BRIEF COMMUNICATION



Predicting the response of the dental pulp to SARS-CoV2 infection: a transcriptome-wide effect cross-analysis

Johnah C. Galicia ¹ · Pietro H. Guzzi² · Federico M. Giorgi³ · Asma A. Khan ¹

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Abstract

Pulpitis, inflammation of the dental pulp, is a disease that often necessitates emergency dental care. While pulpitis is considered to be a microbial disease primarily caused by bacteria, viruses have also been implicated in its pathogenesis. Here, we determined the expression of the SARS-CoV2 receptor, angiotensin converting enzyme 2 (ACE2) and its associated cellular serine protease TPMRSS2 in the dental pulp under normal and inflamed conditions. Next, we explored the relationship between the SARS-CoV-2/human interactome and genes expressed in pulpitis. Using existing datasets we show that both ACE2 and TPMRSS2 are expressed in the dental pulp and, that their expression does not change under conditions of inflammation. Furthermore, Master Regulator Analysis of the SARS-CoV2/human interactome identified 75 relevant genes whose expression values are either up-regulated or down-regulated in both the human interactome and pulpitis. Our results suggest that the dental pulp is vulnerable to SARS-CoV2 infection and that SARS-CoV-2 infection of the dental pulp may contribute to worse outcomes of pulpitis.

Introduction

SARS-CoV2 is a highly aggressive coronavirus, which has infected over 6 million people to date [1]. Most infections (81%) produce only mild symptoms or are asymptomatic. Fifteen percent of infections are severe and require hospitalization. Transmission of this disease is produced by asymptomatic carriers, symptomatic patients, as well patients who are in the incubation period. Human-to-human transmission occurs via close contact of respiratory droplets, direct contact with infected individuals, or by contact with contaminated objects and surfaces.

- Asma A. Khan khana2@uthscsa.edu
- Department of Endodontics, Arthur A. Dugoni School of Dentistry, University of the Pacific, San Francisco, CA 94103, USA
- Department of Surgical and Medical Sciences, Magna Graecia University, Campus S. Venuta, Catanzaro 88100, Italy
- Department of Pharmacy and Biotechnology, University of Bologna, Bologna 40126, Italy
- Department of Endodontics, School of Dentistry, University of Texas Health and Sciences Center, San Antonio, TX 78229, USA

Viral entry into the target cells requires angiotensin converting enzyme 2 (ACE2) and its associated cellular serine protease TPMRSS2 [2]. ACE2, a negative regulator of the renin-angiotensin system, functions as the key SARS coronavirus receptor and stabilizer of neutral amino acid transporters [3]. Viruses found to use this protein for cell entry include Influenza virus and the human coronaviruses HCoV-229E, MERS-CoV, SARS-CoV, and SARS-CoV-2. It is postulated that the pattern of expression of ACE2 in human respiratory epithelia and oral mucosa explains the rapid human-human transmission [4]. TMPRSS2, a serine protease, facilitates entry of viruses into host cells by proteolytically cleaving and activating viral envelope glycoproteins. While a number of studies have examined the expression of ACE2 and TPMRSS2 in various tissues, their expression in the dental pulp is yet to be examined.

Pulpitis, inflammation of the dental pulp, is a disease that often necessitates emergency dental care. Over 90% of dental emergency visits are due to pulpitis pain [5]. In the United States alone, over 22 million procedures are performed annually to treat diseased dental pulps [6]. While pulpitis is considered to be a microbial disease primarily caused by bacteria [7], viruses have also been implicated in its pathogenesis [8]. The complex interaction between the 31 SARS-CoV2 and human proteins has been recently

reported [9], but the correlation between this interactome and pulpitis is yet to be explored.

Here, we first used existing gene expression data (53,000 genes) from our previously published study on pulpitis (GEO NCBI accession number GSE77459; ID: 20007745) [10]. Then, with the data and methods used in a recently published study on the transcriptome-wide effects on coronavirus infection in human cells [11], a master regulator analysis (MRA) [12] was performed to identify genes whose expression values are correlated (upregulated or downregulated) in both the human interactome [11] and pulpitis datasets [10]. With these techniques, we endeavored to answer two important questions: how would the dental pulp respond to SARS-CoV2 infection, and how would ACE2 and TPMRSS2 expression change during SARS-CoV2 infection?

Results and discussion

We identified 75 relevant genes whose expression values are either upregulated or downregulated in both human interactome and pulpitis datasets (Table 1). Of particular interest amongst these genes are ACE2 and TMPRSS2, which were shown to be exploited by SARS-CoV-2 for cell entry and for spike (S) protein priming, respectively [9].

In the human dental pulp, both ACE2 and TMPRSS2 are expressed consistently in biopsies of normal and inflamed tissues (Fig. 1a, b). The expression levels of both ACE2 and TMPRSS2 remain unchanged under conditions of inflammation. These findings are similar to expression patterns in other tissues. For example, both of these viral entry molecules are expressed in the ileum and colon and, expression levels in mucosal biopsies of these tissues do not differ between patients with active Irritable Bowel Disease and those of control patients [13]. Similarly, the expression level of ACE2 in lung tissues does not differ between biopsies taken from patients with chronic respiratory diseases such as chronic obstructive pulmonary diseases and asthma compared to those from healthy volunteers [14].

It is important to note that the consistent expression of both ACE2 and TMPRSS2 in the dental pulp confers its vulnerability to SARS-Cov2 infection. The oral cavity stands at the entry of the respiratory system where its fluids like saliva have been reported to harbor and transmit SARS-CoV2 [15]. This vulnerability may also increase the risk of infection in dental personnel. While several studies have documented the risk of COVID-19 in health care workers, they have been mostly limited to those in medicine and surgery. To our knowledge the risk of acquiring SARS-CoV2 or developing COVID-19 in dental personnel is yet to be documented.

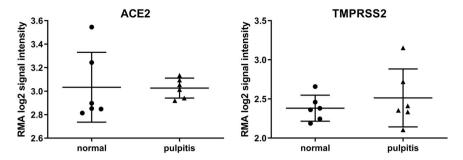
Table 1 Master regulator analysis (MRA) between the gene microarray datasets of inflamed human dental pulp tissue cells and SARS-Cov2 transcriptome in human lung tissue cells.

September Sept		MRA_INTEGRATED	NAME
MIF4GD	EEF1A1		EEF1A1
EIF4B			
DCTN2			
NDUFA10 ACE2 EIF3F AS876092 EIF3F 3.881669285 EIF3F 3.8825013524 SFTPD OCIAD2 BTF3 3.287748138 BZW2 BCL2L2 3.036538169 BRF1 RPS20 PFDN5 -2.942695302 PFDN5 VKORC1 CAV1 PPIH CAMLG -2.171439376 CAMLG C2007f27 PPIA C2.097660662 PPIA TMPRSS2 MARK3 FAHD1 UBE2I H.62592879 UBE2I MNAT1 ATP6V1G1 T.1596010101 MNAT1 ATP6V1G1 T.1584289102 ATP6V1G1 VWHAE SGTA BCL2L1 CHMP2B LAS3L L-1095536157 LAS3L CHEK2 LOREA LOR			
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Table	TMPRSS2	-1.950913709	TMPRSS2
UBE2 1.625592879 UBE2 UMNAT1 1.596010101 MNAT1 ATP6V1G1 VWHAE 1.392488514 VWHAE SGTA 1.290957934 SGTA CL2L1 1.176653696 BCL2L1 CHMP2B L.102816779 CHMP2B LAS1L 1.095536157 LAS1L CHEK2 1.082909434 CHEK2 IKBKB 1.082420145 IKBKB CLEC4G NAE1 1.03567167 NAE1 ISLR 0.980194767 SLR CD209 -0.8171606 CD209 SLC46A3 PSMA2 0.71908742 PSMA2 RCAN3 -0.71908742 PSMA2 RCAN3 -0.71908742 PSMA2 RCAN3 -0.590351578 SERPING1 C110f74 -0.513118793 C110f74 NPH93 -0.381046915 NPHP3-ACAD11 POLR2B -0.350218246 POLR2B XPA -0.33597822 XPA LCP1 -0.333421252 LCP1 H2AFY2 -0.264829439 TBCB NABP2L2 CLEC4M IRF3 0.171350307 IRF3 BAP1 ALB 0.578252442 ALB NMB 0.617598222 NMB NMB 0.617598223 NFRN2 DMAP2 DMAP2 DMAP2 DMAP2 DMAP3 DM	MARK3	-1.720091248	MARK3
MNAT1 ATP6V161 BEL381 BEL2L1 -1.176653696 BEL2L1 -1.176653696 BEL2L1 CHMP2B LAS1L -1.095536157 LAS1L CHEK2 IKBKB -1.082909434 CHEK2 IKBKB -1.082909434 CHEK2 IKBKB -1.082909434 CHEK2 IKBKB -1.03567176 TABE1 ISLR -0.980194767 ISLR CD209 -0.8171606 CD209 SLC46A3 -0.790643856 SLC46A3 PSMA2 RCAN3 -0.711262906 RCAN3 TERF1 SERPING1 -0.590351578 SERPING1 C110474 -0.513118793 C110474 NPHP3 -0.381046915 NPHP3-ACAD11 POLR2B XPA -0.335997822 XPA ICP1 -0.333421252 LCP1 H2AFY2 TBCB -0.264829439 TBCB N4BP2L2 -0.096942088 N4BP2L2 CLEC4M IRF3 -0.171350307 IRF3 BAP1 ALB -0.578252442 ALB NMB -0.617598222 NMB MKRN2 -0.680489923 MKRN2 -0.691965724 DDAH2 BRF1 -0.697516152 BTF3 RYBP -0.085916348 ARL4D TPSAB1 -0.085916348 -0.19851344 -0.198516348 -0.1			
ATP6V1G1 YWHAE -1.392488514 YWHAE SGTA GC22L1 -1.176653696 BCL2L1 CHMP2B LAS1L -1.095536157 LAS1L CHEK2 -1.082909434 CHEK2 IKBKB CLEC4G -1.070002283 CLEC4G NAE1 ISLR -0.980194767 ISLR CD209 -0.8171606 CD209 SLC46A3 -0.790643856 SLC46A3 PSMA2 -0.717908742 PSMA2 RCAN3 -0.711262906 RCAN3 TERF1 SERPING1 -0.590351578 SERPING1 C110rf74 NPHP3 -0.38104691 POLR2B XPA -0.333997822 XPA LCP1 -0.333421252 LCP1 H2AFY2 -0.279673123 H2AFY2 TBCB N4BP2L2 -0.096942088 N4BP2L2 CLEC4M 0.156476249 CLEC4M IRF3 0.171350307 IRF3 BAP1 ALB 0.578252442 ALB NMB 0.617598222 NMB MKRN2 DDAH2 0.689489923 MKRN2 DDAH2 BRF1 0.6997516152 BRF3 RVBP PIG 1.049955368 PPIG ARL4D 1.088916348 ARL4D TPSAB1 DEDD2 1.279555758 DEDD2 BCL2 HGS LR7899235 ATFS SMOC1 BRSVASO MARK2 2.497359666 NARK2 2.5409886 MARK2 2.7985013 DDX5			
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	IVICL1	4.043126478	IVICLI

Underexpressed genes are highlighted in blue, overexpressed genes in red.

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Fig. 1 ACE2 and TMPRSS2 expression in normal and inflamed human dental pulps. Differences in RMA log2 signal intensity between samples were analyzed using Student's *t* test. No statistical difference was found in the expression of both genes in normal and inflamed dental pulps.



The MRA correlation analysis between the pulpitis microarray dataset and the human SARS-Cov2 transcriptome-wide effects shows that both ACE2 and TMPRSS2 values are underexpressed (Table 1). SARS-CoV infection in other tissues have shown marked decrease in ACE2 expression [16]. Furthermore, underexpression of ACE2 was associated with worse outcomes of SARS-CoV2 infection in patients with inflammatory bowel disease [17].

One of the advantages of studies like the present one is that by using omic tools, one can answer several biological questions, without the need of collecting more samples. Our original studies on gene expression in inflamed human pulps was conducted several years ago. We then took advantage of having the sequenced data to explore expression of ACE2 and TPMRSS2 in inflamed and normal human pulps. This was an efficient and quick way to answer a time-sensitive question [10].

Taken together, our results suggest that the dental pulp is vulnerable to SARS-CoV2 infection. The predicted underexpression of ACE2 during SARS-CoV infection in the dental pulp may contribute to worse outcomes of pulpitis.

Materials and methods

Our analysis started by assessing a published study that utilized a dataset describing the transcriptome-wide effects of coronavirus infection in human cells [11]. The study employed a system [18] that probed the transcriptome-wide effects of SARS-CoV2 and its implication on human interactome by applying a MRA, which was performed by comparing infected and mock samples in both MERS and SARS datasets separately with the corto algorithm [18]. With these tools, an MRA correlation analysis of the gene microarray dataset of pulpitis [10] can be performed using a known platform in managing microarray binary data [19].

We first calculated a gene-by-gene signature of differential expression of genes caused by viral infections. In brief, a gene-by-gene signature of viral-induced differential expression is generated, and combined value for each coexpression network is generated by weighting every gene's likelihood in the network, providing a final Normalized Enrichment Score for each genes of the human/Sars-Cov2 integrated interactome. The value is positive when the network is unregulated by the infections, and vice-versa. In this study, we hypothesized that the effects of the viral infection are the same for the dental tissue, therefore we merged the data published in human airway cells [11] with that in dental pulp tissue cells [10]. Consequently, we were able to predict a possible regulator effect for the same genes. This study may therefore suggest some possible effects that should be tested in the future by extracting dental tissue samples from Covid-19 infected patients.

Gene expression analysis of ACE2 and TMPRSS2 in normal and inflamed dental pulps were from our previous study's existing public gene expression database on pulpitis (GEO NCBI accession number GSE77459). Differences in RMA log2 signal intensity between samples were analyzed using Student's *t* test. Statistical significance was set at 0.05.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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