Proceedings of the 2nd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/15/20240465

TREM2 mediated Aβ clearance dysfunction in microglia cells by circadian disruption in Alzheimer's disease

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Abstract. Genome-wide association studies (GWAS) have shown that the Trem2 gene is a risk factor associated with the onset of Alzheimer's Disease (AD). The Trem2 gene is highly expressed on the surface membrane of microglia cells in the central neuron system (CNS), which mediates neuron inflammation and the clearance of axons and synapses. As a growing amount of evidence is connecting Circadian disruptions with increased levels of CNS inflammation, this review aims to find a connection between circadian disruption and amyloid-leading Alzheimer's disease through Trem2 in Microglia cells. This review summarizes past research independently about the circadian disruption with microglia activation, microglia activation with Trem2, and Trem2-affected MG cells impacting the development of Alzheimer's Disease. Further research may focus on specifying the importance of Trem2 microglia cells caused neuron inflammation in the development of Alzheimer's pathology, for whether the early A-beta plaquing is triggered by Trem2 microglia cells, or Trem2 is just contributing but not the causation of AD in its Mild Cognitive impairment (MCI) stage.

Keywords: Circadian Disruption, Microglia, Trem2, Beta-Amyloid.

1. Introduction

Alzheimer's Disease (AD) is a degenerative Neurological disorder, with typical symptoms of poor cognitive status, affective symptoms, psychomotor dysregulation, etc [1]. The pathology of AD is associated with β-amyloid (Aβ) protein plaquing and tau protein hyperphosphorylation [2]. AD as a Central Neural System (CNS) disorder has affected 26.6 million people worldwide and is estimated to increase in the population for 1 out of 85 people by reaching 2050 [3]. Neuron inflammation has been suspected as one causing factor for AD. Microglia cells, as the majority cell in CNS for neuron pruning, and its surface receptor Trem2, have come into sight.

Triggering receptor expressed on myeloid cell 2 (TREM2) is a protein coded by the Trem2 gene, which is widely expressed on the surface membrane of microglia cells in CNS and macrophages in the peripheral neural systems. The extracellular immunoglobin (Ig) site of Trem2 can be activated in multiple ways, which include phospholipids, low and high-density lipoproteins, and amyloid β proteins [4]. The downstream of Trem2 protein is related to inositol polyphosphate-5'-phosphatase (INPP5D/SRC), which is in charge of phosphorylase in microglia cells and is verified controlling Aβ endocytosis and production of proinflammatory cytokines in cells [4]. Thus, it is vital to find the upper stream that regulates the level of Trem2 expression, hence controlling the clearance of Aβ protein.

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Earlier Alzheimer's' Disease could be exacerbated through a chronic inflammatory response. As Aβ accumulated, the cytokines and reactive oxygen intermediate, etc. provided by the microglia cells could be toxic to neurons [5]. However, as microglia cells are categorized into M1, M2, and Disease-associated Microglia phenotypes, Trem2 KO mice showed different microglia compositions compared to Wild type mice [4], indicating that specific types of microglia, or transition of status in microglia play an important role on the results of Aβ protein clearance.

In AD cases, mathematical correlation via sleep quality and Trem2 level have shown a positive correlation [4], and pathological testing shows that sleep deprivation worsens Trem2-dependent mice in microglia activity [6]. However, linking sleep disorders to the development of Alzheimer's disease and their connection to microglia cells remains unclear.

This review summarizes the previous research on the correlation between circadian disruption and substance level fluctuation in the cerebral spinal fluid, focuses on sTrem2 as an indicator of Trem2 receptors on microglia cells, as well as the contribution of tau-mediated Trem2 dementia. Noticing the potential risks of inflammatory-caused AD, this article is dedicated to finding the causation of microglia activation and connecting daily behaviors as sleep-awake patterns leading to molecular activation of Trem2 receptors.

2. Sleep, Circadian Disruption, and Microglia cells

2.1. Correlation of Trem2 level with sleep

As sleep provides the CNS with restoring and cleaning its neurons, nocturnal sleeping becomes a period that consolidates memories and removes metabolites for a day [7]. One of the consequences of sleep loss or sleep deprivation is the activation of microglia cells, and at the molecular level, disruptions in the circadian system regulate the expression of inflammatory-related genes [8]. Studies have revealed that circadian regulation via Trem2 can prevent related-plaquing in the CNS [9]. Hu et al. did experiments among the population of Aβ positive (A+) and normal adults of a variety of ages [10]. They have qualified the sleep efficiency of individuals through the Pittsburgh Sleeping Quality Index (PSQI), and analyzed through non-linear regression to conclude a U-shaped relationship between sleep quality, bedtime, sleep duration, and the level of sTrem2 in the cerebral spinal fluid (CSF). The results showed that in all ages of cognitive normal(A-) populations, earlier bedtime with normal sleeping period caused a upraise in CSF sTrem2 level, as well as later bedtime with normal sleeping period and groups that have poor self-reported sleeping qualities [10]. It could be concluded that the decreasing sleep quality has activated the microglia cells in secreting cytokines in microglia, aggregating the inflammation response and damaging the entirety of CNS [11]. However, the specific pathway of circadian disruption activating microglia cells was to be discovered. Interestingly, the study showed that in A+ populations, the fluctuation of CSF sTrem2 level was not as significant as in the cognitively normal group, which seems the Aβ plaques have attenuated the elevation of sTrem2 [10]. This could be caused by the speeding up of amyloidogenesis in loss Trem2 situation [12], or the barrier theorem proposed that sTrem2 circulates the plaques until it fails to function (Figure 1) [6].

Noticeably, the testing of Trem2 is not able to be viewed directly in CNS, the Trem2 protein will be cleavage by ADAM 10 or ADAM 17 to remove the extracellular immunoglobin section, which is named soluble TREM2 (sTrem2), and hence can pass through inter-cellular space and detected in the cerebral spinal fluid, as a marker of Trem2 expression on microglia cells [10].

2.2. Sleep deprivation impacts Trem2 expressing in Microglia

In priority, the regulation between Microglia cells and Circadian rhythm is not mutual, Experiments have shown that feeding mice with PLX3397, a CSF1R inhibitor that depletes the microglia cells, did not affect the locomotor activity in the mice population, whenever the mice were experiencing a free-running rhythm under whole day darkness (DD), or testing for the inter-daily stability of mice to completely re-entrainment the new light and dark schedule under a jet-legged condition [6].

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Further studies have shown that the evoking of microglia activity is Trem2 dependent [13]. Through examining the changes in homeostatic markers of microglia cells, researchers have observed a significant reduction of P2RY12 and TMEM119 expressing microglia, and through ionized calcium-binding adaptor 1(IBA1) coloring. The results showed that compared to 5xFAD/$T2^{KO}$ mice, groups of 5xFAD/$T2^{CV}$ mice have IBA1+ bindings around the plaque of Aβ proteins, which the sleep-deprived 5xFAD/$T2^{CV}$ group shows a prominent number of coloring surrounding the plaques (Table 1) [4]. Thus, Trem2 may act as a regulatory gene for microglia cells after circadian disruption, in specific, sleep deprivation.

Morphologically, sleep-deprived Trem2 neurons also showed a difference with the normal functioning Trem2 mice group, which revealed a smaller number of branches and a larger volume of soma body of the cell. Testing this same group with CD68 lysosomal immunoglobin, a lower activity was shown in the sleep-deprived group. Hence, Trem2-dependent microglia were in a less functioning state after sleep deprivation [14].

3. Microglia cells' activation

3.1. The activation of Microglia and its relationship with circadian disruption

The activation of the microglia cells is related to the Purinergic receptor $P2X_7$($P2X_7R$) pathway [13], which is an ATP-sensitive cation pore protein. At the conventional status, the CNS neuron cells and microglia release ATP, promoting the sensory CNS system of surrounding ATP level, which in turn amplifies the $P2X_7R$ proliferation on the microglia cells and changes morphologically the microglia cells with more lamellipodia [6]. As a consequence, there would be more contractile distribution of the soma body. Circadian disruption has been proven to impair psychomotor tasks through insufficient AMP-activated protein kinase(P-AMPK) and loss of the regulation of ATP in the Basal Forebrain and Frontal cortex region after sleep deprivation of mice for three hours [15, 16].

Further experiments using oxidized ATP (oxATP), an antagonist substance of ATP-sensitive $P2X_7R$, have shown that the fluorescence of GFP in Glial Fibrillary Acidic Protein (GFAP) is inconspicuous after treatment with oxATP [13]. Analogically, a mutation at the G345Y site of microglia cells only inhibits the formation of $P2X_7$ receptors on the surface of glial cells. Intergroup comparisons have shown that the wild-type microglia cells have a significantly higher rate of activation than the mutated group. Through time-latent electron-microscope, showing that the mutated microglia cells have been influenced during the mitotic period [6]. Thus, ATP activation is vital to both cytokine cascading and proliferation of activated microglia cells (Figure 1).

3.2. Microglia cells and neuroinflammation.

Categorize of microglia cells include M0, M1 and M2 status. Before inflammatory effects occurred, all microglia cells were considered to be in a 'resting' state under healthy conditions [17]. The M0 phenotype microglia cells may extend or retract their ramified soma body when the absence of any inflammatory activation molecules.

Alternatively, M1 and M2 phenotypes were classified as their pro-inflammatory and anti-inflammatory process in the CNS. Depending on the milieu of the microglia cells, the activation can be separated into classical activation(M1) and Alternative/Acquired activation (M2) [18]. For the M1 phenotype, the presence of Lipopolysaccharide (LPS) and interferon-γ (IFN-γ) activate the M0 microglia cells, and transit into the M1 phenotype, producing pro-inflammatory cytokines via induced nitric oxide synthase (iNOS) and NF-κB pathways [16]. Hence, the production of cytokines such as Tumor necrosis factor-α (TNF-α) was considered to be both beneficial and detrimental as it can clean neuron debris and myelin sheath, while overexpression of pro-inflammatory cytokine could lead to neuron apoptosis.

M2 phenotypical microglia cells are functioning to halt the exceeding pro-inflammatory cytokines produced by the M1 microglia cells. Interleukin 4,10 and 13(IL-4,10,13) are all mutual with the transition of M2 microglia cells and being produced by M2 cells to balance intercellular

DOI: 10.54254/2753-8818/15/20240465

communication [16]. Most products from the M2 phenotype are suppressive to the cytokines produced by the M1 microglia cells. Besides the regulatory function of M2 cells, M2 microglia cells also produce Chitinase-3-like-3(Chi3L3) for tissue reconstruction and insulin-like growth factor 1(IGF-1) for neurotrophic supplements [15].

Through single-cell RNA sequencing(scRNA-seq), the researchers have separated the microglia cells into 14 clusters [19]. Via comparison of the normal adult group, researchers have concluded that a cluster of Disease Associated Microglia cells (DAM), existed in all clusters for more than 25%, Trem2, APOE, etc [19]., have been revealed to have the ability to upregulate DAM cells. Wang et al showed that compared to common variant Trem2 expressive mice, the knock-out group and the R47H mutation group present a lesser amount of microglia cells that differentiate to their final state [20].

Hence, specific to the activation of DAM cells, the TREM2-DAP12 transmembrane signaling has been focused on through research [21]. Trem2 activation by lipopolysaccharides etc. needed to be signaled through the DAP ITAM region, which recruits Spleen Tyrosine Kinase (SYK) and activated Phosphatidylinositol-3-kinase (PI3K). PI3K can phosphorate a protein kinase B(AKT), and respond for phosphorylation and suppression of molecules such as BAD, IKK-alpha, etc. to improve microglia cells' apoptosis. Besides, PI3K can inhibit the suppressive GSK3β pathway to regulate cell proliferation [20].

4. Microglia cleaning of Aβ amyloid protein

4.1. Normally functioning Microglia cells

The Amyloid protein is a-n activator of Trem2 receptors on microglia cells. The Aβ proteins resemble monomers (oligomers) into dimers and eventually into aggregative plaques. The plaque of Aβ may cause synaptic pruning disorders in the CNS. And cause the activation of microglia cells via deposits interacting with receptors on microglia cells, receptors such as RAGE and MSR that secrete chemokines and growth factors will navigate the microglia cells around the plaques as well as activate Trem2 pathways [22].

After locating and activating the microglia cells, there still needs to be an opsonization effect to close the distance between the deposit and glial cells [12]. Testing for the activation level of lysosome has shown via CD86 marking that a phagocytic process occurred to engulf and digest the Aβ proteins inside the MG cells. Some researchers question the effectiveness of MG cells cleaning the profuse amount of Aβ inside the CNS. However, the bulk of evidence has indicated that in the early stage of dementia, groups with functioning Trem2 microglia cells show a significantly slower rate of developing cognitive disorders [22].

4.2. Abnormal expression of Trem2 affecting the Microglia on cleaning

Instead of directly inhibiting the Trem2 expression on microglia cells, Wang et al. created a Cre-Loxp line of 5xFAD mice to eliminate the Syk, a downstream molecule of the Trem2-DAP12 pathway (Table 1) [20]. After feeding a normal chow diet after the full development of neurons in the second week, the mice revealed Aβ accumulation till the nice week of the experiment. Anatomical results using the Allograft Inflammatory Factor1(IBA-1) marker for noting the cytoskeleton of MG cells showed that the density of Syk floxed group had a lower density of MG cells, but a higher accumulation of amyloid protein via Methoxy-X04 marker [20]. These results indicated that Trem2 could be an important factor for maintaining the MG cells around the plaque and creating a barrier for the Aβ proteins.

Besides the losing function of isolating the Aβ plaques, the disfunction of phagocytoses in MG cells was also shown by CD68 lysosomal marker, showing that although both Syk^{fl}/Syk^{wt} have the process of engulfing the Aβ proteins. However, the fluorescent markers have shown that in the Syk^{fl} group, there were no lytic signs of the engulfing debris [21, 23]. Thus, lacking Trem2 would not only affect the formation of MG barriers around the Aβ plaques but also disrupt the function of MG cells to phagocyte and lysis the deposits.

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Table 1. Trem2 treated Alzheimer's Disease (AD) models.

Topic/Aims	Subjects	Treatment	Results	References
Trem2 Pathway of Microglia clearance	5x FAD mice with Syk locus deleted.	Cre-loxp transcription modifying	Trem2 can bind to two adaptors of DAP10 and Syk, and both can drive to the microglia clearance of Aβ	[20]
Sequencing RNA of microglia cells to find risk genes for AD	16242 brain cells from 14 patients and three cortex samples.	DLPFC RNA sequencing and modelling	According to the heatmap, Trem2 received a high Z-score in presenting. Trem2 is annotated as an upregulating gene for DAM cells.	[19]
The relationship of Microglia cells and circadian rhythm	CSF1R inhibited PLX3397 mice.	Coronal brain immunoglobin marker IBA1 fluorescence test. And locomotor activity of mice.	The ablation of microglia cells did not affect the circadian rhythmicity of mice. And mice with ablated microglia cells can still habit the new DL pattern.	[6]
Relationship of aging and the microglia phenotypic change.	6-month-old and 18-month-old PS1xAPP mice.	Using astromicroglial culturing to extract Aβ 42 and other extractions testing the activation of phenotype change in microglia cells	The early-aged extractions are unable to activate the accumulation of Aβ oligomers. However, the cytotoxic extractions from the 18-month group are able to participate in neuron loss of the AD process.	[16]
Differentiating the roles of M1 and M2 type microglia cells.	Review article.	Cell lines and mice as CD4+, vector AAV2-Syn and mSOD1^{G93A} mice in use.	Separated the ways of activation from M0 cells into Pro or Anti-inflammatory cells. Concluded the neurotoxins of M1 that can cause neuro loss in AD.	[17]
Sleep deprivation related to Aβ accumulation of Trem2 mice.	5xFAD mice model use. Control-variable experiment.	Knocking out Trem2 gene. SD mice groups. Using CD68 and IBA1 florescence dye to identify microglia cells of transaction samples of mice groups.	In Trem2 knocking out groups, the SD have led to further Aβ deposition than the control group.	[4]
P2X7 receptor and the activation of microglia cells.	Sprague Dawley rats in use.	Transfection of primary hippocampus neurons. Tagging EGFP on both mutated G345Y and WT mice for the P2X7 receptors.	When using oxATP for triggering the immune activation of microglia cells, WT mice review morphologically difference with G345Y mutate group and antagonist treated WT group.	[13]

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Abbreviations: DLPFC, Dorsolateral Prefrontal Cortex; DAM, Disease-Associated Microglia; SD, Sleep Deprivation; WT, Wild Type.

On the other hand, excessive activation of Trem2 doesn't mean speeding up an inflammatory response in cleaning neuron debris. Xu et al. have shown their results of activating excessive microglia via Trem2 by introducing IFNγ to 5xFAD late AD pathological mice. Which is the over-suppression of the PI3K/NF-κB signaling pathway, and shows immunity tolerance in these mice, revealing blocking of the MG immune surveillance and the clearing functions [24].

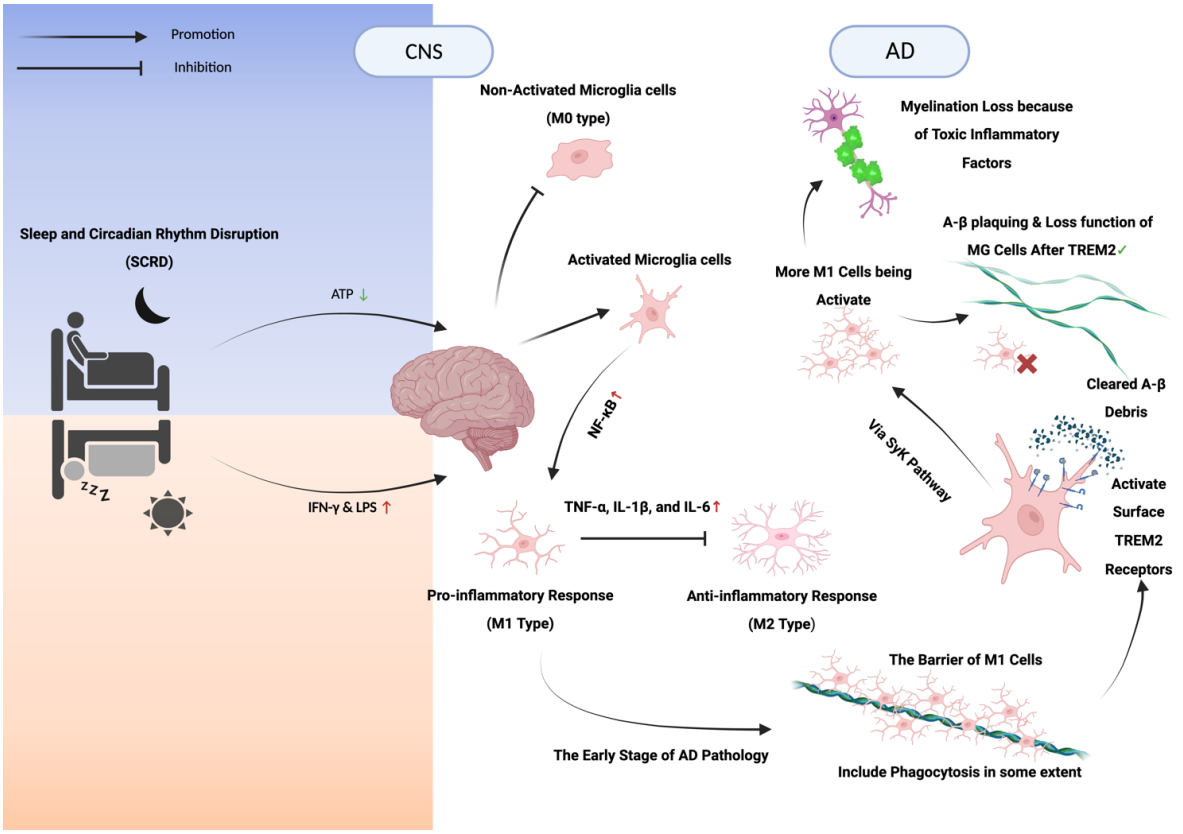

Figure 1. Demonstration of how SCRD affects the progress of AD pathology. The disruption of circadian rhyme down-regulates the ATP level in the cerebrum and raises levels of IFN-γ and LPS (lipopolysaccharide). Hence inhibits the development of M0 cells and directs activated microglia cells to differentiate into M1 cells. Which surrounds monomer Aβ and phagocytes slightly. Then the phagocytic debris activates TREM2 on microglia cells, causing more M1 phenotype forming and deteriorating AD pathology. Figure credit: original, created using Biorender.com.

5. Dis-functioned microglia cells contribute to Alzheimer's' disease

5.1. Speeding Amyloid protein plaquing

Using different dyes in the color of fluorescence, as marking the homeostatic MG cells with transmembrane protein 119(TMEM-119) and DAM cells with c-type lectin domain containing 7A(Clec-7a), the results showed that in the Syk normal group, the section of Clec-7a increases, as an up-regulation of disease associate microglia cells to impede the amyloid protein. However, in the Syk floxed group, Clec-7a was revealed a down-regulation, instead of up-regulating in TMEM-119-related homeostatic MG cells, which boosted the section of Methoxy-X04 marked amyloid protein. Thus, the dysfunction of microglia cells would boost the plaquing of Aβ proteins (Figure 1) [8, 20, 25].

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5.2. Affecting metabolism

Aligned with the side-effect that sleep deprivation causes Trem2-related Aβ plaquing changes. In the mouse group of 5xFAD/$T2^{CV}$ group, multiple pathways, including leptin-insulin signaling and glycolysis, are all prominent in the early onset of AD patients. The impaired metabolism system caused by circadian disruption can add severity to the development of AD despite the Trem2 signaling of MG cells.

6. Conclusion

Through SCRD, the level of Trem2 is affected in taken samples. As Trem2 clearly has the function of controlling inflammatory responses, with the results of increasing amount of M1 microglia cells and dropping cognitive scores in patients, it is worthy to suspect that Trem2 is one of the contributing factors for AD. Through sleep deprivation testing, the turbulence circadian rhythm would cause a lower rate of ATP and a higher proportion of interleukin 4,10 and 13 to be secreted in the CNS, which the previous inhibits the activation of microglia cells, and the latter helps the transition of homeostatic MG cells into M1-inflammatory phenotype. In the prior period levitating the symptoms of AD, but as the Aβ plaquing activated Trem2 receptors causing proliferation and missing of apoptosis of MG cells via Trem2-DAP12 pathway, and the missing of halting of M1 phenotype with M2 anti-inflammatory phenotypes. The microglia cells in CNS began to transit fully into M1 or DAM cells. Hence in the later stage of AD, where MG cells are less functioning to the symptom, the activated MG cells by circadian disruption will also be pruning needing myelin sheath and neuron branches, companioned with toxic cytokines released into the CNS, disrupting the CNS metabolism and assisting the growth of dense Aβ plaques, speeding up the development of AD and cause clinical dementia symptoms. Further research may focus on the effect of microglia inflammation in different stages of AD and detail the pathway of how activated M1 microglia cells could cascade as more A-Beta plaquing. Moreover, the impact of tau protein hyperphosphorylation on MG cells, as defining the importance of neuron inflammation at the later stage of AD.

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