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White matter-associated microglia: New players in brain aging and neurodegenerative diseases

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ABSTRACT

There has been growing interest in brain aging and rejuvenation. It is well known that brain aging is one of the leading causes of neurodegenerative diseases, such as Alzheimer's disease, but brain aging alone can cause cognitive decline. Microglia are thought to act as 'conductors' of white matter aging by modulating diverse glial cells and phagocytosing white matter-derived myelin debris. A recent study identified a specific subpopulation of microglia in the white matter of aged mice, termed white matter-associated microglia (WAM). Additionally, senescent microglia show impaired phagocytic function and altered lipid metabolism, which cause accumulation of lipid metabolites and eventually lead to myelin sheath degeneration. These results suggest that senescent WAM could be pivotal players in axonal loss during brain aging. The aim of this review is to assess the current state of knowledge on brain aging, with an emphasis on the roles of the white matter and microglia, and suggest potential approaches for rejuvenating the aged brain.

1. Introduction

Life expectancy has steadily increased over time and may reach over 90 years from birth by 2030 in several countries (Kontis et al., 2017). Taken together with a decrease in birth rate, this has resulted in a marked augmentation of elderly in the population age distribution.

There is a term called 'normal brain aging' that implies that brain aging without neurodegenerative disease is not a pathological state, but rather is simply part of a natural process. However, recent research suggesting that the aged brain is a pathological state has challenged this concept. Age is the greatest risk factor for some major neurodegenerative diseases, such as Alzheimer's disease (AD) (Association, 2016). Additionally, age-related changes in the brain negatively affect cognitive reserve and prognosis in stroke (Umarova, 2017). Moreover, brain aging alone can cause significant impairment in various domains of cognition, including inductive reasoning, spatial orientation, and verbal memory (Hedden and Gabrieli, 2004). In this context, median scores of Mini-Mental State Examinations (MMSE) start to decline from middle age, reaching 25 by 80 years of age (Crum et al., 1993) (Fig. 1).

Numerous studies have focused on rejuvenation of the aging brain (Wyss-Coray, 2016). Injecting circulatory factors from young mice into old mice has been shown to enhance synaptic plasticity, neurogenesis, and cognitive function in old mice (Katsimpardi et al., 2014; Villeda et al., 2014). Conversely, injecting aged blood plasma into young mice negatively affects neurogenesis and cognitive function (Villeda et al., 2011). Soluble factors, such as insulin-like growth factor, gonadotropin-releasing hormone, and growth hormone-releasing hormone intensify hippocampal neurogenesis in the aged brain (Baker et al., 2012; Stern et al., 2014; Trejo et al., 2001; Zhang et al., 2013). Caloric restriction and exercise are also well-known strategies for reducing age-related brain changes (Colcombe et al., 2006; Erickson et al., 2011; Ingram et al., 1987; Wahl et al., 2016, 2017, 2018). Most of these previous efforts have focused on neurogenesis in the gray matter. Only a few studies have been conducted on brain rejuvenation in relation to white matter.

The aim of this review is to provide an assessment of the current state of knowledge on brain aging, with an emphasis on the roles of white matter and microglia, with the ultimate goal of identifying potential strategies for rejuvenating the aged brain.

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2. Brain aging and white matter loss

2.1. Age-related white matter loss: a macroscopic view

It is well known that aged individuals exhibit diffuse atrophy of the brain (Drayer, 1988). One could suppose that neurodegenerative diseases are accelerated forms of brain aging. However, the significant differences between brain aging and neurodegenerative diseases challenge this concept. For example, neuronal loss is not a principal hallmark of brain aging.

In AD, there are significant reduction in cortical thickness and the number of cortical neurons that are associated with a corresponding decline in cognitive function (Ossenkoppele et al., 2019). Decrements of the cortical thickness and the volume of gray matter were also found among general aging process (Irimia, 2021; Lee et al., 2016; Terry et al., 1987). However, AD and general aging show distinct pattern of atrophy. AD-related atrophy is known to be prominent in specific region, especially in hippocampus, amygdala, entorhinal cortex and inferior temporal cortex (Habes et al., 2021; Ossenkoppele et al., 2019). In contrast, aging-related atrophy shows widespread modest decrements of cortical thickness, and pronounced in the frontal operculum, superior temporal, insular, and frontal and inferior parietal cortex (Habes et al., 2021).

Also, studies which counted cortical neuronal numbers demonstrated that cortical neuronal loss was less significant than the volume loss of gray matter in aged brain (Pakkenberg and Gundersen, 1997; Peters and Kemper, 2012; Terry et al., 1987). Only 10% loss in the total number of neurons in the cortex was observed between 20 and 90 years of age (Pakkenberg and Gundersen, 1997). Autopsy studies identified the age-dependent shrinkage of cortical neurons, which might explain the discrepancy between cortical thickness and cortical neuronal loss (Terry et al., 1987). Several monkey studies support these human data, supporting that rather than cortical neuronal loss, shrinkage of neuronal body and morphological dystrophy are the main features of cortical aging process (Peters and Kemper, 2012; Peters et al., 1994, 1996, 1998; Smith et al., 2004).

Throughout adulthood, the pattern of white matter volume changes shows a u-shaped curve with decreases appearing in middle age (Fotenos et al., 2005; Giorgio et al., 2010; Habes et al., 2021; Liu et al., 2016) (Fig. 1). White matter volume loss is also observed in AD (Habes et al., 2021; Pini et al., 2016; Salat et al., 2009). But volumetric analysis had revealed out that white matter volume reduction of AD was only restricted in several regions compared with general aging process (Salat et al., 2009, 1999). Also, gray-white matter volume ratio at prefrontal cortex in young healthy human was 1.7, that in elderly with normal cognitive function was 2.3, but that in AD patients was 1.9, indicating that white matter loss is more predominant than gray matter loss in general aging process, compared with AD (Salat et al., 1999).

In addition to the volumetric analysis, white matter lesions (WML) and cerebral microbleeds (CMBs) could also represent white matter aging. WML and CMBs, which are the indicators of small vessel disease burden in the brain, are known to be increased during aging process (Graff-Radford et al., 2020; Habes et al., 2021; Vinke et al., 2018).

2.2. Age-related white matter loss: a microscopic view

Most axons residing in cerebral white matter are myelinated. During the aging process, several age-related defects appear in the myelin sheath, the most common of which is a split in myelin lamellae (Peters, 2002). In this setting, the sheath fills with fluid and balloons and myelin debris accumulates (Feldman and Peters, 1998). These degenerative changes cause delayed conduction velocity of axonal fibers, affecting cognitive functions (Felts et al., 1997).

Age-related changes also appear in oligodendrocytes. Oligodendrocytes remodel the myelin sheath in axon fibers throughout life, a process called myelin plasticity (Hill et al., 2018). Oligodendrocytes in the cerebrum of aged primates are swollen and contain dense intracellular inclusions (Peters, 1996). A recent study reported that the enzyme TET1 (ten-eleven-translocation 1) could be the key to explaining the decrease in the myelin-repair function of oligodendrocytes (Moyon et al., 2021). Researchers found that TET1 is essential for myelin repair in

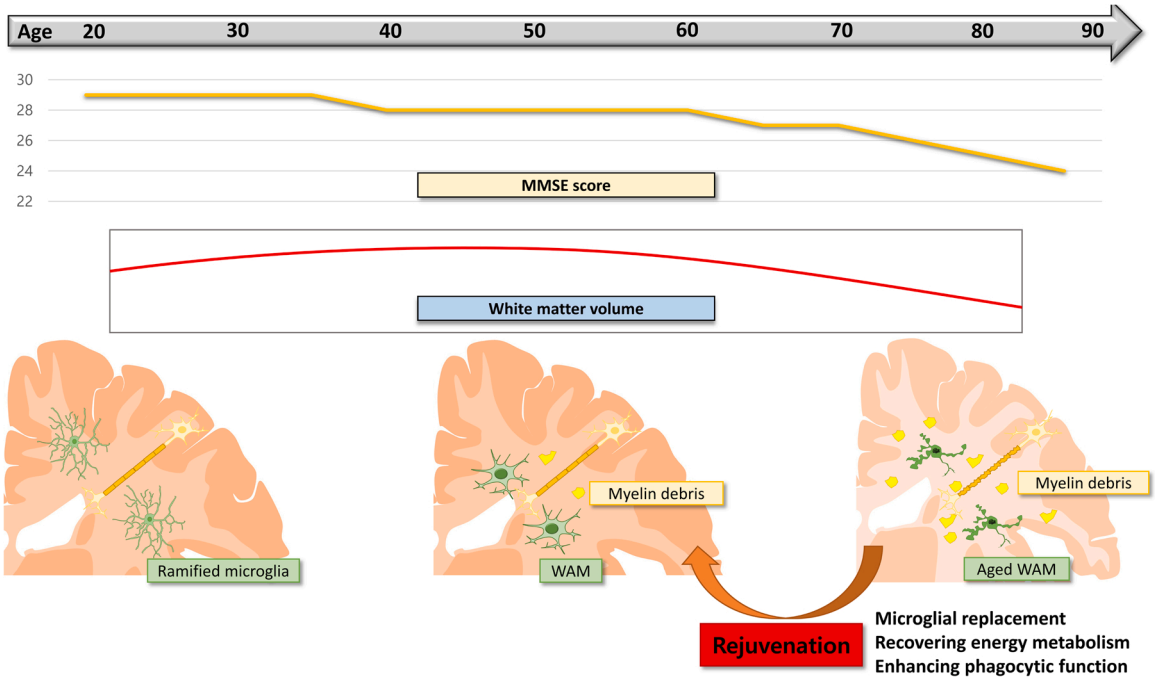

Fig. 1. Hypothesis of white matter aging in the brain. Numbers on the age arrow indicate years. Mini Mental Status Examination (MMSE) scores were used to represent cognitive function. Decreases in mean MMSE scores begin in the 40 s and eventually reach 24 by the late 80 s. White matter volume shows a u-shaped pattern, with decreases appearing after middle-age, as is also the case for cognitive function. Ramified microglia are converted to white matter associated microglia (WAM), which phagocytose myelin debris. As individuals age, senescent WAM are unable to efficiently clear myelin debris, resulting in accumulation of damaged myelin and leading to cognitive dysfunction. However, microglial replacement could reverse this damage.

oligodendrocytes, and showed that its function is decreased in aged mice. The number of oligodendrocytes also decreases after 13 months of age in mice (Hill et al., 2018; Wang et al., 2020). This decrease in oligodendrocyte number combined with loss of function contribute to age-related myelin degeneration and diminished renewal. Conversely, acceleration of oligodendrocyte differentiation promotes re-myelination of axons in white matter, leading to recovery from the cognitive decline associated with aging. The fact that the number of oligodendrocyte precursor cells (OPCs) is unchanged during aging has spurred efforts to determine which factors are associated with age-related change in oligodendrocytes (Wang et al., 2020). Recent data predict that microglia could be the preponderant driver of age-related changes in oligodendrocytes.

Recently, diffusion tensor imaging (DTI) allows novel approach to investigate microscopic features of white matter aging. In DTI, using fractional anisotropy (FA) and mean diffusivity (MD) can estimate the integrity of white matter (Liu et al., 2017). In aged brain, decrement of FA and increment of MD are observed, suggesting the age-related decrement of white matter integrity (Pietrasik et al., 2020; Vinke et al., 2018). Among them, MD showed the highest sensitivity in order to explain brain aging compared with FA and white matter volume (Vinke et al., 2018). Cognitive function including episodic memory, semantic memory and frontal executive function are proportionate to regional white matter integrity (executive function to frontal lobe white matter, episodic memory to temporal and parietal lobe white matter), but not associated with regional cortical thickness, emphasizing the importance of white matter in brain aging (Ziegler et al., 2010). A recent functional connectome study has elaborated on this trend (Damoiseaux, 2017), reinforcing the importance of white matter in brain aging.

3. White matter and microglia in the aged brain

3.1. Microglia and aged brain

Similar to neurodegenerative diseases, inflammation is expected to be a cardinal aspect of the pathogenesis of brain aging (Koellhoffer et al., 2017). Considering that microglia mediate inflammatory responses in the brain, these cells are likely to be among the most important players in brain aging (Angelova and Brown, 2019; Mattson and Arumugam, 2018). Recent human data determined number and morphology of aged microglia (Shahidehpour et al., 2021). The data revealed out that total number of microglia and proportion of hypertrophic microglia were proportional to the age. In another study, dendrites of aged microglia are also shorter and less branched than those of young microglia (Damani et al., 2011; Koellhoffer et al., 2017). In the other hand, numerous studies examined functional aspect of aged microglia. In the aged brain, the phagocytic function of microglia is decreased (Bliederhaeuser et al., 2016; Yanguas-Casas et al., 2020). Notably, senescent microglia are more likely to produce pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)− 1β, IL-6, and IL-10 (Angelova and Brown, 2019; Sierra et al., 2007; Sikora et al., 2021).

In transcriptome analysis of microglia in aged mice, expression of proteins associated with inflammatory response such as lipid-related phagocytosis, pattern recognition, and antigen presentation are upregulated (Pan et al., 2020; Raj et al., 2017). Single-cell RNA sequencing also identified several microglia clusters which were associated with aging, present pro-inflammatory phenotype (Hammond et al., 2019). In addition to their inflammatory and phagocytic properties, microglia modulate the functions of other glial cells or directly affect neurons. Recent studies suggest that microglia function as ‘conductors’ of oligodendrocytes through immune modulation, manipulating the recruitment, differentiation, and re-myelination of OPCs (Lee et al., 2019). In addition, microglia are known to play a role in synaptic plasticity by participating in synaptic pruning (Kim et al., 2013). They are also thought to induce a specific subtype of astrocytes called A1 astrocytes, which are deficient for phagocytosis of myelin debris and exert highly neurotoxic effects (Liddelow et al., 2017).

3.2. Microglia in white matter of the aged brain

Previously, monkey study had revealed out that inflammatory response, such as microglial activation is upregulated in aged individuals (Sloane et al., 1999). In human studies, it has been shown that the increase in the number of microglia during aging is concentrated in the white matter (Gefen et al., 2019; Raj et al., 2017). Furthermore, the number of microglia positive for MAC-2, an indicator of phagocytic microglial subpopulations, is significantly upregulated in white matter, but not in gray matter (Raj et al., 2017). Interestingly, old adults who had better cognitive function than other elderly people, named “Superagers”, had significantly less microglia in cortical white matter than in other old adults (Gefen et al., 2019).

Myelin debris accumulates in aged white matter. This debris is phagocytosed by microglia, which keep the white matter clean. A previous study showed that, after treatment with cuprizone, a copper-chelating agent that stimulates demyelination, microglia in aged mice contained more internalized myelin debris than microglia in young mice (Safaiyan et al., 2016).

TREM2 (triggering receptor expressed on myeloid cells 2), an important factor in immune responses in microglia, is thought to be a key protein involved in clearing myelin debris. TREM2 is considered an important genetic risk factor for diverse neurodegenerative disorders, including AD (Carmona et al., 2018). In addition, TREM2 promotes phagocytosis of amyloid beta (Aβ) protein in AD (Baik et al., 2016; Kim et al., 2017). Recent work showing that re-myelination after cuprizone treatment is impaired in *Trem2*-knockout mice compared with normal mice (Poliani et al., 2015) suggests that TREM2 is also associated with brain aging, especially as related to clearing myelin debris in white matter. The number of cells positive for Iba-1 (ionized calcium-binding adaptor molecule 1), a macrophage marker, increases in normal mice during aging, but is not significantly increased in *Trem2*-knockout mice.

The fact that phagocytosis is upregulated only in white matter in aged mice has led to the hypothesis that microglia present in white matter might be different from those in gray matter. To test this, Safaiyan et al. performed single-cell RNA sequencing of the mouse brain and compared gene expression in microglia between gray and white matter (Safaiyan et al., 2021). They discovered a subset of microglia that was present only in white matter and exhibited a distinct gene expression pattern compared with that in previously identified subsets, namely homeostatic microglia, activated microglia, and disease-associated microglia (DAM). This specific subset of microglia, termed ‘white--matter associated microglia’ (WAM), is characterized by upregulation of DAM-associated genes encoding proteins related to lipid metabolism and phagocytosis. But unlike the case for DAM, formation of WAM is independent of APOE (apolipoprotein E) expression. WAM also show downregulation of genes expressed in homeostatic microglia, such as checkpoint genes. The WAM subtype was also found in re-analyses of pre-existing data obtained by other researchers.

WAM clear myelin debris exuded from myelinated axons in white matter, and TREM2 is a key protein involved in resolving the resulting internalized myelin debris. Two major findings were observed in *Trem2*-knockout mice: absence of WAM and accumulation of myelin fragments in myelinated axons. These observations suggest that TREM2 is essential for formation of WAM. Moreover, the percentage of WAM among microglia in white matter is closely proportional to age. These results indicate that WAM provide a ‘defensive force’ in white matter against demyelinating stress associated with the aging process.

Microglia with an accumulation of lipid droplets and distinct transcriptional patterns compared with previously reported microglial states are observed in the aged brain, (Jung and Mook-Jung, 2020; Marschallinger et al., 2020). Investigators named this subset of microglia ‘lipid-droplet-accumulating microglia’ (LDAM). These microglia show impaired phagocytic function, increased release of reactive oxygen

species (ROS), and pro-inflammatory cytokines.

Thus, it is possible to speculate that the observed cognitive decline and white matter degeneration during brain aging could be caused by dysfunction of senescent, lipid-laden WAM. This raises the question of whether replacing microglia could rejuvenate the aged brain.

4. Can aged brain-associated white matter degeneration be reversed by replacing microglia?

CSF1R (colony-stimulating factor 1 receptor) is thought to be essential for microglial survival. Brain microglia have been successfully eliminated by inhibitors of CSF1R and shown to recover several days after cessation of CSF1R inhibitor treatment (Elmore et al., 2014). Thus, several studies have investigated the possibility of using CSF1R inhibitors to repopulate microglia (Beckmann et al., 2018; Elmore et al., 2018; Henry et al., 2020; Willis et al., 2020). In a mouse model of multiple sclerosis created using cuprizone, treatment with a CSF1R kinase inhibitor (BLZ945) significantly suppressed demyelination (Beckmann et al., 2018), indicating that repopulating microglia can reduce the demyelination burden. It is also thought to increase neuronal survival and neuroprotection by inducing IL-6 in neurons (Willis et al., 2020). IL-6 is known to have neuroprotective effects and induce nerve regeneration (Rothaug et al., 2016).

Another study using the CSF1R inhibitor PLX5622 in aged mice showed that age-related changes in the morphology of microglia were reversed after repopulation of microglia (Elmore et al., 2018), restoring both cognitive and synaptic functions to levels similar to those in young mice.

Restoring microglial metabolism might also be important in rejuvenating the aged brain. Prostaglandin E2 (PGE_2) synthesis in myeloid cells is increased with age (Wu and Meydani, 2004). In human monocyte-derived macrophages (MDM), PGE_2 specifically binds the prostaglandin E receptor, EP2, and inhibits energy production in aged myeloid cells. Blocking EP2 signaling in aged microglia was shown to rescue energy metabolism in these cells and reverse cognitive aging (Minhas et al., 2021).

Rejuvenating microglial phagocytic function has also been considered as a therapeutic strategy. Treatment of AD model mice with interferon-γ was shown to restore inflammatory responses of microglia and increase phagocytic function (Baik et al., 2019). It has recently been discovered that expression of CD36, a protein important in phagocytosis of lipid metabolites by macrophages (Podrez et al., 2002), is markedly decreased in senescent microglia (Rawji et al., 2020). Moreover, overexpression of CD36 in cultured microglia appeared to increase phagocytosis of myelin debris. Niacin (vitamin B3) is known to up-regulate CD36 expression in monocytes (Rubic et al., 2004), resulting in enhanced phagocytosis of myelin debris and recovery of cognitive function in aged mice (Rawji et al., 2020).

5. Unresolved questions

5.1. How does brain aging differ between mice and humans?

As mentioned above, microstructural studies had shown that human and mice share similar aspects of age-related white matter degeneration. Also, DTI study in mouse model revealed that age-related decrement of white matter integrity was observed in wild type mice, even it was less severe than that in AD transgenic mice (Praet et al., 2018; Song et al., 2004).

However, age-related white matter degeneration is not significant in the macrostructural studies of mice. First, the volume of white matter does not decrease significantly in mice like it does in humans (Maheswaran et al., 2009; Rattray et al., 2017). Also, CMBs which were mentioned to be increased in healthy aged human population, are not increased in aged wild-type mice (Sumbria et al., 2018). The interesting finding is that white matter lesions were not observed even in extremely old mice, such as 20months old (Wei et al., 2020). These findings indicate that, unlike humans, microstructural white matter damages do not lead to macrostructural white matter damages in mice. Why macroscopic age-related white matter degeneration is more prevalent in humans than in mice remains unclear, but understanding the basis for this difference could be a key for efforts to rejuvenate the aging brain. Considering that WAM play an important role in the white matter aging process, we tentatively speculate that WAM could be central to answering this question. Thus, further studies are needed to determine whether WAM are present in the brains of aged humans and compare WAM in humans to those in mice.

Also important, considering differences between mice and humans with respect to brain aging, is the need for a specific mouse model that reproduces features of human brain aging. Among possible models are senescence-accelerated mouse (SAM) strains. These non-transgenic mouse models originate from the AKR/J strain and comprise senescence-resistance strains (SAMRs) and senescence-prone strains (SAMPs) (Shimada and Hasegawa-Ishii, 2011). SAMP strains include SAMP1, SAMP6, SAMP8, and SAMP10. Of these, SAMP10, derived from SAMP3, exhibits age-related phenotypes such as deficits in learning/-memory and brain atrophy (Shimada et al., 1994; Takeda, 2009). In contrast to SAMR models, SAMP10 mice show significant age-related decreases in brain weight, with about a 10% loss at 15 months of age. Such age-related brain atrophy is observed predominantly in the frontal cortex, especially the prefrontal cortex, resembling findings in the aging human brain (Giorgio et al., 2010). Thus, SAMP10 mice could prove useful for studying brain aging.

5.2. Comparing aged WAM versus young WAM

WAM in mice brains appear as early as 1 month of age; however, at this age, the proportion of WAM in microglia in white matter is only 1–2% (Safaiyan et al., 2021). The proportion of WAM increases as mice age, reaching ~9% at 24 months of age. However, how senescent WAM differ from young WAM is unclear. Comparing phagocytic function and expression of inflammatory cytokines in WAM between young mice and aged mice could be a good approach. A senescence-accelerated model could also be helpful for addressing these issues. For instance, microglia in the SAMP10 model show early age-related changes, even at 12-months of age (Page et al., 2002).

5.3. Is WAM a precursor to DAM?

WAM share several characteristics with DAM found in AD mouse models. The proportion of WAM is also up-regulated in AD model mice compared with normal mice, reaching ~20% in 21-month-old AD model mice (Safaiyan et al., 2021). Notably, as is the case for DAM, TREM2 is essential for formation of WAM. These findings suggest that WAM are precursors to DAM. Confirming this could provide important clues for understanding the pathogenesis of AD.

6. Hypothesis

We can summarize the findings highlighted in this review in five comments.

First, changes in white matter are crucial for brain aging. Second, senescent microglia produce pro-inflammatory cytokines and exhibit decreased phagocytic function. Third, inflammatory responses driven by microglia are concentrated in the white matter of the aged brain. Fourth, specific forms of microglia called WAM are observed in the white matter of the aged brain, and this microglial subpopulation is active in clearing myelin debris. Last, repopulation of microglia has neuroprotective and neuroregenerative potential in the damaged or aged brain.

On the basis of these observations, we hypothesize that cognitive decline and white matter degeneration of the aged brain are caused by impaired function of senescent WAM, and that recovery of

malfunctioning senescent WAM can rejuvenate the aged brain (Fig. 1).

Author contributions

KA: Conceptualization, Writing – original draft. **SJL:** Methodology, Writing – review & editing, Supervision. **IMJ:** Writing – review & editing, Supervision.

Declaration of Competing Interest

None

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