Introduction

- Parkinson's disease
  - Dopaminergic neuronal loss in the substantia nigra pars compacta.
  - Intracellular inclusions named Lewy bodies or Lewy neurites.
  - Neuroinflammation has been known to be one of the risk factors for the pathogenesis of Parkinson's disease (PD).
- Microglial Phagocytosis
  - Critical for the uptake and degradation of infectious agents and senescent cells.
  - Participated in development, tissue remodeling and contributes to the immune response and inflammation.
  - The rapid and efficient removal of apoptotic cells before cell debris prevents the release of potentially toxic.
- α-Synuclein
  - A major component of Lewy bodies and plays a key role in the pathogenesis of Parkinson's disease.
  - Detected in extracellular biological fluids and known to function extracellularly.
  - Parkinson's disease patients exhibit progressive spreading of aggregated α-synuclein in the nervous system.

Aim

- In the previous study (Park et al., 2008), extracellular monomeric α-synuclein increases phagocytosis, but the aggregated α-synuclein inhibits phagocytosis of microglia.
- The aim of this study is elucidating (1) which type of AS (aggregated α-synuclein) inhibits microglial phagocytosis and (2) how AS inhibits it, in the context of professional phagocytic receptors' signaling.

Results

Figure 3: Aggregated α-syn induced SHP-1 phosphorylation

B6 cells (A) and primary microglia (B) were incubated with 1 μM aggregated α-syn for 30 min. Then, incubated with 0.5 μg/mg IgG for 5 min. BV-2 cells were incubated with 1 μM aggregated α-syn for 30 min, then fixed and permeabilized with 0.5% Brij 35 and blocked with PBS containing 2% goat serum. The cells were then incubated with primary antibody for 1 h, washed with PBS, and then incubated with Alexa Fluor 532-conjugated secondary antibody for 1 h. After washing, the cells were mounted on a glass slide and visualized with a confocal microscope. Scale bars indicate 5 μm.

Figure 4: SHP-1 knockdown and treatment with NSC23766 reduced the inhibitory effect of aggregated α-syn on microglial phagocytosis.

(A) BV-2 and BV-2-SHP-1 KO cells were treated with 1 μg/mg IgG for 1 h, washed, and then incubated with 1 μM aggregated α-syn for 1 h. The cells were then fixed and permeabilized with 0.5% Brij 35 and blocked with PBS containing 2% goat serum. The cells were then incubated with primary antibody for 1 h, washed with PBS, and then incubated with Alexa Fluor 532-conjugated secondary antibody for 1 h. After washing, the cells were mounted on a glass slide and visualized with a confocal microscope. Scale bars indicate 5 μm.

Figure 5: FcγRIIB specifically interacted with aggregated α-syn.

(A) COS cells were incubated with indicated doses of aggregated α-syn and fluorescent microspheres for 1 h. (B) BV-2 and BV-2-SHP-1 KO cells were pre-incubated with 0.5 μM IgG for 30 min, and then incubated with 1 μM aggregated α-syn and fluorescent microspheres for 2 h. (C) BV-2 and primary microglia were pre-incubated with 20 μM KD-2/BD-2, a SHP-1 inhibitor, for 30 min, then incubated with 1 μM aggregated α-syn and fluorescent microspheres for 1 h. *P < 0.05 against untreated controls.

summary

- Aggregated α-syn inhibits microglial phagocytosis
- The inhibitory effect of aggregated α-syn on microglial phagocytosis is due to the activation of SHP-1
- Aggregated α-syn interacts with FcyRIIB on microglia for activating SHP-1
- The interaction of aggregated α-syn and FcyRIIB and further SHP-1 activation can be a new therapeutic target against PD.