



The application of MARCO for immune regulation and treatment

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Received: 27 October 2023 / Accepted: 30 December 2023
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Abstract

Macrophage receptor with collagen structure (MARCO) is a member of scavenger receptor class A (SR-A) and shares structural and functional similarities with SR-A1. In recent years, many studies have shown that MARCO can trigger an immune response and has therapeutic potential as a target for immunotherapy. Studies have shown that alterations in MARCO expression following pathogen infection cause changes in the functions of innate and adaptive immune cells, including macrophages, dendritic cells, B cells, and T cells, affecting the body's immune response to invading pathogens; thus, MARCO plays a crucial role in triggering the immune response, bridging innate and adaptive immunity, and eliminating pathogens. This paper is a comprehensive summary of the recent research on MARCO. This review focuses on the multiple functions of MARCO, including adhesion, migration, phagocytosis, and cytokine secretion with special emphasis on the complex interactions between MARCO and various types of cells involved in the immune response, as well as possible immune-related mechanisms. In summary, in this review, we discuss the structure and function of MARCO and its role in the immune response and highlight the therapeutic potential of MARCO as a target for immunotherapy. We hope that this review provides a theoretical basis for future research on MARCO.

Keywords MARCO · Immune response · Immune cell activation · Signaling pathway · Immunotherapy

Abbreviations

MARCO	Macrophage Receptor with Collagen Structure
SR-A	scavenger receptor class A
PAMPs	pathogen-associated molecular patterns
PRRs	pattern recognition receptors
TLRs	Toll-like receptors
SRs	scavenger receptors
SRCR	scavenger receptor cysteine rich
TNF α	tumor necrosis factor alpha

IFN- γ interferon-gamma

Introduction

The immune system, including the innate and adaptive immune responses plays a vital role in the body's mechanism of defense. The innate immune response promptly detects invading pathogens and triggers the activation of adaptive immunity. Then, the immune system effectively eradicates pathogens by inflammatory reactions during the early stages of infection [1]. Known as pathogen-associated molecular patterns (PAMPs), microbial metabolic products are recognized by pattern recognition receptors (PRRs) within the innate immune system, thereby eliciting an immune response. Examples of PAMPs include lipopolysaccharides, peptidoglycans, lipoteichoic acid, and unmethylated CpG DNA. PRRs exhibit a broad spectrum of specificity and are capable of recognizing numerous diverse ligands [2, 3].

Macrophages serve as the cells that are primarily responsible for executing innate immunity and are crucial elements in the frontline defense against pathogens. The surface PRRs on macrophages are capable of identifying PAMPs

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and initiating intracellular cascade reactions. Through the presentation of antigens, these reactions subsequently activate the adaptive immune system [4, 5]. In recent years, an extensive amount of research has been conducted focusing on macrophage PRRs. Notable examples of these receptors include Toll-like receptors (TLRs), NOD-like receptors, C-type lectin receptors, and scavenger receptors (SRs) [1, 5].

SRs exhibit the ability to bind multiple ligands and participate in various biological processes including phagocytosis, secretion, and adhesion. Additionally, these receptors, as components of the innate immune system, play a vital function in identifying, degrading, and eliminating pathogens. Among the diverse subtypes of SRs, SR-A is particularly important because it contributes to a multitude of biological functions and participates in various pathophysiological processes within the host. In recent years, studies have mainly focused on elucidating the physiological roles of SR-A, such as cell adhesion, apoptosis clearance, lipid metabolism, and antigen presentation. According to the naming criteria established in 2017, there are the following six SR-A subtypes: SR-A1, SR-A1.1, SR-A3, SR-A4, SR-A5 and SR-A6 (also known as MARCO) [6, 7].

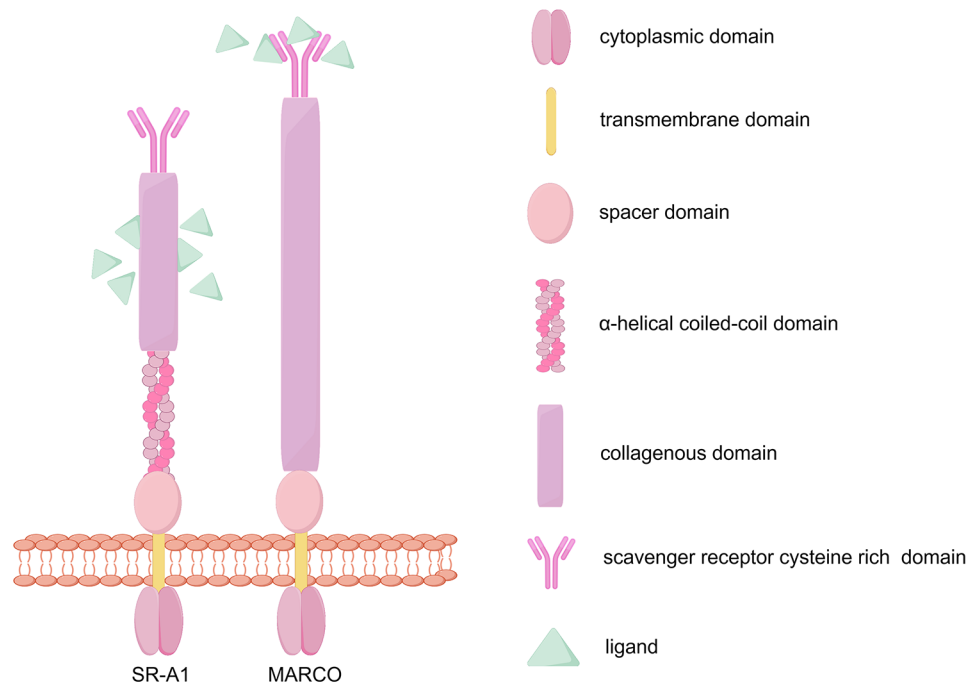
The structure of MARCO

In 1995, Elomaa and colleagues successfully cloned a receptor with a structure similar to SR-A1, now referred to as MARCO, for the first time. This achievement was accomplished by screening a mouse macrophage cDNA

library using a cDNA probe [8]. Subsequently, in 1998, Elomaa's team cloned the MARCO gene from human liver and spleen DNA libraries by employing mouse MARCO cDNA probes. Furthermore, they compared the amino acid sequence of MARCO in humans and mice using the BestFit program. A comparative analysis was conducted based on the amino acid sequences of MARCO in humans and mice, revealing that 68% of the amino acids exhibited consistency, while 77% displayed similarity [9]. Additionally, in 2000, Elshourbagy et al. conducted an expressed sequence tag analysis of human macrophage cDNA libraries, which further confirmed the substantial homology between human and mouse MARCO [10].

MARCO, also known as SR-A6, plays an important role as an SR-A. The MARCO gene is located on chromosome 2 and encodes a transmembrane protein that can form trimer molecules by binding collagenous domains. The following five domains make up MARCO: a short cytoplasmic domain, a transmembrane domain, a spacer domain, a long collagenous domain and a scavenger receptor cysteine rich (SRCR) domain [11]. There are notable structural similarities between MARCO and SR-A1; however, MARCO has a longer collagenous domain and does not have the α -helical coiled-coil domain that is present in SR-A1 (Fig. 1). Additionally, MARCO directly binds ligands via two conserved arginine residues (R x R motifs) within the SRCR domain, whereas SR-A1 primarily binds ligands through its collagenous domain due to the absence of R x R motifs. Furthermore, the SRCR domain of MARCO serves various functions, including ligand binding, cell recognition, the

Fig. 1 The differences between the MARCO and SR-A1 structures (By Figdraw). MARCO has a longer collagenous domain and does not have the α -helical coiled-coil domain that is present in SR-A1; MARCO directly binds ligands via the SRCR domain, whereas SR-A1 primarily binds ligands through its collagenous domain



augmentation of proinflammatory signals, and the regulation of cell adhesion [12–14].

The distribution and ligands of MARCO

MARCO expression and distribution are highly specific; its expression is not ubiquitous among macrophages but rather limited to certain subsets. Previous research has demonstrated that, under physiological conditions, MARCO expression exclusively occurs in macrophages that reside in the spleen, lymph nodes, and peritoneum, while macrophages in other tissues do not have MARCO expression [8]. Yet later studies have shown that MARCO can also be expressed in lung tissue [15]. Nevertheless, upon stimulation by pathogens such as bacteria or viruses, macrophages in various tissues and organs may express MARCO. For instance, in cases of lung infection by *Streptococcus pneumoniae* or the inhalation of environmental particles such as silica, lung macrophages express MARCO [16–20]. Similarly, in autoimmune hepatitis model mice, liver macrophages have higher levels of MARCO expression [21]. Furthermore, in Alzheimer's disease model mice, the presence of MARCO on microglia was detected [22]. Additionally, several studies have indicated that certain subtypes of tumor-associated macrophages express MARCO, and MARCO-expressing tumor-associated macrophages often accumulate around tumor cells [23]. As mentioned above, macrophages are the only cells that express MARCO, according to previous studies. However, according to recent studies, MARCO may also be expressed on dendritic cells and epithelial cells such as keratinocytes, in addition to macrophages [24–26].

Regarding the ligands of MARCO, MARCO possesses cationic residue clusters within its domain that are responsible for ligand binding [27]. Consequently, the ligands of MARCO exhibit a polyanionic structure and can be broadly classified as follows: (1) un-opsonized and environmental particles such as silicon dioxide, latex beads, nanoparticles, and titanium dioxide [17, 18, 28, 29]; (2) chemically modified proteins such as modified low-density lipoproteins (ac-LDL, ox-LDL) [19, 30, 31]; (3) a variety of bacterial products, including oligodeoxynucleotides, lipopolysaccharides, and teichoic acid [21, 32, 33]; (4) polynucleotides, such as polyinosinic acid and polyguanylic acid (polyG) [21]; and (5) other molecules with polyanionic structures, such as fucoidan. In addition, endogenous ligands such as soluble oligomeric amyloid- β peptide have also been reported [22].

The function of MARCO

Cell adhesion and migration

The adherence and migration of immune cells play a crucial role in the normal functioning of both innate and adaptive immunity. Prior studies on SRs have shown a strong correlation between SR-A and the adhesion of macrophages [34, 35]. Due to the similarity in structure to SR-A1, we speculate that MARCO is also involved in cell adhesion and migration. Previous studies have indicated that MARCO might function as the main scavenger receptor for astrocyte and microglia adherence to β -amyloid in Alzheimer's disease [36]. Subsequently, according to Chen et al., MARCO knockout mice displayed notable changes in macrophage structure within the spleen marginal zone, including decreased cell adhesion and a significant decrease in the number of resident macrophages. These observations suggest that MARCO may impact the adhesion and migration of macrophages [37]. Furthermore, a study on dendritic cells revealed that MARCO can influence the adhesion and migration of dendritic cells, as evidenced by the close relationship between MARCO expression and the formation of lamellipodia and dendritic structures in dendritic cells [38, 39]. These results suggest that MARCO can mediate the adhesion and migration of immune cells. Therefore, MARCO may play an important role in the migration, residence and function of immune cells at the invasion site of pathogens. This hypothesis provides a possible direction for study of the activation and initiation of the immune response (Fig. 2a).

Phagocytosis

The primary focus of research on the MARCO is its role in mediating phagocytosis. Notably, MARCO is known to facilitate phagocytosis through the recognition of the following three main ligands: environmental particles, microorganisms, and apoptotic and necrotic cells. Upon ligand recognition, MARCO triggers the reorganization of the macrophage cytoskeleton, upregulates F-actin expression, increases filopodium formation, and promotes macrophages to clear invading pathogens in a noninflammatory manner [40–42]. According to previous studies, there is a significant reduction in the ability of MARCO^{-/-} mouse macrophages to phagocytize bacteria, un-opsonized particles, and apoptotic cells [28, 43–46]. Furthermore, investigations have revealed that MARCO on the surface of lymphatic endothelial cells aids in the capture of viral particles by endothelial cells. The entry of viruses into the bloodstream from the lymphatic system leads to their recognition and subsequent clearance by macrophages expressing MARCO, and

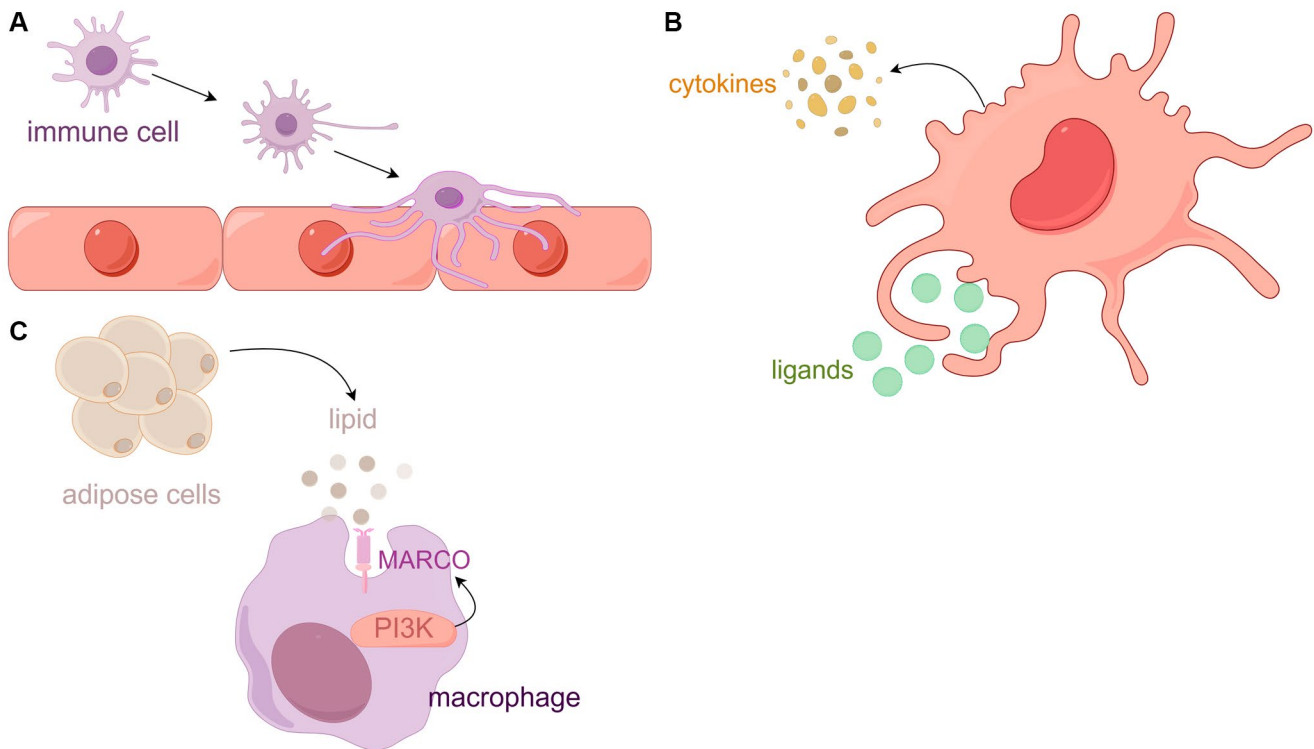


Fig. 2 The function of MARCO (By Figdraw). (a) MARCO is involved in cell adhesion and migration. (b) MARCO mediates phagocytosis and the inflammatory response of immune cells. (c) Macrophages regulate lipid metabolism by regulating MARCO expression through the PI3K pathway

MARCO knockout mice exhibited more severe viremia and more viral spread [47]. Therefore, MARCO plays a key role in macrophage-mediated phagocytosis. The promotion of macrophage phagocytosis by MARCO helps it clear pathogens and maintain internal homeostasis (Fig. 2b).

Inflammation

Inflammation serves as the body's defensive reaction to external stimuli, and there are both infectious and noninfectious forms. Typically, this response is beneficial as it eliminates invading pathogens; however, there are instances where it exacerbates harm. Extensive research has shown that the activation of intracellular signaling pathways, the transcription of inflammation-related genes, and the stimulation of macrophages to produce cytokines associated with inflammation, such as IL-1 α , IL-1 β , IL-15, and tumor necrosis factor alpha (TNF α), can be initiated by the binding of ligands to MARCO. For example, in the context of a silicosis mouse model, alveolar macrophages possessed the ability to identify silica particles via the MARCO receptor, thereby initiating the activation of inflammasomes and subsequently triggering an inflammatory response. Conversely, the absence of MARCO expression in knockout mice significantly diminished the level of inflammation [20]. Additionally, MARCO also plays an important role in augmenting

the bactericidal capabilities of macrophages by promoting cytokine production and recruiting monocytes. Previous studies have indicated that MARCO knockout mice exhibit higher susceptibility to lung infections than abdominal infections [48]. And research has demonstrated that following adenovirus infection, macrophages expressing MARCO are activated. This activation process facilitates the transduction and recognition of adenovirus, augments the proinflammatory immune response and facilitates the elimination of adenovirus and virus-containing cells by macrophages [49]. Nevertheless, some studies have indicated that macrophages lacking MARCO expression are more likely to activate inflammatory responses and release proinflammatory cytokines. This phenomenon is associated with an augmented degree of inflammation in the early stages of lung tissue and an exacerbation of lung injury in MARCO knockout mice [50, 51]. Consequently, the regulation of the inflammatory response by MARCO may be influenced by numerous factors, including the infectious environment, ligand type, and cellular state (Fig. 2b).

Lipid metabolism

Prior research has demonstrated that macrophages modulate lipid metabolism [52], with particular emphasis on the pivotal role of SRs located on macrophage surfaces in the

regulation of lipoprotein cholesterol metabolism. These receptors have the ability to bind and internalize modified lipids, thereby contributing to reduced cholesterol levels and the preservation of optimal lipid metabolism [31, 53]. Rerez et al. found that the increase in LPS-induced macrophage uptake of chylomicrons treated with dalcetrapib was parallel to the expression level of MARCO on its surface, suggesting that there was a correlation between the expression of MARCO and the uptake of chylomicrons treated with dalcetrapib [54]. Recent investigations have further suggested that the presence of MARCO may enhance the binding and internalization of lipids. In a study of MARCO knockout mice, fat uptake by macrophages was reduced, and insulin resistance and glucose tolerance were more likely. This study showed that macrophages can drive the expression of MARCO through the PI3K signaling pathway to promote lipid uptake, decomposition and metabolism, thus promoting metabolic balance [55]. This study further revealed that MARCO plays a critical role in the metabolism of lipids, and these results may provide ideas for the treatment of metabolic diseases (Fig. 2c).

MARCO and the immune response

MARCO regulates the functions of innate immune cells

The innate immune response is recognized as the primary defense mechanism in the body. Numerous studies have linked the level of MARCO expression following pathogen infection to functional modifications in neutrophils, dendritic cells, macrophages, and natural killer cells. Extensive research has demonstrated that MARCO plays a crucial role in regulating the development, activation, and immune response of innate immune cells.

Macrophages are key components of the innate immune response, often being perceived as the “sentinels” and “resident troops” of the immune system. They act as the initial protective line by monitoring pathogen invasion and subsequently initiating relevant responses. Furthermore, macrophages facilitate the recruitment and activation of other innate immune cells, which then collectively combat pathogen invasion. Notably, the expression of MARCO in macrophages can be induced by bacterial, fungal, and viral stimuli, and the role of MARCO in pathogen infection is complex, and distinct types of pathogen infection can induce diverse functional alterations associated with MARCO. MARCO regulates macrophage polarization, adhesion, migration, phagocytosis, cytokine secretion, and other essential biological functions, as mentioned earlier. These studies also

suggest that MARCO may mediate the interaction between macrophages and other immune cells.

When acute injury takes place, macrophages and neutrophils collaborate. Neutrophils constitute the majority of white blood cells in the bloodstream and account for approximately 50-70% of peripheral white blood cells. Neutrophils are among the initial cells that are recruited following pathogen invasion. In instances of local infection or injury, they can swiftly traverse the blood vessel wall and infiltrate the tissue to fulfil their function. Studies have indicated that compared to wild-type mice, MARCO^{-/-} mice exhibit downregulated expression of chemokines or chemokine receptors, resulting in impaired recruitment of neutrophils. As a result, the number of neutrophils remains stable throughout the injury process [56]. This study suggests that MARCO may be involved in the chemotaxis and recruitment of neutrophils, although the mechanism needs to be further explored. In view of the functions of neutrophils in resistance to bacterial invasion, the phagocytosis of pathogens, and inflammation, these studies also indirectly indicate that MARCO may play a role in the above processes.

Monocytes, the largest white blood cells, serve as a crucial defense mechanism against intracellular bacterial and parasitic infiltration in human. Additionally, they contribute to the preservation of overall immune function by identifying and eliminating tumor cells and participating in the immune response. Moreover, monocytes are key in the process of antigen presentation to lymphocytes and they initiate specific immune responses through phagocytosis. According to the findings of Xu et al., compared to MARCO^{+/+} mice, MARCO^{-/-} mice exhibited a notable decrease in the recruitment and accumulation of monocytes in the early stage of *Cryptococcus neoformans* infection. This finding suggests that the expression of MARCO in the lung facilitates the recruitment and accumulation of monocytes, which promotes resistance against pathogen invasion [57]. Therefore, MARCO can affect the innate immune response by modulating the aggregation and function of monocytes; this finding indicates that MARCO plays an important role in initiating the innate immune response.

Mast cells, along with macrophages and dendritic cells are extensively distributed in tissue and are the primary cell populations involved in pathogen recognition and interaction in the immune system. Upon recognizing pathogens, mast cells release inflammatory factors into the cytoplasm, recruit diverse immune cells to combat infection, and initiate the inflammatory process. As stated by Brown et al., mast cells can identify silica, generate cytokines and ROS, and induce proteolytic activity, all of which are closely associated with the abundance of MARCO on their surface. The generation of ROS and TNF α in the bone marrow mast cells of MARCO^{-/-} mice was significantly decreased following

exposure to silica compared to that in the bone marrow mast cells of control mice. Previous research suggests that MARCO plays a more prominent role in promoting the mast cell response to silica than SR-A1 [58]. These findings suggest that mast cells can release inflammatory mediators upon the recognition of silica, and MARCO is believed to augment the mast cell response to silica, thereby contributing to the recruitment of immune cells.

Dendritic cells play a pivotal role in the immune system by serving as the principal cells responsible for antigen presentation. As crucial intermediaries between the innate and adaptive immune systems, dendritic cells present antigens to various immune cells, thereby initiating an immune response. In their investigation of gene expression patterns in tumor lysates, Grolleau et al. observed a significant upregulation of MARCO expression in pulsed dendritic cells compared to non-pulsed dendritic cells. Based on the role of MARCO in ligand binding and phagocytosis in the immune response, they hypothesized that MARCO may be involved in the formation of plate-like structures and dendritic processes in dendritic cells [24]. Furthermore, Granucci et al. demonstrated a correlation between MARCO expression and dendritic cell shape and adhesion, as well as the ability of MARCO to induce cytoskeleton rearrangement in these cells. Transfection of immature dendritic cells with MARCO resulted in the acquisition of mature dendritic cell characteristics, whereas MARCO knockout preserved the morphology of immature dendritic cells [59]. Xu et al. discovered that dendritic cells exhibited reduced recruitment and maturation efficiency in MARCO^{-/-} mice, and MARCO played a crucial role in the phagocytosis of *Cryptococcus neoformans* particles by dendritic cells [57]. The aforementioned studies indicate that the expression of MARCO in dendritic cells significantly influences their functionality. To gain deeper insights into the role of MARCO, Kissick's research team conducted a transcriptome analysis of dendritic cells in MARCO-deficient mice. The study provided evidence that defects in MARCO can impact the function of dendritic cells and various signal transduction pathways, including cell migration, the endocytosis signaling pathway, tight junction signaling, dendritic cell maturation, and the Rho family signaling pathway, among others, and modify the transcription levels of members in the proinflammatory NF- κ B family [60]. These findings suggest that MARCO could serve as a promising target for modulating the morphology and function of dendritic cells to regulate innate immunity.

Moreover, natural killer cells play pivotal roles in the immune system of humans. Functioning as immune cells, they are tasked with eliminating aberrant cells, including those afflicted by aging damage and viral infection. In addition to their formidable cell-killing capabilities, natural killer

cells also have a robust immune regulatory function, which allows them to modulate the body's immune system through interactions with other immune cells. Consequently, natural killer cells exhibit potent cell-killing and immune regulatory functions in the defense against external pathogen intrusion. In clinical investigations, natural killer cells exhibit therapeutic efficacy against several malignant tumors; thus, natural killer cells have promising prospects in diverse applications. Eisinger et al. conducted an experiment in which they stimulated natural killer cell activation in mice by administering antibodies that specifically targeted MARCO. The findings of their study revealed that the administration of MARCO-targeting antibodies resulted in the activation of TNF-related apoptosis-inducing ligands, which subsequently reversed the inhibition of natural killer cell activation by macrophages within the tumor microenvironment. Furthermore, this activation augmented the cytotoxic capabilities of natural killer cells, thereby enhancing their ability to eliminate tumor cells [61]. Following this study, La Fleur et al. discovered a strong association between the expression of MARCO in tumor-associated macrophages and the quantity of natural killer cells in small cell lung cancer. MARCO expression decreased the proliferation and activation of natural killer cells, thereby diminishing their ability to effectively eliminate tumors. Conversely, natural killer cells lacking MARCO exhibited increased antitumor activity [62]. Sarhan et al. further showed that inhibitory tumor-associated macrophages expressing MARCO impeded the infiltration of natural killer cells into tumor tissues, thus impairing their killing function in pancreatic ductal adenocarcinoma, and when macrophages were repolarized by targeting MARCO, natural killer cell function was significantly enhanced [63]. Based on the findings of these studies, the expression of MARCO is likely intricately associated with the functional capacity of natural killer cells. By specifically targeting MARCO, the cytotoxicity of natural killer cells can be enhanced; thus, strategies targeting MARCO offer a viable approach for tumor treatment when combined with other immunotherapeutic strategies.

In summary, MARCO is closely related to the function of various innate immune cells and participates in various processes related to innate immunity, which suggests that MARCO plays a key role in the immune response in the body (Fig. 3).

MARCO mediates the functions of adaptive immune cells

Innate immunity and adaptive immunity are intricately linked. Innate immune cells induce and enhance adaptive immune responses after recognizing invading pathogenic microorganisms. As previously discussed, there is a close

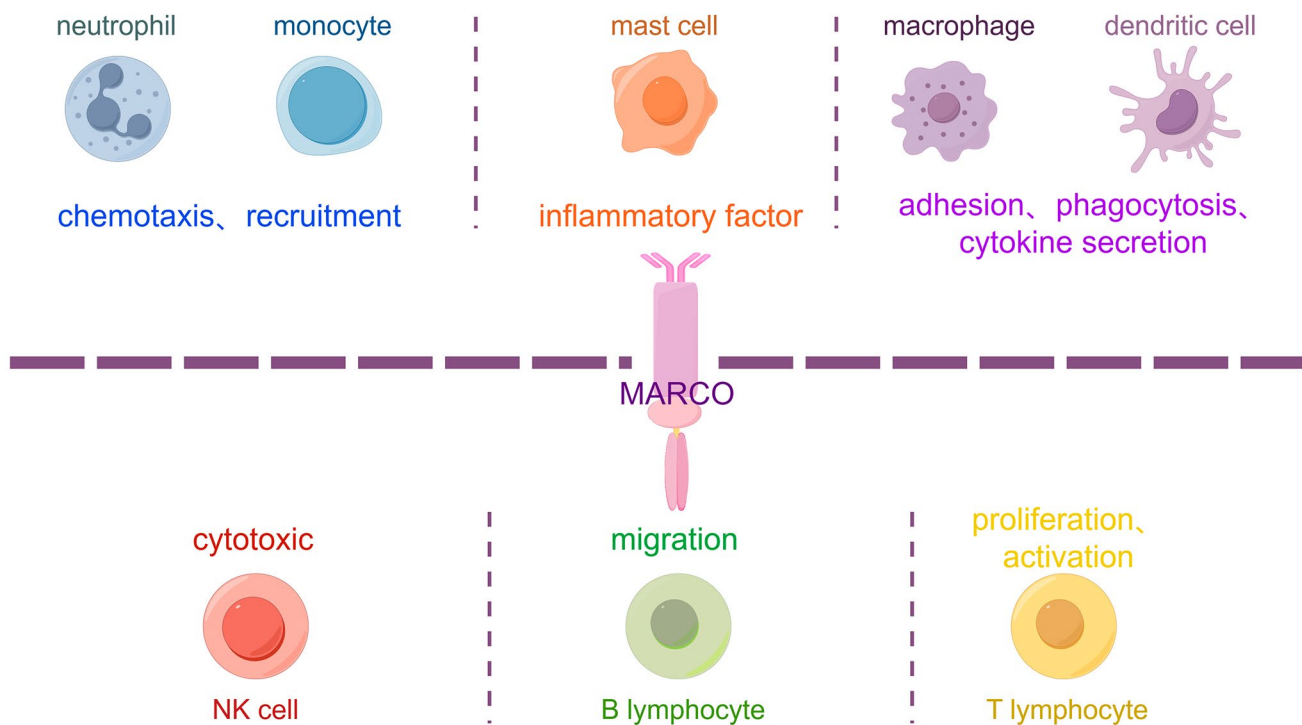


Fig. 3 MARCO regulates the functions of immune cells (By Figdraw). MARCO can regulate the biological functions of innate immune cells such as macrophages, dendritic cells, neutrophils, and adaptive immune cells such as T and B lymphocytes

association between MARCO and the immune system. Furthermore, recent research has elucidated the crucial role of MARCO in governing the function of adaptive immune cells, and established its importance in the context of adaptive immunity. A notable example is the regulation of B-cell activation, function, and antigen recognition by MARCO [64, 65]. Studies have shown that MARCO is important for the localization of B cells in the marginal zone. MARCO can influence the interaction between B lymphocytes in the spleen and macrophages, which consequently impacts the migration of B lymphocytes [66–68]. These investigations propose that MARCO on macrophages governs the functionality of B lymphocytes through an unknown mechanistic process.

Moreover, in addition to B lymphocytes, MARCO can influence humoral immunity by affecting the functionality of T lymphocytes. Matsushita et al. demonstrated that the application of monoclonal antibodies targeting MARCO on dendritic cells can enhance the production of interferon-gamma (IFN- γ) by T cells during cocultivation, thereby augmenting their antimelanoma efficacy [38]. In the context of *C. neoformans* infection, the absence of MARCO led to an elevation in the proportion of TNF α -producing CD4⁺ T cells and a reduction in the proportion of IL-5 and IL-13-producing CD4⁺ T cells, implying that MARCO may influence T-cell polarization and facilitate the development

of a Th2-type immune response [69]. La Fleur et al. found a strong correlation between MARCO expression and T lymphocyte infiltration by analyzing transcriptome data. The findings indicated a positive correlation between the levels of MARCO expression and the presence of regulatory T-cell genes (e.g., FOXP3, TGF- β 1), exhausted T-cell genes (e.g., PDCD1, CTLA4), and cytotoxic T-cell genes (e.g., CD8A, PRF1). Moreover, previous research demonstrated that the expression of MARCO on macrophages can inhibit T-cell proliferation and activation in vitro, leading to a reduction in cytokine production, including that of IFN- γ , and impaired T cell tumor-killing capabilities when cocultured with macrophages [23, 62]. In addition, Sarhan et al. discovered that the expression of MARCO on tumor-associated macrophages hinders the proliferation and activation of T lymphocytes, and targeting MARCO can induce the repolarization of macrophages, thereby enhancing the tumor-killing capabilities of T cells [63].

These studies revealed the important role of MARCO in the interaction between macrophages, T lymphocytes, and B lymphocytes and showed that MARCO plays a crucial role in the bridge between innate immunity, adaptive immunity, and the development and maintenance of the local immune environment; thus, these studies highlight the importance of MARCO in both innate and adaptive immunity (Fig. 3).

MARCO regulates immune signaling pathways

The initial defense against bacterial and viral infections heavily relies on the activation of innate immune cells, and MARCO plays a pivotal role in this activation. Furthermore, a comprehensive analysis of bioinformatics data conducted by a research team revealed a substantial correlation between MARCO and various signaling pathways, including the NF- κ B, PI3K, STAT3, and P53 signaling pathways [70].

When the body is invaded by bacteria or viruses, MARCO plays a crucial role in recognizing and binding to antigenic proteins or products that these pathogens express. This interaction triggers various intracellular signal transduction pathways and leads to alterations in immune cell function, particularly in macrophages and dendritic cells. Additionally, pathogen invasion can also upregulate the expression of MARCO through alternative mechanisms, subsequently inducing changes in cell function. For instance, Wu et al. conducted in vitro cytological experiments where cells were treated with IFN- γ to simulate the effects of influenza. The research revealed that IFN- γ treatment resulted in an upregulation of MARCO expression and an enhancement of MARCO-mediated phagocytosis based on Akt activation [71]. Additionally, *Bacillus baumannii* was found to induce the activation of STAT3 through IL-10, leading to the induction of MARCO expression and the subsequent promotion of macrophage bactericidal activity [72]. Furthermore, tumor-derived extracellular vesicles were augmented macrophage phagocytosis by upregulating MARCO expression through the activation of Akt-STAT3 signaling [46]. Research has demonstrated that PI3K plays a role in regulating lipid uptake through the regulation of MARCO expression, thereby helping maintain metabolic balance [55]. Recent studies have indicated that cancer cells activate the STATA3 pathway via IL-6, IL-10, and other factors to upregulate MARCO expression, leading to macrophage polarization and the immune escape of cancer cells, which occurs as a result of the upregulated expression of IL-10, PD-L1, and other molecules [73].

Activation of MARCO also influences key molecules involved in the inflammatory pathway. For example, activation of the ERK1/2 pathway leads to the production of cytokines associated with inflammation, and research has shown that ERK1/2 is inhibited and cannot produce proinflammatory cytokines in mice lacking MARCO [74]. In addition, MARCO can interact with TLRs to regulate the secretion of cytokines. According to previous research, the inhibition of MARCO expression can significantly downregulate the expression of TLR4 and the activity of the NF- κ B signaling pathway, thereby inhibiting the secretion of inflammatory cytokines [21]. Furthermore, TLRs can regulate the

expression of MARCO through various signaling pathways [75]. Studies have shown that TLR2 significantly promotes the MARCO-mediated inflammatory response by interacting with the SRCR domain of MARCO, and MARCO expression is downregulated after TLR2 knockout [76]. TLR4 can also regulate MARCO expression via a MyD88-dependent pathway [64].

Moreover, the upregulation of MARCO expression can lead to the phosphorylation of Syk kinase, which plays a crucial role in macrophage phagocytosis. This phosphorylation event triggers the phosphorylation of PI3K and Rac, which subsequently activates downstream signaling pathways. Phosphorylated PI3K is involved in the regulation of phagocytic cup formation. The Rac protein can activate the signal for actin polymeric rearrangement, which subsequently activates the signaling pathway of the proximal cell membrane. This activation leads to the nucleation of the actin associated protein 2/3 complex and the polymerization of F-actin. Therefore, macrophage-mediated phagocytosis is promoted through the formation of pseudopods [40, 42, 55, 77].

In conclusion, MARCO, as a crucial element of the innate immune response, plays a role in regulating the phagocytosis of pathogens and the release of cytokines. Thus, further investigation to understand the role of MARCO following bacterial and viral infections and the related mechanisms is warranted (Fig. 4).

The application of MARCO 6.1

Current approaches that target MARCO

When searching the studies on MARCO over the years, we found that a large number of studies did not have specific methods to target MARCO, and as described earlier, some studies showed that the SRCR domain was an important site to target on MARCO. Some previous studies have shown that SRCR is the key domain of MARCO that binds to ligands, activates downstream signaling pathways, and induces changes in cell function by studying the natural variants of MARCO (the SRCR domain contains only the first eight amino acid residues) [13, 78, 79]. In contrast, Sankala et al.'s study showed that if MARCO had only SRCR domain monomers, it would exhibit lower ligand binding activity, indicating that the SRCR domain binding function requires the collagen domain. Subsequently, Chao et al. also found that the collagen domain was closely related to the uptake of dextran-coated superparamagnetic iron oxide nanoparticles by macrophages. However, there are few studies on the collagen domain of MARCO, and MARCO mainly recognizes ligands through the SRCR domain. Therefore, targeting the

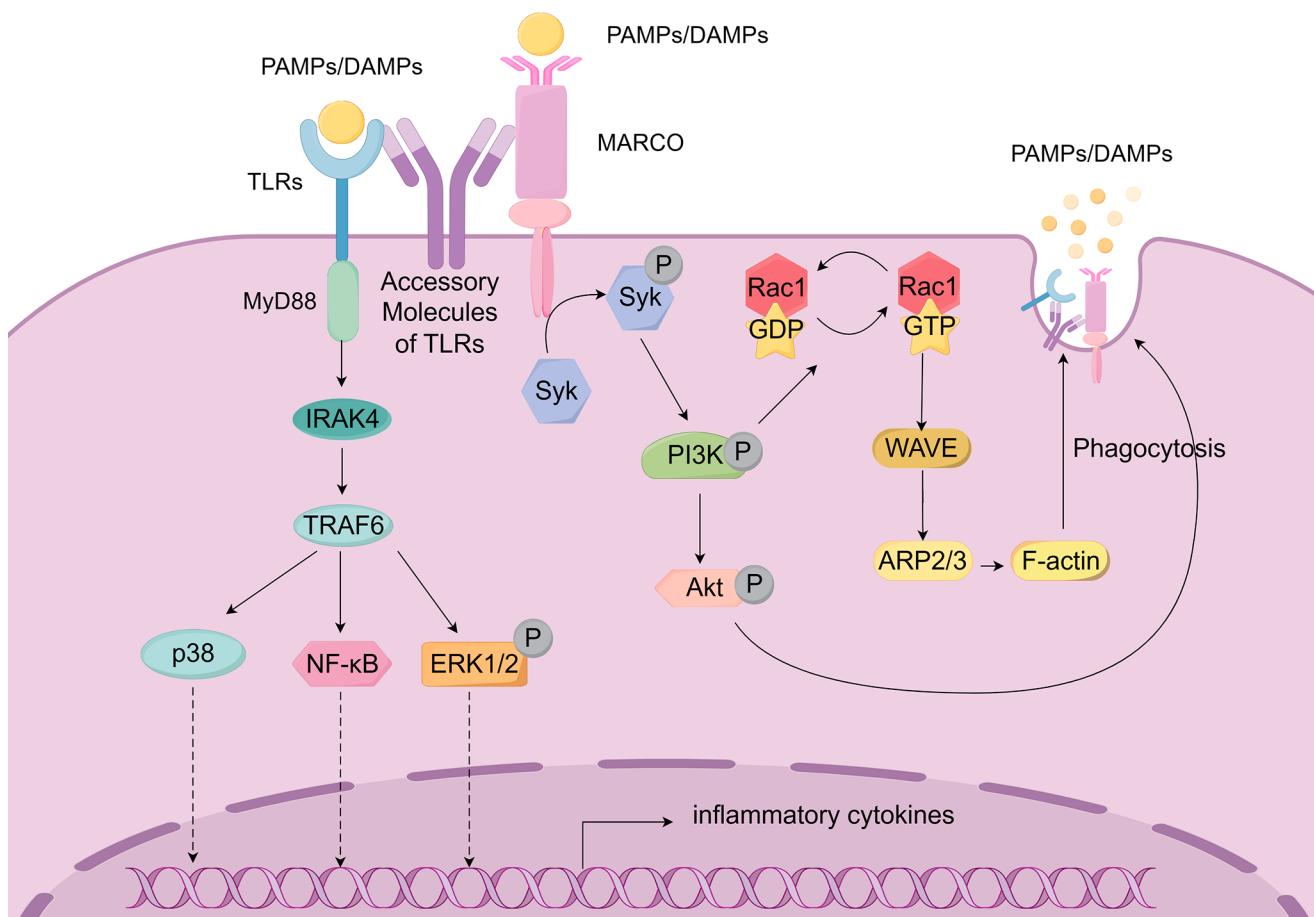


Fig. 4 The role of MARCO in the immune response (By Figdraw). MARCO may exert effects on the immune response by interacting with TLR; the effect of MARCO on gene expression leads to changes in phagocytosis and secretion by cells

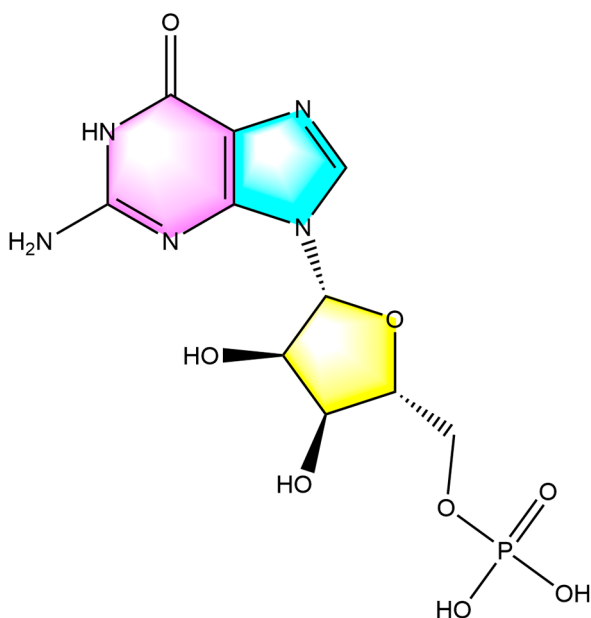


Fig. 5 The structure of polyG drawn in ChemDraw

SRCR domain of MARCO is currently the main strategy used for disease treatment.

PolyG is a common inhibitor used for targeting MARCO. PolyG is a kind of polyguanylic acid potassium salt (Fig. 5) that can form quadruplex structures, and some studies have shown that scavenger receptors can recognize the G-quadruplex secondary structure of polyG [80–82]. In some studies of inflammation, fibrosis, etc., researchers use polyG as a drug to target MARCO. Although we did not find literature that specifically identified the target site of polyG, we found that polyG can compete with other ligands for the binding site on MARCO as one of the ligands of MARCO and thus exert targeted inhibition. Therefore, we speculate that polyG, as a polyanionic compound, targets the SRCR domain of MARCO.

Thus, what are the specific target sites in the SRCR domain of MARCO? Since the discovery of MARCO, a large number of scientists have carried out in-depth studies. As early as 1999, the Pikkarainen team explored the functional fragments of the SRCR domain of MARCO. They demonstrated that the area before the first cysteine residue

of the SRCR domain is decisive for the morphological function of MARCO by transfecting different truncated forms of MARCO [83]. Later, researchers conducted more detailed studies and found that the arginine residues in MARCO's SRCR domain were significant for the activation of macrophages and the ability to bind bacteria [14, 84].

MARCO and disease diagnosis

In the process of pathogen infection, the expression of MARCO significantly changes, and disease progression and prognosis are strongly correlated with MARCO, indicating the potential for the use of MARCO as an early diagnostic marker. In the context of tumorigenesis and development, the levels of MARCO in tumor tissues significantly differ from those in adjacent tissues. For example, in the context of liver cancer, the expression of MARCO in tumor tissues is lower than that in adjacent tissues, which is indicative of a more favorable prognosis. In contrast, upregulated expression of MARCO in breast cancer is associated with an unfavorable prognosis [85–88]. In addition, MARCO plays a crucial role in the identification and eradication of pathogens and inflammatory reactions, as well as the regulation of various signaling pathways and the transcriptional activation of genes. Upon ligand binding, MARCO triggers the activation of macrophages or dendritic cells, thereby initiating innate immune responses. MARCO also facilitates the recruitment of immune cells, enhances the recognition and elimination of pathogens by inducing rearrangement of the actin cytoskeleton in immune cells, and stimulates the production of proinflammatory cytokines, including IL-1, IL-6, IL-15, and TNF α , which consequently activates the adaptive immune response; thus, MARCO plays an important role in limiting virus transmission and clearing pathogens. Moreover, MARCO can downregulate the expression of cytokines associated with inflammation, suppress an exaggerated inflammatory response, reduce the infiltration of immune cells, and mitigate inflammatory pathological damage. Moreover, MARCO can impede the function of immune cells involved in both innate and adaptive immunity; thus, there is a connection between MARCO and unfavorable tumor patient outcomes. These findings collectively propose that aberrant MARCO expression can be utilized as a novel diagnostic and prognostic indicator for disease.

MARCO and disease therapy

The function of MARCO in different diseases is heterogeneous. Currently, studies on the impact of MARCO on the occurrence and progression of disease and its therapeutic potential in the treatment of diverse diseases have yielded disparate and conflicting findings.

In studies of autoimmune diseases, Chen et al. found that MARCO on the surface of macrophages in patients with systemic lupus erythematosus is closely related to the clearance of apoptotic cells. They found that there were anti-SRCR antibodies that targeted the SRCR domain of MARCO in the serum of patients with systemic lupus erythematosus, and compared with the healthy people in the control group, the phagocytosis of apoptotic cells by macrophages in patients with anti-SRCR antibodies was significantly inhibited [89]. In a mouse model of autoimmune hepatitis, the expression of inflammatory factors and MARCO in the liver of mice increased. Targeting MARCO by polyG caused macrophages to polarize from M1 to M2 and reduced the secretion of inflammatory factors [21].

Then, Murthy et al. found that MARCO can recognize asbestos and activate a downstream signaling pathway that polarizes macrophages to the M2 phenotype. Subsequently, after targeting arginine residues in MARCO's SRCR domain, they found that macrophages were less polarized toward the M2 type [84]. These results suggest that MARCO can regulate the fibrotic response to lung injury by regulating the polarization of macrophages, and the arginine residue of MARCO's SRCR domain is a new target for therapeutic intervention in pulmonary fibrosis.

In recent years, an increasing number of studies on MARCO have focused on tumor immunity. Dong et al. conducted a bioinformatics analysis and found that MARCO strongly correlated with immune infiltration in tumor tissues and patient prognosis. Additionally, they observed a positive correlation between MARCO and CD80 and CD86 in most cancer types. Bioinformatics analysis revealed a strong association between elevated MARCO expression and decreased overall survival in colon cancer, prostate cancer, and invasive breast cancer patients. Conversely, in low-grade glioma and cutaneous melanoma patients, upregulated MARCO expression was found to extend progression-free survival [70]. Clinical data analysis further demonstrated that MARCO promotes tumor progression in esophageal cancer, gastric cancer, pancreatic cancer, and breast cancer, leading to a poor prognosis [63, 85, 90–92]. In mouse and cell models, macrophages exhibiting high expression of MARCO activated regulated T cells while deactivating nature killer cells and T cells. Anti-MARCO monoclonal antibodies could also repolarize macrophages, alter their metabolic processes, augment tumor eradication by activating nature killer cells and T cells, and synergize with PD-1/PD-L1 therapy [23, 61–63, 93]. In contrast to previous research, recent studies have demonstrated that elevated levels of MARCO at the tumor site in hepatocellular carcinoma are associated with a more favorable prognosis, whereas low levels of MARCO are strongly correlated with a lower survival rate. Additionally, *in vitro* experiments

have shown that MARCO can induce apoptosis in hepatocellular carcinoma cells and impede their proliferation and metastasis [86, 87, 94]. Furthermore, certain studies have established a significant association between MARCO and macrophage morphology. Macrophages exhibiting elevated expression of MARCO have the capacity to stimulate the generation of pseudopods through the activation of a signaling pathway cascade, thereby enhancing the phagocytic activity of macrophages toward tumor cells. Conversely, when MARCO is depleted, a contrary effect was observed, characterized by a reduction in the number of macrophage pseudopods and a decline in phagocytic functionality. Furthermore, the interaction between MARCO and integrins present on the surfaces of tumor cells supports the involvement of MARCO in the internalization and phagocytosis of tumor cells by macrophages [42].

According to existing research, as a key component of host immune defense, MARCO is crucial, and immunotherapies that target MARCO might have broad implications for preventing the development and occurrence of diseases. Of course, although there are many studies on the treatment of diseases by targeting MARCO, no specific MARCO-targeted drugs have entered clinical trials. Based on our previous description, as an attractive disease target, MARCO plays a pivotal role in initiating innate immunity and modulating adaptive immunity through the regulation of immune cells such as macrophages and dendritic cells. Notably, studies have demonstrated that antibody therapy targeting MARCO holds promise in improving patient prognosis and survival rates. Hence, MARCO, being a pivotal molecule in the regulation of both the innate and adaptive immune responses, holds promise as a prospective target for future therapeutic interventions; thus, it is necessary to continue conducting in-depth research on MARCO.

Conclusion

In conclusion, recent research has demonstrated that MARCO, functioning as a pattern recognition receptor, plays a pivotal role in the initiation and progression of innate immune responses. MARCO is responsible for activating multiple immune cell types and subsequently exerting relevant immunological effects in both the innate and adaptive immune responses. Moreover, MARCO is closely related to the prognosis and treatment of various diseases. Nevertheless, the precise molecular mechanism underlying the role of MARCO in immune responses remains unelucidated undetermined, and the specific method for targeting MARCO is not very clear. In addition, there are no specific drugs that target MARCO in the clinic. Consequently, additional investigation is needed to elucidate the role of

MARCO in antigens uptake, the processing and presentation of immune cells, the secreting of cytokines and the activation of immune responses; further efforts are also needed to develop therapies that specifically target MARCO.

Author contributions Conceptualization: G.Z. and S.S.; Investigation: G.Z.; Writing - Original Draft: G.Z.; Visualization: G.Z.; Resources: L.Z.; Project administration: L.Z.; Funding acquisition: L.Z.; Writing - Review & Editing: S.S.; Supervision: S.S. All authors read and approved the final manuscript.

Funding This work was supported by the National Key Research and Development Program of China (grant numbers [2022YFC2704400]).

Data availability No data was used for the research described in the article.

Declarations

Competing interests The authors declare no competing interests.

Ethical approval Not applicable.

Informed consent Not applicable.

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