

Role of IL6 and TNF α in Hippocampal Neurogenesis of TAM Triple Knockout Mice

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Abstract

IL6 and TNF α 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 TNF α . 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 TNF α 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 TNF α 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, TNF α was examined to see whether it influences neurogenesis as well. According to our results, TNF α 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, TNF α expression in dentate gyrus is much lower than IL6 [29] and therefore it might be less important than IL6 to neurogenesis. Besides, whether TNF α is detrimental to neurogenesis is still not determined. From some in-vitro experiments, TNF α 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 TNF α 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 TNF α '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 TNF α 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.

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