Neurosci. Bull. August, 2019, 35(4):771–774
https://doi.org/10.1007/s12264-018-00335-8

www.neurosci.cn
www.springer.com/12264

RESEARCH HIGHLIGHT

Toll of Mental Disorders: TLR-Mediated Function of the Innate Immune System

Jian-Feng Liu[1] · Ruyan Wu[1,2] · Jun-Xu Li[1]

Received: 5 October 2018 / Accepted: 28 November 2018 / Published online: 10 January 2019

Mental disorder is defined as a syndrome characterized by clinically significant disturbance in an individual's cognition, emotion, or behavior that reflects a dysfunction in the psychological, biological, or developmental processes underlying mental functioning (DSM-V). The economic cost of mental disorders is increasing along with the increased prevalence of mental disorders worldwide. According to the 2016 National Survey on Drug Use and Health, nearly 18.5% of adults are experiencing mental disorders in the United States (http://www.nimh.nih.gov/health/statistics/prevalence/any-mental-illness-ami-among-adults.shtml). However, our poor understanding of the complicated pathology of mental disorders is an obstacle to the development of effective treatments.

Traditional opinions on the pathology of most mental disorders focus on disturbances of specific neurotransmitters [1]. For example, major depression, the most common mental disorder, is linked with abnormal regulation of endogenous serotonin and/or norepinephrine [2]. Most antidepressants have been designed to increase the level of serotonin and/or norepinephrine in the synaptic cleft by inhibiting their transporters in the presynaptic membrane. Although current antidepressants are effective for the first episode of depression, they have major limitations such as slow onset of action, serious side-effects, and loss of efficacy after relapse. Scientists have devoted much effort to uncover novel underpinnings of mental disorders, and it is now clear that several systems and factors beyond neurotransmitters are involved. For example, genetic variation, transcriptional regulation, and the immune system have been demonstrated to participate in the development of mental disorders [2, 3].

Glia *versus* Neurons

The vast majority of studies on mental disorders have focused on deciphering the functional and structural abnormalities of neurons in the brain. It is believed that the maladaptive synaptic plasticity of neurons induced by environmental stress is a critical trigger, if not a cause, of mental disorders such as depression and anxiety [1]. However, the central nervous system (CNS) is not only made of neurons; glial cells make up a large part, and their functions are relatively poorly understood. It has been demonstrated that glial cells (microglia, astrocytes, and oligodendrocytes) are the predominant immune-like cells in the brain and a major component of the CNS. A great number of studies have revealed that the immune system plays a crucial role in modulating the maladaptive synaptic plasticity induced by environmental stress and mental disorders [4]. For example, activation of the peripheral immune system, which produces pro-inflammatory cytokines such as interleukin-1α and β (IL-1α and IL-1β), tumor necrosis factor-α (TNF-α) and IL-6, induces sickness and leads to the symptoms of depression [4]. Recent studies have revealed that glia in the CNS are substantially important in regulating fundamental functions of the brain and participating in general behaviors and brain disorders. However, due to the historically paradoxical assumption

✉ Jian-Feng Liu
jliu66@buffalo.edu

✉ Jun-Xu Li
junxuli@buffalo.edu

[1] Department of Pharmacology and Toxicology, University at Buffalo, Buffalo, NY 14214, USA

[2] School of Medicine, Yangzhou University, Yangzhou 225000, China

that glial cells only function to support and coordinate the growth and the arrangement of neurons in the brain, the roles and functions of glial cells have been ignored for decades and remain largely unknown.

Glial Toll-Like Receptors (TLRs) are Promising Pharmaceutical Targets for Mental Disorders

A recent study by Nie *et al.* [5], showed that a mediator of the innate immune system in the brain contributes to the maladaptive behavioral changes and alterations of synaptic plasticity induced by repeated environmental stress (Fig. 1). The innate immune system, which is the phylogenetically oldest immune system, refers to the first-line barrier to prevent microbial invasion. The TLRs 1–10 are one of the most important mediators of the innate immune system [6]. In this study, Nie *et al.* investigated the role of TLR2 and TLR4 in repeated stress-induced social avoidance.

By using repeated social defeat stress (R-SDS), a clinical model of depression and anxiety, they showed that genetic deletion of TLR2 and TLR4 (TLR2/4) in combination prevented stress-induced social avoidance and anxiety-like behavior [5]. Interestingly, both the TLR2-knockout (KO) mice and TLR4-KO mice, but not the TLR2/4-KO mice, were susceptible to R-SDS-induced social avoidance, indicating that dual deficiency of TLR2/4 is necessary and sufficient to prevent environmental stress-induced behavioral plasticity. TLR2/4 is predominantly expressed in the microglia. They further showed that R-SDS activates microglia in the medial prefrontal cortex (mPFC), a brain region that is involved in repeated environmental stress-induced behavioral alterations [5]. Pro-inflammatory factors such as CD68, Iba-1 (a marker of microglial activation), and CD11b in the mPFC of wild-type animals are upregulated by R-SDS. However, these inflammatory changes do not occur in the TLR2/4 dual-KO animals. To specifically determine whether the effects of TLR2/4 modulation are localized to the microglia, the authors used the "virus-mediated cell-type specific expression of genes" strategy. They microinjected into the mFPC a lentivirus that expressed TLR2/4 microRNA in the microglia and specifically knocked down the expression of TLR2/4. The lentivirus-treated animals were resistant to R-SDS-induced social avoidance [5], indicating that the TLR2/4 in the microglia mediates, at least in part the R-SDS-induced behavioral changes.

As noted above, because only neurons are capable of producing action potentials, the neuronal activity in the brain may be the most important indicator of signal transfer. Thus, whether activation of the immune system is able to affect the activities of neurons remained unclear. Nie *et al.* used the immunofluorescent staining method to analyze the level of c-Fos protein, which is an indicator of neuronal activation. They showed that in TLR2/4-deficient mice, R-SDS attenuated single-SDS-induced neural activation at a level similar to resilient wild-type mice [5].

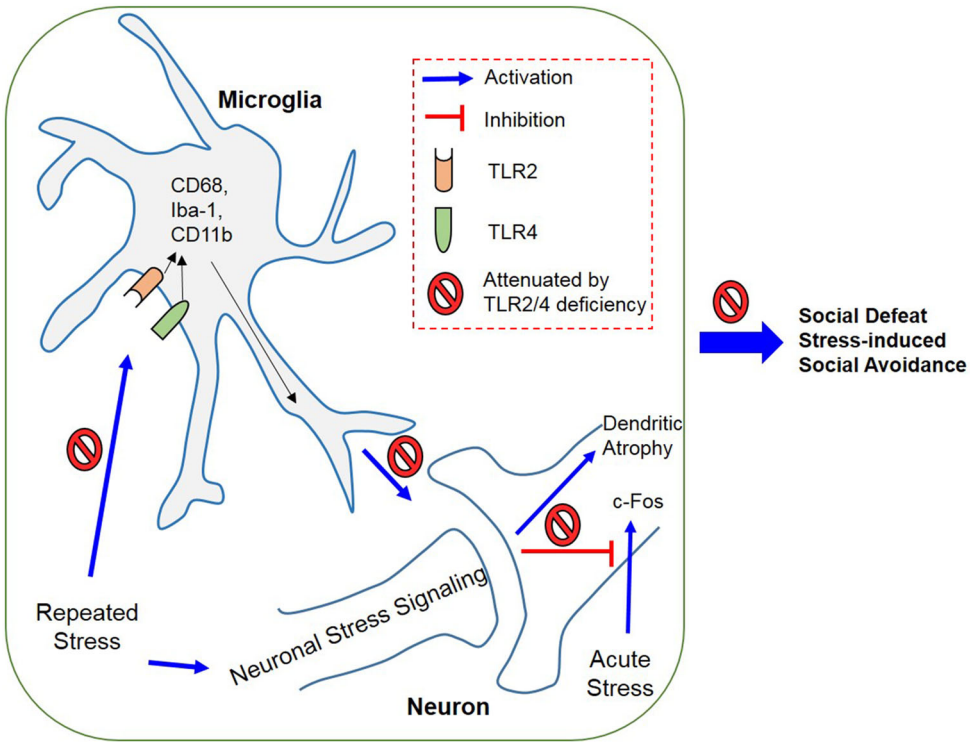

Fig. 1 Graphic summary of the role of TRL2/4 in social avoidance induced by repeated social defeat stress (R-SDS)-induced social avoidance. In the medial prefrontal cortex of TLR2/4-deficient animals, repeated R-SDS-induced accumulation of pro-inflammatory factors was reduced; R-SDS-induced dendritic atrophy of neurons was attenuated; and the inhibitory effect of R-SDS on the single-SDS-induced c-Fos expression was attenuated.

Previous study has also demonstrated that R-SDS induces morphological changes of neurons in the mPFC. For example, repeated stress shortens dendritic length and decreases spine density in the mPFC. These morphological changes induced by stress are believed to influence the connectivity of neurons and the fundamental functions of the PFC such as executive function, and eventually regulate the performance of PFC-mediated tasks. Nie *et al.* showed that the dendritic length of mPFC neurons in TLR2/4 dual-KO mice remains normal after R-SDS [5]. Furthermore, using a transcriptome analysis, they showed that dual-KO of TLR2/4 abolishes R-SDS-induced upregulation of IL-1α and TNF-α in microglia in the mPFC and nucleus accumbens. In addition, they confirmed that IL-1α and TNF-α in the mPFC mediate R-SDS-induced social avoidance [5]. Taken together, they concluded that the innate immune receptors TLR2/4 in the mPFC mediate R-SDS-induced microglial activation and social avoidance. The study was the first to elucidate the mechanism of action of the prefrontal innate immune system in maladaptive behaviors induced by repeated stress. Social defeat stress is widely used as an animal model of depression, so this study sheds light on our understanding of the etiology of depression and stress-related disorders. It should be noted that TLR2/4 in prefrontal microglia may not contribute to SDS-induced anxiety-like behaviors, since systemic but not prefrontal microglial TLR2/4 deficiency attenuates R-SDS-induced anxiety-like behaviors. Future studies are required to identify the brain regions where TLR2/4 participates in anxiety-like behaviors.

Many studies have shown that TLRs also mediate other mental disorders, such as drug addiction [7, 8]. In general, inhibition of TLR4 reduces the dopamine transmission and maladaptive behaviors induced by several abused drugs [7]. Intriguingly, it has been demonstrated that opioids are agonists of TLR4 and the rewarding and reinforcing effects of opioids require the activation of TLR4 [9]. The obstacle to addiction treatment is that patients relapse at a high rate after a period of drug abstinence. Among the triggers of relapse, stress is one of the most important factors. The involvement of TLR2/4 in R-SDS-related behaviors suggests that TLR2/4 may mediate stress-induced drug relapse. Furthermore, TLR2/4 may be an effective target for the treatment of comorbid addiction and depression. However, it should be kept in mind that currently there is no clinical evidence that interfering with the innate immune system is able to control drug addiction and prevent relapse. In addition, modulation of the innate immune system is not effective in regulating drug addiction under some conditions [8]. Therefore, the therapeutic effects may depend on the type of drug, the behavioral assay, and the experimental conditions.

It should be kept in mind that the function of the innate immune system can be sex-dependent [10], and this may affect its role in mental disorders. TLR4 has been demonstrated to play a critical role in regulating pain [11], and further evidence has shown that this is dependent on sex [12]. For example, TLR4 signaling in the periaqueductal gray participates in the sex deference in pain and the antinociceptive effects of morphine, while spinal TLR4 participates in inflammatory and neuropathic pain in male but not female animals [12]. Is sex difference a critical factor that determines the potential therapeutic effects of TLR4 modulators on mental disorders? It seems that the role of TLR4 in mental disorders is not dependent on sex. A study showed that genetic deletion of TLR4 prevents the deleterious effects of ethanol on the brain in both male and female animals [13]. Recently, it was demonstrated that TLR4 regulates anxiety-like behavior similarly in males and females [14]. However, sex difference in the function of TLRs in mental disorders remains largely unknown. Emerging studies are needed to clarify the differences among TLRs in regulating mental disorders in different genders.

Conclusions

The innate immune system plays a crucial role in modulating mental disorders. TLRs may be predominant mediators of this system by regulating the activation of microglia, inflammatory responses, the function of the brain, and consequently the maladaptive synaptic and behavioral changes. TLRs are promising pharmaceutical targets for the treatment of mental disorders. More studies are needed to decipher the detailed mechanisms by which TLRs mediate the innate immune system in mental disorders as well as developing novel compounds that specifically modulate the activity of TLRs.

Acknowledgements This work was supported by the National Institutes of Health National Institute on Drug Abuse (R21DA040777). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflict of interest The authors declare no conflict of interest.

References

1. Sachar EJ, Baron M. The biology of affective disorders. Annu Rev Neurosci 1979, 2: 505–517.
2. Berton O, Nestler EJ. New approaches to antidepressant drug discovery: beyond monoamines. Nat Rev Neurosci 2006, 7: 137–151.

3. Hutchinson MR. 'Convergence' created psychoneuroimmunology, and is needed again to secure the future of the field. Brain Behav Immun 2018, 71: 1–2.
4. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 2008, 9: 46–56.
5. Nie X, Kitaoka S, Tanaka K, Segi-Nishida E, Imoto Y, Ogawa A, *et al.* The innate immune receptors TLR2/4 mediate repeated social defeat stress-induced social avoidance through prefrontal microglial activation. Neuron 2018, 99: 464–479 e7.
6. Bachtell R, Hutchinson MR, Wang X, Rice KC, Maier SF, Watkins LR. Targeting the Toll of drug abuse: the translational potential of Toll-like receptor 4. CNS Neurol Disord Drug Targets 2015, 14: 692–699.
7. Kashima DT, Grueter BA. Toll-like receptor 4 deficiency alters nucleus accumbens synaptic physiology and drug reward behavior. Proc Natl Acad Sci U S A 2017, 114: 8865–8870.
8. Theberge FR, Li X, Kambhampati S, Pickens CL, St Laurent R, Bossert JM, *et al.* Effect of chronic delivery of the Toll-like receptor 4 antagonist (+)-naltrexone on incubation of heroin craving. Biol Psychiatry 2013, 73: 729–737.
9. Hutchinson MR, Zhang Y, Shridhar M, Evans JH, Buchanan MM, Zhao TX, *et al.* Evidence that opioids may have toll-like receptor 4 and MD-2 effects. Brain Behav Immun 2010, 24: 83–95.
10. Sorge RE, Mapplebeck JC, Rosen S, Beggs S, Taves S, Alexander JK, *et al.* Different immune cells mediate mechanical pain hypersensitivity in male and female mice. Nat Neurosci 2015, 18: 1081–1083.
11. Liu T, Gao YJ, Ji RR. Emerging role of Toll-like receptors in the control of pain and itch. Neurosci Bull 2012, 28: 131–144.
12. Doyle HH, Murphy AZ. Sex differences in innate immunity and its impact on opioid pharmacology. J Neurosci Res 2017, 95: 487–499.
13. Alfonso-Loeches S, Pascual M, Guerri C. Gender differences in alcohol-induced neurotoxicity and brain damage. Toxicology 2013, 311: 27–34.
14. Femenia T, Qian Y, Arentsen T, Forssberg H, Diaz Heijtz R. Toll-like receptor-4 regulates anxiety-like behavior and DARPP-32 phosphorylation. Brain Behav Immun 2018, 69: 273–282.