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 Editors

Oral cancer and periodontal disease increase the risk of COVID 19? A mechanism mediated through furin and cathepsin overexpression

COVID-19 was first reported in Wuhan, China in December 2019 [1]. The infectious disease has spread rapidly and was upgraded by WHO to be a pandemic. It commonly presents as fever, dry cough, and dyspnea. In a minor proportion of patients as the disease progresses, it may lead to severe alveolar damage-causing respiratory distress, which can culminate in mortality [2]. The main route of human to human transmission has been suggested to occur by respiratory droplets released by the infected [3], which has necessitated social distancing. Despite numerous measures by health agencies the disease continues to afflict the human race. Understandably, the past couple of months have seen a surge in the number of articles published on SARS-corona virus-2. These articles largely consist of clinical case reports, molecular profiling of the virus, bio-informatic analysis, and hypothesis. Among the hypothesis, the focus has largely been on identifying high-risk group, decoding pathogenic pathways, and in formulating therapeutic strategies.

We present a hypothesis to recognize a potentially high-risk group and to strategize a prophylactic measure to reduce the risk of virus infection in the specific group.

Hypothesis

Studies including bio-informatic analysis have shown the presence of angiotensin-converting enzyme 2 (ACE2) receptors in oral mucosa, including the tongue, buccal mucosa, and gingiva [4]. Similar to SARS-corona virus-1, even the SARS-corona virus-2 exhibits affinity towards ACE2 receptors [2]. Thus, oral mucosa could be a possible route for SARS-corona virus-2 infection. Oral mucosa in pathological states such as chronic periodontitis/oral cancer has shown to exhibit higher levels of osteopontin, which in turn can activate the p38 mitogen-activated protein kinase, stimulating nuclear factor-kappa B signaling and elevating the level of the protease furin [5–7]. In addition to furin, another

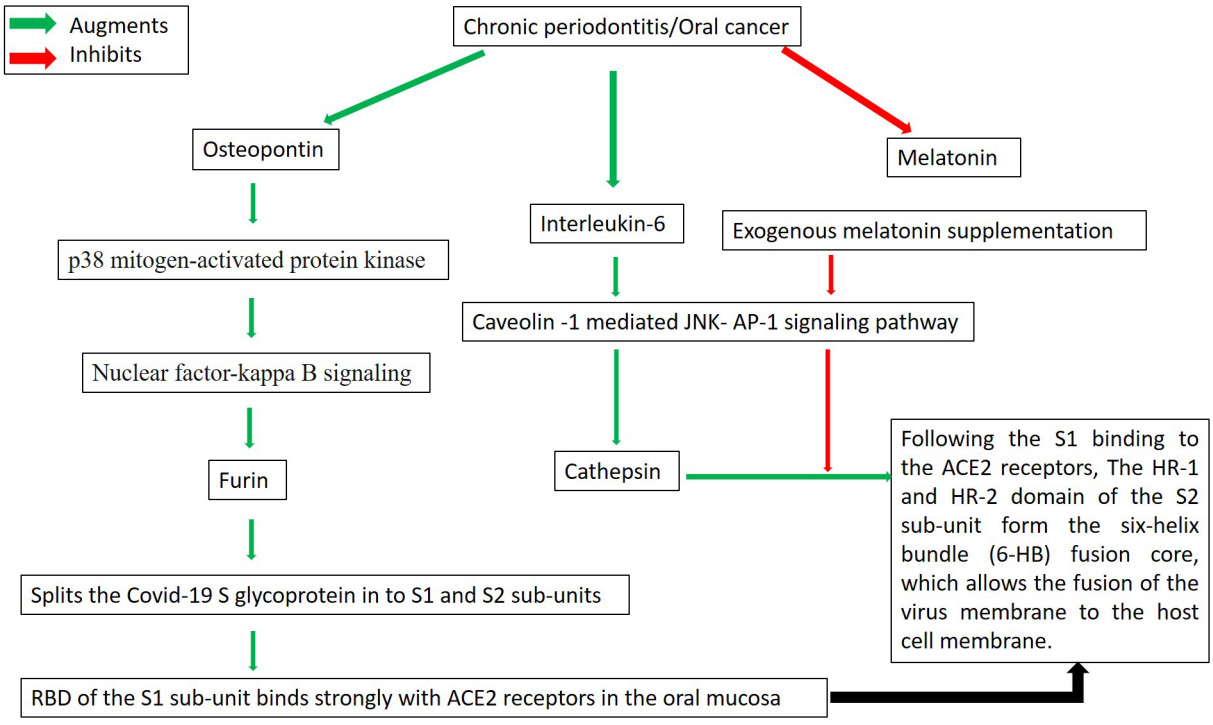

Fig. 1. Oral mucosa mediated SARS-corona virus-2 infection in oral cancer/periodontitis patients.

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protease cathepsin L is also elevated in chronic periodontitis and oral cancer, which in turn could be a result of the interleukin 6 mediated activation of the caveolin-1 mediated JNK-AP-1 signaling pathway [8–10]. Both furin and cathepsin play a major role in enabling the SARS-corona virus-2 to infect the host cells as elaborated in the following steps:

1) Furin pre-cleaves the S glycoprotein of the SARS-corona virus-2 into S1 and S2 subunits [11,12].
2) Following the pre-cleavage of the S glycoprotein, the receptor-binding domain (RBD) of the S1 subunit attaches itself to the angiotensin-converting enzyme 2 (ACE2) present in the host cells [13].
3) Following binding of the S1 subunit to the ACE-2 receptors, the virus fuses with the host cell in two mechanisms: (a) endosomal fusion which is mediated by cysteine proteases cathepsin B/L and (b) plasma membrane fusion mediated by the serine protease TMPRSS2. The heptad repeat (HR) 1 and the HR2 of the S2 subunit form a six-helix bundle (6-HB) fusion core. The formation of this core brings the cell membrane of the virus and the host close allowing cell fusion and infection [12,13].

Based on the above-mentioned data, it can be hypothesized that the increased protease levels in chronic periodontitis and oral cancer could potentially increase the risk of an oral mucosa mediated SARS-corona virus-2 infection (Fig. 1). In addition to increasing proteases, chronic periodontitis, and oral cancer patients have also reported having a low melatonin level [14,15]. Melatonin possesses anti-inflammatory, antioxidant properties [13]. Also, melatonin has shown to inhibit cathepsin L [16]. Thus, exogenous supplementation of the melatonin could aid in reducing the virus-induced inflammation, oxidative stress, and disrupting the cathepsin mediated fusion of virus and host cell.

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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