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Review

The mannose receptor

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ABSTRACT

The MR is a highly effective endocytic receptor with a broad binding specificity encompassing ligands of microbial and endogenous origin and a poorly characterized ability to modulate cellular activation. This review provides an update of the latest developments in the field. It discusses how MR biology might be affected by glycosylation and proteolytic processing, MR involvement in antigen delivery, and the potential contribution of MR to T cell differentiation and cellular activation. Further understanding of these areas will, no doubt, inform the design of novel, therapeutic tools for improved vaccination, control of inflammation, and tumor chemotherapy, which will benefit from exploiting MR-efficient internalization properties and unique pattern of expression. *J. Leukoc. Biol.* 92: 1177–1186; 2012.

Introduction

The MR is a carbohydrate-binding receptor expressed by selected populations of macrophages and dendritic cells (DCs) and nonvascular endothelium. The roles ascribed to this receptor are numerous and include clearance of endogenous molecules, promotion of antigen presentation, and modulation of cellular activation and trafficking. MR is unique because of the presence of two independent carbohydrate-binding domains that recognize sulfated and mannosylated sugars, respectively, and its key role in collagen internalization by macrophages. MR function can be altered through proteolytic cleavage and changes in glycosylation and conformation. Studies on macrophage and DC heterogeneity are closely linked to the study of MR. For instance, ligands of MR are expressed specifically by subpopulations of macrophages in secondary lymphoid organs associated to B cell follicles, and MR itself is only expressed by inflammatory DCs in selected lymphoid organs. The presence of a miR within the MR gene that is coregulated with MR needs be taken into consideration when addressing the effect of MR deficiency in vivo and in vitro, and genetic variants associated with disease within the *Mrc1* gene need to be tested for their effect on the expression of this miR. Finally, in an era of translational-oriented research, the potential for using MR as a target for improved antigen presentation or modulation of macrophage activation cannot be ignored. For this, detailed characterization of MR expression in human primary cells and tissues under normal and pathological conditions needs to be addressed.

STRUCTURAL PROPERTIES OF THE MR

MR (CD206) is the prototype member of the MR family of proteins [1, 2] that, in mammals, also includes the urokinase-type plasminogen activator receptor-associated protein Endo180 (CD280), the M-type PLA2R, and DEC 205 (CD205). All members of this family are endocytic receptors that share a similar structure consisting of an N-terminal CR domain, a FNII, and several CTLDs (**Fig. 1**).

MR is the only member of the MR family that contains a functional CR domain [4]. In MR, the CR domain binds sulfated carbohydrates, particularly, galactose or GalNAc sulfated in Position 3 or 4. Binding takes place through a neutral-binding pocket in a calcium-independent manner [1, 2, 4, 5] and requires Trp^{117} [6]. The region responsible for sugar binding is absent in the CR domain of the other members of the MR family [5].

The FNII domain is the most conserved domain among all members of the MR family [1]. The ability to bind collagen has been demonstrated for the FNII domains of MR and Endo180; the MR FNII domain binds collagens I, II, III, and IV and weakly, collagen V [7, 8], whereas the Endo180 FNII domain binds collagen V > (I and IV) [9, 10]. Cells expressing the M-type PLA2 receptor display binding to collagens I and IV [1]. No information is available regarding the ability of DEC205 to recognize collagen, although this is a likely possibility. MR plays a nonredundant role in collagen internalization in human and mouse macrophages [7, 11] and is also responsible for collagen uptake by liver sinusoidal cells [12].

Abbreviations: CR=cysteine-rich, CR-L=ligands for the cysteine-rich domain of mannose receptor, CTLD=C-type lectin-like domain, FNII=fibronectin type II domain, Galβ1=galactose β1, GalNAc=*N*-acetyl-D-galactosamine, GlcNAc=*N*-acetyl-D-glucosamine, HDM=house dust mite, Met=metallophilic, MiR=microRNA, MR=mannose receptor, *Mrc1*=mannose receptor C-type 1, Muc1=mucin 1, MZ=marginal zone, PPARγ=peroxisome proliferator-activated receptor γ, sMR=soluble MR, SS=subcapsular sinus, TAM=tumor-associated macrophage

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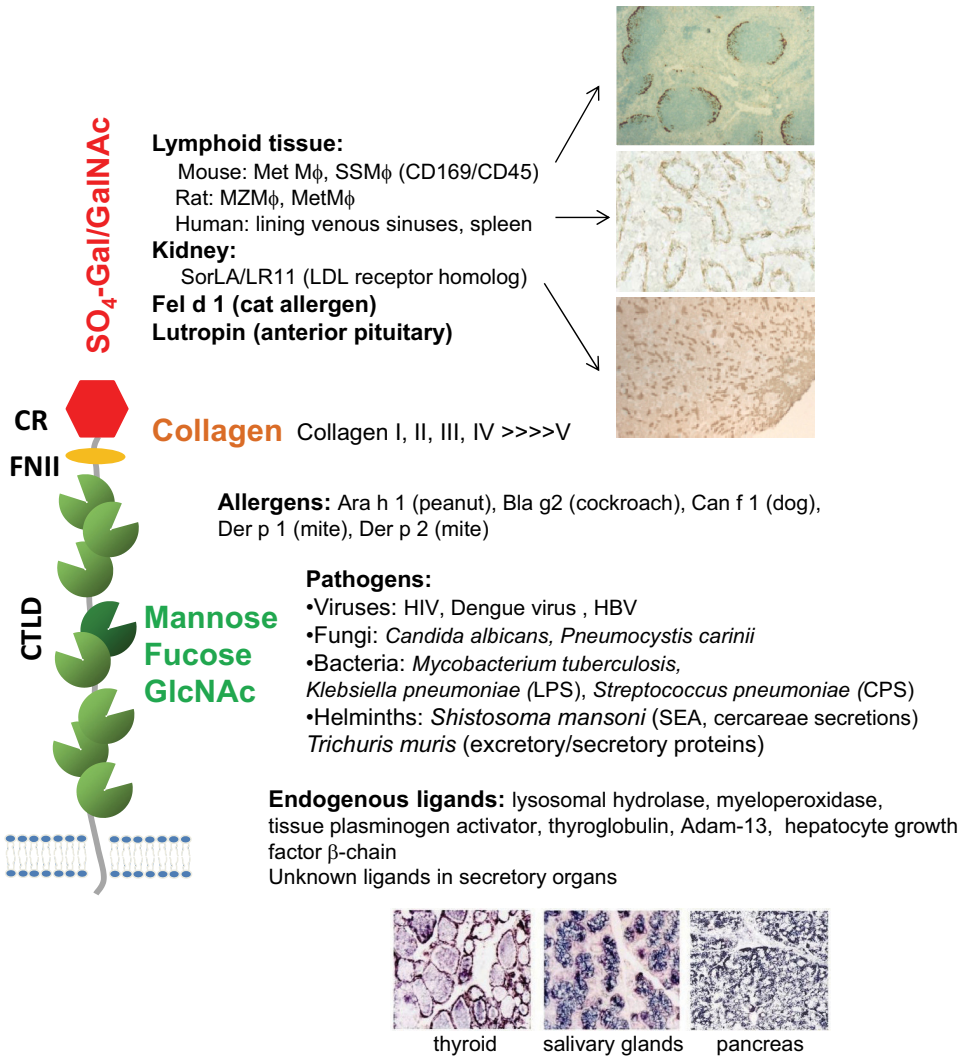

Figure 1. Structural properties of MR. MR is a type I membrane molecule with three types of extracellular domains. Through the CR domain, MR binds sulfated glycans that can be found in lymphoid tissues (see text) and kidney [3], as well as the major cat allergen Fel d 1 and lutropin. The FNII domain binds collagens, and the CTLDs bind endogenous and exogenous molecules, including allergens and microbial products. Mϕ, macrophage; HBV, hepatitis B virus; CPS, capsular polysaccharide; SEA, secreted egg antigen; Adam-13, a disintegrin and metalloprotease 13.

Through the CTLDs, MR binds glycoconjugates terminated in mannose, fucose, or GlcNAc in a calcium-dependent manner [2, 13, 14]. Of the eight CTLDs present in MR, only CLTD4 is capable of carbohydrate binding in isolation [13]. In the case of Endo180, CTLD2 has been shown to be essential for calcium-dependent binding to mannose, fucose, and GlcNAc [15]. The lectin activity of Endo180 facilitates the uptake of glycosylated forms of collagen, indicating a cooperative effect between the FNII and CTLD2 domains [16]. Surprisingly, collagen uptake by MR is independent of collagen glycosylation and the lectin activity of MR [16]. No lectin activity has been ascribed to the CTLDs of the M-type PLA2R or DEC205, but CTLD5 has been involved in the recognition of PLA2 by the former [1].

MR CONFORMATION, GLYCOSYLATION, AND PROTEOLYTIC PROCESSING

Although MR expression is instantly associated to uptake of MR ligands, post-translational modifications can have a drastic effect on MR properties. For instance, MR can adopt a bent conformation, in which the CR domain and the CTLD4 are in close proximity in a pH-dependent fashion [17], and MR binding activities are affected by glycosylation [18, 19]. Further, MR can undergo proteolytic processing [20–22], leading to the formation of a functional, soluble form (sMR). These modifications, discussed in more detail below, need to be addressed to improve the design of targeting strategies for vaccine development or understand the fate of endogenous MR ligands.

Cryoelectron microscopy studies showed close proximity between the main carbohydrate-binding CTLD of MR—CTLD4—and the CR domain [17]. These findings are consistent with a previous report describing a similar arrangement in Endo180 where the CR domain and CTLD2 are in close contact [17, 23]. In view of the finding that collagen glycosylation promotes Endo180-mediated collagen uptake [16], it appears that in MR and Endo180, the adoption of a bent conformation could play a role in modulating ligand selectivity and binding avidity. If, as shown for Endo180, changes in pH could alter the balance between a closed and open conformation in MR, as suggested by results from gel filtration chromatography [17], it is possible that domain

arrangement could influence ligand release during endocytosis.

MR is a heavily glycosylated molecule, and N-glycosylation sites are highly conserved between human and mouse MR [24]. This level of conservation indicates a key role for glycosylation in receptor function. The majority of N-glycans in mouse splenic MR contains sialic acids. These are mainly mono- and disialylated structures in the $\alpha 2 \rightarrow 6$-linkage, although neutral sugar glycans were also detected [18, 24]. In contrast, lung MR contains mostly $\alpha 2 \rightarrow 3$-linked terminal sialic acids, terminal mannose, and probably, Gal$\beta 1 \rightarrow$ 4-GlcNAc [18, 24]. Using stable MR transfectants deficient in specific glycosyl-transferases and the purified sMR (see below) generated in each instance, we demonstrated that lack of terminal sialylation reduces the ability of MR to bind and internalize mannosylated carbohydrates without affecting its subcellular localization, endocytic activity, or proteolytic processing [24]. Subtle differences in the binding and uptake of sulfated sugars were observed [24], and further studies demonstrated that binding of sMR to sulfated sugars was mediated by aggregated forms of the receptor and that nonsialylated MR had an increased tendency to aggregate [24]. Thus, binding to sulfated ligands is highly influenced by multimerization [6, 24, 25], which in turn, is modulated by sialylation, whereas binding to mannosylated sugars requires terminal sialylation [19]. In light of these observations, it is highly plausible that MR could display organ-specific specificity.

MR undergoes proteolytic cleavage, leading to the generation of a soluble form, sMR [20–22]. sMR is produced through the action of metalloproteases and consists of the complete extracellular region of MR [22]. sMR can recognize sulfated and mannosylated carbohydrates [24, 25], and as mentioned earlier, binding to sulfated carbohydrates requires substantial protein multimerization [6, 24, 25]. MR shedding by macrophages was initially considered a constitutive process [22], but we recently found that it can be promoted by fungal pathogens such as *C. albicans* and *Aspergillus fumigatus* [20] and that engagement of the β-glucan receptor, dectin-1, by the β-glucan component of the fungal cell wall was required for this process [20]. These results raise questions regarding the fate of fungal particles and antigens during the course of infection, as the relative abundance of cell-associated and sMR could influence their cellular targeting (see below). We speculate that dectin-1-induced MR shedding could minimize the contribution of cell-associated MR to antifungal responses under specific conditions [20].

THE CELLULAR BIOLOGY OF MR

MR is a highly effective endocytic receptor that recycles constantly between the plasma membrane and the early endosomal compartment [26]. Most of MR is intracellular [26]. MR-mediated endocytosis is clathrin-dependent and requires the internalization motif (FENTLY) [26]. Endosomal acidification is thought to induce ligand release, with the empty receptor recycling back to the cell surface. Unlike other C-type lectin receptors, such as dectin-1 [27], MR does not endow cells with the capacity to phagocytose particles bearing MR ligands [26]. An exception is found in the case of Cos-1 cells, as Cos-1 expressing MR were capable of internalizing *C. albicans* and *P. carinii* [26]. In support of a lack of involvement of MR in phagocytosis, MR expression in mouse macrophages does not affect the uptake of particulate ligands such as *C. albicans* and zymosan [27, 28]. MR was also absent from the phagocytic cup upon uptake of *C. albicans* but was transiently recruited to the maturing phagosome at a later stage [27]. Differentiation between endocytic versus phagocytic uptake in mammalian cells is generally assessed through the requirement for actin polymerization. Cytochalasin D and latrunculin A, which disrupt this process, are widely used for this purpose. During our investigation of the cellular requirements for MR shedding, we observed a drastic reduction in MR expression in the presence of cytochalasin D and latrunculin A [20]. This could be caused by a requirement for actin polymerization for MR recycling, as suggested previously [29]. These results indicate that the levels of MR expression can be regulated by actin polymerization and that the endocytic uptake of sMR ligands could be potentially affected by inhibitors routinely used to inhibit phagocytosis.

The redundancy among lectin-binding specificities presents a challenge to the study of MR-induced signaling using mannose-rich carbohydrate ligands [30]. Potentially, the use of sulfated carbohydrates recognized through the CR domain would resolve this issue, and we have demonstrated their specific uptake by MR-expressing cells [24]. An example of a natural CR domain-targeted antigen is the cat allergen Fel d 1 [31]. Nevertheless, it is safe to conclude that in general, MR does not appear to function as a canonical PRR capable of signal transduction in isolation [2, 26]. MR likely modulates signaling induced by other receptors through the facilitation of recognition by canonical signaling receptors, as suggested for MR and TLR2 [26] or as described for DC-specific ICAM-3-grabbing nonintegrin, which modulates TLR-mediated signaling [32]. This is in agreement with the lack of signaling motifs at the cytoplasmic tail of MR. Anti-MR antibodies have been considered a suitable alternative to carbohydrate-based MR ligands for investigating cellular consequences of MR ligation [26]. However, the ability of MR to modulate FcR-mediated cellular activation (ref. [33], and see below) means that caution must be taken when using these reagents, as there is potential for cross-linking MR and FcRs.

TRAFFICKING OF MR LIGANDS WITHIN DCs AND CROSS-PRESENTATION

MR was identified originally as a major system for antigen internalization in immature, cultured human DCs that facilitates antigen presentation through the MHC II and CD1b pathways. Indeed, MR targeting has been subsequently considered as a way to increase antigen immunogenicity [2, 26]. For this, mannosylated antigen preparations have generally been used, but recently targeting strategies based on the addition of sulfated carbohydrates [34] or the use of antigens fused to anti-MR antibodies [35–37] have been described. In the case of the cancer antigen NY-ESO-1, MR targeting promoted activation of NY-ESO-1-specific $CD4^+$ and $CD8^+$ T cells [36]. Recent studies using peptides conju-

gated to antibodies against MR, DEC205, or CD40 indicate that cross-presentation is reduced if antigens are targeted to late endosomal compartments [37], which indicates that it might be possible to modulate of the efficiency of antigen cross-presentation by altering the avidity of the targeting reagent for the relevant receptor.

A specialized role for MR in promoting cross-presentation and cross-priming in an endotoxin-dependent manner has been proposed [38–40]. In this model (processing and presentation of OVA by bone marrow-derived DCs), endotoxin promotes cross-presentation by inducing relocalization of transporter associated with antigen processing/presentation to early endosomes [40]. Recently, a TLR-independent mechanism for MR-mediated cross-presentation has been suggested [34]. In this instance, the antigens used were OVA-derived neoglycoconjugates bearing 3-sulfo-Lewis^A and tri-GlcNAc [34]. It is intriguing that differences in the nature of the MR ligand could affect the route of antigen processing. These results resemble earlier reports using oxidized and reduced forms of mannosylated Muc1 [41]. In this case, aldehyde groups generated during the conjugation of oxidized mannan to Muc1 with periodate promoted MR-mediated cross-presentation [42]. Additional work into the mechanism behind MR-mediated cross-presentation supports a role for MR polyubiquitination [43] in facilitating the translocation of antigen from endosomes to the cytoplasm. MR polyubiquitination is required for recruitment of p97 AAA ATPase to endosomes. p97 AAA ATPase is part of the endoplasmic reticulum-associated degradation machinery and promotes antigen translocation to the cytosol [43]. MR-mediated CD8 T cell activation is inhibited by PPARγ agonists, which in spite of increasing MR expression, antigen uptake, and processing, inhibit the activation of naïve CD8 T cells through the up-regulation of B7H1 [44]. This work further reinforces the concept of uncoupling between antigen uptake and processing and T cell activation. Key aspects of the cellular biology of MR are shown in **Fig. 2.**

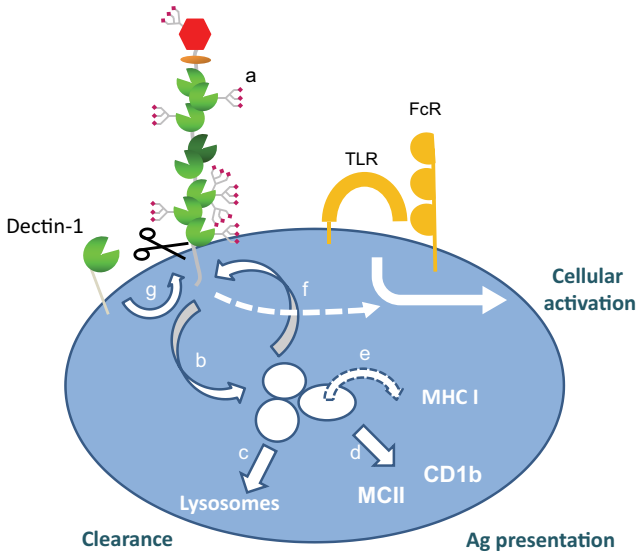

Figure 2. MR and cellular targeting. Sialylation controls the aggregation state of MR (a) and can influence MR binding to sulfated sugars. Sialylation is required for binding to mannosylated sugars. MR recycles constantly between the plasma membrane and the early endosomal compartment (b) and can deliver ligands for degradation in the lysosomes (c), presentation through MHC II (MCII) and CD1b (d), and cross-presentation (e). MR can modulate cellular activation through TLR and FcR (f). MR cleavage is promoted by dectin-1 (g).

MR AND INDUCTION OF IMMUNE RESPONSES

The study of MR involvement in antigen presentation in vivo requires a clear understanding of MR expression in professional APCs. Whereas MR expression is a hallmark of immature human monocyte-derived DCs and mouse bone marrow-derived DCs [2, 26], expression of MR in DCs in vivo is ill-defined. MR$^+$ DCs are present in selected LNs [45, 46] with numbers increasing after innate stimulation [46]. Evidence has been provided in support of MR-mediated cross-presentation in splenic monocyte-derived inflammatory DCs [47], but there is disagreement regarding MR expression in splenic CD8$^+$ DCs under steady-state conditions [47–49]. It has been suggested that lack of MR detection in CD8$^+$ DCs might be caused by MR internalization after binding to collagen fragments released during collagenase digestion [48], which would hamper detection; this has been argued against [49]. Histological studies demonstrate lack of MR expression in splenic T cell areas in naïve [45, 46] and LPS- and flagellin-stimulated animals [46]. Together with further flow cytometric analysis [46], this argues against a role for cell-associated MR in T cell activation in spleen under steady-state conditions [46], which would be in agreement with a major scavenging role in naïve animals. Additionally, our unpublished work suggests that collagen does not affect MR-mediated endocytic activity or MR expression at the cell surface (unpublished results).

The presence of sMR should be taken into consideration when investigating MR involvement in antigen presentation, as sMR could, in principle, directly compete with cell-associated MR for binding to CTLD ligands. This scenario would be less likely in the case of CR domain and FNII ligands, as in this instance, binding is highly dependent on protein multimerization (see above and refs. [2, 24, 25]). An intriguing possibility is that the MR-mediated antigen cross-presentation observed in vivo [39] could be mediated by sMR by means of its ability to target Met macrophages (see below and **Fig. 3**) [6]. These cells in turn could transfer antigen to bona fide CD8$^+$ DCs for cross-presentation, as shown for antigens targeted to Met macrophages using anti-CD169 mAb [49, 50]. Finally, and in contrast to spleen, in the peritoneal cavity, MR expression is restricted to a population of 12/15 lipoxygenase-deficient resident myeloid cells that could represent a novel DC population [51]. These observations further highlight the likelihood of site-specific involvement of MR in antigen presentation.

In spite of their potential limitations as MR ligands, the used of anti-MR antibodies has provided insight into the fate of MR ligands delivered to peripheral tissues [46]. In the absence of stimulation, rat anti-MR antibodies [52] tar-

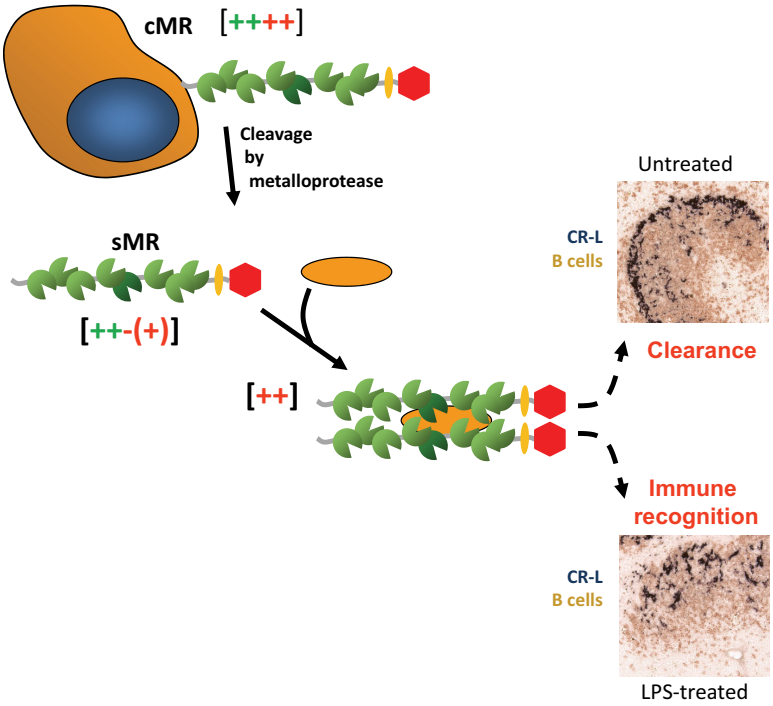

Figure 3. CR-L ligands and immune recognition. Cell-associated MR (cMR) can bind to mannosylated (through CTLDs) and sulfated sugars (through CR domain), symbolized here by the presence of plus signs in green and red, respectively. Upon cleavage by proteases, sMR is produced. sMR would only bind mannosylated sugars, as multimerization is required for efficient binding to sulfated sugars. Binding to multimeric mannosylated ligands promotes multimerization of sMR [25], and this would enhance sMR avidity for sulfated sugars (CR-L). Under steady-state conditions, sMR antigen targeting to CR-L+ cells will probably lead to clearance, whereas in the presence of LPS, when CR-L+ cells migrate into the follicles, this might lead to enhanced immune recognition. Additional CR-L have also been described in mouse kidney (see Fig. 1 and ref. [3]).

get medullary macrophages in draining LNs and fail to induce anti-rat IgG humoral responses [46]. These observations suggest that in the absence of stimulation, MR targeting leads to clearance. When anti-MR antibodies were injected in the presence of endotoxin, substantial targeting to T cell areas was observed alongside targeting to medullary areas [46]. The timing of the antibody targeting provides an indication of the mechanism behind the delivery of anti-MR antibodies to LNs; whereas targeting to the medullary region occurred within minutes, targeting to the T cell areas required 18–24 h [46]. These results indicate that free anti-MR antibody reaches the LNs within minutes and is internalized by medullary cells. On the other hand, delayed targeting of anti-MR antibodies to the T cell areas could be mediated by a population of migratory inflammatory DCs [46]. Under these conditions, there was selective induction of anti-rat IgG humoral responses [46]. Thus, immune recognition of MR ligands is affected by the site of administration, as well as the presence of adjuvants. Several TLR agonists were tested for their ability to induce the presence of MR+ cells in T cell areas on LNs. Whereas LPS and flagellin and to some extent, palmitoyl-3-cysteine-serine-lysine-4 promote MR expression in this location, polyinosinic:polycytidylic acid did not have any effect [46], suggesting that innate immune stimulation through MyD88 is required. The requirement for additional immune stimulation to achieve optimal MR-mediated immune recognition in humans is supported by results obtained using the anti-MR, antibody-based anticancer vaccine CDX-1307. In this instance, immune responses were boosted by the presence of GM-CSF and TLR agonists [35].

TISSUE DISTRIBUTION

Whereas MR expression in murine tissue has been investigated in great detail [2], knowledge of its expression pattern in human tissues is sparse. A critical limitation is the inability of MR-specific antibodies to work in parafilm-embedded tissues, which are the basis for pathological studies in clinical samples. In general, MR is expressed by subpopulations of macrophages and DCs, as well as hepatic, splenic, lymphatic, and dermal microvascular endothelia [53] and specialized cells, such as kidney cells, mesangial cells, trachea smooth muscle cells, and retinal pigment epithelium [2]. It was generally considered that monocytes lacked MR expression but rapidly up-regulated it upon maturation, and this is the case in our experience with CD14+ human monocytes (unpublished results). This is in disagreement with a recent reports showing MR expression in human monocytes [54]. The reasons behind this disagreement are not clear at this stage. It is important to address this issue, as monocytes are key effector cells, and MR expression will have major implications for their interaction with serum proteins, many of them MR ligands, and blood-borne pathogens.

Whereas in most organs MR is present as a 170- to 180-kDa molecule [18], in the small intestine an additional form recognized by several anti-MR antibodies has been detected [18]. The observed 40-kDa relativeMW differences between this peptide and MR would correspond to cleavage of ~400 aa, and it has been suggested that it lacks the CR domain. No information regarding the cellular distribution, regulation, or function of this smaller form is currently available. To determine the contribution of MR to disease in the small intestine, further investigation is required about the potential for a shorter, intestine-specific spliced form of the MR mRNA or an alternative

proteolytic process specific to this organ. Species differences between human and mice expression of MR in tissue macrophages need to be taken into consideration; for instance, human splenic macrophages, unlike their mouse counterparts [45], lack MR expression [55].

THE DISTRIBUTION OF ENDOGENOUS CR-L HIGHLIGHTS MACROPHAGE SPECIALIZATION IN SECONDARY LYMPHOID ORGANS

In mice, CR-L are expressed by MZ Met macrophages in the spleen and SS macrophages in LNs, both of which express the macrophage marker CD169 or sialoadhesin [2]. CD169 is itself a CR-L, together with CD45, when expressed by these cells [56]; i.e., in Met and SS macrophages, CD169 and CD45 undergo specialized post-translational modifications leading to the addition of sulfated N-linked glycans that are recognized by the CR domain of MR. CR-L+ cells are closely associated to B cell follicles, lack MR expression, and migrate into the follicles upon stimulation with endotoxin and during the germinal center reaction [2]. Follicular dendritic cells also bear CR-L during the germinal center reaction [2]. These observations led us to propose the sMR-mediated antigen-delivery pathway (see Fig. 2 and ref. [2]). According to this hypothesis, sMR released from cells that express the cell-associated form of the receptor would transport antigen to the cells bearing CR-L. CR-L+ cells can be targeted in vivo using proteins bearing the CR domain [6], which indicates that CR-L are exposed to the circulation. There are multiple reports in support for a role of CR-L+/CD169+ macrophages in antigen handling in secondary lymphoid organs [57]. These cells have been shown to transport or mediate translocation of native antigen into the follicles for delivery to B cells, promoting B cell activation, and in the activation of invariant NKT cells and CD8 T cells [57]. Recently, CD169+ macrophage cells have been found to be permissive to viral infection through increased expression of Usp18, an inhibitor of the type I IFN signaling pathway [58]. Viral replication within CD169+ macrophages promotes immune recognition [58]. Thus, the detection of CR-L in secondary lymphoid organs acted as an early indicator of the unique role of selected macrophage populations in antigen handling [59].

Conservation of function for the CR-L/MR interaction in rodents is suggested by the presence of CR-L in Met and outer MZ macrophages in rat spleen [55]. On the contrary, in human spleen, there is a perfect colocalization between CR-L and MR expression in venous sinuses [55]. This, together with the lack of MR expression in human splenic macrophages (see above), suggests differential handling of blood-borne MR ligands between rodents and humans.

CONTRIBUTION OF MR TO DISEASE

The generation of MR-deficient animals was a breakthrough in the investigation of the role of MR in immunity, and multiple studies have now demonstrated that in most instances, MR deficiency does not translate into increased susceptibility to infection [2, 26]. The jury is still out in the case of humans, as MR has been implicated in the production of IL-17 in response to *C. albicans* [54, 60]. Contribution of MR to chronic inflammation is suggested by the association of genetic variants in the MR gene (*Mrc1*) to susceptibility to asthma [61] and sarcoidosis [62], although no mechanisms have been proposed.

Recent interest has focused on the potential contribution of human MR to the recognition of endogenous serum components [63] and therapeutic agents [64, 65] as a means to provide a mechanism for the induction of pathological immune responses. As many endogenous MR ligands are autoantigens it is highly plausible that the scavenging role of MR in vivo could be subverted for enhanced antigen presentation during infection [2, 46]. Recent results in support of a role for MR in the promotion of Th2 responses and glomerulonephritis are discussed below.

MR binds to a wide range of allergens through both lectin domains (refs. [31, 66] and Fig. 1), and accordingly, lack of MR leads to reduced allergen uptake by mouse and human APCs [31, 66]. MR-deficient animals sensitized with cat dander and purified Fel d 1 produce less total IgE and Fel d 1-specific IgE and IgG1 [31]. These in vivo results are a likely consequence of the fact that the main allergen used, Fel d 1, bears sulfated glycans and specifically binds to the CR domain of MR [31], and that priming took place in the peritoneal cavity, where MR is expressed by resident DCs [51]. No information regarding the presence of additional MR ligands in the cat dander extract is available. HDM extracts are currently being used for induction of allergic inflammation in animals [67, 68]. In addition to Der p 1 and Der p 2 [66], these complex preparations contain further ligands for the CTLD4-7 region of MR (unpublished results). This, together with the involvement of other C-type lectin receptors in the immune recognition of HDM extracts [69, 70], complicates the dissection of the receptors involved in the promotion of allergic diseases. Whereas this appears a defeatist attitude, comfort can be drawn from studies on parasite-secreted proteins, as these preparations have yielded specific compounds with the capacity to modulate immunity [71]. In support for a role of MR in Th2 polarization in humans, MR deficiency reversed Th2 differentiation in response to purified Der p 1 in cocultures of DCs and T cells [66]. This effect correlated with increased IDO activity in MR-deficient DCs [66] and could be reversed by IDO inhibitors [66]. In agreement with these observations, addition of IDO metabolites, such as L-kynurenine, to control cocultures also promoted Th1 polarization in response to Der p 1 [66]. This suggests that MR could modulate the response to L-kynurenine in DCs.

Additional support for a role of MR in promoting Th2 polarization has been obtained during the investigation of early events during infection with *S. mansoni* cercariae [72]. MR binds excretory/secretory material released during transformation of cercariae into schistosomula and contributes to early Th2 polarization in response to *Schistosoma* infection. Infected MR knockout animals had reduced numbers of hematopoietic cells containing secreted material in draining LNs and IFN-γ

levels, and percent of IFN-γ-producing CD4 T cells were significantly higher, whereas the opposite was true in the case of IL-4 and IL-4-producing CD4 T cells [72]. Nevertheless, under some circumstances, MR engagement has been shown to promote Th1 differentiation [34]. In this instance, the authors used the model antigen OVA linked to two MR ligands—3-sulfo-Lewis^A and tri-GlcNAc [34]. These neoglycoconjugates were also shown to promote cross-presentation. It is possible that as mentioned above, reactive groups generated during the coupling reaction could play a role in modulating T cell differentiation.

One of the most remarkable effects of MR deficiency in mice is the complete protection of MR-deficient animals to accelerated nephrotoxic nephritis [33]. This appears to occur through the interplay between two major effects caused by MR deficiency. Absence of MR expression leads to reduced FcR-mediated responses in macrophages and kidney mesangial cells [33], which would be highly relevant in an immunocomplex-induced disease model. Additionally, MR recognizes Fab_2 fragments of the sheep IgG in the nephrotoxic serum [33]. This observation resembles early reports describing recognition by MR of a form of IgG associated to several autoimmune diseases, agalactosyl IgG [73], and further supports a major role for glycation in the effector functions of Igs [74]. In addition to this anti-inflammatory effect, lack of MR led to increased apoptosis in mesangial cells in vitro and in vivo [33]. Investigation of the consequences of apoptotic cell recognition by macrophages in the presence of LPS demonstrated that MR promotes inflammation under these conditions [33].

THE REGULATORY ROLE OF *Mrc1* TRANSCRIPTS

Macrophage activation has a major effect on MR expression. In vitro, MR is expressed at increased levels in macrophages undergoing alternative, M2-like activation, such as in the case of macrophages treated with IL-4, IL-13, and IL-10 or glucocorticoids, whereas IFN-γ and LPS have a negative effect [2]. MR is considered a highly reliable indicator of M2 activation in mouse and humans, but because of its up-regulation by IL-10 [52, 75] and glucocorticoids [2], in this instance, the term M2 activation must be used in its broader sense, largely as a mean to exclude proinflammatory and microbicidal M1-activated macrophages. A role for PPARγ in the promotion of MR expression in response to IL-13 has been demonstrated, and this correlates with enhanced protection against *C. albicans* infection [76, 77]. In vivo, MR has been observed in M2 TAMs [78, 79] and macrophages recruited to *S. mansoni* granulomas [75, 80]. Recent studies in human TAMs suggest that MR is more than a marker of macrophage activation but also contributes to their immunosuppressive activity [78]. MR, expressed by lymphatics, has been involved in the promotion of cancer metastasis [81].

An unexpected angle in the understanding of how MR expression modulates cellular activation in TAMs has been the identification of a novel miR within the human and mouse *Mrc1* gene (ref. [82] and **Fig. 4**). This miR, termed miR-511-3p, is coregulated with the MR mRNA and protein in TAMs and cultured macrophages. miR-511-3p is predicted to control a wide range of genes involved in multiple cellular processes, including cellular morphogenesis, metabolism, protein localization, and gene transcription [82]. The intriguing observation is that similarly to other M2-associated markers that have a negative effect on Th2-mediated inflammation [83–85], miR-511-3p acts as a negative regulator of the tumor-promoting activities of TAMs [82]. Forced expression of miR-511-3p in hematopoietic precursors has major effects in tumor vasculature and inhibits tumor growth [82].

Linked expression of MR and miR-511-3p has also been demonstrated in MR+ tissue macrophages, including lung, spleen, and adipose tissue [82]. These novel findings suggest that *Mrc1* expression can modulate cellular activation during

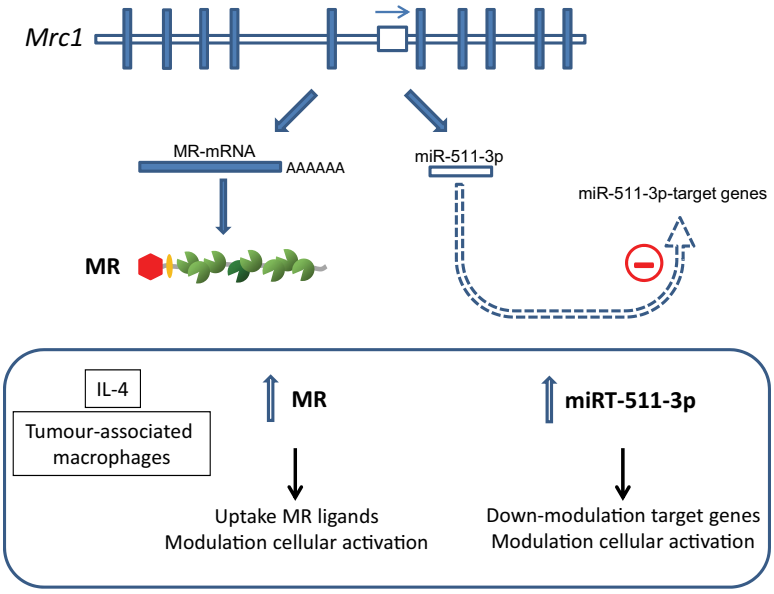

Figure 4. Regulation of cellular activation by *Mrc1* transcripts. The *Mrc1* gene contains a miR (miR-511-3p) located in the fifth intron. miR-511-3p is coregulated with the MR and inhibits the expression of a wide range of genes. Therefore, cells with high MR expression, such as IL-4-treated macrophages and TAMs, express higher levels of miR-511-3p. In these cells, cellular activity can be the result of the endocytic activity of MR, as well as the inhibitory effect of miR-511-3p on gene transcription.

steady-state and inflammatory conditions by two mechanisms: MR synthesis and miR-511-3p transcription. MR expression will enable uptake of a wide range of ligands, and this will have major consequences on their accessibility to endosomal compartments. miR-511-3p will directly control expression of multiple genes at the RNA level.

A key consideration is how these findings could impact on the interpretation of previous work involving MR-deficient models. Are the effects observed a direct consequence of lack of MR or deregulated miR-511-3p expression? miR-511-3p can be detected, albeit at lower levels, in bone marrow macrophages derived from MR-deficient mice [86], indicating transcription of the *Mrc1* gene in these cells (unpublished results). These results imply that it is possible to decouple MR and miR-511-3p expression and that dissecting the contribution of each of these components to the biology of myeloid and endothelial cells is a feasible option.

CONCLUDING REMARKS

Ongoing interest on MR for the last 20 years has generated a vast number of publications that underscore the unique attributes of this multitalented molecule. The field has moved on from the early studies using mannan and Ca^{2+} chelators to the use of stable transfectants, MR-specific small interfering RNA, and cells from knockout animals to investigate MR involvement in specific processes. These developments, together with (1) the adoption of MR-specific ligands, such as sulfated sugars and antibodies, (2) a clearer understanding of MR biochemical properties and distribution in human and murine tissues, and (3) the generation of experimental models to discriminate between MR- and miR-511-3p-mediated effects, will enable us to harness the unique targeting properties of MR for vaccine development and modulation of inflammatory processes.

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