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REVIEW OPEN ACCESS

Targeting Macrophages as a Novel Therapy to Treat Triple-Negative Breast Cancer: A Literature Review

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Abstract

Triple-negative breast cancer (TNBC) is a highly aggressive form of cancer which lacks the traditional cellular targets of other types of breast cancer. As such, it is increasingly important to find alternative targets to treat this deadly disease. Recently, tumour-associated macrophages (TAMs) have become an exciting area of focus for cancer research and may provide a source of treatment options for TNBC. Macrophages are an important part of the innate immune response and also play a crucial role in tumour progression, inflammation, and metastasis. TAMs fall along a spectrum and are generally presented as either M1 type or M2 type. M1 macrophages are considered anti-tumorigenic whereas M2 macrophages are considered pro-tumorigenic, promoting tumour growth and inhibiting T-cell response. A search of the University of Alberta's online library database was carried out with a specific emphasis on clinical research. Search efforts focused on the effects of macrophages on the progression of breast cancer. Further searches were performed to determine the efficacy of targeting macrophages to treat cancer. Increasing the relative ratio of M1 to M2 macrophages or depletion of macrophages may lead to a better prognosis in TNBC. TAMs may be repolarized to M1 phenotype using metformin, inhibition of SerpinE2, YAP/STAT3, or MED1/PPARγ. Macrophage recruitment to the tumour microenvironment may be inhibited by targeting chemokines such as CCL2. Current methods could not efficiently deplete macrophages at such a high abundance. The abundance of macrophages and their phagocytic properties could instead be exploited to increase tumour cell phagocytosis by targeting the CD47-SIRPα axis. Exciting opportunities have been revealed regarding inhibition of macrophage recruitment, repolarization of M2 to M1 type, and through exploitation of phagocytic properties of macrophages. However, conflicting results can be found for all these emerging treatment strategies. Worsening matters is the lack of knowledge regarding macrophage functions and the confusing landscape of macrophages current naming conventions. As such, further research is required to determine the efficacy of macrophages as a target in breast cancer treatment.

Keywords: macrophage; immune response; tumour microenvironment; breast cancer; metformin; cell surface markers; inhibition; activation

Introduction

Overview of Breast Cancer

Breast cancer is one of the most common solid-tissue cancers and the leading cause of cancer death in women worldwide [1,2]. There are several types of breast cancer; however, the most aggressive form, known as triple-negative breast cancer (TNBC), accounts for 15-25% of diagnoses in women [1]. TNBC is characterised by the lack of estrogen (ER), progesterone (PR) and human epidermal growth factor 2 (HER2) receptors on tumour cells; these are the traditional targets of breast cancer treatment, making TNBC extremely difficult to treat [1]. The lack of traditional drug targets contributes to a mortality rate of around 40% within 5 years of diagnosis [3]. Additionally, TNBC has a higher rate of distant metastasis compared to other breast cancer subtypes, further contributing to its aggressiveness [1,3]. TNBC is unique among breast cancer subtypes in that it is more immunologically hot compared to other subtypes [4]. The high immune cell infiltration of TNBC makes it a prime target for immune-based treatment; furthermore, the approval of PD-1 blockers to treat TNBC suggests targeting immune cells may be a feasible treatment option [5]. TNBC has been associated with a heavy presence of $CD163^+$ macrophages [2,6]. High abundance of M2 macrophages within the tumour microenvironment has been associated with tumour growth and poor prognosis overall in breast cancer [7–9]. M1 macrophages are known to have anti-tumorigenic effects via pro-inflammatory and phagocytic functions. In this review we will discuss the role macrophages play in immune response as well as their effects on cancer progression. We will also examine how targeting macrophages could potentially be used to limit breast tumour growth by describing several potential treatment options.

Overview of Macrophages

Macrophages are innate immune cells that maintain tissue homeostasis, resist pathogenic invasion, and repair damaged tissue [9]. Macrophages exist on a phenotypic spectrum with two recognized extremes: M1, or classically activated, and M2, or alternatively activated [8,9]. M1 macrophages are pathogen fighters and promote pro-inflammatory responses; they are activated in response to Th1 cytokines such as interferon-γ (IFN-γ) and antigens such as lipopolysaccharide (LPS). M1 macrophages produce pro-inflammatory mediators such as IL-6, IL-2, reactive oxygen species (ROS), reactive nitrogen species (RNS), and tumour necrosis factor α (TNF-α) [8,10,11]. M2 macrophages are anti-inflammatory and promote tissue repair by promoting angiogenesis and by scavenging dead cells [9]. Tumour-associated macrophages (TAMs) are macrophages specifically associated with tumour cells. Due to the nature of the tumour microenvironment (TME) they are exposed to immunosuppressive stimuli and tend to have a M2-like phenotype [8]. This polarisation can be explained largely by the acidic nature of the TME—the TME tends to be more acidic than healthy tissue which activates immunosuppressive cells and inhibits anti-tumour, pro-inflammatory immune cells [11]. This acidity is, at least partially, caused by an increased reliance on glycolysis due to the anoxic conditions of the TME [11]. Since TAMs tend to resemble M2 macrophages, they preferentially perform anti-inflammatory tasks and promote growth and invasion of cancer cells [8]. Macrophage subsets can be differentiated based on cell-surface markers. M1 typically presents with high levels of CD14, CD16, CD64, CD86, HLA-DRα, among others. Validated surface markers for M2 macrophages include CD200R, CD86 and CD163 [8] (Table 1, Fig. 1). Furthermore, macrophages are plastic cells, and through the alteration of key surface markers, they can effectively change phenotype in response to environmental stimuli [9,12].

Table 1. Summary of the different macrophage types and their properties

Macrophage Type	General Properties	Cell Surface Markers	Activation	Secretion
M1	-Pathogen fighters -Pro-inflammatory responses -Wound healing and tissue regeneration	CD14, CD16, CD64, CD86, HLA-DRα	IFN-γ, LPS, TNF-α	IL-1β, CXCL9, IL-6, IL-12, IL-23
M2a	-Wound healing -Release of matrix remodelling cytokines	CD200R, CD86, CD206	IL-4, IL-13	TGF-β, IGF, fibronectin
M2b	-Wound healing	CCL1, TNFSF14, IL-1β, IL-6, TNF-α	IL-1β, LPS, IL-10, IC or TLR agonists	IL-10, low levels of IL-12
M2c	-Immunosuppressive factors	CD163, MerTK	IL-10, TGF-β	TGF-β, IL-10

Along with T-cells, they are involved in the anti-tumour immune response. Within the tumour microenvironment (TME), T-cells can influence the polarisation of macrophages into either the M1 or M2 type [13]. Similarly, macrophages can affect the differentiation of T-cells by secreting cytokines and presenting different antigens [13]. In cancer, M2 macrophages inhibit effector T-cells while activating regulatory T-cells which can impede the efficacy of immunotherapeutic treatments due to the immunosuppressive properties of regulatory T-cells [13,14]. M1 macrophages can promote anti-tumour immune responses by recruiting effector T-cells to the TME and secrete factors that can induce apoptosis in cancer cells. Despite the growing evidence showing the effects of macrophages on tumour progression, the complexity of the TME makes it a poor pharmacological target [15]. However, in recent years, there have been promising advancements in inhibiting macrophage recruitment, repolarizing macrophages away from M2 type, and in exploiting the phagocytic function of macrophages.

Methods

In this literature review we examined the role of macrophages in immune response in the context of cancer with a specific emphasis on their role in human breast cancer. We then researched various cancer therapies to ascertain the efficacy of targeting macrophages as a cancer treatment using the relative keywords listed in our article, such as breast cancer, macrophages, among others. For this review, we only used peer-reviewed research articles published on, or after, 2010. Though we focused on breast cancer, we used other articles that targeted other cancers as a way to compare and contrast the efficacy of each treatment. For our article search, we primarily used the University of Alberta database, which utilizes a more modified and refined version of Google Scholar that filters out unrelated and inaccessible articles. We then moved on to other databases and journals; PubMed, ScienceDirect, Nature, and Springer as the main ones. All articles cited were acquired from the University of Alberta's online library database, Google Scholar, and PubMed.

Inhibition of Macrophage Recruitment

Signals occurring in the extracellular matrix (ECM) influence macrophage polarisation, as it acts alongside TAMs to help them infiltrate tumours [9]. In cancer, tumours can alter the composition of the ECM to polarize M1 macrophages towards an M2 phenotype [16]. TAMs can adhere to collagen and fibronectin present in the ECM to assist with motility and function. The ECM can also act as a reservoir for soluble factors such as chemokines, which can explain why CCL2 plays such a pivotal role in TAM recruitment. CCL2, a chemokine that is highly secreted by tumour cells, has a major role in the recruitment of monocytes, macrophages, T-cells, B-cells, and other immune cells [17]. The use of anti-CCL2 antibodies in breast cancer models has shown varying results. Some studies have shown that inhibiting CCL2 can reduce tumour growth and metastasis, while others have shown that inhibition of CCL2 has little to no effect [18,19]. Still, inhibition of CCL2 can be an interesting strategy for immunotherapeutic treatment of breast cancer by limiting macrophage recruitment towards the TME. Inhibition of macrophage recruitment/depletion is difficult due to the abundance of macrophages and consistent replenishment of macrophages in the TME. Rather than depleting macrophages, there has been a shift in immuno-oncology to repolarize these immunosuppressive cells to a pro-inflammatory state to promote anti-tumour immune responses.

Repolarization of Macrophages

The protein serine protease inhibitor E2 (SerpinE2) has become more recognized as having a role in breast cancer metastasis [20]. Found in the TME, SerpinE2 has a critical role in regulating the ECM composition, and its overexpression leads to increased M2 polarisation in human breast cancer cells [9] (Figure 1). A study shows SerpinE2 may promote tumour growth by increasing the amount of blood travelling to the tumour through the creation of more extracellular networks while also acting as an anticoagulant [21]. Inhibition of SerpinE2 in mouse breast cancer models decreases CCL2 expression and increases M1 polarisation [20]. However, SerpinE2 inhibition in human trials remains unexplored, but could be a potential immunotherapeutic target in the future.

Targeting the Hippo signalling pathway is also a possibility for treatment. Another study found that the interaction between hippo-yes-associated protein (YAP) and signal transducer and activator of transcription 3 (STAT3) are highly expressed in breast cancer tissues, leading to an increase in macrophage polarization towards the M2 type [22] (Fig. 1). There was also evidence that the interaction between YAP/STAT3 leads to a decrease in $CD8^+$ T-cell viability, which plays an important role in tumour suppression. Inhibition of YAP leads to inhibition of M2 macrophage polarization, while also indirectly increasing the viability of $CD8^+$ T-cells.

The mediator subunit 1 (MED1) gene is involved in macrophage differentiation and DNA repair and has been shown to be upregulated in various cancers [23]. In breast cancer specifically, overexpression of MED1 has shown to polarize macrophages into the M2 type [23]. MED1 does so by inhibiting the release of pro-inflammatory cytokines whilst promoting the release of anti-inflammatory cytokines from macrophages [23] (Fig.1). This results in the promotion of malignant behaviours in breast cancer cells. MED1 can polarize macrophages towards the M2 type by increasing the activity of the nuclear transcription factor peroxisome proliferator-activated receptors γ (PPARγ) [9]. PPARγ can be another interesting target, as it has been shown to regulate many activities in macrophages [24]. The use of PPARγ antagonists is currently being explored in clinical trials, showing effectiveness in inhibiting the growth of various cancers in preclinical and clinical trials. The use of PPARγ antagonists is not without challenges as there are side effects and patient heterogeneity that need to be addressed [24]. PPARγ and MED1 inhibition show a future in immunotherapeutic treatments for breast cancer, but the side effects must be addressed, and further testing needed.

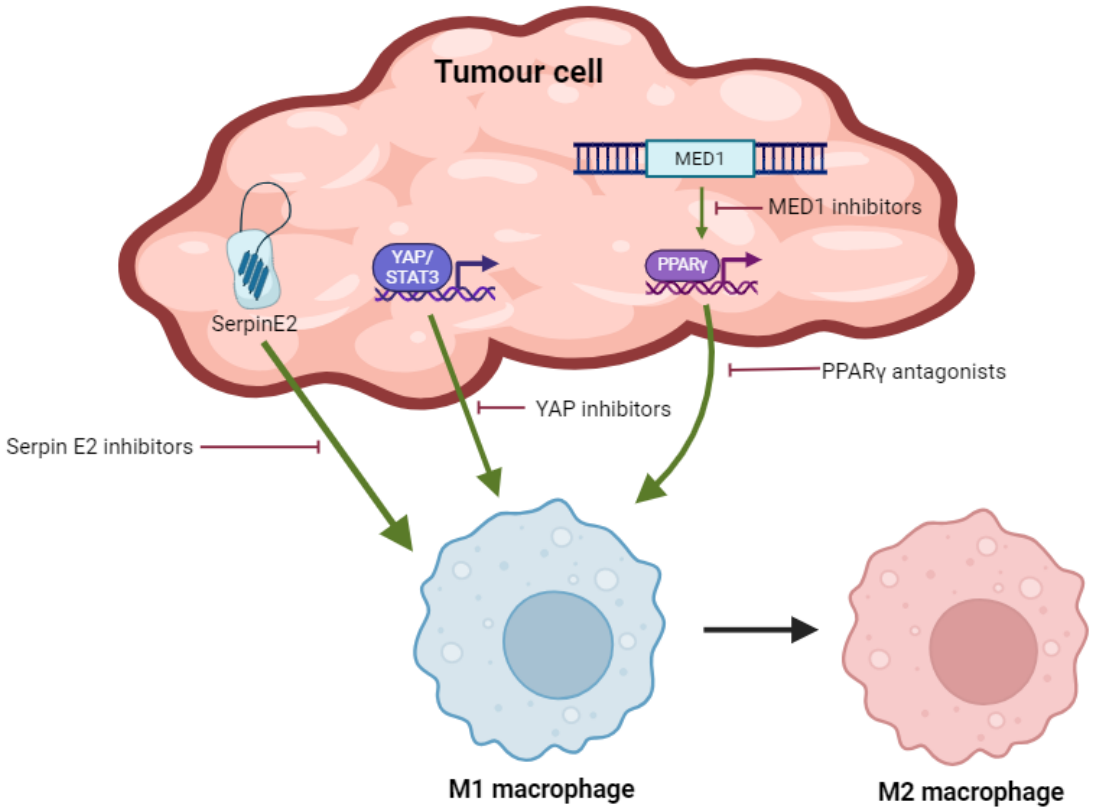

Figure 1. Summary of the signals and pathways involved in polarisation of macrophages in the tumour microenvironment. Utilizing protein inhibitors (SerpinE2 inhibitors, YAP inhibitors), gene expression inhibitors (MED1 inhibitors), and gene transcription inhibitors (PPARγ inhibitors, STAT3 inhibitors) can prevent the polarization of M1 macrophages towards the M2 type. The use of these inhibitors have shown promising results in inhibiting tumour proliferation. Figure created using Biorender.com.

Metformin is a biguanide drug commonly used to treat type 2 diabetes. Within diabetes, the drug works primarily by increasing glucose consumption in the liver—through the targeting of the oxidative phosphorylation (OXPHOS) pathway—and suppresses hepatic gluconeogenesis [15, 25]. Aside from diabetes, metformin is also used as a cancer drug—it has been shown to reduce the recurrence of colorectal polyps and increase overall survival rates for colorectal cancer patients [15]. Metformin's anti-tumour capabilities are found primarily through its ability to activate AMP-activated protein kinase (AMPK) [15]. AMPK is a regulatory enzyme which controls many of the metabolic pathways involved in tumour metabolism. When activated, AMPK inhibits mTOR, an important regulator of growth factors and of the PI3K/protein kinase and B/Akt pathway in cancer [15, 26]. Furthermore, through inhibition of electron transport chain complex 1, metformin reduces the efficiency of the tricarboxylic acid (TCA) cycle and OXPHOS [15,26].

Multiple studies have shown that metformin can decrease the number of M2 macrophages in colorectal cancer cells, as well as decrease the number of colonic tumours *in vivo* [15, 26, 27]. However, the effect of the drug on breast cancer is less clear, and current research on the topic is conflicting. Metformin was shown to inhibit mTOR-mediated phosphorylation of S6K1 and 4E-BP1 proteins in both MCF7 and 4T1 breast cancer cell lines [28]. Cell proliferation and colony formation were inhibited in MCF7 and 4T1 cell lines *in vitro* when treated with metformin [28]. Moreover, 4T1 *in vivo* tumour growth was suppressed with the treatment of metformin in mice [28]. In an indirect study, metformin-induced AMPK activation led to a downregulation of DVL3 and β-catenin in MCF-7, MDA-MB-231 and T-47D breast cancer cells *in vitro*, resulting in suppressed cell growth and slowed tumour progression [29]. Despite the apparent success of *in vitro* studies, clinical trials have proved less promising. Two independent studies of non-diabetic females with breast cancer found that metformin did not significantly affect the rate of disease-free survival or overall survival compared to the control group [30, 31].

Exploiting the Phagocytic Function of Macrophages

In addition to targeting macrophages by repolarizing them, the phagocytic function of macrophages may be exploited to target tumour cells. Therapeutics targeting the CD47/SIRPa axis have shown promising results to date

[32, 33]. CD47 is a transmembrane protein that is ubiquitously expressed on all cells and inhibits phagocytosis when it engages with SIRP-α on phagocytes [32, 33]. CD47 is overexpressed in several cancers, including TNBC. The CD47-SIRP-α axis can promote immune evasion by phagocytosis of tumour cells [32, 33]. CD47 and SIRP-α interaction also play a role in T-cell recruitment in inflammatory sites [34]. The interaction between CD47 and SIRP-α has been shown to inhibit macrophage chemokine secretion in human myeloid cells, preventing T-cells from entering the tumour site [33]. Inhibition of CD47 using monoclonal antibodies has shown promising results, as it prevented further tumour metastasis and growth in breast cancer [35]. Moreover, inhibition of SIRP-α on phagocytes can also be an important immunotherapeutic target in the future [33]. Several studies have shown that using anti-CD47 antibodies in conjunction with other treatments such as chemotherapy, radiotherapy, and tumour-targeting antibodies can decrease tumour growth and proliferation in breast cancer [36–38]. However, inhibition of this signal may lead to non-tumour cells being phagocytosed after cytotoxic or inflammatory therapy [35]. There are also side effects with the use of anti-CD47 antibodies, such as anemia, but these side effects can be minimized by using bispecific antibodies, allowing for targeting only CD47-positive tumour cells [37]. Exploration of more molecules and signalling pathways is necessary for establishing a new standard of care.

Discussion

In this study, we sought to explain macrophage's vital role within the immune system and their effect on tumour growth. From there, we set out to determine if targeting macrophages could be a viable pathway for treating breast cancer. Macrophages occupy a phenotypic spectrum with two extremes, ranging from the anti-tumour M1 to the pro-tumour M2 [8,9]. There are many pathways and cell surface markers that can be targeted in immunotherapeutic treatments, many of which involve the polarisation of macrophages towards the M2 type that can lead to increased tumour growth and metastasis. Thus, tumour progression could be slowed by either reducing the number of M2 macrophages, increasing the number of M1 macrophages or by harnessing the inherent ability of macrophages to phagocytose cancer cells. Metformin, traditionally a diabetes drug, has been shown to decrease the number of M2 macrophages and inhibit the growth of colorectal and breast tumours [15, 29]. However, despite this evidence, the current research is conflicting and uncertain. AMPK activity is more complex than previously thought and may selectively protect tumours from cytotoxicity [39]. Additionally, multiple clinical trials have found metformin to have little effect on the survival of breast cancer patients [30,31]. Part of this conflict may stem from the complexity of macrophages themselves; macrophage polarisation is more complex than the simplified M1-M2 dichotomy proposed in this, and many other studies, and is still not fully understood [40]. Further confounding matters is the sheer breadth of terms used to describe macrophages and their polarisation states; the lack of standardisation on this front may cause future researchers to draw erroneous conclusions [40]. Although inhibition of SerpinE2 has been shown to have a significant role in macrophage polarisation and increase M1 expression in murine models of breast cancer, human trials remain limited and further research is required [9, 20]. Our findings suggest that targeting MED1/PPARγ is possibly the most promising treatment strategy, as inhibiting MED1/PPARγ has been shown to decrease M2 polarisation and Gleevec, a drug targeting PPARγ, has already been approved as an anti-cancer drug [9, 24]. Side-effects and patient heterogeneity are still issues, but current research is promising. Finally, we discussed exploiting the phagocytic function of macrophages through inhibition of CD47 and SIRP-α. Using monoclonal antibodies to target these proteins decreased tumour metastasis in breast cancer; however, side effects such as anaemia and rampant phagocytosis pose a challenge for clinical applications [35,37]. Macrophages are clearly important mediators in tumour growth, and while there is little doubt that they could be effective targets for cancer therapy, further investigation is required. Elucidating the mechanisms underlying polarisation is required before effective treatments can be formulated. Furthermore, conflicting studies of metformin treatment on breast cancer prove further research is necessary to determine how this drug reacts with macrophages and the TME.

Conclusions

This review summarized the role of macrophages in the body's immune response and reviewed the primary types of macrophages and their effects on cancer progression, Multiple studies have examined targeting macrophages as a possible adjuvant therapy for TNBC. Possible treatments include limiting macrophage recruitment through inhibition of CCL2, repolarizing macrophages to M1 type through inhibition of MED1/PPARγ, serpinE2, YAP/STAT3, and metformin-induced AMPK activation, as well as harnessing the phagocytic function of macrophages through the CD47/SIRP-α pathway. CCL2 inhibition and metformin-induced AMPK activation have shown promise in reducing breast tumour growth; however, the literature is conflicting, and further investigation is required. Inhibition of serpinE2 and YAP/STAT3 are interesting targets, but limited information is available on their efficacy and further exploration is required. Targeting CD47 has been shown to decrease tumour growth and proliferation in breast cancer when paired with traditional treatments; although phagocytosis of non-tumour cells remains an issue. Inhibiting MED1/PPARγ shows the most promise of the treatments explored in this study. The use of PPARγ antagonists is already being explored in clinical trials and

showing positive results. Ultimately, all of these therapies present unique challenges to researchers; minimizing side effects, using combination therapy, and more clinical testing for breast cancer will be key to maximizing the effects of immunotherapy.

List of Abbreviations Used
4E-BP1: eukaryotic translation initiation factor 4E-binding protein 1
AMPK: AMP-activated protein kinase
B/Akt: protein kinase B
CCL2: chemokine ligand 2
COX-2: cyclooxygenase-2
CXCL9: chemokine ligand 9
DVL3: dishevelled protein 3
ECM: extracellular matrix
ER: estrogen
HER2: human epidermal growth factor 2
HLA-DRα: human leukocyte antigen-DR isotope α
IC: Immune complex
IFNγ-: interferon-γ
IGF: insulin-like growth factor
IL-1β: interleukin 1β
IL-10: interleukin 10
IL-13: interleukin 13
IL-2: interleukin 2
IL-23: interleukin 23
IL-6: interleukin 6
LPS: lipopolysaccharides
MAPK: mitogen-activated protein kinase
MED1: mediator subunit 1
MerTK: MER proto-oncogene, tyrosine kinase
mTOR: mammalian target of rapamycin
OXPHOS: oxidative phosphorylation
p-AMPK: phosphorylated AMP-activated protein kinase
PD-1: programmed cell death protein 1
PPARγ: peroxisome proliferator-activated receptor gamma
PR: progesterone
RNS: reactive nitrogen species
ROS: reactive oxygen species
S6K1: ribosomal protein S6 kinase beta-1
SerpinE2: serine protease inhibitor E2
SIRP-α: signal regulatory protein α
STAT3: signal transducer and activator of transcription 3
TAM: tumour associated macrophage
TCA: tricarboxylic acid
TGF-β: transforming growth factor-β
TLR: toll-like receptors
TME: tumour microenvironment
TNBC: triple-negative breast cancer
TNF-α: tumour necrosis factor-α
TNFSF14: tumour necrosis factor superfamily 14
YAP: hippo-yap associated protein

Conflicts of Interest
The authors declare that they have no conflicts of interest.

Ethics Approval and/or Participant Consent
Due to the nature of this manuscript as a literature review, there was no requirement for ethics approval or participant consent.

Authors' Contributions
CT: made contributions to the design of the study, collected and analysed data, drafted the manuscript, and gave final approval of the version to be published.
JM: made contributions to the design of the study, collected and analysed data, drafted the manuscript, and gave final approval of the version to be published.
MS: made contributions to the design of the study, collected and analysed data, drafted the manuscript, and gave final approval of the version to be published.

Acknowledgements
Figures were generated with BioRender.com. Additionally, the authors would like to sincerely thank Megan Hong for her guidance and feedback during the creation of this paper.

Funding
This study was not funded.

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Article Information
Managing Editor: Jeremy Y. Ng
Peer Reviewers: Megan Hong, Sara Pishyar, Dusan Pesic
Article Dates: Received Dec 03 23; Accepted Mar 03 24; Published Apr 19 24

Citation
Please cite this article as follows:
Todrick C, Ma J, Singh M. The role of disease-associated microglia in neurodegenerative disease: A review. URNCST Journal. 2024 Apr 19: 8(4). https://urncst.com/index.php/urncst/article/view/558
DOI Link: https://doi.org/10.26685/urncst.558
