When Oral Pathogens Meet the Brain: Exploring *Porphyromonas gingivalis* in Alzheimer's Disease

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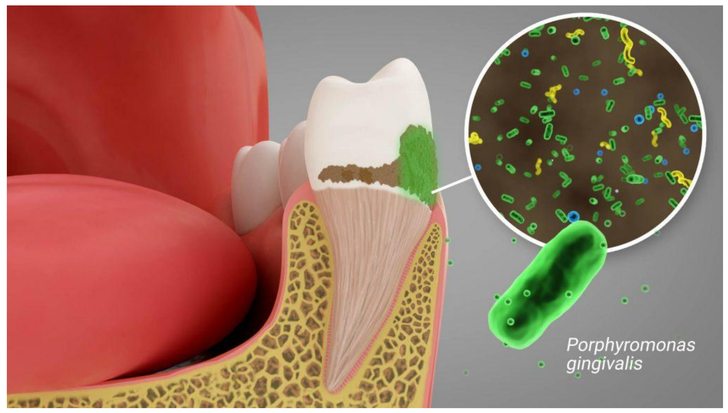
Introduction

One of the main pathogens in periodontitis known as *P. gingivalis* produces major virulence factors called gingipains- cysteine proteases. If left untreated, the effects of the bacteria result initially in the local area but can also spread throughout the body. *P. gingivalis has been implicated in* neurodegenerative diseases such as Alzheimer's disease. Blocking gingipain activity with short peptides lowers *P.gingivalis* virulence and could be a potential treatment for neuronal damage that results from periodontitis.

Objectives

- Evaluate the presence of *P. gingivalis* in Alzheimer's patients with periodontitis vs. Alzheimer's patients without periodontitis.
- Identify the role of gingipain load and its linkage to Alzheimer's disease pathogenesis
- Assess the role of small-molecule gingipain inhibition as a potential disease-modifying therapy in Alzheimer's disease.



Denteric. *Precision Immunotherapies for chronic P. gingivalis Infections.* 2024.

Method

A literature review was conducted through primary sources to understand the biology of *P. gingivalis,* gingipains, and their associations with neurological conditions. Key subtopics included the biology of gingipains, neuroinflammation, and current potential treatments.

Results

- The presence of Kgp protein and *p. gingivalis* DNA was confirmed in both Alzheimer's disease and most non-demented control brains, suggesting that *p.gingivalis* and gingipain presence occur in the brain (Figure 1).
- Some studies reported a correlation between *p. gingivalis* infection, increased amyloid beta levels, and neuroinflammation (Figure 2)
- Both in vitro and in vivo, studies suggest that gingipains from P. gingivalis induce neuronal toxicity and degeneration while selective gingipain inhibitors effectively block these harmful effects and protect neuronal cells (Figure 3).

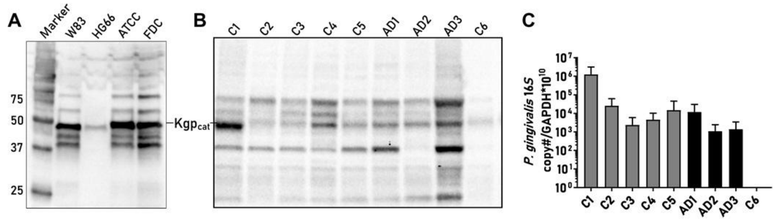


Figure 1: Identification of *P. gingivalis*- specific protein and DNA in cortex from control and Alzheimer's Disease patients

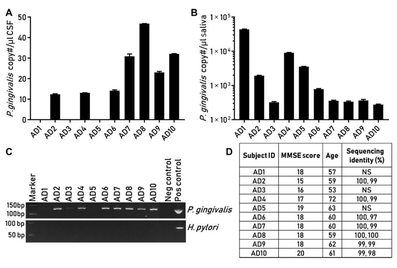


Figure 2: Detection of *P. gingivalis* in CSF and oral biofluids from clinical AD subjects.

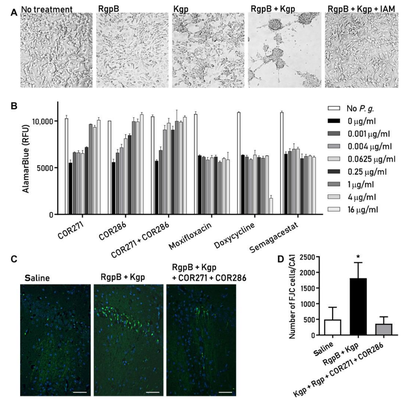


Figure 3: Small-molecule gingipain inhibitors protect neuronal cells against *P. gingivalis*– and gingipain-induced toxicity in vitro and in vivo.

Conclusion

- Gingipains may play a role in the aetiology of Alzheimer's Disease and inhibitors targeting the proteases are offering promising therapy
- The presence of *p.gingivalis* in the brain and cerebral spinal fluid in subjects diagnosed with Alzheimer's disease suggests a diagnostic role for gingipains.
- Small-molecule gingipain inhibitors may have potential in modifying the neurodegenerative effects in Alzheimer's disease.

Future Direction

- There is a need for clinical studies
- The mouse models here are very young, which don't reflect the typical age or condition of humans diagnosed with Alzheimer's disease. Geriatric mice of about 8 months or older would be a better fit for this experiment to mirror progression of disease in similar age groups
- Very high concentration of bacteria in the models used to see if the bacteria would seed; its multiple orders of magnitude are substantially greater than one would possibly encounter outside of a lab
- Have models exposed to the bacteria in a more typical environment and then complete harvesting of brain tissue after the models are a year old to better emulate the disease process that is being suggested

References