

LAG3 Antibody Alleviates Parkinson’s Disease Pathology by Inhibiting Neuronal and Astrocytic LAG3 via Brain Shuttle–Mediated Delivery

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Abstract

Neuronal lymphocyte-activation gene 3 (LAG3) binds to misfolded α -synuclein (α -syn) and facilitates its endocytosis and cell-to-cell transmission. The LAG3 and amyloid β precursor-like protein 1 (APLP1) interaction appears to exacerbate Parkinson’s disease pathology. On the other hand, astrocytic LAG3 promotes α -syn propagation through mediating sleep-deprivation induced glymphatic dysfunction. LAG3 antibodies provide a possible therapy for Parkinson’s disease dopaminergic cell death and motor deficits by preventing LAG3 from facilitating α -syn pathology. With the blood-brain barrier restricting antibody transportation to the brain parenchyma, brain shuttle technology offers a possible solution. A 2x1 format CD98hc brain shuttle LAG3 antibody may allow the delivery of LAG3 antibodies to either neuronal or astrocytic LAG3.

Introduction

Parkinson’s disease (PD) is a progressive neurodegenerative disorder characterized by debilitating motor deficits, and it affects more than 8.5 million individuals worldwide [1]. This disease is marked by the spread of alpha-synuclein (α -syn) aggregates, misfolded proteins that drive dopaminergic cell death. LAG3 receptors on neurons and astrocytes facilitate the propagation of α -syn that is associated with neurodegeneration and motor symptoms [2]. Most current therapeutic strategies such as levodopa or exercise only alleviate motor symptoms rather than addressing the underlying neurodegeneration [3]. LAG3 antibodies that target LAG3 receptors offer a promising approach. Therefore, this review addresses this question: **How might LAG3 antibodies targeting astrocytes or neurons alleviate α -syn propagation in Parkinson’s disease, and what mechanisms could allow this treatment to reach the human brain?**

Methods

- Searched through online scientific journals and academic databases (ex: PubMed) with search terms LAG3, α -synuclein, Glymphatic System, Parkinson’s disease, and brain shuttles, and a published date between 2010 to 2026
- Included peer-reviewed sources
- Organized studies based on researched mechanisms: neuronal LAG3, astrocytic LAG3, and brain shuttles

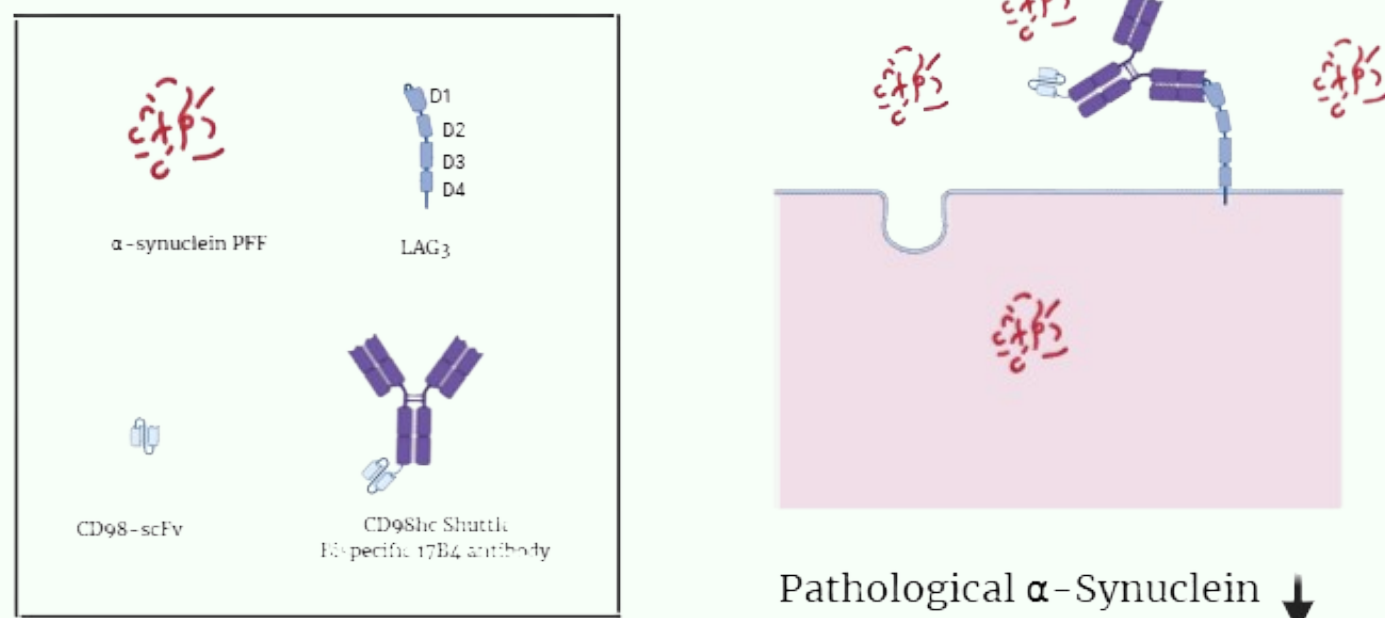


Fig. 1 Schematic of CD98hc shuttle bispecific 17B4 antibody inhibiting the D1 LAG3 domain, preventing α -syn PFF binding and endocytosis into neurons. (Created with BioRender.com)

Results

- The D1 domain of LAG3 binds to α -syn and promotes its endocytosis and neuron-to-neuron transmission [4]
- The APLP1 and LAG3 interaction enhances α -syn uptake [5]
- Neuronal LAG3 knockdown reduced α -syn propagation, neurodegeneration, and motor deficits in mice [5]
- Under sleep deprivation, astrocytic LAG3 impairs glymphatic clearance responsible for removing α -syn, and LAG3 knockdown restored glymphatic function [6]
- CD98hc-shuttled antibodies lead to longer brain retention and cell-type specificity compared to TfR-1 [7]

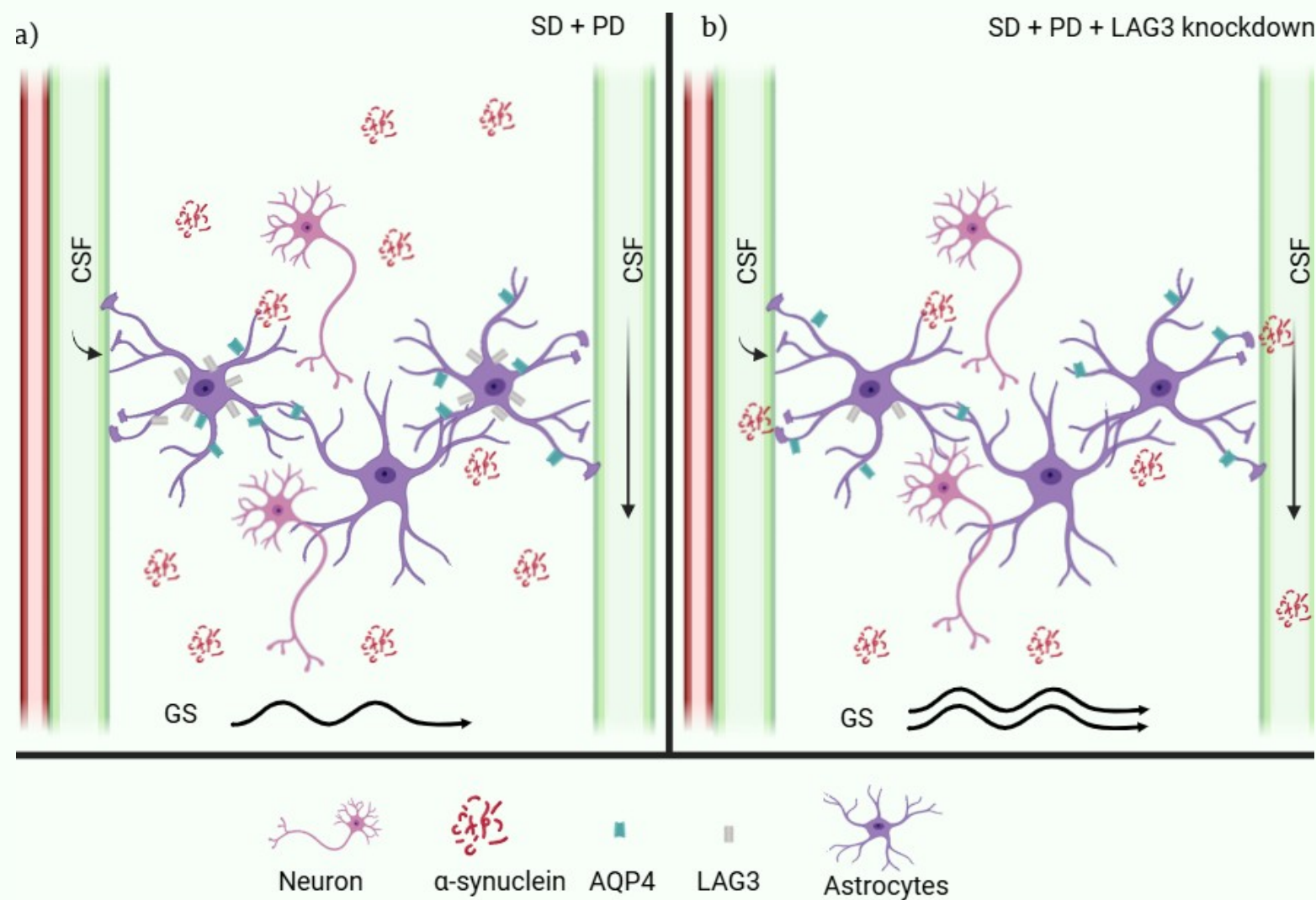


Fig. 2 Astrocytic LAG3 is identified as a target for antibody-mediated inhibition, since its knockdown restores glymphatic clearance and reduces α -syn accumulation (Created with BioRender.com)

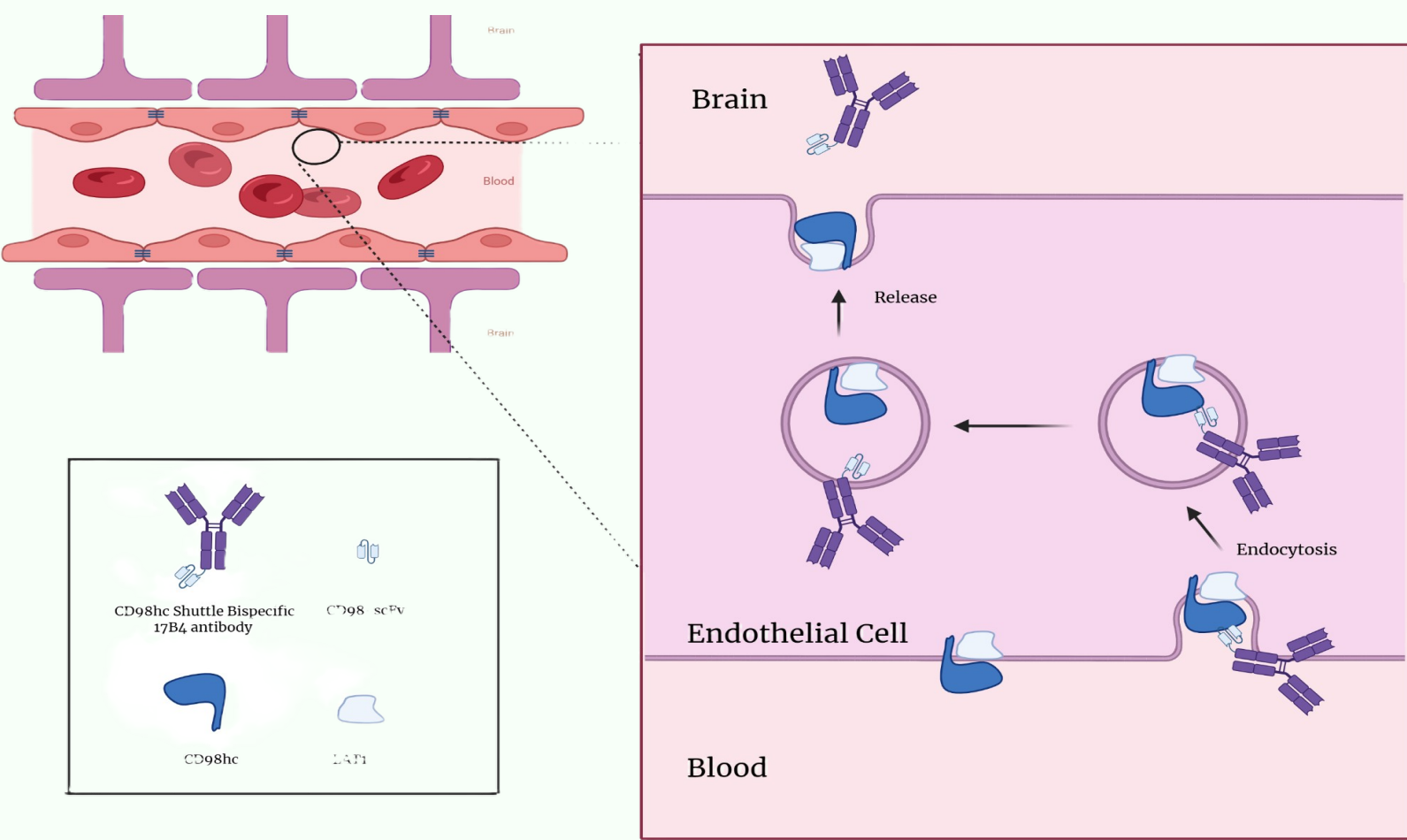


Fig. 3 CD98hc shuttle bispecific 17B4 antibody binds to CD98hc on the luminal surface of endothelial cells and crosses the BBB via receptor-mediated transcytosis (Created with BioRender.com)

Discussion

Unlike many treatments for PD that only target symptoms, LAG3 antibodies inhibiting neuronal or astrocytic LAG3 address the underlying pathology of PD by targeting two distinct pathways that lead to substantial α -syn accumulation which exacerbates neurodegeneration and motor deficits. Brain shuttle-mediated delivery would enable the antibody’s transportation across the blood-brain barrier (BBB). The CD98hc shuttle would be the preferable option; however, CD98hc receptors are also found in some non-brain organs [7]. It is also important to consider that all results found were based on mice studies and can’t be generalized to humans without clinical trials. LAG3 is also found on T cells, so inhibiting it may cause problematic immune responses [8].

Conclusion

Since LAG3 facilitates α -syn propagation through astrocytes and neurons, LAG3 antibodies may alleviate those harmful effects. 17B4 is a potential candidate for a LAG3 antibody as it targets the LAG3 D1 domain where α -syn PFF typically binds [9]. The BBB restricts LAG3 antibodies’ entry into the brain, but designing the antibody into a bispecific CD98hc shuttle LAG3 antibody offers a possible solution. The design was proven to effectively deliver an IgG antibody with cell-type specificity [7]. Still, both LAG3 antibodies and CD98hc shuttles must be tested clinically to ensure that it is a viable PD therapy for humans.

References

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