REVIEW

ACE2 & TMPRSS2 Expressions in Head & Neck Tissues: A Systematic Review

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Abstract

To review the data regarding the expression of angiotensin converting enzyme-2 (ACE2) and transmembrane protease serine-2 (TMPRSS2) in head and neck tissue. Scopus, Cochrane Library, Medrxiv, Google Scholar and PubMED/MEDLINE were searched by four independent investigators for studies investigating ACE2 or TMPRSS2 expressions in head and neck tissues. The following outcomes were considered: sample origin (animal versus human); detection method; anatomical location and cell types. PRISMA checklist and modified population, intervention, comparison, outcome, timing and setting (PICOTS) framework were used to perform the review. Of the 24 identified studies, 17 met our inclusion criteria. Thirteen studies were conducted during the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic. ACE2 and TMPRSS2 were expressed in oral, pharyngeal, sinusonasal human mucosa. The following cell types expressed ACE2: basal, apical, goblet, minor salivary, and endothelial cells. TMPRSS2 was found in goblet and apical respiratory cells. ACE2 and TMPRSS2 were found in the olfactory region, especially in sustentacular non-neural and neural stem cells. Animal studies suggested that ACE2 expression may vary regarding age. There was an important heterogeneity between studies in the methods used to detect ACE2 and TMPRSS2, leading to a potential identification bias. The SARS-CoV-2 receptors, ACE2 and TMPRSS2, are both expressed in many head and neck tissues, enabling the viral entry into the host organism.

Keywords ACE2 · TMPRSS2 · SARS-CoV-2 · COVID · Coronavirus · Head Neck

Introduction

The renin angiotensin aldosterone system is one of the most important systems regulating the homeostasis of cardiovascular and pulmonary function; this involves many molecules including angiotensin converting enzyme-2 (ACE2) [1]. ACE2 is also known to be the functional receptor of some coronavirus species as initially discovered in 2003 during the severe acute respiratory syndrome coronavirus (SARS-CoV) epidemic [2]. The current pandemic of coronavirus disease 2019 (COVID-19) has brought to light the importance of ACE2 regarding development of infection, viral spread and the development of the clinical COVID-19 [3]. At the same time, another SARS-CoV-2 receptor has been identified: the transmembrane protease serine-2 (TMPRSS2) [4].

ACE2 and TMPRSS2 tissue expressions are particularly important to identify viral entry pathways and to better understand the organ-related clinical presentation of the disease [3, 4]. Further evaluation of ACE2 and TMPRSS2 expression in ear, nose and throat mucosa is warranted to shed light on the pathophysiology of disease in the head and neck [5–7].

The aim of this systematic review is to summarize the current data about the expression of ACE2 and TMPRSS2 in head & neck tissue.

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Methods

The review was conducted regarding the Preferred Reporting Items for a Systematic Review and Meta-analysis (PRISMA) checklist [8]. A modified population, intervention, comparison, outcome, timing and setting (PICOTS) framework was used to structure the review process [9]. For this review, the PICOTS structure was kept but adapted to experimental/basic research studies on human and animal tissues.

Studies

Animal and human experimental published studies in English-language peer-reviewed journals were considered. Preprint studies were also considered in light of the current pandemic and the significant wealth of knowledge derived over the last few months. All studies where investigators assessed ACE2 or TMPRSS2 expressions in head & neck tissues through immunochemistry (IHC), in situ hybridization, Western Blot, RNA sequencing (RNA-seq), or reverse transcription polymerase chain reaction (RT-PCR) were evaluated.

Participants and Inclusion Criteria

The papers had to include either human or animal subjects. The authors extracted substantial information about the sample characteristics (including species involved) and ACE2 and TMPRSS2 identification method.

Outcomes

The primary outcome studied was tissue expression of ACE2 and TMPRSS2. The anatomical location; the types of cells that expressed both receptors were recorded. Particular attention was paid to the method used to detect ACE2-TMPRSS2 in tissues. Additional useful information, such as viral impact on the functioning of the tissue/cell that expressed the receptor or inter-individual differences, were also collected.

Intervention and Comparison

Because the aim of the study was to investigate the tissue ACE2 and TMPRSS2 expression, we did not consider potential intervention on patient or animal models.

Timing and Setting

We included the studies where the receptor analysis was made on normal subjects and/or infected patients.

Search Strategy

The PubMed/MEDLINE, Google Scholar, Medrxiv, Scopus and Cochrane search was conducted by 5 independent authors (JRL, TR, CCH, GD, CMCE) to identify papers published between January 1990 and April 2020. The authors screened publications with database abstracts and available full texts referring to the condition. The following keywords were used for the search strategy: 'ACE2'; 'TMPRSS2'; 'COVID-19'; 'COVID'; 'SARS'; 'coronav'; 'coronavirus'; 'salivary'; 'gland'; 'Receptor'; 'Head'; 'Neck'; 'Nasal'; 'ear, nose throat (ENT)'; 'Tissue' and 'Cell'. The authors investigated papers for number of samples/individuals, study type & design, inclusion criteria and ACE2/TMPRSS2 detection outcomes.

Results

The electronic search identified 24 papers, of which 17 met our inclusion criteria (Table 1) [10–26]. A total of 16 studies investigated the expression of ACE2 and TMPRSS2 in human head and neck tissues, while five papers focused on mouse and two on monkey samples respectively (Table 1). One study focused on ACE2 genetic analysis, without reporting site-specific anatomical expression [17]. The flow chart of the study process is available in Fig. 1. Five studies were preprint [15, 18–20, 25].

Tissue Expression in Human

ACE2 Expression

ACE2 was assessed in 16 studies [11–26]. The expression of ACE2 was found in all mucosa of the respiratory upper tract, including trachea [12, 13, 20, 22, 25], sinus and nasal cavities [11, 16, 20]. Among the respiratory mucosa, ACE2 was expressed in several types of cells, including epithelial, goblet and endothelial cells [11, 12, 26]. One study reported that ACE2 was expressed on ciliated epithelial cells and not on non-ciliated (goblet) cells [20]. Butowt et al. compared the intensity of expression of ACE2 in the upper and lower respiratory tract [16]. They found that nasal epithelial cells had lower levels of ACE2 expression compared with epithelial cells of the lower respiratory tract [16]. Among the nasal region, two studies investigated the ACE2 expression in the

Table 1 Studies reporting ACE2 or TMPRSS2 head and neck expression

Authors	Design	Samples	Methods	ACE2 & TMPRSS2 expression	Findings
Vaarala 2001 [10]	Mixed Study	Human Mouse	TMPRSS2 RNAseq	Salivary glands *TMPRSS2 (human)*:+	1. TMPRSS2 is expressed in human salivary gland tissues
Hamming 2004 [11]	Human Study	Human	ACE2 IHC	Oral, Nasal, Nasopharyngeal Epithelium & endothelium *ACE2 human*:+ (*all mucosa*)	1. ACE2 was found in endothelial (arteries & veins) and epithelial cells of nasal, rhinopharyngeal and oral mucosa. Precisely, the epithelium expression concerned the basal layer cells
Jia 2005 [12]	Human Study	Human	ACE2 IHC & biotinylation	Tracheal Epithelium & endothelium *ACE2 (human)*:+	1. ACE2 was more expressed on the apical than the basolateral surface of polarized airway epithelia
Liu 2011 [13]	Experimenal Study	Monkey	ACE2 IHC	Naso- Oro- Hypopharyngeal & Tracheal Epithelium *ACE2 Monkey*:+ Virion in Saliva:+	1. ACE2 is expressed in salivary gland ducts of the pharyngeal glands 2. ACE2 was expressed in epithelial cells (lamina propria, respiratory tract) 3. Virus was found in saliva of infected monkeys
Bilinska 2020 [14]	Animal Study	Mouse	ACE2 & TMPRSS2 RNAseq, RT-PCR, In situ hybridization, WB & IHC	Olfactory Epithelium *ACE2: sustentacular cells* *TMPRSS2: sustentacular cells*	1. ACE2 & TMPRSS2 are expressed in sustentacular cells of the olfactory epithelium but not/much less in most olfactory receptor neurons 2. Expression of the entry proteins increases in animals of old age
Brann 2020 [15]	Mixed Study	Mouse Human	ACE2 & TMPRSS2 RNAseq	Olfactory Epithelium *ACE2 & TMPRSS2 Mouse: non-neuronal cells* *ACE2 & TMPRSS2 Human: glial and neuronal stem cells*	1. In human, ACE2 & TMPRSS2 were not identified in purified olfactory neurons 2. ACE2 was identified in glial cells & olfactory stem cells
Butowt 2020 [16]	Mixed Study	Mouse Human	ACE2 & TMPRSS2 RNAseq	Olfactory Epithelium *ACE2 Mouse & Human: non neuronal cells* *TMPRSS2 Mouse & Human: neuronal & non-neuronal cells* Respiratory Epithelium *ACE2 & TMPRSS2 Human*:+ (*Lower Airway > Nasal*)	1. Nasal epithelial cells have lower levels of ACE2 & TMPRSS2 compared with epithelial cells of the lower respiratory tract 2. ACE2 has non-neuronal expression in olfactory epithelium 3. The expression of ACE2 & TMPRSS2 (mouse) were increased in elderly mouse
Cao 2020 [17]	Human Study	Human	ACE2 gene Genetic Analyzis	No localization provided	1.15 unique expression quantitative trait loci variants were found for ACE2 2. The genotypes of ACE2 gene polymorphism may be characterized by higher expression levels of ACE2 in East Asian population 3. There would be different susceptibility or response to SARS-CoV2 in different populations
Chen 2020 [18]	Human Study	Human	ACE2 RNAseq	Salivary glands *ACE2 human*:+	1. ACE2 is expressed in human granular cells of salivary glands
Hikmet 2020 [19]	Human Study	Human	ACE2 IHC	Nasopharyngeal Epithelium ACE2 (human): no expression in nasopharynx	1. There was no ACE2 expression in nasopharyngeal cells
Lee	Human	Human	ACE2	Tracheal, Nasal & Sinusal Epithelium	1. ACE2 is expressed in ciliated epithelial cells (cilia organelle)

Table 1 (continued)

Authors	Design	Samples	Methods	ACE2 & TMPRSS2 expression	Findings
2020 [20]	Study		IHC	*ACE2* (*human*):+	2.There was no ACE2 expression in the non-ciliated goblet cells
					3. ACE2 expression is influenced by patient demographics, clinical characteristics, co-morbidities, or medication use. The use of ACE inhibitor drugs did not increase ACE2 protein expression
Li	Human	Human	ACE2	Thyroid	1. ACE2 is expressed by thyroid cells
Hikmet	Human	Human	ACE2	Nasopharyngeal Epithelium	1. There was no ACE2 expression in nasopharyngeal cells
2020 [19]	Study		IHC	ACE2 (human): no expression in nasopharynx	
2020 [21]	Study		RNAseq	ACE2 human:+	
Sungnak	Human	Human	ACE2 & TMPRSS2	Airway & Nasal epithelium	1. ACE2 was expressed in airway epithelial cells
2020 [22]	Study		RNAseq	*ACE2 human*:+	2. ACE2 is more expressed in nasal epithelial cells compared with other respiratory cells (goblet & ciliated cells)
				TMPRSS2 (*human*): *subset of ACE2 cells*	
					3. TMPRSS2 is only expressed in a subset of ACE2+cells
Xu	Human	Human	ACE2 & TMPRSS2	Oral Epithelium	1. ACE2 is expressed in the oral cavity epithelial cells
2020 [23]	Study		RNAseq	*ACE2 human*:+	2. ACE2 expression was higher in tongue than buccal and gingival tissues
				Oral T cells, B cells & fibroblasts	
				ACE2 human:+	
Xu	Human	Human	ACE2	Minor salivary glands	1. ACE2 is expressed in minor salivary glands
2020 [24]	Study		RNAseq	*ACE2 human*:+	
Wu	Human	Human	ACE2	Nasal & Oral Epithelium	1. ACE is expressed in nasal epithelial cells
2020 [25]	Study		RNAseq	ACE2 (human):+	2. The was a higher virus concentration in the nasal-swab comparing with throat-swab, which is attributed to ACE2-expression in nasal epithelial cells
Ziegler	Mixed	Human	ACE2 & TMPRSS2	Sinusal & Nasal goblet epithelial cells	1. ACE2 & TMPRSS2 are co-expressed in nasal goblet secretory cells
2020 [26]	Study	Monkey	RNAseq	*ACE2 & TMPRSS2 Human*:+	

ACE2 Angiotensin Converting Enzyme-2, *IHC* Immunohistochemistry, *RT-PCR* reverse transcription polymerase chain reaction, *SARS-CoV-2* severe acute respiratory syndrome coronavirus-2, *TMPRSS2* transmembrane protease serine-2, *WB* Western Blotting

mucosa of the olfactory region, including olfactory bulb [15, 16]. The ACE2 receptor was identified in sustentacular/non-neuronal cells of the olfactory tissues. Moreover, ACE2 was found in a low proportion of neuronal stem cells in the olfactory bulb [15, 16]. The expression of ACE2 in olfactory neurons (non-stem cells) remains uncertain because Butowt et al. and Brann et al. observed that ACE2 has only non-neuronal expression pattern in olfactory epithelium [15, 16].

Five studies investigated ACE2 expression in oral and pharyngeal regions, including oral, and hypo- oro- and nasopharyngeal spaces [11, 19, 23–25]. The study that explored ACE2 expression in human nasopharynx [19], did not exhibit significant ACE2 immunostaining in nasopharyngeal cells [19]. ACE2 receptor was identified in oral endothelial [11], epithelial [11, 23, 25], and salivary [24] cells. Xu et al. found that ACE2 was also expressed in T and B cells as well as fibroblasts of the oral cavity [23]. Moreover, ACE2 was expressed in major salivary gland tissues [18] and thyroid tissue [21]. In many publications, authors reported the type of cells (goblet versus epithelial versus stem cells) that expressed ACE2 or TMPRSS2 (Table 2). Interestingly, Xu et al. almost as much ACE-2 expression in the thyroid as in the lungs [23].

The genetic analysis of Cao et al. reported that there are 15 unique expression quantitative trait loci variants in the East Asian population, supporting a gene polymorphism and tissue-related differences between individuals [17].

Fig. 1 Flow chart. *ACE2* Angiotensin Converting Enzyme-2, *TMPRSS2* transmembrane protease serine-2
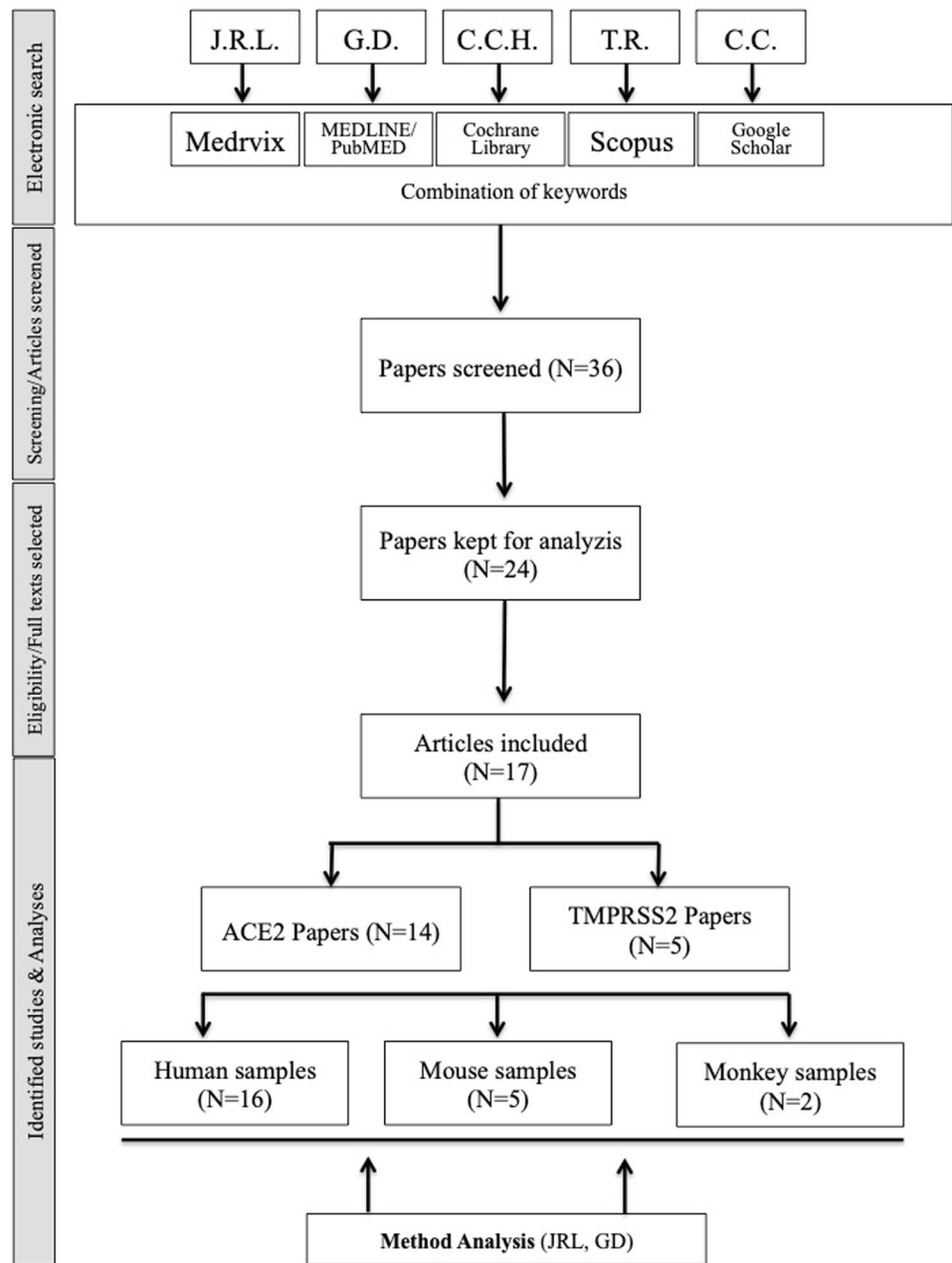
TMPRSS2 Expression

TMPRSS2 expression was investigated in 5 studies [10, 15, 16, 22, 26]. Similarly to ACE2, TMPRSS2 was identified in nasal [16, 22, 26] and respiratory mucosa cells [22], including both epithelial and goblet cells, with higher expression in lower airway compared with upper airway [22]. Moreover, TMPRSS2 receptor was identified in sustentacular and neuronal olfactory cells [15, 16] but not in olfactory neurons [15]. TMPRSS2 was also identified in salivary major gland tissue [10].

ACE2 & TMPRSS2 Tissue Expression in Mouse and Monkey

Six studies used animal models to assess ACE2 or TMPRSS2 expressions in head and neck tissues [10, 13–16, 26]. The mouse studies of Butowt et al. and Bilinska et al. revealed that elderly mice had higher expression of both ACE2 and TMPRSS2 in nasal mucosa compared with younger mice [14, 15]. In olfactory tissue, ACE2 was identified in sustentacular/non-neuronal and neural stem cells of mice [14–16]. Liu et al. analyzed ACE2 expression in monkeys [13],

Table 2 Summary of Cell Expression of ACE2 and TMPRSS2

Authors	Samples	Tissue	Cell types	ACE2	TMPRSS2
Bilinska [14]	Mouse	Olfactory	Sustentatorial	+	+
Brann [15]	Human & Mouse	Olfactory	Sustentatorial	+	+
			Neuronal	-	-
			Stem Neuronal	+	+
Butowt [16]	Human & Mouse	Nasal	Epithelial	+	+
		Olfactory	Sustentatorial	+	−
			Neuronal	−	−
Chen [18]	Human	Major Salivary Gland	Granular	+	NA
Hamming [11]	Human	Oral, Nasal, Nasopharyngeal	Basal layer	+	NA
			Endothelial	+	NA
Hikmet [19]	Human	Nasopharyngeal	Epithelial	−	NA
Jia [12]	Human		Apical Epithelial	+	NA
			Endothelial	+	NA
Lee [20]	Human	Tracheal, Nasal, Sinusal	Apical Epithelial	+	NA
			Goblet	−	NA
Li [21]	Human	Thyroid	Unspecified	+	NA
Liu [13]	Monkey	Pharyngeal	Minor salivary ductal	+	NA
		Tracheal	Basal layer	+	NA
Sungnak [22]	Human	Tracheal & Nasal	Goblet	+	+
			Apical Epithelial	+	+
Vaarala [10]	Human & Mouse	Major Salivary Gland	Unspecified	NA	+
Xu [23]	Human	Oral	Apical Epithelial	+	NA
			Fibroblast	+	NA
			T- and B-cells	+	NA
Xu [24]	Human	Minor Salivary Gland	Unspecified	+	NA
Wu [25]	Human	Nasal	Unspecified	+	NA
		Oral	Basal layer	+	NA
Ziegler [26]	Human, Mouse & Monkey	Nasal & Sinusal	Goblet	+	+

ACE2 Angiotensin Converting Enzyme-2, *NA* not available, *TMPRSS2* transmembrane protease serine-2

reporting a higher ACE2 expression in tracheal, naso-, oro- and hypopharyngeal tissues as well as in the salivary ducts of the pharyngeal gland, and, consequently, in saliva. In this study, the cell expression was mainly localized in the lamina propria. In the same vein, Vaarala et al. reported TMPRSS2 expression in mouse salivary tissues [10].

Cell Detection Methods

The following methods have been used for detecting ACE2 and TMPRSS2 in cells of human and animal tissue: RNAseq (N=11); IHC (N=6); RT-PCR (N=1); in situ hybridization (ISH) (N=1) and WB (N=1). Different detection approaches were used in 2 studies [12, 14]. One study reported specific genetic analysis [17]. There were significant differences between studies regarding methods used. While Ziegler et al. and Sungnak et al. detected ACE2 by RNAseq in goblet cells, Lee et al. did not find any immunohistochemical labeling

[20, 22, 26]. However, the results reported in sustentacular cells agree in the same direction whatever the technique used, whether by RNAseq or by ISH and immunocytochemistry [14–16]. The discrepancies are rather observed between studies having performed immunohistochemistry. Indeed, using two different antibodies, Hikmet did not find ACE2 expression in nasopharynx epithelium whereas others demonstrated the staining of the apical surface of epithelia and ciliated epithelial cells [12, 19, 20]. Interestingly, all the studies which carried out RNAseq found an expression of ACE2 or TMPRSS2 at the epithelial level which implies that the technique used could generate biases between the studies [10, 18–20, 22–25].

Discussion

The presentation of COVID-19 infection may be in several clinical forms ranging from anosmia in isolation to severe multiple organ failure and death. The mechanisms underlying the COVID-19 polymorphism are still unknown. To infect tissues, SARS-CoV2 needs to entry into the cells, which is allowed through ACE2 and TMPRSS2 receptors [4]. The identification of virus receptor expression in the tissues makes particularly sense to better understand the clinical expression of the disease. This systematic review sheds light on many points.

First, ACE2 and TMPRSS2 receptors are expressed in epithelial and non-epithelial cells throughout the head and neck. The head and neck expression may support the otolaryngological clinical picture of the disease, which was recently found in European and North American COVID-19 patients [6, 7, 27, 28]. By entering the body via the epithelial cells of the upper aerodigestive tract mucosa, the SARS-CoV-2 virus leads to an inflammatory reaction and the development of otolaryngological symptoms. Nasal entrance of the virus through high ACE2 expression was supported in the study of Wu et al. who found a higher virus concentration in nasal swabs compared with throat swabs [25].

The olfactory cleft is a nasal region that has drawn the attention of many researchers over the past few weeks. Indeed, recent data supported that more than 70% of COVID-19 patients developed subjective olfactory dysfunction, especially when patients suffered from mild-to-moderate forms of the disease [5, 7, 28, 29]. Because ACE2 and TMPRSS2 are both expressed in the nasal mucosa of the olfactory cleft, entrance into the olfactory bulb seems plausible. Once in the bulb, according to some human studies [15, 16], the virus could infect cells that express ACE2 or TMPRSS2, namely glial and neuronal stem cells (Fig. 2).

Integrating the molecular, clinical and radiological characteristics of SARS-COV-2 olfactory loss may shed light about its pathophysiological process. Taking into account that the loss is often temporary, SARS-COV-2 may primarily infect the sustentacular cells supporting the olfactory sensory neurons. This infection may cause rapid disruption of the olfactory epithelium structure and function with a possible inflammatory response inducing sudden onset smell loss. This inflammation is observed in a minority of patient with congested olfactory cleft who underwent CT scan [5, 7, 28, 30–32].

ACE2 and TMPRSS2 are also found in horizontal basal olfactory stem cells located in the basal layer. They are less exposed to the external environment, thus less likely to be infected in first line; the loss would have been more
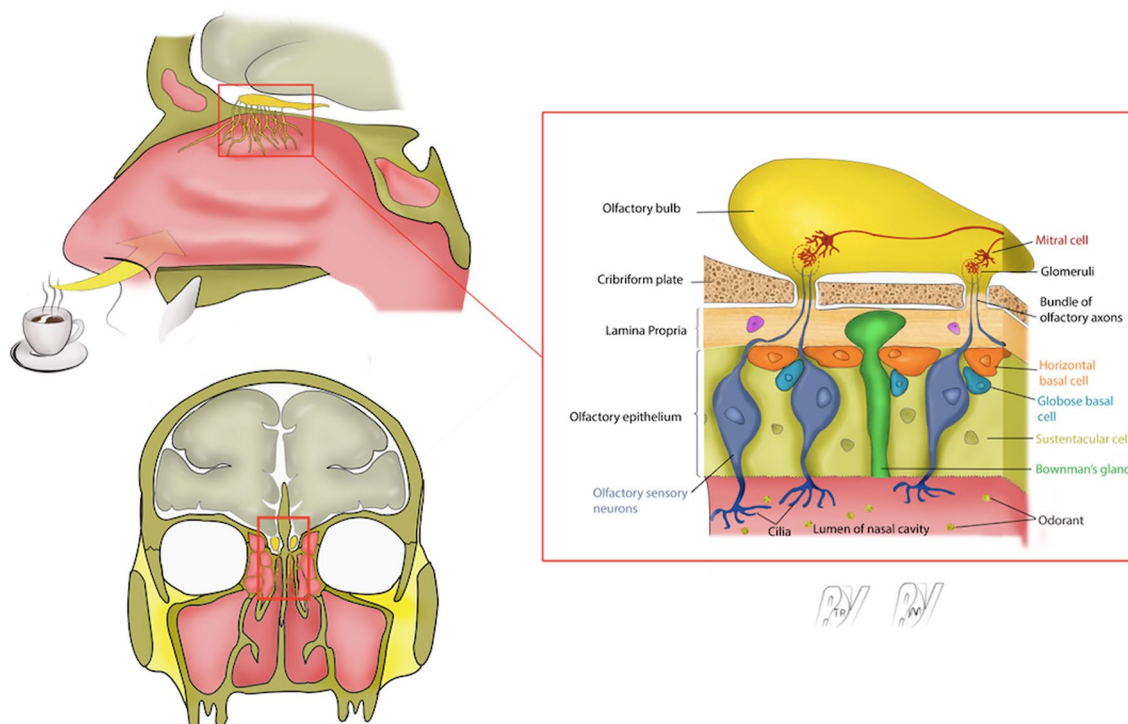

Fig. 2 Epithelium of Olfactory Cleft. The figure summarizes the olfactory cleft epithelium

progressive. However, once infected, they might slow down recovery time because horizontal basal cells give rise to many cell type in the olfactory epithelium. They may also contribute to virus spread to the olfactory bulb vascular pericytes. Magnetic resonance imaging (MRI) studies of the olfactory bulb [33, 34], in which ACE2 are only expressed in vascular pericytes but not in neurons, may show inflammatory signs suggesting that the infection process can extend more centrally and promote inflammatory response [35]. Inflammatory causes are often quickly reversible for example after a one-week trial of high dose of corticosteroids or simply days after the resolution of the viral infection suggesting that the olfactory neurons and bulbs are still somewhat intact. This seems to be the case for a majority of patients. In contrast, with more sustained destruction of neuronal olfactory structures, the recovery time is much longer and may take 2–3 years, given the slow neuroregeneration process [36, 37].

In this systematic review, we found that three studies reported high ACE2 expression in major or minor salivary gland human tissues [10, 18, 24]. These data corroborate the literature findings that reported a salivary pattern of SARS-CoV-2 and related parotitis [38, 39]. Moreover, the virus spread into the salivary gland tissues allows us a better understanding the mechanisms underlying salivary transmission. Interestingly, in 2011, Liu et al. observed that monkeys infected by SARS-CoV had a salivary viral spread, which was associated with a salivary virion excretion [13]. These data support the need to conduct future studies investigating the presence of SARS-CoV-2 in the saliva of infected human and to corroborate the saliva findings with the ACE2 salivary gland expression.

The head and neck expression of ACE2 and TMPRSS2 and the related otolaryngological symptom pattern seems obvious but could vary across individuals and populations. In support of this, Lee et al. observed that ACE2 expression is influenced by patient demographics, clinical characteristics, co-morbidities and medication [20]. As reported in the genetic analysis of Cao et al., there would be different susceptibilities or responses to SARS-CoV2 in different populations [17]. The polymorphism of ACE2 and TMPRSS2 expression could explain the clinical differences between individuals. Indeed, many physicians reported in clinical and epidemiological studies different clinical presentation of the disease [28, 30], which could be associated with virus mutations [40, 41]. The virus mutations and the related impact on receptor binding and infectivity is another point that has to be considered in future studies. Otherwise, according to the Bgee database (https://bgee.org/), expression of ACE2 and TMPRSS2 evaluated in murine models may increase with age. These findings have to be confirmed in humans, but could explain more severe clinical pictures in the elderly.

The present study has several limitations. First, the heterogeneity between studies about the detection method may lead to detection bias as some approaches are more sensitive than others. Some studies interrogate gene expression at mRNA level and others at protein levels, both types of analysis having their advantages and limitations. Compared to transcriptomic analyzes, immunohistochemistry brings additional important spatial information in tissue samples but recently Sorokin et al. demonstrated high and statistically significant correlations between the RNA sequencing and immunohistochemical measurements [42]. Interestingly, they highlighted the complementarity of both techniques for measuring cancer biomarkers in FFPE samples. However, differences observed across IHC studies suggest the involvement of many parameters. The antibody specificity is a big challenge to ensure reproducibility of antibody-based studies and given the high homology between ACE1 and ACE2, cautions must be taken regarding antibody selection. Besides, a report from the International Working Group for Antibody Validation (IWGAV) proposed five scientific approaches to validate antibody specificity [43], then such strategies must be considered in future investigations to confirm the published observations. In addition, it seems essential to enlarge and diversify patient cohorts and to combine transcriptomic and proteomic strategies as well as colocalize different markers of SARS-CoV-2, such as ACE2 and TMPRSS2, to provide an accurate representation of ACE2 expression through all head and neck areas of the whole population.

Second, the majority of studies that were conducted during the SARS-CoV-2 pandemic did not consider many demographic and clinical factors such as the age of patients from who the tissues were extracted or the use of ACE inhibitor medications among others. Third, some otolaryngological regions remain uninvestigated such as the vocal folds. The investigation of these remaining regions may shed further light on some recently reported unusual clinical phenomena such as severe dysphonia [44].

Conclusion

ACE2 and TMPRSS2 are both expressed in head and neck tissues, which may explain the otolaryngological clinical pattern of the disease and the entry of SARS-CoV-2 into the host organism. Future studies considering demographical and clinical characteristics of patients from who the tissues are extracted are needed to better understand the cell entry mechanisms of SARS-CoV-2.

for the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. CCH, CMCE, MRB, IG: design, data analysis & interpretation, revising the manuscript for important intellectual content; final approval of the version to be published, final approval, and accountability for the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. LS, SH, GC, GD, JH, LV, GR: design, acquisition of data, data analysis & interpretation, drafting some parts of the manuscript; final approval of the version to be published, final approval, and accountability for the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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