

Mediation alpha-synuclein clearance through Complement Component 3

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INTRODUCTION

The complement system is emerging as a critical role in inflammations of neurodegenerative diseases. While our previous study linked plasma Complement Component 3 (C3) levels to Alzheimer's disease biomarkers, the specific interactions between C3 and alpha-synuclein (α -syn) remained unclear. This study aimed to investigate the interactions between α -syn and C3 and its functional roles in α -syn clearances.

METHODS

Measurement C3a and TCC

• To evaluate C3 activation, α -syn was incubated with normal human serum (NHS), and levels of C3a and terminal complement complex (TCC) were measured by commercial ELISA kits.

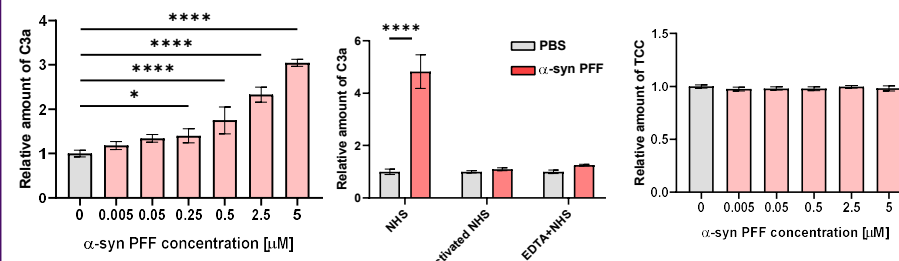
Plasma C3 in PD patients

• Plasma C3 levels were quantified in Parkinson's disease (PD) patients (n=36; Controls, n=38) using ELISA.

Alpha-synuclein clearance in cell

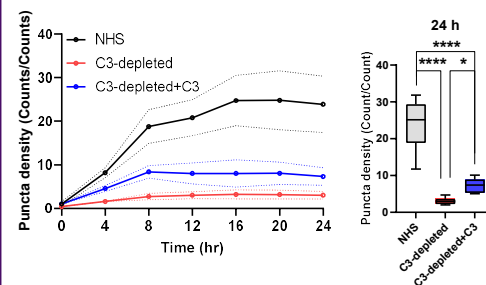
• Fluorescence-labeled α -syn was monitored for 24 hours through live-cell imaging to examine α -syn clearance under various complement-deficient conditions.

RESULTS



α -syn PFF induces dose-dependent C3a activation without TCC changes

• Significant increased C3a levels were observed upon α -syn addition to NHS in a concentration-dependent manner, whereas this activation was abolished in heat-inactivated NHS and upon the addition of EDTA to NHS. TCC levels remained as unchanged regardless of α -syn concentrations

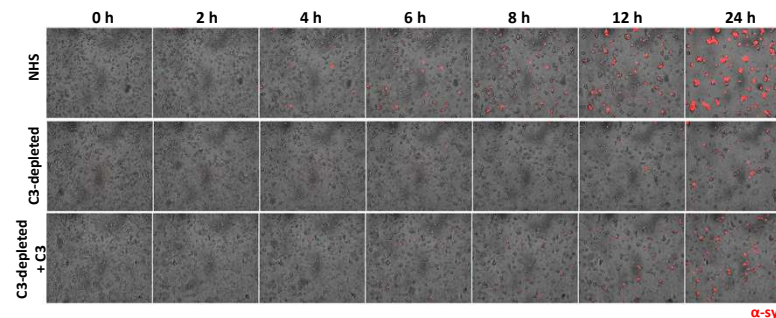
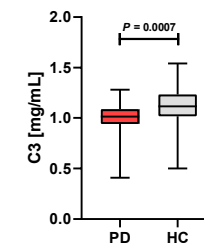


C3 status critically regulates α -syn clearance

• In live-cell imaging, α -syn uptakes and clearances increased over time in the presence of NHS, but the significant reduced effects were observed in C3-depleted serum. Interestingly, the addition of C3 to C3-depleted serum increased the α -syn fluorescence within the cell.

Reduced plasma C3 levels in PD patients

• Plasma C3 levels are significantly lower in PD patients compared to HC.



CONCLUSIONS

This study demonstrated a link between α -syn and C3 activation. The selective C3a increases in without TCC elevation suggested the α -syn triggers in an early-stage complement activation rather than the full cascade, potentially to facilitate the engulfment of extracellular aggregates. The observed reductions of plasma C3 in PD patients likely reflected the systemic complement consumption, as C3 was continuously recruited to process of α -syn accumulation. Critically, the impairment of α -syn clearances in C3-depleted conditions proved that C3 was an important mediator of α -syn proteostasis. These findings indicated that complement-mediated phagocytosis was a protective mechanism against α -syn toxicity, suggesting that modulating C3 activity could offer a novel therapeutic strategy to enhance the clearance of pathological protein aggregates in PD.

CONTACT

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