The protective and pathogenic roles of CD36 in multiple sclerosis

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Abstract

CD36 is a transmembrane protein receptor expressed on various cell types, including immune cells and endothelial cells. It plays a complex role in multiple biological processes, such as lipid metabolism, inflammation, and phagocytosis, and has been implicated in mechanisms in diseases like multiple sclerosis (MS). It is involved in myelin uptake by macrophages and microglia. However, elevated expression in MS has been reported to correlate with both protective and pathogenic effects.
This thesis examines this dual role of CD36 in MS based on a review of recent literature. Despite its potential for both protective and pathogenic effects, the prevailing evidence suggests that CD36 primarily exerts a protective influence. CD36 demonstrates anti-inflammatory properties, attenuating neuroinflammation, and promoting myelin debris clearance, thereby fostering central nervous system (CNS) repair and remyelination. CD36's pathogenic implications are acknowledged, however most of these findings are merely correlations and there is no direct connection. Its predominantly beneficial impact highlights its potential as a therapeutic target to mitigate MS progression. This analysis provides insights into the intricate interplay of CD36 in MS, mostly highlighting the protective role CD36 plays in MS, encouraging further research to harness its protective mechanisms for innovative therapeutic strategies.

Introduction

CD36, also known as cluster of differentiation 36, is a protein that is primarily found on the surface of various cells in the body(Park Y., 2014). It is a multifunctional transmembrane glycoprotein that plays a crucial role in various physiological processes, including lipid metabolism, inflammation, and immune responses. CD36 is widely expressed in different tissues, including adipose tissue, skeletal muscle, heart, liver, and immune cells such as macrophages and dendritic cells. As described below, it is a multifunctional protein that acts as a receptor for a diverse range of ligands. CD36 is encoded by the *CD36* gene, which is located on chromosome 7 in humans.

One of the primary and best described functions of CD36 is in lipid metabolism. It binds to and facilitates the uptake of fatty acids and lipoproteins, such as low-density lipoproteins (LDL) and oxidized LDL (oxLDL), into cells. CD36-mediated fatty acid uptake is particularly important in tissues such as adipose tissue and skeletal muscle, where it helps in the storage and utilization of fatty acids as an energy source(Park Y., 2014).
CD36 also has an important role in inflammation and the immune response. It functions as a pattern recognition receptor (PRR), recognizing pathogen-associated molecular patterns (PAMPs) and triggering immune responses against infectious microorganisms(Park Y., 2014). Thereby, CD36 is involved in phagocytosis, allowing immune cells to engulf and eliminate pathogens. Additionally, under certain conditions, and depending on the ligand and engagement of other receptors, CD36 can initiate intracellular signaling pathways that lead to inflammation, promoting the production of pro-inflammatory cytokines. For example, in the context of atherosclerosis, CD36 contributes to foam cell formation upon binding to oxidized

low-density lipoproteins (LDL) and the release of inflammatory mediators within plaques. Furthermore, CD36 plays a role in angiogenesis, which is the formation of new blood vessels(Park Y., 2014). It is expressed in endothelial cells, where it contributes to various aspects of the angiogenic process. CD36 helps facilitate the migration and organization of endothelial cells, promoting the formation of new blood vessels. It also mediates adhesion between endothelial cells and other cell types involved in angiogenesis. CD36's interactions with ligands such as thrombospondin-1, collagens, and oxidized LDL helps stabilize endothelial cell contacts. CD36 is also involved in regulating vascular permeability, influencing the leakage of fluid and molecules from blood vessels during angiogenesis. Additionally, CD36 can impact endothelial cell survival and apoptosis, potentially affecting the stability of newly formed blood vessels. CD36's interaction with angiogenic factors like angiopoietin-like 4 (ANGPTL4) modulates endothelial cell junction integrity and influences vascular permeability. It can also regulate angiogenic factors such as vascular endothelial growth factor (VEGF) and transforming growth factor-beta (TGF-β), controlling their availability and signaling pathways. In summary, CD36's involvement in angiogenesis encompasses endothelial cell migration, tube formation, adhesion, vascular permeability, survival, and the regulation of angiogenic factors.

Emerging research suggests its involvement in multiple inflammatory and autoimmune diseases, including MS(Grajchen et al., 2020)

MS is a chronic autoimmune disease that affects the central nervous system (CNS), which includes the brain and spinal cord. It is characterized by inflammation, demyelination, and the formation of scar tissue (sclerosis) in various areas of the CNS. MS is believed to result from an abnormal immune response where the body's immune system mistakenly attacks the protective covering of nerve fibers, called myelin.

Myelin is essential for the proper transmission of nerve signals. When it becomes damaged or destroyed in MS, communication between nerve cells is disrupted, leading to a wide range of neurological symptoms. Some common symptoms of MS include fatigue, difficulty walking, muscle weakness, numbness or tingling, problems with coordination and balance, vision problems, bladder and bowel dysfunction, cognitive impairments, and mood disturbances. The severity and progression of MS can vary greatly among individuals, and the specific symptoms experienced depend on the location and extent of the damage within the CNS.

MS is typically diagnosed based on a combination of clinical symptoms, neurological examinations, and the use of diagnostic tests such as magnetic resonance imaging (MRI) to detect areas of inflammation and demyelination in the CNS.

The exact cause of MS is not yet fully understood, but it is thought to involve a complex interplay of genetic and environmental factors. Certain genetic variations are associated with an increased risk of developing MS, but environmental factors, such as viral infections, low vitamin D levels, and smoking, also seem to contribute to the development of the disease.

There is currently no cure for MS, but various treatment options are available to manage symptoms, slow disease progression, and modify the course of the disease. These treatments include medications to reduce inflammation, manage symptoms, and modify the immune response, such as fingolimod and niacin treatment. Additionally, rehabilitation therapies, such as physical therapy and occupational therapy, can help improve function and quality of life for individuals with MS. However, these treatments do not cure the disease and more research needs to be done for new treatments to improve the quality of life further.

As will be explained in detail below, CD36 has been implicated in the pathogenesis of several neurodegenerative diseases like Alzheimer's disease (Dobri et al., 2020) and MS by various scientific papers through its involvement in various aspects of the disease process. However, as will be discussed below, both protective and pathogenic roles for CD36 have been reported. This raises the research question of this thesis:
How can CD36 be both protective and pathogenic in the disease process of MS?

CD36 as a protective protein in MS

One of the articles about CD36 in MS discusses a study that investigated the effects of fingolimod, an oral immunomodulatory drug used in the treatment of MS, on peroxisome proliferator-activated receptors (PPAR) and CD36 gene expression (Ferret-Sena et al., 2022). PPARs are transcription factors involved in lipid metabolism and immune functions, while CD36 expression is regulated by PPAR signaling. The study aimed to determine whether fingolimod treatment influences PPAR signaling and *CD36* gene expression in MS patients.

The researchers analyzed serum lipoprotein profiles and PPAR and CD36 gene expression levels in peripheral leukocytes of 17 female MS patients before treatment initiation and at 6 and 12 months after starting fingolimod therapy. They observed that fingolimod treatment increased high-density lipoprotein cholesterol (HDL-C) and apolipoprotein E levels and also resulted in elevated PPARγ and CD36 gene expression in leukocytes, suggesting that CD36 has a protective role in MS. As explained above, CD36 acts as a scavenger receptor for oxidized lipids, including oxLDL, and is implicated in phagocytosis of myelin debris within MS lesions (Ferret-Sena et al., 2022). Elevated circulating levels of oxLDL in MS have been linked to unfavorable clinical outcomes. Interestingly, fingolimod therapy did not affect oxLDL levels or ratios. Dysfunctional HDL, potentially present in MS, might stimulate the PPARγ/CD36 pathway, though correlations with HDL-C levels and ALCs were not observed.

While the study provides preliminary insights into the potential involvement of PPARγ and CD36 in the therapeutic effects of fingolimod in MS, further research is needed to explore the specific role of the PPARγ/CD36 pathway, its relation to the clinical efficacy of the drug, and its involvement in the underlying mechanisms of MS pathogenesis.

A different article discusses the decline in remyelination efficiency in the central nervous system (CNS) with age and explores the role of macrophages and microglia in this process (Rawji et al., 2020). The study focuses on the decreased phagocytic activity of aging mouse microglia and human microglia, which is associated with reduced expression of CD36. The researchers found that overexpression of CD36 in microglia rescues the deficit in phagocytosis of myelin debris, again suggesting CD36 is protective in MS. Through screening for medications that stimulate macrophages and microglia, they discovered that niacin (vitamin B3) upregulates CD36 expression and enhances myelin phagocytosis in these cells.

Using a mouse model of demyelination, the researchers treated middle-aged mice with niacin and observed improved myelin debris clearance, increased recruitment of oligodendrocyte progenitor cells (OPCs), and enhanced remyelination in the treated mice. They propose that niacin could be a safe and potentially effective regenerative therapy for chronic demyelinating diseases like MS.

The article highlights the impaired macrophage and microglia response in the aging CNS and its contribution to deficient remyelination. The authors confirm the beneficial roles of these cells in remyelination, such as myelin debris clearance and growth factor release. They address concerns about potential neurotoxicity associated with niacin treatment but provide evidence suggesting its safety and potential clinical utility. Niacin's safety is indicated by comparable axon density and IL-1β expression in lesions of mice treated with niacin and those treated with saline, despite its potential to elevate cytokines in culture. The study concludes that niacin can stimulate macrophages and microglia through overexpression of CD36, promote remyelination, and may have implications for other conditions where stimulating these cells is desirable.

A similar article focuses on the role of the receptor CD36 in the clearance of myelin debris by macrophages and microglia in MS (Grajchen et al., 2020). The researchers aimed to understand the impact of CD36 on phagocyte phenotype and lesion progression.

Using flow cytometry, quantitative PCR, and immunohistochemistry, the study examined the abundance of CD36 in myelin-containing phagocytes. The results showed that CD36 is necessary for the uptake of myelin debris by macrophages and microglia, and the internalization of myelin increased CD36 expression through a transcription factor called NRF2, yet again suggesting CD36 is protective.

To investigate the functional consequences, the researchers used the pharmacological inhibitor sulfo-N-succinimidyl oleate(SSO) of CD36 and bone marrow-derived macrophages lacking NRF2. They found that inhibiting CD36 or knockout of NRF2 promoted inflammatory properties in myelin-containing macrophages and microglia in vitro, accompanied by reduced activity of anti-inflammatory receptors.

In the experimental autoimmune encephalomyelitis (EAE) model, which mimics the demyelination of neurons in MS, the study demonstrated that CD36 is essential for myelin debris clearance in vivo. Importantly, inhibiting CD36 significantly increased neuroinflammation and disease severity in the EAE model. Using immunohistochemical analysis they showed that treatment with SSO increased immunoreactivity for degenerated myelin.

In conclusion, the research establishes the critical role of CD36 in clearing myelin debris and suppressing neuroinflammation in demyelinating disorders such as MS. The findings suggest that CD36 may be a potential therapeutic target for promoting myelin clearance and reducing neuroinflammation in these conditions.

Another article explores the effects of glatiramer acetate (GA) treatment on the phagocytic activity of human blood monocytes, focusing on MS patients (Pul et al., 2012). GA is an immunomodulator medication, which is used for MS treatment. Since it is a mixture of several peptides present in myelin basic protein, it acts as a decoy for attacking immune cells. The researchers used flow cytometry to analyze the phagocytic response in vivo and in vitro. They found that GA treatment increased the phagocytic activity of monocytes in MS patients. In vitro experiments showed that even at low GA concentrations, microglial phagocytosis was induced, and it was particularly enhanced in a subset of monocytes expressing CD14 and CD16. Blocking experiments using monoclonal antibodies suggested the involvement of multiple surface proteins/receptors, and CD36 appeared as a promising candidate.
However, two different anti-CD36 antibodies had contrasting effects on DiO-OxLDL endocytosis: one did not impact the endocytosing cell count, while the other significantly increased the number of non-endocytosing cells. However, both of these antibodies did not reverse the effects of GA on phagocytosis of polystyrene beads, suggesting their inhibition was likely non-specific and unrelated to GA's mode of action. The study also observed a decrease in CD11c expression, a receptor associated with phagocytosis, and GA blocked the phagocytosis of beads coated with a CD11c ligand. These findings again suggest CD36 is protective in MS.

Another study investigated the role of the transient receptor potential vanilloid 1 (TRPV1) in demyelinating diseases, particularly MS (Sun et al., 2022). TRPV1 is a cation channel activated by capsaicin, found in chili peppers. The researchers used a cuprizone-induced demyelination mouse model and found increased TRPV1 expression in the corpus callosum during demyelination. Surprisingly, TRPV1 deficiency worsened motor dysfunction and demyelination in the mice, while the TRPV1 agonist capsaicin (CAP) improved behavioral performance and facilitated remyelination.

TRPV1 was predominantly expressed in Iba1+ microglia/macrophages in human brain sections of MS patients and in the mouse corpus callosum under demyelinating conditions. TRPV1 deficiency in mice led to reduced microglial recruitment to the corpus callosum and increased accumulation of myelin debris. On the other hand, CAP activation of TRPV1 enhanced

microglial recruitment and improved myelin debris clearance. Live imaging confirmed increased phagocytic function of microglia following CAP treatment.

Furthermore, CAP treatment increased the expression of CD36, which is known to be involved in phagocytosis and clearance of myelin debris as described above. The study suggests that TRPV1 plays an important role in regulating microglial function during demyelination, and the activation of TRPV1, with the subsequent increase in CD36 expression, may have therapeutic potential for demyelinating diseases like MS. This also suggests that CD36 is protective in MS.

A different study investigated the expression of adhesion molecules on the endothelial surface of the blood-brain barrier (BBB) and their relevance to MS and cerebral malaria (CM) (Dobbie et al., 1999). The researchers found that the immortalized human umbilical vein endothelial cell line, ECV304, expresses intercellular adhesion molecule-1 (ICAM-1) and low levels of CD36. However, it did not express vascular cell adhesion molecule-1 (VCAM-1) or E-selectin. The study highlights CD36 involvement in the context of BBB integrity and its potential implications for disease pathogenesis, particularly in CM and MS. However, there is no conclusion on whether it is protective or pathogenic.

CD36 as a pathogenic protein in MS

One article explores the potential role of PPAR in the mechanisms of action of Natalizumab (NTZ) therapy for autoimmune encephalomyelitis and MS (Ferret-Sena et al., 2016). NTZ is a humanized monoclonal antibody against α4 integrin, which inhibits leukocyte transmigration to the CNS and induces immune function changes in peripheral circulation. The study analyzed gene expression of PPAR in peripheral blood mononuclear cells (PBMC) of women with MS before and after NTZ treatment. As mentioned above, PPARs are antiinflammatory receptors that function as transcription factors to regulate gene expression.

The results showed that NTZ therapy led to selective alterations in the gene expression of PPARβ/δ and PPARγ in PBMC. PPARγ and CD36 gene expression decreased, possibly due to the drug-induced systemic inflammation, while PPARβ/δ gene expression increased, which may be linked to the protective effects of NTZ. PPARα levels remained unchanged, and further investigations are suggested to explore its potential role in NTZ therapy. The study acknowledges the small sample size of 12 individuals and short follow-up period of 6 months, suggesting the need for larger studies to confirm the findings. Overall, the results suggest that PPAR could serve as potential biomarkers for monitoring MS patient responses to NTZ therapy. Moreover, the decreased CD36 gene expression could suggest that CD36 is pathogenic in MS, however this is merely a correlation and there is no direct evidence in this study.

Another article researched the effects of progranulin in mice (Schmitz et al., 2020). Progranulin, a secreted neurotrophin, plays a vital role in autophagolysosomal pathways involved in MHC-mediated antigen processing, pathogen removal, and autoimmunity. In MS patients,

significantly higher levels of circulating progranulin have been observed than in healthy patients, around 10 ng/ml higher. Depleting progranulin using a monoclonal antibody in a mouse model exacerbated MS-like EAE. Surprisingly, mice lacking progranulin (Grn-/-) were found to be resistant to EAE, but this resistance was restored when they received bone marrow transplantation from wild-type mice.

Further analysis revealed that Grn-/- mice had fewer MHC-II-positive antigen-presenting cells and a reduced number of CD8+ and CD4+ T-cells, while the number of scavenger receptor class B (CD36+) phagocytes increased, suggesting defects in antigen presentation alongside increased phagocytosis. Bone marrow-derived dendritic cells from Grn-/- mice displayed heightened antigen uptake but failed to induce antigen-specific T-cell proliferation.

The increase in CD36+ phagocytes in Grn-/- mice was associated with enhanced local inflammation at the immunization site, increased morphological transformation of bone marrow-derived macrophages to phagocytes, elevated phagocytosis of particles, and impaired clearance of material. These findings indicate that CD36 is pathogenic in demyelinating disease in mice.

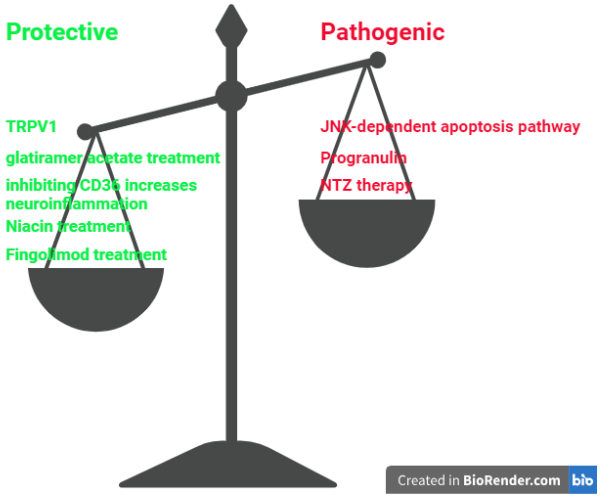
Another study investigated the role of immune cell subsets in relapsing-remitting MS (RRMS) (Ferrandi et al., 2010). The researchers evaluated the immunomodulatory effect of AS602801, a JNK inhibitor, on activated PBMCs from healthy volunteers and purified CD4+, CD8+, and CD11b+ cells from RRMS patients and healthy volunteers. AS602801 was found to block T-lymphocyte proliferation and induce apoptosis in activated PBMCs from healthy volunteers. In RRMS CD4+ and CD8+ cells, AS602801 induced apoptosis genes and surface marker expression, while in RRMS CD11b+ cells, it induced expression of innate immunity receptors and co-stimulatory molecules.

Furthermore, untreated cells from RRMS patients in the active phase released interleukin-23 (IL-23) and interferon-gamma (IFN-γ) and expressed fewer apoptosis markers compared to cells from healthy volunteers. Gene expression analysis revealed significant differences between cells from RRMS active-phase patients and healthy volunteers. A specific genomic signature for RRMS was identified by comparing RRMS PBMCs in the active and stable phases. Several genes, including CASP8AP2, CD36, ITGAL, NUMB, OLR1, PIAS-1, RNASEL, RTN4RL2, and THBS1, were associated with the active phase of RRMS for the first time.

The study might suggest that CD36 is pathogenic in MS, since it is associated with the active phase of RRMS.

Discussion

The findings of these studies shed new light on the intricate role of CD36 in the disease process of MS, revealing a potential dual nature where CD36 exhibits both protective and potentially pathogenic effects. This dichotomy underscores the complexity of immune responses and highlights the multifaceted interactions within the context of MS pathology. The discussion below elaborates on the implications of these findings and their significance in the broader context of MS research.



CD36, a multifunctional scavenger receptor, has been implicated in various cellular processes, including lipid metabolism, inflammation, and immune regulation. In the context of MS, this review of the literature demonstrates that CD36's impact on the disease process seems to be characterized by an interplay between protective and pathogenic pathways, however its protective role seems to be more evident.

The protective role of CD36 is evident through its association with immune regulatory pathways. Published findings suggest that CD36 is involved in mediating anti-inflammatory responses, potentially acting as a modulator of immune cell activation(Park Y., 2014). It seems to be mainly involved in myelin uptake and phagocytosis. These findings highlight CD36's role in dampening pro-inflammatory signals, thereby attenuating immune-mediated damage within the CNS. The activation of CD36-mediated pathways may represent a promising avenue for therapeutic interventions aimed at harnessing its protective potential to mitigate MS progression, such as PPAR agonists to increase CD36 expression.

Conversely, CD36's potential pathogenic effects underscore its involvement in myelin debris clearance and potential contributions to immune cell activation(Park Y., 2014). The increased expression of CD36 observed in certain conditions may lead to enhanced phagocytosis of myelin debris, a process implicated in remyelination. However, an excessive activation of CD36-mediated pathways could potentially result in the presentation of self-antigens, triggering autoimmune responses and exacerbating disease severity(Park Y., 2014). However, most of the articles suggesting CD36 is pathogenic find merely a correlation, and no direct evidence to suggest CD36 is the cause of this observation.

It is noteworthy that this study suggests a prevalence of protective pathways over pathogenic ones associated with CD36 in the context of MS. This observation underscores the potential for therapeutic targeting of CD36 to harness its protective effects, thereby offering new strategies for treating MS. By modulating CD36-related pathways and increasing CD36 expression(Park Y., 2014), it may be possible to bolster immune regulation while minimizing the risk of

autoimmune reactions, ultimately contributing to the development of more targeted and effective therapeutic interventions for MS.

Studying the role of CD36 in MS can benefit from insights gained through the investigation of other neurodegenerative diseases where CD36 is implicated. By examining its involvement in neurodegenerative disorders like Alzheimer's disease and Parkinson's disease, researchers can potentially draw parallels to its functions in MS. Exploring how CD36 modulates disease progression, neuroinflammation, and the clearance of cellular debris in these conditions may provide valuable clues about CD36's intricate role in MS pathogenesis. Comparing CD36-related mechanisms across different neurodegenerative diseases could shed light on its dual nature, being both protective and pathogenic, in the context of MS and aid in the development of novel therapeutic strategies.

MS is also characterized by a slow progression, prompting the question of whether patients would need to take anti-CD36 medication throughout their entire lives. This raises important considerations. While the potential benefits of targeting CD36 in MS are intriguing, the long-term use of any therapeutic intervention requires careful evaluation of both its effectiveness and potential side effects. Given CD36's multifaceted role in various cellular processes, its continuous inhibition might have broader implications beyond MS, impacting lipid metabolism, immune responses, and phagocytosis. These off-target effects could potentially lead to adverse events. Thus, a comprehensive assessment of the risks and benefits, as well as the potential impact on overall health, would be crucial before considering lifelong anti-CD36 treatment for MS patients.

In conclusion, these studies provide valuable insights into the dual nature of CD36 in the disease process of MS. The intricate balance between CD36's protective and pathogenic effects highlights its complex role within the context of immune responses and CNS pathology. These findings have implications for the development of novel therapeutic strategies that leverage CD36-mediated pathways to promote immune regulation and myelin repair in the treatment of MS. Further research into the precise mechanisms underlying CD36's effects and its potential as a therapeutic target is warranted to fully harness its therapeutic potential in the context of MS and related neuroinflammatory disorders.

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