Dental Insights — Why does periodontitis develop? And does it associate with neurodegenerative diseases?

1. The key drivers of periodontal pathogenesis

Drivers of periodontal dysbiosis: primarily inflammation-driven environmental changes.

Tissue breakdown products are being used as nutrients by pathogenic bacteria, such as degraded proteins, aminoacids and heme-containing compounds (source of iron). This favors selectively periodontitis-associated bacteria, at the expense of the commensal health-associated bacteria. Host response is a huge factor in pathogenesis.

P. gingivalis is an inflammophilic keystone pathogen.

P. gingivalis has very sophisticated strategies to avoid getting killed by the host in 2 ways:
1) Inhibition of bactericidal mechanisms, fx by blocking an antimicrobial peptide (Myd88) that is used by the immune cells for bacterial clearance, and by blocking phagocytes.
2) Promotion of inflammation to obtain nutrients.

Dysbiosis cause inflammation, AND inflammation cause dysbiosis (a reciprocal reinforcement that drives periodontitis). It's vicious cyclic process with both dysbiosis and inflammation. Inflammation in itself is not strong enough without dysbiosis, and dysbiosis cannot become fullblown without inflammation.

Complement involvement in periodontitis
Complement is involved in both:
1) The dysbiotic transformation of the periodontal microbiota, and
2) The inflammatory response that leads to destruction of alveolar bone.

It's possible to break the vicious cycle by targeting C3 complement, the central component of the complement cascade. John D. Lambris invented a C3 complement inhibitor Cp40 (AMY-101), that can block C3 complement.

2. Periodontitis leads to epigenetic rewiring

There is a strong rationale for host-modulation therapy in periodontitis:
1) Significant public health and economic burden,
2) Current standard-of-care therapy is not always effective, particularly in highly susceptible patients,
3) Increased risk of systemic inflammatory comorbidities (fx cardiovascular disease, arthritis, Alzheimer disease).

Periodontal inflammation is not just local!

Periodontal inflammation in the mouth —>
Bacterial translocation to vasculature in the gums —>
Induction of inflammatory cytokines in the gums —>
Bacteremia and systemic inflammation.

Periodontitis —>
Epigenetic inflammatory memory —>
Comorbidities.

Epigenetic rewiring
Epigenetic rewiring of bone marrow progenitors as a result of one inflammatory disease (periodontitis) can enhance susceptibility to another distinct disease (arthritis). This creates hyperresponsive myeloid cells with inflammatory memory (responds faster and stronger in future inflammatory challenges) generated in the bone marrow, and they populate both oral tissue but also extraoral tissues such as joints as exacerbates the inflammatory reaction of arthritis.
The C3 complement inhibitor Cp40 (AMY-101) can block C3 in humans and non-human primates only (not in mice).

It took 7 years to move from mice to non-human primates for testing the C3 complement-targeted intervention with AMY-101 in periodontitis. In 2021 they started a trial on humans.
Primary outcome: AMY-101 significantly reduces gingival inflammation in humans. The protection of AMY-101 remained until 90 days after treatment.
Next step: Phase 3 trial on humans with C3-targeted therapy in periodontitis.

Summary:
1) Dysbiosis and inflammation reciprocally reinforce each other in a feed-forward loop that constitutes the actual driver of periodontal disease,
2) An effective way to break this vicious cycle is by targeting complement activation as shown in preclinical models and more recently in a Phase 2a clinical trial at the Forsyth Institute.

3. Periodontitis develops only if both risk factors are present: dental biofilm and an inflammatory host response

A lack of oral hygiene AND a susceptible inflammatory host response will initiate the vicious cycle that drives periodontitis.

There are people that are resistant to periodontitis, and will never develop it in their life, even if they don’t brush their teeth.

A syndrom called Job Syndrom HIS-syndrome have a genetic deficiency in the trascription factor that creates TH-17 cells. These people have healthy gingiva and alveolar bone, even better than healthy people. TH-17 cannot become activated and create inflammation and alveolar bone loss in these people. TH-17 is also important against fungal infections, and therefore they can get fungal infection trush in their mouths, and still have healthy gums and alveolar bone.

Periodontitis is a complicated disease with 3 levels:
1) Microbial level,
2) Host level,
3) Environmental level.

You cannot have inflammation without dysbiosis, and you cannot have dysbiosis without inflammation. Dysbiosis and inflammation work together. The host response can either protect you or contribute to driving the inflammatory process.

Dysbiosis also happens in gingivitis, most often by accumulation of biofilm (dental plaque). Not everybody changes their microbiome if they don't brush. You still need a disturbance in the host response to develop periodontitis.

Discussion
We don't know if amoeba also travels from the periodontal pockets to the bloodstream. We don't teach dental students enough about microbiology. We don't hear much about other microorganisms, such as viruses, in periodontal disease.

The C3 complement inhibitor ANY-101 is a small molecule (14 aminoacids), and it's possible that it can penetrate the gingival epithelial barrier, and be added to fx toothpaste or local gel applied professionally by the dentist/dental hygienist in the future, but we don't know yet.

Diet is also a big factor. If you reduce carbohydrates in your diet, you reduce the systemic inflammation in your body. Very little research is done on that so far. We should focus on what we eat.

Good resources
Maladaptive innate immune training of myelopoiesis links inflammatory comorbidities, Cell 2022.
Phase 2a clinical trial (Forsyth Institute, by Hatice Hasturk et al, Clinicaltrials.gov: NCT0394444, " Phase 2a clinical trial of complement C3 inhibitor AMY-101 in adults with periodontal inflammation", Journal of Clinical Investigation.

4. Neurodegeneration and periodontitis

Neurodegenerative diseases: motor neurone disease, multiple sclerosis, Parkinsons, Alzheimers, Huntingtons, prion diseases.

Parkinsons disease
Parkinsons disease is the 2nd most common neurodegenerative disease.
Lewy body pathology.

A higher IL-6 is associated with higher risk of Parkinsons disease.

Taiwan National Health Insurance Research Database = a fantastic database!

Patients with periodontal disease have a higher risk of developing Parkinsons disease.
Patients with periodontal disease and metabolic disease have a higher risk of developing Parkinsons disease.

Alzheimers disease
Alzheimers disease is the most common cause of dementia.
The 2nd most common cause is vascular dementia due to diabetes.

There's a higher risk of tooth loss when cognitive function decreases.
Brain cytokine response to a peripheral infection.

Kamer et al 2015, Neurobiology of the brain:
Amyloid accumulation is associatied with gum disease.

Severe periodontitis give a higher risk of Alzheimers disease.

Cognitive decline is associated with diabetes, mental disorders, and stroke.

P. gingivalis migrates to the brain and develops gingipain.
There is new medicine that inhibits/slows this (lysine-gingipain inhibitor).

P. gingivalis can be internalized by neurons.
There are brain changes much earlier than clinical signs of cognitive decline.

Oral interventions – what is the optimal timing and indications?

Good resources
”Ermini et al 2020”
”Dominy et al 2019, P. gingivalis in Alzheimers disease brains”
”Kang et al 2020, … relationship between cognitive function and oral health in ageing persons”
”Iwasaki et al 2016”
”Orlandi et al 2022, Impact of the treatment of periodontitis on systemic health and quality of life – a systematic reiew”
”Holmes et al 2009, Systemic TNFalfa and rate of cognitive decline in 300 AD cases”
”Johansson et al 2015, Alzheimers microglia function”
”Ma et al 2022, Dementia and the risk of periodontitis – a population-based cohort study”
Treatment of Stage I-III Periodontitis EFP S3 Clinical Practice Guidelines
”Olsen et al 2020, Parkinsons and periodontal health”
”Parkinsons and periodontal disease, Chen et al, 2017”
”Parkinsons and periodontal disease, Jeong et al 2021”
”Kang et al 2019, Cognitive function and oral health among ageing adults”
”Lee et al 2020, Risk of dementia in patients with periodontitis and related protective factors”
”Epidemiology of Parkinsons disease, Tysnes and Storstein, 2017”
”Periodontitis and cognitive decline in Alzheimers disease”
Kamer et al 2015, Neurobiology of the brain

Top 4 Dental Insights — Key Take Aways

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Sources

EuroPerio10 15-18.06.2022

That was Dental Insights. Thank you for being here. ❤

Dental love, Anne Mette