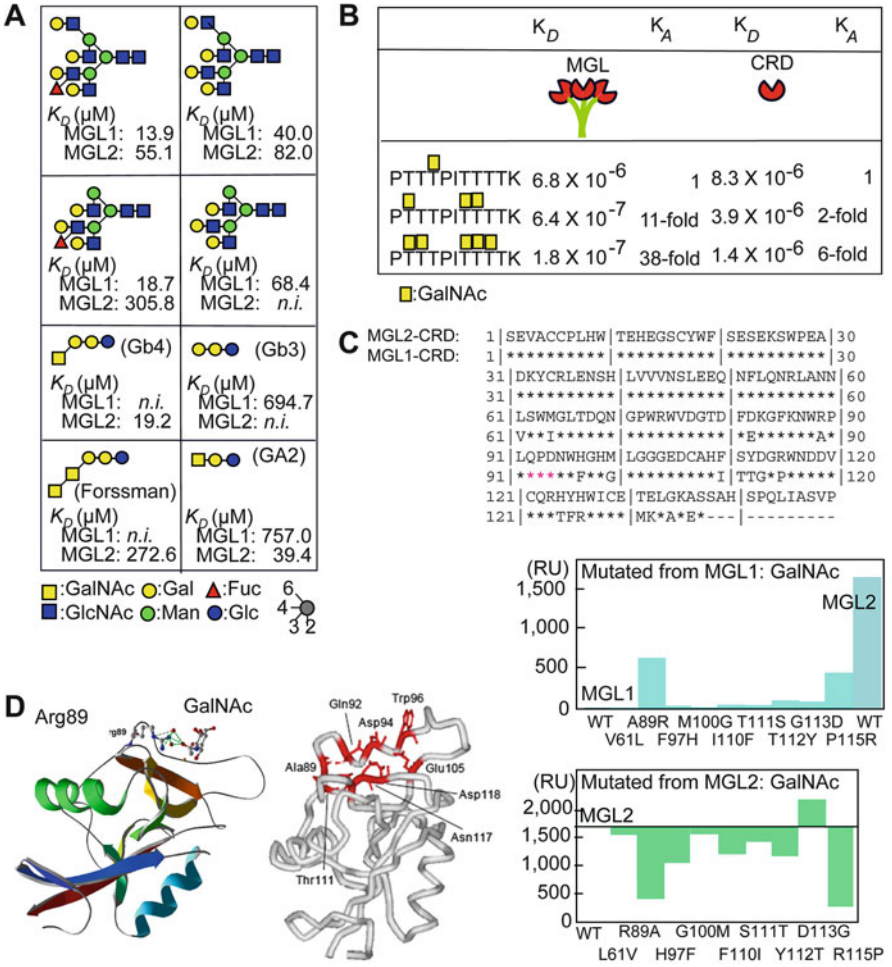

Fig. 11.1 Structural model and carbohydrate specificity of MGL1 and MGL2. (**a**) Oligosaccharide specificities of MGL1 and MGL2 analyzed by frontal affinity chromatography. A smaller K_D value indicates a higher affinity. (**b**) Cluster effects of GalNAc observed in human MGL. Human MGL interacting with Tn-bearing glycopeptides representing a sequence within the tandem repeats of MUC2. The cluster effect was more prominent with the oligomeric form of MGL. (**c**) *Upper panel*: Amino acid sequence of MGL1 and MGL2 CRD. *Two lower panels*: The binding of chimeric MGL1 and MGL2 CRD to GalNAc-polyacrylamide polymers based on the surface plasmon resonance data. Significant increase in GalNAc binding was observed by single mutation of Ala-89 to Arg of MGL1. Likewise, mutation of Arg-89 to Ala of MGL2 CRD resulted in the loss of GalNAc binding. (**d**) Predicted molecular interactions between MGL2 and GalNAc by the molecular modeling technique. These figures have been adapted from a previously published version (Oo-Puthinan et al. 2008)

counter receptors for MGL1 or MGL2 existed within LNs. By the use of affinity chromatography with immobilized MGL1, a few predominant proteins were purified from the lysates of LNs (Kumamoto et al. 2004). Mass spectroscopic analysis

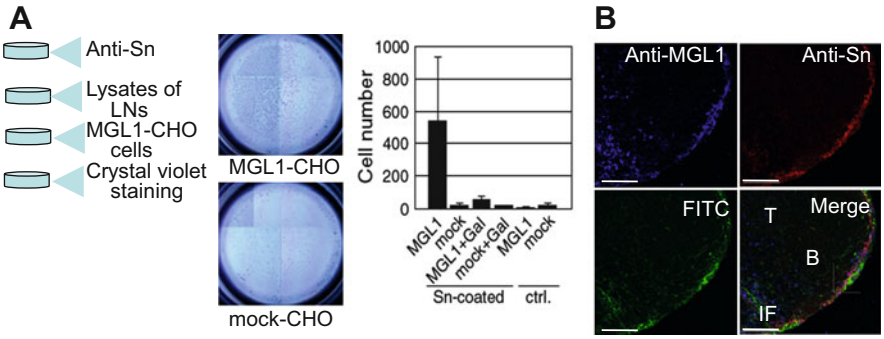

Fig. 11.2 Counter receptor in LNs for MGL1. (**a**) (*Left*) Schematic protocol to investigate the adhesion of cells expressing MGL1 (CHO-MGL1) to surfaces coated with sialoadhesin (Sn) from LNs. (*Middle*) Cell binding was monitored using a phase contrast microscope. (*Right*) Cell binding was shown as the number of adherent cells per well divided by 10. (**b**) Distribution of MGL1+ cells, Sn+ cells, and FITC in FITC-sensitized LNs. The merged image shows partial colocalization of MGL1 and Sn. Interfollicular regions (*IF*), and the border between T-cell areas (*T*) and B-cell areas (*B*) is shown. *Bars* indicate 100 μm. Figure 11.2a, b has been adapted from a previously published version (Kumamoto et al. 2004)

of one of these proteins indicated that the band corresponded to CD169, Siglec-1/sialoadhesin (Sn), which was known to be expressed on subcapsular sinus MØs. Sn purified from lysates of LNs was immobilized on microtiter plates precoated with anti-Sn monoclonal antibody, and binding of recombinant MGL1 as well as adhesion of cells expressing MGL1 was tested. The binding of recombinant MGL1 to Sn was shown to be dependent on Ca^{2+} and *N*-glycans present on Sn. MGL1-transfected Chinese hamster ovary cells adhered to the Sn-coated plates, whereas mock transfectants did not (Fig. 11.2a). Immunohistochemical localization of anti-Sn monoclonal antibody in LNs coincided with the subcapsular sinus area to which recombinant MGL1 was bound. Furthermore, after sensitization with fluorescein isothiocyanate (FITC), the distribution of MGL1-positive cells was demonstrated to overlap with that of Sn within the subcapsular sinus of draining LNs (Kumamoto et al. 2004) (Fig. 11.2b). These results suggest that Sn acts as an endogenous counter receptor for MGL1. Because the trafficking of cells expressing MGL1 was thought to be involved with the initiation phase of contact hypersensitivity, we investigated the distribution of MGL1-positive cells within the regional LNs with Sn knockout mice developed by Crocker and coworkers and the importance of the interaction on the development of hypersensitivity. The results revealed that despite the strong affinity of Sn with MGL1 and MGL1-positive cells, Sn was not involved with the regulation of trafficking of these cells to and within the regional LNs (unpublished data).

Apart from skin, MGL1 is also responsible for the signaling in intestinal MØs. Intestinal MØs express MGL1 to recognize commensal bacteria and down-modulate inflammatory responses by inducing IL-10 production as we previously reported (Saba et al. 2009). Although the counter receptor molecules in this

scenario remain to be identified, it seems highly likely that they are bacterial components with a structure different from those previously investigated.

Infectious enveloped viruses are known to use MGL to attach to and/or enter mammalian cells. Well-known examples for human diseases are Ebola and Influenza (Takada et al. 2004; Upham et al. 2010). The counter receptors for MGL on these viruses are combination products of viral genes and glycosyltransferases of human cells. Thus, variations in the oligosaccharide portions of MGL counter receptors responsible for the viral infection should be limited to human glycans. From these results, it is still a mystery how MGL and its counter receptors evolved as in the examples seen in the evolution of infectious parasites and the immune system.

11.3 Cells Expressing MGL/CD301

As stated above, the cells expressing MGL are MØs and DCs. Although this statement sounds simple, it may not be the case due to the fact that both MØs and DCs comprise highly heterogeneous populations of cells potentially having diverse origins and tissue-specific differentiation. In mice, the situation is even more complex because of the presence of MGL1 and MGL2. We were successful in preparing monoclonal antibodies specific for mouse MGL1, MGL2, and human MGL, respectively. When anti-mouse MGL1 antibody was initially generated, MGL2 was not yet discovered. Among several antibodies prepared against mouse MGL purified from a cell line (Kimura et al. 1995), we later found that mAb LOM-14 was cross-reactive between MGL1 and 2, whereas mAb LOM-8.7 strictly bound MGL1 (Tsuiji et al. 2002). We also generated an MGL2-specific mAb URA-1. The distribution of the binding sites for mAb LOM-8.7 and mAb URA-1 was compared by immunohistochemistry (Denda-Nagai et al. 2010; Kumamoto et al. 2009). Both mAbs bound to cells in the connective tissue of almost all organs except for the brain, and the binding profiles were similar to those previously shown using cross-reactive mAb LOM-14. The number of cells that reacted with mAb URA-1 seemed to be similar to the number of cells that reacted with mAb LOM-8.7 in most organs as far as the results of immunohistochemistry were concerned; however, clear differences between the cell populations expressing MGL1 and MGL2 were shown by flow cytometry as discussed below.

In LNs, $MGL1^+$ cells were mainly observed in the medullary and subcapsular sinuses, whereas $MGL2^+$ cells were restricted to the cortical areas (Kumamoto et al. 2009). In spleens, $MGL1^+$ cells appeared to have a more widespread distribution than $MGL2^+$ cells, and the binding of these antibodies was limited to the white pulp (Denda-Nagai et al. 2010). In lung alveolar spaces, the number of $MGL2^+$ cells appeared to be slightly greater than the number of $MGL1^+$ cells, which was different from any other site (Denda-Nagai et al. 2010). Surface expression of MGL1 and MGL2 on cells from bone marrow (BM), LNs, spleen, and lung was analyzed by flow cytometry using mAb LOM-8.7 and mAb URA-1 in a cell

suspension after exclusion of dead cells and $CD3^+$ or $CD19^+$ cells (Denda-Nagai et al. 2010; Kumamoto et al. 2009). These mAbs were found to bind subsets of $CD11c^+$ cells. BM, LNs, and spleen were populated with more $MGL1^+$ cells than $MGL2^+$ cells. All $MGL2^+$ cells appeared to co-express MGL1. MGL1 and MGL2 double-positive cells were $CD11c^+CD8^{-/low}CD11b^+MHCII^+F4/80^{low}$ conventional DCs. In BM, LNs, and spleen, a significant portion of MGL1 single-positive cells was observed and contained $CD11c^+B220^+$ plasmacytoid DCs.

It was found recently that $MGL2^+$ cells in the skin represent a unique subset of dermal DCs that skews the immune response toward Th2 (Murakami et al. 2013). Cells expressing MGL2 were found to be distinct from migratory Langerhans cells or $CD103^+$ dermal DCs (dDCs). Transfer of $MGL2^+$ dDCs but not $CD103^+$ dDCs from FITC-sensitized mice induced a Th2-type immune response in vivo in a model of contact hypersensitivity. Targeting $MGL2^+$ dDCs with a rat monoclonal antibody against MGL2 efficiently induced a humoral immune response with Th2-type properties, as determined by antibody subclass analysis.

Colonic lamina propria mononuclear cells were prepared from mice and analyzed by flow cytometry for the expression of cell surface markers using mAb LOM-8.7 and other antibodies (Saba et al. 2009). Cells expressing MGL1 were shown to express CD11b, CD11c, a high level of F4/80, and MHC class II. When we sorted cells with CD11b and F4/80, they also expressed *Mgl1* and *Mgl2* mRNA by RT-PCR. *Mgl1* expression was detected in $CD11b^+F4/80^{high}$ cells but not in $CD11b^+F4/80^{intermediate}$ cells. Sorted cells that expressed a combination of high levels of CD11b and F4/80 were shown to be $MGL1^+$ and incorporated FITC-labeled latex beads in vitro. These cells were also positively stained for nonspecific esterase. Therefore, the predominant populations of cells expressing MGL1 in the colonic wall were considered to be MØs, although they expressed CD11c.

From the above findings, $MGL2^+$ cells appeared to be a portion of $MGL1^+$ cells, mostly comprising conventional DCs. $MGL1^+$ cells were more diverse than $MGL2^+$ cells and included MØs and pDCs. Although several mouse myeloma cell lines, such as RAW264.7 cells and J774 cells, express MGL1, no cell line with surface expression of MGL2 or human MGL was identified so far (unpublished data). There is some reason to speculate that MGL1 and MGL2 form hetero-oligomers because $MGL2^+$ cells appear to also express MGL1, and because a homologous C-type lectin expressed on hepatocytes, hepatic asialoglycoprotein receptor, is known to form a hetero-oligomer.

11.4 MGL Knockout Mice and the Molecular Function of MGL/CD301

In the early days of MGL studies, we expected that the biological phenotypes of *Mgl1*−/− mice or *Mgl2*−/− mice should be easily interpretable because the expression profiles of these molecules are rather simple and limited to DCs and

MØs. However, contrary to our expectation, the molecular properties of MGL and the function of cells expressing MGL are not a straightforward matter.

Mgl1−/− mice were generated by Hedrick's group and by our group around the same time, when the presence of MGL2 was not yet published. Because there was no obvious phenotype observed with *Mgl1*−/− mice, it was estimated by Hedrick's group that the biological role of this molecule might be redundantly carried out by multiple homologous gene products (Onami et al. 2002). Although this hypothesis remains to be confirmed, MGL2 is obviously not the answer, since, as partially explained above, it shows different expression profiles and different molecular properties. MGL1 has a so-called hemITAM motif in its cytoplasmic tail, suggesting signaling functions.

The first tangible observations regarding the phenotypic effects of *Mgl1* deficiency were the delay in the repair of damage in embryos caused by the irradiation of pregnant mice (Yuita et al. 2005) (Fig. 11.3a) and the lack of inflammatory tissue formation in an air pouch model (Sato et al. 2005). In the second model, the presence of granulation tissue induced by immunization with a chemically modified foreign protein antigen observed in wild-type mice was diminished in *Mgl1*−/− mice (Fig. 11.3b). Administration of anti-MGL1 antibody similarly suppressed granulation tissue formation in wild-type mice. A large number of cells, present only in the pouch of *Mgl1*−/− mice, were not myeloid or lymphoid lineage cells and the number significantly declined after administration of interleukin 1-alpha (IL-1α) into the pouch of *Mgl1*−/− mice. Furthermore, granulation tissue was restored by this treatment, and the cells obtained from the pouch of *Mgl1*−/− mice were incorporated into the granulation tissue after injection of IL-1α. Therefore, MGL1 expressed on a distinct subpopulation of MØs or DCs that secrete IL-1α seemed to regulate specific cellular interactions crucial to granulation tissue formation.

Almost opposite effects on inflammatory tissue formation were observed in an experimental colitis model (Saba et al. 2009). When dextran sulfate sodium salt (DSS) was orally administrated to *Mgl1*−/− mice and their wild-type littermates, *Mgl1*−/− mice showed significantly more severe inflammation than wild-type mice. $MGL1^+$ cells in colonic lamina propria corresponded to MØ-like cells with $F4/80^{high}$, $CD11b^+$, and $CD11c^{intermediate}$ cells. In *Mgl1*−/− mice, these cells produced a lower level of IL-10 mRNA compared with wild-type mice after administration of DSS for 2 days. Recombinant MGL1 was found to bind both *Streptococcus sp*. and *Lactobacillus sp*. among commensal bacteria isolated from mesenteric LNs of DSS-treated mice. Heat-killed *Streptococcus sp*. induced an increase in IL-10 secretion by $MGL1^+$ colonic lamina propria MØs in wild-type mice but not by MØs from *Mgl1*−/− mice (Fig. 11.3c). These results strongly suggest that MGL1/CD301a plays a protective role against colitis by effectively inducing IL-10 production by colonic lamina propria MØs in response to invading commensal bacteria. It appears that the signal generated through MGL1 leads to the production of cytokines that play a crucial positive or negative role in the process of inflammatory tissue formation in these two examples.

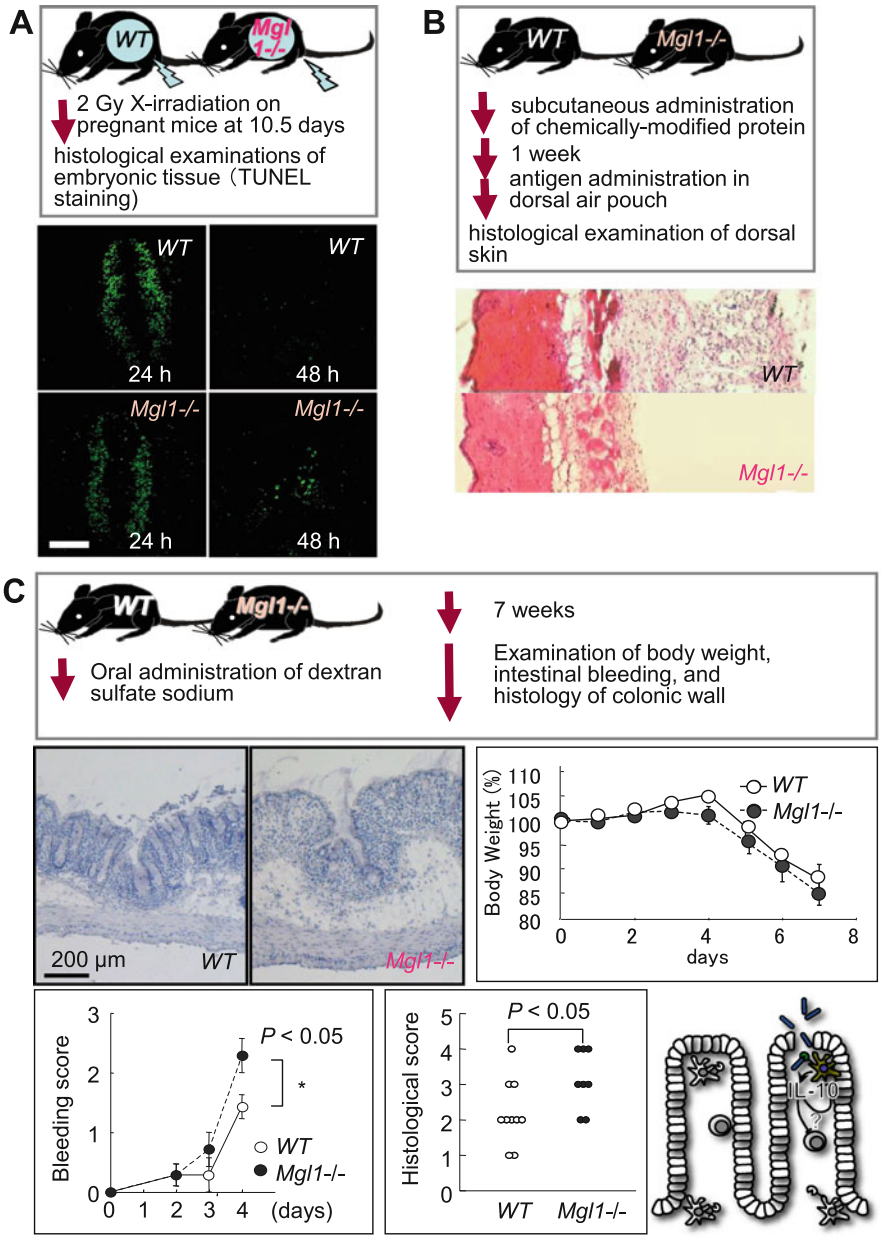

Fig. 11.3 Phenotypes observed with MGL1/CD301a knockout mice. (**a**) Histochemical localization of TUNEL-positive apoptotic cells (*green*) in neural tubes of *Mgl1*+/+ mice and *Mgl1*−/− mice in histological sections 24 or 48 h after X-ray irradiation at 1 Gy. The bar represents 200 μm. The images in Fig. 11.3a are adapted from a previous paper (Yuita et al. 2005). (**b**) Lack of granulation tissue formation after re-challenge with chemically modified protein (azobenzene arsonate-conjugated acetylated bovine serum albumin) in pre-immunized *Mgl1*−/− mice. The images in Fig. 11.3b are adapted from a previous paper (Sato et al. 2005). (**c**) MGL1/CD301a plays

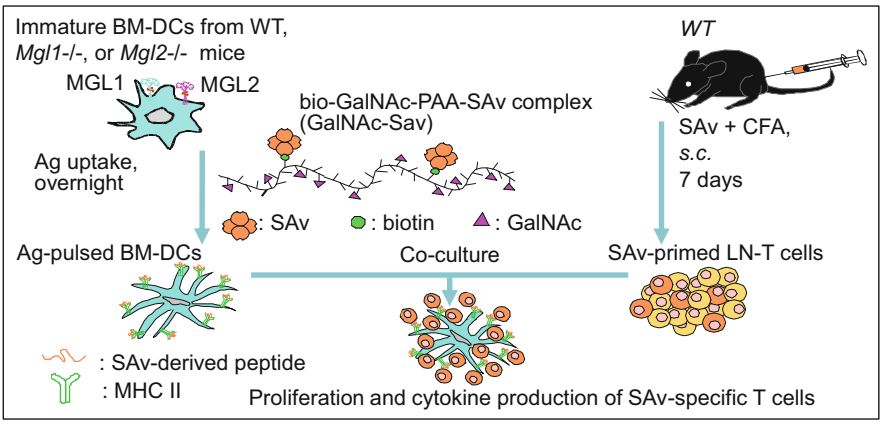

Fig. 11.4 Involvement of MGL1 and MGL2 in uptake of antigens with GalNAc residues by BM-DCs and presentation to T cells. The effects on T cell activation are examined according to this scheme as explained in the text

The function of MGL1 and MGL2 expressed on DCs in antigen uptake and presentation was examined using BM-DCs generated from BM cells of *Mgl1*−/− and *Mgl2*−/− mice. Wild-type BM-DCs expressed both MGL1 and MGL2. Streptavidin conjugated with biotinylated GalNAc-polyacrylamide polymer (GalNAc-SAv) was used as a model of glycosylated antigens (Fig. 11.4). GalNAc-SAv was more efficiently internalized and presented by wild-type BM-DCs to SAv-primed $CD4^+$ T cells than GlcNAc-SAv or SAv alone. MGL2 was suggested to be responsible for efficient binding and uptake of GalNAc-SAv by a comparison of *Mgl1*−/− and *Mgl2*−/− BM-DCs with wild-type BM-DCs (Denda-Nagai et al. 2010).

11.5 Concluding Remarks

MGL/CD301 is a unique C-type lectin expressed by DCs and by MØs for MGL1 in mice. Studies conducted in the past revealed that the roles of MGL are diverse depending on the DC and MØ subsets. The origins and diversity of these subsets are not yet fully understood. MGL will contribute to understand the diversity and

Fig. 11.3 (continued) an anti-inflammatory role in murine dextran sulfate sodium salt (DSS)-induced experimental colitis. Body weights (*Middle-right panel*), hematoxylin/eosin-stained sections of colon (*Middle-left panel*), bleeding score in stools (*Lower-left panel*), and histological scores for the damage of colonic walls (*Lower-middle panel*) are shown. Conceptual representation of MGL1's anti-inflammatory role (*Lower-right panel*). Upon bacterial invasion into the lamina propria, MGL1-expressing MØs initiate IL-10 secretion to combat inflammation. Figure 11.3c has been adapted from a previous paper (Saba et al. 2009)

diverse regulatory roles of DCs and MØs in different organs, which may require distinct types of immunological defense.

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