SEMMELWEIS EGYETEM
Fogorvostudományi Kar

Helyreállító Fogászati és Endodonciai Klinika
Igazgató:
Dr. Vág János egyetemi tanár

Munkacsoport neve: **Fogászati gyulladások és kezelésük**

1. Csoport tagjai:

- Vezető: dr. Lohinai Zsolt, PhD, med. habil, dr. Vasziné Szabó Enikő, PhD, dr. Herczegh Anna, PhD
- PhD hallgatók: Dr. Mikaela Aresti, Dr. Caroline Kelly
- TDK:
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2. Vizsgálat címe:

- **A lizin centrális szerepe a fogágygyulladás kialakulásában**
- **A fogágygyulladás és következményes betegségeinek genetikai fogékonyságának tesztelése**
- **A klórhexidin, nátrium-hipoklorit és a hipertiszta klórdioxid antimikrobiális hatékonysága gyökércsatorna-fertőtlenítésben és a szájüreg egyéb gyulladásainak kezelésénél**
- **A fog struktúrbiológiája**

3. Absztrakt:

Bacterial lysine decarboxylase influences human dental biofilm lysine content, biofilm accumulation, and subclinical gingival inflammation Background: Dental biofilms contain a protein that inhibits mammalian cell growth, possibly lysine decarboxylase from Eikenella corrodens. This enzyme decarboxylates lysine, an essential amino acid for dentally attached cell turnover in gingival sulci. Lysine depletion may stop this turnover, impairing the barrier to bacterial compounds. The aims of this study are to determine biofilm lysine and cadaverine contents before oral hygiene restriction (OHR) and their association with plaque index (PI) and gingival crevicular fluid (GCF) after OHR for 1 week. Methods: Laser-induced fluorescence after capillary electrophoresis was used to determine lysine and cadaverine contents in dental biofilm, tongue biofilm, and saliva before OHR and in dental biofilm after OHR. Results: Before OHR, lysine and cadaverine contents of dental biofilm were similar and 10-fold greater than in saliva or tongue biofilm. After 1 week of OHR, the biofilm content of cadaverine increased and that of lysine decreased, consistent with greater biofilm lysine decarboxylase activity. Regression indicated that PI and GCF exudation were positively related to biofilm lysine after OHR, unless biofilm lysine exceeded the minimal blood plasma content, in which case PI was further increased but GCF exudation was reduced. Conclusions: After OHR, lysine decarboxylase activity seems to determine biofilm lysine content and biofilm accumulation. When biofilm lysine exceeds minimal blood plasma content after OHR, less GCF appeared despite more biofilm. Lysine appears important for biofilm accumulation and the epithelial barrier to bacterial proinflammatory agents. Inhibiting lysine decarboxylase may retard the increased GCF exudation required for microbial development and gingivitis.

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Biofilm Lysine Decarboxylase, a New Therapeutic Target for Periodontal Inflammation Background: Lysine, a nutritionally essential amino acid, enters the oral cavity in gingival crevicular fluid (GCF). During oral hygiene restriction (OHR), lysine decarboxylase (LDC) in dento-gingival biofilms converts lysine to cadaverine. Lysine depletion impairs the dental epithelial barrier to bacterial proinflammatory products. Antibodies to LDC from Eikenella corrodens (Ecor-LDC) inhibit LDC activity and retard gingival inflammation in beagle dogs. Whether E. corrodens is the major source of LDC in dental biofilms and whether the lysine analog tranexamic acid (TA) inhibits LDC activity, biofilm accumulation, and GCF exudation in a human gingivitis model were examined. Methods: Antibodies raised in goats to LDC-rich extracts from E. corrodens cell surfaces were used to inhibit Ecor-LDC and detect it in biofilm extracts using Western blots. Ecor-LDC activity was measured at pH 4.0 to 11.0 and its TA dissociation constant (Ki) at pH 7.0. Young adults used a 5% or 10% TA mouthwash three times daily during OHR for 1 week. Results: Ecor-LDC antibodies and TA inhibited biofilm LDC. Ki of TA for Ecor-LDC was 940 μM. TA reduced plaque index (PI) by downshifting the PI correlation with biofilm lysine content after OHR without TA. GCF was correspondingly suppressed. However, greater TA retention in saliva partially relieved GCF suppression but not biofilm lysine depletion. Conclusions: TA slightly inhibits LDC but strongly reduces biofilm by inhibiting bacterial lysine uptake. Unfortunately, TA may impair dental epithelial attachments by also inhibiting lysine transporter uptake. Ecor-LDC inhibitors other than lysine analogs may maintain sufficient lysine levels and attachment integrity to prevent periodontal inflammation.

Low Biofilm Lysine Content in Refractory Chronic Periodontitis Background: Chronic periodontitis is controlled without antibiotics by scaling and root planing (SRP) to remove dental biofilm. It has been previously reported that the epithelial barrier to bacterial proinflammatory products is impaired when biofilm lysine falls below the minimal content of normal blood plasma. Aims were to examine whether being refractory and requiring antibiotics to supplement SRP were associated with low biofilm lysine contents. Methods: Sixteen patients with periodontitis and six periodontally healthy volunteers (HVs) (respective mean ages: 57 ± 6 and 36 ± 8 years) were examined. Patients with periodontitis received SRP and surgery, and HVs received prophylaxis. At quarterly maintenance or prophylaxis visits during the subsequent year, therapeutic response was good (GR, n = 9) or poor (PR, n = 7; including five cigarette smokers). Biofilm cadaverine, lysine, and other amino acid (AA) contents were determined by liquid chromatography. Cadaverine mole fraction of lysine plus cadaverine (CF) indicated biofilm lysine decarboxylase activity. Results: Biofilm lysine was 0.19 ± 0.10 and 0.20 ± 0.09 μmol/mg in GRs and HVs, but 0.07 ± 0.03 μmol/mg in PRs (Kruskal-Wallis: $P < 0.01$). All AAs were depleted in biofilm from smokers, but only lysine was depleted in biofilm from non-smokers. CF was inversely associated with clinical attachment level (CAL) at baseline before therapy in all patients ($R2 = 0.28$, $P < 0.01$) and with CAL change after therapy in GR ($R2 = 0.49$, $P < 0.05$). Lysine and cadaverine contents discriminated PRs from GRs and HVs (Wilks' $\lambda = 0.499$, $P < 0.012$). Conclusions: Refractory responses requiring antibiotic therapy result from smoking and/or microbial infections that starve the biofilm and epithelial attachment of lysine. Biofilm CF is associated with periodontitis severity pretherapy and extent of therapeutic response post-therapy.

Zinc chloride inhibits lysine decarboxylase production from Eikenella corrodens in vitro and its therapeutic implications Objectives: Dentifrices containing zinc reduce gingival inflammation and bleeding better than control dentifrices (no zinc). How zinc might work is not understood. We have shown that lysine decarboxylase (LdcE), an enzyme from Eikenella corrodens, converts lysine to cadaverine in dental biofilms. The lack of lysine impairs the dentally attached cell barrier to biofilm, causing biofilm products to leak into junctional epithelium and stimulate inflammation. In year-old beagle dogs, immunization with LdcE, induces antibodies that inhibit LdcE activity and retard gingivitis development. We therefore examined whether a zinc-mediated loss of LdcE activity could explain the beneficial effect of zinc dentifrices. Methods: We grew E. corrodens in modified tryptic soy broth with or without zinc chloride, and extracted LdcE from the cell surface using a Potter Elvehjem homogenizer. Results: Up to 0.96 mM zinc chloride in the bacterial growth medium did not change cell yield, but reduced the extracted protein content by 41% ($R2 = 0.27$, $p < 0.05$) and LdcE activity/mg extracted protein by 85% ($R2 = 0.90$, $p < 0.001$). In extracts from cells grown without zinc, 78

times this zinc chloride concentration (73 mM) was required to reduce LdcE activity by 75%. Conclusions: Zinc ions inhibit the production of protein with LdcE activity at E. corrodens cell surfaces. The zinc ions may attach to cysteine residues that are unique to the N-terminal region of LdcE by interfering with the non-covalent polypeptide assembly that produces enzyme activity. Clinical significance: Zinc ion-mediated inhibition of LdcE assembly may provide a rationale for the improved control of gingival inflammation by zinc dentifrices.
Resolving the Contradictory Functions of Lysine Decarboxylase and Butyrate in Periodontal and Intestinal Diseases Periodontal disease is a common, bacterially mediated health problem worldwide. Mastication (chewing) repeatedly traumatizes the gingiva and periodontium, causing traces of inflammatory exudate, gingival crevicular fluid (GCF), to appear in crevices between the teeth and gingiva. Inadequate tooth cleaning causes a dentally adherent microbial biofilm composed of commensal salivary bacteria to appear around these crevices where many bacteria grow better on GCF than in saliva. We reported that lysine decarboxylase (Ldc) from *Eikenella corrodens* depletes the GCF of lysine by converting it to cadaverine and carbon dioxide. Lysine is an amino acid essential for the integrity and continuous renewal of dentally attached epithelium acting as a barrier to microbial products. Unless removed regularly by oral hygiene, bacterial products invade the lysine-deprived dental attachment where they stimulate inflammation that enhances GCF exudation. Cadaverine increases and supports the development of a butyrate-producing microbiome that utilizes the increased GCF substrates to slowly destroy the periodontium (dysbiosis). A long-standing paradox is that acid-induced Ldc and butyrate production support a commensal (probiotic) microbiome in the intestine. Here, we describe how the different physiologies of the respective tissues explain how the different Ldc and butyrate functions impact the progression and control of these two chronic diseases.

4. Elnyert pályázat:

5. Kongresszusi részvétel a témában:

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