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学　位　論　文　要　旨

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論　文　題　名　Effects of miR-128-3p on Renal Inflammation in a Rat Periodontitis Model
ラット歯周炎モデルにおけるmiR-128-3pによる腎臓の炎症への影響

論文内容の要旨（2000字程度）

Introduction

Extracellular vesicles (EVs) are lipid-encapsulated vesicles and have the capacity to transport bioactive molecules, including DNA, RNA, lipids, and proteins, to other cells to regulate their biological functions. EVs mediate a complex intercellular communication network in sepsis, shuttling a variety of key mediators, such as microRNAs (miRNAs). MiRNAs regulate gene expression by inhibiting translation or promoting mRNA degradation. Some miRNAs have organ-specific expression and can circulate from one organ to an-other, potentially changing the expression of specific genes, including the promotion or suppression of inflammatory pathways in the kidney. One specific miRNA, miR-128-3p, has a significant role in inflammation, and contributes to sepsis-associated acute kidney injury. However, whether miR-128-3p from periodontitis can cause renal inflammation re-mains unclear. The study aim was to investigate the role of miR-128-3p from EVs associated with in periodontitis in renal inflammation and to identify the associated target genes of miR-128-3p in the rat periodontitis model.

Methods

Male Wistar rats aged 10 weeks old (Japan SLC, Inc., Hamamatsu, Japan) were used in this study. The rats were randomly divided into two groups: a control group (n = 8) and a LPS group (n = 8). The LPS group received LPS derived from *Porphyromonas gingivalis* and 10 μL injection of LPS was administered between the maxillary first and second molars on both sides of the rats every 2 days for a total of 7 days. The control group received an equivalent volume of distilled water without LPS at the same intervals. At the end of the experiment, plasma, gingival tissue, and kidney samples were collected. Hematoxylin and eosin (H&E) staining was performed to evaluate the glomerular tissue injury score. Bioinformatic analysis was conducted to identify potential target genes of miR-128-3p. The reverse transcription-quantitative polymerase chain reaction (RT-qPCR) was performed to evaluate miR-128-3p, cytokine, chemokine and predicting gene expression. Welch's *t*-test was used and p-values < 0.05 were considered to indicate statistical significance.

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Results

Histological analysis using H&E staining revealed a higher infiltration of inflammatory cells (eosinophils and neutrophils) in the glomerular area of renal tissues in the LPS group compared with the control group. The expression of miR-128-3p was significantly higher in the gingival tissue and plasma of the LPS group compared with the control group. Gene expression of *Interleukin (IL)-1β*, *tumor necrosis factor (TNF)-α*, *C-X3-C motif chemokine ligand 1 (CX3CL1),* and C-X-C motif chemokine ligand 7 *(CXCL7)* was significantly higher in the kidney of LPS group. The potential target genes of *activin A receptor type I* (*Acvr1*), *ribosomal protein S6 kinase B1 (Rps6kb1)*, and *transforming growth factor beta receptor type 1 (Tgfbr1)* were significantly lower in the kidneys of the LPS group.

Discussion

In the present study, the expression levels of miR-128-3p in gingival tissue and blood plasma were significantly higher in the LPS group, suggesting that miR-128-3p may be originated from EVs derived LPS-induced periodontitis. Higher infiltration of inflammatory cells in the glomerular area of renal tissues in the LPS group were observed. The inflammatory gene *COX2* and pro-inflammatory cytokine and chemokine genes *IL-1β*, *TNF-α*, *CX3CL1*, *CXCL7*, and *CCL5* were upregulated in the kidney. In addition, target genes (*Rps6kb1*, *Tgfbr1*, and *Acvr1*) of miR-128-3p were significantly downregulated in the LPS group compared with the control group. TGF-β signaling pathway was associated with three mRNAs (*Rps6kb1*, *Tgfbr1*, and *Acvr1*) as a potential target gene of miR-128-3p, which may play a role in promoting inflammation in the kidney. In conclusion, EV-derived miR-128-3p from LPS-induced periodontitis may cause renal inflammation and be mediated by the *Rps6kb1*, *Tgfbr1*, and *Acvr1* genes through the TGF-βsignaling pathway. Our findings could be used for further study in the context of renal inflammation linked to periodontitis.