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Immune senescence and brain aging: can rejuvenation of immunity reverse memory loss?

Noga Ron-Harel and Michal Schwartz

Department of Neurobiology, The Weizmann Institute of Science, 76100, Rehovot, Israel

The factors that determine brain aging remain a mystery. Do brain aging and memory loss reflect processes occurring only within the brain? Here, we present a novel view, linking aging of adaptive immunity to brain senescence and specifically to spatial memory deterioration. Inborn immune deficiency, in addition to sudden imposition of immune malfunction in young animals, results in cognitive impairment. As a corollary, immune restoration at adulthood or in the elderly results in a reversal of memory loss. These results, together with the known deterioration of adaptive immunity in the elderly, suggest that memory loss does not solely reflect chronological age; rather, it is an outcome of the gap between an increasing demand for maintenance (age-related risk-factor accumulation) and the reduced ability of the immune system to meet these needs.

Introduction

Brain aging is manifested by a deterioration of many aspects of cognitive function, including the reduced speed of information processing, reduced working memory capacity and impaired spatial memory ability. Behavioural indications of brain aging (i.e. memory deterioration) are often already evident by middle age in clinically healthy individuals. Finding ways to restore or even to prevent brain senescence would have a profound effect on the quality of life of these individuals and would reduce their burden on society. To treat or prevent memory loss, mechanisms that contribute to maintenance of brain plasticity and that deteriorate with age but are amenable to manipulation should be identified.

As part of our attempts over the last decade to understand the dialogue between the immune system and the nervous system under pathological conditions, we showed that the adaptive immune system has unique potential to contribute to the maintenance of the brain functional plasticity. This potential is part of a broad role attributed by us to the immune system and is one of the manifestations of the function of the immune system in 'protective autoimmunity' [1] (Box 1). 'Protective autoimmunity' suggests that a network of cellular immune responses, involving $CD4^+$ T cells that recognize self-proteins residing in the brain, provide a mechanism that can sense and respond to various deviations from central nervous system (CNS) homeostasis, thus maintaining its integrity and assisting in its restoration [2–8]. In this article, we suggest a model that attributes to age-related immune compromise a role in age-related brain dysfunction and, specifically, in hippocampus-dependent memory deterioration. According to this view, during old age, when the need for maintenance increases, the senescent immune system fails to provide the support required. The individual onset and rate of age-related memory impairments are determined both by the baseline of cognitive ability (i.e. intelligence) and the rate of cognitive aging [9]. We suggest that the latter is determined by the subject's immune potential at old age, in addition to other known factors including early education and lifelong dietary habits [10–12]. How and where the dialogue between the immune system and the brain takes place, and the prospect of circumventing age-related memory loss by boosting and/or rejuvenating the immune system, are the topics of this article.

Aging: an outcome of impaired maintenance of brain integrity

Complex biological systems are under constant regulation, including maintenance and repair mechanisms. Such mechanisms include various stress responses, antioxidative mechanisms, removal and turnover of defective cellular components and nucleic acid repair. Aging is often viewed as the final manifestation of unsuccessful maintenance (according to the 'homeodynamics' [13] and the 'disposable soma' theories of aging [14]; Box 2) at the molecular, cellular, tissue and system levels.

Like cells in other organ systems, cells in the CNS experience increased levels of oxidative stress, perturbed energy homeostasis, DNA damage and accumulation of non-degradable molecules [15,16]. In fact, expression of stress-associated genes is often seen in aged brains [15]. A variety of mechanisms were identified that contribute to this age-related damage accumulation and the resulting brain dysfunction, among which are perturbation of cellular free Ca^{2+} concentrations and elevation of glutamate-mediated toxicity (for reviews, see Refs [15,16]). The accumulation of these risk factors, together with the reduction in proteolytic systems [17] and in DNA repair mechanisms [18] that are associated with aging, results in a detrimental effect on almost every aspect of cell function [15,19]. Focusing on loss of maintenance as the primary cause for brain aging, rather than on massive loss of neurons [15], leaves open a window for optimism that

Corresponding author: Schwartz, M. (michal.schwartz@weizmann.ac.il).

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Box 1. Immunity to self: a physiological mechanism to protect the healthy and damaged CNS

Our concept of immune-dependent brain maintenance [3,5] is supported by a large amount of evidence accumulated in the past decade, showing that peripheral immune cells, via their direct or indirect interaction with resident microglia and infiltrating blood-borne monocytes, contribute to cell renewal, improve neuronal survival and facilitate restoration of CNS homeostasis under neurodegenerative conditions [7]. The most damage after an acute injury to the mammalian CNS is caused by the gradual secondary degeneration of neurons adjacent to the site of injury. The primary cell death causes an increase in the concentration of toxic physiological substances, such as glutamate and free radicals, creating a hostile environment for neighbouring neurons. The same is true for neurodegenerative diseases in which the primary risk factors include endogenous self compounds that accumulate extracellularly at non-physiological levels. The cells that mediate the neuroprotective immune activity are $CD4^+$ T lymphocytes specific for CNS antigens [1,32,127]. Our studies have shown that such autoimmune T cells locally control resident microglia and boost in a temporal and spatial controlled way infiltrating blood-borne monocytes, helping them to acquire a phenotype that enables them to combat degenerative conditions [48,51,71,79,128]. The activated microglia and macrophages do this by removing dead cells and cell debris, buffering toxic compounds (such as glutamate and reactive oxygen species) and producing growth factors needed for cell survival and renewal, without producing inflammation-associated compounds such as tumor necrosis factor-α, nitric oxide and cyclooxygenase 2 [48,50,68]. In addition, the autoimmune T cells, themselves, upon encountering their specific antigens presented by antigen presenting cells at the lesion site, can produce protective compounds such as cytokines, growth factors and neurotransmitters.

Box 2. Aging as the consequence of unsuccessful maintenance

Life's stability is constantly threatened by a wide array of internal and external stressors, and, under these circumstances, active maintenance is required to protect the integrity of the organism. It is widely accepted that aging is caused by the gradual, lifelong accumulation of a wide variety of molecular and cellular damage. This understanding forms the basis of various theories aimed at explaining the aging process and answering the fundamental question of 'why do we age?' The 'disposable soma' theory, first raised by Kirkwood and colleagues in the 1970s [129], was based on asking how the organism should optimally allocate its metabolic resources between the maintenance and repair of its soma and the other functions that it must carry out, to maximize its Darwinian fitness (i.e. thermogenesis, reproduction). 'Disposable soma' suggests that somatic maintenance needs only to be good enough to maintain the organism in adequate physiological condition for as long as it has a reasonable chance to survive in the wild. According to this theory, aging results from accumulation of unrepaired cellular damage through evolved limitations in somatic maintenance and repair functions, and longevity is therefore controlled primarily through genes that regulate the levels of such somatic maintenance and repair functions [14,130]. Another theory, which makes similar assumptions, is the 'homeodynamics' theory of aging. The concept of homeodynamics accounts for the fact that the internal milieu of complex biological systems is not permanently fixed, is not in equilibrium (as opposed to homeostasis) and is subject to dynamic regulation and interaction among various levels of organization. The homeodynamic machinery consists of different biological pathways such as stress responses, antioxidant mechanisms, protein repair and chaperone functions, removal and turnover of defective proteins, and so on. Aging is seen as the failure of the homeodynamic network owing to progressive accumulation of random damage [13,131].

perhaps there is a room for overcoming maintenance loss, thereby arresting the aging of the brain.

The immune system: a key player in CNS repair and maintenance

The body's major system of tissue maintenance and repair is the immune system. Traditionally, it was believed that the primary role of the immune system is host defence against intruders; thus, the immune response requires the ability to discriminate between self and nonself, to enable a response against any foreign intruders without attacking self tissues [20,21]. Over the years, opinions differed as to whether and why discrimination between self and nonself is actually needed (see Refs [22,23] and others). We suggested that discrimination between self and nonself is required not to completely eliminate the self-recognizing T cells but to ensure a controlled selection of such anti-self T cells (autoreactive T cells) [24]. We demonstrated that such autoreactive ($CD4^+$) T cells are essential for fighting against internal risk factors, as opposed to mediating immunity to nonself, which eliminates external invaders [25]. The constructive role of the anti-self response was first documented after injury. Specifically, we found that $CD4^+$ T cells recognizing CNS-specific antigens are needed for tissue repair after CNS axotomy [1]. These findings formed the basis for our concept of 'protective autoimmunity' (Box 1). Over the years, other studies using various animal models led to results that support this finding [26–31].

In searching for the underlying mechanism by which T cells support CNS recovery, our group discovered that the involvement of self-specific T cells in CNS neuroprotection after CNS insults [32] is part of their much broader physiological role in maintaining plasticity in the healthy CNS [3]. It was proposed that CNS-specific T cells support various aspects of brain function and plasticity at all times, and that their remedial effect under pathological conditions is an extension of the same homeostatic role. Indeed, we found that immune-deficient mice are impaired not only in their ability to cope with acute damage to the CNS [33–36] but also in various aspects of normal brain function and plasticity, including neural cell renewal (neurogenesis) [3], growth factor production [3], cognitive ability [3,5,37] and mental stability [6,38–40] (Figure 1). Importantly, the aging brain is characterized by a decrease in some of these aspects of brain plasticity (as will be discussed later), findings which, in part, created the basis of our current working paradigm.

Neural cell renewal (neurogenesis) and immunity to self

Hippocampal granular cells are among the few neuronal cells that undergo neurogenesis in the healthy adult CNS. Immature neurons from the subgranular zone migrate a short distance into the dentate gyrus granular cell layer, where they develop processes and mature into functioning integrated neurons [41]. Nevertheless, the potential importance of these newly formed neurons to hippocampus-dependent cognitive ability is still a matter of debate [42]. We found that mice deficient in T cells, and particularly in CNS-specific T cells, have reduced rates of progenitor cell proliferation, leading to an overall decrease

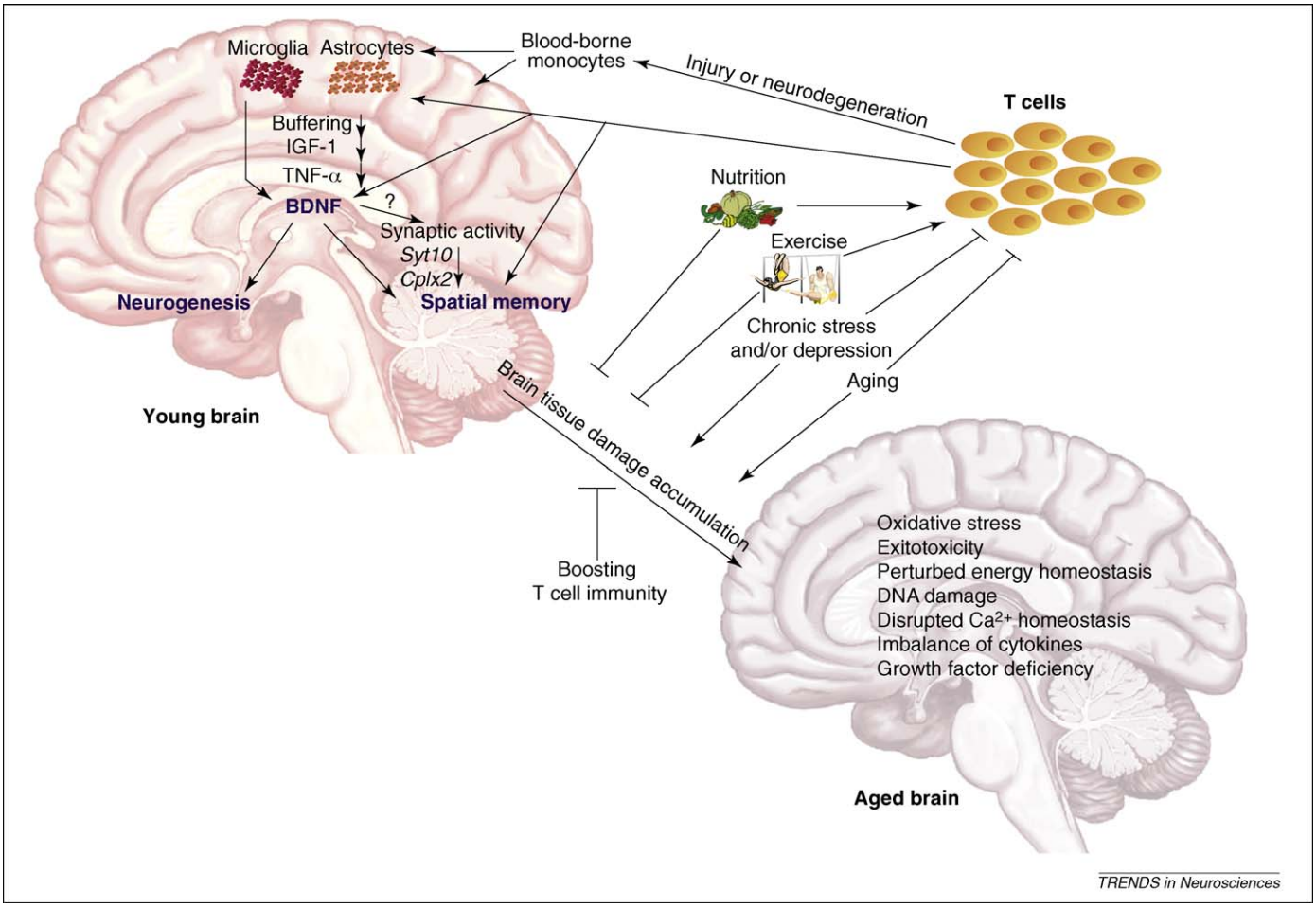

Figure 1. T-cell-mediated maintenance of brain function. There are many parallels between the way factors external to the brain affect brain tissue homeostasis and the way these same factors affect immune potency; whereas aging and mental instability promote damage accumulation in the brain and inhibit T cell immunity, life-style elements including exercise and healthy nutrition contribute to brain tissue homeostasis and increase immune potency. Several mechanisms were identified by which elevation in T cell immunity might contribute to healthy brain function, and specifically to BDNF production, neurogenesis and spatial memory performance. T cells can either secrete BDNF themselves or activate microglia in a manner that promotes BDNF secretion, which is dependent on IGF-1 and tumor necrosis factor (TNF)-α production. BDNF supports both hippocampal neurogenesis and spatial memory capacity. BDNF-independent mechanisms for T-cell-dependent regulation of neurogenesis might also potentially exist. Similarly, T-cell-dependent presynaptic plasticity, exemplified by expression of *Syt10* and *Cplx2*, suggests an additional mechanism for T-cell-dependent maintenance of brain plasticity that could be mediated by BDNF or by another T-cell-secreted factor. Under physiological conditions, T cells contribute to brain maintenance by supporting microglia and astrocytes and helping them contain small deviations from homeostasis. Under pathological conditions, such as acute injury and neurodegenerative diseases, T cells act in recruiting blood-borne monocytes, which in turn migrate to the brain and act together with resident microglia in restoring homeostasis. Boosting the immune system in time of need, and specifically during aging, would attenuate brain tissue damage accumulation, partially through these immune mechanisms. '?' denote a possible pathway, which requires further research.

in the number of new, mature neurons [3]. Yet, T-cell-dependent neurogenesis is most pronounced at early adulthood [43]. In the elderly, there is a substantial reduction in neurogenesis [44]. According to our hypothesis, the reduced neurogenesis that occurs with aging might be an outcome of, among other factors, reduced immune-based maintenance or an overwhelming local inflammatory response that occurs in the elderly.

Immunity maintains lifelong spatial memory

Earlier studies showed that the ability of immune-deficient mice to perform a hippocampus-dependent spatial learning/memory task is impaired [3,37,45]. Recently, we showed that immune-deficient mice are able to acquire a new task that requires spatial navigation, but they are impaired in the subsequent memory of their training [5]. Moreover, we showed that even young, healthy animals suffer from impaired spatial memory as a consequence of sudden T cell depletion [5]. As a corollary, immune-related spatial memory impairment could be partially corrected by immune reconstitution [5]. These results suggested that immunological malfunction has a devastating effect on hippocampus-dependent spatial memory capacity and is reversible by immune activation.

Hippocampus-dependent spatial and episodic memories are severely affected, even during what is considered to be normal aging. Such hippocampal dysfunction is manifested by the reduced ability to retrieve a place map of a familiar environment and to adjust to spatial changes. Some of these neuronal dysfunctions have been attributed to disruptions in Ca^{2+} homeostasis. Higher cellular Ca^{2+} levels in combination with reduced basal cAMP levels cause an increase in the after-hyperpolarization potential, rendering the aged neurons far off their action potential threshold and, therefore, less excitable compared with young cells [46]. An additional aspect of hippocampal aging, possibly contributing to the impairment in spatial memory performance, is the reduction in the number of synaptic

contacts in the aged hippocampus and the dentate gyrus [46] and in the presynaptic density [47]. We found reduced expression of two presynaptic genes, *Syt10* and *Cplx2*, in immune-deficient mice [5]. Moreover, restoration of their expression in response to immune reconstitution was correlated with restoration of spatial memory [5]. Our results further support the possibility that the reduced synaptic activity found in aging is, at least partially, due to immune senescence (Figure 1).

The mechanisms underlying brain maintenance by peripheral immunity

Immune-dependent maintenance of brain plasticity under physiological conditions is mediated by upregulation of beneficial substances including brain-derived neurotrophic factor (BDNF) [3] and insulin-like growth factor-1 (IGF-1) [48] and by improving the ability of glial cells to sense and respond to various deviations from homeostasis [49,50]. Under neurodegenerative conditions, the peripheral immune system can attempt to reverse or limit the adverse local inflammatory milieu [51,52]. Importantly, normal brain aging is also characterized by elevation in microglial activation markers, in association with structural and phenotypic changes [53].

Immune-dependent brain maintenance under physiological conditions

As stated earlier, one possible mechanism by which the immune system maintains brain plasticity is by regulating BDNF expression. BDNF is an important factor in almost all aspects of brain plasticity including hippocampus-dependent learning and memory abilities [54,55], adult hippocampal neurogenesis [56,57] and psychological stability [58]. Our studies have shown that levels of BDNF production by hippocampal neurons are associated with CNS-specific T cell activity; these levels are reduced in immune-deficient mice and in mice deficient in CNS-specific T cells [3] (Figure 1). In addition, T cells contribute to restoration of reduced hippocampal BDNF levels under mental stress and in depression [38,39]. BDNF could also be secreted by T cells themselves [59,60], and it is possible that T cells contribute to BDNF secretion by glial cells [61]. One possible mechanism for the immune-mediated plasticity that is regulated by BDNF is through the role of BDNF in promoting docking of neurotransmitter vesicles in the presynaptic active zone [62]. As mentioned earlier, we have demonstrated in immune-deficient mice a reduction in spatial memory performance [5] that is associated with impaired BDNF production [3] and reduced expression of genes encoding presynaptic proteins involved in synaptic vesicle docking [5]. Deficient BDNF activity was also demonstrated in the aged; an age-dependent reduction was documented in the high-affinity BDNF receptor TrkB [63]. Moreover, reduced BDNF levels in the hippocampus were correlated with poor memory performance in aged rats [64].

T-cell-dependent maintenance of the CNS is also mediated by their crosstalk with resident glial cells. Under physiological conditions, microglia and astrocytes act as active sensors of their microenvironment and have the ability to identify and respond to any disturbance of tissue homeostasis, for example by regulating ionic composition, clearing neurotransmitter (i.e. glutamate) excess from synaptic clefts and providing growth factors and nutrients to neurons [65–68]. Naïve microglia can acquire a phenotype capable of presenting antigens and engaging in dialog with T cells [48,50,69]. Such microglia, depending on the nature of the T-cell-derived cytokines they encounter, can be activated to achieve various beneficial phenotypes. For example, activation with interferon-γ (IFN-γ) enhances glutamate buffering [50], whereas activation with interleukin (IL)-4 induces secretion of IGF-1 [48,69], which supports cell renewal [70] and cognitive ability. Similarly, recent findings demonstrated that astrocytes acquire a neuroprotective phenotype after their coculture with T cells [49]. Together, these findings suggest that the peripheral immune system supports the ability of microglia and astrocytes to contain and correct small deviations from homeostasis (Figure 1).

Importantly, infiltrating blood-borne immune cells can scarcely be detected in the healthy CNS parenchyma [71–73], raising the question of how T cells interact with CNS resident cells and how they contribute to CNS maintenance. Recent models presented by us and others suggest that such communication occurs through T cell activation by antigen-presenting cells that populate the borders of the CNS (i.e. the meninges, the choroid plexus and the perivascular spaces) or at the adjacent cervical lymph nodes [7,8,74]. Such activated T cells can then secrete cytokines and neurotrophic factors that activate resident glial cells or even operate directly on neurons.

Our concept of immune-dependent brain maintenance is consistent with evidence from other systems in which immune cells contribute to tissue homeostasis, for example T-cell-dependent regulation of bone homeostasis. Some T-cell-derived cytokines are pro-osteoclastogenic, whereas others inhibit bone formation. The identity of the cytokines secreted is thought to be determined by the manner by which the T cells were activated [75]. Moreover, T-cell-deficient mice suffer from osteopenia as a result of increased osteoclastic bone resorption [76].

Immune-dependent brain maintenance under neurodegenerative conditions

When the deviation from homeostasis exceeds the capacity of resident microglia to eliminate the risk factors [52], as is the case in various neurodegenerative diseases and might be the case in aging [77], microglial activation is no longer supportive but becomes detrimental. Under such conditions, a well-controlled T cell response might act to repair and restore homoeostasis by controlling microglial activation [48,51,78], either directly or via the recruitment of blood-borne monocytes that, in turn, regulate the microglial response [71,79]. Blood-borne monocytes were shown to contribute to CNS repair by efficient removal of plaques [51,52], by mediating a regulatory role [79] and by providing growth factors such as IGF-I and BDNF [71] (Figure 1).

Additional independent studies have supported the contention that local neuroinflammation supports brain plasticity under various pathological and/or neurodegenerative conditions [80]. For example, increased neurogenesis is found in the spinal cord in an experimental model of

multiple sclerosis (MS) [81]. Similarly, inhibition of post-ischemic inflammation by minocycline reduces neurogenesis [82]. Likewise, treatment with limiting amounts of IFN-γ in a model of Alzheimer's brain enhances neurogenesis [83]. Moreover, it was shown that intrahippocampal injection of lipopolysaccharide (LPS; a prominent component in the outer membrane of gram-negative bacteria that induces a strong innate inflammatory response), which gave rise to long-lasting microglial activation, affected the fate of the hippocampal neural progenitor cells and the properties of the newly formed neurons [84].

Immune-related pathological conditions impair brain plasticity

Despite all that has been said earlier regarding the contribution of peripheral immunity to the maintenance of CNS homeostasis and thus to cognitive ability, the devastating effect of an overwhelming autoimmune response or innate inflammatory response on brain function cannot be denied. Thus, for example, MS is a progressive autoimmune disease of the CNS that is characterized by neuropsychiatric symptoms. The common cognitive symptoms include deficits in complex attention, reduced efficiency of information processing, impaired executive functioning and a decline in long-term memory abilities [85]. Moreover, a substantial proportion of MS patients exhibit depressive symptoms [86]. Importantly, a robust peripheral inflammatory response might also impair brain function, given that elevated levels of proinflammatory cytokines such as IL-6, IL-1β and TNFα were all shown to mediate negative behavioural consequences [87]. Furthermore, repeated injection of LPS results in an accumulation of Aβ1–42 in the hippocampus and cerebral cortex of mouse brains and in memory dysfunction [88]. Despite the distinct etiology of these conditions, many of the factors that are associated with the inflammatory response and are responsible for the cognitive impairment are common to the different paradigms, including elevation of oxidative stress and increased levels of pro-inflammatory cytokines [89].

Additional aspects of brain plasticity are impaired under an overwhelming local inflammatory response. Thus, for example, inflammation has been linked to stem cell dysfunction [90], and chronic brain inflammation has been linked to a non cell-autonomous dysfunction of the endogenous CNS stem cell compartment [91]. Accordingly, immune activation aimed at maintaining and/or restoring brain homeostasis should be carefully designed and tightly regulated to avoid the devastating effect of overwhelming inflammation.

Characteristics of the aging immune system

The results, discussed earlier, suggested that T cell malfunction could have a devastating effect on memory capacity. Alterations in T lymphocyte activities underlie much of the age-related decrease in the protective immune response [92]. The T cell population is maintained by thymic release of nascent naïve T cells throughout life; bone-marrow-derived T lymphocyte precursors migrate to the thymus where they acquire their specificity through a series of gene recombination events that result in a mature T cell receptor (TCR) [93]. Several factors have been linked to the decline in T cell function with age; however, it seems that chronic age-induced thymic atrophy, which results in decreased output of naïve T cells with impaired functional activation properties, is the most important factor. Thymic involution was attributed to various mechanisms including defects in the T cell progenitor pool and changes in the thymic microenvironment (e.g. loss of thymic epithelial cells, decreased capacity to induce TCR rearrangement and altered production of growth factors and hormones). In addition to thymic involution, age-related changes are observed in the hematopoietic compartment of the bone marrow and in peripheral lymphoid tissues and lymphocytes [94]. The hematopoietic compartment of the bone marrow decreases and is replaced by adipose tissue. Such a reduction in bone marrow cellularity could be due to the reduction in the levels of systemic growth hormones and impairment in local secretion of cytokines essential for the development of lymphoid cells [94]. Age-related changes, mostly in architecture, are also observed in the secondary lymphoid tissues, the spleen and lymph nodes. Such changes, which include a decrease in lymphocyte cellularity and an increase in adiposity, result in a decreased ability to provide the proper environment for immune response to take place [94].

Another factor contributing to the reduced T cell immunity in the aged is increased peripheral suppressor cell activity [94]. One such population of suppressor cells is that of the regulatory T cells (Tregs), a T cell subset that regulates effector T cells, and in particular those recognizing self-antigens, both in rodents and in humans, to prevent excessive damage to host tissue. These regulatory cells are crucial for controlling the activity of self-reactive T cells [95,96]. In fact, in young healthy animals it was proposed that Tregs provide a regulatory mechanism that enables the recruitment of autoreactive effector T cells, without encountering the risk of inducing autoimmune diseases [24,40]. A recent study showed an age-dependent increase in the levels of Tregs in the lymphoid organs of mice and in the peripheral blood of human subjects. These accumulating cells maintain their suppressor activity and their depletion in aged mice improves T cell immunity; this is manifested by enhanced secretion of the pro-inflammatory cytokine IFN-γ by effector T cells in response to immunological challenge [97]. Together, these results suggest that Tregs accumulation contributes to the peripheral immune suppression associated with aging. It should be noted that additional types of suppressor cells (e.g. myeloid suppressor cells) were also shown to contribute to immune senescence. Similarly to Tregs, ablation of these cells, which accumulate with age, restores T cell immunity [98]. Because regulatory cells play a part in the balance between the need for adaptive immunity and the risk of an overwhelming response, these cells serve a neuroprotective role under conditions of excessive inflammation or neuroinflammation [99]. Importantly, a careful distinction should be made in this regard between suppression of adaptive immunity in the periphery versus local inhibition; suppression in the periphery eliminates the potential ability to recruit immune cells to sites of inflammation that might be needed for local immunomodulation.

Immunological age: a non-chronological factor in brain senescence

The findings that the aging brain suffers more from functional deficits rather than from substantial anatomical defects or cell death [46], together with our observation that adaptive immunity maintains CNS plasticity, suggest that aging of the immune system is a factor in age-related cognitive loss that might be amenable to restoration. We suggest that the age-associated damage accumulation and the increased need for peripheral intervention are not addressed with an appropriate immune response, owing to the aging of the immune system itself. Accordingly, brain senescence, and specifically memory loss, does not necessarily reflect chronological age but, rather, the 'immunological age' of the affected individual. This view might explain (in addition to other factors including lifelong nutrition, physical fitness and genetic factors) the individual and variable nature of brain senescence, both in terms of the age of occurrence and the nature of the functional loss (Figure 1). It might also provide an answer to the key mystery: why do some people age better than others? We believe that this is a reflection of the aging of the immune system and its genetic regulation. According to this view, risk factors accumulating in the brain will leave their age-related signature if the immune system fails to contain them.

Based on our results, immunity and immunity-to-self are systems that participate in two complementary roles; although immunity primarily provides host defence and resilience to pathogens, immunity to self primarily provides a maintenance function and resilience to internal risk factors [24]. The adaptive arm of the immune system that is needed to maintain and protect the organism from damage to the tissue as a result of either internal or external threats is of T cells that recognize self-antigens. We, therefore, propose that assessing the individual's immune potency before old age could serve a function in predicting future memory impairments. Such immunological assessment should focus on evaluating thymic output and measuring the amount and functionality of peripheral suppressor cells, the two main factors in age-dependent deterioration of T cell immunity. Specifically, thymic atrophy could be monitored by quantifying the amount of naïve T cells in the peripheral blood, possibly by polymerase chain reaction analysis of TCR excision circles (sjTRECs), an episomal DNA characteristic of recent thymic emigrant T cells [100]. The frequency of regulatory T cells can be assessed by fluorescence-activated cell sorting (FACS) analysis of mononuclear cells isolated from the blood, using antibodies against foxp3, a transcription factor uniquely expressed by this population [101]. Other markers characteristic of immune senescence could also be tested, for example, the $CD4^+$:$CD8^+$ T cell ratio [92].

Immunization against memory loss: fantasy or reality?

The long process of age-dependent damage accumulation in the brain creates a neurotoxic environment that strongly resembles the conditions created as a result of acute CNS injury or neurodegenerative disease. These common characteristics include elevation in oxidative stress, ionic imbalance and excitotoxicity. This similarity, together with the facts that (i) immune compromised mice suffer from impaired spatial memory that is amenable to repair by restoring normal T cell levels, (ii) T cell immunity deteriorates with age, and (iii) boosting of peripheral immunity improves the ability of the CNS to fight the toxicity that is created as a result of an injury or a neurodegenerative disease, suggest that rejuvenation of peripheral immunity might be a feasible approach to prevent brain aging. Indeed, we found that aged mice, in which peripheral immune potency was manipulated, performed better than non-treated aged mice in a hippocampus-dependent spatial memory test [5]. These results are in line with other studies showing how factors such as physical activity [102] and nutrition [103], including calorie restriction [104], alleviate some symptoms of brain aging (Figure 1).

Exercise facilitates cognitive ability [105], protects from neurodegeneration [106–108] and improves mental stability [109]. These beneficial effects are mediated by elevation in growth factor production [110,111] and in neuronal plasticity [112] (for reviews, see Refs [113,114]). Calorie restriction was shown to protect neurons against genetic and environmental factors through its effect on energy and oxygen radical metabolism and various cellular stress response systems [104]. Immune-related activity might, thus, be the missing link between exercise and brain plasticity (Figure 1); moderate exercise was shown to enhance immune function and specifically T cell immunity [115,116]. Similarly, calorie restriction delayed T cell senescence manifested by increased levels of naïve T-cells and preservation of the TCR repertoire [117]. Recently, it was suggested that the beneficial effects of exercise and dietary restrictions act through hormesis mechanisms [118–120]. Accordingly, the mild stress induced by low intensity exercise or diet improves the individual's ability to cope with cytotoxic elements such as oxidative stress. We suggest that mild stress could be viewed as a preconditioning effect as far as the ability of the immune system to cope with breaching of homeostasis. According to this contention, the effect of diet or exercise can be replaced by vaccination, aimed at boosting the relevant immune response as a way of overcoming an insufficient physiological preconditioning that might characterize the aging immune system.

Immunization to boost peripheral immunity against memory loss might be a future therapy for maintaining functional plasticity in the elderly. Such an approach might be viewed as a multi-dimensional treatment for restoration of brain homeostasis needed for normal function. The choice of the immune-based vaccination should take into consideration the nature of the immunological deficit in aging and, therefore, might involve inhibition of suppressor cells. Such immunization protocols that involve downregulation of immune suppression together with activation of the relevant T cell population were successfully tested in various animal models of cancer [121,122].

A similar approach has been demonstrated as effective in animal models of acute injuries [28,30], neurodegenerative diseases [29,51,123], amyotrophic lateral sclerosis [124–126] and of psychological stress [37–39], further supporting the notion that boosting immunity to self might

help to strengthen and maintain the physiological mechanisms of maintenance when balance is lost.

Conclusion

Brain aging does not always coincide with the rate of aging of the rest of the body. This leads to an enigma: might the brain be more vulnerable to the aging of a master system that maintains the entire body, the deterioration of which affects brain function? Here, we present a novel idea suggesting that brain aging is a reflection of insufficient maintenance, constitutively provided by the peripheral immune system. These findings suggest an approach for preventing or arresting aging of the brain in a non-invasive manner and without any direct manipulation of the brain.

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