Neurological Disorders

Huang et al., J Neurol Disord 2014, 2:4
DOI: 10.4172/2329-6895.1000170

Review article Open Access

Reversal of Neuronal Atrophy: Role of Cellular Immunity in Neuroplasticity and Aging

Zhi Huang, Grace K. Ha and John M. Petitto*

Departments of Neuroscience and Psychiatry, McKnight Brain Institute, University of Florida, Gainesville, FL, USA

***Corresponding author:** John Petitto, McKnight Brain Institute, UF, 100 South Newell Drive Gainesville, FL 32611, USA, Tel: 352-294-0416; E-mail: jpetitto@ufl.edu

Rec date: Mar 07, 2014, **Acc date:** Jun 30, 2014, **Pub date:** Jul 04, 2014

Abstract

Emerging evidence indicates that neuroimmunological changes in the brain can modify intrinsic brain processes that are involved in regulating neuroplasticity. Increasing evidence suggests that in some forms of motor neuron injury, many neurons do not die, but reside in an atrophic state for an extended period of time. In mice, facial motor neurons in the brain undergo a protracted period of degeneration or atrophy following resection of their peripheral axons. Reinjuring the proximal nerve stump of the chronically resected facial nerve stimulates a robust reversal of motor neuron atrophy which results in marked increases in both the number and size of injured motor neurons in the facial motor nucleus. In this brief review, we describe research from our lab which indicates that the reversal of atrophy in this injury model is dependent on normal cellular immunity. The role of T cells in this unique form of neuroplasticity following injury and in brain aging, are discussed. The potential role of yet undiscover intrinsic actions of recombination activating genes in the brain are considered. Further research using the facial nerve reinjury model could identify molecular signals involved in neuroplasticity, and lead to new ways to stimulate neuroregenerative processes in neurotrauma and other forms of brain insult and disease.

Keywords: Neuroimmunology; Immunodeficiency; Recombination activating genes; Cellular immunity; T cells; Injury; Axotomy; Neuronal atrophy; Cognitive behavior; Aging

Atrophied Neurons have the Potential to Regenerate their Phenotype

In their seminal studies, Hagg and colleagues showed that neuronal atrophy and the loss of the choline acetyltransferase (ChAT) phenotype of axotomized medial septal cholinergic projection neurons could be reversed with NGF treatment [1,2]. Reversal of neuronal atrophy and phenotype has also been demonstrated in the axotomized septum of rodents and non-human primates [1-6]. The processes involved are complex and may differ in different neurons and regions of the CNS. Increasing evidence suggests that in some forms of motor neuron injury, neurons may not actually die following nerve injury, but reside in an atrophic state for an extended period of time. Kwon and colleagues [3] showed that following rubospinal axotomy, BDNF acting at the neuronal cell bodies, can induce reversal of atrophy up to one year later.

In mice, facial motor neurons undergo a protracted period of degeneration or atrophy following peripheral resection of the facial nerve. Reinjuring the facial nerve stimulates a reversal in the atrophic status of the injured neurons, causing an increase in both their size and number [7]. As described below, data from our research suggests that under normal physiological conditions, the reversal of atrophy and the ability of reinjured facial motor neurons to regain their normal phenotype is dependent on a normal functioning cellular immune system [8,9]. To our knowledge, this is the only model of neuronal atrophy reversal that has been studied in the context of immunity or linked to immune function. In this brief review, we describe the status of research using the facial nerve reinjury model, data from which indicates that the species-typical reversal of axotomy-induced neuronal atrophy in mice is dependent on normal cellular immunity. We also discuss the implications of these findings for discovering new insights into brain aging.

The Neuroprotective Effects of Cellular Immunity

A growing body of research has established that in certain contexts T cells act together with glial cells to promote neuroprotection and survival [8-13]. Although it has long been known that during pathogenic conditions (e.g., multiple sclerosis, brain infection), the presence of T cells in the CNS is associated with an increased risk of neuronal damage [14,15]. Emerging evidence shows that T cells have proneuronal effects in the brain, effects that appear to eminate from both the periphery (e.g., cytokine release and regulation) and within the brain [8,13-19].

Immune surveillance of the CNS occurs by small numbers T lymphocytes trafficking in and out of the brain, and it is now recognized that under normal physiological conditions, T lymphocytes have important effects on neuronal integrity and function [20,21]. Cellular immunity has been shown to have beneficial effects on neuronal outcomes in various models of trauma (e.g., mechanical, toxic, ischemic, hemorrhagic) [22]. One of the most notable examples of the neuroprotective role of adaptive immunity is facial nerve axotomy, where T cells have been found to slow the rate of neurodegeneration and neuronal loss after axons are disconnected from their target muscle [12,23]. Following facial nerve axotomy in mice, T cells cross the blood–brain-barrier (BBB) and traffic to the neuronal cell bodies in the facial motor nucleus [18]. Immunodeficient mice such as severe combined immunodeficient (SCID) and recombination activating gene knockout (RAG-KO) mice, which both lack functionally mature T and B lymphocytes, exhibit a faster rate of neuronal death than wild-type (WT) mice [12,23]. The neuroprotective activity resides clearly within the T cell population, as

B cells appear to have no effect and are not found within the facial motor nucleus following facial nerve axotomy [8,11,12]. Likewise, in some animal models, impairments in cognitive and emotional behavior have also been reported to be modulated, in part, by T cell homeostasis [13,19,24-26]. Moreover, indirect evidence suggests that proinflammatory conditions regulated by T cell homeostasis are associated with reduced levels of neurogenesis [27]. As T cells are pivotal in modulating overall immunological homeostasis, T lymphocytes and the cytokines that they secrete and/or modulate have been implicated in processes associated with neurogenesis and other steps involved in neuroplasticity [28-36].

Chronic Axotomy of Facial Motor Neurons, T Cells and Atrophy Reversal

Our research has demonstrated that cellular immunity is required to reverse the atrophic status of injured motor neurons [8]. We used the facial nerve reinjury model to test the hypothesis that the reversal of motor neuron atrophy (i.e., increase in cell number and size) elicited by nerve reinjury would be abnormal in immunodeficient RAG2-KO mice. It is important to emphasize that the facial nerve reinjury model differs from the widely studied facial nerve axotomy paradigm (noted in the paragraph above), where single axotomy is performed. By contrast, in the facial nerve reinjury model in mice – the neuronal atrophy model that is discussed in this review - the facial nerve is first axotomized by resection and the nerve endings are separated and not able to reconnect. They remain in this "chronically axotomized" state for 10 weeks, and then subsequently the proximal nerve (the stump that is still connected to the neuronal cell bodies of origin in the facial motor nucleus) is reinjured. As noted earlier, reinjuring the facial nerve stimulates a reversal in the atrophic status of the injured facial motor neurons, inducing an increase in both their size and number [7,8].

Using the facial nerve reinjury model, we found that whereas a substantial portion of chronically resected facial motor neurons reside in an atrophied state that can be reversed at 14 days following reinjury in WT mice, atrophy reversal was abnormal in immunodeficient RAG2-KO mice. In the facial nerve axotomy model, microglial proliferation is most pronounced 3 days after facial nerve axotomy. Thus, we recently extended our research by comparing WT and immunodeficient RAG2-KO mice in the facial nerve reinjury paradigm at day 3, and at a significantly later point in time, at day 28 post-reinjury. This study was designed to test our hypothesis that the normal regeneration of atrophied motor neurons is dependent on normal adaptive immunity, and to determine if there were differences in kinetics of the reversal response between the groups. We compared motor neuron survival and size between WT and RAG2-KO mice in the facial nerve reinjury paradigm at 3 and 28 days post-reinjury [9]. Our results showed that in WT mice, facial motor neurons that were resected for 10 weeks and subsequently reinjured were able to regain fully an apparent 40% loss of countable neurons at 3 days post-reinjury, and nearly half of the magnitude of that that robust increase in neurons was sustained at 28 days post-reinjury. Thus, whereas WT mice recovered all of the apparent loss of countable neurons (due to atrophy) at 3 days post-reinjury stimulation, by contrast, RAG2-KO mice did not exhibit any increase in neuronal number whatsoever at either both 3 or 28 days post-reinjury (as we saw previously at day 14 post-reinjury). Size measurements showed that the surviving neurons of both WT and RAG2-KO mice actually exhibited motor neuron hypertrophy at 3 days post-reinjury, and surviving motor neurons regained normal size by 28 days following reinjury. Among the immunologically intact WT mice, small numbers of T lymphocytes where found in the re-injured facial motor nucleus and were significantly higher at 3 days, but return to baseline levels by 28 days in the reinjury group (compared to the sham-reinjury control group). No differences were seen between the WT and RAG2-KO mice in overall microglial cell activity using CD11b expression following reinjury. Together, our research indicates that a large percentage of resected motor neurons did not survive the initial resection in RAG2-KO mice, whereas in the immunologically intact WT mice they atrophied and could be restimulated by reinjury to regenerate their phenotype [8,9].

Is this Form of Neuroplasticity Associated with T Cell Function?

Together, our studies using the facial nerve reinjury model in immunodeificient mice indicate that normal T cell function is essential for activating regeneration programs of atrophied motor neurons. The research described above showed that many resected motor neurons did not survive the initial facial nerve resection in immunodeficient RAG2-KO mice, whereas in WT mice motor neurons atrophied and could be restimulated by reinjury to robustly regenerate their phenotype. In WT mice of the C57BL/6 background, the duration of the atrophy reversal response peaks between days 3 to 7 post-reinjury, and decreases between day 14 to 28 following the reinjury stimulus [7-9]. Following the reinjury stimulus, resected WT neurons disconnected from their target tissue were able to maintain nearly half the robust gain in the numbers that they exhibited at day 3 post-reinjury. Although almost all of the available researches using the facial nerve reinjury model have been conducted in C57BL/6 WT mice to date [7-9], one studying showed that Balb/c mice (which are known to have distinctly different Th1/Th2 bias than C57BL/6 mice) have less robust atrophy reversal [7].

We have tested the possibility that the increase in neurons following reinjury could be attributable to a yet undescribed neurostem cell proliferation in the reinjured FMN, but have failed to find any neurons co-labeled with BrdU and doublecortin in the reinjured FMN model [9]. Thus, all the available evidence is consistent with the fact that the increase in countable neurons following reinjury is due to atrophy reversal by the reinjury stimulus where more normal sized neurons are detectable. Moreover, the complete lack of reinjury-induced regeneration in RAG2-KO immunodeficient mice (tested at days 3, 14, and 28) suggests that normal T cell function in the CNS and/or the periphery could be essential for activating regeneration programs of atrophied motor neurons [9,10]. It will be important to determine if immune reconstitution of immunodeficient mice with T cells from WT mice will enable the immunodeficient mice to exhibit atrophy reversal similar to immunologically intact WT mice. If so, then further assessment using this model can determine what subtype(s) of T cells are responsible, and by what mechanism(s).

T Cells and Aging

The actions of T cells in neuronal recovery and function may have important implications for aging. Our lab has found, for example, that even as early as late middle-aged, axonal injury induces a marked increase in T cell trafficking to the neuronal cell bodies of origin in the brain [37]. As mice age, exaggerated neuroinflammatory responses occur in the brain following infection and lipopolysaccharide (LPS) administration, and aging mice also exhibit higher expression of

certain T cell related immune response genes following immune challenge with LPS [38,41,42]. Impairments in cognitive and emotional behavior may also be modulated, in part, by T cell homeostasis [13,19,24-26]. It has been found, for example, that proinflammatory conditions regulated by T cell homeostasis are associated with reduced levels of neurogenesis [27]. T cells are pivotal in modulating overall immunological homeostasis, and T lymphocytes and the cytokines that they secrete and/or modulate have been implicated in processes associated with neurogenesis [28-36]. A decline in neurogenesis underlies deterioration in context-dependent learning in aging, and decreased neurogenesis has been associated with deficits in contextual fear discrimination and related forms of fear-based learning as well [43-46].

Several lines of evidence suggest that changes in T immunity during aging may have important implications for brain aging. Age-dependent deficits in T cell function in the adaptive arm of the immune system coexist with age-related changes within the innate immune system; however, innate immunity is better preserved, while more severe and often detrimental age-dependent changes occur in the adaptive immune system [47]. As aging is associated with decreased T cell function [48-52], older T cells may be less effective at protecting aging or injured neurons, and be less capable of supporting neurogenesis. Neurogenesis is altered in aging animals as well [44,53]. Moreover, in the baseline unchallenged state, aging mice have markedly increased basal levels of T cells in the hippocampus [54]. Thus, aging alters the neuroimmunological milieu of the brain (e.g., cytokine balance, T cell and microglial function), which in turn may contribute to reduced hippocampal neurogenesis found with brain aging [27,40,55]. Manipulating T cell age and/or neurogenesis will be important to establish this linkage more directly in future studies to build upon these intriguing observations in the literature [26].

Is the Neuroplasticity Involved in Atrophy Reversal Modulated by the Intrinsic Actions of the RAG genes in the Brain?

In addition to the testing the role of T cells, it will be necessary to determine if the aforementioned effects on atrophy reversal following injury may be attributable to some yet unknown function of the RAG-1 and RAG-2 genes in the brain. RAG-1 mRNA has been identified in mouse brain, but RAG-2 has not been found to be expressed by in situ hybridization or at appreciable levels using other methods [56]. In our initial study of RAG-1 knockout mice [24], we postulated that RAG-1 may be involved in processes associated with learning and memory given that mRNA was detected in the hippocampus by in situ hybridization [57]. Although RAG-2 gene expression was found to be expressed by mouse CNS tumor cell lines [58], there has not been work to our knowledge that has assessed further the status of the RAG-2 gene in the normal brain. One the other hand, despite the intriguing idea that it could be involved in some form of DNA recombination in the brain, there is no evidence that the RAG-1 gene is translated into a protein or is associated with any known function in the CNS [56,59]. Given the preponderance of evidence in the immunology literature demonstrating that RAG-1 and RAG-2 synergistically activate V(D)J recombination and are concordantly transcribed [60-62], the literature suggests that it is unlikely that RAG-1 would act alone in the brain. A well designed studies by McGowan et al. [63,64] showed that, compared to littermates, RAG-1 knockout mice had impaired social recognition memory at a 60 min delay, whereas RAG-2 mice did not show this impairment. Similar outcomes were seen when the strains were intercrossed to mix the backgrounds. Further investigation is warranted to determine if some yet unknown function of the RAG-1 gene may be operative in the CNS.

Concluding Remarks

Neuroimmunology is beginning to uncover unique mechanisms whereby the peripheral immune system protects brain neurons and/or augments brain processes (e.g., glia cells, neurotrophins) that protect neurons from age-related neurodegeneration. One important area of investigation in our estimation is to disentangle the relative contribution of T cell aging from intrinsic mechanisms of brain aging. Our lab is engaged in approaches, for example, to test directly our hypothesis that T cell immunosenescence alters neuroplasticity and neurobehavioral performance by manipulating the immune system of mice. As diminished T cell function associated with normal aging could be involved in brain aging and repair, greater understanding of brain-immune interactions in aging could have important implications for treating neurodegenerative diseases (e.g., Alzheimer's disease), and improving outcomes for elderly individuals with vascular insults and other forms of CNS trauma. Likewise, new research approaches are continually being sought to impact the progression of neurodegeneration, and to intervene in brain injury to rescue or regenerate damaged brain neurons. Further research using models such as the facial nerve reinjury model, could identify the molecular signals involved in this powerful and unique form of neuroplasticity, and lead to new ways to induce or augment neuroregeneration in patients with neurotrauma and other forms of CNS insult and disease [65,66]. Neuroimmunological approaches could provide needed new insights into the interactions between complex systems, insights that may be essential to move through barriers to devise more effective treatments for clinical neurological disorders.

Acknowledgements:

Funding for this study was provided by NIH RO1 NS055018.

References

1. Hagg T, Fass-Holmes B, Vahlsing HL, Manthorpe M, Conner JM, et al. (1989) Nerve growth factor (NGF) reverses axotomy-induced decreases in choline acetyltransferase, NGF receptor and size of medial septum cholinergic neurons. Brain Res 505: 29-38.
2. Hagg T, Manthorpe M, Vahlsing HL, Varon S (1988) Delayed treatment with nerve growth factor reverses the apparent loss of cholinergic neurons after acute brain damage. Exp Neurol 101: 303-312.
3. Kwon BK, Liu J, Messerer C, Kobayashi NR, McGraw J, et al. (2002) Survival and regeneration of rubrospinal neurons 1 year after spinal cord injury. Proc Natl Acad Sci U S A 99: 3246-3251.
4. Fischer W, Björklund A (1991) Loss of AChE- and NGFr-labeling precedes neuronal death of axotomized septal-diagonal band neurons: reversal by intraventricular NGF infusion. Exp Neurol 113: 93-108.
5. Hefti F (1986) Nerve growth factor promotes survival of septal cholinergic neurons after fimbrial transections. J Neurosci 6: 2155-2162.
6. Lazo OM, Mauna JC, Pissani CA, Inestrosa NC, Bronfman FC (2010) Axotomy-induced neurotrophic withdrawal causes the loss of phenotypic differentiation and downregulation of NGF signalling, but not death of septal cholinergic neurons. Mol Neurodegener 5: 5.
7. McPhail LT, Fernandes KJ, Chan CC, Vanderluit JL, Tetzlaff W (2004) Axonal reinjury reveals the survival and re-expression of regeneration-associated genes in chronically axotomized adult mouse motoneurons. Experimental neurology 188: 331-340.

8. Ha GK, Huang Z, Parikh R, Pastrana M, Petitto JM (2007) Immunodeficiency impairs re-injury induced reversal of neuronal atrophy: relation to T cell subsets and microglia. Exp Neurol 208: 92-99.
9. Huang Z, Petitto JM (2013) Motor Neurons Exhibit Sustained Loss of Atrophy Reversal in Immunodeficent Mice. J Neurol Disord 1.
10. Byram SC, Carson MJ, DeBoy CA, Serpe CJ, Sanders VM, et al. (2004) CD4-positive T cell-mediated neuroprotection requires dual compartment antigen presentation. J Neurosci 24: 4333-4339.
11. Ha GK, Huang Z, Streit WJ, Petitto JM (2006) Endogenous T lymphocytes and microglial reactivity in the axotomized facial motor nucleus of mice: effect of genetic background and the RAG2 gene. J Neuroimmunol 172: 1-8.
12. Jones KJ, Serpe CJ, Byram SC, Deboy CA, Sanders VM (2005) Role of the immune system in the maintenance of mouse facial motoneuron viability after nerve injury. Brain Behav Immun 19: 12-19.
13. Kipnis J, Derecki NC, Yang C, Scrable H (2008) Immunity and cognition: what do age-related dementia, HIV-dementia and 'chemo-brain' have in common? Trends Immunol 29: 455-463.
14. Martino G, Hartung HP (1999) Immunopathogenesis of multiple sclerosis: the role of T cells. Curr Opin Neurol 12: 309-321.
15. Nau R, Brück W (2002) Neuronal injury in bacterial meningitis: mechanisms and implications for therapy. Trends Neurosci 25: 38-45.
16. Ha GK, Huang Z, Petitto JM (2007) Prior facial motor neuron injury elicits endogenous T cell memory: relation to neuroregeneration. J Neuroimmunol 183: 111-117.
17. Meola DM, Huang Z, King M, Petitto JM (2013) Loss of cholinergic phenotype in septohippocampal projection neurons: relation to brain versus peripheral IL-2 deficiency. Neurosci Lett 539: 60-64.
18. Raivich G, Jones LL, Kloss CU, Werner A, Neumann H, et al. (1998) Immune surveillance in the injured nervous system: T-lymphocytes invade the axotomized mouse facial motor nucleus and aggregate around sites of neuronal degeneration. J Neurosci 18: 5804-5816.
19. Schwartz M, Kipnis J, Rivest S, Prat A (2013) How do immune cells support and shape the brain in health, disease, and aging? J Neurosci 33: 17587-17596.
20. Cose S, Brammer C, Khanna KM, Masopust D, Lefrançois L (2006) Evidence that a significant number of naive T cells enter non-lymphoid organs as part of a normal migratory pathway. Eur J Immunol 36: 1423-1433.
21. Hickey WF (1991) Migration of hematogenous cells through the blood-brain barrier and the initiation of CNS inflammation. Brain Pathol 1: 97-105.
22. Graber JJ, Dhib-Jalbut S (2009) Protective autoimmunity in the nervous system. Pharmacol Ther 121: 147-159.
23. Serpe CJ, Sanders VM, Jones KJ (2000) Kinetics of facial motoneuron loss following facial nerve transection in severe combined immunodeficient mice. J Neurosci Res 62: 273-278.
24. Cushman J, Lo J, Huang Z, Wasserfall C, Petitto JM (2003) Neurobehavioral changes resulting from recombinase activation gene 1 deletion. Clin Diagn Lab Immunol 10: 13-18.
25. Wolf SA, Steiner B, Akpinarli A, Kammertoens T, Nassenstein C, et al. (2009) CD4-positive T lymphocytes provide a neuroimmunological link in the control of adult hippocampal neurogenesis. J Immunol 182: 3979-3984.
26. Ziv Y, Ron N, Butovsky O, Landa G, Sudai E, et al. (2006) Immune cells contribute to the maintenance of neurogenesis and spatial learning abilities in adulthood. Nat Neurosci 9: 268-275.
27. Kohman RA, Rhodes JS (2013) Neurogenesis, inflammation and behavior. Brain Behav Immun 27: 22-32.
28. Bauer S, Rasika S, Han J, Mauduit C, Raccurt M, et al. (2003) Leukemia inhibitory factor is a key signal for injury-induced neurogenesis in the adult mouse olfactory epithelium. J Neurosci 23: 1792-1803.
29. Beck RD Jr, Wasserfall C, Ha GK, Cushman JD, Huang Z, et al. (2005) Changes in hippocampal IL-15, related cytokines, and neurogenesis in IL-2 deficient mice. Brain Res 1041: 223-230.
30. Farbman AI, Buchholz JA (1996) Transforming growth factor-alpha and other growth factors stimulate cell division in olfactory epithelium in vitro. J Neurobiol 30: 267-280.
31. Hastings NB, Gould E (2003) Neurons inhibit neurogenesis. Nat Med 9: 264-266.
32. Mahanthappa NK, Schwarting GA (1993) Peptide growth factor control of olfactory neurogenesis and neuron survival in vitro: roles of EGF and TGF-beta s. Neuron 10: 293-305.
33. Newman MP, Féron F, Mackay-Sim A (2000) Growth factor regulation of neurogenesis in adult olfactory epithelium. Neuroscience 99: 343-350.
34. Satoh M, Yoshida T (1997) Promotion of neurogenesis in mouse olfactory neuronal progenitor cells by leukemia inhibitory factor in vitro. Neurosci Lett 225: 165-168.
35. Tham TN, Lazarini F, Franceschini IA, Lachapelle F, Amara A, et al. (2001) Developmental pattern of expression of the alpha chemokine stromal cell-derived factor 1 in the rat central nervous system. Eur J Neurosci 13: 845-856.
36. Vallières L, Campbell IL, Gage FH, Sawchenko PE (2002) Reduced hippocampal neurogenesis in adult transgenic mice with chronic astrocytic production of interleukin-6. J Neurosci 22: 486-492.
37. Dauer DJ, Huang Z, Ha GK, Kim J, Khosrowzadeh D, et al. (2011) Age and facial nerve axotomy-induced T cell trafficking: relation to microglial and motor neuron status. Brain Behav Immun 25: 77-82.
38. Henr CJ, Huang Y, Wynne AM, Godbout JP (2009) Peripheral lipopolysaccharide (LPS) challenge promotes microglial hyperactivity in aged mice that is associated with exaggerated induction of both pro-inflammatory IL-1beta and anti-inflammatory IL-10 cytokines. Brain Behav Immun 23: 309-317.
39. Huang Y, Henry CJ, Dantzer R, Johnson RW, Godbout JP (2008) Exaggerated sickness behavior and brain proinflammatory cytokine expression in aged mice in response to intracerebroventricular lipopolysaccharide. Neurobiol Aging 29: 1744-1753.
40. Jurgens HA, Johnson RW (2012) Dysregulated neuronal-microglial cross-talk during aging, stress and inflammation. Exp Neurol 233: 40-48.
41. Richwine AF, Parkin AO, Buchanan JB, Chen J, Markham JA, et al. (2008) Architectural changes to CA1 pyramidal neurons in adult and aged mice after peripheral immune stimulation. Psychoneuroendocrinology 33: 1369-1377.
42. Terao A, Apte-Deshpande A, Dousman L, Morairty S, Eynon BP, et al. (2002) Immune response gene expression increases in the aging murine hippocampus. J Neuroimmunol 132: 99-112.
43. Garthe A, Kempermann G (2013) An old test for new neurons: refining the Morris water maze to study the functional relevance of adult hippocampal neurogenesis. Front Neurosci 7: 63.
44. Lazarov O, Marr RA (2013) Of mice and men: neurogenesis, cognition and Alzheimer's disease. Front Aging Neurosci 5: 43.
45. Nakashiba T, Cushman JD, Pelkey KA, Renaudineau S, Buhl DL, et al. (2012) Young dentate granule cells mediate pattern separation, whereas old granule cells facilitate pattern completion. Cell 149: 188-201.
46. Shors TJ, Townsend DA, Zhao M, Kozorovitskiy Y, Gould E (2002) Neurogenesis may relate to some but not all types of hippocampal-dependent learning. Hippocampus 12: 578-584.
47. Weiskopf D, Weinberger B, Grubeck-Loebenstein B (2009) The aging of the immune system. Transpl Int 22: 1041-1050.
48. Franceschi C, Bonafè M, Valensin S, Olivieri F, De Luca M, et al. (2000) Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci 908: 244-254.
49. Linton P, Thoman ML (2001) T cell senescence. Front Biosci 6: D248-261.
50. Miller RA (1996) The aging immune system: primer and prospectus. Science 273: 70-74.
51. Nikolich-Zugich J (2008) Ageing and life-long maintenance of T-cell subsets in the face of latent persistent infections. Nat Rev Immunol 8: 512-522.

52. Pawelec G, Effros RB, Caruso C, Remarque E, Barnett Y, et al. (1999) T cells and aging (update february 1999). Front Biosci 4: D216-269.
53. Kalm M, Karlsson N, Nilsson MK, Blomgren K (2013) Loss of hippocampal neurogenesis, increased novelty-induced activity, decreased home cage activity, and impaired reversal learning one year after irradiation of the young mouse brain. Experimental neurology 247: 402-409.
54. Stichel CC, Luebbert H (2007) Inflammatory processes in the aging mouse brain: participation of dendritic cells and T-cells. Neurobiol Aging 28: 1507-1521.
55. Lynch MA, Johnson RW (2012) The impact of aging on the brain--risk, resilience and repair. Brain Behav Immun 26: 714-716.
56. Chun JJ, Schatz DG, Oettinger MA, Jaenisch R, Baltimore D (1991) The recombination activating gene-1 (RAG-1) transcript is present in the murine central nervous system. Cell 64: 189-200.
57. Chun J, Schatz DG (1999) Developmental neurobiology: Alternative ends for a familiar story? Curr Biol 9: R251-253.
58. Aoki T, Tashiro K, Miyatake S, Nakano T, Oda Y, et al. (1991) Expression of the RAG-2 gene in murine central nervous system tumor cell lines. Biochem Biophys Res Commun 181: 151-158.
59. Schatz DG, Chun JJ (1992) V(D)J recombination and the transgenic brain blues. New Biol 4: 188-196.
60. Oettinger MA, Schatz DG, Gorka C, Baltimore D (1990) RAG-1 and RAG-2, adjacent genes that synergistically activate V(D)J recombination. Science 248: 1517-1523.
61. Ohmori H, Hikida M (1998) Expression and function of recombination activating genes in mature B cells. Crit Rev Immunol 18: 221-235.
62. Sadofsky MJ (2001) The RAG proteins in V(D)J recombination: more than just a nuclease. Nucleic Acids Res 29: 1399-1409.
63. McGowan PO, Hope TA, Meck WH, Kelsoe G, Williams CL (2011) Impaired social recognition memory in recombination activating gene 1-deficient mice. Brain Res 1383: 187-195.
64. McGowan PO, Hope, TA, Kelsoe G, Meck WH, Williams CL (2003) Social memory is impaired in RAG1- but not Rag2-deficient littermates. Society for Neuroscience Abstracts Program Number 860.4.
65. van Kesteren RE, Mason MR, Macgillavry HD, Smit AB, Verhaagen J (2011) A gene network perspective on axonal regeneration. Front Mol Neurosci 4: 46.
66. Yamamoto S, Kohsaka S, Nakajima K (2012) Role of cell cycle-associated proteins in microglial proliferation in the axotomized rat facial nucleus. Glia 60: 570-581.