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Influence of the mannose receptor in host immune responses

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Abstract

Mannose receptor (MR) is a C-type lectin primarily expressed by macrophages and dendritic cells. Its three distinct extracellular binding sites recognise a wide range of both endogenous and exogenous ligands, therefore MR has been implicated in both homeostatic processes and pathogen recognition. However, the function of MR in host defence is not yet clearly understood as MR-deficient animals do not display enhanced susceptibility to pathogens bearing MR ligands. This scenario is even more complex when considering the role of MR in innate immune activation as, even though no intracellular signalling motif has been identified at its cytoplasmic tail, MR has been shown to be essential for cytokine production, both pro-inflammatory and anti-inflammatory. Furthermore, MR might interact with other canonical pattern recognition receptors in order to mediate intracellular signalling. In this review, we have summarised recent observations relating to MR function in immune responses and focused on its participation in phagocytosis, antigen processing and presentation, cell migration and intracellular signalling.

Keywords: Antigen processing and presentation; Immune response; Intracellular signalling; Mannose receptor; Phagocytosis

Contents

Domain structure and binding properties of the mannose receptor

The mannose receptor (MR, CD206) is a member of the MR family which is a subgroup of the C-type lectin

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superfamily, that comprises transmembrane and soluble proteins such as selectins and collectins (East and Isacke, 2002). There are three additional members: the M-type phospholipase A_2 receptor (mPLA$_2$R), DEC205 and Endo-180. All these molecules differ from other superfamily members in having multiple C-type lectin-like domains (CTLDs) within a single polypeptide backbone, eight in the case of MR, PLA$_2$R and Endo 180 and ten in the case of DEC205.

MR was the first MR family member to be discovered. It was initially identified in the late 1970s as a 175 kDa endocytic receptor on rabbit alveolar macrophages (Mϕ) involved in the clearance of endogenous glycoproteins. MR expression is not Mϕ-restricted; it is also expressed by hepatic and lymphatic endothelia and kidney mesangial cells (East and Isacke, 2002; Martens et al., 2006; Taylor et al., 2005a). MR, like the other MR family members, is a type-I membrane protein with a single transmembrane domain and a cytoplasmic domain that mediates receptor internalisation and recycling. It contains three types of domains at its extracellular region, an *N*-terminal cysteine-rich (CR) domain capable of qCa^{2+}-independent binding to sulphated sugars terminated in SO_4-3-Gal or SO_4-3/4-GalNAc (Taylor et al., 2005a), a fibronectin type II (FN II) domain involved in collagen binding especially collagen types I, II, III, and IV (Martinez-Pomares et al., 2006; Napper et al., 2006), and eight tandemly arranged CTLD responsible for Ca^{2+}-dependent binding to sugars terminated in D-mannose, L-fucose or *N*-acetyl glucosamine (Taylor et al., 2005a).

The MR binds and internalises material of both exogenous and endogenous origin. The CR domain recognises glycoprotein hormones produced in anterior pituitary, lutropin and thyrotropin, chondroitin sulphate A and B and sulphated oligosaccharides of blood group Lewis^a and Lewis^x types. Also CR domain ligands have been identified in specialised Mϕ subpopulations adjacent to B-cell follicles in secondary lymphoid organs and on follicular dendritic cells during the germinal centre reaction. Expression of CR domain ligands in these cells is dependent on the presence of B cells. These sugars are considered to act as counter receptors for a soluble form of the MR (Taylor et al., 2005a).

Through the CTLD region MR binds thyroglobulin, lutropin hormone, myeloperoxidase and lysosomal hydrolases. The interaction of MR with lysosomal hydrolases and myeloperoxidases suggests a crucial role for the MR during the resolution of inflammation.

Unlike the CR domain, the CTLD region can also bind to ligands of microbial origin, as mannose is frequently found on the surface of many microorganisms. In this way MR is considered a pattern recognition receptor (PRR). Pathogens recognised by MR include *Candida albicans* (Marodi et al., 1991; Martinez-Pomares et al., 1998), *Leishmania* (Chakraborty et al., 1998, 2001), *Mycobacterium tuberculosis* (Tailleux et al., 2003), HIV (Nguyen and Hildreth, 2003), *Pneumocystis carinii* (Ezekowitz et al., 1991; O'Riordan et al., 1995), Dengue virus (Miller et al., 2008) and selected strains of *Klebsiella pneumoniae* (Zamze et al., 2002) *Cryptococcus neoformans* (Dan et al., 2008) and *Streptococcus pneumoniae* (Zamze et al., 2002).

However, pathogen recognition does not appear to translate into enhanced susceptibility of MR-deficient animals to infection. MR-knock-out (MR-KO) mice showed no differences in *C. albicans* phagocytosis, recruitment of inflammatory cells or humoral response to *Candida* antigens (Lee et al., 2003). Similarly, these animals did not display enhanced susceptibility to *P. carinii* (Swain et al., 2003) but in this instance there was a significantly enhanced number of Mϕ recruited to the alveolar space indicating that while Mϕ lacking MR might have become less efficient in clearing *P. carinii* this might have been compensated for through increased numbers of Mϕ recruited to the site of infection. Similar results were obtained in the case of experimental leishmaniasis (Akilov et al., 2007). Furthermore, it has been recently reported that the mannose cap of LAM does not have a major influence on the interaction of Mycobacteria with the host (Appelmelk et al., 2007). When analysing these results it should also be taken into consideration that MR is not the only receptor with specificity for mannose; other receptors sharing similar pattern of ligand binding, include SIGNR1 (mouse)/DC-SIGN (human) and Endo-180 (Taylor et al., 2005b). Interestingly, a recent work by Levitz and co-workers shows that MR contributes to protection against pulmonary challenge with *Cryptococcus neoformans*_ with MR-KO mice dying faster and having a higher lung fungal burdens after 4 weeks of infection. In this model it appears that MR is required for the induction of T cell responses against cryptococcal mannoproteins, which would be required for protection against *C. neoformans* infection (Dan et al., 2008). This work supports a major role for MR in Ag presentation to the acquired immune system *in vivo* (see below).

The MR as an endocytic receptor

The MR constitutively recycles between the plasma membrane and the early endosomal compartment, even in the absence of any ligand. At the steady state 10–30% of the receptor is found at the cell surface and the remaining 70% is localised intracellularly. The MR is internalised and delivered into the endosomal system via clathrin-coated vesicles which involves the polymerisation of clathrin (a fibrous protein with three-limbed

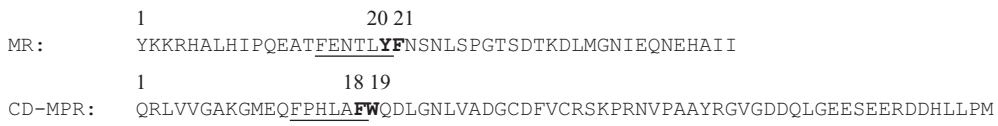

Fig. 1. Comparison of the cytoplasmic domains of mouse MR and mannose-6-phosphate receptor (CD-MPR) precursors. The amino acid sequences are written in single letter code. The di-aromatic motifs FW (CD-MPR) and YF (MR) (both in bold) are located almost at the same distance from the trans-membrane domain. Underlined sequences indicate the amino acid sequence required for receptor internalisation. In both proteins, the signals required for internalisation and endosomal sorting overlap. No intracellular signalling motif has been identified on the cytosoplasmic domain of MR (adapted from Schweizer et al., 2000).

shape) in association with adapter protein complexes, which select cargo proteins to be transported by binding to the cytosolic face of membrane proteins. A polygonal lattice with an intrinsic curvature is then formed as a result of clathrin polymerisation. The resultant vesicle is then released into the cell, during the final step of bud formation.

Studies involving different MR chimeric constructs revealed that the Y residue in the FENTLY sequence motif, similar to that present in the low density lipoprotein receptor, and the di-aromatic Y–F motif in MR cytoplasmic domain are important for receptor internalisation and correct endosomal sorting, respectively (Schweizer et al., 2000). A similar di-aromatic motif is also present almost at the same distance from the trans-membrane domain in the cation-dependent mannose-6-phospate receptor (Schweizer et al., 2000) which is a type-I integral protein that recycles between the trans-golgi network, endosomes and plasma membrane while transporting naïve acid hydrolases from the trans-golgi network to endosomes (Fig. 1).

Role of MR in antigen processing and presentation

Material endocytosed by antigen presenting cells (APC) is targeted to the endocytic pathway which is composed of three increasingly acidic compartments: early endosomes; late endosomes and lysosomes. As well as the acidic nature of the endocytic cycle, hydrolytic enzymes in the lysosomal compartment also contribute to the degradation of internalised material into shorter oligopeptides appropriate for recognition by class II MHC molecules.

On the other hand, endogenous proteins are processed through the cytosolic pathway which involves the same pathways involved in the normal turnover of intracellular proteins. After processing, peptides derived from endogenous antigens are transported to the endoplasmic reticulum and associate with class I MHC molecules.

Cross-presentation allows some extracellular antigens to stimulate $CD8^+$ cells via the class I MHC pathway. This is essential for immune response against viruses not infecting APC directly and against not endogenously expressed tumour antigens. The exact mechanism is not yet clear; however, it is thought to include the rescue of antigen from lysosomal degradation (Burgdorf et al., 2007).

Fluorescence microscopy analysis revealed that the intracellular MR is dominantly expressed in Rab5a positive early endosomes in both, untreated Mϕ and Mϕ cultured under MR up-regulating conditions (IL-4 and prostaglandin E_2) (Martinez-Pomares et al., 2003; Schreiber et al., 1990; Stein et al., 1992; Wainszelbaum et al., 2006). However, in cytokine-treated Mϕ MR could also be detected in late endosomes (Rab7 positive). These results suggest that, under these conditions, MR might also be transported with its ligands into the late endocytic compartment where Ag becomes associated with cell surface molecules required for Ag presentation. In the same work partial co-localisation of MR with Rab11, a recycling endocytic compartment, was also observed in cytokine-treated cells.

Similar MR localisation was also observed previously by early studies of Engering et al, Sallusto et al. and Prigozy et al. which implicated MR in Ag internalisation and presentation by cultured human DC in the context of MHCII and CD1b (Engering et al., 1997; Prigozy et al., 1997; Sallusto et al., 1995). Prigozy et al. observed co-localisation of MR with CD1b and LAM in MIIC, the cellular compartment where peptides are loaded on MHCII molecules. In contrast, Engering et al. found distinct localisation of MR and MHC class II molecules which would be in agreement with the recycling nature of the receptor and release of Ag in the early endosomal compartment. It could be argued that these differences could be due to the type of MR ligand employed by the researchers, mannosylated-BSA vs. LAM, and the differential engagement of additional PRR in each experimental model. MR involvement in Ag presentation through MHCII is supported by recent data by Dasgupta et al. that implicated MR in the presentation of therapeutic factor VIII (Dasgupta et al., 2007) and by the generation of isotype-switched Ab in response to immunisation with anti-MR mAb *in vivo* (McKenzie et al., 2007).

It is currently being argued that for a receptor to play a major role in Ag processing and presentation by MHCII molecules, Ag would have to be effectively transported to the MCII compartment and since MR recycles back to the cell surface from the early endosomes it might not route its ligands effectively for MHCII presentation. By contrast, CD205 which is known to function as an Ag uptake receptor on murine DC was shown to be located to the late endosome/lysosome vesicles. CD205 is known to lack the di-aromatic motif that enables MR to recycle back to the membrane surface but contains an acidic amino acid sequence (EDE) that is crucial for the transport of the receptor from early endosome to the late endosome/lysosome compartment (Mahnke et al., 2000). These data agree with the results obtained by Burgdorf et al. (2007) who found that MR-internalised Ag (the model Ag ovalbumin, OVA) is targeted into early endosome where it co-localised with the early endosomal markers Rab5 and EEA1 (early endosome antigen-1), but not into late endosomes or lysosomes indicated by Rab7 and lysosome-associated membrane protein-1 (LAMP-1) staining. In this study it was shown that while pinocytosed Ag (Lucifer yellow) and scavenger receptor (SR)-internalised OVA co-localised specifically with lysosomal MHC class II, MR-endocytosed OVA co-localised with MHC class I. The involvement of MR in OVA cross-presentation was further supported by staining with Ab 25-D1.16 which recognises the OVA-derived peptide SIINFEKL in the context of the class I MHC molecule $H-2^b$. This Ab labelled OVA-treated MR^+ DC and Mϕ but was negative for APC lacking MR expression. Therefore, it was concluded that MR leads OVA into the stable early endosome compartment for cross-presentation. In contrast Berlyn et al. (2001) using human DC showed that mannosylation of prostate-specific Ag enhanced $CD4^+$ T-cell responses without affecting $CD8^+$ responses.

Other studies showing the influence of MR on MHC class I antigen presentation involve the work by Apostolopoulos et al. (1995) that showed that the tumour-associated Ag MUC1 linked to oxidised rather than reduced mannan was more efficiently targeted towards the class I pathway. Selective passage of oxidised mannosylated Ag to the class I pathway appeared to occur after the internalisation step, since both ligands bound MR, and was due to the presence of aldehyde groups in the oxidised form of the Ag (Apostolopoulos et al., 2000).

Therefore, as well as recycling back to the cell surface after reaching the early endosome compartment, MR may also direct the ligands to the compartments involved in Ag presentation (through either class I or class II MHC molecules). These events will probably be determined by the nature of the Ag and the state of activation of the cell. Accordingly, while both, endotoxin-contaminated and endotoxin-free OVA, are internalised by MR, only OVA preparations containing endotoxin were effectively presented through the MHCI pathway. This enhanced presentation correlated with the translocation of the peptide transporter TAP to the early endosomal compartment under these conditions (Hotta et al., 2006; Norbury et al., 2004; Rodriguez et al., 1999). The recruited TAP would be involved in the re-import of the processed Ag into the early endosome for loading onto MHC class I molecules and subsequent transport to the cell surface (Burgdorf et al., 2008). This process represents a novel mechanism for the selective presentation of exogenous Ag associated with the presence of infection in the context of MHCI.

MR as a phagocytic receptor

Phagocytosis is an actin-mediated process which involves, in response to interaction with the foreign material, the formation of membrane extensions (pseudopodia) that surrounds and eventually encloses the material in a large vesicle called a phagosome. After been internalised, the F-actin depolymerises and the phagosome starts to move toward the cell interior through the endocytic pathway.

MR has been shown to be involved in the phagocytosis of pathogens, such as *Mycobacterium kansasii* (LeCabec et al., 2005), *M. tuberculosis* (Kang et al., 2005), *Francisella tularensis* (Schulert and Allen, 2006) and *C. albicans* (Marodi et al., 1991). MR has been found responsible for the delay in phagosome maturation after phagocytosis of both pathogenic and non-pathogenic mycobacteria (Astarie-Dequeker et al., 1999). These results were further supported by the fact that the glycopeptidolipid component of *M. avium* complex also inhibited phagosome–lysosome fusion in THP-1 cells via its binding to MR (Shimada et al., 2006).

There are early descriptions in the literature in support of MR acting as a professional phagocytic receptor when transfected into Cos 7 cells (Taylor et al., 2005a). In contrast, CHO cells expressing human MR were found unable to phagocytose *M. kansasii* or mannosylated latex beads (LeCabec et al., 2005) even though they could endocytose mannosylated glycoproteins. Therefore, it appears that the capacity of MR to mediate phagocytosis could depend on which additional components of the phagocytic pathway are present in different cell lines.

MR and cell migration

Bone marrow-derived Mϕ deficient in MR have been shown to have increased random migration and a

normal chemotatic response to a gradient of CSF-1 (Sturge et al., 2007). In this work the authors relate this observation to the increased Mϕ recruitment observed in the lungs of MR-KO animals infected with *P. carinii* (Swain et al., 2003) and to the newly described ability of MR to bind collagens (Martinez-Pomares et al., 2006; Napper et al., 2006). These observations are suggestive of a putative role for MR in the function of podosomes, which are subcellular structures used by myeloid cells for migration and able to mediate degradation of collagen and other matrix components.

Intracellular signalling through MR

MR is considered as a 'non-canonical' PRR able to bind endogenous molecules as well as pathogens that mediates physiological clearance and acts as a bridge between homeostasis and immunity. As such, MR adds an additional level of complexity to the cellular activation process in response to PRR ligation as it can facilitate access to and/or modulate PRR-induced responses.

Accordingly, although the MR was shown to participate in intracellular signalling leading to target gene expression (Chieppa et al., 2003; Fernandez et al., 2005; Lopez-Herrera et al., 2005; Tachado et al., 2007; Yamamoto et al., 1997; Zhang et al., 2004, 2005), it appears to require the assistance from other receptors in order to trigger any signalling cascade which is also consistent with the lack of signalling motifs in its cytoplasmic domain. For instance Shibata et al. (1997) demonstrated that phagocytosable mannose-coated beads and chitin induced TNF-α, IFN-γ and IL-12 secretion by murine spleen cells while non-phagocytosable ones did not. Addition of soluble mannan could not induce the above cytokines, but it was able to inhibit the IFN-γ secretion induced by chitin particles which indicates that the mechanism(s) of chitin particle-induced cytokine production involve MR-mediated phagocytosis. Additionally, work by Zhang et al. (2005) revealed the participation of MR in NF-κB-mediated gene expression in response to *P. carinii* in alveolar Mϕ which would be in agreement with the study by the same group (Tachado et al., 2007) demonstrating that when human HEK-293 cells were transfected with cDNA encoding for human toll-like receptor 2 (TLR2, a PRR) or human MR cDNA alone, there was no IL-8 secretion in response to *P. carinii (jirovecci)*. In contrast, when MR and TLR2 were co-expressed on the same cell IL-8 secretion was detected. In the same work, the authors demonstrated pathogen-induced interaction of MR and TLR2 through co-precipitation studies, which indicates that MR, after

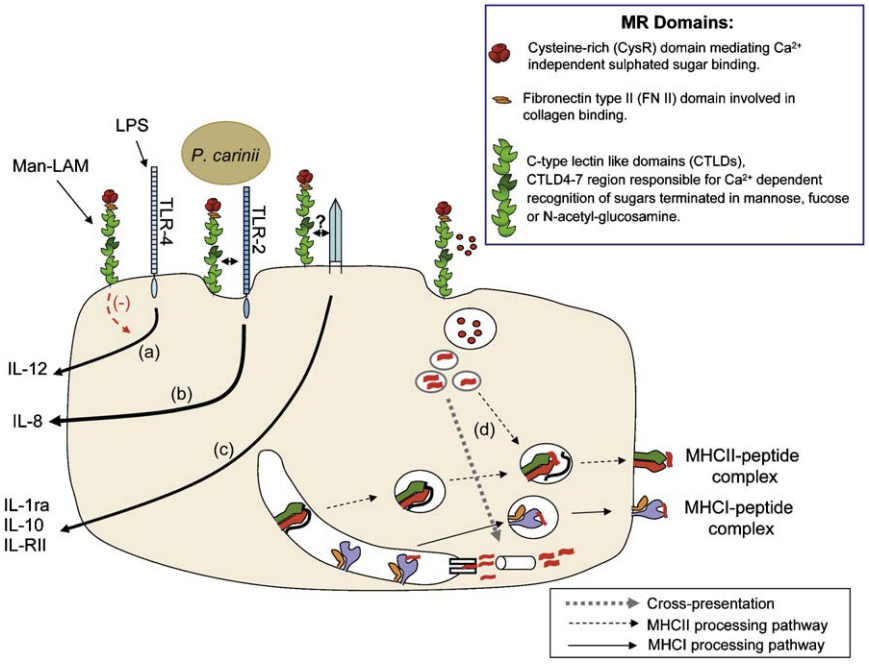

Fig. 2. MR as a complex regulator of immunity. MR is speculated to cooperate with other signalling receptors in the modulation of cytokine secretion. It has been shown that MR engagement by Man-LAM has a negative effect on the production of IL-12 in response to LPS in human DC (a). On the other hand, co-expression of MR and TLR2 is required for IL-8 production in response to *P. carinii* (b). Additionally, engagement of MR by a specific mAb or selected ligands leads to the production of anti-inflammatory mediators (c). Finally, there is strong evidence in support of MR-mediated internalisation favouring cross-presentation (d) in addition to MHCII-mediated presentation of exogenous antigens.

binding with the pathogen, might form a functional complex with TLR2 on the cell surface and facilitate signal transduction.

In a different model, MR has been found directly involved in the triggering of a regulatory-promoting phenotype in human DC (Chieppa et al., 2003). DC treated with mAb PAM-1 specific against MR were unable to produce Th-1 recruiting chemokines but able to release Th2- and T regulatory cell recruiting chemokines, which are negative regulators of Th1 responses, and anti-inflammatory cytokines (IL-1ra, IL-RII). Surprisingly, not all MR ligands had the same functional effects on these cells; while mannan and thyroglobulin had no significant effect on cytokine production, others like mannose-capped LAM (Man-LAM) and biglycan significantly increased IL-10 and decreased IL-12 production in LPS-maturing DC. The Man-LAM mediated cytokine secretion was concluded to be due to MR activation. However, MR is not the only DC receptor capable of recognition of Man-LAM. Other possible receptors are Dectin-2 (Sato et al., 2006) and DC-SIGN (Gringhuis et al., 2007), both of which are shown to signal. The absence of any significant cytokine production in response to mannan, which is a strong MR ligand, further supports this interpretation.

A mechanism that could account for the negative effect of MR ligation on pro-inflammatory cytokine production is the up-regulation of IRAK-M (an inhibitor of TLR signalling that blocks the dissociation of IRAK1 and IRAK-4 from MyD88) as this regulator could be induced by treatment with the MR ligand mannan (Pathak et al., 2005) (Fig. 2).

Conclusions

Mannose is not a ‘danger signal’; it is a signal for effective and, probably quiet or even anti-inflammatory clearance. Endogenous molecules bearing terminal mannose are meant to have a short half life in the extracellular milieu. Consequently, it is not surprising if when looking at the role in immunity of the receptor largely involved in the elimination of these compounds, MR, we encounter a rather complex scenario in which MR ligation does not lead to a hard wired response but to an array of downstream effects largely associated to the reduction of pro-inflammatory cytokines and resolution of inflammation. Probably, the form in which MR ligands are provided, the presence of ligands for other PRR, and the nature of the cells expressing MR are factors that will greatly influence the contribution of MR to cellular activation. As with everything in science, we might have to take it apart further, before we can put it back together again.

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