Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the editor

Biological behavior of oral squamous cell carcinoma in the background of novel corona virus infection

Oral squamous cell carcinoma (OSCC) is the most common malignancy of the oral cavity with increasing incidence and mortality [1]. It is known that tumor microenvironment can modulate the biological behavior of tumor cells. One of the such important modulator is the presence of functional renin-angiotensin system (RAS). Angiotensin II (Ang II), a crucial component of RAS has been reported to have pro-tumoral roles in carcinogenesis [2].

Ang II is produced from the peptide, Angiotensin I (Ang I) by a protease enzyme, angiotensin converting enzyme (ACE). Ang II exerts its functions by attaching to its receptors Ang II receptor type 1 (AT1R) and Ang II receptor type 2 (AT2R). The ACE is known to be a pivotal enzyme in controlling the renin-angiotensin system. ACE2, a homolog of ACE, is another key enzyme of the RAS, which breaks down Ang II to form Ang 1-7 [3]. ACE2 and Ang 1-7 counterbalance the effects of ACE and Ang II respectively. Ang II is reported to play a vital role in carcinogenesis and apart from its systemic actions, it also exerts local effects. It can promote angiogenesis and cellular proliferation [2]. It also mediates the invasion of OSCC cells, thus facilitating its metastasis. Ang II provokes the stromal-tumor paracrine interaction [2]. AT1R mediates the actions of Ang II by receptor phosphorylation and subsequently triggering a chain of intra and extracellular events. ACE, Ang II and AT1R facilitate the pathogenesis of the disease, on the other hand ACE2, Ang 1-7 and AT2R inhibit the progression of the disease and antagonize the actions of ACE, Ang II and AT1R [3]. Thus, it is quite evident that ACE2 maintains the balance of RAS as a negative controller.

Recent studies on Covid19 have indicated that the path of entry of 2019-nCov into a host cell is through the ACE2 cell receptor [4]. The virus attaches itself to this receptor through the S-spike present on the virus surface [5]. ACE2 has been identified as the co-receptor for the corona virus. Intriguingly, ACE2 receptor of this virus is highly expressed on the oral mucosal epithelial cells [6]. The single cell RNA sequence of four samples of oral mucosal tissues were observed and the expression of ACE2 was recorded higher in epithelial cells of tongue than buccal and gingival tissues [6]. The virus expresses a protein, which is known as SPIKE (S protein). This protein contains a receptor binding region, which attaches to the extracellular part of the ACE2. The S protein is broken down into two subunits- S1 and S2 by a host protease TMPRSS2 [6]. The virus fuses with the membrane and is incorporated via endocytosis with ACE2 into the host cell. Thus, COVID-19 infection causes exhaustion of ACE2 cell receptors. In situations of COVID-19 infection in OSCC patients, there will be reduction in availability of ACE2. This situation will increases the concentration of Ang II, thus could be promoting a pro-tumoral effect mediated by Ang II.

Exposure to tobacco has always been regarded as a vital risk factor for the development of OSCC. Smokers, besides being at high risk of developing OSCC, are also very much prone to acquire the COVID-19 viral infection. Studies have revealed that smoking increases the expression of ACE2 receptor, the potential attachment site of 2019-nCoV [7]. There could be a high possibility that expression of ACE2 increases even in the oral mucous membrane by consistent use of tobacco. If the consistent use of tobacco increases the ACE2 expression in the oral mucosa, then it would act like a protective mechanism against the progression of the tumor. This could be one the defense mechanisms of the body against the carcinogens which is not yet explored in the literature. We believe that even if tobacco increases the expression of ACE2 in the oral mucosa, detrimental effects of tobacco (DNA damage, gene mutations) are more severe than the protective mechanism of ACE2. However, exact outcome of the complex interaction between tobacco, COVID-19 and tumor cells is very difficult to speculate. Future studies are warranted in this direction to better understand the mystical association of tobacco, ACE 2, OSCC and COVID-19.

Angiotensin converting enzyme inhibitors (ACEIs) and Angiotensin receptor blockers (ARBs) are quite known to be used as treatment regime in carcinoma patients to manage hypertension [8]. The production of Ang II is inhibited by ACEIs and thus subsequently the pro-tumoral effects of Ang II and the effects of Ang II binding with AT1R and AT2R are also inhibited. Studies have indicated that ARBs can suppress the development of tumors and can even prevent their invasion [8]. A school of thought believes that the use of ACEIs and ARBs upregulates the expression of ACE2 thus making the individual susceptible to COVID-19 complications. Another group of researchers believe that ACEIs and AT1R inhibitors might reduce the effects of Ang II. The binding of the virus with ACE2 reduces ACE2 expression on one hand, on the other hand it increases the concentration of unconverted Ang II which finds that its receptor AT1R is blocked by the drug, thus it proceeds to bind with its second receptor AT2R and triggers a chain of protective mechanism [9]. Thus, the use of ARBs (AT1R antagonists) might have a protective effect. While on the other hand, ACEIs inhibit ACE to form Ang II, hence, reducing its negative results brought about by binding with AT1R and also the protective effects mediated by binding with AT2R [9]. However, there is still a doubt and controversy regarding the use of ACEIs and ARBs in this present pandemic situation. Clinical studies and research need to be carried out regarding their use in the treatment of carcinomas in the setting of COVID-19. ACEIs and ARBs have shown to improve renal, prostate and breast cancer conditions but there is insufficient evidence about their effects in OSCC. Since studies have indicated the presence of a functional RAS in the oral mucosa, there might be a possibility of improving OSCC conditions by the use of ACEIs and ARBs. This hypothesis needs to be addressed. Moreover, it is still a matter of concern whether or not to use these medications for patients in this pandemic condition.

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Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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