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The Role of DKK-1 in HIV-Associated Neurocognitive Disorder: A Clinically Relevant Therapeutic Target

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ABSTRACT

Introduction: HIV-Associated Neurocognitive Disorder (HAND) remains a prevalent and debilitating complication in people living with HIV, even in the era of effective antiretroviral therapy. The condition not only compromises cognitive function but also significantly impairs quality of life, daily functioning, and treatment adherence. Increasing evidence implicates chronic neuroinflammation, neuronal injury, and dysregulation of signaling pathways including the Wnt/β-catenin pathway in HAND pathogenesis. ***Objection:*** This review explores the role of Dickkopf-related protein 1 (DKK-1), a potent endogenous inhibitor of the Wnt signaling pathway, in the context of HAND. DKK-1 has emerged as a critical modulator of neuroinflammatory processes and synaptic integrity. ***Discussion:*** Elevated DKK-1 expression has been associated with neuronal apoptosis, synaptic loss, and blood-brain barrier dysfunction hallmarks of HAND. The interplay between HIV proteins (e.g., gp120, Tat), host immune activation, and DKK-1 signaling may exacerbate neuronal damage. Importantly, preclinical studies suggest that inhibition of DKK-1 can restore neuroplasticity and reduce inflammation, offering a promising therapeutic strategy. ***Conclusion:*** DKK-1 contributes to HAND development by antagonizing the Wnt signaling pathway, leading to synaptic dysfunction and neuronal apoptosis. Modulation of DKK-1 and restoration of Wnt signaling represents a promising therapeutic approach for mitigating HIV-associated neurodegeneration. Nevertheless, further research is essential to clarify the precise molecular mechanisms by which DKK-1 contributes to HAND.

Keywords: HIV-Associated Neurocognitive Disorder (HAND); Dickkopf-1 (DKK-1); Wnt/β-catenin signaling; Cognitive impairment; Therapeutic target.

INTRODUCTION

Human immunodeficiency virus (HIV) infection is a major global health problem, not only because of its systemic effects but also because of its long-term impact on the central nervous system (CNS). Although often unrecognized leading to delayed diagnosis, HIV-associated neurocognitive disorder (HAND) is one of the most devastating complications of chronic HIV infection. HAND is a cognitive impairment caused by HIV infection, clinically ranging from mild asymptomatic deficits to severe dementia-like deficits that significantly impact the patient's quality of life, especially in daily functioning and also adherence to antiretroviral therapy.[1,2,3,4]

Due to significant advances in antiretroviral therapy (ART), the life expectancy of individuals living with HIV has increased substantially.[5] Despite the efficacy of combined antiretroviral therapy, approximately 50% of individuals infected with HIV are estimated to experience varying degrees of HAND. Based on these facts, it is suggested that HAND is not solely the result of active viral replication, but involves a more complex multifactorial pathophysiological mechanism.[2,6]

The suspected underlying mechanisms as the main contributors are chronic neuroinflammation and progressive neurodegeneration.[7] Recent studies have suggested molecular pathways that may be involved in these mechanisms, one of which involves the related protein Dickkopf-1 (DKK-1), DKK-1 is a secreted glycoprotein that functions as an endogenous antagonist of the Wnt signaling pathway.[8] Wnt signaling is critical for maintaining synaptic plasticity and neuronal survival[9], DKK-1 has been shown to disrupt this process, subsequently resulting in neuronal apoptosis and synaptic loss, both of which are hallmarks in neurodegenerative conditions. High levels of DKK-1 have been reported also in other neurodegenerative diseases, such as Alzheimer's disease.[10] Raising questions about its role in HAND neuropathogenesis.[11]

Understanding the involvement of DKK-1 in HAND is important to advance knowledge of the molecular mechanisms driving HIV-related cognitive decline, and hopefully to drive the development of therapeutic interventions. In this study, we aimed to explore the relationship between DKK-1 and HAND and its potential as a therapeutic target in HAND.

Role of Dickkopf-related protein 1 (DKK-1) in Central Nervous System

DKK-1 is known to play a role in neuroinflammation, neurodegeneration, and synaptic integrity through its inhibitory effects on Wnt signaling.[11,12] In the process of maintaining neuronal homeostasis, synaptic plasticity, and neurogenesis, the function of the Wnt signaling pathway has been shown to be important. DKK-1 acts as an antagonist of the Wnt signaling pathway by binding to LRP5/6 which is a Wnt protein coreceptor. This interaction prevents Wnt from activating its downstream signaling cascade and causes β-catenin instability and suppression of Wnt target genes.[11] It has been shown previously that dysregulation of Wnt signaling has been associated with various neurodegenerative conditions or disorders where increased levels of DKK-1 contribute to synaptic loss and neuronal apoptosis. [13,14]

Neuroinflammation is a characteristic feature of HAND, increased levels of DKK-1 in response to increased release of pro-inflammatory cytokines such as TNF-α and IL-1β in the CNS of individuals with HIV infection.[12] Elevated DKK-1 will exacerbate neuroinflammation through increasing microglia activation and the release of additional pro-inflammatory mediators, this condition causes neuronal damage and further compromises the integrity of the central nervous system.[15] Studies have shown that DKK-1 expression is significantly increased in the brains of HIV-infected individuals, especially in areas associated with cognitive function. This suggests a direct role for DKK-1 in HIV-induced neuropathology.[14] HIV proteins such as gp120 and Tat are able to increase the expression of DKK-1 in neurons and glial cells. DKK-1 then inhibits activation of the Wnt pathway by binding to LRP5/6 receptors, causing synaptic dysfunction and neuronal apoptosis. A study by Avdoshina et al. (2016) showed that the increase in DKK-1 induced by gp120 exacerbates neuronal damage through this pathway. In addition, high levels of DKK-1 were found in the brain tissue of HIV patients with cognitive impairment, strengthening the hypothesis that DKK-1 plays a role in the pathogenesis of HAND.[16,17]

Synaptic damage is a major characteristic of HAND and other neurodegenerative disorders. DKK-1 causes synaptic loss by inhibiting Wnt signaling, which is essential for maintaining synaptic structure and function. DKK-1 interferes with the process of synaptogenesis by inhibiting Wnt signaling and causes synaptic degeneration and impaired neuronal communication, Wnt signaling promotes synapse formation and stabilization through the regulation of synaptic proteins such as PSD-95 and synaptophysin.[18] In HIV infection, upregulation of DKK-1 in response to viral proteins (e.g., Tat and gp120) further exacerbates synaptic damage, contributing to the cognitive and motor impairments seen in HAND.[12] In Alzheimer's Disease (AD), increased DKK-1 levels are associated with increased amyloid-β production and hyperphosphorylation of tau, both of which contribute to neuronal death.[11] Similarly in HAND, inhibition of Wnt signaling mediated by DKK-1 is thought to lead to neuronal apoptosis and loss of important neuronal populations, especially in the prefrontal cortex and hippocampus which are important regions for memory and executive function.[19]

Role of DKK-1 in HIV infection

HIV infection induces extensive immunological activation and neuroinflammation, even in individuals undergoing antiretroviral therapy, hence facilitating the onset of HIV-associated neurocognitive disorder (HAND).[2,20] The disruption of essential neuronal signaling pathways, particularly the canonical Wnt/β-catenin pathway, constitutes a crucial mechanism, as this route is vital for preserving neuronal integrity, synaptic plasticity, and blood-brain barrier (BBB) function.[21] DKK-1 is a glycoprotein that is secreted and is a well-characterized antagonist of the Wnt/β-catenin signaling pathway. DKK-1 functions by binding to the cell surface co-receptor LRP5/6, thereby obstructing Wnt ligands from interacting with the Frizzled receptor complex.[8,22] The dissociation of Wnt from the Frizzled receptor complex results in β-catenin degradation via the GSK3β–Axin–APC destruction complex, hence diminishing the transcription of Wnt target genes linked to neuroprotection and synaptic maintenance. HIV infection induces the production of DKK-1 in neurons and glial cells through viral proteins such as gp120 and Tat, resulting in synaptic degradation and neuronal apoptosis.[23,24] Gp120 can particularly activate oxidative stress pathways and proinflammatory cytokine cascades, resulting in increased DKK-1 synthesis, inhibition of the Wnt pathway, and subsequent degradation of β-catenin.[25,26] Gp120 triggers a cascade leading to calcium influx and oxidative stress, which activates transcription factors such as NF-κB and promotes the transcription of DKK-1 via its interaction with chemokine receptors including CXCR4 and CCR5.[23]

The viral protein Tat directly enhances DKK-1 expression by activating the mitogen-activated protein kinase (MAPK) pathway.[24] Inhibiting Wnt/β-catenin signaling, which supports synaptic disassembly, dendritic spine loss, and neuronal apoptosis features commonly observed in HAND the previously stated processes raise DKK-1 levels in the central nervous system (CNS)[17]. The synaptic damage is intensified by DKK-1-mediated activation of glycogen synthase kinase-3β (GSK3β), which degrades β-catenin and phosphorylates tau protein, possibly connecting HAND to the tauopathy observed in Alzheimer's disease.[14,27] Furthermore, it is established that Wnt signaling is crucial for preserving the integrity of the blood-brain barrier, and the inhibition of this pathway by DKK-1 leads to the disruption of endothelial junctions, thereby promoting the infiltration of peripheral immune cells into the central nervous system and exacerbating neuroinflammatory responses.[28,29] The activation of microglia and astrocytes enhances the synthesis of pro-inflammatory cytokines, including IL-1β and TNF-α, which collaborate with viral proteins to sustain DKK-1 expression in a detrimental cycle.[30,31]

The findings indicate that HIV-induced overexpression of DKK-1 represents a pathway in the molecular cascade resulting in neuronal dysfunction, blood-brain barrier breakdown, and chronic inflammation in HAND. Consequently, DKK-1 serves as both a biomarker for disease progression and a potential treatment target for neuroprotective strategies in patients infected with HIV.[32]

Role of DKK-1 in HIV-associated Neurocognitive Disorder

Wnt/β-catenin pathway plays a key role in axonal remodeling and the regulation of synaptic connectivity in the central nervous system (CNS), and inhibition of the Wnt/β-catenin signaling cascade by DKK-1 causes impairment of synaptic transmission, neuronal survival, and plasticity. Inhibition of Wnt signaling due to increased DKK-1 levels leads to impaired neuronal synapses that are essential for cognitive functions such as memory and attention. On the range of cognitive deficits that are reported in HIV-Associated Neurocognitive Disorder (HAND), there is a possibility that disruption of synaptic connections is a contributing factor.[33,34]

In the central nervous system (CNS), the Wnt/β-catenin signaling pathway is essential for the regulation of synaptic plasticity, neuronal survival, and neurogenesis.[21] The negative regulation of this pathway is primarily influenced by DKK-1, a secreted glycoprotein that binds to the LRP5/6 co-receptors, thereby preventing Wnt ligands from activating the Frizzled receptor complex.[22] Under physiological conditions, this pathway promotes neural resilience and homeostasis; however, dysregulation through the overexpression of DKK-1 disrupts these protective mechanisms.[17]

In the context of HIV infection, viral proteins including gp120 and Tat have been demonstrated to stimulate DKK-1 production in neurons and glial cells, leading to synaptic deterioration and neuronal death.[23,24] Specifically, HIV gp120 can activate oxidative stress pathways and proinflammatory cytokine cascades, which in turn upregulate DKK-1 expression, leading to Wnt pathway inhibition and subsequent β-catenin degradation.[25,26]

Loss of Wnt/β-catenin signaling as a result of DKK-1 activity results in reduced transcription of neuroprotective genes and impaired synaptic maintenance, particularly in hippocampal and cortical neuron regions critical for cognition and frequently affected in HAND.[35,36] Moreover, elevated levels of DKK-1 have been detected in cerebrospinal fluid and postmortem brain tissue from patients with neurodegenerative conditions, including those with HIV-related neurocognitive impairment, further supporting its pathogenic role.[14,37]

Beyond synaptic disruption, DKK-1 contributes to blood-brain barrier (BBB) dysfunction by modulating endothelial cell tight junctions through Wnt signaling inhibition, thereby facilitating the entry of inflammatory cells and viral proteins into the CNS.[28,38] This compromise in barrier integrity exacerbates neuroinflammation, a key driver of HAND pathology. Several previous studies have found that Wnt/β-catenin acts as a restriction factor for HIV in astrocytes and affects glutamate metabolism and uptake in astrocytes through inhibition of Wnt/β-catenin signaling.[39,40,41,42]

HIV induces the opening of Cx43 hemichannels leading to dysregulated secretion of DKK-1. Secretion and expression of DKK-1 causes a reduction in the number and length of neuronal processes and neuronal processes contribute importantly to maintaining synapse formation and stability, and reduction of neuronal processes causes synaptic dysfunction.[43]

Previous research found that DKK-1 has the potential as a biomarker for evaluating cognitive impairment in people with HIV infection, indicating that there is involvement of the Wnt pathway in HIV neuropathogenesis. The study found that compared to HIV-negative individuals, cognitive impairment was more severe in people living with HIV (PLWH), particularly those with HIV RNA levels ≤50 units/mL.[44] This is in line with other studies that found a relationship between HAND and plasma DKK-1 levels. The risk of HAND is 2.82 times higher when the plasma DKK-1 level is more than 313.5 pg/mL.[34]

DKK-1 role as a therapeutic target of HAND

DKK-1 is increasingly acknowledged as a viable target for neuroprotective strategies in HIV-associated neurocognitive disorders (HAND) due to its established role in neuronal damage. The utilization of monoclonal antibodies particularly designed to target DKK-1 is among the various treatment strategies explored to alleviate the adverse consequences of DKK-1. The potential of these antibodies to inhibit DKK–1–induced neurodegeneration and promote the restoration of synaptic function was initially investigated in Alzheimer's disease models.[14] An additional potential approach is to activate the Wnt/β-catenin signaling pathway, agents such as lithium which act as glycogen synthase kinase-3 beta (GSK-3β) inhibitors, have demonstrated the ability to activate β-catenin and mitigate the adverse effects of DKK-1. Preclinical models of HIV-associated neurotoxicity have shown supportive evidence for the neuroprotective potential of this technique.[45]

A potential technique involves manipulating transcriptional regulators that control DKK-1 expression. Transcription factors such as p53 and FOXO are recognized for their role in regulating DKK-1 expression, and modifying these regulatory pathways presents a viable approach to inhibit DKK-1 production. Significant challenges persist in the development of DKK-1-targeted therapies.[46] This involves managing potential systemic effects, achieving adequate penetration across the blood-brain barrier, and ensuring target specificity. The majority of information currently derives from preclinical studies, whereas clinical trials involving HAND patients are limited.

In light of its multifaceted role, which encompasses synaptic loss and BBB disruption, DKK-1 is a promising therapeutic target and an emergent biomarker of neurodegeneration. Experimental inhibition of DKK-1 has shown promise in restoring Wnt signaling, enhancing synaptic resilience, and reducing neuroinflammation in various neurodegenerative models, underscoring its relevance in the treatment of HAND as well.[17,47,48,49]

CONCLUSION

This narrative review highlights the emerging role of Dickkopf-related protein 1 (DKK-1) as a risk factor in the pathogenesis of HIV-associated neurocognitive disorder (HAND). Despite substantial progress in suppressing systemic viral replication through antiretroviral therapy (ART), the prevalence of HAND remains high, primarily due to persistent neuroinflammation, synaptic damage, and neurodegeneration driven by residual immune activation, latent viral reservoirs in the central nervous system (CNS), and the neurotoxic effects of viral proteins.

Evidence from recent studies suggests that DKK-1 contributes to HAND development by antagonizing the Wnt signaling pathway, leading to synaptic dysfunction and neuronal apoptosis. Elevated DKK-1 levels in both cerebrospinal fluid and plasma have been associated with increased risk and severity of cognitive impairment in people living with HIV (PLWH), supporting its potential as a biomarker for HAND. Furthermore, the modulation of DKK-1 and restoration of Wnt signaling represents a promising therapeutic approach for mitigating HIV-associated neurodegeneration.

Nevertheless, further research is essential to clarify the precise molecular mechanisms by which DKK-1 contributes to HAND. A deeper understanding of the interplay between DKK-1, Wnt signaling, and HIV-mediated neuropathology will be critical in developing targeted therapies that may improve cognitive outcomes and overall quality of life in PLWH.

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