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COVID-19 and oral cancer: Critical viewpoint

Gopalakrishnan D *et al.* COVID-19 and oral cancer

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Abstract

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has marked the beginning of a new pandemic named coronavirus disease 2019 (COVID-19). The World Health Organization has announced it as a health emergency which is of international concern. The disease has been reported to cause respiratory illness, pneumonia and even hinder the immunity of an individual. Individuals with disturbed immune responses have been found to be quite susceptible to this viral infection. Oral cancer patients are also at high risk in this pandemic situation and might encounter severe detrimental outcomes. Angiotensin receptors, documented in studies as the path of entry of this virus, are highly expressed in the epithelial cells of oral mucosa, making the group of individuals with oral cancers even more vulnerable. Extracellular matrix metalloproteinase inducer (EMMPRIN) is another potential target for SARS-CoV-2. An exhaustion of angiotensin converting enzyme 2 cell receptors leads to pro-tumoral effects, whereas a downregulation of EMMPRIN leads to anti-tumoral effects. Thus, it causes a variation of the biological behaviour of the tumor. This article focusses on the molecular mechanisms, effects and pathophysiology of COVID-19 in oral squamous cell carcinoma (OSCC) patients. The different molecular changes in OSCC in the background of COVID-19 will modify various environmental factors for this pathology and have an effect on the carcinogenesis process. Understanding the behaviour of the

tumor will help plan advanced treatment strategies for OSCC patients in the background of COVID-19.

Key Words: COVID-19; SARS-CoV-2; Oral cancer; Head and neck carcinomas

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Core Tip: ¹ The outbreak of the coronavirus disease 2019 (COVID-19) pandemic has evoked a huge concern world-wide. The rapid spread of the disease during the first and the second waves have caused severe respiratory illness; individuals are also facing a serious suppressed immune response. An impaired immune response has made patients with head and neck cancer highly susceptible to the viral infection. Moreover, the two most potential receptors of severe acute respiratory syndrome coronavirus 2, that is, angiotensin receptors and extracellular matrix metalloproteinase inducer have contrasting effects on cancer progression. Thus, the molecular mechanisms and the biological behaviour of oral squamous cell carcinoma show varying effects in the background of COVID-19.

TO THE EDITOR

³ The outbreak of coronavirus disease 2019 (COVID-19) pandemic has posed a major health impact, affecting population all over the world with significant morbidity and mortality. With the introduction of second wave in many countries, the doubling time of infectivity has reduced drastically. This also means that we should doubly prepare for all the consequences that we faced in the first wave. Individuals with disturbed immune responses have been found to be quite susceptible to this viral infection. Cancer patients have been considered to be at high risk in this pandemic situation because of immunosuppression^[1]. Not only the underlying malignant condition but

also co-morbidities, advanced age and poor host response have been held responsible for the vulnerability of cancer patients during COVID-19 pandemic^[2,3].

Studies have identified the angiotensin converting enzyme 2 (ACE2) cell receptors as the path of entry of 2019-novel corona virus (2019-nCov) into a host cell^[4]. ACE2 receptors are reportedly found to be highly expressed on the epithelial cells of oral mucosa making the group of individuals with oral cancers even more vulnerable. ACE2, a key enzyme of renin-angiotensin system (RAS), breaks down **Angiotensin II (Ang II)** into **Angiotensin 1-7 (Ang 1-7)**^[5]. **Ang II** is a pro-tumoral agent which plays a major role in carcinogenesis^[6]. It helps in tumor cell proliferation and angiogenesis. It also facilitates the metastasis of cancer cells. Thus, Ang II aids in progression of the disease while ACE2 and Ang 1-7 inhibit the progression. ACE2 maintains a balance of RAS^[5]. However, these propositions might alter due to change in the viral component, specially mutation in the spike protein.

The novel corona virus takes help of the ACE2 cell receptors and gets attached to them through the S-spikes on the virus surface. The SPIKE (S protein) expressed by the virus **attaches to the extracellular part of ACE2 receptors and the S protein breaks down into subunits S1 and S2**^[7]. The virus gets fused with the cell membrane and gets entry into the cell *via* endocytosis. An exhaustion of ACE2 receptors takes place due to the viral infection. ACE2 receptors being highly expressed in tongue, gingiva and buccal epithelial cells, oral squamous cell carcinoma (OSCC) patients are at high risk during this pandemic^[7]. The viral infection will cause a reduction in ACE2 concentration leading to an increase in Ang II concentration^[5]. This could have a pro-tumoral effect facilitating the progression of OSCC.

Besides ACE2 receptors, **extracellular matrix metalloproteinase inducer (EMMPRIN)**, also known as **BASIGIN/CD147** has been identified as another potential target for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)^[8]. EMMPRIN is a cell surface glycoprotein **belonging to immunoglobulin family**. It helps in activation of molecules of several matrix metalloproteinases. Thus, it helps in proliferation of tumor cells, their invasion and also migration^[9]. EMMPRIN also promotes angiogenesis by

stimulating vascular endothelial growth factors in tumor microenvironment^[10]. It can be quite well speculated that EMMPRIN expression is increased in oral carcinogenesis. The upregulation of EMMPRIN expression in OSCC patients might make them more susceptible to COVID-19 infection^[8]. The virus attaches itself to EMMPRIN receptors through S receptors, thus, COVID-19 in OSCC patients will lead to downregulation of EMMPRIN receptors. This will inhibit the progression of the tumor due to scarcity of EMMPRIN receptors.

² The COVID-19 infection in OSCC patients will reduce the availability of ACE2 receptors. This will lead to upregulation of Ang II concentration, thus, promoting carcinogenesis. In such situations of non-availability of ACE2 receptors, SARS-CoV-2 gets attached to its next potential target, EMMPRIN receptors to get entry into the host cells^[8]. This in turn causes downregulation of EMMPRIN receptors leading to anti-tumoral effects. The two potential receptors of SARS-CoV-2 have contrasting effects on OSCC progression.

COVID-19 infections in OSCC patients modulate the events of carcinogenesis and control the biological behavior of the tumor. Future molecular studies are required to have a better insight into the role of the two receptors in the pathophysiology of OSCC. Moreover, ¹ angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) which are administered in cancer patients have been thought to have varying effects on tumor progression. The use of these drugs in OSCC patients during this pandemic still remains doubtful and requires clinical studies.

The expression of ACE2 in various pathologies like oral cancer, oral submucous fibrosis and periodontitis modulate their disease process. The biological behavior of not only OSCC, but also other oral potentially malignant disorders, in the background of COVID-19 requires in-depth studies and researches. This can only be achieved by representative clinical material *i.e.*, COVID-19 positive OSCC patients, appropriate disease model and their long term follow-up. While keeping these interactions in mind, one should not forget the delay in cancer treatment worldwide. COVID-19 pandemic has caused deviation of attention from many medical emergencies; cancer and OSCC is

not an exception to it. Thus, it is mandatory to formulate guidelines for safe and effective delivery of therapeutics to cancer patient in this difficult time.

Impact of pandemic on cancer management

Due to mandatory lockdown during pandemic, many healthcare speciality services get affected including cancer management. Many countries reported more than 50% reductions in the registration of new cancer patients^[11]. These repercussions of pandemic are mainly related to travel restrictions, conversion of hospitals to COVID-19 centres, fear in the mind of patients, human resource shortage, *etc.* To mitigate the reduction in number of cases many cancer hospitals have started telecommunication and teleconsultations, but it is premature to comment on its effectiveness especially for head and neck cancer.

Due to compromised primary medical and dental services across the world, the early detection of oral cancer is at stake. Already head and neck cancers are detected at advanced stages; further delay in the detection would lead to extremely poor prognosis. According to one study in US, there was 25% reduction in the newly diagnosed oral cancer cases^[12]. Currently, COVID-19 is at declining stages in many countries and this opportunity should be exploited to perform maximum screening for early detection.

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