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LAG3-Targeting Therapy for Parkinson's Disease: Unlocking Biomarkers, Autoimmunity, and Blood Brain Barrier Strategies

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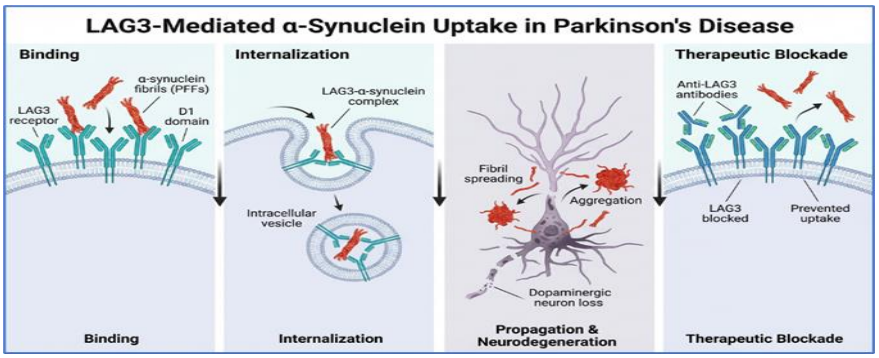
ABSTRACT:

LAG3-targeting therapy represents a promising therapeutic approach for the treatment of neurodegenerative diseases such as Parkinson's Disease (PD) through modulation of immune responses and attenuation of neuroinflammatory processes. This therapy leverages the role of lymphocyte-activation gene 3 (LAG3) in the uptake and propagation of pathological α-synuclein, a key protein implicated in PD. However, significant challenges remain, including the identification of reliable biomarkers for early diagnosis and treatment monitoring, understanding the autoimmune implications of LAG3 modulation, and developing effective strategies for crossing the blood-brain barrier (BBB). Addressing these obstacles is crucial for advancing LAG3-based therapies from preclinical studies to clinical applications. This review highlights the potential of LAG3-targeting therapies, elucidates the mechanisms of α-synuclein modulation, and emphasizes the need for further research to enhance precision medicine approaches in PD treatment. By overcoming these challenges, LAG3-targeting therapies may offer new hope for patients and clinicians in managing Parkinson's disease. Inm summary, addressing the complexities surrounding LAG3-targeting therapies is essential for their successful implementation in clinical settings for Parkinson's disease.

GRAPHICAL ABSTRACT:



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1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder [1] characterized by the degeneration of dopaminergic neurons in the substantia nigra, leading to motor and non-motor symptoms that significantly impair quality of life [2]. The etiology of PD remains complex and multifactorial, involving genetic, environmental, and immunological factors. In recent years, there has been growing interest in the role of immune system dysregulation in the pathogenesis of PD, particularly the potential contributions of neuroinflammation [3] and autoimmunity [4]. Specifically, aberrant α-synuclein aggregation, a pathological hallmark of PD, has been shown to incite microglial activation and subsequent inflammatory responses [5].

One promising avenue of research in this context is the targeting of lymphocyte-activation gene 3 (LAG3), an immune checkpoint regulator known for its role in modulating T-cell responses. Originally explored in oncology, LAG3-targeting therapies have shown potential in enhancing anti-tumor immunity, prompting investigations into their applicability in neurodegenerative diseases such as PD. Given LAG3's involvement in the uptake and propagation of pathological α-synuclein, a hallmark of PD, targeting this pathway may offer a novel therapeutic strategy to mitigate disease progression and neurodegeneration [6].

Despite the promising prospects of LAG3-targeting therapies [7, 8], significant challenges remain, particularly in transitioning these treatments from oncology to neurodegenerative contexts [5, 9]. These include the need for reliable biomarkers for early diagnosis and therapeutic monitoring, as Parkinson's disease currently lacks objective biomarkers to track disease progression [5, 8, 10]. Additionally, a deeper understanding of the autoimmune implications of LAG3 modulation is critical, as the blockade or deficiency of this receptor has been linked to severe autoimmune manifestations and a loss of self-tolerance in preclinical models [11–13]. Finally, the development of effective strategies to facilitate the crossing of the blood-brain barrier is a major hurdle, as the low CNS exposure of large-molecule therapeutics like monoclonal antibodies often results in sub-therapeutic concentrations at target sites in the brain [7, 14, 15].

This review aims to explore the potential of LAG3-targeting therapies in the treatment of Parkinson's disease, elucidating the mechanisms underlying α-synuclein modulation, the implications for immune regulation, and the necessary advancements in biomarker discovery and BBB penetration strategies. By addressing these critical areas, we hope to contribute to the evolving landscape of precision medicine in neurodegenerative disorders, ultimately offering new hope for patients affected by Parkinson's disease.

Exploring LAG-3 as a Therapeutic Target: From Oncology to Neurodegenerative Disorders

A key immune checkpoint regulator that has become well-known for regulating T-cell responses is lymphocyte-activation gene 3 (LAG-3). LAG-3-targeting therapy currently holds efficacy in oncology, especially when used in conjunction with programmed death-1 and its ligand inhibitors to boost anti-tumor immunity in malignancies including non-small cell lung cancer and melanoma [16]. These results have prompted scientists to investigate the possibility of LAG-3 regulation in conditions other than cancer, especially in neurodegenerative disorders like Parkinson's disease (PD) [5, 8, 17, 18]. Hence leveraging knowledge from cancer therapies targeting LAG3 presents a promising avenue for developing novel treatments for PD.

Targeting LAG3: A Promising Therapeutic Approach in Parkinson's Disease Through α-Synuclein Modulation:

The rationale for targeting LAG3 in PD is justified by a number of mechanisms. LAG3 interacts selectively with pathological α-synuclein (α-syn) fibrils, facilitating their transmission and contributing to neurodegeneration in PD. Although it binds to monomeric α-syn only moderately, it has a high affinity (~77 nanomolar) for α-syn preformed fibrils (PFFs). This interaction is mediated by LAG3's D1 domain, which specifically recognizes the fibrillar conformation of α-syn. LAG3 facilitates the endocytosis of α-syn fibrils into neurons and glial cells after binding, which aids in the spread of disease from cell to cell. Studies show that LAG3-deficient models have delayed dopaminergic neuron loss and reduced α-syn spread, indicating its role in disease progression. When phosphorylated at serine 129 (pS129), the acidic C-terminal segment of α-syn (residues 118–140) is bound by the D1 domain of LAG3 and further promotes binding and internalization. This mechanism underscores LAG3's role in α-syn propagation and PD pathogenesis [19]. Beyond facilitating α-syn transmission, LAG3's involvement in

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immune regulation suggests a link between α-syn pathology and neuroinflammation. The interaction between LAG3 and α-syn may influence microglial activation and peripheral immune responses, contributing to the inflammatory milieu observed in PD [17]. Disrupting the interaction between LAG3 and α-syn using anti-LAG3 antibodies has been shown to block neurodegeneration induced by α-synuclein, suggesting that LAG3-targeting therapies, initially explored in cancer, present a promising trajectory for PD's treatment [18].

Exploring the Potential of LAG-3 Inhibition in Neurodegenerative Disease Treatment

It is essential to conduct a thorough assessment of the potential for LAG-3 inhibition to be implemented in clinical settings for the treatment of neurodegenerative diseases. While preliminary findings from preclinical studies indicate that a more robust body of evidence is needed to validate its efficacy and safety in human subjects. Several significant challenges that remain, including understanding the autoimmune implications of LAG-3 modulation [20, 21], developing effective strategies to cross the blood-brain barrier [9], and identifying reliable biomarkers for patient stratification and therapeutic monitoring [5]. Comprehensive clinical trials will be critical to confirm the therapeutic benefits and identify any potential risks associated with this intervention. Hence, I emphasize the need for research to address critical challenges related to the development of biomarkers, autoimmunity, and blood-brain barrier penetration for the usage of LAG3-targeting therapies in PD.

Biomarkers and Therapeutic Insights in Parkinson's Disease: The Role of LAG3

Identifying biomarkers such as LAG3 genetic variants, soluble LAG3 (sLAG3) levels and co-expression with another immune checkpoint that predict responsiveness to LAG3-targeting therapies in PD is a burgeoning area of research. Particularly in some groups, certain single nucleotide polymorphisms (SNPs) of the LAG3 gene have been linked to an elevated risk of PD. In a Chinese female cohort, for illustration, research discovered that LAG3 SNPs raised the chance of PD [5]. This suggests that genetic differences in LAG3 may affect disease susceptibility and might be useful biomarkers for medication response. Multiple conditions have been linked to elevated sLAG3 levels, which might indicate immune system activation. Monitoring sLAG3 concentrations could potentially serve as a biomarker to predict and monitor responses to LAG3-targeting therapies in PD patients [10]. LAG3 functions alongside other inhibitory receptors, such as PD-1, to modulate immune responses. The expression patterns of these molecules could provide insights into the immune landscape of PD patients and help identify those who may benefit from LAG3-targeting therapies [9]. Some studies have questioned the expression of LAG3 in neurons and its role in α-synuclein pathology. In this regard, research found that LAG3 does not modify α-synucleinopathies and is not expressed in human or murine neurons, indicating that LAG3's involvement in PD may be more complicated than initially anticipated [22]. Some Research indicates that the absence of LAG3 may delay the progression of neurodegenerative diseases in certain models [17]. More study is required to confirm these indicators and completely understand the role of LAG3 in PD pathophysiology, even though soluble versions of LAG3 [9] and genetic variants [5, 23] provide intriguing pathways as biomarkers for predicting response to LAG3-targeting therapeutics in PD. A precision medicine strategy may probably be required due to the pathophysiology of PD's heterogeneity.

LAG-3-Targeting Therapies: Autoimmune Risks and Monitoring Needs

It's important to note that while LAG-3-targeting therapies hold promise, their modulation can have complex effects on immune regulation. For instance, deficiencies in LAG-3 pathways have been linked to the development of autoimmune diseases, highlighting the delicate balance required in therapeutic interventions [24]. Numerous skin-related autoimmune adverse reactions were found in an extensive investigation that focused on the cutaneous adverse effects linked to LAG-3 blockers in the therapeutic management of cancer. Complications entailed vitiligo, dry skin, erythema, rash, stomatitis, and pruritus. These manifestations suggest that LAG-3 inhibition can disrupt normal immune regulation, potentially leading to autoimmune-like skin conditions [25]. There is further evidence that autoimmune disorders are associated with deficits in LAG-3 pathways. This correlation highlights the vital function of LAG-3 in sustaining immunological tolerance, and its suppression may precipitate or worsen autoimmune reactions [26]. These findings highlight the importance of monitoring for autoimmune-related side effects when administering LAG-3-targeting therapies. To completely comprehend the mechanisms underlying

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these negative occurrences and develop prevention methods, further research is required. Therefore, in order to fully understand the possible immune-related side effects and therapeutic advantages of LAG-3-targeting medicines in PD, meticulous monitoring and extensive clinical studies are necessary.

Challenges and Innovations in Delivering LAG-3 Targeted Therapies Across the Blood-Brain Barrier

The blood-brain barrier (BBB), which restricts big molecules, like traditional antibodies, from entering the brain, limits the effectiveness of LAG-3 targeted therapeutics in curing disorders of the central nervous system (CNS), such as PD. Therefore, permeability of blood vessels and neural access are potentially possible pathways that restrict immune responses to checkpoint inhibitors. There is currently insufficient evidence that LAG-3 targeting therapy may successfully penetrate the blood-brain barrier [9]. Intranasal administration, Fc fragment engineering, and nanobody-based techniques are among those that are newer approaches to BBB penetration. In a study, researchers developed nanobodies derived from heavy-chain-only antibodies found in camelids that bind to the transferrin receptor (TfR), facilitating the transport of therapeutic agents across the blood-brain barrier (BBB) [27]. The BBB can be avoided by using intranasal administration, a non-invasive method of delivering therapeutic compounds directly to the central nervous system. According to recent research, intranasal infusion of LAG-3 antibodies can reverse depression-like behaviors in animal models caused by prolonged stress [28]. Advancements in protein engineering have led to the development of Fc fragments capable of exploiting receptor-mediated transcytosis to cross the BBB. These engineered fragments can serve as vehicles to deliver therapeutic proteins [29]. These methods may hold promises for extending the therapeutic benefits of LAG-3-targeting agents to neurological conditions. Further research and novel delivery methods are necessary to enhance their CNS accessibility and therapeutic potential for neurological conditions. Additionally, research must clarify whether peripheral immune modulation alone is sufficient for disease modification or if direct CNS penetration is necessary for therapeutic efficacy.

Conclusion

LAG-3-targeting therapy, originally developed for cancer, presents a promising opportunity for Parkinson's disease by repurposing existing drugs to modulate immune responses and neuroinflammation, paving the way for innovative treatment approaches. Preclinical evidence supports the potential of LAG-3 inhibitors to mitigate α-syn spread and neuronal toxicity. As of now, there are no registered clinical trials specifically investigating LAG-3-targeting therapies in PD patients. Key challenges in Parkinson's research include understanding autoimmunity mechanisms, improving blood-brain barrier penetration, and identifying reliable biomarkers for disease progression and treatment response. In conclusion, while targeting LAG-3 represents a promising avenue for Parkinson's disease, these significant gaps must be addressed before clinical translation. A multidisciplinary approach involving neurologists, immunologists, and clinical trial experts is essential to evaluate and validate both the efficacy and safety of LAG-3-targeting therapies in neurodegeneration. Future studies should also focus on identifying biomarkers that predict immune-related toxicity and investigating whether combination therapies can mitigate adverse effects while preserving potential neuroprotective benefits. I look forward to further research addressing these challenges and appreciate the opportunity to contribute to this important discussion. This comprehensive review underscores the imperative for continued investigation into the multifaceted roles of LAG-3 in both neuroinflammation and α-synuclein pathology, which could inform the development of novel therapeutic strategies for Parkinson's disease [7, 8, 30]. Specifically, further exploration is warranted into the mechanisms by which LAG-3 influences microglial activation and α-synuclein processing, as its depletion has been shown to reduce microglial activation and potentially diminish neurodegeneration [17].

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