CD206 as a pattern recognition and prognostic marker for immune regulation and cancer

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Abstract

CD206, also known as the mannose receptor (MR), is a type-C lectin receptor predominantly expressed on the surfaces of macrophages, dendritic cells, and liver endothelial cells. This review will discuss its function in immune surveillance, antigen presentation, and endocytosis as both a scavenger receptor and pattern recognition receptor. It will focus on the mechanism of how it binds mannose-rich glycans as a means of clearing pathogens. Furthermore, the review will focus on the role of CD206 in cancer progression. In the tumor microenvironment (TME), CD206 is highly expressed on M2-polarized tumor associated macrophages (TAMs), contributing to immunosuppression, angiogenesis, and metastasis. Elevated CD206 expression is associated with poor prognosis in various cancers, suggesting its potential as a prognostic marker in cancer progression. However, emerging evidence also suggests that CD206 can exert antitumor effects by recruiting cytotoxic immune cells through chemokine secretion.

Keywords: CD206, tumor-associated macrophages (TAMs), tumor microenvironment (TME), M2 polarization

Introduction

CD206, also referred to as the mannose receptor (MR) is a specialized pattern recognition receptor involved in the immune system's ability to detect and process pathogens (Gazi & Martinez-Pomares, 2009).

Found on the surface of macrophages, dendritic cells, and liver endothelial cells, CD206 is essential for endocytosis and antigen presentation, thereby contributing to immune surveillance and regulation (Gazi & Martinez-Pomares, 2009). As a type-C lectin receptor, CD206 binds to mannose-rich glycans on the surface of pathogens, facilitating their uptake and clearance (Feinberg et al., 2021). Beyond its normal function, CD206 has gained attention for its involvement in cancer progression, particularly through its association with tumor-associated-macrophages (Haque et al., 2019; Heng et al., 2023). In the tumor microenvironment (TME), CD206 is highly expressed and serves as a marker of M2-polarized macrophages such as tumor associated macrophages (TAMs), inflammatory dendritic cells in selected lymphoid organs, and liver, splenic, lymphatic, and dermal microvascular endothelial cells (Haque et al., 2019). These macrophages exhibit immunosuppressive and pro-tumorigenic properties, promoting tumor immune evasion, facilitation of angiogenesis, and driving metastasis (Heng et al., 2023). High expression of CD206 in multiple myeloma has been linked to poor prognosis in patients and worse clinical outcomes (Kvorning et al., 2020). Additionally, M2 macrophages are preferentially enriched in acute myeloid leukemia (AML) and other blood cancers, which means CD206 may serve as a new prognostic marker (Xu et al., 2020). While $CD206^+$ TAMs are often linked to immunosuppression, recent studies show they can also exert anti-tumor effects by producing CXCL9, which recruits $CXCR3^+$ $CD8^+$ T cells and NK cells to the tumor site. This recruitment supports the cDC1–NK–$CD8^+$ T cell axis, enhancing cytotoxic responses and improving outcomes with immunotherapies (Modak et al., 2022).

This review will focus on elucidating the structural biology, ligand-binding mechanisms, and immunological functions of CD206, with an emphasis on its dual role in the TME as both an anti-tumor and pro-tumor agent.

CD206 Structure

CD206 is a type I transmembrane protein found on macrophages and dendritic cells that plays a crucial role in both adaptive and innate immunity (Kazuo et al., 2019). It functions by binding and internalizing various glycoproteins through carbohydrate recognition. Its structure consists of an intracellular domain, a transmembrane segment, and an extracellular domain. Its extracellular structure is an integral part of pathogen recognition, consisting of an N-terminal cysteine rich (CR)

domain that binds glycoproteins containing sulfated sugars, a fibronectin II (FNII) domain, and eight carbohydrate recognition domains (CRDs) that bind sugars like mannose and fucose (Azad et al., 2014). These structures allow it to scavenge foreign mannose N-linked glycoproteins since many pathogens are coated with mannose-containing structures (Nielsen et al., 2020).

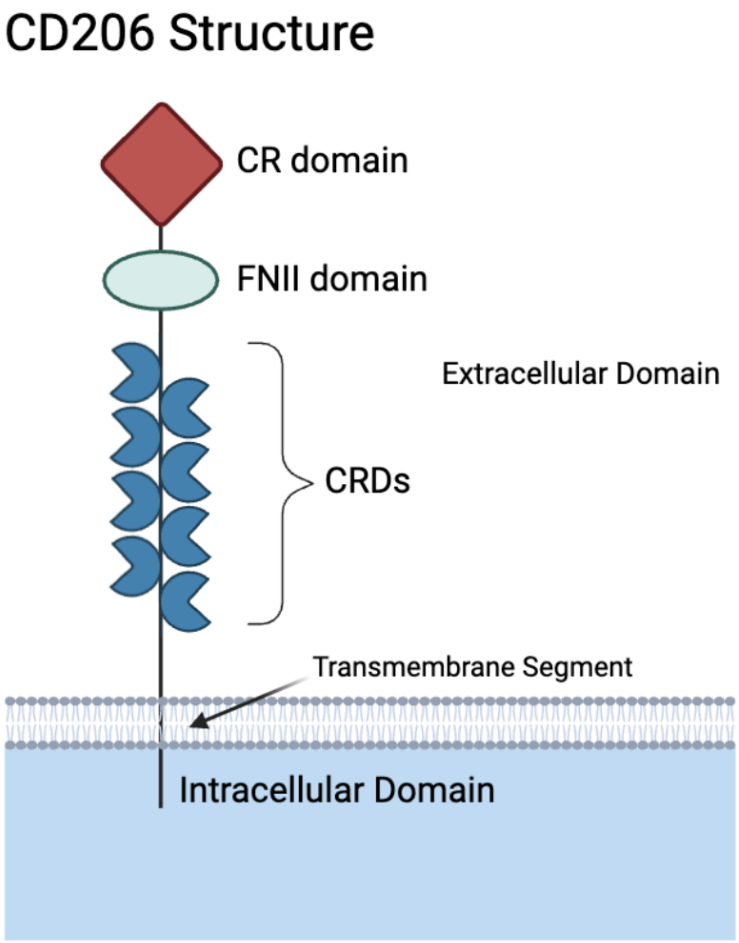

Figure 1. Depiction of mannose receptor. CRD4 interacts with mannose-rich glycans, including D-mannose, L-fucose, and N-acetylglucosamine.

CD206 Function

CD206 acts as both a pattern recognition receptor (PRR) and a scavenger receptor. As a PRR, CD206 helps detect danger signals as part of the innate immune response. CD206 is a type of PRR called a C-type lectin receptor, which binds to various sugars found on the surface of pathogens (Cummings, 2022). Specifically, it recognizes mannose, fucose, and N-acetylglucosamine. At a molecular level, the carbohydrate-recognition domain 4 (CRD4) of the receptor requires Ca^{2+} molecules to bind sugars (Feinberg et al., 2021). For mannose, it binds to the receptor using its 3rd and 4th hydroxyl group (OH^-) to attach to a specific Ca^{2+} ion in CRD4, the Ca^{2+} holding the sugar in place. In Manα1-2Man, a disaccharide made of two mannose units linked together, supplementary interactions take place with the second mannose, making the binding stronger. Fucose residues can bind in several orientations, using either its 2nd/3rd or 3rd/4th OH^- group. In oligosaccharides containing fucose, additional interactions occur with the other sugars which increase the affinity (Feinberg et al., 2021). These mechanisms are responsible for its role in pathogen recognition and binding.

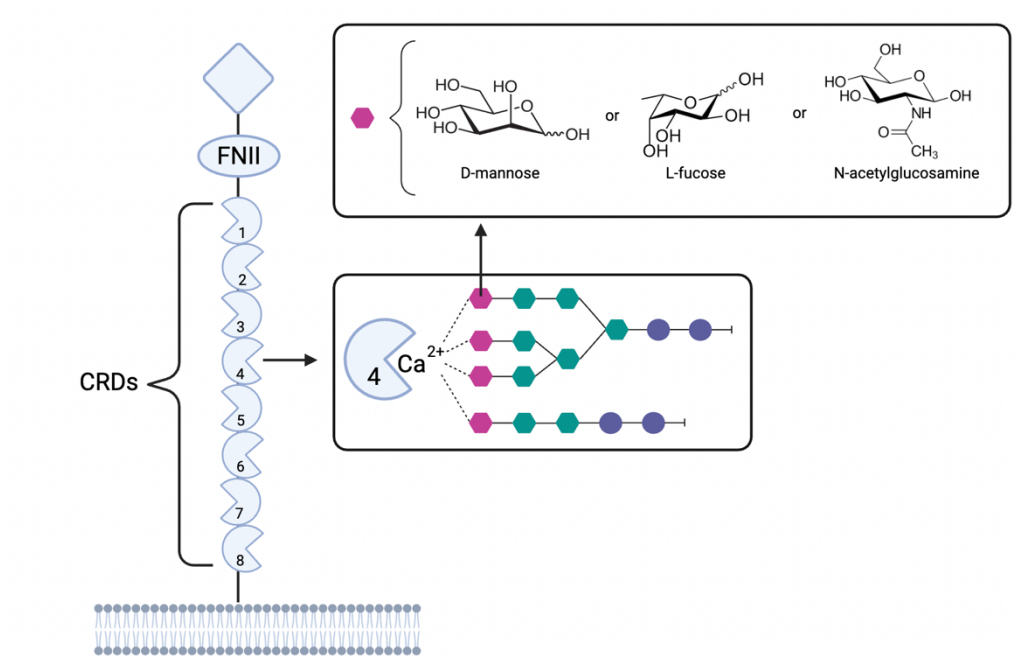

Figure 2. Depiction of mannose receptor. CRD4 interacts with mannose-rich glycans, including D-mannose, L-fucose, and N-acetylglucosamine.

CD206 is a highly expressed scavenger receptor by M2 macrophages that facilitates in the uptake and clearance of pathogens through endocytosis, phagocytosis, adhesion and signaling (Nielsen et al., 2020). It undergoes several rounds of endocytosis and membrane recycling between the cell membrane and endosomal compartments, as the receptor is pulled into the cell once it binds to a sugar (Nielsen et al., 2020). Inside the cell, the acidic pH levels cause ligand dissociation. After releasing the ligand, the receptor is cycled back to the membrane, allowing it to process many molecules continuously (Bellato et al., 2022). CD206 expression is upregulated by IL-4 and IL-3 through the STAT6 pathway (Borriello et al., 2015). Once CD206 binds to its target, it initiates signaling pathways within the macrophage. This process involves the phosphorylation of tyrosine residue and Syk, which transmit the signal downstream (Rajaram et al., 2017). The signaling pathways activated lead to the rearrangement of the actin skeleton to induce phagocytosis.

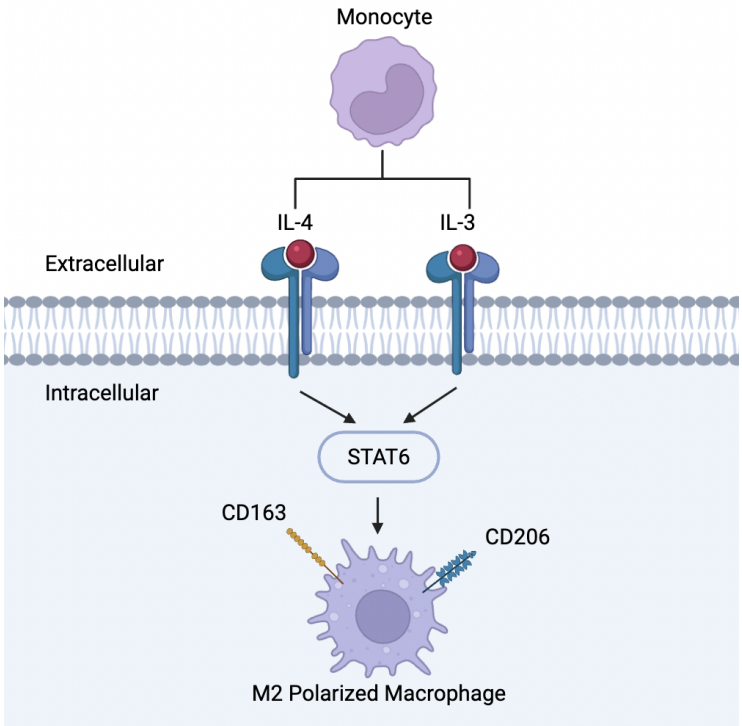

Figure 3. M2 macrophage polarization highlighting CD206 and CD163 expression in M2 phenotype through STAT6 pathway

Furthermore, the mannose receptor mediates antigen presentation to $CD4^+$ and $CD8^+$ T-cells. MR internalization directs antigens into non-degradative endosomes, where they avoid lysosomal degradation. From this compartment, MR-internalized antigens are mostly used for cross-presentation on MHC I molecules, which activate $CD8^+$ cells. If MR is cross-linked, it instead sends antigens to lysosomes for MHC II presentation, which activate $CD4^+$ cells (van der Zande et al., 2021). This triggers the immune response.

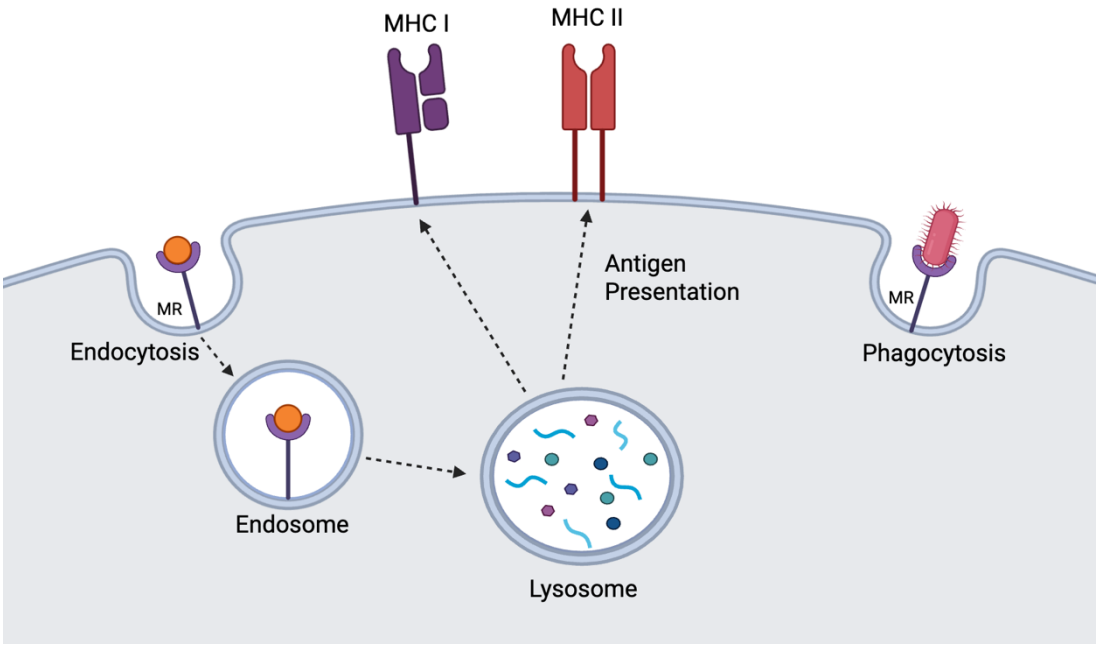

Figure 4. Cellular functions of the mannose receptor. The membrane-bound MR detects extracellular ligands and internalizes them. The engulfed antigens are delivered to early endosomes, where they are primarily processed for cross-presentation on MHC I molecules, leading to the activation of $CD8^+$ T cells. Membrane-bound MR undergoes phagocytosis to eliminate pathogens. MHCII and CD4 T cell activation

CD206 in the TME

In the tumor microenvironment (TME), CD206 is highly expressed on M2-like tumor-associated macrophages (TAMs). It contributes to immunosuppression by suppressing T cell activity, especially $CD8^+$ killer T-cells. CD206 is a marker of M2 macrophages, which secrete anti-inflammatory cytokines like IL-10 and TGF-β (Mia et al., 2014).

$CD206^+$ TAMs promote tumor growth and cancer cell proliferation through their angiogenic properties. In solid tumors, TAMs secrete extensive amounts of proangiogenic growth factors. They cluster around tumors to form a protective niche. In oral squamous cell carcinoma (OSCC), $CD206^+$ TAMs support tumor growth and cancer cell proliferation through EGF production. EGF acts as a chemotactic factor in the TME and promotes the motility and invasion of tumor cells, driving metastasis (Haque et al., 2019). In blood cancers such as acute myeloid leukemia (AML) and multiple myeloma (MM), CD206 is highly expressed on M2 TAMs (Xu et al., 2020). Thus, CD206 correlates with worse prognosis in various cancers and may serve as a clinically useful biomarker.

Conversely, recent studies prove that CD206 also display anti-tumor properties. Specifically, these TAMs can robustly express CXCL9, a chemokine that recruits $CXCR3^+$ $CD8^+$ T cells and natural killer (NK) cells into the tumor microenvironment. These lymphocytes, once recruited, release FLT3L and XCL1, which are crucial for the survival and expansion of conventional type 1 dendritic

cells (cDC1s)(Modak et al., 2022). cDC1s are potent antigen-presenting cells that stimulate cytotoxic T cell responses. This cDC1–NK–CD8$^+$ T cell axis is associated with stronger immune activity against tumors and better responses to immunotherapies like immune checkpoint blockade (Ray et al., 2025). This duality suggests that CD206's role is tumor-context-dependent; they may either suppress immunity or organize key immune modules that enhance tumor rejection.

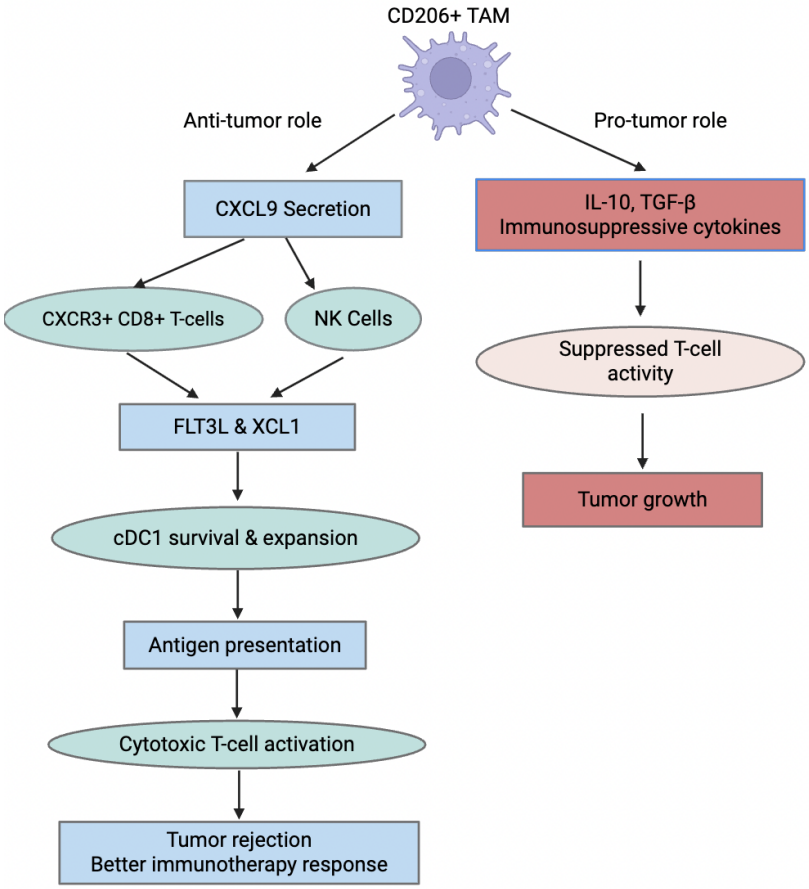

Figure 5. Dual role of CD206$^+$ TAMs in tumor immunity. M2-polarized macrophages promote tumor growth via secretion of IL-10 and TGF-β. M2-polarized macrophages promote tumor rejection via recruitment of CXCR3$^+$ CD8$^+$ T cells and NK cells through CXCL9 to support cDC1 survival.

CD206 Potential in Cancer Immunotherapy

Targeting CD206 with specific therapies is a potential strategy for cancer immunotherapy. Activating CD206 can potentially reprogram M2-like macrophages towards a more anti-tumor phenotype (ref). Manipulating its expression could be a potential strategy to either deplete immunosuppressive TAMs or enhance the function of CD206$^+$ APCs (Ray et al., 2025). Targeting CD206 could be combined with other cancer therapies, like chemotherapy or checkpoint inhibitors, to enhance their effectiveness. It can also be used as a target for imaging techniques, such as positron emission tomography (PET), single-photon emission computed tomography (SPECT) and near-infrared fluorescence (NIRF), to visualize and quantify M2-like macrophages in tumors, which could help in predicting post-chemotherapy tumor relapse and metastasis (Zhang et al., 2017).

Conclusion

CD206 plays a critical role in shaping the immune response through its involvement in antigen recognition, immune cell recruitment, and regulation of macrophage polarization. Its expression on tumor-associated macrophages not only reflects an immunosuppressive microenvironment but also

holds significant prognostic value across various cancers. In recent research, reports on CD206 hold promising anti-tumor properties by stimulating anti-tumor chemokines. Future research should clarify the molecular signals that dictate whether CD206 promotes or suppresses tumors, as this will be critical for designing effective CD206-targeted therapies.

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