Review

Extended and bent conformations of the mannose receptor family

O. Llorca

Centro de Investigaciones Biológicas, Spanish National Research Council (CSIC), Ramiro de Maeztu 9, Campus Universidad Complutense, 28040 Madrid (Spain), Fax: +34-91-5360432, e-mail: ollorca@cib.csic.es

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Abstract. In mammals, the mannose receptor family consists of four members, Endo180, DEC-205, phospholipase A\textsubscript{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\textsubscript{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\textsubscript{2} receptor (PLA\textsubscript{2}R) (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
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, PLA2R 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 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.](image-url)