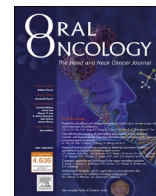




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Is prognostic monitoring of high-risk populations at risk for oral cancer necessary after infection with COVID-19?

Dear Editor,

COVID-19 disease is a pandemic that has been ravaging humankind for a few years. The physiological, psychological, and financial toll inflicted by this disease on people is severe [1]. COVID-19 has an inflammatory pathophysiology characterized by a cytokine storm, which refers to a huge inflammatory engagement as an infection response [2]. COVID-19 has a tremendous impact on the global health scenarios affecting all domains of human survival. Cancer patients have an alarming risk of contracting COVID-19 infection owing to their immunocompromised and inflammatory state. Cancer patients are highly susceptible to COVID-19 but whether SARS-CoV-2 can cause cancer in cancer survivors, susceptible populations (with altered lifestyles such as tobacco use), and patients with premalignant disorders is not yet known. So there is a need for studies unravelling the following questions: (a) whether SARS-CoV-2 infection increases cancer risk? (b) Does the infection affect tumor initiation and progression, and (c) What is the molecular basis of interconnectivity between cancer and COVID-19? Oral cancer is the sixth most frequent cancer across the globe, with a five-year survival rate of under 50%. As a result, it's crucial to understand the biology of oral cancer and look into alternate prognostic and therapeutic targets. Oral cancer patients encounter inflammatory bursts that may aggravate oral cancer prognosis.

We have reviewed various works of literature with a vision of whether COVID-19 and cancer share common molecular events/signatures that increase the risk of cancer. Certainly, we found that both these disease conditions share similar miRNA signatures.

Human coronaviruses alter antiviral immune responses by co-opting with host miRNAs. SARS-CoV-1 infection alters the circulating host miRNA signatures. Host miRNAs, by binding to viral RNA, actively modulate the replication and pathogenesis processes. Alternatively, SARS-CoV-2 encoded miRNA was found to hijack host miRNA to alter human gene expression involved in apoptosis, inflammation, and immune response. Alterations in these genes result in irregularities in the cell cycle and cancer. miRNAs are single-stranded, short (~22 nucleotides in length), and non-coding RNAs participate in the post-transcriptional regulation of mRNAs. A single miRNA can target the expression of multiple mRNAs and the expression pattern is likely to be altered in different disease conditions. Interactions of miRNAs with SARS-CoV2 resulted in increased expression of several functionally important miRNAs in immune cells, which could contribute to gene deregulation and modification of the host immune response, allowing viral infection to progress [3]. The SARS-CoV-2 genome has been shown to hijack the genes for hsa-miR-146b and hsa-miR-939, two critical modulators of immune responses. Some host miRNA changes caused by SARS-CoV-2 were substantially related to comorbidities. For example, hsa-miR-3611 has been linked to an increased susceptibility to viral

respiratory infections in opioid users. TGF-pathways, inflammatory response, cytokine-cytokine receptor interaction, and oxidative stress have all been related to hsa-miR-8066, hsa-miR-1307-3p, hsa-miR-3691-3p, and hsa-miR-5197-3p, all of which are hallmarks of pulmonary injury.

Several host miRNA genes were also activated during COVID-19. IFN, TGF, interleukins (IL), IGF1 (insulin-like growth factor 1), tumour necrosis factor-related apoptosis-inducing ligand (TRAIL), and toll-like receptors (TLRs) signalling have all been shown to be downregulated by these human miRNAs, resulting in immune suppression in the host. Another study found that the SARS-CoV-2 genome titrated 22 human miRNAs, resulting in altered and dysregulated post-transcriptional processes in infected cells such as CD8 + T, CD4 + T, and natural killer (NK), CD14, and mast cells. Noncoding SARS-CoV-2 RNAs may dysregulate and inhibit human miRNA levels, such as miR-99b-5p, miR-376a-3p, miR-10a-5p, miR-548av-5p, miR-376a-3p and miR-99b-5p, which are implicated in immune responses, by functioning as host miRNA sponges [4]. The tumour suppressor p53 gene is targeted and inhibited by the SARS-CoV-2 altered host miRNA MD3-3P. p53 is a key inducer of apoptosis during viral infection and is involved in innate immune activation. By sponging and depleting the human miR-376b-3p, SARS-CoV-2 might increase the activity of the mammalian target of rapamycin (mTOR) and inhibit the autophagy process [5].

Smokeless tobacco use, such as maras powder, has been linked to increased expression of miR-31 and miR-138, as well as decreased expression of miR-10b, miR-200b, miR-92a, miR-372, miR-378a, miR-375, and miR-145; tobacco chewing has been linked to increased expression of miR-155 and decreased expression of miR-542. Tobacco smoking has been linked to lower expression of miR-23a,b, miR200b, miR-203a, and miR-375. Pan-masala chewers had higher levels of miR-21 expression; areca nut chewers had higher levels of miR-23a and miR-155 expression, and alcoholics had higher levels of miR-34a, miR-183, and miR-375 expression. In receiver operating characteristic (ROC) curve analysis, miR-21 is considerably overexpressed in 62–89 percent of oral tumors, with a 4.345 – 39.51 fold change in expression and a testing accuracy of more than 90%. Oral cancer patients had higher amounts of miR-21 in their plasma and saliva than healthy controls, allowing for a non-invasive diagnosis [6].

Studies have shown that miR 21, miR 21-3p, miR 29a, miR 155-5p, miR 155, and miR 182 upregulation and miR 17 downregulation are common in oral cancer and COVID-19 disease [7]. These upregulated miRNA's are involved in both cancer initiation and malignant transformation. Therefore, the individuals classified as a high-risk population for oral cancer would be vulnerable to cancer following COVID-19 owing to miRNA dysregulation. Since COVID-19 affects the cytokine pathways and immunoregulatory mechanisms, there is a considerable

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likelihood that oncogenic microRNAs can be triggered to initiate cancerous transformation. Hence, patients with COVID 19 disease should be considered a significant risk group for oral cancer acquisition and should be monitored periodically for oral cancerous transformation using suitable biomarkers.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Dhanraj Ganapathy^{*}, Saravanan Sekaran, Sivaperumal Pitchaiah
*Department of Prosthodontics, Saveetha Dental College and Hospitals,
 Saveetha Institute for Medical and Technical Sciences, Chennai 600077,
 Tamil Nadu, India*

^{*} Corresponding author.

E-mail address: ghanraj@saveetha.com (D. Ganapathy).