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Review

Extended and bent conformations of the mannose receptor family

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Abstract. In mammals, the mannose receptor family consists of four members, Endo180, DEC-205, phospholipase A_2 receptor and the mannose receptor. The extracellular domains of all these receptors contain a similar arrangement of domains in which an N-terminal cysteine-rich domain is followed by a single fibronectin type II domain and eight or ten C-type lectin-like domains. This review focuses on the three-dimensional structure of the receptors in the mannose receptor family and its functional implication. Recent research has revealed that several members of this family can exist in at least two configurations: an extended conformation with the N-terminal cysteine-rich domain pointing outwards from the cell membrane and a bent conformation where the N-terminal domains fold back to interact with C-type lectin-like domains at the middle of the structure. Conformational transitions between these two states seem to regulate the interaction of these receptors with ligands and their oligomerization.

Keywords. Mannose receptor, Endo180, DEC-205, phospholipase A_2 receptor, conformation, electron microscopy.

The mannose receptor family of receptors and their functions

C-type lectin receptors are proteins that bind endogenous and exogenous ligands containing carbohydrates in a calcium-dependent manner. Several families of these receptors have been identified that typically contain one domain capable of recognizing the carbohydrate, such as DC-SIGN and dectin-2 [1, 2]. The mannose receptor (MR) family represents one family among these receptors, and contains molecules with several, either eight or ten, lectin-like domains, although only some of these are actually functional in carbohydrate recognition [3–6]. The MR family comprises four members in mammals: the MR (CD206), Endo180 (also known as the urokinase-type plasminogen activator receptor-associated protein uPARAP and CD280), the dendritic cell receptor DEC-205 (CD205) and the M-type phospholipase A_2 receptor (PLA_2R) (Fig. 1). FcRY, an avian yolk sac IgY receptor, was recently discovered and found to be a homolog of the MR family [7]. Each of these receptors can recognize a distinct set of ligands, and, consequently, each performs very specific functions. Nonetheless, a common functional feature of the whole family is that they are all recycled between the plasma membrane and the endosomal machinery allowing the internalization of extracellular ligands and delivery to the interior of the cell [3, 8].

The MR can bind a range of pathogens, such as bacteria and viruses, by the recognition of sugars that are frequently found in their surface but which are less common in mammalian glycoproteins [3, 9–12]. More recently it has also been firmly established that the

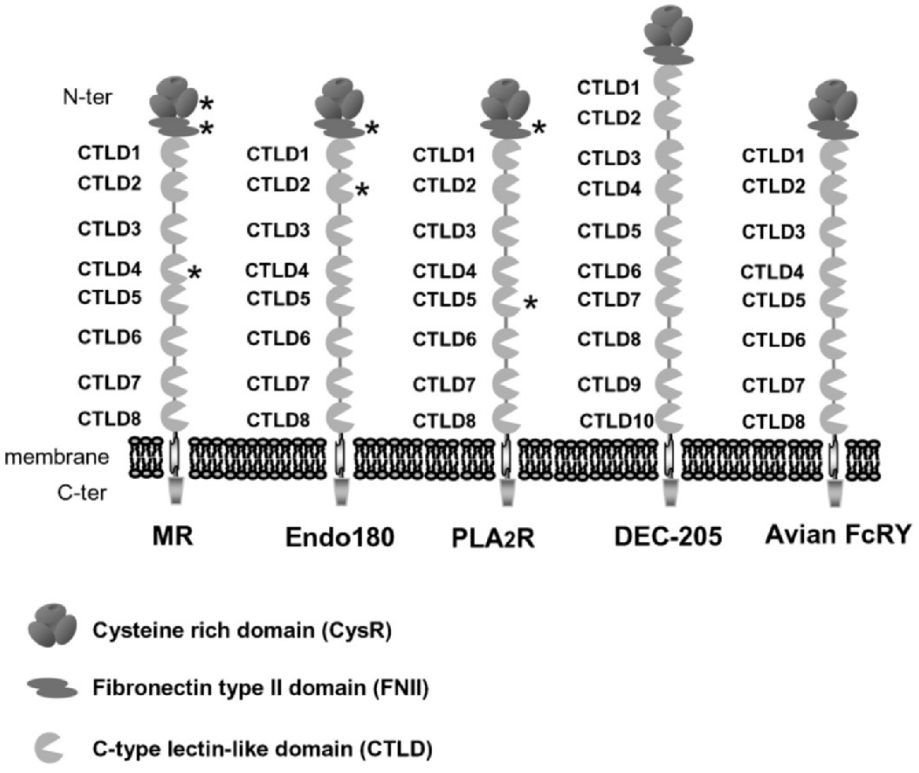

Figure 1. Domain organization of the mannose receptor (MR) family. The functional domains in each receptor have been labeled with an asterisk at its right side, considering only those domains for which there are clear data supporting their interaction with a ligand.

MR binds and internalizes collagen and gelatin in a carbohydrate-independent mechanism [13] and that it can function as an antigen-acquisition system in a subset of dendritic cells [14]. The MR has also been implicated in the regulation of macrophage migration during different stages of pathogenesis [15]. Endo180 also binds to collagen and it has been shown to cooperate in the degradation of collagen [16–24]. In addition, the Endo180-mediated pathway of intracellular collagen degradation seems to be a major path of extracellular matrix turnover during malignancy [25, 26]. Several other functions have been recognized for Endo180 [27–34]. DEC-205 is specific to dendritic cells and regulates the presentation of antigen among other functions [3, 35–40]. Finally, PLA_2R is a receptor for the secreted phospholipases A2, a family of lipolytic enzymes that cleave the fatty acid bond of membrane glycerophospholipids, and it has been implicated in several biological functions [3, 41]. A more in-depth and detailed review on the functions of the receptors in the MR family can be found elsewhere [1–3, 5, 6, 42].

Structural domains of the MR family

All members of the MR family are structurally organized into a linear sequence of globular domains to compose a roughly 180-kDa receptor [2, 3, 5, 43] (Fig. 1). A cysteine-rich (CysR) domain is located at the extreme N terminus, followed by a single fibronectin type II domain (FNII) and eight (ten in the case of DEC-205) C-type lectin-like domains (CTLDs). After a single transmembrane segment, a short cytosolic domain contains motifs capable of recognizing components of the endocytic pathway. This allows their recycling between the plasma membrane and the endosomes, therefore delivering the receptors and their bound ligands towards the interior of the cell.

This collection of domains permits the members of the MR family to work as multi-functional transmembrane receptors that interact with various types of ligands (see below for further details) [4, 12, 13, 41, 44–46]. Nevertheless, not all these domains are actually functional in every receptor and only specific ligand activities have been described in each case (Fig. 1; functional domains labeled with an asterisk). The preservation of the ligand-binding capabilities of each domain type in each receptor was first evaluated by sequence analysis to detect the conservation of key residues required for interaction with their ligands [3]. Subsequently, the predicted functionalities for each domain were confirmed experimentally (see below). These studies revealed that, in the MR, only the CysR domain [47], the FNII [13, 45] and CTLD4 (with cooperation from CTLD5) are functional [12, 48], whereas only FNII [20] and CTLD2 [44] seem to be active in Endo180. On the other hand, analysis of the

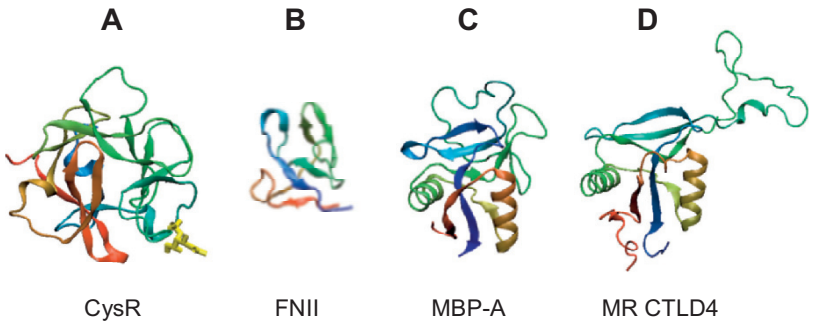

Figure 2. Atomic structures of the domains comprising the extracellular segments of the MR family. Each structure has been represented as a cartoon colored by index order from the N to the C terminus. (*A*) Cysteine-rich domain (CysR) of the mannose receptor (PDB file 1DQG) [49]. Sulfated ligand is displayed in yellow. (*B*) Fibronectin type II domain (FNII) (PDB file 2FN2) [51]. (*C*) Mannose binding protein A (MBP-A) (PDB file 1MSB) [55]. (*D*) C-type lectin-like domain (CTLD) from the CTLD4 of the mannose receptor (PDB file 1EGI) [47]. The extended loop present in this structure seems to be specific of the CTLD4 domain in the MR not being present in the other CTLD domains. All representations in this figure have been performed using VMD (http://www.ks.uiuc.edu/Research/vmd/).

sequences of the domains in DEC-205 predicts that none of its CTLDs have a classical binding activity and in fact no *in vivo* ligands of DEC-205 have yet been found [3]. Interestingly, the PLA_2R has lost all calcium-dependent carbohydrate-binding properties, but its CTLD5 seems to have transformed into a protein-protein interaction module used to bind phospholipase A2 [41, 46].

The CysR domain

The CysR domain was originally identified in the MR as a region with no homology to domains in other proteins and that was able to bind specific sulfated glycoproteins [12]. Subsequently, the crystal structure of this domain bound to a sulfated ligand was resolved revealing a β-trefoil structure reminiscent of the fold found in other unrelated proteins, such as ricin B or the soybean trypsin inhibitor [49] (PDB files 1DQG and 1DQO) (Fig. 2A). The CysR domain comprises 12 anti-parallel β-strands, 4 for each unit in a three-lobe structure. Binding of the sulfated ligands takes place through the most C-terminal lobe and the regions implicated are not conserved in any other member of the family. Accordingly, to date, only the CysR domain of the MR has been demonstrated to be functional in ligand binding.

The FNII domain

FNII is the most conserved of the extracellular domains of the MR family (44–63 % sequence identity) and it can bind several forms of collagen [3] (Fig. 2B). FNII receives its name from a domain found in fibronectin, a large glycoprotein present in the extracellular matrix that can bind denatured collagen [50]. Several structures of this domain solved at atomic resolution show a four β-strand structure arranged into two double-stranded β-sheets and containing several highly conserved aromatic residues [51] (PDB file 2FN2). Although the exact nature of the interactions between FNII and collagen are not clear, sequence analysis suggests that the residues needed for collagen binding might be conserved in all the family. Endo180 was demonstrated to bind collagen through the FNII domain [4, 20, 21, 25] and to actively participate in collagen degradation pathways [4, 20, 21, 25]. A clear verification of collagen recognition *in vivo* by the MR has only been found recently [13, 45, 52]. Also, PLA_2R mediates adhesion to collagen but it is unclear how this relates to the main biological function of the protein as PLA_2R.

The CTLD

Initial characterization of the MR family described these proteins as having multiple C-type carbohydrate recognition domains (CRDs). However, the majority of these domains do not have C-type lectin activity [8, 32, 44, 46, 53, 54], so a more accurate term to refer to these structures is C-type lectin-like domains (CTLDs) [54]. A unique characteristic of the receptors in the MR family is the presence of several of these CTLD, most of which lack sugar-binding activity. The atomic structure of CTLD4 from the MR shows a conserved fold comprising two β-sheets and two short α helices [47, 54] (PDB file 1EGI) (Fig. 2D). This atomic structure is very similar to that solved for the rat serum mannose-binding protein (MBP-A) [55] (PDB file 1MSB) (Fig. 2C). Functional CTLD can bind mannose, fucose and *N*-acetylglucosamine and such interactions require coordination with Ca^{2+}. The residues needed for Ca^{2+}-dependent sugar recognition

are only conserved in those CTLDs that are functional. In the MR, only CTLD4 binds sugars, although several lines of evidence indicate that CTLD5 might contribute somehow to ligand recognition by CTLD4 [3]. Interestingly, the CTLD4 of the MR contains an extended loop that is not found in any other CTLDs of the members of the family and it seems, therefore, to be a unique feature [47] (Fig. 2D). Endo180 also binds mannose, fucose and *N*-acetylglucosamine in a Ca^{2+}-dependent manner, but its sugar-binding activity is restricted to CTLD2 [44] and this is the only CTLD domain containing the conserved amino acids found in functional C-type lectins. PLA_2R does not posses Ca^{2+}-dependent sugar-binding functions but its CTLD5 appears to have evolved to mediate protein-protein interaction as part of its function as a receptor for PLA_2. In the case of DEC-205, analysis of its sequence predicts that none of its CTLD retains sugar-binding functionality.

Extended and bent conformations of the MR family members influence ligand binding

One of the most fascinating issues concerning the three-dimensional organization of the receptors of the MR family has been the recent discovery that these can probably display significantly distinct conformations. Initial suspicions suggesting that the conformation of the MR could not be as simple as an extended linear conformation were suggested by the fact that the functional ligand binding CTLD4 and CTLD5 are located in the middle of the linear structure of the molecule [43]. Other receptors usually have the ligand binding domains positioned at their further end, away from the plasma membrane so that putative interactions can be more easily achieved. Napper et al. [43] conducted the first investigations to determine the overall conformation of the MR. Using hydrodynamic measurements on analytical ultracentrifugation they tested two alternative models, either an extended or a U-shaped-folded and more compact conformation. These authors showed that their experimental results were more compatible with a structural model based on an extended and fairly rigid conformation of the MR. Another important contribution (partially confirming previous suggestions) revealed that CTLD1 is in close contact with CTLD2, as is the case for CTLD4 and CTLD5. On the other hand, the linker between CTLD2 and CTLD3 and that between CTLD5 and CTLD6 were found to be more susceptible to protease cleavage.

This apparently settled issue concerning the conformation of the MR regained interest when a low-resolution study on the three-dimensional structure of the most N-terminal domains in Endo180 was reported by our group in collaboration with Prof. Clare M. Isacke (ICR, London). This work used single-particle electron microscopy (EM) techniques [56, 57] to visualize and reconstruct the three-dimensional structure of the CysR, FNII, CTLD1 and CTLD2 domains of Endo180 [58] (Fig. 3B). Strikingly, it was revealed that the polypeptide chain was bent and that the CTLD2 contacted the CysR domain. Subsequent EM work confirmed that the N-terminal domains of Endo180 are arranged as a globular structure at the tip of an extended tail containing the remaining CTLDs [59]. Notably, CTLD2 is the only functional CTLD in Endo180 and these initial structures therefore indicated that such conformational arrangement could be implicated in the regulation of ligand binding by the receptor.

A further turning point in the structural characterization of the MR family took place when a close structural homolog (FcRY) was discovered in chicken [7]. In mammals, acquired immunity is passed from the mother to the offspring by the transport of certain immunoglobulins across a cellular barrier by specific receptors [60]. This transportation is pH dependent so that either binding or the release of the immunoglobulins by the receptor at the required compartment is accomplished by the different pH environment at each location by means of chemical changes. Interestingly, West et al. [7] found that chicken yolk sac membranes contained a receptor playing a role in the transfer of passive immunity to the young in a pH-dependent manner. This receptor was found to be an avian homolog of the MR family containing a CysR domain, a single FNII and eight CTLDs with a sequence identity between 29% and 55% with its mammalian homologs. Surprisingly, a collection of elegant experimental approaches revealed that at acidic pH this avian receptor displayed a bent conformation capable of binding ligands, whereas an extended conformation was observed at basic pH, which was incapable of ligand binding. Using a series of truncated versions of the receptors, the authors concluded that the compact ligand-competent conformation at acidic pH was formed by the interaction between the N-terminal CysR-FNII domains folded back upon the CTLD1–8 region. Another interesting finding was the discovery, using analytical ultracentrifugation, that the extended conformation of the avian receptor (at basic pH) behaved as monomer, while the ligand-binding compact conformation (at acidic pH) seemed to form dimers. The oligomerization of several molecules of receptors has also been described for the MR [59, 61, 62], and it is possible that such multimerization phenomena could somehow contribute to the regulation of the activity of the

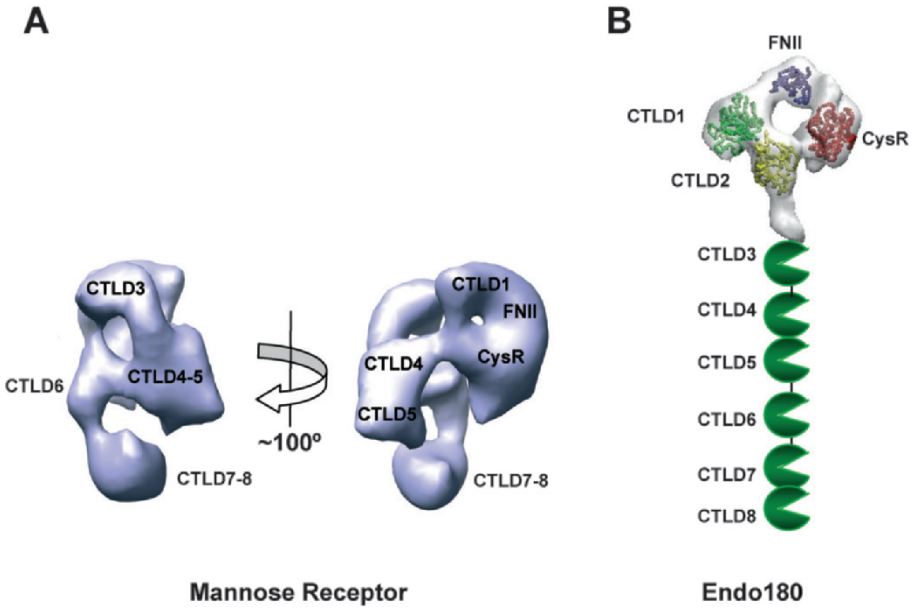

Figure 3. Three-dimensional reconstructions of the MR and Endo180. These three-dimensional structures are derived from data collected using a transmission electron microscope as input for image processing and three-dimensional reconstruction techniques [56, 57]. (*A*) Two views of the bent conformation of the MR structure at 33 Å resolution (EMD code 1213) [59]. (*B*) Three-dimensional model of Endo180 modified from Boskovic et al. [59]. Rendering of the EM reconstructions in this figure has been performed using UCSF chimera [73].

receptors *in vivo*. Whatever the case, the data derived from this avian homolog strongly suggested that the receptor could alternate between extended and folded conformations, only one of which is capable of binding their ligands [7].

Could this structural model be extended to other members of the MR family? Initial structural analysis of Endo180 using EM suggested that a bent conformation can, indeed, exist in these receptors, in contrast to the first reports on the extended conformation of the MR [58]. When preparations of soluble versions of purified MR lacking the transmembrane and cytosolic segments were observed in the electron microscope and reconstructed in three dimensions, the MR was found to display a twisted S-shaped conformation (Fig. 3A). A globular head encloses the N-terminal CysR, FNII and CTLD1 to CTLD4 domains arranged into a compact region followed by a tail decorated by globular domains assigned to CTLD5 though CTLD8 [59] (EMD code 1213 at http://www.ebi.ac.uk/msd/) (Fig. 3A). This structure reveals that CTLD1 and CTLD2 and CTLD4 and CTLD5 are close together, a pattern coincident with that already proposed by Napper at al based on the susceptibility of the MR to cleavage by proteases [43]. Significantly, this bent conformation is different to that of Endo180 since the CysR and FNII domains of the soluble MR contact CTLD4 rather than CTLD2. CTLD2 in Endo180 and CTLD4 in MR are the only domains active in calcium-dependent sugar binding and these structures strongly indicate that such three-dimensional arrangement must somehow contribute to the regulation of ligand binding properties of the receptor. The discrepancy between the conformational models for the MR could reflect that the conformation of these receptors and also their oligomerization state could be extraordinarily sensitive to the experimental conditions [43, 59]. An interesting difference between the mammalian receptors of the MR family and FcRY, the avian yolk sac IgY receptor, is that FcRY binds IgY at low pH [7], whereas the mammalian receptors seem to be active at neutral pH [12, 44, 46]. Interestingly, FcRY shows a compact conformation at acidic pH [7], compatible with the bent conformations of the mammalian members of the family at neutral pH. Hence, the avian IgY receptor might have adapted its structure and its response to environmental changes in the pH conditions of the two compartments between which immunoglobulins must be transported.

Putting all this information together, it is therefore clear that the MR can appear in at least two conformations, extended and bent, similar to the avian homolog of the MR family. Likewise, Endo180 shows a compact folded conformation at the most N-terminal region. Interestingly, changing pH conditions seems to affect the conformation of the MR, Endo180 and the avian receptor [7, 58, 59]. Therefore, a structural model is starting to emerge where two conformations of the MR family of receptors, extended and bent, regulate either ligand recognition and/or oligomerization (Fig. 4). A direct proof of this relation between conformation and ligand binding has only been firmly establish for the avian receptor but the MR has also been shown to migrate as different species in a gel filtration chromatography displaying differential selectivity towards ligands [59, 61, 62]. Has this model any reminiscence to the behavior found in other types of cell receptors? Some findings

have revealed that the activation of integrin could involve a transition between a bent and an extended conformation [63–66]. At least three different conformations of integrin ectodomain have been solved by EM and X-ray crystallography and it is suggested that a bent conformation of integrin is inactive, whereas the active form is extended. More recently, several structures of the insulin receptor have been solved at atomic resolution showing that the extracellular segments of this receptor adopt a bent conformation that potentially regulates its activation [67–69]. A more detailed picture of the mechanistic implications of such conformational transitions has come from crystallographic studies performed with the extracellular domains of the epidermal growth factor (EGF) receptor (EGFR, also known as ErbB) [69, 70]. Inactivated EGFR structures show an "auto-inhibited" conformation where N-terminal regions of the receptor interact with the C-terminal segments of the ectodomain. This conformation can bind ligand, but ligand binding establishes an extended conformation in which the N-terminal region has rotated upwards and is now capable of interacting with other activated receptor to constitute a dimeric activated complex. Therefore, it seems plausible that transitions between "bent" and "extended" conformations could be a general structural mechanism in receptors to regulate accessibility to ligand binding and/or oligomerization domains, although the specific regulatory details will surely be different for each family of receptors. Moreover, many proteins, not only receptors, actually regulate their activation by controlling the access to a catalytic site by other domains in the protein. For instance, an either open or closed conformation of the Vav3 guanosine exchange factor (GEF) controls the interaction of its Rho/Rac substrate with the catalytic domain [71].

How can the three-dimensional arrangement of the receptors in the MR family regulate their function? A possible clue to this puzzle comes from the fact that in Endo180 and MR the extent of the compactness of the "bent" conformation relates to which CTLD is functional in each receptor. In Endo180, the N-terminal domains fold back to interact with CTLD2 [58], whereas in the MR they do so to contact CTLD4 and CTLD5 [59]. These three-dimensional structures of Endo180 and MR were derived from preparations that were shown to be capable of binding ligands *in vitro*, so it is likely that such a compact conformation is actually functional. The experiments with the avian receptor revealed that the compact conformation seems to be the only one that can bind its ligand [7]. Hence, it seems possible that the bent conformation could serve to spatially arrange the ligand-competent domains specifically for each receptor to allow

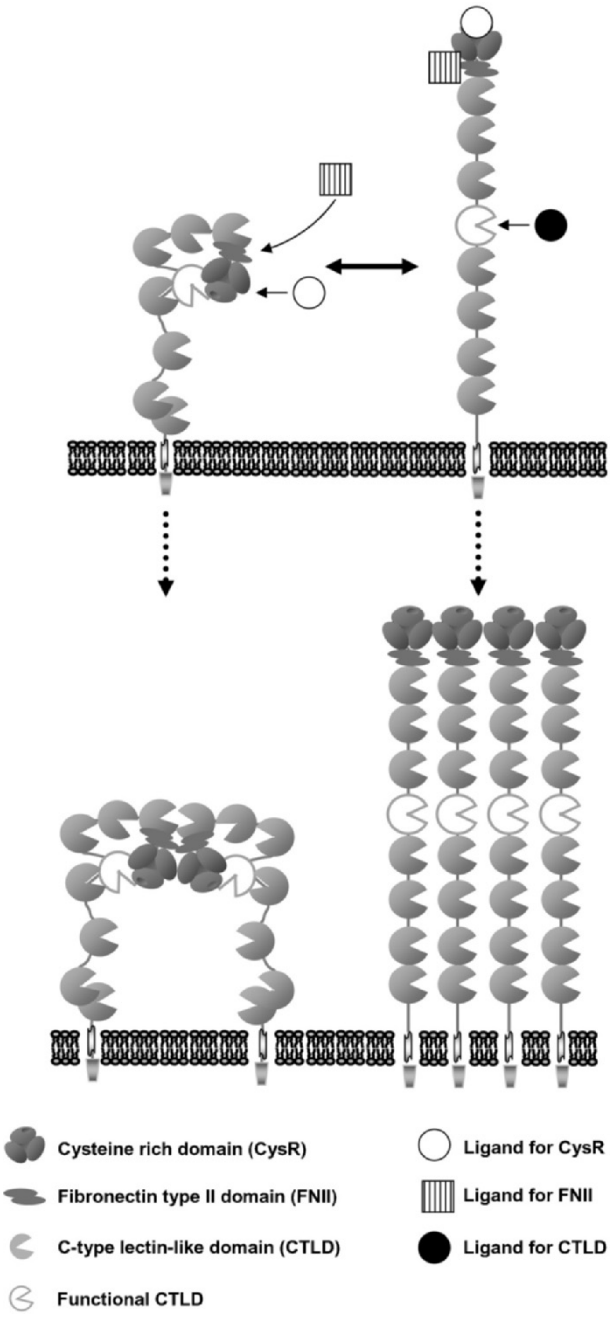

Figure 4. Model for the conformational transitions between an extended and a bent conformation of the MR family. For simplicity, only the mannose receptor is used as a model. In the bent conformation, some ligands could bind to specific domains of the receptor, whereas others would not interact with the receptor if the access to the binding site has been occluded. A hypothetical possibility could be that the interaction between the N-terminal domains in the MR with the functional CTLD (CTLD4–5 in MR) would spatially block ligand binding to these CTLDs, while still allowing the interaction of the CysR and FNII domains with substrates. Changes in the conditions of the environment or recognition of some of the ligands could trigger a switch to the extended conformation releasing the auto-inhibition and exposing previously occluded ligand-binding sites. Moreover, depending on the actual member of the MR family, each of the two possible conformations (bent and extended) could have a distinct tendency to form multimers, adding a new level of regulation of their functions.

substrate recognition. Also, since the functional CTLDs are found in the middle of the polypeptide chain, the bent conformation could serve to project these domains closer to their possible ligands. An alternative and probably more provocative model could be one inspired by our present understanding of the role of similar conformational changes in the EGFR [69, 70, 72] (Fig. 4). The receptors in the MR family display several ligand-binding properties: sulfated sugars by the CysR domain, collagen by FNII domain and C-type lectin activity by some of their CTLDs. Extensive work on Endo180, the MR and PLA_2R has demonstrated that these domains in isolation are necessary and sufficient to bind their specific ligands (sugars or collagens) [3]. It is therefore possible that the bent conformation, as in the case of the EGFR, can expose some of these domains, making them accessible for binding, while "auto-inhibiting" others. One possibility might be that collagen, for instance, could bind the FNII domain, while binding of ligands to the functional CTLD (CTLD2 in Endo180 and CTLD4–5 in MR) would be spatially blocked by the N-terminal domains. Changes in the conditions of the environment such as pH or recognition of one ligand could trigger a switch to the extended conformation. As in EGFR, the extended conformation could allow the appearance of new binding properties, maybe allowing binding of ligands to the specific CTLD domain, that were "auto-inhibited" in the bent conformation. The EGFR shows that only the extended conformation could dimerize to further activate the receptor. Similarly, for the MR family, the extended and bent conformation could have a distinct propensity to interact to form larger oligomers or multimers that could add a further regulatory level to their functions [61, 62]. Nevertheless, the precise role of each conformation in oligomerization and each protein remains to be defined.

In conclusion, an alternation between bent and extended conformations in the MR family, somehow regulated by either differences in the pH or other mechanisms, might serve as a "conformational switch" to regulate ligand binding, the oligomerization state and/or selectivity in different compartments and functional states. The details of this structural model and how this contributes to regulating ligand binding and selectivity remain to be investigated. Still missing is a clear link between the three-dimensional conformation of these receptors, and the intimate mechanism to control recognition of the ligand. Furthermore, these receptors can be affected by differential glycosylation and can be found in several oligomerization states, adding a further level of complexity. Also, the structure-function relationships proposed for the MR family are based on experiments performed with the MR, Endo180 and the avian homolog, whereas fewer data are available for DEC-205 and PLA_2R. Hence, this extended/bent model must serve as an initial framework to start understanding the structural basis regulating the receptors of the MR family, but the actual detailed mechanisms should be further explored.

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