ROLE OF IL-33/ST2 AXIS IN CHRONIC INFLAMMATORY NEUROLOGICAL DISORDERS

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ULOGA IL-33/ST2 SIGNALNOG PUTA U HRONIČNIM ZAPALJENSKIM NEUROLOŠKIM OBOLJENJIMA

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ABSTRACT

Interleukin-33 (IL-33) is a member of IL-1 family of cytokines, produced constitutively by fibroblasts, endothelial cells, and epithelial cells. IL-33 can be released passively from cells during tissue damage and cell necrosis, suggesting that it may act as an alarmin. Function of IL-33 is mediated by its interaction with ST2 molecule that is expressed on many immune cells: Th2 lymphocytes, NK, NKT and mast cells, monocytes, dendritic cells and granulocytes. IL-33/ST2 pathway plays, often dual, roles in different physiological and inflammatory processes, mediating both, pathological immune responses and tissue repair. Expression of IL-33 in the central nervous system (CNS) is significantly enhanced during various pathological processes, indicating its important role in the pathogenesis of neurological inflammatory and degenerative diseases. In this review the biological features, expression of IL-33 and its ligand ST2 in CNS, and the role of IL-33/ST2 pathway in development of Alzheimer's disease and multiple sclerosis are discussed.

Keywords: IL-33, ST2, Alzheimer's disease, Multiple Sclerosis, EAE.

SAŽETAK

Interleukin-33 (IL-33) je član citokinske porodice IL-1, konstitutivno eksprimiran u fibroblastima, endotelnim i epitelnim ćelijama. Ćelije mogu pasivno da oslobađaju IL-33 tokom oštećenja tkiva i nekroze ćelija, kada ima ulogu alarmina. IL-33 svoju funkciju ostvaruje putem interakcije sa ST2 molekulom koji je eksprimiran na mnogim imunskim ćelijama: Th2 limfocitima, NK ćelijama, NKT ćelijama, mastocitima, monocitima, dendritskim ćelijama i granulocitima. IL-33/ST2 signalni put često ima dvostruku ulogu u različitim fiziološkim i zapaljenskim procesima, učestvujući tako u patološkim imunskim odgovorima i reparaciji tkiva. Ekspresija IL-33 u centralnom nervnom sistemu (CNS) je značajno pojačana tokom različitih patoloških procesa, što ukazuje na važnu ulogu u patogenezi neuroloških zapaljenskih i degenerativnih oboljenja. U ovom radu će se diskutovati o biološkim karakteristikama, ekspresiji IL-33 i njegovog liganda ST2 molekula u CNS-u, kao i o ulozi IL-33/ST2 signalnog puta u razvoju Alchajmerove bolesti i multiple skleroze.

Ključne reči: IL-33, ST2, Alchajmerova bolest, multipla skleroza, EAE.

INTRODUCTION

Interleukin-33 (IL-33), is a member of the IL-1 cytokine family. Initially described as a nuclear protein (1), later it has been shown that by binding to the ST2 molecule. The receptor complex for IL-33 consist of a ST2 subunit and IL-1RAcP. The ST2 subunit exists in two forms, the soluble sST2 isoform and ST2L isoform. (2) The sST2 form is found constitutively in human serum and binds excessive free IL-33 (3). ST2L isoform represents full-length protein which consists of extracellular Ig-like domains, short extracellular spacer, transmembrane domain and an intracellular TIR domain. IL-33 binds between two distal domains (D1D2) and membrane proximal third domain (D3), and recruits IL-1RAcP, a shared signaling component of receptors for IL-1 family (3, 4). IL-1RAcP signaling induces recruitment of myeloid differentiation primary response protein 88 (Myd88), IL-1R associated kinase 1 (IRAK1), IRAK4 and TRAF6 (Tumor Necrosis Factor Acceptor Associated Factor 6) to the receptor complex (5-7). This leads to activation of signaling proteins including extracellular signal-regulated kinase 1 (Erk1/2), p38 and c-Jun N terminal kinase (JNK), activation of AP-1 transcription factors and degradation of inhibitor of nuclear factor- κ B (I κ B α), leading to translocation of NF κ B to the nucleus (8). The activation of these signaling pathways results in the production of cytokines and chemokines specific for the cell type activated by interleukin-33 (7-9). Cells of innate immunity stimulated by interleukin-33 produce pro-inflammatory mediators that recruit other cells of the immune system and induce inflammation. Full length IL-33 is bioactive and can be released by the living cells (10) or by the necrotic cells following the tissue damage, acting as an endogenous danger signal or alarmin (11). In apoptotic cells, IL-33 is inactivated by released caspases which contributes to the process of maintaining immune tolerance (12). In the states of inflammation, serine proteases released by neutrophils cleave IL-33 into smaller fragments that exhibit 10 times higher biological activity than the complete protein. Chymases and tryptases released by activated mast cells also cleave IL-33 to make forms that have 30 times higher biological activity (13). These data indicate that IL-33 activity is enhanced in the inflammatory environment. IL-33 is expressed by many types of cells, in particular stromal and tissue barrier cells and in some innate immune cells, while ST2 is expressed by various immune cells including T cells, B cells, macrophages, dendritic cells and innate lymphoid cells (1). IL-33 and its ligand ST2 is constitutively expressed within brain and spinal cord, which indicate a unique role of IL-33/ST2 signaling pathway within CNS (14). IL-33, by mediation interactions between cells of nervous tissue, immune and endothelial cells, plays the role in the nervous tissue development and CNS homeostasis, but is also involved in neuroinflammation and pathogenesis of many neurological diseases such as Alzheimer's disease (AD) and multiple sclerosis (MS). This indicates that IL-33/ST2 pathway has pleiotropic functions in a range of physiological processes and inflammatory diseases often with dual roles, mediating both, pathological immune responses and tissue repair (15-19).

EXPRESSION OF IL-33 AND ITS LIGAND ST2 IN CNS

IL-33 is synthesized in the CNS in the first two to three weeks of postnatal development, and is expressed in developing and adult brain (20-22). It has been shown that IL-33 is constitutively expressed in the brains of adult healthy mice, predominantly in gray matter astrocytes and postmitotic oligodendrocytes (20, 22). Levels of IL-33 expression across brain and spinal cord regions are not constant and uniform, which potentially reflects specific functions of the IL-33/ST2 signaling pathway in neuronal activities and disorders (20). IL-33 expression is distributed throughout the white matter areas such as corpus callosum (CC), anterior forceps of the CC, anterior commissure, hippocampal fringe and stria terminalis (15, 21). It has been shown that expression of IL-33 increases significantly after brain tissue injury leading to monocyte recruitment and tissue repair due to alternative macrophage activation (15). IL-33 is also present in the zone of the olfactory cortex, motor and somatosensory cortex (14). In the region of cerebellum, IL-33 is present in the granular layer as well as in the white matter layers, while the molecular layer is characterized by the absence of IL-33 production (14). The hippocampal zone, often affected by pathological processes in various neurodegenerative diseases, is characterized by low expression of IL-33 (15, 20, 23). When it comes to co-localization IL-33 with different resident cells in the central nervous system, it has been shown that the dominant sources of production are astrocytes and oligodendrocytes in the corpus callosum (23, 24). Low expression of IL-33 is associated with astrocytes in the molecular layer of the dentate gyrus, as well as in the region of the stratum oriens and the stratum radiatum of the hippocampus (23, 24).

In the spinal cord IL-33 is present in the gray matter, while its expression in the white matter is significantly lower (25). This situation may indicate a different functions of the IL-33/ST2 axis in the spinal cord as opposed to that in the brain because the expression of IL-33 in the zone of white matter of the brain is higher. IL-33 is produced by astrocytes, oligodendrocytes, and a limited number of NeuN⁺ neurons and Iba1⁺ microglial cells (20).

In the brain, ST2 is expressed in the same zones as IL-33, which includes olfactory bulb, hippocampus and hippocampal fringe, anterior commissure, corpus callosum and somatosensory regions (14). The expression of ST2 in the cerebellum is different and is characterized by low levels in the granular layer and the white matter layer (14). ST2 is highly expressed throughout all regions of hippocampus (14). Within CC region, ST2 is expressed by some astrocytes, with lower expression level observed in neuron cell bodies and microglia (14).

ROLE OF IL-33/ST2 AXIS IN CNS DEVELOPMENT

It is still unclear whether IL-33 has protective or destructive effects on the growth and function of neurons. Previous studies have shown that administration of lower doses of recombinant IL-33 to cultures of mouse glial cell and neurons

reduces the number of neurons with decreasing signs of neuritis, while higher doses do not affect the growth and viability of neurons and axons (26). The IL-33/ST2 signaling axis also influences the process of myelination of axons. Studies conducted on rat oligodendrocyte culture showed that administration of recombinant IL-33 enhances oligodendrocyte differentiation and maturation, but reduces the process of axon myelination (24, 27, 28). Such knowledge indicates the important influence of the IL-33/ST2 signaling pathway in the process of myelination of the CNS during development, but also in various pathological conditions characterized by the inability to repair myelin, such as in the case of multiple sclerosis (24, 27, 28). Recent report indicates that IL-33 deficiency affects the expression of neural activity indicators (cFos proteins), thereby disrupting the development and maturation of neural circuits. IL-33 deficient mice have an excess of excitatory synapses and show the signs of a sensory-motor reflex disorder. This indicates the significant role of IL-33 in the process of synapse formation within the thalamus and spinal cord *via* microglia activation and stimulation of phagocytosis of synaptic elements (20, 21).

ROLE OF IL33/ST2 AXIS IN ALZHEIMER'S DISEASE

Alzheimer's disease is a neurodegenerative disease characterized by progressive dementia and other cognitive dysfunctions, such as judgment, loco motor ability, and reasoning (29). The main characteristics of the disease are the extracellular accumulation of amyloid plaques and the intracellular formation of neurofibrillary tangles (NFTs) (29). Important feature in pathogenesis and progression of neurodegenerative diseases, such as Alzheimer's disease is neuroinflammation characterized by elevated levels of proinflammatory cytokines, activation of microglia, and astrogliosis (30, 31-33). Studies have shown that the presence of a peripheral infection accompanied by inflammation increases the risk of developing sporadic cases of Alzheimer's disease (34-36). One of the most important animal model of peripherally induced neuroinflammation and neurodegeneration is lipopolysaccharide (LPS) treated mice (37). It has been shown that after peripheral administration of LPS in mice, astrogliosis develops with microglia activation leading to increased production of proinflammatory cytokines in the brain (37-40). Microglia as the main effector cells of the immune system in the brain by releasing a neurotrophic factor like BDNF participate in remodeling synapses and maintaining homeostasis in the brain (41). In inflammatory conditions, microglial cells are activated and produce proinflammatory cytokines, disrupting the relevant circuits leading to neuronal damage (41). Besides microglia, after the application of LPS, the number of glial fibrillary acidic protein (GFAP)-positive cells increases, which is referred to as astrogliosis, which can worsen neuroinflammation and tissue damage (40). Increased activity of two proinflammatory enzymes, COX-2 and iNOS, also contributes to neurodegeneration. In physiological conditions, iNOS is not detected in the brain, while COX-2 was found to be expressed, thus contributing to memory consolidation and synapse remodeling (42). Increased expression of iNOS

increases local production of NO, which causes damage to axons and synapses, as well as inhibition of the mitochondrial respiration, which causes neuronal apoptosis. Studies have shown increased expression of COX-2 and iNOS at the level of mRNA and protein in mice treated with LPS. COX-2 induction was observed primarily at the level of the brain endothelium, as well as in activated astrocytes, but not in microglial cells (43).

It is still unknown how the expression of IL-33 and its receptor plays a role in the pathogenesis of Alzheimer's disease. Studies have shown increased expression of IL-33 and ST2 in the zone of amyloid plaque and neurofibrillary tangles, whereas at the level of the entire brain, IL-33 expression is reduced compared to the healthy population (44, 45). Following applications of recombinant IL-33 to transgenic APP/PS1 mice that spontaneously develop Alzheimer's disease like pathology, it was observed that IL-33 promotes activation of microglia and macrophages in the direction of the M2 anti-inflammatory phenotype, thereby enhancing the phagocytic activity of microglia (17). This, in turn, leads to a decrease in the level of soluble $\text{A}\beta$ and a reduced accumulation of amyloid plaques, thereby improves cognitive deficiency and stabilizing synaptic transmission (17). The protective role of endogenous IL-33 is present only in a state of limited inflammation and can potentially slow the progression of the disease in its early stage (46). If the inflammation is prolonged, it further stimulates the expression of IL-33, as well as other proinflammatory and neurotoxic mediators that damage neurons leading to neuronal death (47). IL-33 stimulates the proliferation of microglial cells that produce IL-1 β , TNF- α , as well as anti-inflammatory IL-10, and thus could promote the inflammatory processes in the CNS (45). IL-33 can exert its proinflammatory effect by autocrine or paracrine mechanism on glial cells and its presence in lesion zones may exacerbate neuroinflammation (45). A study comparing the levels of inflammatory cytokines and receptors of the IL-1 family in the serum of patients with Alzheimer's disease, patients with mild cognitive impairment, subjective memory complaints, and healthy subjects showed that IL-33 and its soluble inhibitor receptor sIL-1R4 were significantly increased in patients with AD (48). An increase of serum's level of IL-33 in patients with AD could be endogenous attempt for preventing neuroinflammation. In contrast to patients with AD, IL-33 is almost not detected at all in the sera of healthy individuals, as well as in those who show symptoms of mild cognitive impairment and subjective memory complaints. In addition to sIL-1R4, an increase in other IL-1 inhibitors was detected in AD patients, such as IL-1Ra, sIL-1R1, sIL-1R3, as well as IL-18 inhibitor IL-18BP compared to the health control group. The increase in anti-inflammatory receptors is one way to limit the inflammation present in the brain of patients with AD and negatively correlate with the seriousness of cognitive dysfunction (11, 48). A study that examined the role of IL-33 in the Alzheimer's disease, by measurement concentrations of IL-33 and sST2 in serum and cerebrospinal fluid (CSF) in AD and patients with mild cognitive impairment comparing the results to healthy controls showed that IL-33 was significantly decreased in serum

and CSF of AD and mild cognitive impairment, while sST2 was increased in serum, but was undetectable in CSF (48). This study also examined concentration of IL1 β , IL-6, and IL-10 in serum and CSF. IL-1 β concentration was significantly increased in serum and CSF and IL-10 was reduced in AD and mild cognitive impairment, whereas no differences were observed in IL-6 (49). Application of IL-33 to the culture of LPS+A β 42-stimulated monocytes resulted in a decrease of IL-1 β synthesis in cell cultures isolated from mild cognitive impairment and healthy control, and an increase in IL-10 synthesis only in healthy control group (49). The use of IL-33 caused a decrease in the nuclear translocation of NF κ B in LPS + A β 42-stimulated monocytes only in healthy subjects (49). Another clinical study which examined the correlation between levels of IL-33 in human blood and cognitive preservation in patients with amnesic mild cognitive impairment (aMCI) and Alzheimer's disease revealed that the peripheral IL-33 expression showed a positive trend among controls, amnesic mild cognitive impairment, and AD, but the longitudinal changes of IL-33 expression was unclear in aMCI and AD (50). Patients who expressed IL-33 preserved their cognitive function compared to those who do not express IL-33 (50). The cognitive preservation was not associated with the lower levels of A β , tau, and ApoE ϵ 4, while higher levels of ApoE ϵ 4 and phosphorylated tau were associated with cognitive decline (50).

Most models examining the pathogenesis of Alzheimer's disease are transgenic animal models, which show similarities to the disease that develops in humans (48, 51). The similarity is reflected in the damage and loss of neurons in the cerebral cortex and hippocampus with tau protein abnormalities and impaired cognitive function in old age. Aging of neurons is characterized by damage to DNA, accumulation of reactive oxygen species and old organelles (52-54). Stress-impaired neurons stimulate astrocytes to enhance IL-33 expression, which promotes neuronal repair and cellular waste autophagy, thus ensuring neuronal rejuvenation (21). Studies have shown that the accumulation of tau protein and amyloid occurs due to impaired autophagy (55, 56). The inability to repair damaged neurons in the hippocampal and cerebral cortex zones could lead to AD-like dementia in old age (22). It has been shown that astrocytes with aging increase expression of IL-33, which plays a key role in neuronal repair, and that mice with deletion of the IL-33 gene with aging show significant neuronal loss in the cortex and hippocampus due to increased deposition of tau protein, which causes neurodegeneration (24). The results of these studies indicate that the IL-33/ST2 signaling pathway could modulate neuroinflammation and consequently affect the development of tauopathy and the amount of amyloid in the brain (22).

Recent research has shown that components of inflammasome play an important role in the neuroinflammation that accompanies Alzheimer's disease (57). Nucleotide-binding domain and leucine-rich repeat (NLR)-protein 3 (NLRP3) is an intracellular multiprotein complex that activates proinflammatory caspase 1 and thus participates in the maturation and release of cytokines IL-1 β , IL-18, and IL-33 (58). An *in*

vitro and *in vivo* study showed that amyloid plaques and neurofibrillary tangles activate NLRP3 inflammasome present in microglial cells (59, 60). Peptides present in amyloid plaques further disrupt the functioning of Na⁺ / K⁺ ATPase and cause disruption of the Na⁺ and K⁺ ions gradients in neurons, leading to cytotoxicity and neuronal death (61). Deficiency of NLRP3 inflammasome and absence of caspase 1 activity in a transgenic model of mice with chronic deposition of amyloid plaques (APP /PS1 mice) showed reduced accumulation of amyloid due to polarization of microglia in the direction of the M2 phenotype. It has also been observed that increased expression of caspase 1 is present in the hippocampal zone in patients with Alzheimer's disease (60). It has been shown that application of IL-33 suppress inflammation in the brains of APP/PS1 mice by reducing gene expression for the proinflammatory cytokines IL1 β , IL-6, and NLRP3 (18).

ROLE OF IL33/ST2 AXIS IN MULTIPLE SCLEROSIS AND EAE

Multiple sclerosis (MS) is chronic inflammatory disease of CNS characterized by immune-mediated demyelination and axonal loss, resulting in impaired impulse delivery through the nervous system (26). Damage to the myelin sheath causes a different range of symptoms and signs of the disease (26). The pathogenesis of MS is elusive, but it is generally considered that MS is an autoimmune disease initiated by auto-reactive CD4⁺ T cells specific for myelin antigens that perpetuate an inflammatory cascade, which finally results in demyelination and axonal loss (62). The immense range of different clinical presentations in patients with MS and in the histopathological findings in the CNS tissue indicates that multiple immunopathological pathways contribute to MS development. Results obtained in clinical studies indicate that cytokines play an essential role in the pathogenesis of MS (63, 64). However, the most findings about pathogenesis of MS have been obtained by analogy to EAE, an animal model of MS (65, 66.).

Enhanced expression of IL-33 and ST2 in the brain of MS patients, in the active lesions has been previously shown, indicating the potential modulating properties of IL-33 both on the immune and resident CNS cells (26, 45). Astrocytes, neurons, oligodendrocytes and activated microglia have been identified as the major source of IL-33, whereas ST2 receptor is predominantly present on neurons and oligodendrocytes (23). A study comparing serum concentrations of IL-33 in healthy subjects and patients with MS showed that MS patients had higher concentrations of IL-33 and that cytokine level correlated with disease severity (67). Serum values of IL-33 were significantly higher in patients with severe disease compared to those with milder forms of MS (67). A study conducted in subjects with relapsing-remitting form of the disease (RRMS) showed that these patients had enhanced intracellular expression of IL-33 and histone deacetylase (HDAC3), an enzyme involved in epigenetic regulation of genes activated during inflammation, compared to healthy subjects and subject with other neurological diseases, while there was no statistically significant difference in the

expression of circulating IL-33 between patients and control subject (68). Results from another study that compared the plasma levels of IL-33 in patients with RRMS and healthy control subjects showed increased concentration of IL-33 in patients with RRMS (69). Also, in the same study, it was shown that patients treated with interferon beta (IFN- β) had lower concentrations of IL-33 compared to untreated patients (69). Reduced serum level of IL-33 after treatment of MS patients with IFN- β was reported in several studies (70-72).

Results obtained from experimental studies in animal models of MS show often opposite effects of IL-33 on severity of the disease depending on the experimental settings. Significantly enhanced expression of IL-33 and ST2 in the spinal cord of mice during myelin oligodendrocyte glycoprotein 35-55 (MOG₃₅₋₅₅) peptide-induced EAE has been reported (73). Treatment of mice with a blocking anti-IL-33 antibody during induction phase of EAE significantly attenuated severity of EAE, while treatment with recombinant IL-33 worsened the disease (73). Changes in EAE severity after treatment with a blocking anti-IL-33 antibody or recombinant IL-33 were accompanied with changes in the expression of cytokines that play the roles in EAE pathogenesis, IFN- γ and IL-17 in spinal cord (73). In other study protective role of IL-33 released from resident cells of CNS during onset and peak of EAE has been described (74). Blockage of the CNS-derived IL-33 during onset and peak of the disease exacerbated EAE (74). Also treatment with recombinant IL-33 after disease onset attenuated clinical and histological parameters of EAE induced with MOG₃₅₋₅₅ peptide (25). Data obtained in studies with mice with targeted disruption of *Il1rl1* (ST2) and *Il33* genes indicate protective role of IL-33 in EAE. The clinical score of EAE and more severe demyelination were reported in *Il33* knockout mice compared with the wild-type mice (74). Exacerbated EAE in IL-33 deficient mice was accompanied with a transition from the dominantly pathogenic Th17 and Th1 immune response to the protective Th2 immune phenotype in CNS (74). We have previously shown that deficiency of the ST2 molecule attenuates the inborn resistance of BALB/c mice to EAE induction with MOG₃₅₋₅₅ peptide by stimulation the development of proinflammatory antigen-presenting cells and encephalitogenic T lymphocytes that cross the blood brain barrier and induce CNS tissue damage (25, 75).

Further, it has been reported that protective effects of several potential therapeutics in EAE are accompanied with modulated expression of IL-33 and ST2 in CNS. The treatment with anti-CD52 antibodies following onset of the disease reduces EAE severity and attenuates protein level of extracellular IL-33 and percentage of ST2 positive cells in spinal cord (76). On the other hand attenuation of EAE in mice treated with quinolizidine alkaloid, matrine, during induction of EAE has been recently linked with matrine induced attenuation of IL-33 and ST2 mRNA levels in spinal cord (77). Similarly attenuation of EAE after treatment with ginger extracts after immunization of mice with MOG₃₅₋₅₅ peptide is accompanied with attenuated expression of IL-33 at mRNA level (78). Beneficial effects of infections with helminths in

EAE has been recently linked to increased production of IL-33 and Th2 responses induced by helminth products (79).

Recently it has been shown that relative resistance of males to sex-dependent autoimmune diseases, such as multiple sclerosis could be due to enhanced production of IL-33 (80). Selective induction of IL-33 in male SJL mice was found after immunization with PLP₁₃₉₋₁₅₁ peptide accompanied with promotion of nonpathogenic Th2 myelin-specific response, while female mice without increase of IL-33 generate encephalitogenic Th17 cells (80).

CONCLUSION

A large number of reports suggest often opposite effects, protective or deleterious, of IL-33/ST2 signaling axis in inflammatory and degenerative neurological diseases. The precise roles and relative contributions of the IL-33/ST2 signaling in the development and progression of neurological diseases are still elusive. Since IL-33/ST2 axis might be potential therapeutic target in CNS diseases, additional research in this field is required in order to elucidate the precise role of IL-33/ST2 signaling in the pathogenesis of neuroinflammatory and neurodegenerative diseases.

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LITERATURE

1. Schmitz J, Owyang A, Oldham E, Song Y, Murphy E, McClanahan TK, et al. IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. *Immunity*. 2005; 23: 479-90.
2. Yanagisawa K, Takagi T, Tsukamoto T, Tetsuka T, Tominaga S. Presence of a novel primary response gene ST2L, encoding a product highly similar to the interleukin 1 receptor type 1. *FEBS Lett*. 1993; 318(1): 83-7.
3. Kuroiwa K, Li H, Tago K, Iwahana H, Yanagisawa K, Komatsu N, et al. Construction of ELISA system to quantify human ST2 protein in sera of patients. *Hybridoma*. 2000; 19(2): 151-9.
4. Liu X, Hammel M, He Y, Tainer JA, Jeng US, Zhang L, et al. Structural insights into the interaction of IL-33 with its receptors. *Proc Natl Acad Sci USA*. 2013; 110(37): 14918-23.
5. Ali S, Huber M, Kollewe C, Bischoff SC, Falk W, Martin MU. IL-1 receptor accessory protein is essential for IL-33-induced activation of T lymphocytes and mast cells. *Proc Natl Acad Sci U S A*. 2007; 104: 18660-5.
6. Cayrol C, Girard JP. Interleukin-33 (IL-33): A nuclear cytokine from the IL-1 family. *Immunol Rev*. 2018; 281(1): 154-168.

7. Chackerian AA, Oldham ER, Murphy EE, Schmitz J, Pflanz S, Kastelein RA. IL-1 receptor accessory protein and ST2 comprise the IL-33 receptor complex. *J Immunol.* 2007; 179: 2551–5.
8. Andrade MV, Iwaki S, Ropert C, Gazzinelli RT, Cunha-Melo JR, Beaven MA. Amplification of cytokine production through synergistic activation of NFAT and AP-1 following stimulation of mast cells with antigen and IL-33. *Eur J Immunol.* 2011; 41(3): 760-72.
9. Dunne A, O'Neill LA. The interleukin-1 receptor/Toll-like receptor superfamily: signal transduction during inflammation and host defense. *Sci STKE.* 2003; 2003(171):re3.
10. Kakkar R, Hei H, Dobner S, Lee RT. Interleukin 33 as a mechanically responsive cytokine secreted by living cells. *J Biol Chem.* 2012; 287(9): 6941-8.
11. Liew FY, Pitman NI, McInnes IB. Disease-associated functions of IL-33: the new kid in the IL-1 family. *Nat Rev Immunol.* 2010; 10(2): 103-10
12. Oboki K, Ohno T, Kajiwara N, Arae K, Morita H, Ishii A, et al. IL-33 is a crucial amplifier of innate rather than acquired immunity. *Proc Natl Acad Sci U S A.* 2010; 107:18581–6.
13. Kamijo S, Takeda H, Tokura T, Suzuki M, Inui K, Hara M, et al. IL-33-mediated innate response and adaptive immune cells contribute to maximum responses of protease allergen-induced allergic airway inflammation. *J Immunol.* 2013; 190:4489–99
14. Fairlie-Clarke K, Barbour M, Wilson C, Hridi SU, Allan D, Jiang HR. Expression and Function of IL-33/ST2 Axis in the Central Nervous System Under Normal and Diseased Conditions. *Front Immunol.* 2018; 9:2596.
15. Gadani SP, Walsh JT, Smirnov I, Zheng J, Kipnis J. The glia-derived alarmin IL-33 orchestrates the immune response and promotes recovery following CNS injury. *Neuron.* 2015; 85:703–9.
16. Yang Y, Liu H, Zhang H, Ye Q, Wang J. ST2/IL-33-dependent microglial response limits acute ischemic brain injury. *J Neurosci.* 2017; 37:4692–704.
17. Fu AK, Hung KW, Yuen MY, Zhou X, Mak DS, Chan IC, et al. IL-33 ameliorates Alzheimer's disease-like pathology and cognitive decline. *Proc Natl Acad Sci U S A.* 2016; 113(19): E2705-13.
18. Wicher G, Wallenquist U, Lei Y, Enoksson M, Li X, Fuchs B, et al. Interleukin-33 promotes recruitment of microglia/macrophages in response to traumatic brain injury. *J Neurotrauma.* 2017; 34(22): 3173–82.
19. Cao K, Liao X, Lu J, Yao S, Wu F, Zhu X, et al. IL-33/ST2 plays a critical role in endothelial cell activation and microglia-mediated neuroinflammation modulation. *J Neuroinflammation.* 2018; 15(1): 136.
20. Dohi E, Choi EY, Rose IVL, Murata AS, Chow S, Niwa M, et al. Behavioral Changes in Mice Lacking Interleukin-33. *eNeuro.* 2017; 4(6).
21. Vainchtein ID, Chin G, Cho FS, Kelley KW, Miller JG, Chien EC, et al. Astrocyte-derived interleukin-33 promotes microglial synapse engulfment and neural circuit development. *Science.* 2018; 359(6381): 1269-1273.
22. Carlock C, Wu J, Shim J, Moreno-Gonzalez I, Pitcher MR, Hicks J, et al. Interleukin33 deficiency causes tau abnormality and neurodegeneration with Alzheimer-like symptoms in aged mice. *Transl Psychiatry.* 2017; 7(7): e1164.
23. Pichery M, Mirey E, Mercier P, Lefrancais E, Dujardin A, Ortega N, et al. Endogenous IL-33 is highly expressed in mouse epithelial barrier tissues, lymphoid organs, brain, embryos, and inflamed tissues: in situ analysis using a novel IL-33-LacZ gene trap reporter strain. *J Immunol.* 2012; 188(7): 3488-95.
24. Natarajan C, Yao SY, Sriram S. TLR3 Agonist Poly-IC Induces IL-33 and Promotes Myelin Repair. *PLoS One.* 2016; 11(3): e0152163.
25. Jiang HR, Milovanović M, Allan D, Niedbala W, Besnard AG, Fukada SY, et al. IL-33 attenuates EAE by suppressing IL-17 and IFN- γ production and inducing alternatively activated macrophages. *Eur J Immunol.* 2012; 42(7): 1804-14.
26. Allan D, Fairlie-Clarke KJ, Elliott C, Schuh C, Barnett SC, Lassmann H, et al. Role of IL-33 and ST2 signalling pathway in multiple sclerosis: expression by oligodendrocytes and inhibition of myelination in central nervous system. *Acta Neuropathol Commun.* 2016; 4(1): 75.
27. Kempuraj D, Khan MM, Thangavel R, Xiong Z, Yang E, Zaheer A. Glia maturation factor induces interleukin-33 release from astrocytes: implications for neurodegenerative diseases. *J Neuroimmune Pharmacol.* 2013; 8(3): 643-50.
28. Glenner GG, Wong CW. Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. 1984. *Biochem Biophys Res Commun.* 2012; 425(3): 534-9.
29. Heneka MT, Kummer MP, Latz E. Innate immune activation in neurodegenerative disease. *Nat Rev Immunol.* 2014; 14(7): 463-477.
30. Luteran JD, Haroutunian V, Yemul S, et al. Cytokine gene expression as a function of the clinical progression of Alzheimer disease dementia. *Arch Neurol.* 2000; 57(8): 1153-1160.
31. Serrano-Pozo A, Mielke ML, Gómez-Isla T, et al. Reactive glia not only associates with plaques but also parallels tangles in Alzheimer's disease. *Am J Pathol.* 2011; 179(3): 1373-1384.
32. McGeer PL, McGeer EG. The amyloid cascade-inflammatory hypothesis of Alzheimer disease: implications for therapy. *Acta Neuropathol.* 2013; 126(4): 479-497.
33. Holmes C, Cotterell D. Role of infection in the pathogenesis of Alzheimer's disease: implications for treatment. *CNS Drugs.* 2009; 23(12): 993-1002.
34. Holmes C. Review: systemic inflammation and Alzheimer's disease. *Neuropathol Appl Neurobiol.* 2013; 39(1): 51-68.
35. Su X, Federoff HJ. Immune responses in Parkinson's disease: interplay between central and peripheral immune systems. *Biomed Res Int.* 2014; 2014:275178.
36. Qin L, Wu X, Block ML, et al. Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. *Glia.* 2007; 55(5): 453-462.

37. Erickson MA, Banks WA. Cytokine and chemokine responses in serum and brain after single and repeated injections of lipopolysaccharide: multiplex quantification with path analysis. *Brain Behav Immun.* 2011; 25(8): 1637-1648.
38. Park SM, Choi MS, Sohn NW, Shin JW. Ginsenoside Rg3 attenuates microglia activation following systemic lipopolysaccharide treatment in mice. *Biol Pharm Bull.* 2012; 35(9): 1546-1552.
39. Biesmans S, Meert TF, Bouwknecht JA, et al. Systemic immune activation leads to neuroinflammation and sickness behavior in mice. *Mediators Inflamm.* 2013; 2013:271359.
40. Tremblay MÈ, Stevens B, Sierra A, Wake H, Bessis A, Nimmerjahn A. The role of microglia in the healthy brain. *J Neurosci.* 2011; 31(45): 16064-16069.
41. Dubois RN, Abramson SB, Crofford L, et al. Cyclooxygenase in biology and disease. *FASEB J.* 1998; 12(12): 1063-1073.
42. Brown GC. Mechanisms of inflammatory neurodegeneration: iNOS and NADPH oxidase. *Biochem Soc Trans.* 2007; 35(Pt 5): 1119-1121.
43. Chapuis J, Hot D, Hansmannel F, Kerdraon O, Ferreira S, Hubans C, et al. Transcriptomic and genetic studies identify IL-33 as a candidate gene for Alzheimer's disease. *Mol Psychiatry.* 2009; 14(11): 1004-16.
44. Xiong Z, Thangavel R, Kempuraj D, Yang E, Zaheer S, Zaheer A. Alzheimer's disease: evidence for the expression of interleukin-33 and its receptor ST2 in the brain. *J Alzheimers Dis.* 2014; 40(2): 297-308.
45. Yasuoka S, Kawanokuchi J, Parajuli B, Jin S, Doi Y, Noda M, et al. Production and functions of IL-33 in the central nervous system. *Brain Res.* 2011; 1385:8-17.
46. Marx CE, Jarskog LF, Lauder JM, Lieberman JA, Gilmore JH. Cytokine effects on cortical neuron MAP-2 immunoreactivity: implications for schizophrenia. *Biol Psychiatry.* 2001; 50:743-749.
47. Italiani P, Puxeddu I, Napoletano S, et al. Circulating levels of IL-1 family cytokines and receptors in Alzheimer's disease: new markers of disease progression?. *J Neuroinflammation.* 2018; 15(1): 342.
48. Richardson JA, Burns DK. Mouse models of Alzheimer's disease: a quest for plaques and tangles. *ILAR J.* 2002; 43: 89-99.
49. Saresella M, Marventano I, Piancone F, et al. IL-33 and its decoy sST2 in patients with Alzheimer's disease and mild cognitive impairment. *J Neuroinflammation.* 2020; 17(1): 174.
50. Liang CS, Su KP, Tsai CL, et al. The role of interleukin-33 in patients with mild cognitive impairment and Alzheimer's disease. *Alzheimers Res Ther.* 2020; 12(1): 86.
51. Gotz J, Ittner LM. Animal models of Alzheimer's disease and frontotemporal dementia. *Rev Neurosci* 2008; 9: 532-544
52. Obulesu M, Rao DM. DNA damage and impairment of DNA repair in Alzheimer's disease. *Int J Neurosci* 2010; 120: 397-403.
53. Hou Y, Song H, Croteau DL, Akbari M, Bohr VA. Genome instability in Alzheimer disease. *Mech Ageing Dev* 2017; 161: 83-94.
54. Malpass K. Alzheimer disease: DNA damage provides novel and powerful biomarkers of Alzheimer disease. *Nat Rev Neurol.* 2012; 8: 178.
55. Inoue K, Rispoli J, Kaphzan H, Klann E, Chen EI, Kim J et al. Macroautophagy deficiency mediates age-dependent neurodegeneration through a phospho-tau pathway. *Mol Neurodegen.* 2012; 7: 48.
56. Bateman RJ, Munsell LY, Morris JC, Swarm R, Yarasheski KE, Holtzman DM. Human amyloid-beta synthesis and clearance rates as measured in cerebrospinal fluid in vivo. *Nat Med.* 2006; 12: 856-861.
57. Pennisi M, Crupi R, Di Paola R, et al. Inflammasomes, hormesis, and antioxidants in neuroinflammation: Role of NLRP3 in Alzheimer disease. *J Neurosci Res.* 2017; 95(7): 1360-1372.
58. Singhal G, Jaehne EJ, Corrigan F, Toben C, Baune BT. Inflammasomes in neuroinflammation and changes in brain function: a focused review. *Front Neurosci.* 2014; 8:315.
59. Halle A, Hornung V, Petzold GC, et al. The NALP3 inflammasome is involved in the innate immune response to amyloid-beta. *Nat Immunol.* 2008; 9(8): 857-865.
60. Heneka MT, Kummer MP, Stutz A, et al. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. *Nature.* 2013; 493(7434): 674-678.
61. Rubartelli A. DAMP-mediated activation of NLRP3-inflammasome in brain sterile inflammation: the fine line between healing and neurodegeneration. *Front Immunol.* 2014; 5:99.
62. Wu GF, Alvarez E. The immunopathophysiology of multiple sclerosis. *Neurol Clin.* 2011; 29(2): 257-278.
63. Wang K, Song F, Fernandez-Escobar A, Luo G, Wang JH, Sun Y. The Properties of Cytokines in Multiple Sclerosis: Pros and Cons. *Am J Med Sci.* 2018; 356(6): 552-560.
64. Lucchinetti C, Brück W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. *Ann Neurol.* 2000; 47(6): 707-717.
65. Steinman L, Zamvil SS. How to successfully apply animal studies in experimental allergic encephalomyelitis to research on multiple sclerosis. *Ann Neurol.* 2006; 60(1): 12-21.
66. Kuchroo VK, Anderson AC, Waldner H, Munder M, Bettelli E, Nicholson LB. T cell response in experimental autoimmune encephalomyelitis (EAE): role of self and cross-reactive antigens in shaping, tuning, and regulating the autopathogenic T cell repertoire. *Annu Rev Immunol.* 2002; 20:101-123.
67. Kouchaki E, Tamtaji OR, Dadgostar E, Karami M, Nikouejad H, Akbari H. Correlation of Serum Levels of IL-33, IL-37, Soluble Form of Vascular Endothelial Growth Factor Receptor 2 (VEGFR2), and Circulatory Frequency of VEGFR2-expressing Cells with Multiple

- Sclerosis Severity. Iran J Allergy Asthma Immunol. 2017; 16(4): 329-337
68. Zhang F, Tossberg JT, Spurlock CF, Yao SY, Aune TM, Sriram S. Expression of IL-33 and its epigenetic regulation in Multiple Sclerosis. Ann Clin Transl Neurol. 2014; 1(5): 307-318.
 69. Alsahebhosoul F, Rahimmanesh I, Shajarian M, et al. Interleukin-33 plasma levels in patients with relapsing-remitting multiple sclerosis [published correction appears in Biomol Concepts. 2017;]. Biomol Concepts. 2017; 8(1): 55-60.
 70. Christophi GP, Gruber RC, Panos M, Christophi RL, Jubelt B, Massa PT. Interleukin-33 upregulation in peripheral leukocytes and CNS of multiple sclerosis patients. Clin Immunol 2012; 142: 308–19.
 71. Kanda T. Interleukin-33/suppression of tumorigenicity 2 system: can it be a future therapeutic target for neuro-immunological disorders? Clin Exp Neuroimmunol. 2013; 4: 255–6
 72. Wang S, Ding L, Liu S-S, Wang C, Leng R-X, Chen G-M, et al. IL-33: a potential therapeutic target in autoimmune diseases. J Investig Med. 2012; 60: 1151–6.
 73. Li M, Li Y, Liu X, Gao X, Wang Y. IL-33 blockade suppresses the development of experimental autoimmune encephalomyelitis in C57BL/6 mice. J Neuroimmunol. 2012; 247(1-2): 25-31.
 74. Chen H, Sun Y, Lai L, et al. Interleukin-33 is released in spinal cord and suppresses experimental autoimmune encephalomyelitis in mice. Neuroscience. 2015; 308:157-168.
 75. Xiao Y, Lai L, Chen H, et al. Interleukin-33 deficiency exacerbated experimental autoimmune encephalomyelitis with an influence on immune cells and glia cells. Mol Immunol. 2018; 101:550-563.
 76. Barbour M, Wood R, Hridi SU, et al. The therapeutic effect of anti-CD52 treatment in murine experimental autoimmune encephalomyelitis is associated with altered IL-33 and ST2 expression levels. J Neuroimmunol. 2018; 318:87-96.
 77. Zhao X, Zhang X, Lv Y, et al. Matrine downregulates IL-33/ST2 expression in the central nervous system of rats with experimental autoimmune encephalomyelitis. Immunol Lett. 2016; 178:97-104.
 78. Jafarzadeh A, Mohammadi-Kordkhayli M, Ahangar-Parvin R, et al. Ginger extracts influence the expression of IL-27 and IL-33 in the central nervous system in experimental autoimmune encephalomyelitis and ameliorates the clinical symptoms of disease. J Neuroimmunol. 2014; 276(1-2):80-88.
 79. Finlay CM, Stefanska AM, Walsh KP, et al. Helminth Products Protect against Autoimmunity via Innate Type 2 Cytokines IL-5 and IL-33, Which Promote Eosinophilia. J Immunol. 2016; 196(2):703-714.
 80. Russi AE, Ebel ME, Yang Y, Brown MA. Male-specific IL-33 expression regulates sex-dimorphic EAE susceptibility. Proc Natl Acad Sci U S A. 2018; 115(7): E1520-E1529.