Review Article:

Does COVID-19 and oral, lung cancer have a connection? A insight to future investigation; A literature review.

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Abstract

Even though there has been a significant amount of research conducted on the origin of SARS-CoV-2 (SARS-CoV-2) aetiology, very little is known about the disease's long-term effects till the date(1). As with previous viral infections, SARS-CoV-2 may raise the risk of developing cancer by altering tumour suppressor genes and expression of various pro-oncogenic proteins. We will conduct a comprehensive review of the available research on it,because an infection with SARS-CoV-2 might have a potential to cause cancer in the long run, researchers are looking at the likelihood of this happening, precisely on likeliness of occurring oral and pulmonary malignancies in this work. We speculate that one of these long-term impacts may be the SARS-carcinogenic CoV-2 virus. The viral proteins Nsp-15 or Nsp-3 are hypothesised to have pro-oncogenic effects when they interact with two essential tumour suppressors, pRB and p53 inhibitors.

Keywords: SARS-CoV-2 virus; Viral infections; Oral and pulmonary malignancies.

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Introduction

According to the World Health Organization (WHO), the total number of COVID-19 cases worldwide is estimated to be 492,189,439 as of April 4, 2022, with 6,1594,74 deaths[2]. Additionally, as of April 4, 2022, the total number of COVID-19 cases that have been registered in Bangladesh stood at 4,27,0000, with 35,160 deaths, according to the Bangladesh Ministry of Health's COVID-19 information centre[3]. SARS-CoV-2 is the virus that causes COVID-19, and the World Health Organization describes it as an airborne infection spread through close contact with infected droplets and aerosols by asymptomatic, pre-symptomatic, and symptomatic patients[4,5]. Although SARS-CoV-2 can be transmitted via close contact activities such as talking, breathing, coughing, sneezing, and even singing, the nasal-lung axis has received the most attention[6,7]. However, approximately half of all COVID-19 cases report decreased taste, dry mouth, and mouth sores, it is unknown whether SARS-CoV-2 can be transmitted directly to and replicated in oral tissues such as salivary glands (SGs) or mucosa[7-9]. This is important because, if the initial infection occurs in the salivary glands, saliva can contribute to viral infections in the oral cavity and lungs by the virtue of unique morphology (Figure 1).

The SARS-CoV-2 virus is an RNA virus with a single

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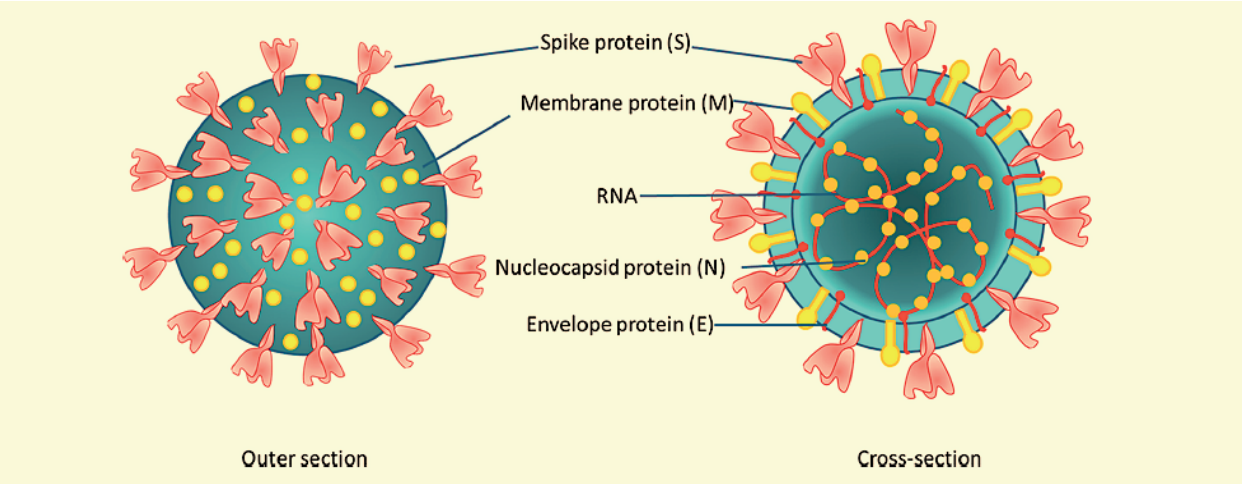

Figure1: SARS-CoV-2 virus morphology.

strand, which measures 29,903 base pairs and is~50 - 150 nanometers in diameter. Novel viruses can take on a variety of shapes, from spherical to oval to pleomorphic. It is a member of the betacronavirus genus and the cervicovirus subgenus. RNA's structure is as follows: 5'-leader-UTR-replicase S-E-M-N 3'-UTR-Poly (A) The open reading frame of the tail is unknown, where S represents spike, E represents envelope, M represents membrane, and N represents nucleocapsid (Figure 2).It has a sequence identity of 80.26 percent and genome coverage of 98.6 percent of the SARS-CoV genome infected population. SARS-CoV-2 utilizes the Angiotensin-converting enzyme 2 (ACE2) receptor to enter host cells1[0,1]

SARS-CoV-2 replication in human cell cytoplasm

In bronchial tissues or cells, the SARS-CoV-2 spike attaches to the protein ACE2 receptor, allowing the virus to enter the cell. Spike (S) protein is a homotrimer glycoprotein made up of two subunits responsible for virus-host cell membrane fusion and binding to host cell receptors[12]. The envelope protein (E) is found in a site of intracellular traffic, such as the golgi complex, where it assists in the golgicomplex's self-assembly. Additionally, it is believed to be required for the formation and maturation of viral particles. The nucleocapsid protein directs the genome to replicate, replicate, and package (N)[13]. Membrane protein (M) is also involved in the stabilisation of nucleocapsids within internal membrane structures such as the golgi complex, as well as the delivery of nutrients to the transmembrane, virion secretion, and envelope structure. Near the cell membrane's edge, the S protein is degraded into S1 and S2 do not contain distinct subunits[14]. The S1 subunit binds to the receptor, while the S2 subunit (which contains the fusion instrument) continues to generate perfusion in preparation for membrane fusion with the host cell. S protein priming, or the degradation of S protein at the S2'site by a cellular protease, is required for SARS-CoVfusion. It facilitates protein activation by irreversibly altering the S protein's extensive decoration with linked confirmation glycans, which aids in proper folding and thus access to host proteases[15]. It begins replication once the viral DNA has been translated into two polyproteins and structural proteins within the cytoplasm. When envelope (E) glycoproteins are introduced into the Golgi endoplasmic reticulum membrane, nucleocapsids are formed. This location contains the enzyme Furin, which enables effective S protein activation via protein conversion. Furin is a calcium-dependent membrane-bound protease that is created in large quantities as 794 amino acid zymogens. In order to become fully active, these zymogens must first undergo automatic cleavage. These vesicles contain viral particles and replicate the virus within the host cell's cytoplasm (Figure 3). Type I and II epithelial cells produce ACE2 receptors in the lungs. The viral receptor ACE2 and 20 other genes involved in virus replication and infection are enriched in alveolar type II epithelial cells, according to RNA profiling data. Only 0.64 percent of all human lung cells expressed ACE2, which is significant. Variations in the expression of ACE2 in epithelial cells are associated with disease. Completely differentiated cells (those that produce a high level of ACE2) are more susceptible to viral infections, hence, subsequently infected weakly

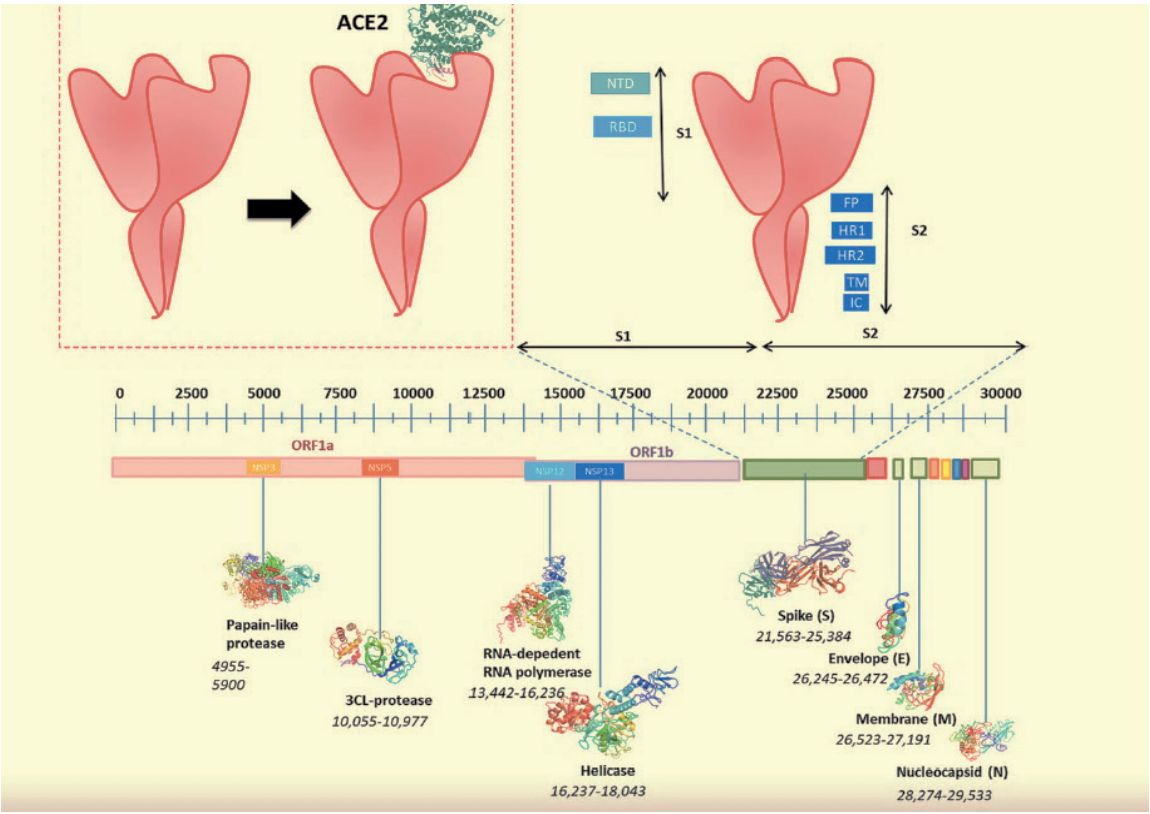

Figure 2: Spike proteins that bind to the SARS-CoV-2 genome.Codified proteins, and ACE2 receptors are depicted in Figure 2. SARS-CoV-2 ACE2 interaction with RBD image (inset). NTD represents N-terminal domain; RBD symbolises receptor binding domain; FP reflects fusion peptide; HR1 denotes heptad repeat 1; HR2 signifies heptad repeat 2; S1 represents receptor binding subunit; S2 represents membrane fusion subunit; IC represents intracellular tail; NSP represents non-structural protein., non-structural proteinSARS-CoV-2 enters host cells via the angiotensin-converting enzyme 2 (ACE2) receptor. This receptor is prominent in the lungs, upper esophageal epithelial cells, ileum, and colon enterocytes, as well as kidney tubules. As a result, the infection has the potential to spread across the respiratory and digestive systems.

differentiated cells (those that produce a low level of ACE2)[16,17].

Infections with SARS-CoV-2 and cancer incidences

In humans, cancer can develop as a result of a series of random mutations. Cancer cases are associated with genomic events that accelerate the rate of genetic mutations. UV exposure, for example, causes mutations in melanocytes, which can eventually result in the development of melanoma1[8,19]. Cancer and viral infections are two events that may be particularly significant. The connection between viruses and tumours is one of the most significant discoveries in contemporary biology[20]. A viral infection can progress to cancer in a variety of ways, from a persistent inflammatory response to immune system suppression to active host cell reprogramming[21]. In general, a virus can transform normal cells directly into malignant cells in the following ways: by introducing an external oncogene, activating intrinsic suppressing human oncogenes, and/or tumour suppressors[22]. The human papilloma virus is a textbook example of an oncogenic being suppressed by a virus (HPV). HPV-infected cells express two viral proteins, E6 and E7, which bind to and inhibit the tumour suppressor proteins p53 and pRB(23). Regrettably, SARS-CoV-2 infection has been associated with cancer via a variety of mechanisms. The most critical first step is to investigate the possibility of suppressing oncosupressorsof Sars-CoV-2-infected cells(24). Increased expression of endoribonuclease non-structural protein 15 (Nsp15) in response to SARS-CoV infection, which interacts via an LXCXE motif with the pRB tumour suppressor gene. Nsp15-pRB interactions result in nuclear export and widespread degradation of pRB(25). Sars-CoV-1 may enhance p53, G1 checkpoint depletion

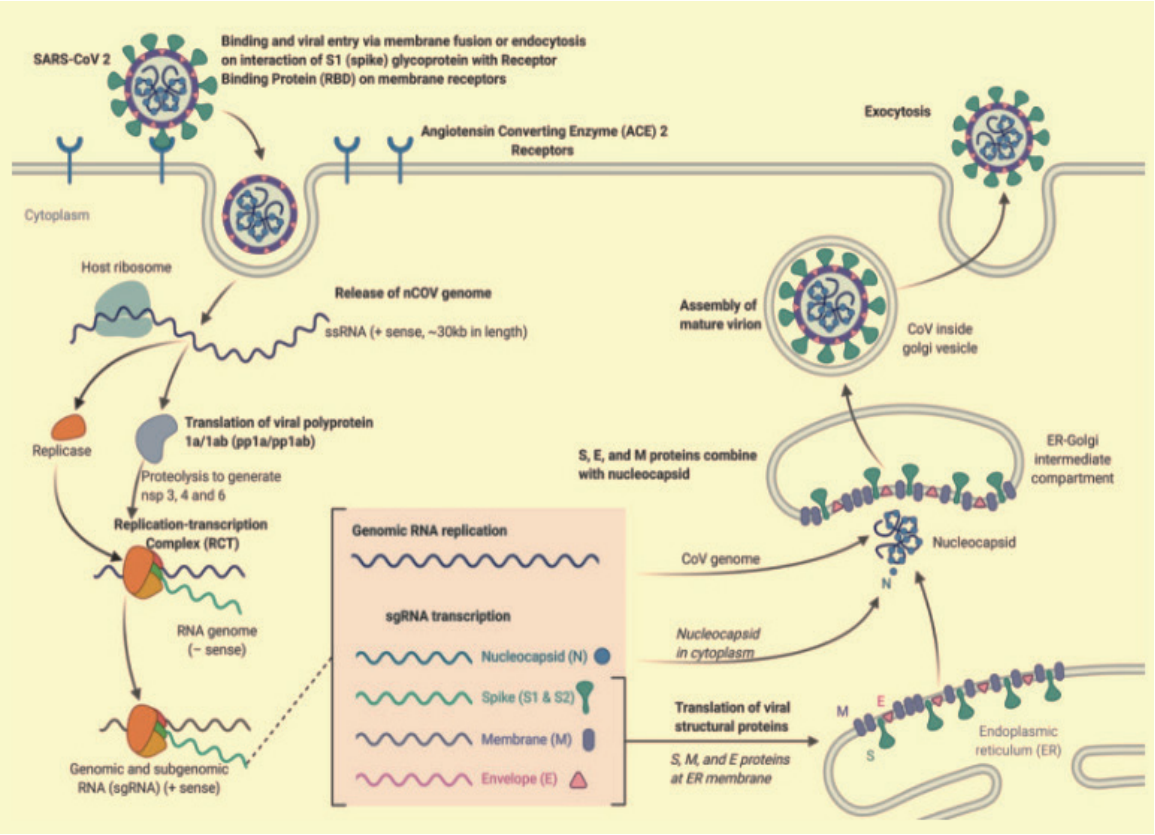

Figure 3: Steps involve in SARS-CoV-2 replication in human cell cytoplasm.

caused by non-structural protein 3 (Nsp3) proteins, and pRB resistance. Nsp3 is highly conserved (76 percent sequence similarity) between SARS-CoV-1 and SARS-CoV-2, implying that Nsp3 from SARS-CoV-2 may reduce p53 levels, thereby increasing the likelihood of malignant transformation(26). Both p53 and pRB are widely recognised as critical tumour suppressor genes, with the p53 gene undergoing the most frequent mutations in humans(27). Human cancer frequently results in the loss of pRB. SARS-CoV-2 proteins (e.g., Nsp15 and Nsp 3) indicate that both p53 and pRB inhibit SARS-CoV-2, which may have oncogenic potential via a process analogous to HPV(28, 29). However, cells infected with SARS-CoV-2 may have insufficient control of the tumour suppressors pRB and p53, which compete with virus-mediated cell cycle arrest and SARS-direct CoV-2's oncogenic potential(30, 31). After analysing RNAseq data from public databases, it was discovered that both paracarcinoma and normal tissue have elevated ACE2 levels in facial and gum tissue. Several previous studies discovered that ACE2 was highly concentrated in epithelial cells of the tongue based on single-cell RNAseq data from patients' oral tissue, and that the epithelial cell layer of the salivary glands, as well as the ducts, are the primary target cells of severe acute respiratory syndrome coronavirus infection of the upper respiratory tract, according to a previous animal model developed by the same group of researchers(32, 33). Additionally, increased expression of Furin has been observed in a number of different types of cancer. In the majority of malignancies, furin proteins are involved in the hallmark processes of proliferation, migration, and invasion, as well as neovascularization. Furin overexpression was associated with invasiveness in cancer and was recommended as a marker for advanced or high-grade disease. Furin expression was found to be increased in approximately 90% of patients with oral squamous cell carcinoma (OSCC), and all squamous cell carcinomas of the oesophagus are evaluated using microwave technology. Furin expression was significantly increased in most precancerous lesions and OSCC when compared to normal epithelium (Figure 4). Additionally, it was discovered that furin expression was increased in post-radiotherapy recurrent laryngeal cancer samples obtained following radiation, implying that radiation may induce increased production of furin in recurring or resistant malignancies(34).

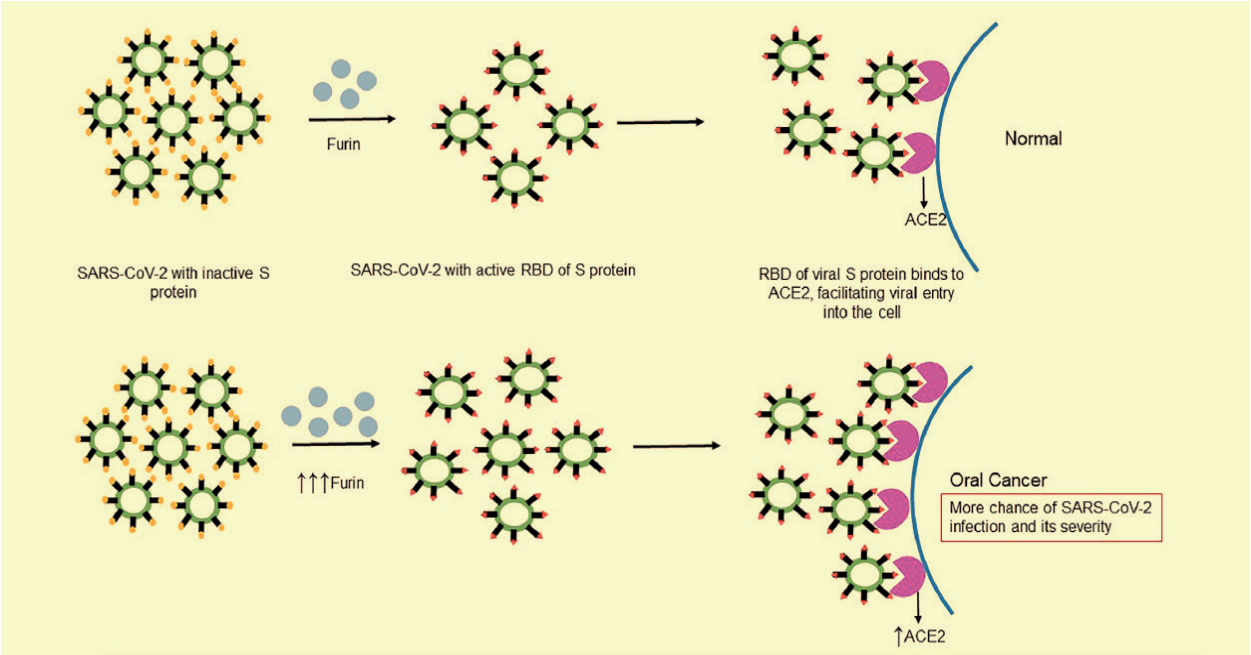

Figure 4: Under normal conditions, activation of the SARS-CoV-2S protein's receptor binding domain (RBD), and the host enzyme furin attaches to the active RBD host cell. The membrane receptor ACE2 enhances viral entrance into the host tissue by fusing viral particles with the host cell membrane. Increased expression of furin leads to greater activation of S protein RBD in SARS-CoV-2, and increased expression of ACE2 promotes greater binding in the case of oral cancer. The greater the amount of SARS-CoV-2, the more likely an infection will occur and the severity of the infection will increase.

Conclusion

According to an increasing amount of scientific research, there may be long-term repercussions following resolution of primary SARS-CoV-2 infections. We hypothesize that one of these long-term effects could be the SARS-carcinogenic CoV-2 virus, the viral protein Nsp15 or Nsp3 have been expected to have pro-oncogenic effects when it interacts with two critical tumour suppressors, pRB and p53 inhibitors. Numerous studies have revealed that host furin, a critical enzyme for initiating furin-like cleavage, may have exacerbate expressionslevels in oral cancer. SARS CoV2's S Spike site is being found. Attachment of viral particles to their receptors, such as ACE2 is pivotal factor to initiation, transformation, proliferation and malignant transformation.

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