International Journal of Advance Innovations, Thoughts & Ideas

Lingbin et al., Int J Adv Innovat Thoughts Ideas 2014, 3:1
DOI: 10.4172/2277-1891.1000155

Mini Review Open Access

Role of IL6 and TNFα in Hippocampal Neurogenesis of TAM Triple Knockout Mice

Lingbin Meng[1], **Xin Jiang**[2] **and Rui Ji**[3*]

[1]*Department of Anatomical Sciences and Neurobiology, University of Louisville School of Medicine, Louisville, KY4020, USA*

[2]*Department of Radiation Oncology, The First Hospital of Jilin University, Changchun, 130021, China*

[3]*Department of Biochemistry and Molecular biology, University of Louisville School of Medicine, Louisville, KY 40202, USA*

Received date: June 03, 2014; **Accepted date:** June 10, 2014; **Published date:** 19 June, 2014

[*]**Corresponding author:** Dr. Rui Ji, University of Louisville School of Medicine, 319 Abraham Flexner Way, Louisville, KY 40202, USA, E-mail: r0ji0001@louisville.edu

Abstract

IL6 and TNFα are two main proinflammatory factors in brain. Both of them are found to play an important role in neurogenesis. However, in a chronic inflammatory disease model, TAM triple knockout mice, severe loss of neurogenesis is observed and this reduction is found to be only relevant to IL6 instead of TNFα. This finding indicates IL6 could be a promising target for treatment of some neurodegenerative diseases which are accompanied with severe neuroinflammation.

Abbreviations

NSCs: Neural Stem Cells; DG: Dentate Gyrus; TAM: Tyro3, Axl, and Mertk, TKO: Triple Knockout; BrdU: 5-bromo-2'-deoxyuridine

Review

Neurogenesis is a process by which new neurons are produced from neural stem cells (NSCs) [1,2]. Initially, neurogenesis is considered to happen only during early postnatal development, but recently the adult brain has been demonstrated to also continuously generate new neurons mainly in two locations: the subventricular zone (SVZ) lining the lateral ventricles [3,4] and the subgranular zone (SGZ) of dentate gyrus in the hippocampal complex [5,6]. Neurogenesis consists of multiple differentiation stages and is regulated by sequential intrinsic gene regulation events [7], including Notch [8] and Wnts [9] signaling. Adult NSCs with differentiation potential provide a rich source for the replacement of cells lost during normal cell turnover and after brain injury [10-13]. Interruption of adult neurogenesis leads to impairment of hippocampus-dependent learning and behavior [10,12,14-19].

TAM receptors are tyrosine kinase receptors that play multiple functional roles, either providing intrinsic trophic support for cell growth or regulating the expression of pro-inflammatory cytokines [20]. Our lab firstly found mice lacking all the three receptors show a significant loss of hippocampal neurogenesis [21,22]. Since Inflammation has been recognized as a major negative impact on adult neurogenesis [23,24], we showed that hyperactive microglia in the Tyro3, Axl and Mertk triple knockout (TKO) mice produced increased level of pro-inflammatory cytokines that are detrimental to NSCs proliferation and differentiation [21]. Among these pro-inflammatory cytokines, IL6 and TNFα are previously thought to be two main factors responsible for brain inflammation and loss of neurogenesis. However, in our study, IL6 is found to be the main factor for impaired neurogenesis while TNFα is not. Medium from TKO microglia was cytotoxic to NSCs, decreasing their proliferation and differentiation into neurons but increasing apoptosis. But medium from TKO/IL6-/- microglia lost the cytotoxicity. More importantly, Axl and Mertk double knockout mice (DKO) also had a decreased neurogenesis and elimination of IL6 in DKO could largely restore neurogenesis [21,22]. All these results indicate IL6 is a major factor detrimental to adult hippocampal neurogenesis in TKO mice. Nevertheless, it is worth mentioning IL6 might protect neurogenesis under normal conditions since IL6 knockout mice have a decreased hippocampal neurogenesis [25]. A recent study even showed, activated microglia, which have been demonstrated to inhibit adult neurogenesis after radiation or LPS induced inflammation [26,27], could enhance neurogenesis in the early postnatal SVZ [28]. IL6 was indicated to play the protective role in the early neurogenesis of SVZ.

In addition to IL6, TNFα was examined to see whether it influences neurogenesis as well. According to our results, TNFα does not contribute to loss of neurogenesis in TKO mice since knocking out TNF-R1/2 did not rescue neurogenesis in DKO mice [21]. In fact, TNFα expression in dentate gyrus is much lower than IL6 [29] and therefore it might be less important than IL6 to neurogenesis. Besides, whether TNFα is detrimental to neurogenesis is still not determined. From some in-vtro experiments, TNFα was found to exert detrimental effects on NSCs differentiation into neurons and on neuronal survival and apoptosis [30,31]. However, it has also been proposed as a positive regulator of neurogenesis. In vitro treatment with TNFα improved proliferation of SVZ neurospheres, as shown by increased volume and BrdU incorporation [32]. Moreover, in-vivo experiments also give us a contradictory conclusion about TNfa's role in neurogenesis. Robert et. al. observed elevated new hippocampal neuron numbers in TNF-R1(-/-) and TNF-R1/R2(-/-) mice, whereas no significant changes were detected in TNF-R2(-/-) mice. Consistently, after status epilepticus (SE), the TNF-R1(-/-) and TNF-R1/R2(-/-) mice produced more new neurons. In contrast, the TNF-R2(-/-) mice showed reduced SE-induced neurogenesis [33]. Their data revealed different role of TNF-R1 and TNF-R2 signaling in adult hippocampal neurogenesis and identified TNF-R1 as a negative regulator of neural progenitor proliferation. However, Chen et. al. found loss of TNF-R1 has no protective effects on neurogenesis and loss of TNFR2 worsened the

effects of radiation injury on neurogenesis [**34**]. Therefore, it is still controversial whether TNFα improves or reduces adult neurogenesis.

In summary, IL6 might be the main factor microglia use to inhibit adult neurogenesis under condition of chronic inflammatory disease. As a result, IL6 could be a promising target for treatment of some neurodegenerative diseases which are accompanied with severe neuroinflammation.

References

1. Emsley JG, Mitchell BD, Kempermann G, Macklis JD (2005) Adult neurogenesis and repair of the adult CNS with neural progenitors, precursors, and stem cells. Prog Neurobiol 75: 321-341.
2. Gage FH (2000) Mammalian neural stem cells. Science 287: 1433-1438.
3. Reynolds BA, Weiss S (1992) Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. Science 255: 1707-1710.
4. Richards LJ, Kilpatrick TJ, Bartlett PF (1992) De novo generation of neuronal cells from the adult mouse brain. Proc Natl Acad Sci U S A 89: 8591-8595.
5. Gage FH, Coates PW, Palmer TD, Kuhn HG, Fisher LJ, et al. (1995) Survival and differentiation of adult neuronal progenitor cells transplanted to the adult brain. Proc Natl Acad Sci U S A 92: 11879-11883.
6. Palmer TD, Takahashi J, Gage FH (1997) The adult rat hippocampus contains primordial neural stem cells. Mol Cell Neurosci 8: 389-404.
7. Ming GL, Song H (2011) Adult neurogenesis in the mammalian brain: significant answers and significant questions. Neuron 70: 687-702.
8. Imayoshi I, Sakamoto M, Yamaguchi M, Mori K, Kageyama R (2010) Essential roles of Notch signaling in maintenance of neural stem cells in developing and adult brains. J Neurosci 30: 3489-3498.
9. Lie DC, Colamarino SA, Song HJ, Désiré L, Mira H, et al. (2005) Wnt signalling regulates adult hippocampal neurogenesis. Nature 437: 1370-1375.
10. Zhao C, Deng W, Gage FH (2008) Mechanisms and functional implications of adult neurogenesis. Cell 132: 645-660.
11. van Praag H, Schinder AF, Christie BR, Toni N, Palmer TD, et al. (2002) Functional neurogenesis in the adult hippocampus. Nature 415: 1030-1034.
12. Zhang CL, Zou Y, He W, Gage FH, Evans RM (2008) A role for adult TLX-positive neural stem cells in learning and behaviour. Nature 451: 1004-1007.
13. Deng W, Aimone JB, Gage FH (2010) New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? Nat Rev Neurosci 11: 339-350.
14. Monje ML, Mizumatsu S, Fike JR, Palmer TD (2002) Irradiation induces neural precursor-cell dysfunction. Nat Med 8: 955-962.
15. Madsen TM, Kristjansen PE, Bolwig TG, Wörtwein G (2003) Arrested neuronal proliferation and impaired hippocampal function following fractionated brain irradiation in the adult rat. Neuroscience 119: 635-642.
16. Shors TJ, Miesegaes G, Beylin A, Zhao M, Rydel T, et al. (2001) Neurogenesis in the adult is involved in the formation of trace memories. Nature 410: 372-376.
17. Dupret D, Revest JM, Koehl M, Ichas F, De Giorgi F, et al. (2008) Spatial relational memory requires hippocampal adult neurogenesis. PLoS One 3: e1959.
18. Balmer J, Ji R, Ray TA, Selber F, Gassmann M, et al. (2013) Presence of the Gpr179(nob5) allele in a C3H-derived transgenic mouse. Mol Vis 19: 2615-2625.
19. Yan XB, Wang SS, Hou HL, Ji R, Zhou JN (2007) Lithium improves the behavioral disorder in rats subjected to transient global cerebral ischemia. Behav Brain Res 177: 282-289.
20. Lemke G, Rothlin CV (2008) Immunobiology of the TAM receptors. Nat Rev Immunol 8: 327-336.
21. Ji R, Tian S, Lu HJ, Lu Q, Zheng Y, et al. (2013) TAM receptors affect adult brain neurogenesis by negative regulation of microglial cell activation. J Immunol 191: 6165-6177.
22. Ji R (2012) Tyro-3, Axl, and Mertk (TAM) Receptors Maintain Adult Hippocampal Neurogenesis: University of Louisville.
23. Monje ML, Toda H, Palmer TD (2003) Inflammatory blockade restores adult hippocampal neurogenesis. Science 302: 1760-1765.
24. Carpentier PA, Palmer TD (2009) Immune influence on adult neural stem cell regulation and function. Neuron 64: 79-92.
25. Bowen KK, Dempsey RJ, Vemuganti R (2011) Adult interleukin-6 knockout mice show compromised neurogenesis. Neuroreport 22: 126-130.
26. Monje ML, Toda H, Palmer TD (2003) Inflammatory blockade restores adult hippocampal neurogenesis. Science 302: 1760-1765.
27. Ekdahl CT, Claasen JH, Bonde S, Kokaia Z, Lindvall O (2003) Inflammation is detrimental for neurogenesis in adult brain. Proc Natl Acad Sci U S A 100: 13632-13637.
28. Shigemoto-Mogami Y, Hoshikawa K, Goldman JE, Sekino Y, Sato K (2014) Microglia enhance neurogenesis and oligodendrogenesis in the early postnatal subventricular zone. J Neurosci 34: 2231-2243.
29. Liebetanz D, Gerber J, Schiffner C, Schütze S, Klinker F, et al. (2012) Pre-infection physical exercise decreases mortality and stimulates neurogenesis in bacterial meningitis. J Neuroinflammation 9: 168.
30. Guadagno J, Xu X, Karajgikar M, Brown A, Cregan SP (2013) Microglia-derived TNFÎ± induces apoptosis in neural precursor cells via transcriptional activation of the Bcl-2 family member Puma. Cell Death Dis 4: e538.
31. Liu YP, Lin HI, Tzeng SF (2005) Tumor necrosis factor-alpha and interleukin-18 modulate neuronal cell fate in embryonic neural progenitor culture. Brain Res 1054: 152-158.
32. Widera D, Mikenberg I, Elvers M, Kaltschmidt C, Kaltschmidt B (2006) Tumor necrosis factor alpha triggers proliferation of adult neural stem cells via IKK/NF-kappaB signaling. BMC Neurosci 7: 64.
33. Iosif RE, Ekdahl CT, Ahlenius H, Pronk CJ, Bonde S, et al. (2006) Tumor necrosis factor receptor 1 is a negative regulator of progenitor proliferation in adult hippocampal neurogenesis. J Neurosci 26: 9703-9712.
34. Chen Z, Palmer TD (2013) Differential roles of TNFR1 and TNFR2 signaling in adult hippocampal neurogenesis. Brain Behav Immun 30: 45-53.