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Is Alzheimer disease a failure of mobilizing immune defense? Lessons from cognitively fit oldest-old

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Multifaceted evidence supports the hypothesis that inflammatory mechanisms contribute to Alzheimer disease (AD) neuropathology and genetic association of several immune specific genes (REM2, CR1, and CD33) suggests that aladaptive immune responses may be pivotal drivers of AD pathogenesis. We reviewed microglial-related data from postmortem AD studies and examined supporting evidence from AD animal models to answer the following questions: i) What is the temporal sequence of immune activation in AD progression and what is its impact on cognition? ii) Are there discordant, “primed,” microglial responses in AD vs successful cognitive aging? iii) Does central nervous system (CNS) repair in aging depend on recruitment of the elements of cellular adaptive immune response such as effector T cells, and can the recruitment of systemically derived immune cells ameliorate AD neuropathology? iv) How effective are the immune-system-based therapeutic approaches currently employed for the treatment of AD?

Keywords: Alzheimer disease; gene expression; immune response; inflammation; macrophage; microglia, oldest-old; T cell

Integration of the immune response in the central nervous system

Vigilant immune defenses against infection and injury ensure the endurance of the organism by setting in motion a discrete, localized inflammatory response to thwart a variety of pathogenic and pathophysiologic threats. These responses must be tuned and scaled precisely, because insufficiency or excesses of responses such as prolonged inflammation can cause morbidity and mortality, shortening lifespan and compromising health. Homeostasis and health are restored when inflammation is resolved by rapid and reversible anti-inflammatory actions dependent on paired antigen clearance, persistence of inflammation triggers, activated macrophages, and the development of adaptive immune responses.

The mammalian nervous system integrates inflammatory responses by gathering information about invasive events, mobilizing defenses, and restoring homeostasis, and creates memory to improve likelihoods of survival. Microglia, derived from primitive myeloid progenitors that populate the developing brain during mid-embryogenesis, are the resident immune/inflammatory cells of central nervous system (CNS). Additional subtypes of macrophages (reviewed in ref 3) are positioned at brain boundaries and show diverse transcriptional profiles. These cell populations include perivascular, subdural, and choroid plexus macrophages which are distinct from parenchymal microglia and are likely derived from hematopoietic precursors. Throughout this review we will discuss brain injury responses of adult microglia, the functions of which may be inherently different from the role(s) of other immune cells.
of microglia during prenatal periods when microglia regulate the wiring of brain circuits, influence the outgrowth of dopaminergic axons, impact the laminar positioning of subsets of neocortical interneurons, and effect functional connectivity.\(^6\)

Under homeostatic conditions microglia are ramified cells with multiple branches and processes. Microglia extend processes to contact neurons, macroglia (astrocytes and oligodendrocytes), and blood vessels and constantly monitor and remodel the functional state of synapses. Highly activated microglia transform from a ramified to an amoeboid shape in response to injuries or inflammatory stimuli and are characterized by enlarged cell bodies and shortened processes with restricted coverage. Amoeboid morphology is associated with phagocytosis and proinflammatory functions. Additional differently shaped activated microglia are recognized (e.g., bipolar, rod-shaped etc)\(^8\) possibly reflecting their diverse responses and movement toward injury or “toxic” stimuli.

Activated parenchymal and perivascular microglial cell populations express variable levels of extracellular markers of myeloid lineage in which some resemble tissue macrophages attesting to microglial heterogeneity.\(^7\) It remains unclear whether hemato poetic-derived progenitors contribute to the expansion of adult parenchymal microglia-like cells when homeostasis is disrupted, such as during brain injury, or whether microglia can maintain and transform their function independently of hemato poetic-derived progenitors throughout adult life in the absence of temporary disruption of the blood-brain barrier (BBB). The experimental manipulation of lethally irradiated and bone marrow-transplanted mice have provided contradicting views regarding the recruitment of lethally irradiated and bone marrow-transplanted mice. While some studies show that donor-derived cells can replace considerable population of microglia in parabiotic chimeras. While some studies show that donor-derived cells can replace considerable population of microglia in parabiotic chimeras. While some studies show that donor-derived cells can replace considerable population of microglia in parabiotic chimeras. While some studies show that donor-derived cells can replace considerable population of microglia in parabiotic chimeras.

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Under the inflammatory conditions of an active immune response, microglia must moderate the potential damage to the nervous system by supporting tissue repair and remodeling, including the maintenance and restoration of synaptic connections. Microglia achieve neuroprotection by clearing debris, suppressing inflammation, and promoting cortical synaptogenesis/neurogenesis by stripping inhibitory synapses.\(^{21}\) To protect from attacking its own antigens, microglia maintain self-tolerance of neural cell types. How ever, examination of the effector myeloid cells derived from microglia or monocytes in animal models of autoimmune disease has shown that microglia-derived myeloid cells are protective and oriented toward resolving neuroinflammation, whereas monocyte-derived myeloid cells are highly phagocytic and proinflammatory suggesting that self-immune tolerance may be an inherent feature of microglia.
Additionally, it has been shown that locally secreted immune suppressive cytokines (eg, TGFβ, G-CSF, and IL-10) by immune cells may promote immune tolerance to self-associated antigens. It is plausible that self-tolerance mechanisms in the brain contribute to the accumulation of toxic signals in neurodegenerative disorders such as AD.

We will discuss whether the engagement of systemic adaptive immune responses can overcome self-tolerance suppression of the brain immune response in order to ameliorate AD neuropathology. We will additionally sum arize microglia-related data from postmortem AD studies and examine supporting evidence from AD animal models to answer the following questions: i) What is the temporal sequence of microglia activation in AD progression and what is its impact on cognition? ii) Are there discordant, “primed,” microglia activation states revealed by transcriptomic approaches? iii) How effective are the immune-system-based therapeutic approaches currently employed for the treatment of AD? iv) How effective are the immune-system-based therapeutic approaches currently employed for the treatment of AD?

Brain inflammatory response – relevant factor in Alzheimer disease and successful cognitive aging: evidence from neuropathology and molecular studies

Alzheimer disease and its associated dementia is the most common type of neurodegenerative disorder, with age and aging representing the greatest risk factors. The neuropathological hallmark of AD include neuronal loss, abnormal neuronal cytoskeletal changes, known as neurofibrillary tangles (NFT) and extracellular protein deposits called neuritic plaques (NP) and NFTs. In addition to the NFTs and NPs, evidence from multiple dom ains suggest the hypothesis that inflam matory responses in AD may be contributing to AD neuropathology. Elevated levels of the inducers of acute phase response, such as inflammatory cytokines and acute phase reactants, are identified in CSF, plasma and in am yloid-laden plaques; the presence of reactive microglial cell clusters around senile plaques and com plexes in vicinity of dystrophic neurites and NFTs are well-documented in postmortem studies of individuals with AD. Additionally, changes in gene expression of inflammatory signaling pathways and regulatory gene networks and microglia have been consistently found in brains of individuals with AD.

Given the evidence of genetic linkage of several immune specific genes (TREM2, CR1, and CD33), the immune-inflammatory processes may be pivotal drivers of AD pathogenesis suggestive of a feed-forward self-amplifying cycle model of AD. This model proposes that immune-inflammatory mechanisms to CNS insults may be imperative for understanding, and potentially treating, the contribution of inflammatory processes to neurodegeneration and impairment of cognitive function in AD. Recent imaging studies aiming to assess longitudinal changes in microglial activation and

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am yloid deposition in m ild cognitive im pairment and AD provided some clues regarding the temporal sequences and trajectories of m icroglia activation in the progression of AD.35 Initial activation during m ild cognitive im pairment followed by longitudinal (>14 m onths) reduction of m icrog lia activation was observed during prodromal AD. A second wave of activation of m icroglia was observed in individuals with definite AD, suggesting the prevalence of proinflam m atory phenotype of m icroglia in advanced stages of AD. The vulnerability of cholinergic neurons, cholinergic atrophy, and decline of acetylcholine release in AD may be at least in part responsible for proinflam m atory phenotype in definite AD as acetylcholine directly m odulates imune responses by acting on the α7 nicotinic acetylcholine receptor and suppressing the proinflam m atory responses in m icroglial and in blood-borne m acrophages.

Acquired anti-inflamm atory protective phenotype during prodromal AD may be tied to self-tolerance mechanism5,29 or it may exemplify chronic para-inflamm atory response (low-grade inflam m atory) switched on due to cellular m alfunction as a result of genetic variance and gene-by-exposom e interactions such as age-associated low level of physical activity, high-calorie diet, and environm ental toxin exposure, rather than tissue injury/infection.50 Divergent imune responses along with age-related imune senescence may suppress the anti-inflamm atory protective phenotype of m icroglia during the prodrom al phase of AD and enable progression to frank dem entia, synaptic loss, neurodegeneration, and AD. In contrast, m icroglia activation will dem and a high rate of m etabolic activity necessary for synthesis and production of imune m odulating factors, such as cyto kines and other cellular proteins associated with m icroglial hypertrophy im unophenotype. The well-documented m etabolic activity of m icroglia in brain atrophy is associated with the microglia transcriptome signature in blood-borne m acrophages. The well-documented m etabolic activity of m icroglia in brain atrophy is associated with the microglia transcriptome signature in blood-borne m acrophages.

Advanced age is the greatest risk factor in AD and is associated with replicative senescence (loss of mitotic ability after repeated rounds of replication) in m yeloid cells. Morphological assessment of microglia in the brains of elderly humans has provided evidence of structural deterioration of microglia and age-associated reduced expression of genes related to motility, adhesion, and chromatin organization. Moreover, in vitro studies have shown that m icroglia are subject to replicative senescence in aging. Together these observations raise the possibility that advanced age-associated factors adversely affect the viability and self-renewal capacity of m icroglia, resulting in m ild senescence/or dysfunctional immune-related cells.19,67 In this regard, investigation of immune responses in persons surviving beyond the 9th decade of life who remain cognitively intact may shed light on the contribution of m icroglia to successful cognitive aging with scarce presence of AD neuropathology.58-70 Investigation of system imune responses in centenarians suggests that immune function is not compromised by extreme age, but rather undergoes remodeling processes in which innate immune responses are preserved, while adaptive immune responses manifest profound m odifications suggestive of elevated levels of regulatory T cells and their m unsuppressive activities. Moreover, assessment of the m icroglial transcriptome in healthy adults shows that during physiological aging the m icroglial transcriptome undergoes disproportionate downregulation of genes involved in sensing endogenous ligands and upregulation of genes associated with alternative neuroprotective m icroglial priming states suggesting that aging is associated with the m icroglia transcriptome signature shifting toward neuroprotection by downregulating debris-sensing receptor signaling. Thus, it can be argued, and studied further, that neuroprotection processes assisted by active m icroglia are likely central to the cognitive resilience.7 The presence of ubiquitin-imune m unoreactive dystrophic neurites in the neocortex of non-demented old and est-old (90+ years old) humans brains and granular degeneration of m yelin in white m atter in the absence of m yloid deposition and neocortical neurofibrillary degeneration support activation of imune responses. However, extrapolation from m ume to humans m ust be approached with caution. A recent purified m icroglia study in human brains found little overlap between genes differentially expressed during aging in humans and those of m ouse brain suggesting that the m icroglia of physiologically aged mice do not necessarily recapitulate the effect of aging on human m icroglia.

Extrapolating to the CNS m icroglia and successful cognitive aging, one may hypothesize that robust imune responses involving ubiquitination m ay promote intact cognitive function in extreme age and protect against accumulation of toxic m olecules and Aβ deposition. Evaluation of transcriptional profiles from hum an postmortem brains...
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show support for contribution of immune activation to the cognitive resilience in aging. Direct comparison of neocortex transcriptomes from young-old (64 to 86 years old) and oldest-old (87 to 103 years old) cognitively normal and demented individuals suggest that inability to scale up robust immune activation that typify oldest-old individuals who evaded dementia (Figure 1) may be directly associated with cognitive decline in the oldest-old.

One working hypothesis may be that successful aging is associated with an enhanced immune-related signature resulting from priming of microglia, similar to the mechanisms known to occur in peripheral macrophages. The “prim ed” microglia would respond to triggering stimuli more rapidly and to a greater degree than would be expected from non-prim ed microglia presumably by modulating accessibility of microglia-specific transcriptional enhancers and promoters (work in transgenic mice suggests that senescent-like dysfunctional neurons are sufficient to induce progressive priming responses in microglia). This hypothesis stands in contrast to, and is underscored by, the fact that there is general consensus that acute and chronic systemic inflammation is detrimental to brain function, impedes adult neurogenesis, and is associated with cognitive decline in AD. This “paradox” may be more apparent than real, however, and may be a result of a too-simplistic or too-binary model of immune/inflammation and microglial function. As we have discussed above, microglia assume diverse phenotypes and can promote both harmful and advantageous/neuroprotective outcomes. Findings in animal models show that upon receiving triggering stimuli, microglia in their classical primed state will release excessive concentration of inflammatory cytokines (IL-1β, IFNγ, TNFα etc) associated with neurotoxicity and neurodegeneration, while in the alternative primed state microglia release anti-inflammatory agents that may aid in this effort.
with protection and neuroplasticity. Transcription study of isolated microglia in rodents suggested that during aging the m icroglial phenotype shifts toward an alternative neuroprotective prim ing state. Survey of protein levels of 30 cytokines in cortical grey m atter of nondem ented oldest-old when com pared with cognitively intact younger individuals showed that only a sm all set of cytokines (G-CSF, IL-6, 8, and 15) were significantly upregulated in brain tissue hom ogenates (Brodm ann area 22) from nondem ented oldest-old (refer to ref 74 for unpublished data derived from the same dataset). At least two of these factors (IL-6 and IL-15) can be considered to elicit both pro- and anti-inflam m atory responses implying that this sim plistic subdivision of cytokine responses m ay also be inadequate to classify their function and necessitate further examination with respect of neuronal and glial responses in the h um an CNS.

It is critical to keep in m ind that m icroglia and the other cell-types of the CNS do not function independently. Rather, neurons, microglia, astrocytes, oligodendrocytes, and m icrovascular endothelial cells interact extensively and function in unison. Notably, the most upregulated cyto kine in the brain of nondem ented oldest-old is granulocyte colony stimulating factor (G-CSF) which has been shown to induce neurogenesis, neuroplasticity to counteract apoptosis, and is known as a factor involved in vasculogenesis. G-CSF is currently under investigation for the development of treatments of neurological diseases such as acute cerebral ischemic stroke. In this respect, participation of brain m icrovascular endothelial cells in inflam m atory responses is highly critical as they can initiate the release of cytokines/chem okines, reactive oxygen species capable of inducing neurotoxicity, expression of antigen presentation m olecules (MHC class II), phagocytosis-related Fc receptors, and m atrix m etallo peptidases. In contrast, M2 (a,b,c) phenotypes are central for inflammation resolution, imm unom odulation, angiogenesis, tissue repair/remodeling and associated with release of neurotrophic/pro-survival factors and anti-inflam m atory cytokines. These phenotypes are not static, however, and exhibit dynamic changes at different ages, stages of evolution of diseases such as AD, and in response to different environm ental stimuli. Novel approaches such as single-cell and cell-type-specific transcriptomics have revolutionized m odern immunology and suggests that classification systems such M1 and M2 phenotypes may be inadequate for the advanced understanding of m icroglia diversity in health and disease. Recent advances in next-generation sequencing and single-cell transcriptomics show that m icroglia activation states associated with development, aging and different neuropathologies are varied, display unique m ultiple transcription signatures that are not only distinct from m yeloid cells/m acrophages in peripheral tissue, but also m uch m ore com plex than those im pelled by M1 vs M2 dichotom ies/taxonomy. For exam ple, a com prehensive m apping of all m icroglial specific genes com pared with the other neural cell types are the m ost reliable predictors of biological aging in the human brain. Intriguingly, the distinct gene signature of human endothelial cells treated with VEGF-A, a critical pro-angiogenic factor, shows the upregulation of inherent inflam m atory subset of genes attesting to the cross-regulation of angiogenesis, systemic inflam m ation, and m icroglial activation during neovascularization and BBB m aintenance. Feasibility of cognitive function im provem ent and reduction of amyloid pathology due to im proved circulation and adaptive activation of inflam m atory pathways around plaques and the vasculature involving perivascular m acrophages and potential BBB modifications has been dem onstrated in AD m icroglia.

**Microglia plasticity - different states of activation and altered immune cell composition in Alzheimer disease**

Activation of m icroglia is frequently categorized by the M1-classical and M2-alternative phenotypes similar to the categorizations attributed to m acrophages. The M1 phenotype is considered a proinflam m atory state characterized by elevated levels of cytokines/chem okines, reactive oxygen species capable of inducing neurotoxicity, expression of antigen presentation m olecules (MHC class II), phagocytosis-related Fc receptors, and m atrix m etallo peptidases. In contrast, M2 (a,b,c) phenotypes are central for inflammation resolution, imm unom odulation, angiogenesis, tissue repair/remodeling and associated with release of neurotrophic/pro-survival factors and anti-inflam m atory cytokines. These phenotypes are not static, however, and exhibit dynamic changes at different ages, stages of evolution of diseases such as AD, and in response to different environm ental stimuli. Novel approaches such as single-cell and cell-type-specific transcriptomics have revolutionized m odern immunology and suggests that classification systems such M1 and M2 phenotypes may be inadequate for the advanced understanding of m icroglia diversity in health and disease. Recent advances in next-generation sequencing and single-cell transcriptomics show that m icroglia activation states associated with development, aging and different neuropathologies are varied, display unique transcriptional signatures that are not only distinct from m yeloid cells/m acrophages in peripheral tissue, but also m uch m ore com plex than those im pelled by M1 vs M2 dichotom ies/taxonomy. For exam ple, a com prehensive m apping of all m icroglial specific genes com pared with the other neural cell types are the m ost reliable predictors of biological aging in the human brain. Intriguingly, the distinct gene signature of human endothelial cells treated with VEGF-A, a critical pro-angiogenic factor, shows the upregulation of inherent inflam m atory subset of genes attesting to the cross-regulation of angiogenesis, systemic inflam m ation, and m icroglial activation during neovascularization and BBB m aintenance. Feasibility of cognitive function im provem ent and reduction of amyloid pathology due to im proved circulation and adaptive activation of inflam m atory pathways around plaques and the vasculature involving perivascular m acrophages and potential BBB modifications has been dem onstrated in AD m icroglia.
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of that analysis was the identification of TREM2-dependent activation of gene networks specific to the novel disease-associated microglial subtype, which is consistent with genetic evidence of TREM2 polymorphism and dysregulation associated with increased risk of AD. Recent meta-analysis of m yeloid transcriptional responses from the fusiform gyrus of individuals with AD and controls, and animal models of different pathological states provided additional information about m yeloid population-wide transcriptional changes indicating upregulation of not only the TREM2-dependent core neurodegeneration-related subtype, but also additional cell-type clusters including phenotypes related to neutrophil/m onocyte, which were absent in AD m ouse m odels and a subtype related to the acute response to endotoxin lipopolysaccharide. It is not clear whether m ultiple m yeloid cell clusters represent various dynamic phenotypes of activated microglia, such as phagocytic, antigen presenting cells (APC), and/or whether they include CNS-infiltrating m onocyte-derived m acrophages and Aβ-reactive T cells. What these more recent studies reveal is a remarkable diversity in m yeloid cell phenotypes that requires reassessment of functional distinctions and perhaps even a new taxonomy.

While the functions of microglia as APC for adaptive immune responses has not been characterized in AD, the appearance of perivascular and intraparenchymal dendritic cells (DC) - classical APCs - has been demonstrated in brains of patients suffering from epilepsy and encephalopathies. These findings are consistent with data acquired in adult transgenic mice showing prominent appearance of DCs in CNS regions exhibiting plasticity and adult neurogenesis with the m orphologic characteristics of immune/microglia cells. However, these CD11c-positive DC cells express low levels of MHC class II genes suggesting that their function as APC may be flawed, or that within the CNS their functions may be different or possess features in addition to classical antigen presentation. It is possible that these DC-like cells within the CNS may not infiltrate from the periphery. It has been suggested that adult m icroglial progenitors may differentiate into m ature DCs in the presence of granulocytic-m acrophage colony-stimulating factor and express extracellular m ark ers distinct from the rest of microglia. These DC-like cells can m ature fully into DC upon CD40 ligation. Consistent with this hypothesis, T cell-based vaccination in AD mice induced the appearance of a DC-like CD11c m icroglia phenotype which was associated with increased neurogenesis and improved spatial learning and m em ory suggesting that DC-like m onocytes m ay be of benefit to the brain’s resistance to AD by aiding T helper cells to induce T cell activation as APC.

Limited work in postmortem human brains also suggests elevated appearance of T cells (T cell receptor expressing m ature T lymphocytes are part of the adaptive immune system) in the brain parenchyma of the elderly and individuals with AD. More comprehensive tissue m ouse n o staining using m ultiple T cell m arkers have confirmed increased frequencies of T cells in the hippocampus, the entorhinal cortex and associated brain regions of individuals with AD compared with other types of dementia and controls. These observations have supported the view that brain parenchymal T cells are likely m em ory T cells rather than naïve T cells based on the cell-surface m arkers staining. The absence of the IL-2 receptor subunit (CD25), proliferation m arkers, and CD11b staining in CD8+ cells argues against clonal expansion of T cells in AD brains, and their complete differentiation into effector cells. Taken together, these findings suggest ineffective activation of T lymphocytes or a brain-specific T lymphocyte phenotype in AD brain.

A subtype of T cells, regulatory/suppressor T cells (Tregs), is another component of the immune system, critical for the modulation of inflammatory responses, and usually difficult to distinguish from effector T cells. Modulation by Tregs of overall systemic inflammation is critical for moderating microglia-related brain disease. The mechanism involved in this interaction and the infiltration of circulating immune cells into the CNS is a controversial topic and a question that needs to be addressed with high priority. It has been hypothesized that elevated activity of Tregs, key m unsuppressors, and protectors of system ic m une tolerance, is permissive of cerebral plaque pathology and cognitive decline in AD, and m ay contribute to the limited efficacy of anti-inflammatory treatment trials of AD. Under neurodegenerative conditions CNS recruitment of circulating immunoregulatory cells, such as T cells, m ay be critical for m oderating m icroglia-mediated neuroinflammation and enhance CNS activation-resolving cells in the brain parenchyma, which was
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associated with reduced brain protein levels of soluble β amyloid and reversed cognitive decline in transgenic AD mice. Simlarly, early vaccination experiments with CNS antigens showed enhanced recovery after axonal injury and subsequently boosting levels of CNS-specific circulating T cells facilitated the recruitment of m onocyte-derived macrophages from the periphery to the CNS sites of injury where they differentiate locally into resolving macrophages. The blood-CSF barrier of the choroid plexus is a likely candidate for a selective site of m onocyte CNS infiltration and is characterized by distinct population of effector-m emory T lymphocytes expressing T-cell receptors specific for CNS antigens. The cellular composition of CSF is different from that of peripheral blood and constitutively predisposed towards a tissue injury healing, pro-resolving, m ilieu characterized by elevated levels of anti-inflammatory cytokines, untraceable levels of pro-inflammatory factors and inhibition of development of cytotoxic T lymphocytes. Studies in human and m ice have shown that age-induced dysfunction of the choroid plexus and cognitive decline are associated with elevated expression of type I interferon (IFN) responses interfering with IFN-type II regulation of leukocytes homing, rolling, and migration, which m ay act as perm issive m echanism allowing leukocyte infiltration through the choroid plexus. Blocking of brain IFN-I signaling improved neurogenesis and partially restored cognitive function in aging m ice. Diverse Tregs subpopulations are responsible, at least in part, for limited and conflicting information about systemic composition of Tregs subpopulations in AD. Some studies have reported strong increases of the subset of Tregs negative for the immunosuppressive programmed death receptor 1 in individuals with m onocyte-derived m acrophages from the periphery to the CNS sites of injury where they differentiate locally into resolving m acrophages. The blood-CSF barrier of the choroid plexus is a likely candidate for a selective site of m onocyte CNS infiltration and is characterized by distinct population of effector-m emory T lymphocytes expressing T-cell receptors specific for CNS antigens. The cellular composition of CSF is different from that of peripheral blood and constitutively predisposed towards a tissue injury healing, pro-resolving, m ilieu characterized by elevated levels of anti-inflammatory m atory cytokines, untraceable levels of pro-inflammatory factors and inhibition of development of cytotoxic T lymphocytes. Studies in human and m ice have shown that age-induced dysfunction of the choroid plexus and cognitive decline are associated with elevated expression of type I interferon (IFN) responses interfering with IFN-type II regulation of leukocytes homing, rolling, and migration, which m ay act as perm issive m echanism allowing leukocyte infiltration through the choroid plexus.

The exposome, its individual constituents, and sex are additional factors influencing adult m icroglia and need special attention. Ex vivo and in vitro experiments show profound environmental dependence of human m icroglia transcriptomes and epigenetic landscapes from surgically resected tissue. Recent data also suggest that adult m icroglia go through transcriptional and epigenetically distinct differentiation stages, which can diverge as a function of sex. For example, m icrobion e depletion and antibiotic treatment in m ice has sexually dimorphic effects on m icroglia highlighting the importance of the interplay between sex-dependent m icroglia features and environmental factors.

The studies and observations discussed above all point to the centrality of m icroglia to AD, cognitive compromise, and successful aging. But they also highlight the immense complexity of m icroglia, their phenotypic diversity and the myriad of responses that can and are evoked depending on factors such as age, sex, environment, and their CNS milieu, all of which are ripe with their own complexities. It seems unlikely that we will be able to make significant gains in AD therapies andPrompt the successful cognitive ageing without a more detailed understanding of the mechanisms that govern the myriad roles and responses of m icroglia and the ways in which they influence and modulate the functions of the other cells of the CNS. As daunting a task as this m ay seem, recent advances in cell-type specific omics provides the light at the end of the tunnel.

Challenging immune responsiveness in central nervous system – therapeutic approaches to Alzheimer disease

Current immunotherapeutic approaches to AD aim to reduce amyloid burden and reduce or slow the rate of cognitive decline by increasing amyloid β clearance and m icroglial phagocytic activity, while dampening pro-inflammatory m atory response and retaining m icroglial phagocytic activity. Suppression of inflammation alone through non-steroidal anti-inflammatory m atory drug therapy has been disappointing, or had adverse effects in advanced AD. With hindsight, this is not surprising given that, as described above, m icroglial activation phenotypes are contextually different and evolve at different stages of AD progression (reviewed in ref 118 and ref 119). The anti-inflammatory m atory steroid, prednisone, was explored in a randomized, m ulticenter trial with no positive outcome and with some adverse reactions. Minocycline-antibiotic immunomodulation, neuroprotective in neurodegenerative models and hum an chronic neurological disorders, showed reduced production of proinflammatory m atory cytokines, while showing conflicting results for amyloid clearance. Recent clinical trial in patients with m oderate-severe traumatic brain injury showed detrimental effect of chronic phase minocycline treatment – increasing neurodegeneration, while decreasing inflammation.
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One line of defense against toxic amyloid subspecies could be natural neutralizing antibodies, which can be expanded upon by univalent antibodies to Aβ peptides (active vaccination). The first active vaccine (AN1792, consisting of pre-aggregate Aβ Elan Pharmaceutical) was termed inactivated because it induced autoimmune encephalitis in humans. Postmortem tissue examination showed T cell infiltration and inflammation around leptomeningeal blood vessels, near vascular amyloid and infiltration of macrophages in white matter. Despite these negative consequences, immunized patients also showed improvements in amyloid clearance and reduced measures of plaque-associated neuritic dystrophy in the hippocampus, which were associated with increased expression of microglial markers reminiscent of the phagocytic phenotype.

Another approach has focused on passive vaccination by administering antibodies against Aβ. Several anti-Aβ monoclonal antibodies (e.g., bapineuzumab, solanezumab, and mAb158) have been developed. The cognitive benefits of the initial clinical studies with bapineuzumab are still unclear and concerns on the safety of these antibodies have been raised. Solanezumab, a humanized monoclonal antibody directed against the mid-region of the Aβ peptide, was shown to neutralize soluble Aβ. Initial evaluation from two pooled phase III studies suggest a positive trend toward slowing of cognitive decline in the mild AD subgroup. A monoclonal antibody, mAb158 has high selectivity for soluble Aβ protofibrils, which are toxic to neurons. A humanized version of mAb158, BAN2401, has now entered a clinical phase IIb trial for Aβ immunotherapy in early AD with some, but limited positive outcomes. Despite these encouraging trends, none of the trials to date have led to meaningful and substantial clinically significant outcomes.

Experimental approaches toward utilizing cellular mechanisms of adaptive immune responses against Aβ are supported by detection of elevated levels of Aβ in healthy elderly and individuals with AD, suggesting that either these cells are either positively selected, or that they have escaped central and peripheral tolerance. A recent animal study provided convincing evidence that activated CD4 positive T cells polarized toward the Th1 phenotype (but not Th2 or Th17 subsets) and injected into the lateral ventricles can effectively migrate and target amyloid plaques in the parenchyma of hippocampus, and the cerebral cortex by proving neurogenesis and alleviating amyloid burden. Interestingly, T cell function and migration within the brain parenchyma was dependent on IFN gamma signaling in neural tissue, which is consistent with IFN gamma regulation of adhesion and migration, which act as a permissive mechanism allowing immune cells infiltration through the choroid plexus. T cells migrate was associated with upregulation of MHC class II on ependymal cells in choroid plexus revealing that MHC-T cell receptor interactions may be a prerequisite for T cell transmigration to the CNS and agrees with hypotheses that suggest that Aβ induces adaptive immune in response in the periphery. While the exact source and functional characteristics of CNS perivascular antigen presenting dendritic cells remains elusive in humans, animal studies favor the recruitment of blood-derived macrophages and their differentiation into dendritic cells.

Hyperphosphorylation of tau at specific sites transforms normal tau into misfolded tau within paired helical filaments and leads to the canonical NFTs of AD. When secreted by affected neurons, misfolded tau may propagate pathology by inducing tau aggregation in neighboring neurons. Preclinical studies suggest that active univalent antibodies specific to Aβ may be effective against misfolded tau in AD animal models. Very few preclinical studies of passive univalent antibodies specific to an tau pathological phosphorylation site have been conducted. Animal studies showed that IgG2a/kappa, but not an IgG1/kappa antibody, reduced hyperphosphorylation of tau and NFT burden in two independent mouse models of tau pathology.

Despite the meager effects of current clinical trials of Aβ and anti-inflammatory treatments, the prospect for effective immune system-based approach for treatment of AD will be enhanced as we expand our knowledge of microglia-mediated immune responses, their phenotypic and functional diversity, and their role(s) in modulating cognition, successful aging, and cognitive decline during AD progression.

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