Review

SARS-CoV-2 and other respiratory viruses in human olfactory pathophysiology

Serigne Fallou Wade [1,*], Abou Abdallah Malick Diouara [2 *], Babacar Ngom [1], Fatou Thiam [2] and Ndongo Dia [3]

[1] Ecole Supérieure des Sciences Agricoles et de l'Alimentation, Université Amadou Makhtar MBOW, Dakar, Sénégal; serigne.wade@uam.edu.sn; babacar.ngom@uam.edu.sn
[2] Groupe de Recherche Biotechnologies Appliquées & Bioprocédés environnementaux (GRBA-BE), École Supérieure Polytechnique, Université Cheikh Anta Diop, Dakar, Sénégal; malick.diouara@ucad.edu.sn; fatou54.thiam@ucad.edu.sn
[3] Institut Pasteur de Dakar, Unité de Virologie Médicale, Dakar, Sénégal; ndongo.dia@pasteur.sn
* Correspondence: SFW, serigne.wade@uam.edu.sn ; AAMD, malick.diouara@ucad.edu.sn

Simple Summary: The human olfactory dysfunction following COVID-19 and other acute respiratory viruses is now accepted as a hallmark symptom in affected patients. Recent studies have pointed out the relationship between COVID-19 and altered or loss of smell in infected patients. This mini review provides an overview of the role of SARS-CoV-2 and the other respiratory viruses in the development the human olfactory pathophysiology. Based on the recent investigations, it is crucial to decipher the molecular mechanisms underlying the olfactory dysfunction for the discovery of new drugs to restore the altered or loss of smell due to SARS-CoV-2 infection in human.

Abstract: The novel coronavirus disease 2019 (COVID-19) known as severe acute respiratory syndrome - coronavirus 2 (SARS-CoV-2) has emerged in China in 2019, and caused an outbreak of unusual viral pneumonia. The olfactory dysfunction following the infection of different variants of SARS-CoV-2 is now accepted as a hallmark symptom in patients. Recent studies have pointed out the relationship between COVID-19 and altered or loss of smell in infected patients. This mini review provides an overview of the role of SARS-CoV-2 and the other acute respiratory viruses in the development the human olfactory pathophysiology. We highlight the importance of deciphering the molecular mechanisms underlying the olfactory dysfunction caused by SARS-CoV-2 to help design new drugs to restore the altered or loss of smell in affected patients.

Keywords: Respiratory viruses; Anosmia; Olfaction Disorders; loss of smell; COVID-19.

1. Introduction

In December 2019, a novel coronavirus designated as SARS-CoV-2 (severe acute respiratory syndrome - coronavirus 2) emerged in the city of Wuhan, China, and caused an outbreak of unusual viral pneumonia. Being highly transmissible, this novel coronavirus disease, also known as coronavirus disease 2019 (COVID-19), has spread fast all over the world [1, 2]. The new emerging virus has overwhelmingly surpassed SARS and MERS in terms of both the number of infected people and the spatial range of epidemic areas [3]. On 11 March 2020, the WHO officially characterized the global COVID-19 outbreak as a pandemic [4]. As of 12 April 2023, 763 million confirmed cases and 6,8 million deaths have been reported globally [5]. SARS-CoV-2 is transmitted to humans through buccal and nasal cavities mainly through

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respiratory droplets from sneezes or coughs of infected people and spread to those nearby [6]. A key factor in the transmissibility of COVID-19 is the active virus replication in upper respiratory tract tissues and therefore its massive excretion [7]. Regarding symptoms reported in patients with COVID-19 infection the most common are fever, dry cough, shortness of breath (dyspnoea), myalgia, malaise, chills, confusion, headache, sore throat, rhinorrhea, chest pain, diarrhea, conjunctival congestion, nasal congestion, sputum production, hemoptysis, runny nose, fatigue and sneezing [8-11]. Several studies have reported olfactory dysfunction and hypogeusia in COVID-19 patients [12, 13]. Interestingly, a clustering clinical data have shown that neurological symptoms like persistent headache was noticed in 50% of patients who suffered from olfactory dysfunction after months of recovery from SARS-CoV-2 infection suggesting in part a strongly link between the pathophysiological substrate of both cognition and olfaction related disorders [14]. A recent study has documented the effect of the use of personal protective equipment, especially by healthcare workers in preventing the spread of COVID-19. Their findings demonstrated that wearing a face mask significantly improves the daily health issues related to the disease symptoms and the working performance of those workers who have adhered to safety guideline rules [15]. Humans have developed five senses, traditionally vision, hearing, smell, taste and touch, to gather information from their surroundings and to benefit from where they live. Even though several factors, such as ageing, drug, and respiratory pathogens, are shown to lead to neurological invasiveness, different variants of SARS-CoV-2 have been considered a leading cause of anosmia in humans [14, 16-18] . The respiratory coronavirus transmission throughout the nasal cavity and its consequence in impairing odorant detection have gained attention recently [19-21]. The first step of molecular detection occurs when a chemical odorant is recognized by one or several olfactory receptors (ORs) in the olfactory sensory neurons (OSN). The process of this odour recognition takes place in the nasal cavity before reaching the upper part of the human brain [22-24]. The importance of sensing and tasting is often shed in light only when a subject is facing difficulties in discriminating odours via food intake or the environment [25]. As smell is somehow not vital daily for humans and its loss may not be directly life-threatening, the loss of functional olfactory responses, in the long term, could be accounted for the poor quality of life, at worst, lead to death [14, 26]. Since the beginning of this pandemic, a lot of reports have shown the issues of olfactory disorders in patients affected by COVID-19 [16-19]. This review mainly focuses on the loss of smell and particularly on understanding the molecular signaling underlying the olfactory pathophysiology in human patients from COVID-19 infection and the importance of using such mechanisms to find potential targets to overcome the loss of smell.

2. Methods

The present study synthesizes the current knowledge regarding the relationship of the respiratory viral pathogenesis of the olfactory system and the mechanisms underlying the loss of smell in patients infected by respiratory viruses in general and COVID-19 in particular in the last three years. A deep search has been performed using mostly the database PubMed, PMC and ScienceDirect to parse both original and review articles that

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have tackled the animals and human respiratory viruses having a negative impact on the olfactory system functionality. For our search, we used the combination of the following keywords: respiratory virus, coronavirus, rhinovirus, influenza viruses, parainfluenza viruses, respiratory syncytial virus (RSV), coxsackievirus, adenoviruses, poliovirus, enteroviruses (EVs), herpesviruses, anosmia, olfactory epithelium, human, mouse, hamster, loss of smell or olfactory dysfunction were considered in this review. Only the papers that have met the keyword criteria listed above were considered in this work.

3. Olfactory receptor and odorant detection

Odorant perception is fundamental for survival in most animals. In humans, the sense of smell is important to appreciate our environment. Therefore, a functional olfactory system detects and discriminates among diverse chemical stimuli. Odours are important for behaviours such as feeding, mating, and avoiding dangerous smells, such as smoke, leaking propane gas, and spoiled food [25, 27, 28]. Processes of learning and memory are associated with these behaviours. This leads to a strong belief that the loss of olfactory function is indirectly related to human life-threatening [29, 30] . The sense of smell, which is fundamental for their survival, is developed in most animals. Mostly, two different olfactory systems have been developed in mammals such as rodents: the main olfactory epithelium (MOE or OE), also called olfactory mucosa, connected to the main olfactory bulb , and the accessory system called vomeronasal organ (VNO) connected to the accessory olfactory bulb [22, 31-34]. Here, the VNO will not be discussed. The configuration of the olfactory epithelium (OE) presents unique cytological characteristics as it contains different cell types such as the ciliated olfactory receptor neurons (ORNs), the sustentacular supporting cells, and the cells of Bowman's glands (Fig. 1). The ORNs reside in the intermediate layer of the olfactory mucosa while the sustentacular cells and sensory cilia are located in the apical layer where the dendrites of olfactory neurons are extended [35, 36].

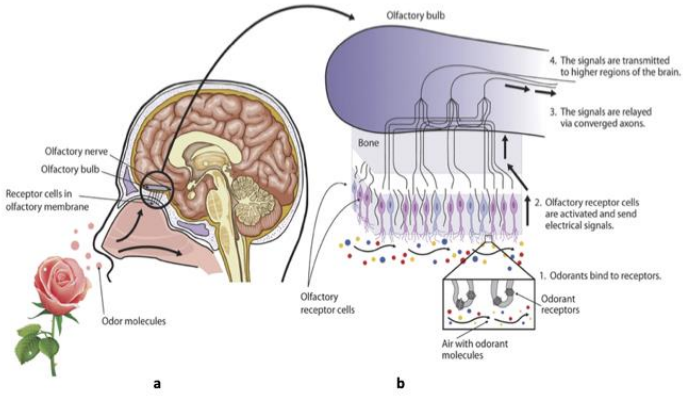

Figure 1: Functional anatomy and structure of the human olfactory system

(a) The human olfactory system contains multiple organs, including the olfactory epithelium (OE), the olfactory tract (OT). Odorants enter the nasal cavity (NC) and access the OE during inhalation, by being pumped through the sasal conchae. (b) Sensory neurons of the OE project to the olfactory bulb (OB) (taken and modified from

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https://sites.google.com/a/edmail.edcc.edu/savannatest/literature-research/pheromones-and-neurocircuits) (Accessed on November 18, 2022).

A deep understanding of the molecular signaling of the smelling recognition is required to understand the basis of the olfactory system and, consequently, the loss of olfactory function. In the last decade, pioneers have developed and studied the physiology of the olfactory system based on molecular biology, biochemistry, anatomy, and bioinformatics [23, 25]. At first glance, getting insight into the molecular mechanisms of the perception of odours has emerged from several disciplines such as chemistry, biology and professional odour detectors [23, 25].

In the human genome, around 857 olfactory receptors (OR) genes were identified, but 60% of them are pseudogenes. This high prevalence may be due to internal deletions during evolution, leaving around 390 putative functional ORs while around 465 are pseudogenes [23, 37-39]. Although 1300 OR genes have been identified in the mouse genome, only 20% of these genes are pseudogenes [40, 41]. This difference between humans and mice in the amount and percentage of functional OR genes may originate from the fact that olfaction is more solicited in rodents than in higher primates during evolution. The ORs of mammals are part of the superfamily of GPCRs [42]. They are considered one of the most critical groups in number and are known as rhodopsin-like owing to their structural similarity to rhodopsin. GPCRs in family A share many features, such as an Asp-Arg-Try sequence (DRY motif) in the second intracellular loop and a disulfide bridge from the two cysteines in the first (EC1) and second (EC2) extracellular [42]. In fact, olfaction is the perception of a combination of a myriad of odorant molecules. Odorants are generally known as small components (less than 400 Da) and are mostly hydrophobic volatile molecules. They are commonly aliphatic or aromatic molecules, with various functional groups including aldehydes, alcohols, carboxylic acids, ketones and esters [43]. Odorants can be cyclic, linear, or branched. The detection occurs when the odorants penetrate into the nasal cavity and reach the olfactory mucosa. The odorants then interact with specific OR in the olfactory mucosa. Once an OR is activated by an odorant, a nervous influx is sent to the cortex via the olfactory bulb. In addition, while acting as agonists for certain ORs, odorant stimuli can act as antagonists for other ORs [44, 45], by preventing the activation of the receptors. This could be a plausible argument to explain why certain odours can be masked within some mixtures of odorants [46]. Surprisingly, the perception of an odour can also depend on its concentration. The olfactory response is efficient when odorant concentration is at a moderate level. Instead of activating, the high concentration of odorant inhibits the OR functionality. The OR functional response adaptation strongly depends on the concentration of odorant and has been a subject of debate in the sensing field [47-50]. Readers interested in the mammalian olfactory epithelium and the perception of odour coding are invited to view an excellent review by Kurian and colleagues published in 2020 [51].

4. Viral infection causing loss of smell

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The fact that the olfactory receptor neurons (ORNs) are found in the nasal cavity and expressed in the olfactory epithelium (OE) makes them directly exposed to all kinds of air-bound and air-way pathogens that make the ORNs vulnerable. Whether the cause is physiological or pathological, the lifespan of ORNs is relatively short of few weeks in the OE. Moreover, the stem cell reprogramming ensures the continuous regeneration of new ORNs from OE basal cells in response to inflammation and OE severe damage mediated by neural injury [**52-54**]. Several airway pathogens, such as viruses, are causing damage to OE through particularly the sustentacular cells, triggering anosmia in mammals [**55**, **56**] [**36**, **57**, **58**]. Many respiratory tract infections due to viruses like rhinovirus, influenza viruses, parainfluenza viruses, respiratory syncytial virus (RSV), coxsackievirus, adenoviruses, poliovirus, enteroviruses (EVs), and herpesviruses, have been involved in the development of olfactory disorders such as partial or total loss of smell. Doty and others have termed this pathology as virus-induced olfactory dysfunction as post-viral olfactory disorder (PVOD) [**59-62**]. Chronic viral infection destroys the many cells within the apical layer of the OE that could lead to ORNs functional impairment in the nose. Interestingly, the OE basal cells can constantly replace damaged ORNs to new olfactory neurons allowing patients to recover functional olfactory response [**53**, **54**]. In the following sections, the most common viral infection of the upper respiratory tract leading to olfactory dysfunction in animal models and humans will be discussed.

5. Viruses impacting respiratory system

The respiratory system is exposed to the environment and is in permanent contact with air-way pathogens like viruses. Cytomegalovirus (CMV) belonging to the Herpesviridae family and, also called Human Herpes Virus 5 (HHV-5), is shown to impact mice's olfactory system. The mouse neonatal exhibited an impaired olfactory function following a placental CMV infection. The virus preferentially impacts the sensing system before it deteriorates the hearing system in mice [63]. Moreover, the infection of the hippocampus and the olfactory bulb by CMV triggers a sensorineural handicap that can induce brain malformations at the late stages of gestation [64]. A recent investigation in humans, has identified 18 viruses in patients with post-viral olfactory dysfunction. Particularly, rhinovirus (RV) and coronavirus (CoV OC43) were more predominant suggesting that they are major causative agents of PVOD [65]. The *Sendai* virus (SeV), the murine counterpart of Parainfluenza virus, has been shown to directly infect the mouse brain via the olfactory neurons [66]. Another investigation demonstrated that SeV infection led to impairing mouse olfaction. Interestingly, the virus persists in OE and OB tissues for over two months, and reduces the regenerative power and the functionality of the ORNs [67]. The seasonal changes play a key role in influenza and parainfluenza type 3 infections to induce olfactory loss. This dysfunction occurs most frequently in winter and spring [68]. Preventing the influenza A virus from reaching and infecting the upper brain is crucial for maintaining the process of detecting odours. Mori et *al*. have shown that ORNs undergoing apoptosis after infection may be a preferential mechanism to provide protective effects against invasion of the neurovirulent virus from the peripheral to the CNS [69, 70]. In mice infected with influenza virus, Bcl-2, bax, and iNOS may play a key

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role in apoptosis regulation of ORNs [71]. A recent complementary investigation demonstrated that the homologous vaccination significantly decreased the H5N1 virus replication in the olfactory mucosa, compared to prophylactic oseltamivir and thus hindered subsequent virus spread to the CNS [72]. Another recent study using transcriptomic analysis demonstrated that olfactory signaling is among the altered pathways in patients suffering from RSV infection. This finding further supports previous work that described RSV as a causative agent of post-viral olfactory dysfunction. Interestingly, the authors highlighted that this molecular signaling could be a promising future route to investigate drug targets against RSV infection [29, 60].

6. Mechanisms of SARS-CoV-2 mediating the loss of smell

The post-COVID and the long-term-COVID have both tremendously triggered a lot of complications in different human systems. The loss or reduction of smell, among other complications of the nervous system, is an associated symptom for patients affected by different variants of COVID-19 including omicron variant (Table 1) [73-79]. Moreover, studies reported that the prevalence of olfactory dysfunction differs greatly between populations and approaches [77, 80, 81]. The relationship between the loss of smell and the SARS-CoV-2 infection remains an enigma which could partly explain why the fight against this disorder is difficult. In the emergency context of the pandemic, many COVID-19 vaccines are authorized to help protect and eliminate the virus. Unfortunately, at least, two COVID-19 vaccines have been reported to cause the loss of smell one day after the administration. Also, it remains unclear what drive the occurrence of olfactory dysfunctions as the cases are relatively rare, although the development of a post-vaccine inflammatory reaction in the olfactory neuroepithelium is pointed to play a role in this process [82, 83]. Therefore, this adds more complexity to compare the molecular signaling of the loss of smell driven by COVID-19 infected patients and individuals benefiting from COVID-19 vaccines and later contracting the disease. The COVID-19 pathology and the cellular mechanism by which the olfactory dysfunction occurs, remain unclear and is still under intensive investigation [18, 84]. Earlier in the pandemic, reports hypothesized that five potential mechanisms were considered to get insights into the olfactory dysfunction in COVID-19 patients : (1) obstruction/congestion and rhinorrhea of the nasal airway, (2) damage and loss of ORNs, (3) Olfactory center damage in the brain, (4) damage of the olfactory supporting cells in the OE, and (5) Inflammation-related olfactory epithelium dysfunction [80, 81]. Butowt et *al*, have recently reviewed that at least the following hypotheses (1)-(3) turned out to be implausible, for explaining the olfactory dysfunction in patients [85]. Here, we will particularly review the mechanisms related to the second and the fourth scenarios according the available findings. Healthy sensory cilia of ORNs in the olfactory epithelium are crucial in perceiving odorant molecules before sending the information to the olfactory bulbs and then to the upper parts of the brain [52]. It has been reported in humans that the SARS-CoV-2 may inderectly affects the olfactory cilia, hindering the smelling system's efficacy [86]. Reports suggested that ORNs lack to express the entry proteins of SARS-CoV-2 in the OE. The virus seems to establish a first contact in human nasal epithelia by binding its spike S protein to specific cells in the OE [87]. These reports are confirmed by study based on in-silico data, predicting the that mature ORNs

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do not express the virus entry protein, the angiotensin-converting enzyme 2 (ACE2), and therefore are not likely to be infected by SARS-CoV-2 [88]. Furthermore, supporting data by Bryche et *al*., showed that SARS-CoV-2 was not detected in the ORNs of golden Siryan hamsters [89]. However, in few cases, authors suggested that SARS-CoV-2 could infect ORNs in hamsters [90]. Based on the fact that COVID-19-related loss of smell disappeared within 1-2 weeks, while the regeneration of dead ORNs needs more than 2 weeks, many data tend to conclude that COVID-19-related olfactory dysfunction (OD) is not directly associated with the impairment of the ORNs [13, 80, 81, 87, 91]. Consequently, studying the entry proteins expression within the cells in the OE will help to understand the sensitivity of the OE to SARS-CoV-2 infection-related to the high prevalence of ODs in patients. Many groups are now interested to the organization of the sustentacular cells in the OE and thought that they might play central role in leading to OD. A high level of expression of ACE2 and the transmembrane serine protease 2 (TMPRSS2) is particularly found on the sustentacular cells suggesting a path to the neurotropism of SARS-CoV-2 in the OE. The ACE2 and TMPRSS2 are respectively known as the SARS-CoV-2 receptor and the SARS-CoV-2 cell entry-priming protease. ACE2 is found mainly on different parts of the sustentacular cells both in human and mouse. The ACE2 and TMPRSS2 genes tend to be co-regulated [81, 92-96]. Different approaches using tissues, cells and organ systems in human, golden Syrian hamster, and hACE2 transgenic mouse have been employed to study the pathological impact of the SARS-CoV-2. Here, we discussed findings related particularly to the OE in inducing ODs in human. The spike protein (S protein) of SARS-CoV-2 mediates the passage of the virus into the host cell by fusing the viral and host cell membranes. In fact, via his spike S, SARS-CoV-2 employs the ACE2 as host functional receptor and TMPRSS2 as the cellular priming protease facilitating viral uptake, both signaling being confirmed by Single-cell RNA sequencing (scRNA-seq) datasets from the Human Cell Atlas consortium [97-99]. Another study showed that SARS-CoV-2 Nucleocapsid protein (NP), was observed in human OE through the neuronal marker Tuj1, 9 hours post infection. This data further supported the enrichment of ACE2 in human olfactory sustentacular cells [93, 100]. Earlier in the pandemic, the golden Syrian hamster was used as a model to document the pathology of SARS-CoV-2 in the OE post infection. Reports showed that the sustentacular cells are rapidly infected by SARS-CoV-2. This viral neurtropism is associated with a massive recruitment of immune cells in the OE and lamina propria, which could drive the disorganization of the OE structure [89]. This study is consistent with high level of TNFα observed in OE samples from COVID-19 suffering patients [101]. Furthermore, the inflammation induced by SARS-CoV-2 infected supporting cells may play an important role in the onset and persistence of loss of smell in patients. This SARS-CoV-2-associated inflammation status was confirmed by analyzing the expression of selected targets in the olfactory bulb using RNA-seq and RT-qPCR tools. Interestingly, this study showed that the proinflammatory markers Cxcl10, Il-1β, Ccl5 and Irf7 overexpression continued up to 14 dpi, when animals had recovered from ageusia/anosmia (77). These findings are in line with a very recent study showing the implication of immune cell infiltration and altered gene expression in OE in driving persistent smell loss in a subset of patients with SARS-CoV-2. Moreover, this study

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particularly, demonstrates that T cell–mediated inflammation lasts longer in the OE after the acute SARS-CoV-2 infection has been eliminated from the tissue, suggesting a mechanistic insights into the long-term post–COVID-19 smell loss (78). The OE disorganization is followed by a drastic deterioration of the cilia layer of the ORNs that leads to the impairment of the olfactory capacity of the animal [89]. Investigations in humans and hamsters using respectively, Transmission Electron Microscopy (TEM) studies and Scanning Electron Microscopy (SEM) analysis showed various levels of cilia height that undergo regeneration in the course of patient recovery, including smell restoration. Data using the golden Syrian hamster showed that the regenerated cilia in the epithelium is accompanied by a decreased expression of FOXJ1^{+} highlighting the importance of this marker in the respiratory ciliogenesis. This later finding by Schreiner et *al*., could in part shed light on the inquiry of how could we regenerate cilia during patient recovery, although a lot needs to be done in the roadmap of treating loss of smell related to nasal cilia deterioration by SARS-CoV-2 (75, 76) (Table 1 ; Fig. 2).

Table 1: Summary of the mechanisms of SARS-CoV-2-induced olfactory dysfunction

Effect of SARS-CoV-2 infection on cells in the OE	References
• The virus targets the sustentacular and Bowman gland cells by binding to their ACE2 and TMPRSS2 proteins. • Exponential growth of the virus leading to the destruction of these supporting cells. • Significant reduced thickness of the mucus layer could be related to the Bowman's glands deterioration which are the precursor of the mucus. • Healthy mucus is crucial for odor detection as it enables odorants to diffuse to olfactory receptors. • Retraction of OSN cilia, although the mature OSN are free of SARS-CoV-2 viral load. • SARS-CoV-2 alterates throughout the supporting cells not only the structure of mucus but also the OSN cilia which contribute to the olfactory dysfunction (Fig. 2)	[102] [103] [88] [104] [105] [106] [89] [107]
• Sustentacular cells and Bowman gland cells supply additional glucose to the cilia that is necessary for the ORN to respond to odorants. • Supporting cells infected by SARS-CoV-2 affect	[108] [109] [110]

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the expression of the GLUT1/GLUT3 that interrupt the glucose trafficking to the cilia of the ORN in the mucus.	[110] [85]
• SARS-CoV-2 uses the internal glucose as a fuel to maximize its replication thus preventing the cilia to undergo odorant-inducd reponse of the ORN.	[111]
• Loss of glucose normally supplied by sustentacular cells and Bowman gland cells • SARS-CoV-2 exhibits supporting cells damage that consequently trigger the interruption of the supply of additional glucose to the cilia of the ORN via GLUT1/GLUT3.	[112]

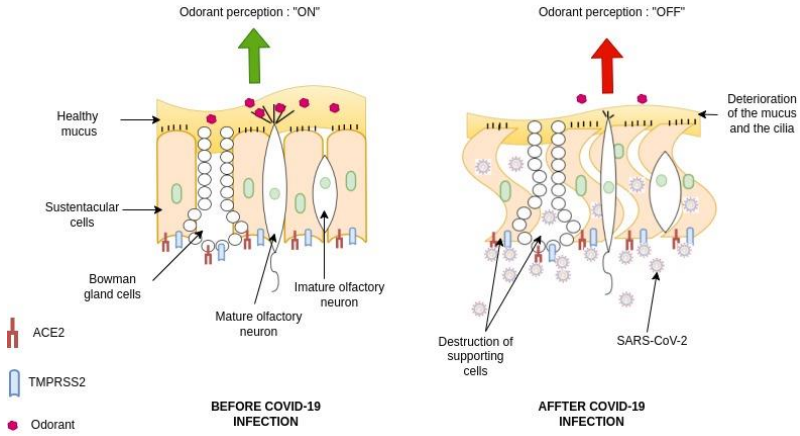

Figure 2: Summary of how SARS-CoV-2 infected support cells induce damage to the mucus and cilia that prevent the olfactory receptor neurons to bind to their odorant molecules.

According to the literature, different variants of SARS-CoV-2 do not directly target particularly the ORNs in the OE, instead they are found in majority expressed in the sustentacular cells [36]. Recent study by Seehusen et al, showed that K18-hACE2 transgenic mouse expressing the human ACE2 is highly sensitive to at least five variants of SARS-CoV-2 that infected not only the supportive cells in OE and the respiratory epithelium but invaded the CNS of the animal five days post infection. Interestingly, the expression of hACE2 seems to convey higher binding affinity when compared to the wild-type mouse [113]. Using this transgenic mouse reveals to be a serious option for therapy development against loss of smell as these animals exhibited low mortality when treated with COVID-19 convalescent antisera [113, 114].

It is now accepted that ACE2 is not the only obligate entry for SARS-CoV-2 as it has been suggested that molecules including PIKfyve or neuropilin-1 (NRP-1) may participate in SARS-CoV-2 entry [115-117]. Like ACE2, NRP-1 is highly expressed in the respiratory and olfactory epithelium which further support the infectivity and entry of SARS-CoV-2 in the

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human OE. NRP-1 is not only found in supportive cells but is expressed in nearly every cell type in the nasal passages including the ORN, therefore giving SARS-CoV-2 a route to access those cells and impair the olfactory response. Interestingly, Daly et *al*., demonstrated that the selective inhibition of the S1-NRP-1 interaction reduces SARS-CoV-2 infection [117-119].

Taken together, the highly expression of ACE2, TMPRSS2 and NRP-1 in supportive and other olfactory cells and their impact in olfactory neurophysiology maintenance and in the development of human olfactory pathophysiology supports them as potential targets for signaling-based therapeutics of anosmia. Finally, for further insight into the molecular signaling and treatments in COVID-19 patients with impaired smelling, readers are invited to explore the following reviews. They have explored many different potential therapeutic agents against olfactory and gustatory dysfunctions [73].

7. Conclusion and perspective

Our literature review further confirms the previous extended investigations showing that loss of smell and taste are among the key associated symptoms with most COVID-19 variants, including the omicron variant which causes runny nose, headache, fatigue, sneezing, and sore throat [11]. The last three years have been an important rush towards deciphering the underlying mechanisms the SARS-CoV-2 deploys to impair the olfaction in infected patients. Still few works have addressed the molecular signaling mediated by SARS-CoV-2-induced loss of smell in human patients. This work pointed the urge and necessity of finding an adequate therapeutic solution against the COVID-19 pathogen in general and the loss of smell affecting patients in particular. In addition, the mechanisms of taste dysfunction due to COVID-19 infection is not discussed in this review. But it would be interesting to decipher the possible pathogenesis between ageusia and anosmia in COVID-19 patients in the future.

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All authors contributed to the literature review, writing the article, revising the manuscript, have read and agreed to the published version of the manuscript.

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The authors declare no conflict of interest.

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