RESEARCH HIGHLIGHT

AHI1: linking depression and impaired antiviral immune response

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Cell Research (2022) 32:869–870; https://doi.org/10.1038/s41422-022-00702-1

***AHI1* is a neurodevelopmental gene, and its expression deficiency was found to correlate with altered stress responses and depressive behaviors in mice. In a recent paper of *Cell Research*, Zhang et al. show that AHI1 reduction is also associated with attenuated antiviral innate immunity, providing an important linker between depression and reduced antiviral immune response**.

The Abelson helper integration site 1 (*AHI1*) gene encodes a multifaceted protein that contains 7 WD40 repeats, an SH3 domain and numerous SH3-binding sites, and is involved in brain development. Nonsense or frameshift mutations in *AHI1* lead to Joubert syndrome, a recessive neurodevelopmental disorder characterized by multi-system abnormalities including motor deficits, cognitive impairment, low muscle tone, and abnormal eye movements.[1] Genetic studies revealed that *AHI1* is also a susceptibility gene for schizophrenia[2] and autism,[3] two important neuropsychiatric disorders associated with abnormal early brain development and depressive behaviors. The potential role of AHI1 in depression was further supported by the findings that Ahi1-deficient mice display depressive phenotypes[4] and resilience to stress.[5] Consistently, Ahi1 was found to participate in maintaining the level of tyrosine kinase receptor B (TrkB) in the mouse brain[4] which is critical for neuronal differentiation and brain development. However, since AHI1's expression is widespread in the brain and peripheral tissues, whether AHI1 in non-neuronal cells also plays a role in depression-associated phenotypes remains elusive.

It has been known that patients with depression have a higher risk of viral infection and that viral infection can promote the development of depression.[6,7] However, the mechanism by which depression affects antiviral innate immunity remains largely unexplored. Zhang and colleagues now provided exciting findings that AHI1 may be an important linker between depression and attenuated antiviral immunity.[8] Several lines of evidence in their study support this novel idea. The authors first found that the levels of *AHI1* mRNA were obviously reduced in the peripheral blood mononuclear cells (PBMCs) of unmedicated patients with major depressive disorder (MDD) and depressive mice. They further showed that both AHI1-deficient cells and Ahi1-knockout mice had a more severe viral infection and reduced antiviral ability. Since the loss of Ahi1 did not affect the numbers of peripheral monocytes/macrophages in mice, the authors investigated whether the reduced level of Ahi1 affected type 1 interferons (IFNs) and their signaling, as IFNs activate intracellular antimicrobial programs and play crucial roles in influencing the development of innate and adaptive immune responses.[9]

Zhang and colleagues revealed that AHI1 deficiency in primary macrophages could inhibit IFNs-induced signaling (expression of ISGs) and antiviral activity. Peripheral macrophages from MDD patients showed significantly reduced AHI1 expression, lower ISG levels, and decreased antiviral ability compared to those from healthy controls.[8] In line with this, Ahi1-knockout mice also showed much lower basal ISGs in the peripheral tissues, suggesting that AHI1 is essential for maintaining basal IFN-1 signaling such that loss of AHI1 attenuates IFN-1-mediated antiviral immunity. IFN-1 signaling activation was critically mediated by Tyk2, whose stability was regulated by the deubiquitinase OTUD1. Mechanistic studies further revealed that AHI1 interacted with OUTD1 to regulate Tyk2 ubiquitination and stability and that the loss of AHI1 led to the reduced level of Tyk2, resulting in diminished IFN-1 signaling and antiviral response.[8]

Although these findings indicate that AHI1 expression deficiency occurs in depression and can attenuate antiviral immune response via inhibiting IFN-1 signaling in the immune system, they also raised a question of how depression can reduce AHI1 in the peripheral tissues. To address this question, the authors examined several hormones, including arginine vasopressin (AVP), in serum, which are secreted from the hypothalamic-pituitary-adrenal system under stress and depressive conditions. They found that AVP could decrease Ahi1 mRNA level in macrophages and PBMCs in mice. Consistently, AVP administration into mice reduced Tyk2 expression, inhibited IFN-1 signaling, and attenuated antiviral activity. To strengthen the idea that AHI1 expression level is key to antiviral immune response, the authors screened available clinical drugs and found that meptazinol, an opioid analgesic, could promote *AHI1* mRNA expression. Subsequent investigation also showed that meptazinol treatment increased Tyk2 protein levels and improved the IFN-1 antiviral activity in primary macrophages from MDD patients and a depressive mouse model.[8] These findings led to a proposed mechanism underlying the association of depression with an attenuated immune response via AHI1 (Fig. 1).

Active research has been focused on how the pathophysiology of depression influences immune inflammatory responses, but the previous studies of MDD patients could be confounded by different disease stages and treatment situations. The current

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Published online: 20 July 2022

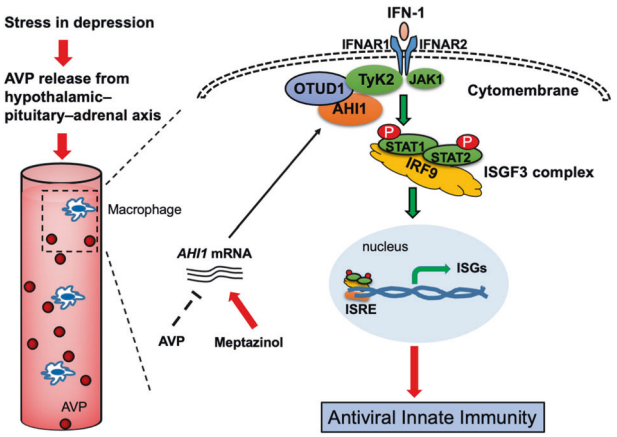

Fig. 1 The proposed model for AHI1 as an important linker between depression and antiviral immune dysfunction. The depression-mediated elevation of AVP in the blood reduces AHI1 expression in macrophages and peripheral tissues and results in the disruption of the interaction of the AHI1/OTUD1/Tyk2 complex, which can lead to the degradation of Tyk2 and the attenuation of IFN-1-mediated signaling for antiviral immune activity. Meptazinol can increase AHI1 mRNA expression to enhance antiviral immune activity.

study by Zhang et al. used the peripheral macrophages from unmedicated MDD patients to provide compelling evidence for the association between reduced AHI1 expression and attenuated antiviral immune activity. The regulation of Tyk2/IFN-1 complex stability by AHI1–OTUD1 interaction in the peripheral tissues is analogous to stabilization of TrkB and glucocorticoid receptor by Ahi1 in the mouse brain.[4,10] In view of the widespread distribution of AHI1, it will be fascinating to see whether AHI1 interacts with cell type-specific proteins to confer divergent functions in different cell types or organisms. The findings of Zhang and colleagues also raised additional issues for further investigation. It remains unknown how AVP can downregulate AHI1 expression in macrophages. Does this regulation also occur in neuronal cells to contribute to the decreased level of AHI1 in depressive mouse models? It is exciting to see that meptazinol can improve antiviral immune activity, but it remains open whether meptazinol can alleviate depressive behaviors of Ahi1-deficient mice. While the work of Zhang and colleagues has presented an additional layer of complexity in the regulation of depression and antiviral activity, their findings provided a strong motivation for further investigation of AHI1 as a therapeutic target for depression-associated antiviral immune dysfunction.

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ADDITIONAL INFORMATION

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