Received: 20 August 2020 | Revised: 31 October 2020 | Accepted: 14 December 2020

DOI: 10.1002/JPER.20-0623

JOURNAL OF Periodontology

ORIGINAL ARTICLE

# MicroRNA-146a and -155, upregulated by periodontitis and type 2 diabetes in oral fluids, are predicted to regulate SARS-CoV-2 oral receptors genes

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**Abstract**

**Background:** Type 2 diabetes and periodontitis predispose to a higher risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Recent studies show upregulation of innate immuno-regulatory microRNA-146a and -155 in oral fluids of patients with type 2 diabetes as well as of patients with periodontitis. The aim was to investigate whether upregulation of these microRNAs may relate to patient susceptibility to the infection via modulation of SARS-CoV-2 cellular entry factors expression.

**Methods:** Due to limited experimental feasibility and health risks in Coronavirus Disease 2019, bioinformatic analyses combining with system biology were used as initial investigation of interaction between microRNA-146 and -155 and genes encoding SARS-CoV-2 entry factors.

**Results:** SARS-CoV-2 cellular entry factors are expressed in salivary glands and masticatory mucosa (tongue) at different expression levels, comparable with those measured in lungs and tonsil. MicroRNA-146 and -155 are widely involved in the regulation of SARS-CoV-2 oral cellular entry factors and may enhance expression of ACE2 and modulate genes involved in host immunity.

**Conclusions:** Diabetes- and periodontitis-induced increase in microRNA-146a and -155 in oral cavity is predicted to upregulate angiotensin-converting enzyme 2 expression, essential SARS-CoV-2 entry receptors, and modulate host antiviral response. As it could suggest increased infectivity of diabetes and periodontitis patients, additional protective measures for periodontists are recommended.

KEYWORDS
microRNAs, periodontitis, SARS-CoV-2, type 2 diabetes

## 1 | INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causes systemic inflammatory response due to release of large amounts of proinflammatory cytokines by immune cells during the infection.[1] Nevertheless, the mechanism of virus invasion and the causes of these aberrant inflammatory responses in SARS-CoV-2 infection remain largely unknown. Moreover, evidence demonstrates that people with underlying metabolic conditions such as type 2 diabetes mellitus, are at higher risk of severe Coronavirus Disease 2019 (COVID-19), associated with more efficient virus entry.[2] A very recent study by Katz et al.[3] showed that dental diseases are associated with increased odds ratio for COVID-19 and that patients with periodontal disease were 4.7 times

  

more likely to have COVID-19, after adjustment for smoking.[3] Based on significant association of periodontitis with diabetes as well as known systemic inflammatory reaction, periodontitis was proposed to be a risk factor for SARS-CoV-2 infection.[4] Infection by human coronaviruses as well as other respiratory viruses highly depends on host microRNA (miR) involvement which maintains the epithelial cell barrier in the respiratory tract and modulates virus entry and replication.[5] miR-146a and miR-155 are the first miRs induced during immune activation and modulate the Toll-like receptor (TLR)-signaling pathways which trigger the production of large amounts of inflammatory cytokines, type I interferons (IFNs), and antiviral proteins via nuclear factor-kappa B (NF$\kappa$B).[6] Regarding SARS-CoV-2, very recent in-silico analyses showed that among 28 human miRs predicted to target at the SARS-CoV-2 genome, miR-146 and the immune response as the function were seriously affected by the virus infection. Furthermore, the authors of the study proposed that miR-146 could be "hijacked" by the virus genome to modulate host biological processes by affecting genes that originally are targeted by this miR.[7]

Recent studies show that states of type 2 diabetes and chronic periodontitis show upregulation of miR- 146a and -155 in oral fluids: patients with type 2 diabetes express higher expression of crevicular fluid miR-146a[8] and salivary miR-146a and miR-155[9] while patients with periodontitis express higher expression of miR-146a and miR-155 in crevicular fluid[8] and saliva.[9,10] These miRs, persisting in body fluids as circulatory and exosomal, could be taken up by diverse oral cavity-neighbor or distant cells such as epithelial cells, endothelial or immune cells acting in local as well as systemic intercellular communication and immune regulatory function.[11] The aim was to investigate whether upregulation of these immunomodulating and oral cavity-circulating miRs in periodontitis and type 2 diabetes could be related to susceptibility of these patients to SARS-CoV-2 infection, by computational analysis of interaction between miR-146 and -155 and genes encoding SARS-CoV-2 oral cellular entry factors.

## 2 | MATERIALS AND METHODS

Due to the limitation of experimental feasibility and health risks during COVID-19, the usage of in-silico target identification algorithms, as an initial strategy with the advantage of fast speed and low cost, could be important for the emerging information aiming to improve dental practice and reduce health risks. In-silico characterization presently was performed by using approaches such as expression profiling of human genes related to SARS-CoV-2 entry, gene/protein-network mapping, protein- protein interactions, and gene expression predictions.

### 2.1 | Expression profiling of SARS-CoV-2 cellular entry factors in oral cavity

The lst of cellular factors regulating SARS-CoV-2 entry into cells is derived from experimental studies of SARS-CoV-2 but also of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). Angiotensin-converting enzyme 2 (ACE2) has been considered the major receptor for SARS-CoV-2 entry into target cells while the transmembrane serine protease 2 (TMPRSS2) cleaves ACE2 and facilitates the entry of SARS-CoV into host cells.[13] Cell surface protein basigin (BSG, also known as CD147) has been proposed as alternative receptor for SARS-CoV-2[14,15] while cathepsins (CTSL/B) and FURIN can also substitute for TMPRSS2 to prime SARS-CoV.[16] Receptors which have been confirmed experimentally to facilitate entry of either SARS-CoV (ANPEP, CD209, CLEC4G/M) or MERS-CoV (DPP4) were included in the investigation as candidates for promoting SARS-CoV-2 entry.[12] To identify the tissue localization of potential SARS-CoV-2 cellular receptors, the publicly available, The Human Protein Atlas online program was used.[17] The Tissue Atlas contains information regarding the expression profiles of human genes both on the mRNA and protein level. The mRNA expression data are derived from deep sequencing of RNA (RNA-seq) from 37 different normal tissue types. Consensus transcript expression levels for each gene were summarized based on transcriptomics data from three sources: HPA, GTEx, and FANTOM5. The consensus normalized expression (NX) value for each gene and organ/tissue represents the maximum NX value in the three data sources.

### 2.2 | Interaction networks

ACE2-associated genes used for constructing interaction networks and miR prediction analyses were extracted from StringApp 1.5.1 (Search Tool for the Retrieval of Interacting Genes/Proteins) database (https://string-db.org) (top 10 ACE2 interactors), Archs4 database (https://amp.pharm.mssm.edu/archs4) (top 10 genes with correlated expression) and Genecards database (https://www.genecards.org) (five interactors). For TMPRSS-2 -interaction network and miR predictions data are based on StringApp 1.5.1 (top 10 TMPRSS2 interactors), Archs4 database (top five genes with correlated expression), and Genecards database (five interactors). To analyze connections between ACE2 and TMPRSS2 genes and their interactors, a protein-protein

**TABLE 1** Normalized gene expression (NX)* of SARS-CoV-2 cellular entry factors in oral, lung, and tonsil as well as small intestine tissues

| Genes (NX) | Salivary glands | Masticatory mucosa | Lung | Tonsil | Small intestine |
|---|---|---|---|---|---|
| ACE2 | 1.1 | 0.5 | 0.8 | 0.2 | 122.0 |
| TMPRSS2 | 52.3 | 3.9 | 20.7 | 10.2 | 75.6 |
| FURIN | 337.9 | 5.5 | 9.5 | 4.1 | 5.9 |
| BSG | 44.0 | 45.9 | 36.1 | 31.2 | 45.5 |
| CD209 | 3.0 | 2.1 | 3.7 | 1.3 | 10.1 |
| DPP4 | 46.9 | 1.4 | 5.4 | 1.1 | 133.1 |
| CLEC4G/M | 4.9 | 0.6 | 0.5 | 0.2 | 0.7 |
| ANPEP | 6.6 | 4.2 | 9.7 | 3.8 | 155.8 |
| CTSL | 22.0 | 9.4 | 53.1 | 10.1 | 12.0 |
| CTSB | 63.7 | 25.9 | 94.3 | 38.4 | 51.2 |

ACE2, angiotensin-converting enzyme 2; ANPEP, alanyl aminopeptidase; BSG, basigin; CD209, cluster of differentiation 209; CLEC4G/M, C-type lectin domain family 4 member G/M; CTSB, cathepsin B; CTSL, cathepsin L; DPP4, dipeptidyl peptidase-4; TMPRSS2, transmembrane serine protease 2.
*Based on the mRNA data obtained from The Human Protein Atlas.

interaction (PPI) network in Cytoscape 3.8.0 were constructed, using human interactome data from StringApp 1.5.1 database, including known and predicted protein–protein interactions. Interaction networks were composed from a set of genes/proteins (nodes) connected by edges which represent functional relationships among these genes/proteins. Connections with edge interaction confidence cut-off > 0.4, (with 1.0 being the highest possible confidence) were considered.

### 2.3 | MicroRNA predictions

To predict miR-146 and miR-155- regulation of SARS-CoV-2 oral cellular entry factors, TargetScan 7.2 is used. TargetScanHuman predicts biological targets of microRNAs by analyzing different miRNA-mRNA seed-site interaction patterns.[18] Predictions are presented as predicted efficacy of targeting, calculated using cumulative weighted context++ scores of the sites representing the sum of the contribution of 14 interaction-relevant features.[19] This score estimates the total repression expected from multiple sites of the same miRNA, for each mRNA target predicted and the more negative the score, the repression is greater.

## 3 | RESULTS

### 3.1 | Tissue-specific expressions of SARS-CoV-2 entry factors

Analysis based on the mRNA data obtained from The Human Protein Atlas revealed that SARS-CoV-2 cellular entry factors are expressed in salivary glands and masticatory mucosa (tongue) at different expression levels. The highest gene expression in masticatory mucosa expresses BSG while CLEC4G/M and ACE2 genes show the lowest expression levels. In salivary glands (samples from minor and major glands), FURIN is expressed at the highest, and ACE2 at the lowest levels. However, even at low expression levels, ACE2 expression levels in the oral cavity were comparable with those measured in lungs and tonsil. The highest expression levels for ACE2 and TMPRSS2 were shown in small intestine (Table 1).

### 3.2 | Prediction of miR-146 and miR-155 targeting SARS-CoV-2 oral cellular entry factors

Firstly, ACE2 and TMPRSS2 interaction networks were analyzed at the first level interactors including virus-related proteins from ACE2 (ACE2, DPP4, ANPEP, CLEC4M) and TMPRSS2 (TMPRSS2, CTSB, CTSL, FURIN) interaction networks. Present in-silico analyses show that miR-146 and -155 are widely involved in the negative regulation of genes encoding SARS-CoV-2 cellular entry factors and their interactors present in the oral cavity (Fig. 1, Table 2). In ACE2 interaction network, miR-146 and miR-155 negatively regulate ACE2-co-expressed genes, AGTR1 and membrane metallo-endopeptidase (MME), as well as prolyl carboxypeptidase (PRCP) gene with highest predicted efficacy of miR-155 targeting AGTR1. In TMPRSS2 interaction network, the highest predictive efficacy miR-146 and miR-155 show in targeting transcription factor NKX3-1 (Fig. 1, Table 2). Importantly, miR-146 is predicted to directly suppress FURIN, BSG, and CTSB genes expression, showing the highest predictive efficacy

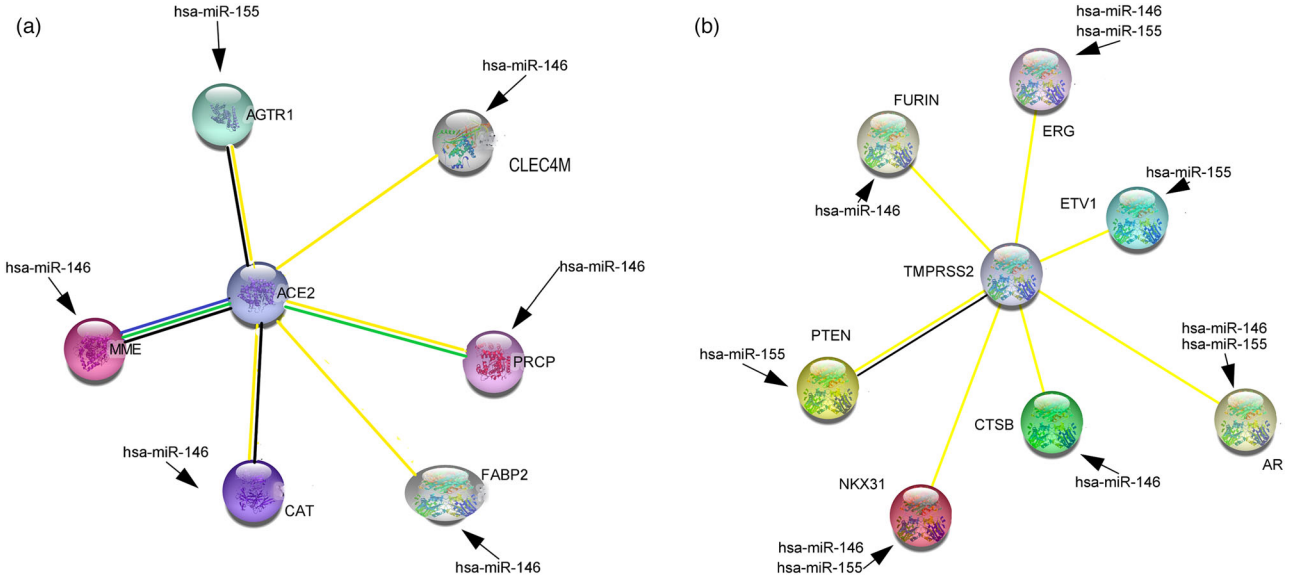


**FIGURE 1** Predicted miR-146 and -155 targeting in ACE2 (a) and TMPRSS2 (b) interaction networks. Nodes represent the first level ACE2 and TMPRSS2 interactors connected by edges which represent functional relationships among these genes/proteins. For clarity, only the edges connecting ACE2 and TMPRSS2 with interactors negatively regulated by miR-146 and/or miR-155 were presented. ACE2, angiotensin-converting enzyme 2; AGTR1, angiotensin II receptor type 1; AR, androgen receptor; CAT, catalase; CLEC4M, C-type lectin domain family 4 member M; CTSB, cathepsin B; ERG, ETS transcription factor; ETV1, ETS variant transcription factor 1; FABP2, fatty acid binding protein 2 (the second level ACE2 interactor); MME, membrane metallo-endopeptidase, neprilysin; NKX3-1, homeobox protein; PRCP, prolylcarboxypeptidase; PTEN, phosphatase and tensin homolog; TMPRSS2, transmembrane serine protease 2. Gene neighborhood (green line); gene co-occurrence (blue line); co-expression (black line); text mining (yellow line)

of targeting BSG (Fig. 2) while miR-146 and -155 could indirectly regulate other alternative SARS-CoV-2 entry regulators: CD209 (by suppressing regulating genes KRAS and NRAS), ANPEP (by suppressing CD33), CLEC4G/M (by suppressing BACE1, CLEC5A, and TYRO3), and DPP4 (by suppressing MME and PRCP) (Fig. 2)

### 3.3 | Prediction of miR-146 and miR-155 targeting viral entry-related, host immune-regulating genes

Host immune-regulating genes being first level interactors within SARS-CoV-2 entry receptor (ACE2, ANPEP, CD209) networks and the predicted effects of their interaction with miR-146 and miR-155 were presented in Table 3. The highest predicted efficacy in repression shows miR-155 targeting CD33 gene (cumulative weighted context++ scores: −0.43) followed by miR-146 targeting NRAS gene (cumulative weighted context++ scores: −0.36) and miR-146 targeting CLEC5A (cumulative weighted context++ scores: −0.22) (Table 3).

Immunomodulatory effects on host antiviral responses by miR-146 and miR-155, mediated by TLRs- downstream effectors and shown in in vitro and in vivo studies with other respiratory viruses, are presented in Table 4.

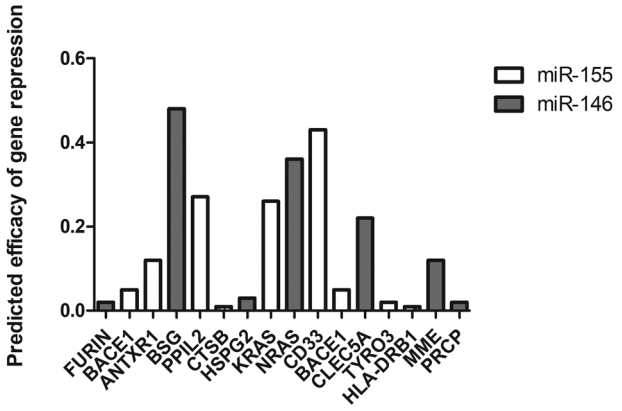


**FIGURE 2** Predicted efficacy of miR-146 and -155 targeting alternative SARS-CoV-2 oral cellular entry factors. Bars represent absolute values of cumulative weighted context++ scores estimating the total repression expected from multiple sites of the same miRNA, for each mRNA target predicted. ANTXR1, anthrax toxin receptor 1; BACE1, beta-secretase 1; BSG, basigin; CD33, siglec-3; CLEC5A, C-type lectin domain family 5 member A; CTSB, cathepsin B; HLA, DRB1 – HLA class II histocompatibility antigen, DR-1 beta chain; HSPG2, heparan sulfate proteoglycan 2; KRAS, Kirsten rat sarcoma viral proto-oncogene; MME, membrane metallo-endopeptidase, neprilysin; NRAS, neuroblastoma RAS viral oncogene homolog; PPIL2, peptidyl-prolyl cis-trans isomerase-like 2; PRCP, prolylcarboxypeptidase; TYRO3, tyrosine-protein kinase receptor TYRO3

**TABLE 2** Predicted efficacy of miR-146 and miR-155 targeting genes from ACE2 and TMPRSS2 interaction networks[a]

| Genes | Gene interaction network | Predicted miR | Predicted efficacy of targeting (cumulative weighted context++ scores) |
|---|---|---|---|
| AGTR1 | ACE2 | miR-155 | −0.27 |
| MME | ACE2 | miR-146 | −0.12 |
| PRCP | ACE2 | miR-146 | −0.02 |
| CLEC4M | ACE2 | miR-146 | −0.22 |
| CAT | ACE2 | miR-146 | −0.12 |
| FABP2 | ACE2 | miR-146 | −0.06 |
| AR | TMPRSS2 | miR-146miR-155 | −0.06−0.03 |
| ERG | TMPRSS2 | miR-146miR-155 | −0.03−0.00 |
| ETV1 | TMPRSS2 | miR-155 | −0.09 |
| PTEN | TMPRSS2 | miR-155 | −0.07 |
| NKX3-1 | TMPRSS2 | miR-146miR-155 | −0.11−0.33 |
| FURIN | TMPRSS2 | miR-146 | −0.02 |
| CTSB | TMPRSS2 | miR-146 | −0.01 |

ACE2, angiotensin-converting enzyme 2; TMPRSS2, transmembrane serine protease 2; AGTR1, angiotensin II receptor type 1; MME, membrane metallo-endopeptidase, neprilysin; PRCP, prolylcarboxypeptidase; AR, androgen receptor; ERG, ETS transcription factor; ETV1, ETS variant transcription factor1; PTEN, phosphatase and tensin homolog; NKX3-1, homeobox protein. The more negative the score, the greater the repression.

[a]TargetScan 7.2.

**TABLE 3** Predicted modulation of host immunity effects by miR-146 and miR-155 via genes related to SARS-CoV-2 entry

| Genes | Gene interaction network | Predicted miR | Predicted miR -146a and -155 modulated host immune responses |
|---|---|---|---|
| CLEC5A | ACE2 | miR-146 | By suppression of CLEC5A/TLR2 signaling-inhibition of production of cytokines (TNF-$\alpha$, IL-1, IL-6, IL-8, IL-17) and chemokines. Overactivation of CLEC5A/TLR2 is detrimental during acute viral infections. |
| KRAS | CD209 | miR-146miR-155 | Inhibition of Ras/NFkB signaling: reduction in production of proinflammatory cytokines: IL-17, IL-22, IFN-$\gamma$, TNF-$\alpha$, IL-6. |
| NRAS | CD209 | miR-146 | Reduction in production of proinflammatory cytokines: IL-17, IL-22, IFN-$\gamma$, TNF-$\alpha$, IL-6. |
| CD33 | ANPEP | miR-155 | Upregulation of proinflammatory cytokines: IL-1$\beta$, IL-8, TNF-$\alpha$ |
| CAT | ACE2 | miR-146 | Oxidative stress |

## 4 | DISCUSSION

Comprehensive overview on cellular factors that could be involved in SARS-CoV-2 entry show that they are expressed in masticatory mucosa as well as in salivary glands located throughout the oral cavity in mRNA expression levels comparable with lungs or tonsil suggesting SARS-CoV-2 tropism for oral tissues. Recent RNA sequencing transcriptome profiling of samples of oral mucosa show that 2% of non-immune mouth tissue cells

**TABLE 4** miR-146a and miR-155- immunomodulatory effects in host defense responses to respiratory viruses

| Respiratory virus (cells/samples used) | miR | Effects | Pathways and targets |
|---|---|---|---|
| Rhinovirus (human bronchial epithelium-in vitro)[40] | miR-155 | Inhibition of viral replication | Promoting IFN signaling and/or direct inhibition of viral genes? |
| Adenovirus Influenza Parainfluenza Respiratory syncytial virus (nasal samples in vivo)[37] | miR-155 | Enhanced antiviral immunity and decreased respiratory disease severity | IFN-$\gamma$ production and enhanced airway TH1 cytokine polarization, pro-inflammatory effects |
| Influenza viruses: H1N1 and H3N3 (human pulmonary epithelium in vitro)[41] | miR-146a | Enhanced viral replication | Inhibiting IFN production by targeting TRAF6, TLRs-downstream effector |
| Influenza viruses: H1N1 and H3N3 (human pulmonary epithelium in vitro)[42] | miR-146a | Decrease in viral production | miR-146a-induced cellular antiviral activity or direct inhibition of viral genes? |
| H3N2 (human nasal epithelium in vitro)[43] | miR-146a | No change in viral titer | Suppression of TRAF6, TLRs-downstream effector |

compared with 2.5% of non-immune nasal tissue cells and 5.6% of non-immune lung tissue cells, express ACE2 expression and that ACE2 is frequently co-expressed with TMPRSS2 in oral tissues.[20] Furthermore, ACE2 receptor mRNA expression level was relatively high in epithelial cells, higher in oral tongue than buccal and gingival tissues, and less pronounced in fibroblasts.[21] Expression of ACE2 protein detected by polyclonal antibody revealed moderate to strong staining covering >75% of the epithelium of oral mucosa and salivary glands, and weak staining in fibroblasts and immune inflammatory cells of oral cavity.[22]

Present in-silico analyses showed that miR-146 and miR-155 are widely involved in the regulation of cellular factors present in oral mucosa and important for SARS-CoV-2 entry. Regulation of essential viral receptor, ACE2, by miRs seems to be indirect, by suppressing co-expressed genes: miR-155 express high efficacy in targeting and suppressing AGTR1 expression while miR-146 suppresses gene expression of membrane metallo-endopeptidase (MME, neprilysin) and prolyl carboxypeptidase (PRCP). As the first level ACE2 interactors, they represent components of renin-angiotensin system, involved in metabolism of bioactive peptides known to regulate vascular homeostasis.[23] Since negative regulation of AGTR1 and lack of PRCP increase ACE2 expression,[24–26] these results imply miR-146 and -155 could promote ACE2 gene expression. In-silico analyses are associated with limitations: the accuracy of the predictions is mainly limited by the amount of data used in the underlying algorithms, thus experimental data are needed. The predicted upregulation of ACE2 expression in periodontitis and diabetes needs to be validated in the clinical studies. Recent data investigating ACE2 expression in lung tissue of patients with type 2 diabetes showed that protein levels of ACE2 were significantly increased in both alveolar tissue and bronchial epithelium of patients with diabetes.[27] Opposite to our predictions, a single study, on a limited number of human gingival samples, showed weaker ACE2 immunostaining in periodontitis compared with healthy gingival samples.[28] Caution must be taken regarding the interpretation of this result since Descamps et al.[22] suggested that lack of ACE2 immunostaining in oral tissues could be explained by the cleavage of ACE2 receptor by disintegrin and metalloproteinase (ADAM 17), activity of which enhances in inflammatory states,[29] such as periodontitis.

Noteworthy, miR-155 and especially miR-146, negatively regulate other potential cellular entry factors. Data suggest TMPRSS2 gene regulation is via androgens and present results show that miR-146 and -155 are suppressors of androgen signaling showing the highest efficacy in suppressing transcription factor homeobox protein (NKX3-1) which negatively regulates androgen receptor (AR) transcriptional activity[30] and indirectly TMPRSS2. miR-146 directly negatively regulates CTSB gene expression and with high predicted efficacy represses expression of alternative viral receptor and activating factor: BSG and FURIN.

Nevertheless, ACE2 seems to be essential and sufficient for SARS-CoV-2 cellular entry since soluble extracellular domain of ACE2 as well as antibodies targeting the receptor binding element can effectively block infection.[31]

The expression pattern of ACE2 in oral tissues in patients with type 2 diabetes and periodontitis need validation in the clinical studies, but based on the epidemiological data, patients with periodontal disease and diabetes are at higher risk for SARS-CoV-2 infection, thus additional protective measures are needed for periodontists.

Besides regulating the SARS-CoV-2 entry receptors genes, overexpressed miR-146 and miR-155 could contribute to viral propagation by affecting antiviral host defense. Presently reported repressive effects of miR-146 and -155 on genes included in SARS-CoV-2 entry revealed also signaling pathways of miR-146 and -155 immunomodulatory effects: by miR-146- suppression of CLEC5A, highly expressed on myeloid lineages, inhibition of production of cytokines and chemokines, and attenuated innate immune response[32] could be proposed. By suppression of KRAS and NRAS-inhibition of RAS signaling pathway, suppression of NFkB-cytokine production[33] by both miR-146 and miR-155 is proposed while by suppression of CD33, transmembrane receptor in myeloid cells, induction of proinflammatory cytokines[34] by miR-155 may be proposed. These results imply miR-146a-suppressive and miR-155-stimulating effects on production of cytokines which combat invading pathogens. Thus, the miR-146a and miR-155 interplay may help maintain the inflammatory response but minimize tissue damage while inducing an effective immune response for viral clearance. Another immunomodulatory effect by miR-146a and miR-155 on host antiviral responses via TLRs-downstream effectors, shown in studies with other respiratory viruses should be considered also. It could be assumed that these miR-146a and -155-regulated inflammatory pathways affect host defense mechanisms against SARS-CoV-2 but may be engaged in the host anti-inflammatory responses to type 2 diabetes and chronic periodontitis also.

Furthermore, it has been pointed out that altered immune response by overexpressed miR-146a can be transferred via exosomes to the neighbor or distant cells making them more susceptible for virus infection.[35] Nevertheless, while miR-155 may stimulate host antiviral defense, immunosuppressive actions of miR-146a could have beneficial effects for the host by counteracting the dangerous excessive inflammatory reaction. Indeed, upregulation of miR-146a contributes to suppression of inflammation-induced acute lung injury.[36] High airway miR-155 levels were found to be strongly linked to a higher production of IFN-$\gamma$ in children and decreased respiratory disease severity.[37]

Besides being the receptor for the virus, ACE2 also represents a protective factor in COVID-19. Namely, the entry of SARS-CoV-2 into the cells through membrane fusion markedly downregulates ACE2 receptors and disbalance between ACE-ACE2 axes could aggravate diabetes and cardiovascular disease and predispose to severe COVID-19.[38] Angiotensin-converting enzyme (ACE) converts angiotensin (Ang) I to Ang II which binds to the angiotensin II receptor 1 (AGTR1), whereas ACE-2 converts Ang I to Ang-(1-7), which binds to Mas receptor. Opposite to activation of ACE- Ang II-AGTR1 axis, ACE2-Ang-(1-7)-Mas axis induces a protective mechanism of anti-inflammatory, anti-fibrotic effects, and anti-hyperresponsiveness in respiratory and cardiovascular system.[38] In addition to angiotensin receptor inhibitors aiming to enhance ACE2 expression, a very recent study proposed benefits from angiotensin receptor/MME (neprilysin) inhibitors in patients with COVID-19, to maximize the anti-inflammatory effects and anti-hyperresponsiveness.[39]

Diabetes- and periodontitis-induced increase in miR-146a and miR-155 in oral cavity is predicted to upregulate ACE2 expression, essential SARS-CoV-2 receptors, and modulate host antiviral response, implying possibility of increased infectivity of these patients. Therefore, additional caution and protective measures are obligatory for periodontists.

## ACKNOWLEDGMENTS

The author would like to thank Mrs Ružica Popović for technical support. The author reports no conflicts of interest related to this study.

## AUTHOR CONTRIBUTIONS

Jelena R. Roganović was responsible for conceptualization, data curation, investigation, visualization, writing, and review of this study

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**How to cite this article:** Roganović JR. MicroRNA-146a and -155, upregulated by periodontitis and type 2 diabetes in oral fluids, are predicted to regulate SARS-CoV-2 oral receptors genes. *J Periodontol*. 2020;1-9.
https://doi.org/10.1002/JPER.20-0623