

# The mechanisms of *Porphyromonas gingivalis*-derived outer membrane vesicles-induced neurotoxicity and microglia activation

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## Abstract

**Background/purpose:** Periodontitis is associated with various systemic diseases, potentially facilitated by the passage of *Porphyromonas gingivalis* outer membrane vesicles (Pg-OMVs). Several recent studies have suggested a connection between Pg-OMVs and neuroinflammation and neurodegeneration, but the precise causal relationship remains unclear. This study aimed to investigate the mechanisms underlying these associations using in vitro models.

**Materials and methods:** Isolated Pg-OMVs were characterized by morphology, size, and gingipain activity. We exposed SH-SY5Y neuroblastoma cells and BV-2 microglial cells to various concentrations of Pg-OMVs. Cell

morphology, a 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay, an enzyme-linked immunosorbent assay, and Western blot analysis were used to evaluate the cellular mechanism underlying Pg-OMV-induced neurotoxicity in neuronal cells and inflammatory responses in microglial cells.

**Results:** Exposure to Pg-OMVs induced neurotoxicity in SH-SY5Y cells, as evidenced by cellular shrinkage, reduced viability, activation of apoptotic pathways, and diminished neuronal differentiation markers. Gingipain inhibition mitigated these effects, suggesting that gingipain mediates Pg-OMVs-induced neurotoxicity in SH-SY5Y cells. Our research on neuroinflammation suggests that upon endocytosis of Pg-OMVs by BV-2 cells, lipopolysaccharide (LPS) can modulate the production of inducible nitric oxide synthase and tumor necrosis factor- $\alpha$  by activating pathways that involve phosphorylated AKT and the phosphorylated JNK pathway.

**Conclusion:** Our study demonstrated that following the endocytosis of Pg-OMVs, gingipain can induce neurotoxicity in SH-SY5Y cells. Furthermore, the Pg-OMVs-associated LPS can trigger neuroinflammation via AKT and JNK signaling pathways in BV-2 cells.

**Keywords:** Gingipain; Lipopolysaccharide; Microglial cell; Neuron; Outer membrane vesicles; Porphyromonas gingivalis.

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