**Abstract:**

Adult neurogenesis is the process of producing new neurons in the adult brain and is limited to two major areas: the hippocampal dentate gyrus and the Subventricular Zone (SVZ). Adult neurogenesis is affected by some physiological, pharmacological, and pathological factors. The inflammasome is a major signalling platform that regulates caspase-1 and induces proinflammatory cytokines production such as interleukin-1β (IL-1β) and IL-18. Inflammasomes may be stimulated through multiple signals, and some of these signaling factors can affect neurogenesis. In the current review, “adult neurogenesis and inflammasome” were searched in PubMed, Scopus, and Google Scholar. Reviewing various research works showed correlations between inflammasome and neurogenesis by different intermediate factors, such as interferons (IFN), interleukins (IL), α-synuclein, microRNAs, and natural compounds. Concerning the significant role of neurogenesis in the health of the nervous system and memory, understanding factors inducing neurogenesis is crucial for identifying new therapeutic aims. Hence in this review, we will discuss the different mechanisms by which inflammasome influences adult neurogenesis.

**Keywords:** Inflammasome, Neurogenesis, Neural stem/progenitor cells, Subgranular zone, Subventricular zone, Hippocampal dentate gyrus.

1. **INTRODUCTION AND STATEMENT OF THE PROBLEM**

Throughout life, neural stem/progenitor cells [NSPCs] can produce new neurons in specific areas in the mammalian’s brain [1]. Adult neurogenesis contributes to physiological brain activities and is crucial for specific learning and memory processes and a critical factor in adult brain plasticity. Adult neurogenesis is limited to the Subventricular Zone (SVZ) and the hippocampal Dentate Gyrus [2] (Fig. 1). Adult neurogenesis is an active process done with high accuracy and can be affected by pharmacological intervention, different physiological and pathological conditions [3]. Inflammasomes are the main signalling platforms that recognize sterile factors and pathogenic microorganisms [4]. During inflammasome activation, caspase-1, the prominent inflammatory mediator [5], releases interleukin-18 and interleukin-1β (IL-18/IL-1β), and these products cause pyroptosis and cells death [6, 7]. The innate immune system cells express Pattern Recognition Receptors (PRRs) to specify two molecular classes: Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs). NOD-Like Receptors (NLRs) are a subclass of PRRs which are found in the cytosol. There are numerous NLRs proteins that contribute to inflammasome pathways [8]. The oligomerization of NLRs (NLRP1, NLRP3, and NLRC4) can form multi-protein inflammasome complexes [9] (Table 1).

Toll-like Receptors (TLRs) are PRRs on immune cells which detect pathogens and stimulate IL1-β production [10] (Fig. 2). As inflammasome causes pyroptosis, it is possible that inflammasome may reduce neurogenesis. Several studies showed that IL1-β, the product of inflammation and IL-6, and the downstream target of IL1-β, can potentially prevent neurogenesis [2]. IL1-β, a potent pro-inflammatory cytokine, is important for host-defense reactions to injury and infection and is released and produced by many cell types [11]. It was reported that IL1-β had preventive effects on hippocampal cells in the dentate gyrus and NPCs of adult rats [12]. According to the Ryan study, IL1-β reduced neurogenesis and proliferation, while co-treatment with IL1-β receptor antagonist inhibited the adverse impact of IL1-β on the proliferation of cells [13].

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Fig. (1). Zones of adult neurogenesis: SVZ; Sub Ventricular Zone/ SGZ; Sub Granular Zone/ NSC; Neural Stem Cell.

Fig. (2). Inflammasome: PAMPs, pathogen-associated molecular patterns/ DAMPs, damage-associated molecular patterns / TLRs; Toll like receptors / NLRS, NOD-Like Receptors / IL, Interleukin / NF-κB; nuclear factor kappa B.

Table 1. Different factors responsible for active or inactive inflammasome and affect neurogenesis.

| Effect on Neurogenesis | Role in Inflammasome | Factor |
|------------------------|----------------------|--------|
| Inhibits neurogenesis   | It is produced by activation of the inflammasome | IL1β   |
| Inhibits neurogenesis   | It is a downstream target of IL1β                | IL6    |
| Stimulates neurogenesis | Inhibits IL1β, IL6, and TNF-α                  | IL4    |
| Stimulates neurogenesis | Inhibits NLRP3 inflammasome                    | IL10   |
| Inhibits neurogenesis   | It is produced by activation of the inflammasome | IL18   |
| Inhibits neurogenesis   | Activates inflammasome                          | INF-α  |
IL-1β also decreased proliferation and differentiation of rat neonatal DG NPCs to serotonergic (5-hydroxytryptamine) neurons [14]. Since IL-1β is the inflammasome’s ultimate production, therefore neurogenesis may be enhanced by managing the inflammasome and reducing the IL-1β production.

Interleukin-6 (IL-6) is an IL-1β downstream target, increased continuously in patient’s serum with NLRP3 inflammasome mediated conditions [2]. IL-6 reduced neurogenesis and enhanced apoptosis in rat adult DG NPCs, blocking antibodies to IL-6 induced neurogenesis [15].

The crucial role of IL-18 is highlighted in mediating neurodegeneration and neuroinflammation in the CNS under pathological conditions [16]. IL-18 exhibits direct pro-inflammatory properties by increasing inflammatory factors such as TNF-α, IL1-β, and IL-6 [17]. As previously described, TNF-α, IL-1β, and IL-6 have inhibitory effects on neurogenesis. Also, IL-18 increases amyloid precursor protein [18], Beta-secretase 1 (BACE1), and the N-terminal fragment of presenilin-1 and presenilin enhancer-2 protein levels [19]. It has been reported that in the adult SGZ, presenilin (PS) variant expression is correlated to early-onset familial Alzheimer’s [20]. So, IL-18 secreted during inflammasome influences neurogenesis not only by above mentioned inflammatory factors, but also via presenilin expression in adult SGZ.

Another interleukin that, unlike the expressed interleukins, has a protective effect against inflammation is IL-4. It inhibits inflammasome and reduces IL-6, IL1-β, and TNF-α [21]. In many studies, the effect of IL-4 on immunity has been shown. It is also prominent in the normal brain’s functions, involving learning, memory, and neurogenesis [22]. IL-4 increases neuronal and glial differentiation [14]. Changes in microglial status by IL-4 alter their phenotype to enhance neurogenesis [23, 24]. It can be said that IL-4 enhances neurogenesis via inhibiting inflammasomes, IL-1β, TNF-α, and IL-6 and therefore increases neurogenesis. IL-10 also inhibits NLRP3 inflammasome and increases neurogenesis through the inhibition of IL-1β production [25]. It elevates proliferation and decreases neuronal and glial differentiation [14]. According to the Gurung et al. study, IL-10 controls NLRP3 inflammasome activation negatively [26]. It inhibits the signaling of nuclear factor kappa B [NF-kB] during inflammasome [27]. It also prevents TNF-α generation of human monocytes [28]. In neurons, this interleukin receptor signaling is correlated with elevated cell survival [29] and the regulation of adult neurogenesis [30].

Another effective factor in the inflammasome pathway is TLRs. TLRs, as the main regulators of the innate immune system, are receptors that contributed to the inflammasome. The immune signal is activated through NF-κB to prime the NLRP3 inflammasome [31].

IFN-α and IFN-β are inflammasome products and control inflammasome activation [32].

Interferons α and β, in addition to being key players at the start of the inflammasome, are two of its ultimate products [33]. It has been assumed that IFN-α suppresses NSC proliferation directly and, as a result, reduces new neurons generation [34] and inhibits the proliferation of cells in adult rat’s SGZ [35]. Chronic peripheral IFN-α administration suppresses neurogenesis and induces depressive behavioral phenotypes [34]. The impact of IFN-β on neurogenesis depends on its concentration. Low IFN-β concentrations (1000 U/ml) contribute to the survival and proliferation of human NSC, while greater concentrations (more than 100,000 U/ml) reduce the survival and proliferation of human NSC [36]. Controlling IFN-α and IFN-β from various pathways, like inflammasome, can enhance neurogenesis. There are other factors that cause neurogenesis suppression by activating the inflammation. α-synuclein (α-syn) is a ubiquitous protein particularly observed in high amounts in the brain and is assumed to have the main role in the pathogenesis of Alzheimer’s and Parkinson’s disease and other neurodegenerative disorders [37]. In patients with dementia, levels of hippocampal α-syn have been reported to increase [38]. α-syn motivates IL1-β production in a process that is dependent on the NLRP3 inflammasome in monocytes [39]. A53T mutant α-syn inhibited proliferation and differentiation of adult NSC in SVZ through activation of NLRP3/caspase-1/IL1-β signalling axis. Extracellular α-syn may stimulate pathways of pro-inflammatory TLR4 in astrocytes [40]. TLR4 generates IL-1β by the activation of the inflammasome. IL-1β inhibits neurogenesis. A negative effect of α-syn has been detected on newly generated neurons, especially on their dendrite development and spine improvement [38]. Accumulation of α-syn may be involved in the neurodegenerative process via weakening neurogenesis and the existence of differentiating neural progeny [41]. It can be summarized that α-syn causes an inhibitory effect on neurogenesis via activation of the inflammasome. Studies have shown that some microRNA inhibit TLR3 and NLRP3 by hindering α-synuclein. MicroRNA7, microRNA223, and microRNA9 inhibit the activation of NLRP3 inflammasome in NSCs, resulting in increased neurogenesis [42 - 45]. miR-7

| Effect on Neurogenesis | Role in Inflammasome | Factor |
|------------------------|-----------------------|--------|
| Its role is dose-dependent | In the low dose, it inhibits the activation of NLRP1 inflammasome. Activates inflammasome at high doses | INF- β |
| Stimulates neurogenesis | Inhibits α-synuclein and inhibits NLRP3 inflammasome | miR-7 |
| Stimulates neurogenesis | Inhibits NLRP3 inflammasome | miR-9 |
| Stimulates neurogenesis | Inhibits NLRP3 inflammasome | miR-223 |
| Stimulates neurogenesis | Inhibits TXNIP that is one activator of NLRP3 inflammasome | Curcumin |
| Stimulates neurogenesis | Inhibits NLRP3 inflammasome | EGCG |
| Stimulates neurogenesis | Inhibits NLRP3 inflammasome | Quercetin |
| Stimulates neurogenesis | Inhibits NLRP3 inflammasome | Boswellia serrata |
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Goldman controlling SVZ neurogenesis was primarily observed by Brain-Derived Neurotrophic Factor [BDNF]. BDNF regulates significantly increased TLR-3, and TLR-4 protein expression decreases inflammatory cytokines, and suppresses NF-κB p65, in a dose-dependent manner. It decreases IL1-β and TNF-α in inflammatory illnesses. It decreases IL1-β and TNF-α in inflammatory illnesses. It decreases IL1-β and TNF-α in inflammatory illnesses.

It was shown that miR-223 reduced the NLRP3 activity [43, 44] and cell-autonomous suppression of miR-223 in the adult mice dentate gyrus NS/PCs caused a potential rise in immature neurons soma size, dendritic tree size, branch number per neuron, and complexity; however, neuronal migration in the dentate gyus was not affected [45]. miR-9 can also prevent the NLRP3 inflammasome activation [47] and control NS/PC proliferation [45]. Levels of miR-9 expression increase across the transition from neuronal precursors to neurons during the differentiation of embryonic stem cells [48]. miR-7, miR-9, and miR-223 may increase neurogenesis by suppression of inflammasome.

Some natural compounds have stimulant impacts on neurogenesis [49 - 51]. Curcumin [52], Epigallocatechin-3-gallate (EGCG), Boswellia serrate [53], and quercetin are examples of these natural compounds that enhance neurogenesis. Curcumin can decrease the release of IL1-β from microglia, inhibit microglial activation, decrease stroke injury, activate neurogenesis in the hippocampus, and trigger neuronal protective mechanisms like heat shock protein [HSP] elevation [54]. Studies reported that HSP90 inhibition influences the stability of free NLRP3 and pro-IL1-β proteins [55]. Epigallocatechin-3-gallate [EGCG] is the major antioxidant in green tea. EGCG, by activating SHH and suppressing NLRP3 and NF-κB, inhibits IL1-β, TNF-α, and caspase1 and stimulates neurogenesis [56]. Tozser et al. showed that EGCG promotes hippocampal adult neurogenesis [57]. Treatment of EGCG markedly increased BrdU-labeled cells in hippocampal cultures, neural progenitor cell (NPC), and in the adult mice’s dentate gyrus. Other findings showed that EGCG prompts neurogenesis via reduction of IL1-β and SHH pathway and, SHH ameliorates neurogenesis by the suppression of the inflammation pathway.

Boswellia serrate resin extract, which has 3-O-acetyl-11-keto-b-boswellic acid (AKBA), possesses anti-inflammatory features and has significant therapeutic properties to cure inflammatory illnesses. It decreases IL1-β and TNF-α in a dose-dependent manner [58]. It also controls inflammasome, decreases inflammatory cytokines, and suppresses NF-κB p65, TLR-3, and TLR-4 protein expression [59]. Boswellic acid inhibits TNF-α and IL1-β release in monocytes [60] and inhibits IL-1, IL-6, TNFα, and NF-κB [61]. Hippocampal neurogenesis after administration of Boswella extracts significantly increased [53]. Boswellia Serrata up-regulates Brain-Derived Neurotrophic Factor [BDNF]. BDNF regulates adult SVZ neurogenesis [61]. The role played by BDNF in controlling SVZ neurogenesis was primarily observed by Goldmann et al. in the 1990s. They reported that rat SVZ-derived neuroblasts treated with BDNF in vitro survived for a long time [62].

**CONCLUSION**

It is concluded that activation of the inflammasome in the brain can inhibit adult neurogenesis, and drugs or compounds that inhibit the inflammasome platform can improve the neurogenesis process in adults by different pathways.

**CONSENT FOR PUBLICATION**

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**CONFLICTS OF INTEREST**

The authors declare no conflict of interest, financial or otherwise.

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**REFERENCES**

[1] Braun SM, Jessberger S. Adult neurogenesis and its role in neuropsychiatric disease, brain repair and normal brain function. Neuropathol Appl Neurobiol 2014; 40(1): 3-12.
[2] McGeough MD, Pena CA, Mueller JL, et al. Cutting edge: IL-6 is a marker of inflammation with no direct role in inflammasome-mediated mouse models. J Immunol 2012; 189(6): 2707-11.
[3] Ming GL, Song H. Adult neurogenesis in the mammalian brain: significant answers and significant questions. Neuron 2011; 70(4): 687-702.
[4] Latz E, Xiao TS, Stutz A. Activation and regulation of the inflammasomes. Nat Rev Immunol 2013; 13(6): 397-411.
[5] Guo H, Callaway JB, Ting JP-Y. Inflammasomes: mechanism of action, role in disease, and therapeutics. Nat Med 2015; 21(7): 677-87.
[6] Okun E, Grifflen KJ, Mattson MP. Toll-like receptor signaling in neural plasticity and disease. Trends Neurosci 2011; 34(5): 269-81.
[7] Abbasi-Oshaghi E, Mirzaei F, Pourjafr M. NLRP3 inflammasome, oxidative stress, and apoptosis induced in the intestine and liver of rats treated with titanium dioxide nanoparticles: in vivo and in vitro study. Int J Nanomedicine 2019; 14: 1919-36.
[8] Zambetti LP, Mortellaro A. NLRPs, microbiota, and gut homeostasis: unravelling the connection. J Pathol 2014; 233(4): 321-30.
[9] Guo H, Callaway JB, Ting JP-Y. Inflammasomes: mechanism of action, role in disease, and therapeutics. Nat Med 2015; 21(7): 677-87.
[10] Grishman EK, White PC, Savani RC. Toll-like receptors, the NLRP3 inflammasome, and interleukin-1β in the development and progression of type 1 diabetes. Pediatr Res 2012; 71(6): 626-32.
[11] Dinarello CA. Biologic basis for interleukin-1 in disease. Blood 1996; 87(6): 2095-147.
[12] Crampton SJ, Collins LM, Toulouse A, Nolan YM, O’Keeffe GW. Exposure of foetal neural progenitor cells to IL-1β impairs their proliferation and alters their differentiation - a role for maternal inflammation? J Neurochem 2012; 120(6): 964-73.
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[28] Coutuinho-Silva R, Ojcius DM. Role of extracellular nucleotides in the immune response against intracellular bacteria and protozoan parasites. Microbes Infect 2012; 14(14): 1271-7.

[27] Masters SL, Gerlic M, Metcalf D, et al. NLRP1 inflammasome activation induces pyroptosis of hematopoietic progenitor cells. Immunity 2012; 37(6): 1069-72.

[26] Guarda G, Braun M, Staheli F, et al. Type I interferon inhibits interleukin-1 production and inflammasome activation. Immunity 2011; 34(2): 213-23.

[25] Deng LS, Itoshi S, Kaneko N, et al. Mechanisms for interferon-α-induced depression and neural stem cell dysfunction. Stem Cell Reports 2014; 3(1): 73-84.

[24] Netea MG, Kullberg BJ, Verschueren I, Van Der Meer JW. Interleukin-18 induces production of proinflammatory cytokines in mouse liver injury. J Immunol 2015; 194(12): 5715-25.

[23] Rannikko EH, Weber SS, Kahle PJ. Exogenous α-synuclein induces granulocyte infiltration and neuronal activation by inducing NLRP3 inflammasome to modulate neuroinflammation in the hippocampus of transgenic mice. J Neurosci 2008; 28(16): 4250-60.

[22] Carpentier PA, Palmer TD. Immune influence on adult neural stem cell proliferation. Brain Behav Immun 2011; 25(5): 850-62.

[21] Sutinen EM, Pirttilä T, Anderson G, Salminen A, Ojala JO. Pro-inflammation cytokines induce neurogenesis and oligodendrogenesis in adult hippocampal neurogenesis. Science 302(5651): 1760-5.

[20] Guarda G, Braun M, Staheli F, et al. Type I interferon inhibits interleukin-1 production and inflammasome activation. Immunity 2011; 34(2): 213-23.

[19] Lu M, Qiao C, Zhou Y, Ding JH, Hu G. MicroRNA-7 enhances hippocampal damage via inhibiting NLRP1 inflammasome activity through IL-10 mediated regulation of IL-1β expression and neurogenesis in mouse embryonic stem cells and in the hippocampus of transgenic mice. J Neurosci 2008; 28(16): 4250-60.

[18] Bueno R, Regensburg M, Schregelm S, et al. Role of α-synuclein in adult neurogenesis and neuronal maturation in the dentate gyrus. J Neurosci 2012; 32(47): 10966-16.

[17] Benseler T, Layer P, Schmitz A, et al. MicroRNA-7 targets Nod-like receptor protein 3 inflammasome to modulate neuroinflammation in the pathogenesis of Parkinson’s disease. Mol Neurodegener 2016; 11: 28.

[16] Zhu Y, Lu M, Du RH, et al. MicroRNA-7 targets Nod-like receptor protein 3 inflammasome to modulate neuroinflammation in the pathogenesis of Parkinson’s disease. Mol Neurodegener 2016; 11: 28.

[15] Badawy EA, Cha T, Kim K, et al. Amyloid production in human neuron-like cells. J Neuroinflammation 2007; 4: 19.

[14] Masters SL, Gerlic M, Metcalf D, et al. NLRP1 inflammasome activation induces pyroptosis of hematopoietic progenitor cells. Immunity 2012; 37(6): 1069-72.

[13] Ryan SM, O’Keeffe GW, O’Connor C, Keeshan K, Nolan YM. Neurogenesis in the adult hippocampus: A player in neuroprotection. Trends Neurosci 2005; 28(9): 487-93.

[12] Netea MG, Kullberg BJ, Verschueren I, Van Der Meer JW. Interleukin-18 induces production of proinflammatory cytokines in mouse: no immediate role for the cytokines of the tumor necrosis factor family and interleukin-1beta. Eur J Immunol 2000; 30(10): 3057-60.

[11] Du RH, Tan J, Yan N, et al. Kir.2 knockout aggravates lipopolysaccharide-induced mouse liver injury via enhancing NLRP3 inflammasome activation. J Gastroenterol Hepatol 2014; 29(4): 727-36.

[10] Patel PJ, Mandal SK, Figueroa JD, et al. Suppression of cell proliferation by interferon-α through alpha-interleukin-1 production in adult rat dentate gyrus. Neuropharmacology 2006; 51(12): 2619-26.

[9] Qazi O, Parthasarathy PT, Locke R, Kellipati N. Can microRNAs keep inflammasomes in check? Front Genet 2013; 4: 30.

[8] Dziennik S, Domady Z, Nir T, et al. Interleukin-18 increases the expression and neurogenesis in mouse embryonic stem cells and in the hippocampus of transgenic mice. J Neurosci 2008; 28(16): 4250-60.

[7] Zhu Y, Lu M, Du RH, et al. MicroRNA-7 targets Nod-like receptor protein 3 inflammasome to modulate neuroinflammation in the pathogenesis of Parkinson’s disease. Mol Neurodegener 2016; 11: 28.

[6] Masters SL, Gerlic M, Metcalf D, et al. NLRP1 inflammasome activation induces pyroptosis of hematopoietic progenitor cells. Immunity 2012; 37(6): 1069-72.

[5] Masters SL, Gerlic M, Metcalf D, et al. NLRP1 inflammasome activation induces pyroptosis of hematopoietic progenitor cells. Immunity 2012; 37(6): 1069-72.
Virgin coconut oil (VCO) by normalizing NLRP3 inflammasome showed potential neuroprotective effects in Amyloid-β induced toxicity and high-fat diet fed rat. Food Chem Toxicol 2018; 118: 68-83.

Mehdizadeh M, Hashem Dabaghian F, Shojaee A, et al. Protective effects of cyperus rotundus extract on amyloid β-peptide (1-40)-induced memory impairment in male rats: a behavioral study. Basic Clin Neurosci 2017; 8(3): 249-54.

Jalili C, Rodsari BA, Roshankhah S, et al. Effect of curcumin on hippocampus dentate gyrus injury induced by nicotine in rats. Journal of Hermed Pharmacology 2019; 8(4): 320-7.

Chen LC, Hu LH, Yin MC. Alleviative effects from boswellic acid on acetaminophen-induced hepatic injury - Corrected and republished from: Biomedicine (Taipei) 2017; 6(2): 9.

Siddiqui MZ. Boswellia serrata, a potential antiinflammatory agent: an overview. Indian J Pharm Sci 2011; 73(3): 255-61.

Kirschenbaum B, Goldman SA. Brain-derived neurotrophic factor promotes the survival of neurons arising from the adult rat forebrain subependymal zone. Proc Natl Acad Sci USA 1995; 92(1): 210-4.